# The Assessment and Management of Glycaemic Control and Vascular Risk in People with Type 1 Diabetes

Thesis submitted in with the requirements of the University of Liverpool for the degree of Doctor in Philosophy.

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## ABSTRACT

### Introduction:

Type 1 diabetes is a common cause of chronic disease in young people. Over the past few decades a worldwide rise in incidence has been observed, particularly in children under the age of 5 years. Life expectancy is reduced with the major causes of mortality being renal and cardiovascular disease. Good glycaeamic control has been shown to reduce the risk and progression of micro and macro vascular complications in type 1 diabetes. However, in many people, target $HbA_{1c}$ levels are difficult to achieve without increasing the risk of hypoglycaemia. In the past, there has been a tendency to focus on the prevention of microvascular complications, especially in young people with type 1 diabetes. However it is clear that type 1 diabetes is associated with an increased risk of cardiovascular disease and therefore a shift in emphasis towards global risk factor reduction may be indicated. This could include the management of glycaemia and cardiovascular risk factors involving lifestyle and pharmacological interventions.

### Aims:

This thesis consists of four related studies of aspects of glycaemic and cardiovascular risk factor management in people with type 1 diabetes. The aims of these studies were:

(1) Audit: To assess the achievement of glycaemic control and cardiovascular risk factor targets in people with type 1 diabetes attending a routine hospital based diabetes clinic.
(2) Physical activity and glycaemic control: To clarify the relationship between aerobic fitness and glycaemic control in people with type 1 diabetes and identify the management strategies adopted by people with type 1 diabetes to maintain blood glucose control and avoid hypoglycaemia during physical activity.
(3) Nurse led intervention versus routine care: To compare the effects of a nurse-led risk factor reduction clinic with routine diabetes care in achieving glycaemic and cardiovascular risk factor targets
(4) Glycaemic "streaming": To investigate the stability of long term glycaemic control in a group of people with type 1 diabetes over a 5 year period, examining the possible phenomenon of glycaemic "streaming".

### Methods:

The basic investigative methods for the 4 studies were:

(1) Audit: A case note review of 218 people with type 1 diabetes. Demographic and risk factor target information (weight, $HbA_{1c}$, blood pressure, lipid profile and albumin : creatinine ratio) were collected. The same group was reassessed 3.5 years later.
(2) Physical activity and glycaemic control: To assess the relationship between physical activity and glycaemic control aerobic capacity was assessed using the Chester Step Test in 141 people with type 1 diabetes. In addition self reported physical activity, frequency of hypoglycaemia and hypoglycaemic avoidance behaviour was assessed using a simple 'in-house' questionnaire in 50 of the 141 people who had completed the Chester Step Test.

(3) Nurse led intervention versus routine care: To compare the effects of nurse-led intervention with routine care, 81 people with type 1 diabetes with an $HbA_{1c}$ ≥8.0% and at least one other risk factor for the development of cardiovascular disease were randomised to receive either routine care or nurse-led intervention. $HbA_{1c}$, non-fasting lipid profile, blood pressure, weight, BMI and insulin dose were recorded at baseline, 6, 12 and 24 months.
(4) Glycaemic "streaming": To examine long term glyceamic control a retrospective analysis of glycaemic control in a cohort of 181 people with type 1 diabetes (2003-2007) was conducted. Basic demographic data, sequential $HbA_{1c}$, first and last $HbA_{1c}$, and mean $HbA_{1c}$ for the 5 year period was collected.

**Results:**

The results of each of the 4 studies are as follows:

(1) Audit: Mean $HbA_{1c}$ was 9.7±1.9%, mean total cholesterol was 5.1±1.1 mmol/l, mean systolic blood pressure was 113±18 mmHg and mean diastolic blood pressure was 64±10 mmHg. Target $HbA_{1c}$, (≤ 7.5%) was achieved in only 7.9% of those audited, 54.6% had a total cholesterol above target (>4.8 mmol/l), 13.1% had a systolic blood pressure above target (>135mmHg) and 3.8% had a diastolic blood pressure above target (>85mmHg). At re-audit mean $HbA_{1c}$ and total cholesterol had improved significantly and mean systolic and diastolic blood pressure had increased significantly.
(2) Physical activity and glycaemic control: Initial data revealed a positive correlation between aerobic capacity and $HbA_{1c}$ ($r=0.17$, $p<0.05$), indicating that those with good aerobic capacity have poorer glycaemic control. Further investigation, involving 50 people with type 1 diabetes, revealed that 78% of this group took some action to prevent hypoglycaemia during physical activity despite there being no previous experience of serious hypoglycaemia associated with physical activity.
(3) Nurse led intervention versus routine care: Compared with routine care, nurse-led intervention led to significant improvements in $HbA_{1c}$ (10.1±1.4 v 9.3±1.4%, $p<0.001$), total cholesterol (5.8±0.9 v 4.3±1.0 mmol/l, $p<0.001$), systolic (127±22 v 115±13 mmHg, $p<0.001$) and diastolic blood pressure (71±13 v 65±9 mmHg, $p<0.05$) at 12 months. At 24 months improvements were maintained in all variables except diastolic blood pressure. In the control group only total cholesterol improved significantly after 12 months (5.9±0.9 v 5.2±1.0 mmHg, $p<0.001$) and this was maintained at 24 months.
(4) Glycaemic "streaming": Over the 5 year study period there was a small but significant improvement in mean $HbA_{1c}$ in the cohort studied (181 patients) (9.0 ± 1.6 to 8.7 ± 1.5%, $p = 0.003$). This was accounted for by improvements in males (8.9 ± 1.6 to 8.6 ± 1.4%, $p = 0.005$) and those with poor control ($HbA_{1c}$ > 8.0%) (9.4 ± 1.4 to 9.0 ± 1.4%, $p = 0.002$). Females and well controlled patients did not show any improvement in mean glycaemic control.

**Conclusions:**

The basic audit data indicated that the majority of people with type 1 diabetes involved in the study had an $HbA_{1c}$ and lipid profile outside of the target range regardless of being managed in a clinic staffed by a multidisciplinary diabetes team experienced in the management of type 1 diabetes. Although over a 3.5 year follow- up period mean $HbA_{1c}$ and total cholesterol

improved significantly. The majority of patients still had an $HbA_{1c}$ and total cholesterol above target levels.

Life advice such as the encouragement of physical activity is a routine part of diabetes care on the assumption that this will have beneficial effects on glycaemic control and cardiovascular risk factors. However, the study of physical activity and glycaemic control included in this thesis, has demonstrated that increased aerobic capacity, indicating greater physical fitness, was associated with poorer glycaemic control. Further investigation revealed that this may be due to action taken by people with type 1 diabetes to avoid potential hypoglycaemia (increasing carbohydrate consumption, reducing insulin or a combination of both) which may have had a detrimental effect on glycaemic control. These findings indicate that people with type 1 diabetes require more education on the management of blood glucose during physical activity.

Routine diabetes follow up reviews can be complex and time consuming with a focus not only on presenting problems but also on routine screening, risk factor reduction and lifestyle issues. The achievement and maintenance of target $HbA_{1c}$ levels on a long term basis can be difficult for many people with type 1 diabetes. There are several possible reasons for this. Even with modern insulin regimens it is difficult to mimic physiological insulin secretion. In addition it is possible that for some patients the drudge of the day to day self management of type 1 diabetes leads to fatigue of the efforts required. It is also plausible that concern about hypoglycaemia, leading to intentional raised blood glucose levels, may contribute to poor glycaemic control. Furthermore there may be a tendency to a "streaming" effect. In the glycaemic "streaming" study included in this thesis, a small overall improvement in $HbA_{1c}$ was noted over a 5 year time period. However, most patients maintained similar glycaemic control over the study period adding strength to the small body of data on the phenomenon of glycaemic "streaming".

Alternatively poor glycaemic control may reflect the system of health care delivery. It may be that to achieve optimal diabetes care particular problems need to be identified and managed in a specific clinic staffed by experienced health care professionals. Traditionally diabetes specialist nurses have focused mainly on glycaemic control. However many of the lifestyle issues which impact on glycaemic control also influence blood pressure and lipid profile. In the randomised controlled study reported in this thesis nurse led intervention resulted in beneficial effects on glycaemic and cardiovascular risk targets in type 1 diabetes most of which were maintained at 24 months. These improvements may be a feature of being seen more frequently by the same person. Nurse led intervention, particularly in the first 6 months, involved identification of individual goals and regular review of these goals which may have increased motivation. Also a change in focus to global risk factor reduction, rather than just glycaemic control may have had a beneficial effect. In addition improvements in risk factors were associated with a greater use of anti-hypertensive and lipid lowering agents.

The findings reported in this thesis have significant implications for practice. Targeted nurse-led global risk factor reduction may be a more effective system of achieving risk factor targets in patients with type 1 diabetes, freeing medical staff to deal with more complex cases. Adopting a global approach may encourage patients to make lifestyle changes to reduce cardiovascular risk which also have beneficial effects on glycaemic control.

## PREFACE

Following the discovery of insulin, an increase in medical knowledge and screening procedures have resulted in a longer life expectancy for people with type 1 diabetes. A rise in the incidence of type 1 diabetes has been observed worldwide over recent decades and much of this increase has been reported in children particularly in those aged less than 5 years (Schober et al 2008, Patterson et al 2009). In the UK there are currently 2.9 million people (children and adults) with diagnosed diabetes and it is estimated that approximately 15% of these individuals have type 1 diabetes. It is predicted, that by 2025, there will be 5 million people in the UK with diagnosed diabetes (Diabetes UK 2012).

A diagnosis of diabetes can lead to the imposition of substantial lifestyle adjustments and in the long term serious and disabling complications can occur. People with type 1 have to endure lifelong medical follow up and treatment interventions which may impact on their physical and psychological well-being. Effective care depends on the person with diabetes performing a series of self care behaviours which include the injection of insulin several times a day, monitoring blood glucose levels and altering insulin doses according to blood glucose levels and physical activity. This complex and demanding regimen rests primarily with the person with diabetes.

Aside from the burden of diabetes on the effected individual, diabetes also impacts on National Health Service (NHS) resources. It is currently estimated that 10% of the NHS budget, £9 billion per year, is spent on diabetes (Diabetes UK 2012).

Despite advances in medical care type 1 diabetes is still associated with increased morbidity and mortality (Skrivarhaug et al 2006, Secrest et al 2010). However evidence from the Diabetes Control and Complications Trial and the Epidemiology of Diabetes Interventions and Complications study demonstrate that good glycaemic control can reduce the risk and progression of micro and macro vascular complications in type 1 diabetes (Diabetes Control and Complications Research Trial Group 1993, Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Study Research Group 2005). However achieving target glycaemic control whilst minimising the risk of hypoglycaemia remains a challenge and large amounts of nursing and medical time are invested in attempts to improve control often with little or transient effect. In recent years there has been a focus on nurse- led global risk factor reduction, particularly in type 2 diabetes

(Woodward et al 2006) and it is reasonable to assume that such an approach may be effective in type 1 diabetes.

This thesis focuses on the management of glycaemic and cardiovascular risk factors in adults with type 1 diabetes and is organised into the following chapters:-

The first 3 chapters are introductory chapters providing an overview of type 1 diabetes and reviewing the literature on the acute and long term complications of type 1 diabetes and risk factor management.

Chapter 1:- Presents an overview of type 1 diabetes starting with a historical perspective and moving on to consider the aetiology and epidemiology. Clinical management including a critical review of the various types of insulin is presented and education and quality of life issues are considered. The last section of this chapter considers the acute complications of diabetes.

Chapter 2:- This chapter reviews the long term micro and macro vascular complications associated with type 1 diabetes considering both primary and secondary preventative measures. It also includes a section on long term survivors of type 1 diabetes and a section on The Diabetes Control and Complications Study and 'metabolic memory'.

Chapter 3:- Focuses on reducing risk and improving outcomes in type 1 diabetes including lifestyle issues and pharmacological interventions. Risk factor targets are discussed and a review of the various insulin regimens is included.

Chapters 4-7 are the audit and research chapters which consider a variety of aspects of glycaemic and cardiovascular risk factor management in type 1 diabetes. Patients, methods, statistical analysis, results and findings are discussed in each individual chapter. The chapters are divided as follows:-

Chapter 4:- This chapter presents two audit papers. The initial study is an audit of the achievement of risk factor targets in a population of individuals with type 1 diabetes. The aim of this study was to assess 'the size of the problem' locally prior to a review of services. The

chapter states the audit standards, describes the methodology and presents the results. In addition the cohort is reassessed 3.5 years after the initial audit and results are compared.

Chapter 5:- This chapter includes 2 studies of physical fitness and glycaemic control in people with type 1 diabetes. The first study is an assessment of the relationship between aerobic capacity and glycaemic control. Details of the patients and methods are included. The results are presented and discussed. Somewhat surprisingly this study demonstrated that people with type 1 diabetes who have good aerobic capacity have poorer glycaemic control. This prompted further investigation into why this might be. The second study investigated how people with type 1 diabetes manage blood glucose level during physical activity. Methods and results are presented as is a discussion of the findings.

Chapter 6:- This chapter is a randomised controlled study comparing the effects of nurse-led intervention and routine care on glycaemic and cardiovascular risk factor targets. Patients, methods, sample size, statistical analysis, findings and implications for clinical practice are discussed.

Chapter 7:- This chapter investigates the phenomenon of glycaemic "streaming" or "tracking" in a cohort of people with type 1 diabetes over a 5 year period. The chapter includes a brief review of the limited literature available and compares finding with the small number of previous studies.

Chapter 8:- This chapter presents a summary and discussion of the results from the 6 studies. The strengths and weakness of the studies are highlighted and the implications for clinical practice discussed. Finally the last section considers future perspectives and research in the field of type 1 diabetes.

**References to preface:**

Diabetes Control and Complications Trial. The effect of intensive treatment of diabetes on the development and progression of long-term complication insulin-dependent diabetes mellitus. The New England Journal of Medicine 1993; 329: 977-986

Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Study Research Group. Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. New England Journal of Medicine 2005; 353: 2643-2653

Diabetes UK. Diabetes in the UK 2011 / 2012: Key statistics on diabetes. http://www.diabetes.org.uk/Documents/Reports/Diabetes-in-the-UK-2011-12.pdf

Patterson C, Dahlquish GG, Gyurus A, Green A, Soltesz G. Incidence trends for childhood type 1 diabetes in Europe during 1989-2003 and predicted new cases 2005-20: a multicentre prospective registration study. Lancet 2009; 373: 2027-2033

Schober E, Rami B, Waldhoer T. Steep increase of incidence of childhood diabetes since 1999 in Austria. Time trend analysis 1979–2005. A nationwide study. European Journal of Pediatric 2008; 167: 293–297

Secrest AM, Becker DJ, Kelsey SF; LaPorte RE, Orchard J. All-cause mortality trends in a large population-based cohort with long-standing childhood-onset type 1 diabetes: The Allegheny County type 1 Diabetes Registry. Diabetes Care 2010; 33: 2573-2579

Skrivarhaug T, Bangstad TJ, Stene LC, Sandvik L, Hanssen KF, Joner G. Long-term mortality in a nationwide cohort of childhood-onset type 1 diabetic patients in Norway. Diabetologia 2006; 49: 298–305

Woodward A, Wallymahmed M, Wilding J, Gill G. Successful cardiovascular risk reduction in Type 2 diabetes by nurse-led care using an open clinical algorithm. Diabetic Medicine 2006; 23, 780–787

## PUBLICATIONS AND PRESENTATIONS FROM THIS THESIS

### PUBLICATIONS IN PEER REVIEWED JOURNALS:

Wallymahmed ME, Pinkney J, Saunders S, MacFarlane. Vascular risk factors in patients with Type 1 diabetes. Practical Diabetes International 2005; 22: 81-85.

Wallymahmed ME, Morgan C, Gill GV, MacFarlane. IA Aerobic fitness and hand grip strength in type 1 diabetes: relationship to metabolic control and body composition. Diabetic Medicine 2007; 24:1296-1299

Wallymahmed ME, Morgan C, Gill GV, MacFarlane IA. Does hypoglycaemic avoidance behaviour contribute to increased HBa1c levels in physically active people with type 1 diabetes. Practical Diabetes International 2007; 24: 418–421

Wallymahmed ME. The management of Type 1 diabetes : more than just glycaemic control. The 2008 Janet Kinson Lecture Practical Diabetes international 2008;7: 285-289

Wallymahmed ME, Morgan C, Gill GV, Osman-Hicks V, Chamberlain P. MacFarlane IA. Changes in cardiovascular risk factors in a type 1 diabetes population: a 3.5 year study. Practical Diabetes International 2008; 25: 223-227

Wallymahmed ME, Morgan C, Gill GV, MacFarlane IA. Nurse led cardiovascular risk factor intervention leads to improvements in cardiovascular risk targets and glycaemic control in people with type 1 diabetes when compared to routine diabetes clinic attendance . Diabetic Medicine 2011; 28: 373-379

### POSTER PRESENTATIONS AT SCIENTIFIC MEETINGS AND PUBLICATIONS IN ABSTRACT FORM:

Wallymahmed ME, Morgan C, Gill GV, MacFarlane IA. Aerobic fitness, handgrip strength and body composition in type 1 diabetes: relationship to metabolic control. Diabetic Medicine (2005) 22 (suppl 2) P105, Diabetes UK National Conference, Glasgow 2005.

Wallymahmed ME, Morgan C, Gill G, MacFarlane IA. Physically active people with type 1 diabetes have increased Hba1c levels: role of hypoglycaemic avoidance behaviour. DiabeticMedicine 23 (suppl 2) P69, Diabetes UK National Conference Birmingham 2006

Wallymahmed ME, Morgan C, Gill GV, Macfarlane IA.The influence of structured fitness advice on fitness (aerobic capacity), body composition and metabolic control in Type 1 diabetes – a 2 year study. Diabetic Medicine (2007) 24 (suppl 1) P115. Diabetes UK Annual Conference, Glasgow, March 2007.

Wallymahmed ME, Morgan C, Gill G, MacFarlane IA.Cardiovascular risk factors and physical fitness in type 1 diabetes: the impact of a consultant nurse clinic. Diabetic Medicine (2008) 25 (suppl 1) P277. Diabetes UK Annual Conference, Glasgow, March 2008.

Wallymahmed ME, Morgan C, Gill GV, MacFarlane IA. Cardiovascular risk factors in type 1 diabetes: the impact of a nurse led risk factor clinic Diabetic Medicine (2010) 27 (suppl 1) P176 Diabetes UK Annual Conference, Liverpool, March 2010.

Gill GV, Woodward A, Bailey D, MacFarlane IA, Casson IF, Wallymahmed ME. Glycaemic streaming in Type 1 diabetes: is intervention worthwhile Diabetic Medicine (2010) 27 (suppl 1) P228. Diabetes UK Annual Conference, Liverpool, March 2010.

**INVITED ORAL PRESENTATIONS:**

Diabetes UK Annual Professional Conference – Glasgow, March 2008
Janet Kinson Lecture - 'The management of Type 1 diabetes – more than just glycaemic control?

## ABBREVIATIONS

| | |
|---|---|
| ACE | Angiotensin Converting Enzyme |
| ACR | Albumin Creatinine Ratio |
| BMI | Body Mass Index |
| BP | Blood Pressure |
| CGMS | Continuous Glucose Monitoring Systems |
| CSII | Continuous Subcutaneous Insulin Infusion |
| CVD | Cardiovascular Disease |
| DAFNE | Dose Adjustment for Normal Eating |
| DCCT | Diabetes Control and Complications Trial |
| DKA | Diabetic Ketoacidosis |
| DSN | Diabetes Specialist Nurse |
| EDIC | Epidemiology of Diabetes Interventions and Complications Study |
| HbA1c | Glycated Haemoglobin |
| HDL | High Density Lipoprotein |
| LDL | Low Density Lipoprotein |
| NICE | National Institute of Clinical Excellence |
| NPH | Neutral Protamine Hagedorn insulin |
| SMR | Standardised Mortality Ratio |
| UK | United Kingdom |
| USA | United States of America |

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# TYPE 1 DIABETES - AN OVERVIEW

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# TYPE 1 DIABETES- AN OVERVIEW

## 1.1 INTRODUCTION

This chapter presents a critical overview of the most important aspects of the disease of type 1 diabetes. It starts with an historical overview and goes on to discuss the aetiology and possible environmental and genetic risk factors associated with the development of type 1 diabetes. In the past few decades there has been a global increase in the incidence of type 1 diabetes, particularly in children under the age of 5 years and geographical differences are considered. Clinical management of type 1 diabetes is focused around insulin replacement and a variety of different insulin types and delivery systems are reviewed. As with any chronic condition the burden of diabetes can be considerable to the affected individual and issues of education and impact on quality of life are considered.

The main theme of this thesis is the management of risk factors associated with the development of the chronic complications of type 1 diabetes. This chapter will provide an overview of type 1 diabetes generally. Chapter two will focus specifically on the micro and macrovascular complications associated with type 1 diabetes and chapter three will consider the risk factors related to these complications.

## 1.2 HISTORY OVERVIEW - "A MELTING DOWN OF FLESH"

The symptoms associated with diabetes mellitus have been recognised for thousands of years. A clinical description of type 1 diabetes can be dated back to Aretaeus of Cappadocia in the 2$^{nd}$ century AD when he described diabetes as 'a dreadful affliction... a melting down of flesh and limbs into urine' which describes the classical presentation of type 1 diabetes. He also added that 'life is short unpleasant and painful 'referring to the onset of diabetic ketoacidosis which in the absence of exogenous insulin the patient would eventually succumb to. The urine in patients with diabetes was noted to be sweet as early as 400-500 BC by two Hindu physicians Sasruta and Charuka . They also noted that the condition was most common in people who were overweight and gluttonous, alluding to type 2 diabetes. Sweet urine was also

documented by Avicenna in Arabic texts in the 9th-11th centuries, he also described complications such as gangrene.

In the 17th century an English physician Thomas Willis described the urine of people with diabetes as being 'sweet like sugar or honey' (Tattersall 2010a). At the same time Thomas Sydenham speculated that diabetes was a systemic disease arising in the blood where 'chyle' was incompletely absorbed (MacFarlane 1991). Hyperglycaemia was first described by Mathew Dobson, a physician from Liverpool who published a series of observations and experiments on the blood and urine of one of his patients, Peter Dickonson. He concluded that sugar was excreted by the kidneys but it was 'not formed in the secretory organ but previously existed in the serum of the blood' (Dobson 1776 ). The word diabetes is from the Greek word meaning siphon and 'mellitus' from the Latin word meaning honey was added by John Rollo in the 18th century.

In the 19th century Michel Chevreul, a French chemist, introduced chemical tests to aid diagnosis however this was seldom used due to the amount of blood required. Prior to this the only diagnostic tool was tasting the urine to detect sweetness. The 19th century also saw the description of glucose metabolism and storage (Claude Bernard 1813-1878) and recognition that diabetes was associated with the pancreas. This was an incidental finding, by Oskar Minkowski and Josef von Mering, following the removal of a dogs pancreas to investigate fat metabolism. Pancreatic islet cells were identified in 1869 by Paul Langerhans and later named the islets of Langerhans by Gustave Laguesse. At this time there was speculation that pancreatic secretions were the key to a cure for diabetes however attempts to isolate extracts were unsuccessful. Clinical management of diabetes focused on almost starvation regimens which may have prolonged life in type 1 diabetes for a short period of time.

In 1921 an orthopaedic surgeon named Frederick Banting (figure 1.1) , encouraged after reading an article on the pancreas approached Professor James Macleod at Toronto University with an idea involving ligation of the pancreatic ducts to isolate internal secretions. Professor Macleod was initially reluctant but eventually relented and assigned a student Charles Best to help with the work. Their work involved the injection of extracts of atrophied pancreas into dogs with diabetes due to pancreatectomy. Later they obtained active beef extracts from the abattoir. The first person to be treated with insulin was a 14 years old boy named Leonard Thompson, who showed a marked clinical improvement with a reduction in glycosuria and

ketonuria. Subsequently the results of seven cases were published in the Canadian Medical Association Journal. In 1923 the Nobel Prize was awarded to Banting and Macleod. Banting was unhappy with this and announced that he would share his prize with Best and Macleod shared his prize with James Collip, a biochemist who had helped refine the extraction procedure. By 1923 insulin was being produced commercially by a company called Eli Lilly who continue to produce insulin today. Initially insulin was isolated from the pancreases of cows and then pigs however purity issues were a problem. In the late 1980's human insulin was introduced followed more recently by insulin analogues. The events surrounding the discovery of insulin are documented in detail in a book by Michael Bliss (Bliss 1982).

**Figure 1.1** Dr Fredrick Banting and Charles Best

Following the discovery of insulin it was generally felt that a cure for type 1 diabetes had been found. However with the passage of time unpredicted long term complications became evident. An association between diabetes and retinal changes in patients with no other evidence of vascular disease was first described in the 1930's (Wagener 1934). However the effectiveness of laser photocoagulation did not become apparent until the 1970's (Diabetic Retinopathy Group 1978). Renal disease related to diabetes was observed in 1936 by Kimmelstiel and Wilson who also noted the presence of hypertension, albuminuria and renal failure (Kimmelstiel and Wilson 1936). The importance of blood pressure control is now well established in the prevention and progression of renal disease in people with diabetes. In the 1940-50's the sombre nature of type 1 diabetes became apparent following the publication of

two papers outlining the serious long term complications (mainly retinopathy, albuminuria and hypertension) and mortality associated with the condition (Dolger 1947, Reuting 1950). In a cohort of 50 young patients, after a mean duration of 18 years, 30% had died mostly due to cardiovascular and renal disease (Reuting 1950). It was not until 1993 that the Diabetes Control and Complications Trial firmly established that good glycaemic control was associated with the prevention and progression of microvascular complications in type 1 diabetes (DCCT 1993). By this time capillary blood glucose monitoring and glycated haemoglobin were available as tools to aid the achievement of glycaemic targets. Type 1 diabetes continues to be a common cause of chronic disease in young people and despite advances in insulin treatment and screening for complications is associated with significant mortality and morbidity. Cardiovascular and renal disease remain the major causes of morbidity and mortality in type 1 diabetes and prevention and treatment of both long and short term complications remain a challenge for all working in the specialty today.

## 1.3 AETIOLOGY OF TYPE 1 DIABETES

Type 1 diabetes is a T cell mediated autoimmune disease involving destruction of the insulin secreting β cells in the pancreatic islets resulting in insulin deficiency. As normal pancreatic β cells have a capacity to produce insulin beyond that needed for normal carbohydrate, fat and protein metabolism the onset of the symptoms of type 1 diabetes; thirst, polyuria and polydipsia, is preceded by an asymptomatic pre clinical diabetes period. This stage is characterised by 'insulitis' where the islets are infiltrated with mainly T lymphocytes and macrophages followed by a loss of β cell function whilst other islet cells are preserved. During this pre clinical period islet auto antibodies to insulin, glutamine acid decarboxylase (GAD), islet cell antibodies (ICAs) and insulinoma-associated antigen 2 (IA-2) can be detected (Eisenbarth 2007) and are thought to be markers of ongoing β cell destruction . In caucasian populations more than 90% show evidence of autoimmunity where 1 or more islet cell auto antibodies are detected on diagnosis of type 1 diabetes (American Diabetes Association 2007a).

The aetiology of type 1 diabetes is complex and involves both genetic predisposition and environmental factors which are thought to trigger onset of the condition. The

pathophysiological mechanisms in type 1 diabetes include 2 distinct stages in genetically susceptible individuals:

- Triggering of autoimmunity resulting in one or more islet cell auto antibodies associated with β cell destruction.
- Loss of β cell function leading to loss of first phase insulin secretion, reduced C peptide levels, glucose intolerance and hyperglycaemia

### 1.3.1 Islet cell auto antibodies

Antibodies against islet cells (ICA's) were first described in 1974. They were detected using frozen pancreatic sections and immunofluorescence (MacCuish et al 1974) and provided the first evidence for type 1 diabetes being an autoimmune condition. Shortly after ICA was detected in individuals who had not been diagnosed with diabetes but subsequently developed the condition (Bottazzo et al 1974). Auto antibodies against glutamic acid decarboxylase (GAD) are most commonly to the GAD65 isoform and are found in approximately 70-80% of children with newly diagnosed type 1 diabetes (Bonifacio 1995) and remain detectable for many years (Sanjeevi 1998). Insulin autoantibodies (IAA) were first identified in 1983 and found to be present in patients with new onset diabetes before insulin was started (Palmer et al 1983). Detection appears to be age related and has been shown to be present in 90% of children who develop diabetes before the age of 5 but only 40-50% of those over 15 years (Vardi et al 1988).

Recently autoantibodies to another autoantigen, zinc transporter 8 (ZnT8Ab), has been identified. This autoantigen is highly β cell specific and has been detected in 60-80% of patients with newly diagnosed type 1 diabetes of whom 26% were negative for other autoantibodies. Less than 2% of controls and 3% of patients with type 2 diabetes tested positive (Wenzlau et al 2007). When combined with other conventional islet autoantibodies (GAD, IA-2, IAA) autoimmunity detection rates were 98% at the onset of type 1 diabetes (Wenzlau et al 2007).

### 1.3.2 Genetic risk factors for type 1 diabetes

Type 1 diabetes is a genetically influenced and immunologically mediated disease with a prolonged asymptomatic phase known as pre diabetes. This eventually results in progressive β cell destruction, insulin deficiency and overt diabetes. A number of genes have been

implicated in the pathogenesis of type 1 diabetes. These are known as "susceptibility genes" as they increase the risk of developing the condition but do not actually cause it. The human leukocyte antigen (HLA) genes, which are located within the major histocompatibilty complex (MHC) of the short arm of chromosome 6, have been shown to influence susceptibility to type 1 diabetes and other autoimmune diseases (Hermann et al 2004, Kelly et al 2006, Todd et al 2007). The combination of HLA DR3-DQ2 and DR4-DQ8 in particular confers a high risk of type 1 diabetes (Hermann et al 2004, Thomson et al 2007). One or both of these are found in approximately 40-50% of the general population compared to 95% of people with type 1 diabetes under 30 years of age (Notkins and Lernmark 2001). Although a strong link between type 1 diabetes and HLA has been established other non HLA genetic factors are also thought to play a role e.g. INS-VNTR. PTPN22.

Having an affected first degree relative increases the risk of developing type 1 diabetes. By the age of 20 years, approximately 4-6% of siblings of people with type 1 diabetes have been reported to have developed the condition (Gillespie and Gail 2002, Harjutsalo et al 2005) compared to about 0.2-1% of the background population. Children of parents with diabetes have a 6-9% risk of developing the condition if the father is affected compared to 2-4% if the mother is affected and this rises to approximately 30% if both parents are affected (Todd and Farall 1996, Akesson et al 2005). In addition concordance rates for type 1 diabetes have been reported to be higher in identical (50-70%) than in non identical twins (10-19%) (Kumar et al 1993, Redondo et al 2001). However the majority of people diagnosed with type 1 diabetes do not have a known family history of the condition.

### 1.3.3 Environmental risk factors for Type 1 diabetes

Several environmental factors are thought to be associated with the development of type 1 diabetes. These factors may have a role in initiating the autoimmune disease process, modulating the progression from islet autoimmunity to clinical type 1 diabetes or precipitating disease in genetically susceptible individuals .

A number of viruses, including mumps, measles, rubella, rotavirus, cytomegalovirus and enterovirus have been implicated in the aetiology of type 1 diabetes (Kelly et al 2006, Von Herrath 2009). Congenital rubella has also been associated with an increase in the incidence of type 1 diabetes (Menser et al 1978, Forrest et al 2002). However in current times vaccination

programmes now make it an unlikely cause of type 1 diabetes in the western world and the associated risk may have been overstated (Gale 2008). Maternal enterovirus during pregnancy has been associated with an increased risk of childhood onset type 1 diabetes in some but not all studies (Viskari et al 2002). In addition antibodies to Coxsackie viruses have been reported to be more common amongst people with newly diagnosed type 1 diabetes than in healthy controls (Green et al 2004). More recently a study involving post-mortem pancreatic biopsies obtained from young individuals with recent onset type 1 diabetes found positive β cell staining for enterovirus in 44 of 72 cases, only 3 of the 50 controls stained positive (Richardson et al 2009).

It has been proposed that reduced exposure to microorganisms in early childhood limits maturation of the immune system and increases susceptibility to autoimmune disease, the "hygiene hypothesis" (Strachan 1989, Gale 2002). The relationship between level of sanitation, socioeconomic factors and the incidence of autoimmune disease strengthens the case; in addition animal models indicate that those raised in a pathogen free environment are more likely to develop autoimmune conditions (Bach 2005). This is supported by findings that children who attend day care, which is associated with increased exposure to microbial agents, may be at a lower risk of developing type 1 diabetes (Kaila and Taback 2001). However this meta analysis of 11 case controlled studies may have been affected by recall bias as there was no pre-recorded data therefore results must be interpreted with care and further investigation is required. However a recent population based case control study from the USA, involving 1852 people with childhood onset diabetes and 7408 controls (4:1, case :control ratio) utilised pre recorded data from birth and health records (D'Angeli et al 2010). The authors report an inverse relationship between numbers of siblings and type 1 diabetes which they suggest is consistent with the hygiene hypothesis as more siblings may indicate greater exposure to microorganisms at an earlier stage, this has been reported in earlier studies (Bingley et al 2000, Cardwell et al 2005). In addition overcrowding which is associated with an increased risk of exposure to pathogens has also been associated with a decreased risk of type 1 diabetes (Patterson et al 1996, Staines et al 1997). A recent study from Sweden reported a relationship between education, socioeconomic factors and auto immune diabetes. The authors speculate that environmental issues during childhood such as low prevalence of early infections support the hygiene hypothesis (Olsson et al 2011).

Nutritional factors have also been linked to the development of type 1 diabetes. The early introduction of cows milk and a short duration of breast feeding have been associated with the development of islet cell auto-immunity in high risk children in Finland (Kimpimaki et al 2001). However more recently in the largest study so far, involving over 3500 infants with HLA susceptibility to diabetes, there was no significant association between duration of total breast feeding and the development of islet auto antibodies or type 1 diabetes. (Virtanen et al 2006). This is supported by both the Diabetes Auto Immunity Study in the Young (DAISY) and the BABYDIAB studies (Norris et al 1996, Hummel et al 2000) neither of which have shown a relationship between early exposure to cows milk and the risk of diabetes or islet cell auto-antibodies. Other studies have suggested a link between the age of introduction of cereal, gluten, fruits and roots and islet autoimmunity (Norris et al 2003, Ziegler et al 2003, Virtanen et al 2011).

Increased maternal age (over 35years) has been shown to increase the risk of diabetes in offspring by about 20-30% compared to the children of mothers who are aged 25 years or less (Stene et al 2001, Cardwell et al 2005). In addition a recent meta analysis suggests that babies born by caesarean section have a 20% greater risk of developing diabetes in childhood (Cardwell et al 2008). It is speculated that this may be due to differences in the composition of gut microbiota which are thought to play a part in development of the immune system. An alternative explanation may be non specific peri natal stress (Dahlquist et al 1992)

### 1.3.4 Accelerator hypothesis

The global increase in the incidence of type 1 diabetes, especially amongst children, is not fully understood. It has occurred over a relatively short period of time making genetic change an unlikely explanation but implicating environmental factors. Many patients with type 1 diabetes present in adult life and type 2 diabetes is becoming more common in children and young people. In addition on presentation the diagnosis of type 1 versus type 2 diabetes is often a difficult clinical dilemma particularly in younger people. The accelerator hypothesis proposes that type 1 and type 2 diabetes are essential the same condition distinguished only by the rate of β cell destruction and the accelerators responsible (Wilkin 2001). Three accelerators are identified; insulin resistance, the rate of β cell death and beta cell autoimmunity. Insulin resistance and central obesity have long been associated with type 2 diabetes and the global increase in obesity is mirrored by a similar increase in type 2 diabetes. Furthermore obesity

has been shown to be associated with a higher risk for the development of diabetes in childhood. One study found that a 10% increment in relative weight was associated with a 50-60% increase in the risk of type 1 diabetes before 3 years of age and a 20-40% increase from 3-10 years of age (Hypponen et al 2000). The accelerator hypothesis argues that overall increases in weight and body mass index (BMI) are associated with insulin resistance and acceleration to diabetes at an earlier age. A pattern of earlier presentation is reported in type 1 diabetes with the greatest increase being in children under 5 years of age (Patterson et al 2009). It is well documented that puberty, which is associated with weight gain and an increased demand for insulin, is associated with an increase in the incidence of type 1 diabetes (Padaiga et al 1999). In addition a pre-diabetes study in Australia reported that autoantibody positive first degree relatives of individuals with type 1 diabetes who progress to diabetes are significantly more insulin resistant, assessed by homeostasis model assessment of insulin resistance (HOMA-R), than those who did not progress, despite there being no difference in body weight percentile (Forlanos et al 2004).

Several studies have tested the accelerator theory with conflicting results. A study in the UK, involving 168 young people (diagnosed with type 1 diabetes before the age of 16 years of age) demonstrated pre and post onset BMI to be greater than the population mean. In addition waist circumference, a proxy for both visceral fat mass and insulin resistance was found to be substantially greater than for the population (mean value on the 87th centile). Waist circumference measurements were not available prior to onset of diabetes however there was no correlation between waist circumference and duration of diabetes suggesting that visceral fat had accumulated prior to diagnosis and not as a result of treatment with insulin (Betts et al 2004). This study from the UK along with others including a large study of over 9000 patients from Germany and Austria support the accelerator hypothesis reporting an inverse relationship between age at onset and BMI, those diagnosed more recently being heavier than those diagnosed previously (Kibirige et al 2003, Knerr et al 2005, Kordonouri and Hartmann 2005). However a study from the USA reported that this was only the case in those with reduced β cell function measured by fasting C-peptide which was not measured in the other studies (Dabelea et al 2006).

Not all studies support the hypothesis (O'Connell et al 2007, Porter 2004). A recent meta-analysis involving 2658 cases (8 case control studies and 1 cohort study) found that 7 studies

reported a significant relationship between childhood obesity, BMI or percentage weight for height and increased risk of diabetes (Verbeeten et al 2011). The accelerator hypothesis predicts early onset of diabetes rather than an increase in risk which in the long term would not affect overall incidence. This is supported by findings from Europe suggesting that the incidence of diabetes has not increased however initial presentation is at an earlier age (Pundziute–Lycka et al 2002). Furthermore the hypothesis proposes that type 1 and type 2 diabetes are a similar condition, weight loss which is a feature of newly diagnosed type 1 diabetes can also occur in type 2 diabetes, especially with poor control and increased duration of disease; this is usually an indication of β cell failure.

## 1.4 EPIDEMILOGY

A rise in the incidence of type 1 diabetes has been observed worldwide over recent decades (Green and Patterson 2001, DIAMOND Project Group 2006, Patterson et al 2009). Much of this increase has been reported in children particularly in those aged under 5 years (EURODIAB ACE Study Group 2000, Schober et al 2008). The reason for this is largely unknown and has been discussed previously in this chapter but variations in incidence within geographical regions have been noted (figure 1.2). Between the time period from 1990-1999 the incidence of type 1 diabetes worldwide in children 14 years of age or less increased by 2.8%. Statistically significant increases were evident across all continents except Central America and the West Indies were there was a 3.6% decrease in incidence. The age adjusted incidence of type 1 diabetes among 114 populations varied from 0.1 per 100 000/year in China and Venezuela to 40.9 per 100 000 in Finland (DIAMOND Project Group 2006). Recent data from Finland indicates an increased incidence rate to 64.2 per 100 000 in 2005 with a prediction of a doubling of the incidence by 2020 (Harjutsalo et al 2008). In addition updated information from the EURODIAB registers, which includes 17 European countries, demonstrated on overall increase in incidence of 3.9% from 1989-2003 and predicts a 70% rise in children younger than 15 years between 2005-2020 (Patterson et al 2009). Both of these studies report the greatest increase in incidence to be amongst the under 5 years age group. However a shift towards an earlier age of onset is not reported by all. A recent study from Italy reported a similar annual increase in incidence in both children and young adults (3.3%) over a 20 year period (Bruno et al 2009). Similarly a study from the UK reports an annual increase in incidence of 4.4% in children (ages 0-14)

alongside an increase of 2.8% per annum in young adults aged 15 - 34years (Imkampe and Gulliford 2011).

Countries with the highest incidence have been noted to be geographically further away from the equator (both north or south) and are often populations of European origin for example Australia, New Zealand and Canada (Soltesza et al 2007). This may be mediated by the hygiene hypothesis with better levels of sanitation being evident in more westernised countries. An alternative explanation may be exposure to sunshine and vitamin D which may protect again the development of type 1 diabetes (EURODIAB Substudy 2 Study Group 1999, Mohr et al 2008).

The incidence of diabetes in European countries varies widely with Macedonia appearing to have the lowest rate (3.6 per 100 000/year) whereas Sweden has a high incidence rate (30 per 100 000/year) (DIAMOND Project Group 2006). Rates appear to be lowest in eastern European countries although recent data indicates that countries with a previously low incidence rate (below 10 per 100 000/year), such as Lithuania, Romania and Poland, are now reporting rates in excess of 10 per 100 000/year (Patterson et al 2009). In the UK in 2010 it was estimated that there were 2.6 million people, including children, with diagnosed diabetes of which approximately 15% had type 1 diabetes. The estimated prevalence of type 1 diabetes in children was 1 per 700-1000 with a total population of 25 000 people under the age of 25 years with type 1 diabetes (Diabetes UK 2010). It has been suggested that the variation in incidence rates in European populations may be related to national prosperity (Patterson et al 2001).

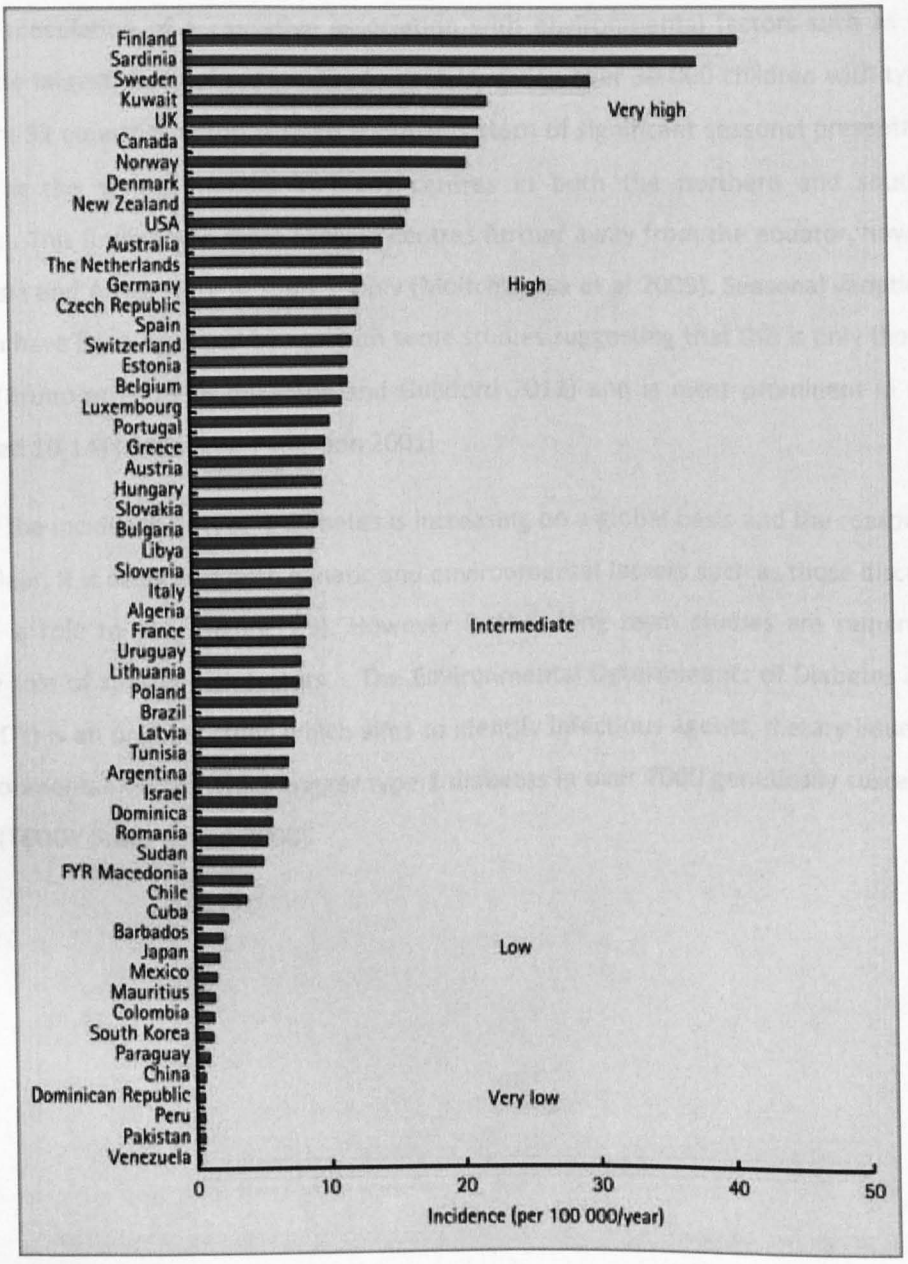


**Figure 1.2** Geographical variation in childhood onset diabetes incidence rate, 1990-1999. Reproduced from Textbook of Diabetes (Holt et al 2010 (eds)) with permission from John Wiley and Sons Ltd, Chichester

Seasonal variations in presentation of type 1 diabetes have been reported in some (Green and Patterson 2001, Svensson et al 2009,) but not all (Ye et al 1998, Padaiga et al 1999) studies. Peak incidence appears to be in the autumn and winter months (Svensson et al 2009) and may

support the speculation of a causative association with environmental factors such as viral infections. The largest study of seasonality to date involving over 30 000 children with type 1 diabetes from 52 countries demonstrated a global pattern of significant seasonal presentation with peaks in the winter months in many centres in both the northern and southern hemispheres . This finding was more likely in centres further away from the equator, however data from Asia and Africa were in short supply (Moltchanova et al 2009). Seasonal variation in presentation have been reported by age with some studies suggesting that this is only the case in children (Bruno et al 1997, Imkampe and Gulliford 2011) and is most prominent in older children (aged 10-14) (Green and Patterson 2001)

In summary the incidence of type 1 diabetes is increasing on a global basis and the reasons for this are unclear. It is likely that both genetic and environmental factors such as those discussed above have a role to play (figure 1.3). However further long term studies are required to confirm the role of specific risk factors. The Environmental Determinants of Diabetes in the Young (TEDDY) is an ongoing study which aims to identify infectious agents, dietary issues and other environmental factors which trigger type 1 diabetes in over 7000 genetically susceptible individuals (TEDDY Study Group 2008).

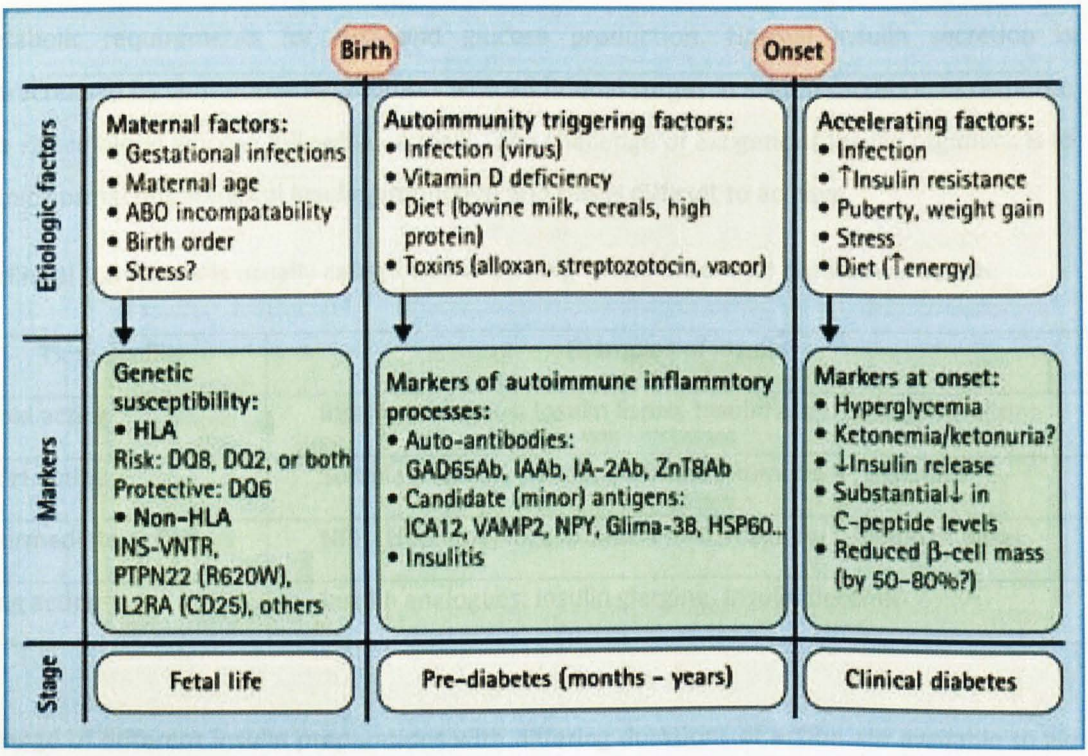


**Figure 1.3** Schematic presentation of the natural history of type 1 diabetes showing possible etiopathologic factors and disease markers. Reproduced from Textbook of Diabetes (Holt et al 2010 (eds)) with permission from John Wiley and Sons Ltd, Chichester

## 1.5 CLINICAL MANAGEMENT OF TYPE 1 DIABETES

Aside from a pancreas or islet cell transplant exogenous insulin replacement, by subcutaneous injection, is the only treatment for type 1 diabetes. However lifestyle issues such healthy eating and physical activity are also important as is education and regular screening to detect complications at the earliest stage.

### 1.5.1 Insulin replacement

The aims of insulin treatment in the management of type 1 diabetes are to relieve the symptoms of hyperglycaemia whilst minimising the risk of hypoglycaemia, reduce the risk of acute and long term micro and macro vascular complications and enable the person to live a long and healthy life.

Normal insulin secretion in a non diabetic healthy person is a dynamic response between the metabolic requirements for fuel and glucose production. Normal insulin secretion is characterised by continuous basal pulses with additional surges in insulin secretion in response to a rise in blood glucose following a meal. The challenge of exogenous insulin regimens is to mimic normal physiological insulin production and this is difficult to achieve.

In clinical use insulin is usually categorised according to the onset and duration of action:

| Time profile | Examples of insulin |
|---|---|
| Rapid acting | Insulin analogues: Insulin lispro, Insulin aspart, Insulin glulisine |
| Short acting | Soluble (regular) insulin: Actrapid, Humulin S , Insuman |
| Intermediate acting | NPH (isophane) insulin: Insulatard, Humulin I, Insuman Basal |
| Long acting | Insulin analogues: Insulin glargine, Insulin detemir |

A range of different insulin preparations with differing durations of action are available to aid clinical management (figure 1.4). The choice of insulin and regimen should be tailored according to individual need taking into account lifestyle issues, dexterity and cognitive function.

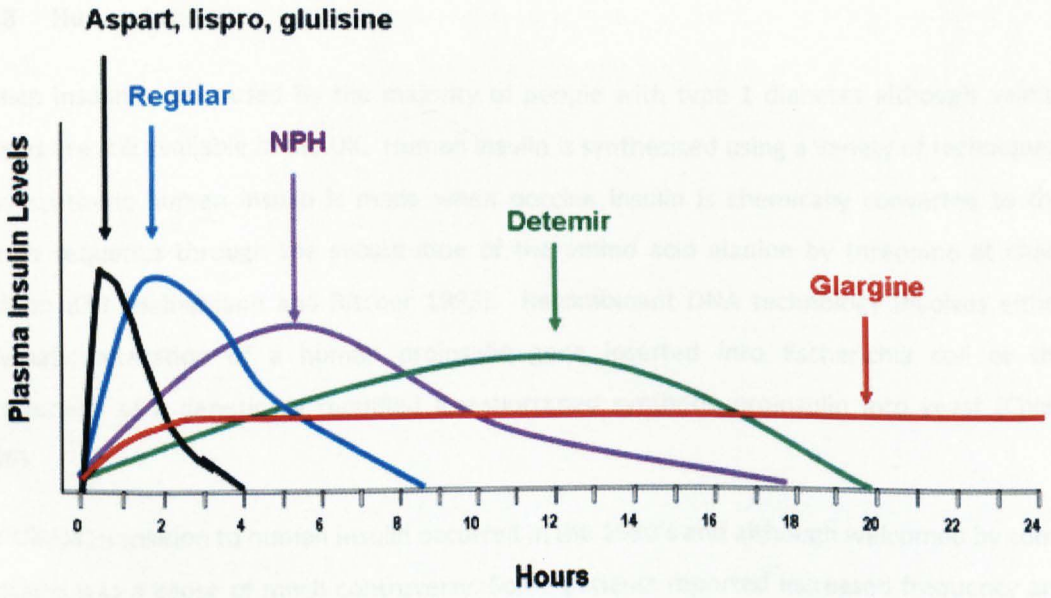


**Figure 1.4** Insulin time profiles following subcutaneous injection. Reproduced with permission from www. ENDOTEXT.Org. Chapter 17, The Management of Type 1 Diabetes (Hirsch IB and Skyler JS, 2009)

### 1.5.2 Animal insulin

The first commercially available insulins were extracted from bovine or porcine pancreas, were impure and led to problems such as allergic reactions and lipoatrophy (Wright et al 1979, Young et al 1981). Crystallisation techniques followed by gel and ion exchange chromatography were associated with improvements in purity and fewer side effects (Wilson et al 1985) however insulin was short acting meaning that several injections had to be given throughout the day to avoid symptomatic hyperglycaemia. Longer acting insulins were developed in the 1930-1940's when Protamine or zinc was added to soluble insulin to become what is now known as Neutral Protamine Hagedorn (NPH) / isophane insulin and zinc or lente insulin. These developments made it possible for diabetes to be managed with one or two injections per day however absorption could be unpredictable leading to erratic blood glucose control and frequent episodes of hypoglycaemia (Holleman and Gale 2007). Biphasic insulin followed shortly when soluble and intermediate acting insulins were combined and commercially produced in fixed mixtures which proved to be clinically beneficial. The use of animal insulin either in fixed mixtures or free mixing of soluble and isophane insulin was the main stay of treatment for type 1 diabetes until the advent of human insulin in the 1980's.

### 1.5.3 Human insulin

Human insulin is now used by the majority of people with type 1 diabetes although animal insulins are still available in the UK. Human insulin is synthesised using a variety of techniques. Semi synthetic human insulin is made when porcine insulin is chemically converted to the human sequence through the substitution of the amino acid alanine by threonine at chain position B30 (Heinemann and Ritcher 1993). Recombinant DNA technology involves either enzymatic alteration of a human proinsulin gene inserted into Escherichia coli or the introduction of a genetically modified foreshortened synthetic proinsulin into yeast (Chien 1996).

The clinical transition to human insulin occurred in the 1980's and although welcomed by some clinicians was a cause of much controversy. Some patients reported increased frequency and reduced awareness of hypoglycaemia (Teusher and Berger 1987, Egger et al 1991) however subsequently a few double blind randomised controlled cross over studies involving patients who had previously reported loss of awareness failed to confirm this (Maran et al 1993, Colagiuri et al 1992). In addition a literature survey involving 39 clinical studies and 12 epidemiological reports comparing human and porcine insulin concluded that the incidence and severity of hypoglycaemia did not differ (Jorgensen et al 1994). However many patients felt that this was the case and opted to go back to animal insulin and the debate continues today. In the UK concern about the safety of human insulin prompted the then British Diabetic Association to investigate sudden deaths in young people with type 1 diabetes. In a series of 50 deaths 22 were unexplained though hypoglycaemia or hypoglycaemic related events were considered to be the most likely cause of death. All of these patients had been using human insulin for over 6 months but type of insulin was not thought to be implicated in the cause of death (Tattersal and Gill 1991). This syndrome has since been coined 'dead in bed' and continues to be reported (Secrest et al 2011).

Furthermore, in studies comparing human insulin with animal insulin there is little evidence of significant benefits in glycaemic control. A meta analysis of 45 randomised controlled studies (58% of which involved people with type 1 diabetes) involving 2156 subjects comparing animal to human insulin did not find any difference in glycaemic control or frequency of hypoglycaemia (Richter and Neises 2009). However the majority of these studies (36 of the 45) used highly purified porcine insulin which may be less immunogenic than bovine insulin, some

were of short duration and patient related outcomes such as health related quality of life were not assessed. The 1980's also witnessed the widespread introduction of home blood glucose monitoring and a focus on patient education. It could be speculated that these factors may have resulted in improvements in glycaemic control, in some individuals, which may have contributed to more hypoglycaemic events.

### 1.5.4 Analogue insulin

Despite the introduction of human insulin many clinical issues relating to the action of subcutaneous insulin injections persist. Such issues are:

- slow absorption and delayed clearance of soluble insulin leading to postprandial rises in blood glucose levels but hypoglycaemia before the next meal
- early peak of isophane insulin given at night increasing the risk of nocturnal hypoglycaemia
- fluctuating blood glucose levels due to erratic insulin absorption (Holleman and Gale 2007).

In an attempt to overcome such problems considerable attention has been devoted to altering the pharmacokinetic profile resulting in the development of insulin analogues, the so called 'designer insulins'. Compared to soluble insulin these rapid acting analogues have specific amino-acid substitutions which lead to conformational and electrical changes within the molecule which decrease hexamerisation (Vajo et al 2001). They are therefore absorbed more quickly and may help reduce post prandial hyperglycaemia. There are currently three rapid acting analogues (Insulin Lispro, Eli Lilly, Insulin Aspart, Novo- Nordisk and Insulin Glulisine- Sanfi- Aventis) commercially available. Lispro swaps proline at position 28 and lysine at position 29 of the B-region (Kucera and Graham 1998). Aspart substitutes proline at B28 with aspartic acid (Setter et al 2000) and Glulisine substitutes lysine at position B3 and glutamic acid at B29 (Becker 2007) .

Two longer acting insulin analogues (Insulin Glargine, Sanofi-Aventis and Insulin Detemir Novo-Nordisk) are also commercially available. They too have amino acid changes (Heinemann et al

1999, Heinmann et al 2000) resulting in a longer duration of action (Bolli et al 1999) and less erratic absorption (Owens et al 2000).

In clinical practice rapid acting analogues have the advantage of being able to be injected either just prior to eating or after eating unlike soluble insulin which needs to be injected 30-40 minutes before eating. This may be more convenient for people with type 1 diabetes who are often injecting rapid acting insulin 3 or more times per day and may be advantageous for parents managing young children with type 1 diabetes were the amount of carbohydrate eaten at each meal cannot be predicted. Longer acting analogues in theory have a more 'peakless' action which could be beneficial in reducing hypoglycaemia.

A recent systematic review, comparing the efficacy and safety of insulin aspart and regular human insulin in 18 studies of type 1 diabetes, concluded that treatment with insulin aspart resulted in moderately better glycaemic control and treatment satisfaction than regular insulin. The same was not true for type 2 diabetes (Rys et al 2011). However the majority of the individual studies included in this analysis did not report statistically significant improvements in $HbA_{1c}$ associated with insulin aspart and this may have been due to small sample size and lack of statistical power. A large prospective, multicentred , randomised parallel group study involving 1070 adults with type 1 diabetes comparing either aspart or human insulin in combination with an NPH basal insulin reported significant improvement in glycaemic control and treatment satisfaction over a 6 months period in the patients randomised to aspart (Home 2000). This improvement in glycaemic control along with no increased risk of major hypoglycaemia was maintained at 30 months ($p<0.05$) (Home et al 2006). Similar results have been reported by another group (Raskin et al 2000). Conflicting results have been reported by other groups with one randomised double blind crossover trial reporting no difference in glycaemic control between analogue and human soluble insulin when used in combination with NPH as basal insulin. However analogue insulin was associated with fewer episodes of nocturnal hypoglycaemia (Gale et al 2000). In addition significant reductions in postprandial glucose levels but no reduction in fasting blood glucose have been reported in several studies (Home et al 2000, Raskin et al 2000, Rys et al 2011). This is important as it has been proposed that lower postprandial blood glucose levels may be associated with a lower risk of cardiovascular disease (CVD) in people with diabetes (Haffner 1998).

Evidence in support of a reduction in the frequency of nocturnal hypoglycaemia in patients with type 1 diabetes using long acting insulin analogues compared to NPH as part of a multiple daily injection regimen appears to more consistent (Garg et al 2004, Vardi et al 2008). This is a significant clinical development for many patients with type 1 diabetes who report frequent disabling nocturnal hypoglycaemia which can adversely affect quality of life and ability to work. However a recent small (25 participants) observational study, investigating nocturnal hypoglycaemia in type 1 diabetes using continuous glucose monitoring, reported that nearly 50% of patients experienced nocturnal hypoglycaemia during the study period (2 separate overnight monitoring periods) and there was no difference in the frequency of nocturnal hypoglycaemia according to type of basal insulin (NPH or long acting analogue) (Woodward et al 2009). Of concern is that only 21% of patients woke up despite the mean duration of episodes being 68 minutes.

In summary, when considering bolus insulin, there is currently little evidence to support improvements in glycaemic control according to the type of insulin. Highly purified animal insulin reduced the occurrence of unsightly lipodystrophies although lipoatrophy has been reported with analogue insulin (see section 1.7). The change to human insulin in the UK was largely imposed by the commercial withdrawal of a wide range of animal insulin although a limited range is still available today. The argument for rapid acting analogue insulin appears to be mainly focused around convenience although many patients on soluble insulin also inject just prior to eating. In a chronic condition such as diabetes convenience should not be overlooked however neither should the cost of convenience. Analogue insulin is considerably more expensive than soluble insulin and this is an important consideration in the current economic climate. There is some evidence for a reduction in nocturnal hypoglycaemia with long acting insulin analogues and this is of great clinical and human benefit to individual patients. The issue of evidence may have been easier if there had been any double blinded clinical trials comparing analogue and standard insulin. This was deemed difficult due to problems with timing of insulin injections and blinding issues with clear long acting insulin analogues (Holleman and Gale 2007). The challenge to the clinician is to work with each person on an individual basis to agree an insulin regime which is suitable for that person and also to ensure that appropriate support is available to help optimise control.

## 1.6 INSULIN DELIVERY

Patients starting on insulin therapy require considerable education, support and supervision. In the UK this is usually the remit of the Diabetes Specialist Nurse (DSN) and dietitian. Most patients now use insulin pens to give insulin injections. The first commercially available pen device, the Novopen (Walters et al 1985), was launched in 1985 and was followed by a variety of other pen devices. The choice of device is usually down to the individual although the decision may be guided by for example dexterity as some pens are more difficult to manage than others. Selection of the most appropriate device is important and in many cases can maintain an individual's independence. Most devices are insulin specific therefore in some cases the choice of insulin is determined by individual ability to manage the device. Insulin pens are discrete, convenient to use and are associated with increased satisfaction and improved quality of life (Hornquist et al 1990, Graf and McCunahan 1998).

### 1.6.1 Insulin injection technique

Whilst there have been many large scale studies investigating the pharmacokinetic and pharmacodynamic properties of insulin and optimal insulin regimens, relatively little attention has been given to the importance of injection technique. However correct injection technique is a crucial factor in achieving optimal glycaemic control. Issues for consideration include: correct use of pen devices, depth of injection, rotation of sites and needle length. Insulin should be injected into subcutaneous tissue as injecting into muscle can lead to more rapid absorption with subsequent hypoglycaemia (Vaag et al 1990, Frid et al 1990) and discomfort at the injection site. To avoid intramuscular injection careful attention should be paid to needle size and the need to lift a skin fold or 'pinch the skin'. Several studies have shown that injections with 4-6mm needles, without a lifted skin fold are suitable for most adults regardless of BMI (Gibney et al 2010, Hirsh et al 2010). Insulin is absorbed at different rates from different injection sites (Koivisto and Felig 1980, Frid and Linde 1992). The abdomen appears to be the preferred site for soluble insulin as it is absorbed fastest there (Henriksen et al 1993) with the thigh or the buttocks being the most appropriate site for NPH as absorption is slowest from these sites (Bantle et al 1993). Therefore to minimise intra site variability injection times and sites should be matched i.e. breakfast insulin always injected in a specific site, although rotation within that site should be encouraged to avoid lipohypertrophy. Recent evidence suggests that rapid acting and long acting analogues may be given at any injection site as

absorption rate does not appear to be site specific (Owens et al 2000, Guerci and Sauvamet 2005) . Injection technique should be assessed on a regular basis particularly in those with sub optimal glycaemic control. New injection recommendations for people with diabetes have recently been published (Frid et al 2010).

### 1.6.2 Continuous subcutaneous insulin infusion

Continuous subcutaneous insulin infusion (CSII), more commonly referred to as the insulin pump, aims to mimic normal physiological insulin secretion by delivering small amounts of insulin on a continuous basis (figure 1.5). The pump is programmed to deliver insulin at a variety of basal rates according to individual need with additional bolus doses given via the pump depending on carbohydrate intake. Insulin pump technology has improved considerably over the years. Aside from basal and bolus insulin settings pumps now have many advanced features including dual and square wave bolus settings and blood glucose reminders. CSII is a relatively expensive method of insulin delivery not only in terms of the cost of the equipment which is approximately £4000 to purchase the initial pump (a replacement is required every 4 years when the warranty expires) plus an annual cost of £1800 for consumables, but also in terms of staff resources. Initial education is time consuming and resource intensive and long term benefits are yet to be proven.

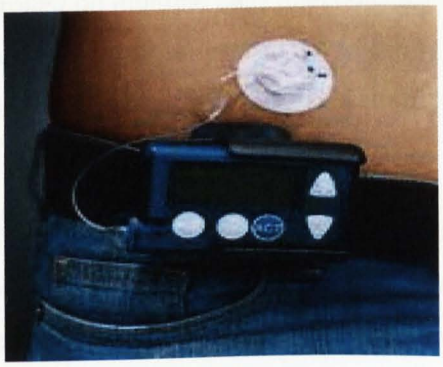

**Figure 1.5** Continuous Subcutaneous Insulin Infusion

Several studies have investigated the effects of CSII on glycaemic control and quality of life with conflicting results. A large randomised controlled crossover study, involving 272 people with type 1 diabetes from 11 European countries, reported that compared to multiple daily injections with lispro and NPH insulin CSII resulted in statistically significant improvements in

$HbA_{1c}$ and quality of life, especially flexibility in eating and general lifestyle (Hooga et al 2006). Furthermore there was a marked reduction in the frequency of hypoglycaemia and less fluctuations in blood glucose levels during the 6 months CSII treatment period. However the basal insulin used in this study was NPH which is known for problematic absorption and undesired peaks which may have contributed to the raised pre breakfast blood glucose levels and increased frequency of hypoglycaemia reported during the multiple daily injection periods. However, another randomised multicentre crossover study, involving 100 adults with type 1 diabetes, comparing CSII with a multiple daily injection regimen using aspart and glargine also reported better glycaemic control, measured by serum fructosamine, during the CSII period (Hirsch et al 2005). This study was of very short duration each treatment phase was only 5 weeks so results need to be interpreted with care. Interestingly although overall frequency of hypoglycaemia did not differ between the treatment periods there were significantly more reported episodes of minor nocturnal hypoglycaemia during the multiple daily injection periods in contrast to significantly more minor daytime hypoglycaemia in the CSII periods. Although episodes of hypoglycaemia were minor, the avoidance of nocturnal hypoglycaemia is clinically important as it may be more difficult to recognise and manage. Another parallel study, evaluated the effect of either CSII or multiple daily injections (using lispro and glargine insulins) on glycaemic control and frequency of hypoglycaemia in 32 adults with type 1 diabetes who were poorly controlled on multiple daily injections using NPH insulin. At the end of the 12 months study period $HbA_{1c}$ had improved significantly and episodes of severe hypoglycaemia decreased significantly in both groups and there were no between group differences (Lepore et al 2003).

A meta analysis published in 2010 concluded that in type 1 diabetes CSII may be more effective in improving glycaemic control and reducing severe hypoglycaemia than multiple daily injections (Misso et al 2010). Earlier meta analyses of the randomised controlled trials indicate that CSII is associated with 0.4-0.5% lower $HbA_{1c}$ than multiple daily injections (Weissberg – Benchell et al 2003, Jeitler et al 2008). Improvements in $HbA_{1c}$ after starting insulin pump therapy appear to be greatest in those with poorer glycaemic control (Retnakaran et al 2004, Pickup et al 2006) However CSII requires intensive self management skills including carbohydrate counting and flexible insulin dosing and is not an option for all. As with any method of self medication it is open to manipulation (Moreau et al 2011).

Currently in the UK CSII is a treatment option for people with type 1 diabetes with poor glycaemic control ($HbA_{1c}$ greater than 8.5% ) despite multiple daily injections or for those with disabling hypoglycaemia (National Institute of Clinical Excellence 2008).

## 1.7 COMPLICATIONS OF INSULIN THERAPY

The most common side effects of insulin therapy are weight gain and hypoglycaemia, both can be a major barrier to achieving optimal glycaemic control. Insulin is also associated with a variety of subcutaneous changes such as lipohypertrophy and lipoatrophy

Insulin can restore fat and muscle mass in newly diagnosed or poorly controlled diabetes and can lead to excessive weight gain. In the Diabetes Control and Complications Trial, after 5 years, patients randomised to intensive insulin treatment had gained a mean of 4.6kg more than those in the conventional group (DCCT 1993). This weight gain was associated with unfavourable changes in lipid profile and blood pressure (Purnll et al 1998) which are independent risk factors for the development of cardiovascular disease. Weight gain is a major concern for many patients and has been associated with deliberate insulin omission (Peveler et al 2005). Factors such as advice from a dietician, tailoring insulin regimens to individual patient needs and avoidance of hypoglycaemia may help to minimise weight gain. More recently long acting insulin analogues have been associated with less weight gain when compared to NPH insulin in patients with type 1 diabetes (De Leeuw et al 2005, Zachariah et al 2011, Szypowski et al 2011).

Lipohypertrophy is a common complication of subcutaneous insulin treatment occurring in 27-57% of patients using insulin injections (Kordonouri et al 2002, Strauss et al 2002, Wallymahmed et al 2004). It is thought to be a result of the local anabolic effects of insulin with promotion of fat and protein synthesis (Holstein et al 2010). Lipohypertrophy is unsightly and can lead to erratic insulin absorption (Thow et al 1990). In addition it is associated with longer duration of diabetes, failure to rotate injection sites, reuse of needles (Strauss et al 2002, Vardar and Kizilci 2007) and poor glycaemic control (Kordonouri et al 2002).

Lipoatrophy is an adverse immunological side effect of insulin therapy usually associated with the use of non purified animal insulin (Reeves et al 1980). However in recent years there has

been several case reports of lipoatrophy associated with rapid and long acting insulin analogues (Hussein et al 2007, Holstein et al 2010, Babiker et al 2011). In some of these cases rotation of insulin injection sites has not resulted in further lipoatrophic lesions (Holstein et al 2010, Babiker et al 2011) however in others further areas have developed at the new injection sites necessitating a change of insulin following which the lipoatrophy resolved (Holstein et al 2010, Babiker et al 2011).

Systematic rotation of injection sites should be encouraged and information reinforced on a regular basis. Self examination of injection sites should include regular palpation of injection sites as lipohypertrophy can often be felt before it becomes visibly evident. If lipohypertrophy is found then consideration should be given to reducing the dose of insulin as well as advice about rotation of injection sites.

## 1.8 WHOLE PANCREAS AND ISLET CELL TRANSPLANTATION

Whole pancreas and more recently islet cell transplantation have been explored as a treatment for type 1 diabetes. Whole pancreas transplantation was first performed in the late 1960's (Kelly et al 1967). Initially problems with peritonitis were encountered due to exocrine drainage from the pancreatic duct. However improved surgical techniques and immunosuppression have led to an increase in the number of whole pancreas transplants with more than 23000 being carried out worldwide. An analysis of pancreas transplants, performed in the USA between 1988-2003, demonstrated a progressive improvement in 1 year graft survival rates in those performed in 1988/1989 compared to those performed in 2002/2003 (75% v 85% for simultaneous pancreas- kidney cases, 55% v 78% for pancreas after kidney cases and 45% v 77% for pancreas transplant alone) (Gruessner et al 2005). Nevertheless pancreas transplantation is not without its risk and careful patient selection is required.

The first islet cell transplants in the 1970's failed to achieve insulin independence however in 1980 there was a case report, involving a 30 year old women with type 1 diabetes in Switzerland, who achieved insulin independence eight months following islet cell transplantation (Largiader et al 1980). However islet cell transplantation really only became a possible option for the management of type 1 diabetes following the publication of a report from Canada in 2000 involving 7 people with type 1 diabetes who had remained insulin

independent after a mean follow up period of nearly 12 months following islet cell transplantation (Shapiro et al 2000). The technique used involved multiple infusions of fresh human islet cells from brain dead donors and steroid free immunosuppression and became known as the Edmonton Protocol. In 2005 the same group reported that of 65 patients who had received islet cell transplantation less than 10% remained insulin independent at 5 years with a mean duration of insulin independence of 15 months (Ryan et al 2005). However at 5 years 80% demonstrated detectable graft function (C-peptide secretion) which was associated with significantly better glycaemic control than those who did not have detectable graft function. More recently the International Collaborative Islet Cell Transplantation Registry, which includes data from North America, Australia and Europe, reported data on 325 patients who had received islet cell transplantation. Of the 325 patients 70% achieved insulin independence at some stage, 71% of this group remained insulin independent at 1 year and 52% at 2 years (Alejandro et al 2008). In addition as reported by Ryan et al islet cell transplantation was associated with a reduction in the frequency and severity of hypoglycaemia.

Islet cell transplantation is a promising treatment for people with type 1 diabetes, particularly those with disabling hypoglycaemia, however it is not without its problems. The major issue being the long term maintenance of insulin independence. In addition shortage of donors (at least 2 donors are needed for each graft) and the management of immunosuppression remain a challenge as do the yet unknown long terms effects. Alternatives such as bioartificial islet cell transplantation using animal islets are currently being considered (Matsumoto 2010).

## 1.9 MONITORING GLYCAEMIC CONTROL

Blood glucose control in type 1 diabetes is usually assessed clinically in 3 ways:

- Glycated haemoglobin
- Home capillary blood glucose monitoring
- Clinical assessment of osmotic symptoms and episodes of hypoglycaemia

### 1.9.1 Glycated haemoglobin

Haemoglobin $A_{1c}$ was identified by Samuel Rahbar in the 1960's. This led to the development of assays to measure glycated haemoglobin which gives an objective measure of overall glycaemic control and has influenced the quality of diabetes care worldwide (Rahbar 2005). However initially a range of assays were used and there was no agreement over a common reference standard. Following the publication of the Diabetes Control and Complications Trial (DCCT 1993) efforts were made to standardise measurement including external quality control schemes to ensure that measurements between laboratories could be compared, this is known as DCCT alignment (Mbanya 2005).

Glycated haemoglobin is formed when haemoglobin reacts spontaneously with plasma glucose to form glycated derivatives in a non enzymatic pathway. As the half life of haemoglobin is about 120 days it is a useful glycated protein to measure to assess glycaemic control. The extent of glycation is determined by the level of glucose and the duration of exposure (Krishnamurti and Steffes 2001). Haemoglobin A undergoes such glycation to form $HbA_{1c}$ from a reaction between the β-chain of haemoglobin AO and glucose. $HbA_{1c}$ serves as a marker of average blood glucose levels over the previous few months and is widely accepted as the standard measure of glycaemic control. Approximately 50% of the variance in $HbA_{1c}$ is determined by the average blood glucose concentration over the previous month, 25% by the concentration over 30-60 days and the remaining 25% by the concentration from 60-120 days (Farmer 2010). Results can be affected by a number of different conditions including: haemoglobinopathies, uraemia, blood transfusion, haemolytic or iron deficiency anaemia, polycythemia and high vitamin C levels.

Until recently $HbA_{1c}$ was reported as percentage however from October 2011 $HbA_{1c}$ will be reported using a new reference standard agreed by the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) (American Diabetes Association 2007b). The new method uses units expressed as mmol/mol. Current $HbA_{1c}$ targets of 6.5% and 7.5% will therefore be 48 mmol/mol and 59mmol/mol. In addition in January 2011 the World Health Organisation endorsed the use of $HbA_{1c}$ as a diagnostic test for diabetes with 6.5% (48mmol/mol) being the criteria for diagnosis (World Health Organisation 2011).

### 1.9.2 Fructosamine

Fructosamine is formed when albumin reacts non enzymatically with glucose. Fructosamine measurements reflect glucose measurement in the past 1-3 weeks and are useful in situations where glucose levels change rapidly for example during pregnancy or when $HbA_{1c}$ measurements are not indicated due to for example haemoglobinopathies.

### 1.9.3 Self blood glucose monitoring

Self monitoring of blood glucose became a practical option with the introduction of capillary blood glucose strips in the 1970's however it was not widely accessible as initially strips were expensive and not available on prescription. Dextrostix produced by Ames was the first commercially available visually read strip. Strips were impregnated with a chemical reagent which changed colour when exposed to blood. The depth of colour change was dependent on the amount of glucose in the blood and results were read off a colour chart. This was initially a chaotic process as samples had to be timed accurately and blood washed off the strip, there were also issues with individual variations in colour discrimination and the accuracy of readings (Krynski and Logan 1967). Blood glucose meters followed shortly and early clinical studies indicated that self blood glucose monitoring using meters resulted in improvements in blood glucose control, prevented hypoglycaemia, were easy to use and preferred to urine testing (Sonksen et al 1978, Walford et al 1978). The era of home blood glucose monitoring had begun and was to give rise to much debate over its value in improving long term control particularly in type 2 diabetes. However it was a major step forward for those with type 1 diabetes making possible real time blood glucose estimations and facilitating self management.

Once it became clear that good glycaemic control was associated with long term microvacular complications, self monitoring of capillary blood glucose quickly became an intrinsic element of diabetes management. Initial meters were expensive, cumbersome and prone to user error. There are now a wide variety of blood glucose meters available most of which are discrete and easy to use. More recently capillary ketone measurement has been shown to be useful in identifying patients at risk of diabetic ketoacidois (Harris et al 2005). Assessing the impact of self monitoring on glycaemic control in type 1 diabetes is difficult as education and advice on monitoring is usually just a single part of a wider education programme often involving insulin dose adjustment. However capillary blood glucose monitoring is a useful tool in determining blood glucose patterns and informing decisions on treatment changes especially in those who

are using flexible insulin regimens. It is also useful in detecting hypoglycaemia and guiding self management strategies during periods of illness. Frequency of blood glucose monitoring should be determined on an individual basis but testing at least 3 times a day with pre meal target levels of 3.9 – 7.2 mmol/l and post meal levels of less than 10 mmol/l have been suggested (American Diabetes association 2011, Ceriella and Colagiuri 2008) . Monitoring is essential for drivers with type 1 diabetes as recent guidance from the Driving and Vehicle Licensing Agency recommends testing blood glucose before driving even short distances (Driver and Vehicle Licensing Agency 2011).

### 1.9.4 Clinical assessment

$HbA_{1c}$ and capillary blood glucose monitoring are great advances in the management of diabetes before which clinicians were largely working on self reported symptoms which are subjective and dependent on individual recall and interpretation. Both have their own merits. $HbA_{1c}$ provides information on overall control but cannot identify blood glucose patterns which can be identified by capillary blood glucose monitoring. However the importance of skilled clinical assessment must not be overlooked and it must always be remembered that the clinicians' priority is the patient not the $HbA_{1c}$. Clinical assessment involves a review of blood glucose control, arterial risk, screening for complications, lifestyle and educational issues (National Institute of Clinical Excellence 2004). In the current climate of target driven care it is wise to consider targets on an individual basis as overzealous chasing of targets can lead to detrimental effects on an individuals physical wellbeing and quality of life. The challenge is to work in partnership with the person with diabetes to agree specific aims and realistic objectives which are reviewed on a regular basis according to individual circumstances.

## 1.10 CONTINUOUS BLOOD GLUCOSE MONITORING

Recently there has been a focus on continuous blood glucose monitoring systems (CGMS) as a tool to optimise glycaemic control in type 1 diabetes and several devices are now available. These transcutaneous sensors measure and display the glucose concentration in interstitial fluid every 1-5 minutes and results are transmitted to a data storage device. Sensors may be left in place for 3-7 days (Hirsch et al 2008a). However there is some concern about the

accuracy of CGMS due to the physiological lag time between blood glucose and interstitial glucose, particularly when blood glucose levels are changing rapidly and calibration using capillary blood glucose monitoring is required on a regular basis (Hirsch et al 2008a).

Several randomised controlled studies have reported improvements in glycaemic control associated with CGMS. One such study, involving 120 adults and children with type 1 diabetes, reported a statistically significant improvement in $HbA_{1c}$ and less time spent in hypoglycaemia in the group randomised to CGMS compared to those performing conventional blood glucose monitoring at the end of the 6 months study period (Battelino et al 2011). No additional diabetes management advice or written guidance on insulin alteration were given during the study aside from target pre and post meal blood glucose levels which were the same for both groups. However results of this study may not be generalised as all participants had an $HbA_{1c} \leq$ 7.5% before randomisation and all were using intensive treatment regimens (CSII or multiple daily injections). In general they were a highly motivated group who were already performing at least 5 capillary blood glucose measurements per day prior to the start of the study. Furthermore compliance with the protocol, wearing the sensor for at least 6 days per week (86% of study time) for 26 weeks, was higher than reported in other studies (Garg et al 2011). Compliance with CGMS is reported to be especially poor in younger age groups (Juvenile Diabetes Research Foundation 2008). In contrast, a study comparing the effects of CGMS on glycaemic control in subjects with type 1 diabetes on multiple daily injections versus CSII reported no significant change in $HbA_{1c}$ over a 6 months study period. There were however, improvements in other glucose variability indexes including time within blood glucose target range and mean amplitude of glucose excursions (Garg et al 2011). Again this study involved subjects with relatively good glycaemic control with a pre study mean $HbA_{1c}$ of 7.6% in both groups.

A further randomised controlled study of 3 months duration, including 81 adults with poorly controlled type 1 diabetes ($HbA_{1c} > 8\%$) randomised patients to one of three treatment arms; CGMS on a continuous basis, CGMS bi -weekly for 3 day periods or conventional self blood glucose monitoring (Deiss et al 2006). At the end of the study period there was a statistically significant improvement in $HbA_{1c}$, with no significant increase in insulin dose, between the continuous CGMS group and the control group ($p<0.03$) but no other differences between groups were detected. In addition at the end of the study 50% of those randomised to continuous CGMS had a reduction in $HbA_{1c}$ of at least 1% compared to 37% in the intermittent

CGMS group and 15% in the control group. Other studies have demonstrated improvements in glycaemic control only in sub groups of individuals with type 1 diabetes, for example those 25 years of age and over (Juvenile Diabetes Research Foundation 2008), and most studies have included only patients on intensive insulin regimens (Hirsch et al 2008a, Hirsch et al 2008b, Battelino et al 2011).

A recent meta-analysis involving six randomised controlled trials comparing CGMS with self monitoring of blood glucose concluded that CGMS was associated with significant improvements in $HbA_{1c}$ and reduced exposure to hypoglycaemia with the greatest improvements being evident in those with the highest baseline $HbA_{1c}$ and those who used the sensor frequently (Pickup et al 2011).

In the UK CGMS is not currently a routine part of diabetes care for people with type 1 diabetes. This is largely due to lack of clinical evidence for its effectiveness and concern about the accuracy of the readings particularly in relation to detection and treatment of hypoglycaemia (Cheyne et al 2002, Wilson et al 2007). In addition CGMS is currently recommended only as a supplement to capillary blood glucose monitoring as calibration is required a on regular basis and confirmation of results by self monitoring is recommended before any treatment changes are implemented. This obviously has additional cost implications.

## 1.11 EDUCATION

People with type 1 diabetes have to cope with their condition on a day to day basis. It is estimated that the majority of people with diabetes have contact with health care professionals for about 3 hours per year, leaving 8757 hours in which they have to manage on their own (Department of Health 2005a). Education for self management is therefore a vital part of diabetes management and should be delivered on an ongoing basis. The role of education has long been recognised. Dr Elliot Joslin (1869-1962), founder of the Joslin Diabetes Centre in the USA, was the first to advocate patient education. In the early 1900's he published a book 'Diabetic manual - for the Doctor and Patient' advising patients on how to manage their diabetes. A version of this book is still published today. In the UK in 1925 Robin Lawrence published a book 'The diabetic life: Its control by diet and insulin' (Lawrence 1925). This proved to be a big seller and reached its 15th edition in 1944. Lawrence was also the first to suggest that people with diabetes should be managed in special centres specifically for diabetes and

that these centres should have a clinical and educational function and a consistent multidisciplinary team (Lawrence 1951). Diabetes centres became commonplace in the 1980's although there are still many areas that do not have a specific centre. However multidisciplinary teams are now a well established element of diabetes care. In the early days it was usual for people with newly diagnosed type 1 diabetes to be admitted to either a nursing home or hospital, for 2 -3 weeks, to start insulin injections. This admission was to stabilise blood glucose levels and provide basic education (Tattersall 2010b). However over time it became apparent that hospital was not the best place for individuals to start their lives with diabetes and there was a move to starting insulin injections in the home environment. In the UK patient education and home insulin starts really began to gain momentum with the increased numbers of Diabetes Specialist Nurses in the 1980's.

### 1.11.1 Current diabetes education

In 2003 the National Institute for Clinical Excellence (NICE) published a report defining structured education and advocating that all patients with diabetes should have access to educational programmes which should be delivered by multidisciplinary teams (NICE 2003). In addition programmes should meet 4 key criteria; a written curriculum, trained educators, quality assurance and regular audit (Department of Health 2005b). More recently the American Association of Diabetes Educators have identified seven health care behaviours important to enable people with diabetes to self manage these are: healthy eating, being active, monitoring, taking medication, problem solving, reducing risks and healthy coping (Funnell et al 2007). These areas should be built into any educational programme.

The effects of intensive education programmes on glycaemic control and quality of life in people with type 1 diabetes has been investigated on many occasions. Most of these programmes are based on a 5 day inpatient programme originally developed and delivered in Germany. This uncontrolled study, of 78 people with type 1 diabetes, reported a significant improvement in glycosylated haemoglobin over a 22 month study period along with a significant reduction in hospital admissions (Muhlhauser et al 1983). However as with the Diabetes Control and Complications Trial (DCCT 1993), there were more episodes of hypoglycaemia although 76% of these episodes involved 4 patients and were thought to be due to high insulin doses, alcohol excess, pregnancy and kidney failure. Compared to baseline, metabolic control improved over the study period however deterioration in control was noted

between 12 and 22 months. This was a landmark study in the field of patient education but was resource intensive and importantly involved an inpatient admission which is certainly not practical or appropriate in current times. The aim should be for people with diabetes to develop the skills and knowledge in their own environment rather than an artificial hospital environment.

Several other uncontrolled studies, of 12 – 24 months duration, have reported statistically significant improvements in metabolic control, quality of life, knowledge and problem solving skills following intensive education (Everett et al 2003, Lowe et al 2008, Falconnier Bendik et al 2009). These outpatient based education programmes vary in duration and intensity with some programmes running for 4 consecutive days whilst others involve weekly sessions over several weeks. In addition a few randomised controlled studies, of short duration (6-12months), have demonstrated improvements in glycaemic control with no increase or significantly less reported incidents of severe hypoglycaemia after intensive educational intervention (Scavone et al 2010, DAFNE Study Group 2002). However one randomised controlled study failed to replicate these results reporting that glycaemic control improved significantly over a 12 month period in both the intervention and the control group and with no between group differences (George et al 2008). Nevertheless there were statistically significant improvements in measures of treatment satisfaction and empowerment in the intervention group. A cross sectional study from Switzerland in a clinic, where education based flexible intensified insulin therapy is delivered as standard care, reported a median $HbA_{1c}$ of 7.1% in 206 patients with type 1 diabetes (Albrecht et al 2011). This is lower than measures of glycaemic control reported in clinics where intensive education is not routine practice (Saunders et al 2004a, Eeg-Olofsson et al 2007, DCCT/EDIC Research Group 2009).

Only a few studies have investigated the long term effects of intensive education on glycaemic control. In the UK, Dose Adjustment for Normal Eating (DAFNE) is now a well established intensive education programme. This is a skills based 5 day outpatient programme facilitated by trained health care professionals. Long term data revealed that after 44 months $HbA_{1c}$ remained significantly improved when compared to baseline ($p<0.01$) however there was a significant deterioration in control after 12 months ($p<0.05$) (Speight et al 2010). Similar findings have been reported by other authors (Bott et al 1997, Plank et al 2004). However the DAFNE group did report improvements in quality of life which were sustained during the study

period. In a chronic condition such as type 1 diabetes this should not be overlooked. Surprisingly there was a significant decrease in a single quality of life item 'satisfaction to continue with present treatment'. It is possible that this may be related to the deterioration in glycaemic control observed after 12 months although the authors conclude that this may be a ceiling effect. In a qualitative study, involving semi structured interviews with 30 adult patients who had previously completed the DAFNE course, the authors reported that flexible insulin regimens are not without their burdens. Examples being the 'day to day drudge' of carbohydrate counting and increased blood glucose monitoring. However patients generally preferred this approach to diabetes management (Rankin et al 2011).

Attending a course on 5 consecutive days may be difficult for some patients especially in tough economic times. Several centres in the UK have now developed their own versions (Cradock 2003). It should also be remembered that not all patients are comfortable with group education (Wallymahmed and MacFarlane 2005). Therefore one to one education should also be accessible.

Regardless of its effects on glycaemic control education of people with type 1 diabetes is now universally accepted as a vital aspect of any management programme. To ensure day to day relevance the content of such programmes need to be developed in collaboration with people with type 1 diabetes (Woodward et al 2006).

## 1.12 QUALITY OF LIFE AND PSYCHOLOGICAL FACTORS IN TYPE 1 DIABETES

A diagnosis of diabetes may lead to the imposition of substantial lifestyle adjustments and in the long term serious and disabling complications can occur. People with type 1 have to endure lifelong medical follow up and treatment interventions which may impact on their quality of life and psychological well-being. Quality of life in people with type 1 diabetes has been shown to be lower than the general population in some (Wandell et al 1998, Rubin and Peyrot 1999, Hahl et al 2002) but not all (Wallymahmed et al 1999) studies. One study from the Netherlands compared health related quality of life in 274 adults with type 1 diabetes with an age matched group from the general population. Quality of life was assessed using 2 different measures; the RAND-36 questionnaire which measures health related quality of life in 8 domains and the EuroQOL which is a simple questionnaire involving 5 questions using a valuation technique

known as time trade off. The authors report no difference in health related quality of life between the groups as assessed by the RAND questionnaire but those with type 1 diabetes reported significantly worse quality of life measured by EuroQOL (Hart et al 2003). These questionnaires assess different areas of quality of life for example the RAND focuses on general health perception and role functioning whereas the EuroQOL assesses self care and anxiety/depression. To obtain a comprehensive assessment of health related quality of life it is important to consider a variety of areas because quality of life may be compromised only in specific areas according to the medical condition. Interestingly another study, comparing quality of life in adults with type 1 diabetes with an age and sex matched group of adults with growth hormone deficiency and a control group, reported no significant differences in self reported quality of life between the group with diabetes and the control group in any of the areas assessed except depression (Wallymahmed et al 1999). However compared to adults with untreated growth hormone deficiency, patients with type 1 diabetes diabetes reported a significantly better life quality in all areas except anxiety where there was no difference. Type 1 diabetes has been associated with increased levels of anxiety and depression (Engum et al 2005, Barnard et al 2006, Storz et al 2011,). However a study investigating factors associated with depression in patients with type 1 or type 2 diabetes and a control population did not demonstrate a relationship between hyperglycaemia and depression (Engum et al 2005). A subsequent study found that depression was significantly associated with co morbidity in type 2 but not type 1 diabetes. The factors that correlated with depression in people with type 1 or type 2 diabetes were the same as those for the non diabetic population i.e. low levels of education, low physical activity, subjective somatic complaints and physical impairment (Hislop et al 2008). Many people with diabetes have multiple co morbidity and it may be that the general burden of chronic disease is related to depression.

### 1.12.1 Adherence to treatment

Adherence to treatment regimens is known to be difficult for some people with diabetes for a variety of reasons. Omission of insulin is thought to be relatively common with one study reporting that of the 341 females with type 1 diabetes studied, 30% reported deliberate insulin omission with 8.8% reporting frequent omission of insulin (Polonsky et al 1994). Insulin omission was associated with self reported eating disorders, fear of hypoglycaemia and poor glycaemic control. In addition, of those who reported deliberate omission of insulin, half

reported doing so due to concern about weight gain and these patients reported the greatest psychological distress. An 11 year follow up study involving 60% of the original cohort (30% reporting insulin restriction at baseline) demonstrated that insulin restriction was associated with a threefold increase in the risk of death particularly at a younger age. In addition insulin restrictors reported significantly more nephropathy and foot problems than those who reported appropriate use of insulin (Goebal et al 2008). An association between 'weight worry' and poor adherence to insulin, specifically in younger females with type 1 diabetes, has also been reported in the DAWN study (Peyrot et al 2009). A recent internet survey study involving 502 people with diabetes managed by insulin injections (114 type 1) reported that 57% of respondents reported intentionally missing insulin with 20% doing so on a regular basis (Peyrot et al 2010). Subgroup analysis did not show any overall association between age, sex and intentional omission of insulin in patients with type 1 diabetes although students (who tend to be younger) were more likely to miss insulin. The mean age of type 1 respondents to this survey was 47 years. A previous study of adherence to insulin in young people with type 1 diabetes found direct evidence of regular non compliance (collection of insulin from the pharmacy) in 25 (28%) of the 89 young people studied (Morris et al 1997) with no sex differences. In addition non compliance with insulin was associated with acute admissions to hospital with diabetic ketoacidosis.

### 1.12.2 Disordered eating and diabetes

Eating disorders have been reported to be more common in young females with type 1 diabetes than in the general population. It is speculated that this may be in part due to the imposition of dietary restrictions, the cycle of initial weight loss at diagnosis followed by weight gain after initiation of insulin and the availability of intentional omission or under dosing of insulin as a means of weight control (Peveler & Holt 2010). Cross sectional case controlled studies have revealed significantly more disordered eating behaviour in adolescent and young females with diabetes than in age matched control groups (Jones et al 2000, Colton et al 2004). One such study, involving 356 females with type 1 diabetes (aged 12-19 years) and 1098 age matched controls, reported that 10% of those with type 1 diabetes had an eating disorder meeting Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria compared to 4% in the control population. In addition sub threshold eating disorders were also significantly more common in those with diabetes (14% v 8%) (Jones et al 2000). Those with type 1 diabetes

reported significantly more binge eating and less dieting than control subjects. In addition insulin omission was common with 41 (11%) of the whole group with diabetes reporting that they were currently taking less insulin than prescribed as a method of weight control. As would be expected significantly more of those with an eating disorder (42%) reported insulin misuse compared with those in the sub threshold (18%) and non disordered groups (6%). Insulin omission, which is a recognised form of purging behaviour, has been associated with eating disorders in other studies (Colton et al 2004, Peveler et al 2005). The cumulative incidence of eating disorders in females with type 1 diabetes has been investigated and clinical outcomes assessed. One longitudinal study reported a 26% cumulative incidence of disordered eating behaviours in young people with type 1 diabetes over a 12 years period (Peveler et al 2005). The authors report a significant relationship between the development of two or more serious complications and the presence of a probable eating disorder. A previous meta analysis found the risk of developing retinpathy to be greater in those with type 1 diabetes and an eating disorder than in those with type 1 diabetes alone (Neilsen 2002a). Also a 10 year follow up study reported a significantly higher mortality rate in individuals with type 1 diabetes and anorexia nervosa than those with either type 1 diabetes alone or anorexia nervosa alone (Neilsen et al 2002b).

Insulin omission and disordered eating behaviours may be on a similar spectrum to brittle diabetes a condition associated mainly with young female patients with type 1 diabetes whose lives are disrupted by glycaemic instability and frequent admissions to hospital (Gill et al 1996). Brittle diabetes is also associated with excess morbidity and mortality. Early identification of those at risk is important to direct supportive therapies to effected individuals. A recent prospective study investigated predictors of disturbed eating behaviours in adolescent girls with type 1 diabetes (Olmsted et al 2008). Concerns about weight, shape and physical appearance along with low self esteem and depressive symptoms were all significant predictors of the outset of disturbed eating behaviours. In addition the authors report that in a cohort of 101 teenagers 45% developed disturbed eating behaviours over a 5 year period. More recently specific screening tools for detection of disordered eating behaviours in type 1 diabetes have been developed and validated (Markowitz et al 2010). However it has been proposed that asking a single question 'have you ever been overweight' may be a simple first screening tool to identify those at risk of developing disordered eating behaviours (Markowitz et al 2009).

Type 1 diabetes is a complex chronic condition which can affect not only physical but psychological well being. Affected individuals have to adhere to complex treatment regimens that can be difficult to maintain on long term basis. Health care professionals need to be aware of the intricate relationship between diabetes and psychological morbidity and resources directed towards those in need.

## 1.13 ACUTE COMPLICATIONS OF TYPE 1 DIABETES

The two main acute complications of type 1 diabetes are hypoglycaemia and diabetic ketoacidosis (DKA). Both are emergency situations which can be fatal if not managed appropriately. Acute complications have been reported to be the greatest single cause of excess death in individuals with type 1 diabetes under the age of 30 years, with males between the ages of 20-29 years being particularly vulnerable (Laing et al 1999). Some of these deaths may be preventable by ongoing education aimed at improving self management skills.

### 1.13.1 Hypoglycaemia

Good glycaeamic control has been shown to reduce the risk and progression of micro and macro vascular complications in type 1 diabetes (DCCT 1993, DCCT/EDIC 2005). However this improvement in glycaemic control is associated with an increased risk of hypoglycaemia (DCCT 1997). Hypoglycaemia in type 1 diabetes is common with a reported incidence of approximately 2 episodes of mild symptomatic hypoglycaemia per week (Cryer 2008). An observational study from the UK involving 383 subjects (107 with type 1 diabetes) investigated frequency and severity of hypoglycaemia according to treatment type and duration of diabetes (UK Hypoglycaemia Group 2007). Results suggests that patients with type 1 diabetes are at significantly greater risk of hypoglycaemia than those with type 2 diabetes treated with either sulphonylureas or insulin. Duration of type 1 diabetes did not influence the frequency of mild hypoglycaemia however those with the longest duration (more than 15 years) reported the highest frequency of severe hypoglycaemia over the 9-12 months study period. Similar results have been reported elsewhere (Luddeke et al 2007). Interestingly frequency of hypoglycaemia in the UK Hypoglycaemia Study was more than twice that reported in the DCCT.

Hypoglycaemia has been associated with considerable mortality and morbidity with recent studies reporting 6-10% of deaths in type 1 diabetes, diagnosed before the age of 30 years, being due to hypoglycaemia (Skrivarhaug et al 2006, Feltbower et al 2008,). In addition nocturnal hypoglycaemia has been implicated in 'dead in bed' syndrome which is characterised by apparently healthy young individuals being found dead in an undisturbed bed with no evidence of underlying pathology (Tattersall and Gill 1991, Secrest et al 2011). A recent case report involving a 23 year old man, with type 1 diabetes of 12 years duration, found dead in bed is the first to confirm hypoglycaemia at the time of death (Tanenberg et al 2010). Diabetes was managed with an insulin pump and he was wearing a retrospective continuous blood glucose monitor revealing severe hypoglycaemia (blood glucose levels <1.7 mmol/l) around the time of death. Although there was a history of a recent hypoglycaemic seizure, which prompted continuous blood glucose monitoring, there was no indication of seizure activity at the time of death. Interestingly there was evidence of insulin 'stacking' which is a stark reminder of the dangers of overcorrecting hyperglycaemia. Another explanations for dead in bed syndrome is undiagnosed cardiac autonomic dysfunction which like hypoglycaemia can lead to alterations in cardiac repolarisation specifically QT interval prolongation which may trigger ventricular arrhythmias and sudden death (figure 1.6) (Tu et al 2010)

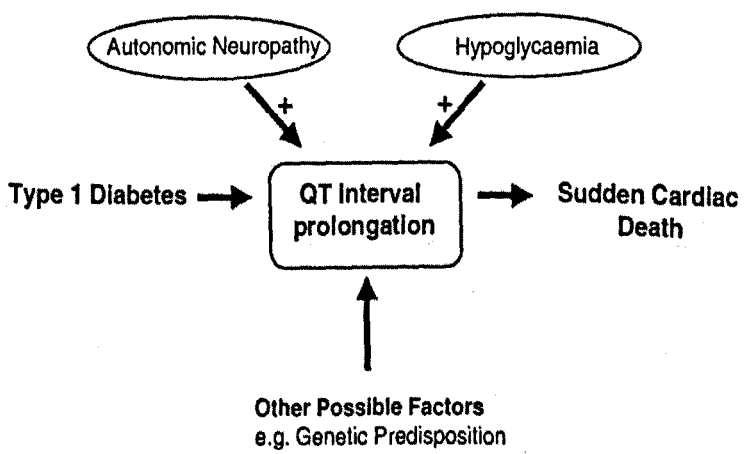


**Figure 1.6** Possible multiple factors involved in sudden cardiac death in young people with type 1 diabetes. Acute onset of nocturnal hypoglycaemia as a precipitant, on a background of cardiac neuropathy and possible genetic factors may all contribute to QT interval prolongation leading to ventricular arrhythmias and sudden death. Reproduced with permission from Elsevier (www.elsevier.com)

A recent observational study, involving 25 adults (aged less than 50 years) with long standing type 1 diabetes, simultaneously recorded 24 hour ECG and continuous blood glucose monitoring on 2 separate occasions (Gill et al 2009). Thirteen individuals (52%) had periods of nocturnal hypoglycaemia lasting a mean of 68 minutes and cardiac rate or rhythm disturbances (ventricular ectopics, sinus bradycardia, atrial ectopics and P wave abnormalities) were noted in eight of these 13 periods (62%). In addition corrected QT interval was significantly more prolonged during periods of nocturnal hypoglycaemia than during normoglycaemic periods. These findings appear to support arrhythmia as an underlying factor in 'dead in bed' syndrome.

Nocturnal hypoglycaemia is thought to be common in long standing type 1 diabetes and in the past rebound hyperglycaemia, aided by counter regulatory hormones, has been considered to be protective. A small study from 1980 involving 22 subjects reported asymptomatic nocturnal hypoglycaemia in 72% of those studied. Further analysis revealed rebound hyperglycaemia, the 'Somogyi effect', in 40% of those with nocturnal hypoglycaemia. Growth hormone, cortisol and glucagon levels were similar in those with apparent rebound hyperglycaemia and those with no rebound hyperglycaemia (Gale et al 1980). The authors suggested that instability in overnight and early morning blood glucose was most likely due to the insulin and regimens available at the time (mostly twice daily free mixed soluble and isophane beef or pork insulin). However despite advances in insulin treatment nocturnal hypoglycaemia persists with a recent small study reporting nearly 50% of patients experiencing blood glucose levels < 3.5 mmol/l assessed by continuous glucose monitoring (Woodward et al 2009).

It is well established that profound hypoglycaemia can lead to brain damage (Aeur 2004) and short term cognitive impairment (Cox et al 2003). However long term follow up (18 years) of the DCCT cohort did not find any evidence of long term cognitive dysfunction compared to baseline despite relatively high rates of recurrent severe hypoglycaemia. Cognitive function was assessed using a battery of cognitive tests and despite 40% of subjects experiencing at least 1 episode of hypoglycaemic coma or seizure, neither frequency nor severity of hypoglycaemia or original allocation to treatment group was associated with a decline in cognitive function (DCCT 2007).

Fear of hypoglycaemia is a common problem for people with type 1 diabetes and can lead to impaired quality of life and poor glycaemic control due to deliberate hyperglycaemia in an

attempt to avoid hypoglycaemic episodes. One study involving 1387 people with type 1 diabetes investigated fear of hypoglycaemia using a previously validated 'Hypoglycaemia Fear Survey' questionnaire. The authors report that fear of hypoglycaemia was significantly associated with frequency of severe hypoglycaemia, number of symptoms during mild hypoglycaemia, hypoglycaemic unawareness and previous attendance at emergency department due to severe hypoglycaemia (Anderbro et al 2010). There was also a positive association between $HbA_{1c}$ and fear of hypoglycaemia confirming the suspicions of many clinicians. Of note was the finding that there was a greater fear of hypoglycaemia amongst females than males in the study but this was not associated with an increase in blood glucose monitoring which may have been expected. It may be that other strategies such as eating more carbohydrate or injecting less insulin are used to avoid hypoglycaemia. The findings in this study need to be considered with care, 45% of those approached to participate in the study did not return the questionnaire and there were significant demographic and clinical differences between the responders and non responders. The non responders were more likely to be men, were significantly younger, with a shorter duration of diabetes and poorer glycaemic control than those who responded to the study. This study identified that the most important factor associated with hypoglycaemic fear is a history of severe hypoglycaemia in the past year. This is important and indicates that additional support and clinical intervention is required following an episode of severe hypoglycaemia. Fear of hypoglycaemia has also been related to duration of diabetes, blood glucose variability and anxiety (Wild et al 2007).

### 1.13.2 Diabetic Ketoacidosis

Diabetic ketoacidosis (DKA) is a serious metabolic emergency caused by insulin deficiency and increased production of the counter regulatory hormones glucagon, catecholamines, cortisol and growth hormone resulting in increased glucose production in the liver and deceased peripheral utilisation in the tissues. This leads to increased lipolysis and the production of ketone bodies eventually resulting in metabolic acidosis. DKA predominately occurs in type 1 diabetes but can also occur in type 2 diabetes (Henriksen et al 2007). The National Diabetes Audit for England and Wales (2009-2010) revealed a 12% prevalence rate of DKA over a 5 years period with 3.9% of people with type 1 diabetes having at least 1 episode of DKA in the 2009-2010 period. The greatest prevalence was in children and young people with 9% of this group

having at least 1 episode of DKA in 2009. Diabetic ketoacidois was more common in girls and teenagers and was often recurrent (National Diabetes Audit 2009-2010).

Mortality rates of up to 4- 5% have been reported and are associated with age, co-morbidity and drug abuse (Laing et al 2005, Kitabchi et al 06, Henriksen et al 2007). DKA is reported to be a major cause of diabetes related deaths in the 20-29 years age group, particularly in young men (Laing et al 1999). Risk factors for the development of DKA include younger age, poor glycaemic control, co-morbidity, clinic non attendance and psychological problems (Wright et al 2009). In addition predominance in females is reported in some (Wright et al 2009, National Diabetes Audit 2009-2010) but not all studies (Henriksen et al 2007). A recent study in the UK, involving five hospitals, reported 278 admissions with DKA involving 137 patients over a nine year period. Of these 137 patients 54 patients (39%) accounted for 70% of the admissions (Wright et al 2009).

Recurrent admissions with DKA is characteristic of 'brittle diabetes' a condition associated mainly with young female patients with type 1 diabetes whose lives are disrupted by glycaemic instability and frequent admissions to hospital. Psychosocial and behavioural factors such as family problems, denial, anorexia, manipulation and compliance issues are thought to be the main contributors to the cause and the condition is thought to affect about 1 person in every 1000 with type 1 diabetes (Gill et al 1996). Most cases resolve spontaneously and this is often related to positive changes in life circumstances (Kent et al 1994). However mortality rates are high with a recent series from the UK reporting 50% mortality at twenty year follow up with 80% of these deaths being diabetes related. This mortality rate must be interpreted with care because from an original cohort of thirty three individuals 13 (39%) could not be traced at follow up (Cartwright et al 2011). Furthermore the authors report a significant excess of nephropathy and autonomic neuropathy in the survivors compared to a non brittle control group. At 20 year follow up none of those who could be traced would have been considered to fit the criteria for 'brittle' diabetes. Brittle diabetes is not exclusive to young females and has been reported in males and the elderly (Gill et al 1996, Thomas et al 2007). In addition presentation is not always specifically related to DKA some patients present with recurrent hypoglycaemia and others with a 'mixed' picture of DKA and hypoglycaemia. This mixed presentation is more likely in the elderly and is thought to be largely due to multiple diabetes and non diabetes related causes with only a minority of cases considered to be due to deliberate manipulation (Benbow et al 2001).

Recurrent admissions with DKA have also been associated with intravenous drug abuse and menstruation (Saunders et al 2004b, Ovalle et al 2008).

DKA is a potentially preventable condition as many cases are precipitated by intercurrent illness e.g. infection or gastrointestinal problems (Wright et al 2009). Education is essential not only for people with type 1 diabetes but also for carers and health care professionals. Those in whom deliberate manipulation of treatment is considered to be a major cause continue to be a challenge and counselling and psychotherapy may be of some value.

## 1.14 PREVENTION AND FUTURE DEVELOPMENTS

Advances in the understanding of the natural history have made it possible to consider prevention of type 1 diabetes particularly in genetically predisposed individuals. Studies are aimed at either preventing the initiation of islet cell immunity (primary prevention) or reducing autoimmune destruction and progression to clinical diabetes (secondary prevention).

Ongoing primary prevention studies include those considering dietary and environmental factors (TEDDY Study Group 2008). The ongoing Trial to Reduce IDDM in the Genetically at Risk (TRIGR) is investigating the effect of excluding cow's milk protein, for the first 6-8 months, from the diet of genetically at risk infants. The study does not report back until 2017 however preliminary data suggest that substitution with hydrolyzed formula milk was associated with fewer autoantibody positive children at 10 years of age (Knip et al 2010). Other studies are considering vitamin D, which is known to have effects on the immune system, and omega 3 fatty acid docosahexanoeic acid which is thought to have anti inflammatory effects on the immune system .

Immune intervention studies have focused on modulation of the immune system in particular T cell activity. It has been proposed that exposure of the immune system to the insulin molecule (an auto antigen) may result in a protective immunity that has the potential to down regulate ongoing destructive immune reactions. However to date randomised controlled studies of both parental and oral insulin in antibody positive relatives of individuals with type 1 diabetes have failed to prevent the onset of type 1 diabetes (Diabetes Prevention Trial 2002, Diabetes Prevention Trial 2005). Although a significant treatment effect was demonstrated in those with the strongest evidence of autoimmunity to insulin (insulin auto antibodies ≥ 80 U/ml) who

were randomised to oral insulin (Diabetes Prevention Trial 2005). Recent follow up of the same cohort suggests that progression to type 1 diabetes even after discontinuation of treatment may have been delayed by 2.2 years in this subgroup compared to placebo (Vehik et al 2011). In addition nicotinamide has been thought to protect β cell function, however a randomised double blind placebo controlled trial involving 552 antibody positive relatives of individual with type 1 diabetes was not effective in preventing type 1 diabetes (European Nicotinamide Diabetes Intervention Trial (ENDIT) Group 2004).

Currently, TrialNet, an international network of clinical research groups is coordinating both natural history and interventional studies (oral insulin) involving first and second degree relatives of people with type 1 diabetes with the ultimate aim of preventing the onset of type 1 diabetes (www.trialnet.org).

Non specific systemic immunotherapy to modulate T cells has also been attempted. Anti CD3 has multiple effects leading to immune tolerance and has been used to preserve β cell function in newly diagnosed type 1 diabetes. However in most individuals endogenous insulin production declines within 2 years and side effects such as fever, arthralgia and a transient reactivation of Epstein Barr virus have been reported (Thrower et al 2011). Other agents under investigation include daclizamab, rituximab, etanercept and anti-thymocyte. In a small double blind randomised controlled study of 18 children / young people (3-18 years of age) with newly diagnosed type 1 diabetes, twice weekly etanercept resulted in a significantly greater improvement in glycaemic control and increased endogenous insulin production than placebo suggesting greater β cell preservation however larger studies are required (Mastrandrea et al 2009).

More recently there has been interest in stem cell therapy to treat type 1 diabetes. Stem cells are self renewing cells which have the ability to differentiate in to a number of specialised cell types. There are 2 main groups: embryonic stem cells derived from the inner mass of mammalian blastocysts and adult stem cells which are known to participate in tissue repair. To date no definite stem cell has been identified in the pancreas but stem cells from a range of tissues including the central nervous system and the spleen have been reported to differentiate into insulin expressing cells (Choudrey et al 2011). Umbilical cord blood contains not only stem cells but also regulatory T cells and it has been suggested that autologous cord

blood may induce immune tolerance and allow for islet cell regeneration (Thrower et al 2011). However a pilot study has failed to show any β cell preservation (Haller et al 2009).

Currently subcutaneous insulin therapy is the only treatment available for type 1 diabetes. Over the past two decades there have been technical advances in insulin delivery systems and equipment for self blood glucose monitoring, for example disposable insulin pens, CSII and continuous blood glucose monitoring systems. Development of a 'closed loop' system involving an integrated external insulin pump and a continuous glucose sensor utilising a variable insulin infusion rate algorithm is underway. Furthermore whole pancreas and islet cell transplantation are options for some patients but are not without risk.

## 1.15 SUMMARY

Type 1 diabetes is a chronic condition caused by β cell destruction resulting in insulin deficiency. It is associated with considerable morbidity and mortality and can seriously impair an individuals quality of life. The discovery of insulin in 1921 was one of the greatest advances in medical science and gave the gift of life to those who would previously have succumbed to diabetic ketoacidosis. However it was not a cure and over time the scourge of unexpected long term complications became apparent and brought new challenges. It became evident that the management of type 1 diabetes was not just about the relief of hyperglycaemic symptoms but about achieving near normoglycaemia. The challenge for those caring for people with diabetes was twofold; how to achieve better glycaemic control and how to detect and treat the emerging complications.

In the years following the discovery of insulin when the burden of injecting fast acting insulin several times a day became apparent the search turned to finding a once daily long acting insulin. This undoubtedly allowed control to deteriorate as erratic absorption led to periods of hyperglycaemia and unpredictable episodes of hypoglycaemia. It is ironic to note that after many years of trying to reduce the number of daily injections that the intensive insulin regimens currently employed to optimise glycaemic control have a lot in common with the regimens of the early days. In fact the trend is now towards more frequent insulin injections particularly in those using flexible insulin regimens who may inject fast acting insulin in excess of 4 times daily depending on carbohydrate intake. In addition, essentially dietary advice has

changed very little and recent years has witnessed the re-emergence of carbohydrate counting, although it is not quite so prescriptive as red (measurement of fat content) and black lines (measurement of carbohydrate content). The sequential move from animal to human to analogue insulin was initially led by the quest for more purified insulin to reduce allergic reactions and lipoatrophy. There was indeed a beneficial reduction in allergic reactions with more purified insulins but little evidence that human insulin was superior in improving glycaemic control. Particularly as it was around this time that home blood glucose monitoring became more commercially available as did intensive insulin regimens. However it was the pharmaceutical industry that finally imposed this change by implementing a widespread withdrawal of animal insulin thus forcing the use of human insulin. The move from human to analogue insulin may be even more difficult to justify as evidence of improvements in glycaemic control, particularly in the case of short acting analogues, is not wholly convincing. The convenience factor was the driving force from the pharmaceutical industry and it remains to be seen if the production of human insulin will be ongoing on a long term basis. Another possible contributory factor in the move to analogue insulin may be the clinicians desire to have something new to offer in the absence of any revolutionary developments. Nevertheless insulin is a lucrative business accounting for £286 million of the diabetes drugs bill in England in 2007, £234 million of which was accounted for by insulin analogues (Gale 2010).

Despite developments in insulin technology, capillary blood glucose monitoring and intensive insulin regimens, the achievement of good glycaemic control without the burden of hypoglycaemia remains an ongoing problem and a dilemma in diabetes care. Insulin pumps have proved to be useful in some individuals but are not an option for all. In the future closed loop systems may be a more attractive option.

One of the greatest advances in diabetes care is the growth and development of the multidisciplinary team and specialist diabetes centres. Multidisciplinary teams are beneficial to people with diabetes (and their relatives/ carers) and health care professionals alike. All can benefit not only from the diversity of individual skills but the wealth of collective skills and knowledge. The Diabetes Control and Complications Trial (DCCT) (DCCT 1993) is a prime example of how multidisciplinary working can influence outcomes in people with type 1 diabetes. Specialist diabetes centres with a clinical and educational function serve not only to house the diabetes team but also to co-ordinate and deliver diabetes care. They are often

centrally based and enable people with diabetes to access multidisciplinary care on a one stop basis. Wider members of the diabetes team can also be accessed via such centres e.g. vascular teams and many are attached to or work collaboratively with research centres.

As the prevalence of both type 1 and type 2 diabetes continues to increase the organisation of care has become a subject of great debate. Historically in many areas the management of type 1 diabetes has been the remit of specialist teams usually based in secondary care settings. However this is now being challenged. There is a move in various parts of the country for uncomplicated type 1 diabetes to be managed in primary care by General Practitioners and practice nurses leaving specialist teams to deal with more complex cases. Whilst on the face of it this may appear to be a practical solution to a growing problem, there are specific areas which need addressing particularly education of health care professionals involved in the care of people with type 1 diabetes. The skills and knowledge required to manage often complex treatment regimens including flexible insulin regimens and carbohydrate counting develop with experience. Maintaining such skills is dependent on ongoing exposure which may not be easy to uphold in primary care settings due to the limited numbers of patients with type 1 diabetes in an individual practice. In addition discussion with other members of the multidisciplinary specialist team on an individual patient basis can contribute to improving the care of that individual. Diabetes is a small element of the role of most practice nurses and this can make it difficult to maintain skills and keep up to date with changes. Type 1 diabetes is a complex condition which is not just about insulin injections. Management particularly in the months after diagnosis is intensive and requires multidisciplinary intervention.

Another major step forward is education and working in partnership with people with type 1 diabetes with the ultimate aim of optimising self management skills and improving both the physical and psychological wellbeing of people with diabetes. For some more traditional health care professionals the change to a shared decision making process has required a change in culture and consultation style which has required considerable adaptation. However in the long term this may not only improve standards of diabetes care but also improve work satisfaction.

This chapter has reviewed the natural history, pathophysiology and aetiology associated with type 1 diabetes. In addition an overview has been given on the history of insulin therapy, clinical management and acute complications. The next chapter will consider the morbidity and

mortality associated with the long term micro and macro vascular complications of type 1 diabetes and chapter two will discuss global risk factor reduction.

## 1.16 REFERENCES


Åkesson K, Nyström L, Färnkvist L, Östman J, Lernmark A, Kockum I. Increased risk of diabetes among relatives of female insulin-treated patients diagnosed at 15–34 years of age. Diabetic Medicine 2005; 22: 1551–1557

Albrecht D, Puder J, Keller U, Zulewski H. Potential of education-based insulin therapy for achievement of good metabolic control: a real-life experience. Diabetic medicine 2011; 28: 539-542

Alejandro R, Barton F, Hering BJ, Wease S. Update from the collaborative islet transplant registry. Transplantation 2008; 86: 1783–8

American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care 2007a; 30: S42-S47

American Diabetes Association, European Association for the Study of Diabetes, International Federation of Clinical Chemistry and Laboratory Medicine, and the International Diabetes Federation. Consensus statement on the worldwide standardization of the HbA1c measurement. Diabetologia 2007b; 50:2042–2043

American Diabetes Association. Standards of Medical Care in Diabetes—2. Diabetes Care 2011; 34, S11-S61

Anderbro T, Amsberg S, Adamson U, Bolinder J, Lins PE, Wredling R, et al. Fear of hypoglycaemia in adults with type 1 diabetes. Diabetic Medicine 2010; 27: 1151-1158

Auer RN. Hypoglycemic brain damage. Metabolic Brain Disease 2004; 19: 169-175

Babiker A, Datta V. Lipoatrophy with insulin analogues in type I diabetes. Archives of Disease Childhood 2011; 96: 101–102

Bach JF. Six questions about the hygiene hypothesis. Cellular Immunity 2005; 233:158-161

Bantle JP, Neal L, Frankamp LM. Effects of the anatomical region used for insulin injections on glycemia in type I diabetes subjects. Diabetes Care 1993; 16:1592-1597

Barnard KD, Skinner TC, Peveler R. The prevalence of co-morbid depression in adults with type 1 diabetes: systematic literature review. Diabetic Medicine 2006; 23: 445–448

Battelino T, Phillip M, Bratina N, Nimri R, Oskarsson P, Bolinder J. Effect of continuous glucose monitoring on hypoglycemia in type 1 diabetes. Diabetes Care 2011; 34: 795-800

Becker RHA. Insulin Glulisine Complementing Basal Insulins: A Review of Structure and Activity. Diabetes Technology & Therapeutics 2007; 9: 109-121

Benbow S, Walsh A, Gill G. (2001).Brittle diabetes in the elderly. Journal of the Royal Society of Medicine 2001; 94:578-580

Betts P, Mulligan J, Ward P, Smith B, Wilkin T. Increasing body weight predicts the earlier onset of insulin-dependent diabetes in childhood: testing the "accelerator hypothesis" (2). Diabetic Medicine 2004; 22: 144-151

Bingley PJ, Douek IF, Rogers CA, Gale EAM; Bart's-Oxford Family Study Group. Influence of maternal age at delivery and birth order on risk of type 1 diabetes in childhood: prospective population based family study. British Medical Journal 2000;321: 420-424

Bliss, M. The discovery of Insulin. McClelland & Steward Inc; 1982

Bolli GB, Di Marchi RD, Park GD ,Pramming S, Koivisto VA. Insulin analogues and their potential in the management of diabetes mellitus. Diabetologia 1999; 42: 1151-1167

Bonifacio E, Genovese S,Braghi S, Bazzigaluppi E, Lampasona V, Bingley PJ, et al. Islet antibody markers in IDDM: risk assessment strategies yielding high sensitivity. Diabetologia 1995; 38: 816-822

Bott S, Bott U, Berger, M, Muhlhauser I. Intensified insulin therapy and the risk of severe hypoglycaemia. Diabetologia 1997; 40: 926–932

Bottazzo GE, Florin-Christensen A, Doniach D. Islet-cell antibodies in diabetes mellitus with autoimmune polyendocrine deficiencies. Lancet 1974; 2: 1279-1283

Bruno M, Merletti F, De Salvia F, Lezo A, Arcari R, Pagano G. Comparison of incidence of insulin dependent diabetes mellitus in children and young adults in the province of Turin, Italy, 1984–91. Diabetic Medicine 1997; 14: 964–969

Bruno G, Novelli G, Panero F, Perotto M, Monasterolo F, Bona G. et al. The incidence of type 1 diabetes is increasing in both children and young adults in Northern Italy: 1984–2004 temporal trends. Diabetologia 2009; 52: 2531–2535

Cardwell CR, Carson DJ, Patterson CC. Parental age at delivery, birth order, birth weight and gestational age are associated with the risk of childhood Type 1 diabetes: a UK regional retrospective cohort study. Diabetic Medicine 2005; 22: 200–206

Cardwell CR, Stene LC, Joner G, Cinek O, Svensson J, Goldacre MJ. et al. Caesarean section is associated with an increased risk of childhood-onset type 1 diabetes mellitus: a meta-analysis of observational studies. Diabetologia 2008; 51: 726–735

Cartwright A, Wallymahmed M, Macfarlane IA, Wallymahmed A, Williams G, Gill G. The outcome of brittle type 1 diabetes—a 20 year study. Quarterly Journal of Medicine. 2011; 104: 575–579

Ceriello A, Colagiuri S. International Diabetes Federation guideline for management of postmeal glucose: a review of recommendations. Diabetic Medicine 2008; 25: 1151–1156

Cheyne EH, Cavan DA, Kerr D. Performance of a continuous glucose monitoring system during controlled hypoglycaemia in healthy volunteers. Diabetes Technology & Therapeutics 2002; 4: 607-613

Chien YW. Human insulin: basic sciences to therapeutic uses. Drug Development and Industrial Pharmacy 1996; 22: 753-789

Choudhary P, Pickup J, Jones P, Amiel SA. A future of glucose-response insulin secretion: bionics versus nature. Diabetes Voice 2011; 56: 22-27

Colagiuri S, Miller J, Petocz P. Double-Blind crossover comparison of human and porcine insulins in patients reporting lack of hypoglucaemia awareness. Lancet 1992; 339, 1432-1435

Colton P, Olmsted M, Daneman D, Rydall A,Rodin G. Disturbed eating behavior and eating disorders in preteen and early teenage girls with type 1 diabetes. Diabetes Care 2004; 27: 1654-1659

Cox DJ, Penberthy JK, Zrebiec J, Weinger K, Aikens JE, Frier B, et al. Diabetes and driving mishaps: Frequency and correlations from a multinational survey. Diabetes Care 2003; 26: 2329–2334

Cradock S. DAFNE, BERTIE, Insight and jigsaw: turning of the tide or breaking of the waves. Practical Diabetes International 2003; 20: 43

Cryer PE. The barrier of hypoglycemia in diabetes. Diabetes 2008; 57: 3169-3176

Dabelea D, D'Agostino RB, Mayer-Davis EJ, Pettitt DJ, Imperatore G, Dolan LM, et al. Testing the accelerator hypothesis: Body size, β-cell function, and age at onset of type 1. Diabetes Care 2006; 29: 290-294

DAFNE Study Group. Training in flexible, intensive insulin management to enable dietary freedom in people with type 1 diabetes: dose adjustment for normal eating (DAFNE) randomized controlled trial. British Medical Journal 2002; 325: 746-751

Dahlquist G, Kallen B. Maternal-child blood group incompatibility and other perinatal events increase the risk of early onset type 1 (insulin-dependent) diabetes mellitus. Diabetologia 1992; 35: 671-675

D'Angeli MA, Merzon E, Valbuena LF, Tirschwell D, Paris CA, Mueller BA. Environmental Factors Associated With Childhood-Onset Type 1 Diabetes Mellitus. Archives of Pediatric & Adolescent Medicine 2010;164 :732-738

Deiss D, Bolinder J, Riveline J, Battelino T, Bosi E, Md, Tubiana-Rufi N. Improved glycemic control in poorly controlled patients with type 1 diabetes using real-time continuous glucose monitoring. Diabetes Care 2006; 29: 2730-2732

De Leeuw I, Vague P, Selam L, Skeie S, Lang H, Draeger E, Elte JWF. Insulin detemir used in basal-bolus therapy in people with type 1 diabetes is associated with a lower risk of nocturnal hypoglycaemia and less weight gain over 12 months in comparison to NHP insulin. Diabetes, Obesity and Metabolism 2005; 7: 72-82

Department of Health. Selfcare- A real choice. Department of Health 2005a

Department of Health. Structured patient education in diabetes: Report from the Patient Education Working Group. Department of Health 2005b

Diabetes Control and Complications Trial. The effect of intensive treatment of diabetes on the development and progression of long-term complication insulin-dependent diabetes mellitus. The New England Journal of Medicine 1993; 329: 977-986

Diabetes Control and Complications Trial Research Group. Hypoglycemia in the Diabetes Control and Complications Trial. Diabetes 1997; 46: 271-286

Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Study Research Group. Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. New England Journal of Medicine 2005; 353: 2643-2653

Diabetes Control and Complications Trial/ Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Study Research Group. Long-term effect of diabetes and its treatment on cognitive function. . New England Journal of Medicine 2007; 356: 1842-1852

Diabetes Control and Complications Trial/ Epidemiology of Diabetes Interventions and Complications and Pittsburgh Epidemiology of Diabetes Complications Experience (1983-2005). Modern-day clinical course of type 1 diabetes mellitus after 30 years duration. Archive of Internal Medicine 2009; 169: 1307-1316

Diabetes Prevention Trial - Type 1 Diabetes Study Group. Effects of insulin in relatives of patients with type 1 diabetes mellitus. New England Journal of Medicine 2002; 346: 1685-1691

Diabetes Prevention Trial - Type 1 Diabetes Study Group. Effects of oral insulin in relatives of patients with type 1 diabetes. Diabetes Care 2005; 28:1068–1076

Diabetic Retinopathy Research Group. Photocoagulation treatment of proliferative diabetic retinopathy. The second report of Diabetic Retinopathy Study Findings. Ophthalmology 1978: 85 82-106

Diabetes UK. Diabetes in the UK 2010: Key statistics on diabetes. Diabetes UK, 2010

DIAMOND Project Group. Incidence and trends of childhood Type 1 diabetes worldwide 1990-1999. Diabetic Medicine 2006; 23: 857-866

Dobson M. Experiments and observations on the urine in diabetes. Medical Observations and Inquiries . 1776; 5: 298-316

Dolger H. Clinical evaluation of vascular damage in diabetes mellitus. Journal of American Medical Association 1947; 134:1289-1291

Driver and Vehicle Licensing Agency. At a glance guide to the current medical standards of fitness to drive. DVLA 2011

Eeg-Olofsson K, Cederholm J, Nilsson PM, Gudbjornsdottir S, Eliasson B. Glycaemic and risk factor control in Type 1 diabetes results from 13612 patients in a national diabetes register. Diabetes Care 2007; 30: 496-502

Egger M, Smith GD, Imhoof H, Teuscher A. Risk of severe hypoglycaemia in insulin treated diabetic patients transferred to human insulin: a case control study. British Medical Journal 1991; 303: 617-21

Eisenbarth GS. Update in Type 1 Diabetes. The Journal of Clinical Endocrinology & Metabolism 2007; 92: 2403–2407

Engum A, Mykletun A, Midthjell K, Holen A, Dahl AA. Depression and Diabetes: A large population-based study of sociodemographic, lifestyle, and clinical factors associated with depression in type 1 and type 2 diabetes. Diabetes Care 2005; 28: 1904–1909

EURODIAB ACE Study Group. Variation and trends in incidence of childhood diabetes in Europe. Lancet 2000; 355: 873-876

EURODIAB Substudy 2 Study Group. Vitamin D supplement in early childhood and risk for Type (insulin-dependent) diabetes mellitus. Diabetologia 1999; 42: 51-54

European Nicotinamide Diabetes Intervention Trial (ENDIT) Group. European Nicotinamide Diabetes Intervention Trial (ENDIT): a randomised controlled trial of intervention before the onset of type 1 diabetes. Lancet 2004; 363: 925–31

Everett J, Jenkins E, Kerr D, Cavan DA. Implementation of an effective outpatient intensive education programme for patients with type 1 diabetes. Practical Diabetes International 2003; 20:51-55

Falconnier Bendik C, Keller U, Moricini N, Gessler A, Schindler C, Zulewski H et al. Training in flexible intensive insulin therapy improves quality of life, decreases the risk of hypoglycaemia and ameliorates poor metabolic control in patients with type 1 diabetes. Diabetes Research and Clinical Practice 2009; 83:327-333

Farmer AJ. Monitoring diabetes. In Holt RIG, Cockram CS, Flyvberg A, Goldstein BJ. Textbook of Diabetes (eds). London: Wiley-Blackwell 2010

Feltbower RG, Bodansky HJ, Patterson CC, Parslow RC, Stephenson CR, Reynolds C. Acute complications and drug misuse are important causes of death for children and young adults with type 1 diabetes: results from the Yorkshire Register of Diabetes in children and young adults. Diabetes Care 2008; 31: 922–926

Forrest JM, Turnbull FM, Sholler GF, Hawker RE, Martin EJ, Doran TT, et al. Gregg's congenital rubella patients 60 years later. Medical Journal of Australia 2002; 177: 664-667

Fourlanos S, Narendran P, Byrnes GB, Colman PG, Harrison LC. Insulin resistance is a risk factor for progression to Type 1 diabetes. Diabetologia 2004; 47:1661–1667

Frid A, Ostman J, Lindeb. Hypoglycemia risk during exercise after intramuscular injection of injectable therapy in thigh in IDDM. Diabetes care 1990; 13: 473-477.

Frid A, Linde B. Intraregional Differences in the Absorption of Unmodified Insulin From the Abdominal Wall. Diabetic Medicine 1992; 9: 236–239

Frid A, Hirsch L, Gaspar R, Hicks D, Kreugel G, Liersch J, Letondeur C, et al. New injection recommendations for patients with diabetes. Diabetes & Metabolism 2010; 36: S3-S18

Funnell MM, Brown TM, Childs BP, Haas LB, Hosey GM, Jensen B, Maryniuk M. National Standards for Diabetes Self-Management Education. The Diabetes Educator 2007; 33: 599-614

Gale, EAM, Kurtz AB, Tattersall RB. In search of the Somogyi effect. Lancet 1980; 316:279-281

Gale EAM for the OK Trial Group. A randomized controlled trial comparing insulin lispro with human soluble insulin in patients with type 1 diabetes on intensified insulin therapy. Diabetes Medicine 2000; 17: 209-214

Gale EAM. A missing link in the hygiene hypothesis? Diabetologia 2002; 45:588–594

Gale EAM. Congenital rubella: citation virus or viral cause of type 1 diabetes. Diabetologia 2008; 51: 1559-1566

Gale EAM. Diabetes in the UK: time for a reality check? Diabetes Medicine 2010;27: 973-976

Garg SK, Paul JM, Karsten JI, Menditto L, Gottlieb PA. Reduced severe hypoglycemia with insulin glargine in intensively treated adults with type 1 diabetes. Diabetes Technology & Therapeutics 2004; 6: 589-595

Garg SK, Voelmle MK, Beatson CR, Miller HA, Crew LB, Freson BJ. Use of continuous glucose monitoring in subjects with type 1 diabetes on multiple daily injection versus continuous subcutaneous insulin infusion therapy. Diabetes Care 2011; 34: 574-579

George JT, Valdovinos AP, Russet I, Dromgoole P, Lomax S, Torgerson DJ, Wells T, Thow JC. Clinical effectiveness of a brief education intervention in Type 1 diabetes: results from the BITES (Brief Intervention in Type 1 diabetes, Education for Self-efficacy) trial. Diabetic Medicine 2008; 25:1447-1453

Gibney MA, Arce CH, Byron KJ, Hirsch LJ. Skin and subcutaneous adipose layer thickness in adults with diabetes at sites used for insulin injections: implications for needle length recommendations. Current Medical Research & Opinion 2010; 26: 1519–1530

Gill GV, Lucas S, Kent LA. Prevalence and characteristics of brittle diabetes in Britain. Quarterly Journal of Medicine 1996; 89:839-843

Gill GV, Woodward A, Casson IF, Weston PJ. Cardiac arrhythmia and nocturnal hypoglycaemia in type 1 diabetes—the 'dead in bed' syndrome revisited. Diabetologia 2009; 52:42–45

Gillespie KM, Gale EAM, Bingley PJ. High familial risk and genetic susceptibility in early onset childhood Diabetes. Diabetes 2002; 51: 210-214

Goebel-Fabbri AE, Fikkan J, Franko DL, Pearson K, Anderson BJ; Weinger K. Insulin restriction and associated morbidity and mortality in women with type 1 diabetes. Diabetes Care 2008; 31: 415-419

Graf MR, McClunahan MA. assessment by patients with diabetes mellitus of two insulin pen delivery systems versus a vial and syringe. Clinical Therapeutics 1998; 20, 486-496

Green, A, Patterson CC. Trends in the incidence of childhood onset of diabetes in Europe 1989-1998. Diabetologia 2001, 45;B3-B8

Green J, Casabonne D, Newton R. Coxsackie B virus serology and Type 1 diabetes mellitus: a systematic review of published case-control studies. Diabetic Medicine 2004; 21: 507–514

Gruessner AC , Sutherland DE, Pancreas transplant outcomes for United States (US) and non US cases as reported to the United Network for Organ Sharing (UNOS) and the International Pancreas Transplant Registry (IPTR) as of June 2004. Clinical Transplantation 2005; 19:433-455

Guerci B, Sauvanet JP. Subcutaneous insulin: pharmacokinetic variability and glycemic variability. Diabetes Metabolism 2005; 31: 4S7-4S24

Haffner SM. The Importance of Hyperglycemia in the Nonfasting State to the Development of Cardiovascular Disease. Endocrine Reviews 1998; 19: 583–592

Hahl J, Hämäläinen H, Sintonen H, Simell T, Arinen S, Simell O. Health-related quality of life in type 1 diabetes without or with symptoms of long-term complications. Quality of Life Research 2002; 11: 427-436

Haller MJ, Wasserfall CH, Mcgrail KM, Cintron M, Brusko Tm, Wingard JR et al. Autologous umbilical cord blood transfusion in very young children with type 1 diabetes. Diabetes Care 2009; 32:2041–2046

Harjutsalo V, Podar T, Tuomilehto J. Cumulative incidence of type 1 diabetes in 10,168 siblings of Finnish young-onset type 1 diabetic patients. Diabetes 2005; 54: 563-569

Harjutsalo V, Sjoberg L, Tuomilehto J. Time trends in the incidence of type 1 diabetes in Finnish children: a cohort study. Lancet 2008; 371: 1777-1782

Harris S, Ng R, Syed H, Hillson R. Near patient blood ketone measurements and their utility in predicting diabetic ketoacidosis. Diabetic Medicine 2005; 22: 221–224

Hart HE, Bilo HJG, Redekop WK, Stolk RP, Assink JH, Meyboom-de Jong B. Quality of life of patients with type 1 diabetes mellitus. Quality of Life Research 2003; 12: 1089-1097

Heinemann L, Ritcher B. Clinical pharmacology of human insulin. Diabetes Care 1993; (Suppl 3) 16: 90-100

Heinemann L, Sinha K, Weyer C, Loftager M, Hirschberger S, Heise T. Time-action profile of soluble, fatty acid acylated, long-acting insulin analogue NN304. Diabetic Medicine 1999; 16: 332-338

Heinemann L, Linkeschova R, Rave K, Hompesch B, Sedlak, M, Heise T. Time-action profile of the long-acting insulin analog insulin glargine (HOE 901) in comparison with those of NPH insulin and placebo. Diabetes Care 2000; 23:644–649

Henriksen JE, Djurhuss MS, Vagg A, Thye-Ronn P, Knudsen D, Hother-Nielsen O, et al. Impact of insulin sites on glycaemic control in type 1 (insulin dependent) diabetic patients treated with multiple insulin injection regimen. Diabetologia 1993; 36: 752-758

Henriksen OM, Røder ME, Prahl JB, Svendsen OL. Diabetic ketoacidosis in Denmark incidence and mortality estimated from public health registries. Diabetes Research and Clinical Practice 2007; 76: 51–56

Hermann R, Bartsocas CS, Vazeou A, Paschou P, Bozas E, Malamitsi-Puchner A, et al. Genetic screening for individuals at high risk for type 1 diabetes in the general population using HLA Class II alleles as disease markers. A comparison between three European populations with variable rates of disease incidence. Diabetes Metabolism Research and Review 2004; 20: 322–329

Hirsch IB, Bode BW, Garg S, Lane WS, Sussman A, Hu P. et al. Continuous subcutaneous insulin infusion (CSII) of insulin as part versus multiple daily injection of insulin aspart/insulin glargine in type 1 diabetic patients previously treated with CSII. Diabetes Care 2005; 28: 533-538

Hirsch IB, Armstrong D, Bergenstal RM, Buckingham B, Childs BP, Clarke WL, et al. Clinical application of emerging sensor technologies in diabetes management: consensus guidelines for Continuous Glucose Monitoring (CGM). Diabetes Technology & Therapeutics 2008a; 10: 232-246

Hirsch IB, Abelseth J, Bode BW, M.D, Fischer JS, Kaufman FR, M.D, Mastrototaro J,et al. Sensor-augmented insulin pump therapy: results of the first randomized treat-to-target study. Diabetes Technology & Therapeutics 2008b; 10: 377-383

Hirsch LJ, Gibney MA, Albanese J, Qu S, Kassler-Taub K. Comparative glycemic control, safety and patient ratings for a new 4 mm x 32G insulin pen needle in adults with diabetes. Current Medical Research & Opinion 2010; 26: 1531–1541

Hislop AL, Fegan PG, Schlaeppi MJ, Duck M, Yeap BB. Prevalence and associations of psychological distress in young adults with type 1 diabetes. Diabetic Medicine 2008; 25: 91–96

Holleman F, Gale EAM. Nice insulin, pity about the evidence. Diabetologia 2007; 50:1783-1790

Holstein A, Stege H, Kovacs P. Lipoatrophy associated with the use of insulin analogues: a new case associated with the use of insulin glargine and review of the literature. Expert Opinion on Drug Safety 2010; 9 : 225-231

Holt RIG, Cockram CS, Flyvberg A, Goldstein BJ (eds). Textbook of Diabetes. London: Wiley-Blackwell 2010

Home PD, Lindholm A, Riis A. Insulin aspart vs. human insulin in the management of long-term blood glucose control in Type 1 diabetes mellitus: a randomized controlled trial. Diabetic Medicine 2000; 17, 762-770

Home PD, Hallgren P, Usadel KH, Sane T, Faber J, Grill V, et al. Pre-meal insulin aspart compared with pre-meal soluble human insulin in type 1 diabetes. Diabetes Research and Clinical Practice 2006; 71: 131–139

Hoogma RPLM, Hammond PJ, Gomis R, Kerr D, Bruttomesso D, Bouter KP, et al. Comparison of the effects of continuous subcutaneous insulin infusion (CSII) and NPH-based multiple daily insulin injections (MDI) on glycaemic control and quality of life: results of the 5-nations trial. Diabetic Medicine 2006; 23: 141–147

Hornquist JO, Wikby A, Andersson P, Dufva AM. Insulin-pen treatment, quality of life and metabolic control: retrospective intra-group evaluations. Diabetes Research and Clinical Practice 1990; 10: 221-230

Hummel M, Füchtenbusch M, Schenker M, Ziegler AG. No major association of breast-feeding, vaccinations, and childhood viral diseases with early islet autoimmunity in the German Babydiab study. Diabetes Care 2000; 23:969–974

Hussein SF, Siddique H, Coates P, Green J. Lipoatrophy is a thing of the past, or is it? Diabetic Medicine 2007; 24: 1470–1472

Hyppönen E, Virtanen SM, Kenward MG, Knip M, Åkerblom HK. Obesity, Increased Linear Growth, and Risk of Type 1 Diabetes in Children. Diabetes Care 2000; 23:1755–1760

Imkampe AK, Gulliford MC. Trends in type 1 diabetes incidence in the UK in 0 to 14 year olds and 15 to 34 year olds, 1991-2008. Diabetic Medicine 2011; 28: 811-814

Jeitler K, Horvath K, Berghold A, Gratzer TW, Neeser K, Pieber TR, at al. Continuous subcutaneous insulin infusion versus daily insulin injections in patients with diabetes mellitus: systematic review and meta-analysis. Diabetologia 2008; 51: 941-951

Jones JM, Lawson ML, Daneman D, Olmsted MP, Rodin G. Eating disorders in adolescent females with and without type 1 diabetes: cross sectional study. British Medical Journal 2000; 320: 1563-1566

Jørgensen LN, Dejgaard A, Pramming SK. Human insulin and hypoglycaemia: a literature survey. Diabetic Medicine 1994; 11: 925-34

Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study Group. Continuous glucose monitoring and intensive treatment of type 1 diabetes. New England Journal of Medicine 2008; 359: 1464-76

Kaila B, Taback SP. The effect of day care exposure on the risk of developing type 1 diabetes. Diabetes Care 2001; 24:1353–1358

Kelly AM, Barnett AH, Bain SC. The aetiology and genetics of type 1 diabetes. In A H Barnett (ed) Diabetes: Best Practice & Research Compendium. Elsevier 2006

Kelly WD, Lillehei RC, Merkel FK, Idezuki Y, Goetz FC. Allotransplantation of the pancreas and duodenum along with the kidney in diabetic nephropathy. Surgery 1967; 61:827-837

Kent L, Gill G, Williams G. Mortality and outcome of patients with brittle diabetes and recurrent ketoacidosis. Lancet 1994; 344: 778-781

Kibirige M, Metcalf B, Renuka R, Wilkin TJ. Testing the Accelerator Hypothesis: The relationship between body mass and age at diagnosis of type 1 diabetes. Diabetes Care 2003; 26: 2865-2870.

Kimmelstiel P, Wilson C. Intercapillary lesions in the glomeruli of the kidney. American Journal of Pathology 1936; 12: 83-97

Kimpimaki T, Erkkola M, Korhomen S, Kupila A, Virtanen SM, Ilonen J, et al. Short-term exclusive breast feeding predisposes young children with increased genetic risk of type 1 diabetes to progressive beta-cell autoimmunity. Diabetologia 2001; 44: 63-69

Kitabchi AE, Umpierrez GE, Murphy MB, Kreisberg RA. Hyperglycemic crises in adult patients with diabetes: A consensus statement from the American Diabetes Association. Diabetes Care 2006; 29: 2739-2748

Knerr I, Wolf J, Reinehr T, Stachow R, Grabert M, Schober E, Rascher W, Holl RW. The 'accelerator hypothesis': relationship between weight, height, body mass index and age at diagnosis in a large cohort of 9,248 German and Austrian children with type 1 diabetes mellitus. Diabetologia 2005; 48: 2501–2504

Knip M, Virtanen SM, Sepp K, Ilonen J, Savilahti E, Vaarala O, et al. Dietary intervention in infancy and later signs of beta-cell autoimmunity. New England Journal of Medicine 2010; 363:1900-1908

Koivisto VA, Felig, P. Alterations in insulin absorption and in blood glucose control associated with varying insulin injection sites in diabetic patients. Annals of Internal Medicine 1980; 92: 59-61

Kordonouri O, Lauterborn R, Deiss D. Lipohypertrophy in young patients with type 1 diabetes. Diabetes Care 2002; 25: 634

Kordonouri O, Hartmann R. Higher body weight is associated with earlier onset of type 1 diabetes in children: confirming the "Accelerator Hypothesis." Diabetic Medicine 2005; 22: 1778-1784

Krishnamurti U, Steffes M. Glycohemoglobin: a primary predictor of the development or reversal of complications of diabetes mellitus. Clinical Chemistry 2001; 47: 1157–1165

Krynski IA, Logan JE. Dextrostix as a Quantitative Test for Glucose in Whole Blood. Canadian Medical Association Journal 1967; 97: 1006-1011

Kucera ML, Graham JP. Insulin lispro, a new insulin analog. Pharmacotherapy 1998; 18: 526-38

Kumar D, Gemayel NS, Deapen D, Kapadia D, Yamashita PH, Lee M, et al. North-Americam twins with IDDM. Genetic, etiological, and clinical significance of disease concordance according to age, zygosity, and the interval after diagnosis in first twin. Diabetes 1993; 42: 1351-1363.

Laing SP, Swerdlow AJ, Slater SD, Botha JL, Burdent AC, Waugh NR, et al. The British Diabetic association Cohort Study, II: cause-specific mortality in patients with insulin-treated diabetes mellitus. Diabetic Medicine 1999; 16: 466-471

Laing SP, Jones ME, Swerdlow AJ, Burden AC, Gatling W. Psychosocial and socioeconomic risk factors for premature death in young people with type 1 diabetes. Diabetes Care 2005; 28: 1618–1623

Largiader F, Kolb E, Binswanger U. A long-term functioning human pancreatic islet Allotransplant. Transplantation 1980; 29:76–77

Lawrence RD. The Diabetic Life: Its control by diet and insulin. J&J Churchill London, 1925

Lawrence RD. Regional centre for the treatment of diabetes . Lancet 1951; 1:1318-19

Lepore G, Dodesini AR, Nosari I, Trevisan R. Subcutaneous insulin infusion and a multiple daily insulin injection regimen with glargine as basal insulin are equally better than traditional multiple daily insulin injection treatment. Diabetes Care 2003; 26: 1320-1321

Lowe J, Linjawi S, Mensh M, James K, Attia J. Flexible eating and flexible insulin dosing in patients with diabetes: results of an intensive self-management course. Diabetes Research and Clinical Practice 2008; 80:439-443

Luddeke HJ, Sreenan S, Aczel S, Maxeiner S, Yenigun M, Kozlovski P. et al. PREDICTIVETM – a global, prospective observational study to evaluate insulin detemir treatment in types 1 and 2 diabetes: baseline characteristics and predictors of hypoglycaemia from the European cohort. Diabetes, Obesity and Metabolism 2007; 9: 428–434

MacCuish AC, Irvine WJ, Barnes EW, Duncan LJ. Antibodies to pancreatic islet cells in insulin-dependent diabetics with coexistent autoimmune disease. Lancet 1974; 2: 1529-1531

MacFarlane, I. A. Mathew Dobson of Liverpool (1735-1784) and the history of diabetes. Practical Diabetes Digest 1991; 2 : 54-58

Maran A, Lomas J, Archibald H, Macdonald IA, Gale EAM, Amiel SA. Double blind clinical and laboratory study of hypoglycaemia with human and porcine insulin in diabetic patients reporting hypoglycaemia unawareness after transferring to human insulin. British Medical Journal 1993; 306: 167-171

Markowit JT, Lowe MR, Volkening LK, Laffel LM. Self-reported history of overweight and its relationship to disordered eating in adolescent girls with Type 1 diabetes. Diabetes Medicine 2009; 26: 1165–1171

Markowitz JT, Butler,DA, Volkening LK, Antisdel JE. Brief Screening Tool for Disordered Eating in Diabetes: Internal consistency and external validity in comtemporary sample of peadiatric patients with type 1 diabetes. Diabetes Care 2010; 33: 495-500

Mastrandrea L, Yu J, Behrens T, Buchlis J, Albini C, Fourtner S. Etanercept treatment in children with new-onset type 1 diabetes: Pilot randomized, placebo-controlled, double-blind study. Diabetes Care 2009; 32:1244–1249

Matsumoto S. Islet cell transplantation for Type 1 diabetes. Journal of Diabetes 2010; 2: 16–22

Mbanya J. The standardization of glycated haemoglobin: is it desirable? Diabetes Voice 2005; 50: 27-30

Menser MA, Forrest JM, Bransby RD. Rubella infection and diabetes mellitus. Lancet 1978; 311:57-60

Misso ML, Egberts KJ, Page M, O'Connor D, Shaw J. Continuous subcutaneous insulin infusion (CSII) versus multiple insulin injections for type 1 diabetes mellitus (Review). The Cochrane Collaboration 2010

Mohr SB, Garland CF, Gorham ED, Garland FC. The association between ultraviolet B irradiance, vitamin D status and incidence rates of type 1 diabetes in 51 regions worldwide. Diabetologia 2008 51:1391–1398

Moltchanova EV, Schreier N, Lammi N, Karvonen M. Seasonal variation of diagnosis of Type 1 diabetes mellitus in children worldwide. Diabetic Medicine 2009; 26: 673–678

Moreau F, Spizzo H, Bursztejn C, Berthoux V, Agins A, Pingett M. Factitious self-manipulation of the external insulin pump in adolescent with Type 1 diabetes. Diabetic Medicine 2011; 28: 623-524

Morris AD, Boyle DIR, McMahon AD, Greene SA, MacDonald TM, Newton RW. Adherence to insulin treatment, glycaemic control, and ketoacidosis in insulin-dependent diabetes mellitus. Lancet 1997; 350: 1505–1510

Muhlhauser I, Jorgens V, Berger M, Graninger W, Gurtler W, Hornke L et al. Bicentric evaluation of a teaching and treatment programme for type 1 (Insulin-Dependent) diabetic patients: Improvement of metabolic control and other measure of diabetes care for up to 22 months. Diabetologia 1983; 25: 470-476

National Diabetes Audit Executive Summary 2009-2010. The NHS Information Centre 2011

National Institute for Clinical Excellence. Guidance on the use of patient-education models for diabetes. NICE; 2003

National Institute for Clinical Excellence. Type 1 Diabetes In Adults: National clinical guideline for diagnosis and management in primary and secondary care. NICE 2004

National Institute for Clinical Excellence. Continuous subcutaneous insulin infusion for the treatment of diabetes mellitus (Review of technology appraisal guidance 57). NICE; 2008

Nielsen S. Eating disorders in females with type 1 diabetes: An update of a meta-analysis. European Eating Disorders Review 2002a; 10: 241–254

Nielsen S, Emborg C, Mølbak A. Mortality in concurrent type 1 diabetes and anorexia nervosa. Diabetes Care 2002b; 25:309–312

Norris JM, Beaty B, Klingensmith G, Yu L, Holliman M, Chase P, et al. Lack of association between early exposure to cow's milk protein and β-cell atoimmunity. Journal of American Medical Association 1996; 276: 609-614

Norris JM, Barriga K, Klingensmith G, Hoffman M, Eisenbarth GS, Erlich HA, et al. timing of initial cereal exposure in infancy and risk of islet autoimmunity. Journal of American Medical Association 2003; 290: 1713-1720

Notkins AL, Lernmark A. Autoimmune type 1 diabetes: resolved and unresolved issues. The Journal of Clinical Investigation 2001; 108:1247–1252

O' Connell MA, Donath S, Cameron FJ. Major increase in type 1 diabetes- no support for the accelerator hypothesis. Diabetic Medicine 2007; 24: 920-923

Olmsted MP, Colton PA, Daneman D, Rydall AC, Rodin GM. Prediction of the Onset of Disturbed Eating Behavior in Adolescent Girls with Type 1 Diabetes. Diabetes Care 2008; 31:1978–1982

Olsson L, Ahlbom A, Grill V, Midthjell K, Carlsson S. High levels of education are associated with an increased risk of latent autoimmune diabetes in adults. Diabetes Care 2011; 34: 102-107

Ovalle F, Vaughan Iii TB, Sohn JE, Gower B. Catamenial diabetic ketoacidosis and catamenial hyperglycemia: case report and review of the literature. The American Journal of Medical Sciences 2008; 335: 298-303

Owens DR, Coates PA, Luzio SD, Tinbergen JP, Kurzhals R. Pharmacokinetics of $^{125}$I-labeled insulin glargine (HOE 901) in healthy men. Diabetes Care 2000; 23:813–819

Padaiga Z, Tuomilehto J, Karvonen M, Dahlquish G, Podar T, Adojaan B, et al. Seasonal variation in the incidence of type 1 diabetes during 1983 to 1992 in the countries around the Baltic Sea. Diabetic Medicine 1999; 16: 736-743

Palmer JP, Asplin CM, Clemons P, Lyon K, Tatpati O Raghu PK, et al. Insulin antibodies in insulin-dependent diabetics before insulin treatment. Science 1983; 222: 1337-1339.

Patterson CC, Carson DJ, Hadden DR; Northern Ireland Diabetes Study Group. Epidemiology of childhood IDDM in Northern Ireland 1989-1994: low incidence in areas with highest population density and most household crowding. Northern Ireland Diabetes Study Group. Diabetologia. 1996;39(9):1063-1069. 40

Patterson, C, Dahlquish GG, Soltesz G, Green A. Is childhood-ondet type 1 diabetes a wealth related disease? An ecological analysis of European incidence rate. Diabetologia 2001; B9-B16.

Patterson C, Dahlquish GG, Gyurus A, Green A, Soltesz G. Incidence trends for childhood type 1 diabetes in Europe during 1989-2003 and predicted new cases 2005-20: a multicentre prospective registration study. Lancet 2009; 373: 2027-2033

Peveler RC, Bryden KS, Neil HAW, Fairburn CG, Mayou RA, Dunger DB. The relationship of disordered eating habits and attitudes to clinical outcomes in young adult females with type 1 diabetes. Diabetes Care 2005; 28:84–88

Peveler RC, Holt RIG. Psychiatric disorders and diabetes. Holt RIG, Cockram CS, Flyvberg A, Goldstein BJ (eds). Textbook of Diabetes. London: Wiley-Blackwell 2010

Peyrot M, Skovlund SE, Landgraf R. Epidemiology and correlates of weight worry in the multinational Diabetes Attitudes, Wishes and Needs study. Current Medical Research and Opinion 2009; 25: 1985–1993

Peyrot M, Rubin R, Kruger D, Travis LB. Correlates of Insulin Injection Omission. Diabetes Care 2010; 33: 240-245

Pickup JC, Kidd J, Burmiston S, Yemane N. Determinants of glycaemic control in type 1 diabetes during intensified therapy with multiple daily insulin injections or continuous subcutaneous insulin infusion: importance of blood glucose variability. Diabetes/Metabolism Research and Reviews 2006; 22: 232-237

Pickup JC, Freeman SC, Sutton AJ. Glycaemic control in type 1 diabetes during real time continuous glucose monitoring compared with self monitoring of blood glucose: meta-analysis of randomised controlled trials using individual patient data. British Medical Journal 2011; 343:d3805

Plank J, Köhler G, Rakovac I,Semlitsc BM, Horvath K, Bock G, Kraly B, Pieber TR. Long-term evaluation of a structured outpatient education programme for intensified insulin therapy in patients with Type 1 diabetes: a 12-year follow-up. Diabetologia 2004; 47: 1370-1375

Polonsky WH, Anderson BJ, Lohrer PA, Aponte JE, Jacobson AM, Cole CF. Insulin Omission in Women With IDDM. Diabetes Care 1994 17 1178-1185

Porter JR. Braking the Accelerator Hypothesis? Diabetologia 2004; 47: 352-356

Purnell JQ, Hokanson JE, Marcovina SM, Steffes MW, Cleary PA, Brunzell JD. Effect of excessive weight gain with intensive therapy of type 1 diabeteson lipid profile and blood pressure; results from the DCCT. The Journal of the American Medical Association 1998; 280: 140-146

Pundziute-Lyckå A, Dahlquist G, Nyström L, Arnqvist H, Björk E, Blohmé G, Bolinder J,et al. The incidence of Type I diabetes has not increased but shifted to a younger age at diagnosis in the 0–34 years group in Sweden 1983 to 1998. Diabetologia 2002; 45:783–791

Rahbar S. The discovery of glycated hemoglobin: A major event in the study of nonenzymatic chemistry in biological system. Annals New York Academy of Science 2005; 1043: 9–19

Rankin D, Cooke DD, Clark M, Heller S, Elliott J, Lawton J. How and why do patients with type 1 diabetes sustain their use of flexible intensive insulin therapy? A qualitative longitudinal investigation of patients' self-management practices following attendance at Dose-Adjustment for Normal Eating (DAFNE) course. Diabetic Medicine 2011; 28:532-538

Raskin P, Guthrie RA, Leiter L, Riis A, Jovanovic L. Use of insulin as part, a fast-acting insulin analog, as the mealtime insulin in the management of patients with type 1 diabetes. Diabetes Care 2000; 23:583–588

Redondo MJ, Yu L, Hawa M, Mackenzie T, Pyke DA, Eisenbarth GS, et al. Heterogeneity of type 1 diabetes: analysis of monozygotic twins in Great Britain and the United States. Diabetologia 2001; 44: 354-362

Reeves WG, Allen BR, Tattersall RB Insulin induced lipoatrophy an immune pathogenesis British Medical Journal 1980; 280:1500-1503

Retnakaran R, Hochman J, Devries JH, Hanaire-Broutin H, Heine RJ, Melki V. Continuous Subcutaneous insulin infusion versus multiple daily injections: The impact of baseline A1c. Diabetes Care 2004; 27: 2590–2596

Reuting RE. Progress notes on fifty diabetic patients followed 25 or more years. Archives of Internal Medicine 1950; 86:891-897

Richardson SJ, Wilcox A, Bone AJ, Foulis AK, Morgan NJ. The prevalence of enteroviral capsid protein vp1 immunostaining in pancreatic islets in human type 1 diabetes. Diabetologia 2009; 52: 1143-1152

Richter B, Neises G. "Human" insulin versus animal insulin in people with diabetes mellitus (Review). The Cochrane Collaboration; 2009

Rubin RR, Peyrot M. Quality of Life and Diabetes. Diabetes/Metabolism Research Review 1999; 15: 205-218

Ryan EA, Paty EW, Senior PA, Bigam D, Alfadhli E, Kneteman NM. Five-year follow-up after clinical islet transplantation. Diabetes 2005; 54: 2060-2069

Rys P, Pankiewicz O, Lach K, Kwaskowski A, Skrzekowska-Barn I, Malecki MT. Efficacy and safety comparison of rapid-acting insulin aspart and regular human insulin in the treatment of type 1 and 2 diabetes mellitus: A systematic review. Diabetes and Metabolism 2011; 37:190-200

Sanjeevi CB, Hagopian WA, Landin-Olsson M, Kockum I, Woo W, Palmer JB, et al. Association between autoimmunity markers and subtypes of DR4 and DR4-DQ in Swedish children with insulin-dependent diabetes reveals closer association of tyrosine pyrophosphate autoimmunity with DR4 than DQ8. Tissue Antigen 1998; 51: 281-286

Saunders SA, Wallymahmed M, Macfarlane IA. Glycaemic control in a type 1 diabetes clinic for younger adults. Quarterly Journal of Medicine. 2004a; 97; 575-580.

Saunders SA, Democratis J, Martin J, Macfarlane IA. Intravenous drug abuse and Type 1 diabetes: financial and healthcare implications. Diabetic Medicine 2004b; 21: 1269–1273

Scavone G, Manto A, Pitocco D, Gagliardi L, Caputo S, Mancini L, Zaccardi F, Ghirlanda G. Effect of carbohydrate counting and medical nutritional therapy on glycaemic control in Type 1 diabetic subjects: a pilot study. Diabetic Medicine 2010; 27: 477-479

Schober E, Rami B, Waldhoer T. Steep increase of incidence of childhood diabetes since 1999 in Austria. Time trend analysis 1979–2005. A nationwide study. European Journal of Pediatric 2008; 167: 293–297

Secrest AM, Becker DJ, Felsey SF, LaPorte RE, Orchard TJ. Characterizing sudden death and dead-in-bed syndrome in type 1 diabetes: analysis from two childhood-onset type 1 diabetes registries. Diabetic Medicine 2011; 28: 293-300

Setter SM, Corbett CF, Campbell RK, White JR. Insulin aspart: A new rapid-acting insulin analog. Ann Pharmacokinet 2000; 34: 1423-31

Shapiro AMJ, Lakey JRT, Ryan EA, Korbutt GS, Toth E, Warnock GL. Islet transplantation in seven patients with type 1 diabetes mellitus using a glucocorticoid-free immunosuppressive regimen. New England Journal of Medicine 2000; 343: 231-238

Skrivarhaug, T, Bangstad HJ, Stene LC, Sandvik L, Hanssen KF, Joner G. Long-term mortality in a nationwide cohort of childhood-onset type 1 diabetic patients in Norway. Diabetologia 2006; 49: 298-305

Soltesza G, Patterson CC, Dahlquis G. Worldwide childhood type 1 diabetes incidence – what can we learn from epidemiology? Peadiatric Diabetes 2007; 8: 6-14

Sonksen P, Judd S, Lowy C. Home monitoring of blood glucose : method for improving diabetic control. Lancet 1978; 1:729-732

Speight J, Amiel SA, Bradley C, Heller S, Oliver L, Roberts S. Long-term biomedical and psychosocial outcomes following DAFNE (Dose Adjustment For Normal Eating) structured education to promote intensive insulin therapy in adults with sub-optimally controlled Type 1 diabetes. Diabetes Research and Clinical Practice 2010; 89: 22-29

Staines A, Bodansky HJ, McKinney PA, et al. Small area variation in the incidence of childhood insulin-dependent diabetes mellitus in Yorkshire, UK: links with overcrowding and population density. International Journal Epidemiology 1997;26 :1307- 1313

Stene LC, Magnus P, Lie RT, Søvik O, Joner G. Maternal and paternal age at delivery, birth order, and risk of childhood onset type 1 diabetes: population based cohort study. British Medical Journal 2001; 323: 1-4

Storz SM, Wylenzek SAM, Matheis N, Weber MM, Kahaly GJ. Impaired psychometric testing in polyglandular autoimmunity. Clinical Endocrinology 2011; 74: 394–403

Strachan DP. Hay fever, hygiene, and household size. British Medical Journal 1989; 299: 1259-1260

Strauss K, De Gols H, Hannet I, Partanen TM, Frid A. A pan-European epidemiologic study of insulin injection technique in patients with diabetes. Practical Diabetes International 2002; 19: 71-76

Svensson J, Lyngaae-Jørgensen A, Carstensen B, Simonsen LB, Mortensen, HB. Long-term trends in the incidence of type 1 diabetes in Denmark: the seasonal variation changes over time. Pediatric Diabetes 2009; 10: 248–254

Szypowski A, Golickiz D, Groela L, Pankowska E. Long- acting insulin analogue detemir compared with NPH insulin in type 1 diabetes. A systematic review and meta-analysis. Polskie Archivum Medycycy Wewetrznej 2011; 121: 237-246

Tanenberg RJ, Newton, CA, Drake AJ. Confirmation of hypoglycemia in the "dead-in-bed" syndrome, ascaptured by a retrospective continuous glucose monitoring system. Endocrinology Practical 2010; 16: 244-248

Tattersall R, Gill G. Unexplained Deaths of Type 1 Diabetic Patients. Diabetic Medicine 1991, 8: 49–58

Tattersall R. The history of diabetes mellitus. In Holt RIG, Cockram CS, Klyvbjerg A, Goldstein BJ (eds) Text book of diabetes. Wiley-Blackwell 2010a

Tattersall R. Patient education and diabetes care: Part 1. Diabetes Digest 2010b; 9: 126-127

TEDDY Study Group. The environmental determinants of diabetes in the young (TEDDY) study. Annals of the New York Academy of Science 2008; 1150: 1-13

Teuscher A, Berger WG. Hypoglycaemic awareness in diabetics transferred to human insulin. Lancet 1987; 2: 382-385

Thrower SL, Bingley PJ. Prevention of type 1 diabetes. British Medical Bulletin 2011; 99: 73–88

Todd JA, Farall M. Panning for gold: genome-wide scanning for linkage in type 1 diabetes. Human Molecular Genetics 1996; 5: 1443-1448

Todd JA, Walker MN, Cooper JD, Smyth DJ, Downes K, Plagnol V, et al. Robust associations of four new chromosome regions from genome-wide analyses of type 1 diabetes. Nature Genetics 2007; 39: 857-864

Thomas C, Majid S, Wilding J, Wallymahmed M, Gill G. An elderly type 1 diabetic patient with life event-related brittle diabetes. Practical Diabetes International 2007; 24: 130-131

Thomson G, Valdes AM, Noble JA, Kockum I, Grote MN, Najman J, et al. Relative predispositional effects of HLA class II DRB1-DQB1 haplotypes and genotypes on type 1 diabetes: a meta-analysis. Tissue Antigens 2007; 70: 110–127

Thow CC, Johnson AB, Marsden S, Taylor R, Home PD. Morphology of palpably abnormal injection sites and effects on absorption of Isophane (NPH) insulin. Diabetic Medicine 1990; 7: 795-799

Tu E, Twigg SM, Semsarian C. Sudden death in type 1 diabetes: The mystery of the 'dead in bed' syndrome. International Journal of Cardiology 2010; 138:91-93

UK Hypoglycaemia Group. The risk of hypoglycaemia in type 1 and 2 diabetes: Effects of treatment modalities and their duration. Diabetologia 2007; 50: 1140-1147

Vaag A,Handberg A, laritzen M et al Variation in absorption of NPH injectable therapy due to intramuscular injection. Diabetes Care 1990; 13: 74-76

Vajo Z, Fawcett J, Duckworth WC. Recombinant DNA technology in the treatment of diabetes: insulin analogs. Endocrine Reviews 2001; 22: 706–717.

Vardar B, Kızılcı S. Incidence of lipohypertrophy in diabetic patients and a study of influencing factors. Diabetes Research and Clinical Practice 2007; 77: 231–236

Vardi P, Ziegler AG, Mathews JH, Dib S, Keller RJ, Ricker AT, et al. Concentration of insulin autoantibodies at onset of type 1 diabetes: inverse log-linear correlation with age. Diabetes Care 1988; 11: 736-739

Vardi M, Jacobson E, Nini A, Bitterman H. Intermediate acting versus long acting insulin for type 1 diabetes mellitus (Review). The Cochrane Collaboration; 2008

Vehik K, Cuthbertson D, Ruhlig H, Schatz D A, Peakman M, Krischer J, et al. Long-term outcome of individuals treated with oral insulin: diabetes prevention trial-type 1 (DRP-1) oral insulin trial. Diabetes Care 2011; 34: 1585-1590

Verbeeten KV, Elks CE, DanemanD, Ong K. Association between childhood obesity and subsequent Type 1 diabetes: a systematic review and meta-analysis. Diabetic Medicine 2011; 28: 10–18

Virtanen SM, Kenward MG, Erkkola M, Kautiainen S, Kronberg-Kippila C, Hakulinen T. Age at introduction of new food and advanced beta cells autoimmunity in young children with HLA-conferred susceptibility to type 1 diabetes. Diabetologia 2006; 49: 1512-1521

Virtanen SM, Takkinen HM, Nevalainen J, Kronberg-Kippila C, Salmenhaara M, Uusitalo L, et al. Early introduction of root vegetables in infancy associated with advanced ß-cell autoimmunity in young children with human leukocyte antigen-conferred susceptibility to Type 1 diabetes. Diabetic Medicine 2011; 28: 965–971

Viskari HR, Roivainen M, Reunanen A, Pitka¨niemi J, Sadeharju K, Koskela P, et al. Maternal first-trimester enterovirus infection and future risk of type 1 diabetes in the exposed fetus. Diabetes 2002; 51: 2568-2571

Von Herrath M. Can we learn from viruses how to prevent type 1 diabetes?: the role of viral infections in the pathogenesis of type 1 diabetes and the development of novel combination therapies. Diabetes 2009; 58: 2-11

Wagener HF, Dry TJS, Wilder RM. Retinitis in diabetes. New England Journal of Medicine 1934; 211:1131-1137

Walford S, Gale EAM, Allison SP, Tattersall RB. Self monitoring of blood glucose: improvement of diabetic control Lancet 1978;1:732-735

Wallymahmed ME, Foy P, MacFarlane IA. The quality of life of adults with growth hormone deficiency: comparison with diabetic patients and control subjects. Clinical Endocrinology 1999; 51: 333-338

Wallymahmed ME, Littler P, Clegg C, Haqqani MT, MacFarlane IA. Nodules of fibrocollagenous scar tissue induced by subcutaneous insulin injections: a cause of poor diabetic control. Postgraduate Medical Journal 2004; 80: 732–733

Wallymahmed ME, MacFarlane I. The value of group insulin starts in people with type 2 diabetes. Journal of Diabetes Nursing 2005; 8: 287-290

Walters DP, Smith PA, Marteau TM, Brimble A, Borthwick LJ Experience with Novopen, an injection device using cartridged insulin, for diabetic patients Diabetic Medicine 1985; 2: 496-497

Wändell PE, Brorsson B, Åberg H. Quality of life among diabetic patients in Swedish primary health care and in the general population: comparison between 1992 and 1995. Quality of Life Research 1998: 7: 751-760

Weissberg-Benchell J, Antisdel-Lomaglio J, Seshadri R. Insulin pump therapy. A meta-analysis. Diabetes Care 2003; 26: 1079–1087

Wenzlau JM, Juhl K, Yu L, Moua O, Sarkar SA, Gottlieb P. et al. The cation efflux transporter ZnT8 (Slc30A8) is a major autoantigen in human type 1 diabetes. Proceedings of the National Academy of Science 2007; 104: 17040-17045

Wild D, Von Maltzahn R, Brohan E, Christensen T, Clauson P, Gonder-Frederick L. A critical review of the literature on fear of hypoglycemia in diabetes: Implications for diabetes management and patient education. Patient Education and Counseling 2007; 68: 10–15

Wilkin TJ. The accelerator hypothesis: weight gain as the missing link between type 1 and type 2 diabetes. Diabetologia 2001; 44: 914-922

Wilson DM, Beck RW, Tamborlane WV, Dontchev MJ, Kollman C, Chase P, et al. The accuracy of the freestyle navigator continuous glucose monitoring system in children with type 1 diabetes. Diabetes Care 2007; 30: 59–64

Wilson RM, Douglas CA, Tattersall RB, Reeves WG. Immunogenicity of highly purified bovine insulin: a comparison with conventional bovine and highly purified human insulins. Diabetologia 1985; 28: 667-670

Woodward A, Dawes S, Dolan D, Wallymahmed M. What education do people with type 1 diabetes want and how should we provide it? Practical Diabetes International 2006; 23: 295-298

Woodward A, Weston P, Casson IF, Gill GV. Nocturnal hypoglycaemia in type 1 diabetes—frequency and predictive factors. Quarterly Journal of Medicine 2009; 102: 603–607

World Health Organisation. Use of Glycated Haemoglobin (HbA1c) in the Diagnosis of Diabetes Mellitus: Abbreviated Report of a WHO Consultation. WHO; 2011

Wright AD, Walsh CH, Fitzgerald MG, Malins JM. Very pure porcine insulin in clinical practice. British Medical Journal 1979; 1 :25-27

Wright J, Ruck K, Rabbitts R, Charlton M, De P, Barrett T, et al. Diabetic ketoacidosis (DKA) in Birmingham, UK, 2000–2009: an evaluation of risk factors for recurrence and mortality. British Journal of Diabetes & Vascular Disease 2009; 9: 278–282

Ye J, Chen RG, Ashkenazi I, Laron Z. Lack of seasonality in the month of the onset of childhood IDDM (0.7 – 15 years) in Shanghai, China. Journal of Pediatric Endocrinology and Metabolism 1998; 11: 461-464

Young RJ, Steel JM, Frier BM, Duncan LJP. Insulin injection sites in diabetes a neglected area? British Medical Journal 1981; 283: 394

Zachariah S, Sheldon B, Shojaee-Moradie F, Jackson NC, Backhouse K, Johnsen S, Jones RH, Umpleby AM, Russell-Jones DL. Insulin detemir reduces weight gain as a result of reduced food intake in patients with type 1 diabetes. Diabetes Care 2001; 34: 1497-1491

Ziegler AG, Schmid S, Huber D, Hummel M, Bonifacio E. Early infant feeding and risk of developing type 1 diabetes–associated autoantibodies. Journal of American Medical Association 2003;290: 1721-1728

## *CHAPTER 2*

## *COMPLICATIONS AND OUTCOME IN TYPE 1 DIABETES*

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# COMPLICATIONS AND OUTCOME IN TYPE 1 DIABETES

## 2.1 INTRODUCTION

Before the discovery of insulin in early 1920's a diagnosis of type 1 diabetes was closely followed by death usually due diabetic ketoacidosis. Insulin treatment led to significant prolongation of life, however over the course of time chronic complications which would influence life quality and expectancy became evident. An early study from Denmark in 1978 reported that of 307 individuals diagnosed with type 1 diabetes prior to 1933, most within a decade of the discovery of insulin, forty years after diagnosis, 50% were deceased (Deckert et al 1978). The mortality rate was 2-6 times that of the general population and renal failure and myocardial infarction were the major causes of death. Despite advances in management, type 1 diabetes is still associated with premature mortality, and renal and cardiovascular disease (CVD) remain the major cause of death in those over the age of 30 years (Laing et al 1999a, Skrivarhaug et al 2006). Acute metabolic complications account for the majority of deaths in people with type 1 diabetes under the age of 30 years (Laing et al 1999a, Skrivarhaug et al 2006). This chapter will focus on the long term complications and outcomes associated with type 1 diabetes.

## 2.2 MICROVASCULAR COMPLICATIONS ASSOCIATED WITH TYPE 1 DIABETES

The long term micro vascular complications of type 1 diabetes are retinopathy, neuropathy and nephropathy. Micro vascular complications are related to prolonged exposure to hyperglycaemia although other risk factors such as hypertension, dyslipidaemia, smoking and life style issues also contribute. The Diabetes Control and Complications Study (DCCT 1993) (see section 2.6), a large scale prospective study of individuals with type 1 diabetes firmly established the relationship between glycaemic control and the risk of development and progression of micro vascular complications.

Hyperglycaemia selectively damages cells that cannot down regulate glucose uptake causing intracellular hyperglycaemia. It is though that there are five major mechanisms by which hyperglycaemia damages tissue hence causing micro vascular complications (Giacco and Brownlee 2010). These mechanisms are:

- Increased flux of glucose and other sugars through the polyol pathway
- Increased intracellular formation of advanced glycation end products (AGEs)
- Increased expression of the receptor for AGE (RAGE) and its activating ligands
- Activation of Protein Kinase C (PKC) isoforms
- Over activity of the hexosamine pathways

### 2.2.1 Retinopathy

Retinopathy is a common long term complication of type 1 diabetes and a major cause of blindness in the working population. National screening programmes are in place throughout the UK with the aim of reducing visual impairment due to diabetic eye disease. In England, local Primary Care Trusts are responsible for implementing screening programmes and establishing call/recall systems. Annual quality controlled digital photography is now the recommended method of screening. However, in the past, other screening methods such as slit lamp indirect ophthalmoscopy and direct ophthalmoscopy have been used.

The English National Screening Programme for Diabetic Retinopathy has proposed the following classification and referral outcome for diabetic retinopathy (Royal College of Ophthalmologists 2010).

**Table 2.1** English National Screening Programme for Diabetic Retinopathy classification of diabetic retinopathy (Royal College of Ophthalmologists 2010)

| Grade | Defining Features | Outcome |
|---|---|---|
| R0 | No diabetic retinopathy | Annual recall in screening programme |
| R1 | Background diabetic retinopathy | Annual recall in screening programme |
| R2 | Pre-proliferative diabetic retinopathy | Refer to ophthalmology (to be seen within 13 weeks) |
| R3 | Proliferative retinopathy / advanced proliferative features (figure 2.1) | Refer to ophthalmology (to be seen within 2 weeks) |
| MO | No lesion within 1 disc diameter or VA better than 0.3LogMAR with no exudates within 1 disc diameter | Annual recall in screening programme |
| M1 | a) exudates within 1 disc diameter of the centre of the fovea<br><br>b) circinate or group of exudates within the macula<br><br>c) any microaneuyrsm or haemorrhage within 1 disc diameter of the centre of the fovea only if associated with a best VA of =0.3 log MAR (6/12) or worse | Refer to ophthalmology (to be seen within 13 weeks |
| P | Photocoagulation scars present | |
| U | Ungradeable | |

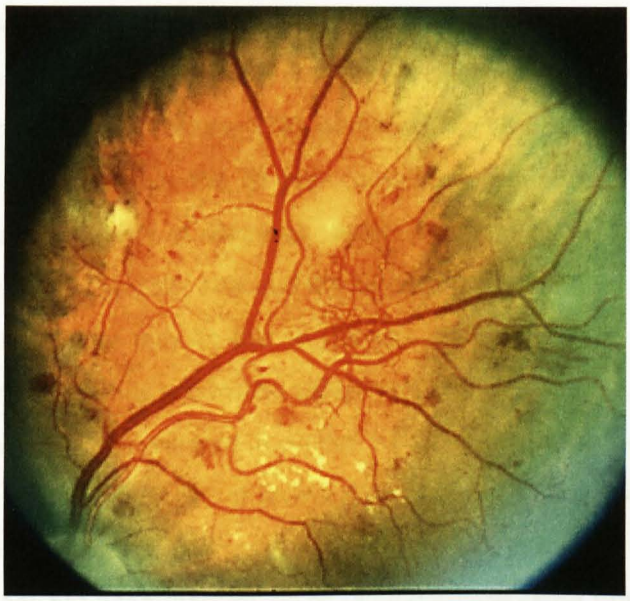


**Figure 2.1** Proliferative retinopathy – downloaded from www.diabeticretinopathy.org.uk

Several studies have assessed the cumulative risk of retinopathy in individuals with type 1 diabetes. An early study from 1984, the Wisconsin Epidemiologic Study of Diabetic Retinopathy, reported that retinopathy of some degree was present in 17% of individuals within the first 5 years of diabetes rising to 97% in those with a duration of 15 years or more. In addition, at 35 years or more duration of diabetes, proliferative retinopathy was present in 67% of individuals with type 1 diabetes diagnosed before the age of 30 years (Klein et al 1984). Twenty five years later follow up data was available on approximately 50% of the original cohort. The cumulative rate of progression to retinopathy was 83% and progression to proliferative retinopathy 42% (Klein et al 2008). Factors associated with progression of retinopathy were, as would be expected, poor glycaemic control, hypertension and duration of diabetes. The 25 year cumulative rate of improvement in diabetic retinopathy was 18% and further analysis revealed that male sex, retinopathy of borderline significance and lower $HbA_{1c}$ at baseline were associated with improvements in retinopathy over 25 years. Finally this study reported a reduction in the prevalence of proliferative retinopathy in those diagnosed in recent years.

A reduction in the cumulative risk of severe retinopathy, according to period of diagnosis, has also been reported by other groups from Finland and Denmark (Hovind at al 2003, Kyto at al 2011). In the Danish study a decrease in the incidence of proliferative retinopathy was

associated with statistically significant trends of decreased $HbA_{1c}$ and lower mean blood pressure along with earlier intervention with anti hypertensive agents (Hovind at al 2003). The more recent study from Finland, involving 3781 people with type 1 diabetes (mean duration of diabetes of 19 years), showed that the 20 year cumulative incidence of severe retinopathy declined according to time frame of diagnosis (before 1975, 1975-79, 1980-84, after 1985). Cumulative incidence was 23%, 33%, 18% and 6% respectively (Kyto at al 2011). The authors suggest that this improvement may be due to changes in diabetes care following the DCCT, specifically carbohydrate counting and insulin adjustment, which is routine in Finland. However the group do not report an improvement in current $HbA_{1c}$. Results of this study do need to be viewed with some care as the diagnosis of severe retinopathy was based on self reported laser treatment rather than photographic images. An improvement in the cumulative incidence of diabetic retinopathy has not been reported by all. A longitudinal study from Pittsburgh did not demonstrate any significant improvements in cumulative incidence of proliferative retinopathy at 25 years duration according to year of diagnosis (Pambianco at al 2006). Furthermore a study from Finland failed to demonstrate any change in the prevalence of retinopathy or in glycaemic control in children and adolescence over a 17 year period (Kubin at al 2011).

Factors associated with the development of retinopathy were investigated recently in a large study involving 8784 adults with type 1 diabetes diagnosed in childhood, adolescence or adult life (Hammes at al 2011). Retinopathy of any degree was present in 27.4% and 8.0% of the cohort had advanced retinopathy. At 40 years duration the cumulative incidence of any retinopathy was 84.1% and severe retinopathy 50.2%. The greatest predictor of retinopathy was good long term control. An $HbA_{1c}$ below 6.5% was associated with a significant delay in the time to clinically significant retinopathy, 32.3 years versus 27.3 years in those with an $HbA_{1c}$ above 6.5%. In addition age at diagnosis was shown to significantly influence the development of any retinopathy with a diagnosis before the age of 5 years being protective of retinopathy and after 15 years being least protective (31.5 versus 26.9 years). Male sex and smoking were also related to the development of any retinopathy. Duration of diabetes, being male, $HbA_{1c}$ above 7.0%, triglycerides above 1.7mmol/l and blood pressure above 140/90mmHg were all significantly related to the development of severe retinopathy. The majority of individuals (84%) in this study were using multiple daily insulin injection regimens indicating that intensive insulin regimens similar to those used in the DCCT are commonly used in routine clinical practice. Retinal screening in this study was with quality controlled direct funduscopy (dilated

pupils) by trained ophthalmologists according to national guidelines. Under reporting is a possibility as photography is known to be more sensitive.

It has been suggested that drugs which block the rennin-angiotensin system may have a beneficial effect on retinopathy. To date studies include a double blind randomised controlled study of the angiotensin converting enzyme (ACE) inhibitor lLsinopril in 530 normotensive individuals with type 1 diabetes (Chaturvedi et al 1998). Lisinopril was associated with a reduction in the progression of retinopathy and a trend to regression. However retinopathy was not a primary endpoint of the study nor was the study powered to detect eye related outcomes and not all participants had gradable photographs. Furthermore and perhaps most importantly there were differences in baseline and final $HbA_{1c}$ favouring the intervention group. In addition intervention with the angiotensin II receptor antagonist candesartan did not demonstrate any significant reduction in the progression of retinopathy although a non significant trend in a reduction in incidence was observed (Chaturvedi at al 2008).

Regardless of improvements in diabetes care retinopathy is still a common and much feared complication of type 1 diabetes (Luckie at al 2007). Currently intensive sustained glycaemic control is the most effective way of reducing the incidence and progression of retinopathy in type 1 diabetes. In addition control of blood pressure, lipids and abstinence from smoking have also been shown to contribute (Hammes at al 2011). Screening is vital in maximising early detection and referral for appropriate intervention for example laser treatment. In England following the publication of the National Service Framework in 2001 (Department of Health 2001) a national screening programme utilising digital retinal photography was introduced. This service is available to everyone with diabetes. However, in the 2009-2010 National Diabetes Audit uptake in type 1 diabetes was only 67.8% (NHS information centre 2011). The reason for this poor uptake is unclear. For some patients, for example the housebound and those who live in rural areas, access may be a problem. In addition many people with diabetes are fearful of the results of screening. It is important for health care professional to discuss the benefits of screening stressing the importance of regular surveillance, early detection and timely intervention when retinopathy is diagnosed.

### 2.2.2 Neuropathy

Diabetic neuropathy is a common complication of diabetes and can lead to considerable morbidity, mortality and impairment of quality of life. It is a heterogeneous condition affecting different parts of the nervous system and has a variety of clinical manifestations which can impact on an individual's life in a diverse manner. Chronic sensorimotor distal symmetric polyneuropathy (DPN) and the autonomic neuropathies, for example erectile dysfunction, are the most common forms of neuropathy in people with diabetes (Tesfaye et al 2010). Sensorimotor neuropathy may be asymptomatic and is characterised by progressive sensory loss predisposing to neuropathic foot ulceration and amputation. In some patients it is associated with pain and in many cases it remains undiagnosed and untreated. An internationally agreed definition of DPN is 'the presence of symptoms and / or signs of peripheral nerve dysfunction in people with diabetes after the exclusion of other causes' (Boulton et al 1998).

Detection methods for DPN include bedside assessment of sensation using simple semi-quantitative bedside tools such as a 10 gram monofilament to assess touch; similar instruments are available to assess temperature and vibration perception. Validated questionnaires such as the Michigan Neuropathy Screening Instrument (Feldman et al 1994) have also been developed to assess the severity of symptoms. In addition, objective measure such as nerve conduction tests and quantitative sensory tests are available in some centres (Ziegler 2010).

Definitions of a minimal criteria for Diabetic Sensorimotor Polyneuropathy (DSPN) have been suggested (table 2.2) (Dyck et al 2011).

**Table 2.2** Definitions for minimal criteria for DSPN (Dyck et al 2011)

| | |
|---|---|
| Possible clinical DSPN | Symptoms or signs of DSPN - symptoms may include: decreased sensation, positive neuropathic sensory symptoms (e.g. 'prickling' or 'burning' pain) predominantly in the toes, feet, or legs. Signs may include: symmetric decrease of distal sensation or unequivocally decreased or absent ankle reflexes. |
| Probable Clinical DSPN | A combination of symptoms and signs of distal sensorimotor polyneuropathy with any two or more of the following: neuropathic symptoms, decreased distal sensation, or unequivocally decreased or absent ankle reflexes. |
| Confirmed Clinical DSPN | An abnormal nerve conduction study and a symptom or symptoms or a sign or signs of sensorimotor polyneuropathy |
| Subclinical DSPN | No signs or symptoms of polyneuropathy but abnormal nerve conduction present |

Neuropathy is generally classified under two main headings (Boulton at al 2005a):

Generalised symmetric polyneuropathies

- Acute sensory
- Chronic sensorimotor
- Autonomic

Focal and multifocal neuropathies

- Cranial
- Truncal
- Focal limb
- Proximal motor (amyotrophy)

More recently there has been suggestion that the generalised symmetric polyneuropathies should be further divided into two sub groups, typical and atypical (Tesfaye et al 2010, Dyck et al 2011).

The prevalence of sensorimotor neuropathy varies according to screening methods used. Rates of 34-40% have been reported (type 1 and type 2 diabetes) recently in community and outpatient populations in Europe (Van Acker at al 2009, Abbott at al 2011). The prevalence appears to be higher in type 2 diabetes and is associated with increased age and duration of diabetes (Young at al 1993, Van Acker at al 2009). In people with type 1 diabetes prevalence rates of 23–28% have been reported with symptoms of painful neuropathy being present in 5.8-13.4% of those screened (Young at al 1993,Tesfaye at al 1996, Van Acker at al 2009, Abbott at al 2011.) In a large study of 3250 individuals with type 1 diabetes from 16 European countries, the EURODIAB Prospective Diabetes Complications Study, 28.5% were found to have evidence of neuropathy on initial assessment (Tesfaye at al 1996). The same cohort was reassessed seven years later when 23.5% of those who did not have evidence of neuropathy at initial assessment subsequently developed neuropathy (Tesfaye at al 2005).

Diabetic painful neuropathy has been defined as 'pain arising as a direct consequence of abnormalities in the somatosensory system in people with diabetes' (Tesfaye et al 2010). It is difficult to estimate the prevalence of painful neuropathy as definitions vary. However it is has been estimated that between 3 and 25% of people with diabetes may be effected (Boulton et al 2004). Patients often report burning pains, tingling in the legs and feet and altered sensation when walking. Symptoms are characteristically worse at night, which leads to sleep disturbance sometimes made worse by contact pain brought on by bedclothes (allodynia).

Unfortunately painful neuropathy is often unreported. In a community study from Liverpool, involving 350 people with diabetes, the prevalence of painful neuropathy, as assessed by a structured questionnaire and examination, was reported to be 16% (Daousi et al 2004). However, 13% of those with painful neuropathy had never reported their symptoms to a doctor and 39% had never received treatment (Daousi at al 2004). At five year follow up despite 96% of those with painful neuropathy reporting pain to a health care professional only 65% had ever received treatment (Daousi at al 2006). Under treatment of painful neuropathy is also highlighted elsewhere (Van Acker at al 2009).

Painful neuropathy has been shown to have significant detrimental effects on the quality of life of people with diabetes when compared to a control group without diabetes and a group of individuals with diabetes but no painful neuropathy (Benbow at al 1998). In this study, quality

of life was assessed using the Nottingham Health Profile, a validated measure of health related quality of life. Painful neuropathy was shown to have a negative effect on measures of energy, pain, physical mobility and sleep. These findings are not surprising as disturbance of sleep due to aggravation of pain at night is characteristic of painful neuropathy and can have a negative effect on overall energy. A reduction in self reported quality of life in adults with diabetes and painful neuropathy, particularly in areas of interference with sleep, enjoyment of life, depression, physical and mental wellbeing has been reported since (Van Acker at al 2009, Galer at al 2000, Vileikyte et al 2009).

Sensorimotor neuropathy is associated with foot ulceration and amputation and it is estimated that up to 85% of all amputations in diabetes could be preventable (Boulton at al 2005b). Factors associated with lower extremity amputations in adults with type 1 diabetes include, being male, smoking, hypertension, poor glycaemic control, neuropathy and retinopathy (Sahakyan at al 2011). However significant reductions in total and major amputation rates have been shown to improve with the introduction of a multidisciplinary team in a large UK district general hospital (Krishnan at al 2008).

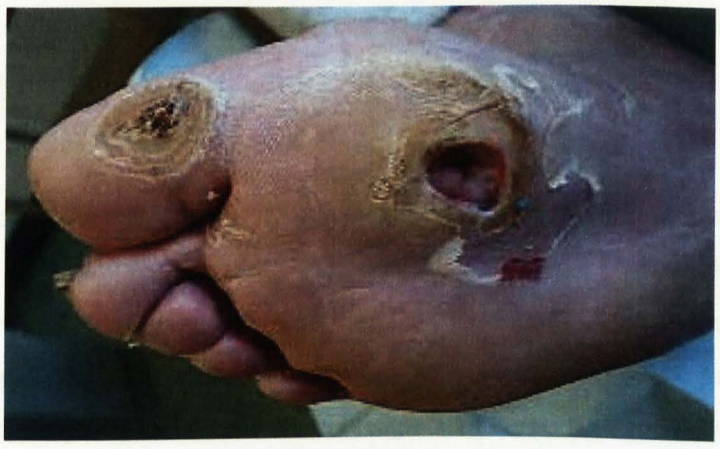


**Figure 2.2** Neuropathic foot ulcer

As with other microvascular complications the DCCT confirmed that improved glycaemic control can have beneficial effects on the development and progression of neuropathy. After a median follow up of 5 years there was a 64% reduction in neuropathy in the intensively treated group compared to the conventional group and this was mainly related to measures of distal symmetrical polyneuropathy (DCCT 1995a). Fourteen years after completion of the DCCT the prevalence of neuropathy had increased in both groups, from 9 to 25% in the former intensive management group and from 17 to 35% in the conventional group. However the difference between the groups remained significant. In addition the incidence of neuropathy remained significantly lower in those originally randomised to the intensive group compared to the conventional group (22% versus 28%, p=0.0125) (Albers at al 2010). Furthermore on completion of the DCCT the prevalence of cardiovascular autonomic neuropathy (assessed by heart rate variability), which is associated with cardiac arrhythmias and sudden death, was reduced in those randomised to intensive treatment compared to the conventional group (4% versus 9%) (DCCT 1995a) and this difference was maintained at 14 year follow up in the EDIC study (Pop- Busui at al 2009). However at follow up, when glycaemic control in both groups was comparable, the prevalence of cardiovascular autonomic neuropathy increased substantially in both groups (28.9% versus 35.2%) but remained significantly lower in the intensive group. Whilst the beneficial effects of a period of intensive management persisted for up to 14 years this was insufficient to prevent the onset and progression of neuropathy in many individuals.

Apart from glycaemic control there is no evidence of any other interventions preventing the development or progression of diabetic neuropathy in type 1 diabetes. However in the EURODIAB cohort, factors significantly associated with development of neuropathy were baseline $HbA_{1c}$, lipid profile, and albumin excretion rate. In addition compared to those who did not develop neuropathy those who did had significantly more retinopathy, hypertension, and abnormal albumin excretion at baseline (Tesfaye at al 2005).

Once neuropathy is established management is aimed at reducing the symptoms and preventing further complications for example foot ulceration. This can be complex particularly in the management of pain which is subjective and can impact on social, psychological and economic well being. Education of health care professionals to encourage early identification of the 'at risk' foot is important as is patient education.

### 2.2.3 Nephropathy

Diabetic nephropathy is a major cause of morbidity and mortality in type 1 diabetes and is associated with cardiovascular disease (Groop et al 2009, Orchard et al 2010). End stage renal failure is devastating to the individual and his or her family and can have serious effects on quality of life, ability to work and financial well being. In type 1 diabetes, recent reports indicate a decline in the progression from nephropathy to end stage renal failure in European populations (ESRD Incidence Study Group 2006, Stewart et al 2007).

Diabetic nephropathy is characterised by a gradual increase in urinary albumin excretion usually accompanied by an increase in blood pressure. Development takes place over a number of years with progression of albumin excretion, usually measured by albumin: creatinine excretion ratio, from the normal to proteinuric range (table 2.3).

| | Normal albumin excretion | Microalbuminuria | Proteinuria |
|---|---|---|---|
| Albumin : creatinine ratio (mg/mmol) | <2.5 (male)<br><3.5 (female) | 2.5-30 (male)<br>3.5 -30 (female) | >30<br>>30 |

**Table 2.3** Definition of normal albumin excretion, microalbuminuria and proteinuria

In the past serum creatinine has been used as an indication of renal function however more recently estimated glomerular filtration rate (eGFR) has been used to stage chronic kidney disease. Results range from >90ml/min indicating normal albuminuria to <15ml/min indicating stage 5 chronic kidney disease.

Progression from normal albumin excretion to microalbuminuria has been assessed in several studies. In a large study of 1134 adults with type 1 diabetes (from 31 European countries) and normal albumin excretion, 12.6% progressed to microalbuminuria over a 7 year time period (Chaturvedi at al 2001). Progression was significantly associated with baseline $HbA_{1c}$, albumin excretion rate, lipid profile and the presence of peripheral neuropathy and any retinopathy. A more recent smaller study involving a younger cohort (median age 17 years) with a short duration of diabetes (median 3 years) reported a progression from normal albumin excretion

to microalbuminuria of 41% over a seven year period (Cobas at al 2011). Progression in this study was not related to baseline $HbA_{1c}$ but was related to a higher BMI and cholesterol : HDL ratio. The rate of progression observed in this study is greater than in other studies and the authors report that final albumin excretion rates in those who progressed to microalbuminuria were close to the normal range (median AER 32.3 µg/min, normal range 20-200 µg/min) and may represent a group of individuals who may regress to normal albumin excretion. Regression of microalbuminuria has been reported previously (Perkins at al 2003). It is generally considered that about one third of people with type 1 diabetes and microalbuminuria will gradually progress to proteinuria, one third will continue to display persistent microlbuminuria and one third will revert to normal albumin excretion (DCCT 1995b, Giorgino at al 2004) (figure 2.3) . However in a recent follow up study of the DCCT / EDIC cohort, after a median follow up of 13 years following the onset of persistent microalbuminuria, regression to normoalbuminuria was 40% and was associated with lower $HbA_{1c}$ and blood pressure. Surprisingly only 46% of those who regressed to normoalbuminuria were taking medication effecting the reninangiotensin- aldosterone system (deBoer at al 2011)

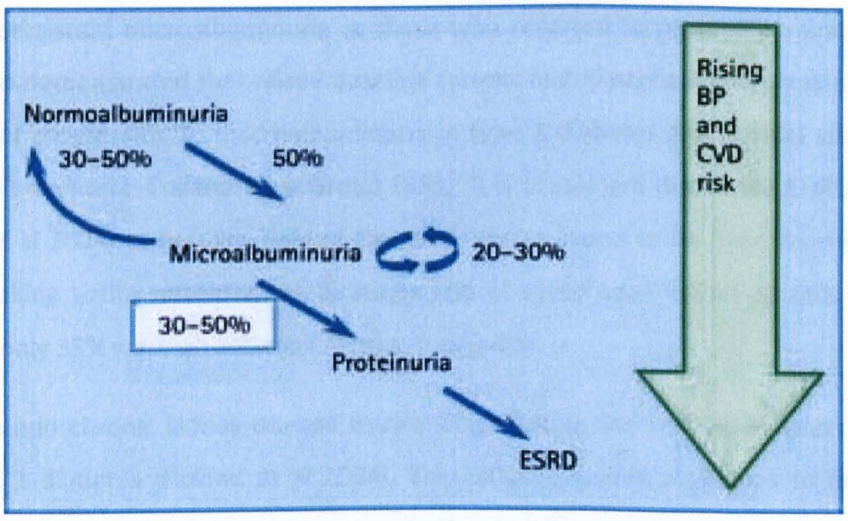



**Figure 2.3** Progression of albuminuria in patients with type 1 diabetes. Reproduced from Textbook of Diabetes (Holt et al 2010 (eds)) with permission from John Wiley and Sons Ltd, Chichester

The cumulative incidence of micro and macro albuminuria at 40 years duration of diabetes has been reported to be 25.4% and 9.4% respectively and there is some evidence of a decline in cohorts diagnosed more recently (Raile at al 2007). A study from Denmark demonstrated a

significant reduction in the cumulative incidence of diabetic nephropathy, defined as urinary albumin excretion greater than 300mg / 24 hours, according to period of diagnosis (Hovind at al 2003). At 20 years duration the cumulative incidence had significantly declined from 31.1% in the cohort diagnosed in 1965-69 compared to 12.5% in those diagnosed in 1979-84. This decline was related to significant improvements in glycaemic control and blood pressure accompanied by greater use of ACE inhibitors in the cohort diagnosed more recently. However data from Pittsburgh did not show any significant difference in cumulative incidence of overt nephropathy at 25 years duration (32%) although a significant decreasing trend in renal failure was evident (Pambianco at al 2006).

In a 7 year follow up study of 352 patients with type 1 diabetes and microalbuminuria the main factor related to progression to macroalbuminuria was $HbA_{1c}$ at baseline (Giorgino at al 2004). Although 46% of the cohort were hypertensive at baseline, there was no significant difference in baseline blood pressure in those who progressed to macroalbuminuria and those who reverted to normal albumin excretion. However at seven year follow up, systolic, but not diastolic, blood pressure was significantly higher in those who progressed to macroalbuminuria than those with persistent microalbuminuria or those who reverted to normoalbuminuria. A previous study has demonstrated that raised baseline systolic and diastolic blood pressure is a strong predictor of progression to macroalbuminuria in type 1 diabetes and normal albumin excretion (Microalbuminuria Collaborative Group 1999). It is of concern that in the EURODIAB study (Giorgino at al 2004) at baseline 46% of the cohort were found to be hypertensive but only 10% were taking antihypertensive medications and at seven year follow up 56% were hypertensive but only 35% were on antihypertensive mediation.

Microalbuminuria and chronic kidney disease usually occur within the first 20-25 years after diagnosis of type 1 diabetes (Hovind et al 2004). Thereafter prevalence appears to decline although this may be explained by premature deaths due to chronic kidney disease or cardiovascular disease. It has been suggested that in type 1 diabetes of long duration (greater than 50 years), abnormal albumin excretion is associated with have a 'benign' form of diabetic renal disease, evident by an absence of stage 5 chronic kidney disease (Gill et al 2009). However a study of 135 patients with longstanding type 1 diabetes (greater than 30 years duration) reported that microalbuminuria and proteinuria still predicted all cause mortality (Arun et al 2003).

More recently the relationship between ambulatory blood pressure and microalbuminuria in young people with type 1 diabetes (mean age 15years) has been investigated (Marcovecchio et al 2009). Baseline $HbA_{1c}$, ACR, 24 hour diastolic blood pressure and day time diastolic blood pressure were reported to be significantly related to progression to microalbuminuria. However there was no difference in nocturnal fall between those who progressed to microalbuminuria and those who did not. It has previously been suggested that reduced nocturnal dipping is a characteristic of early increase in albumin excretion in type 1 diabetes (Poulsen et al 1994).

The risk of developing diabetic nephropathy is reduced greatly by good blood glucose control. In the DCCT, for those with normal albumin excretion at entry to the study, there was a 39% relative risk reduction for the development of microalbuminuria and a 54% relative risk reduction for the development of macroalbuminuria in those randomised to intensive management compared to those in the conventional group (DCCT 1993). There was no threshold below which risk is reduced indicating that any reduction in $HbA_{1c}$ is beneficial. In addition 7-8 years following completion of the DCCT, when glycaemic control was undistinguishable between the groups, benefits persisted with 6.8% and 1.4% of those in the intensive group developing microalbuminuria and proteinuria respectively compared to 15.8% and 9.4% in the conventional group (EDIC 2003). This represents a 59% and 84% reduction in odds for microalbuminuria and proteinuria respectively. In addition significantly fewer of those in the original intensive group developed hypertension.

Two trials have investigated the preventative effect of the rennin angiotensin system inhibitors, lisinopril and candesartan (EUCLID Study Group 1997, Bilous et al 2009), in individuals with type 1 diabetes and normoalbuminuria. Both failed to demonstrate any effect on prevention of progression to microalbuminuria. However treatment with angiotensin converting enzyme (ACE) inhibitors have been shown to significantly reduce progression to macroalbuminuria and increase the chance of regression in normotensive adults with type 1 diabetes and microalbuminuria (ACE inhibitors in Diabetic Nephropathy Trialist Group 2001). This preventative effect is thought to be beyond that expected from a reduction in blood pressure alone. ACE inhibitors are now well established in the management of microalbuminuria in type 1 diabetes. Once renal disease occurs aggressive blood pressure

management has been associated with a regression and remission of albumin excretion (Hovind et al 2001).

Early detection and appropriate management of microalbuminuria is an essential element of diabetes care. Albumin creatinine ratio (ACR) is a simple screening tool to detect the earliest stage of renal damage. However in the 2009-2010 National Diabetes Audit, only 54.4% of people with type 1 diabetes had been screened (NHS information centre 2011). Microalbuminuria is asymptomatic and the relevance of screening, consequences of a positive diagnosis and benefits of treatment need to be carefully discussed with people with diabetes. Diagnosis cannot be made by a single raised ACR and delays due to practical problems associated with repeat samples need to be overcome locally to prevent a delay in treatment. In addition treatment with ACE inhibitors requires careful consideration and counselling in women of childbearing age because of the teratogenic effects. However this should not be a deterrent, as diabetic nephropathy, including persistent microalbuminuria, has been shown to be perhaps the most important marker of mortality risk in people with type 1 diabetes (Groop et al 2009, Orchard et al 2010).

Whilst in adults the use of ACE inhibitors and statins has become routine in the management of microalbuminuria, due to lack of evidence, this is not the case for adolescents and young people with type 1 diabetes. The Adolescent type 1 Diabetes cardio-renal Intervention Trial (AdDIT), a randomised, double blind, placebo controlled trial of ACE inhibitors and statins in high risk adolescent with type 1 diabetes, aims to assess the effect of these agents on albumin excretion, markers of CVD, retinopathy and quality of life (AdDIT 2009). Recruitment to the study began in 2009 and results are expected in 2013.

## 2.3 MACROVASCULAR COMPLICATIONS ASSOCIATED WITH TYPE 1 DIABETES

Compared to the general population people with type 1 and type 2 diabetes have a reduced life expectancy and much of this mortality is due to CVD particularly in those aged over 30 years (Laing et al 1999a, Laing et al 1999b, Skrivarhaug et al 2006, Soedamah-Muthu et al 2006a). A large study from the UK involving 7476 people with type 1 diabetes and 38,116 age and sex matched controls, all of whom were free from CVD at baseline, reported a greater risk of major CVD in those with diabetes compared to the control population (Soedamah-Muthu et

al 2006b). At follow up seven years later, in the years 1992-1999, overall hazard ratios of 3.6 and 7.7 for major CVD were found for men and women with type 1 diabetes respectively compared to those without diabetes. Increased hazard ratios were found for acute coronary events (3.0 and 7.6 in men and women with diabetes), coronary revascularization (5.0 in men and 16.8 in women) and stroke (3.7 in men, 4.8 in women). Sub group analysis revealed this increased risk was evident across all age bands (banded less than 35 years and then at 5 yearly intervals until 75 years) and was higher for women than for men. A previous study involving a similar population, the Diabetes UK cohort, included more than 23000 people with type 1 diabetes diagnosed before the age of 30 years (identified between 1972 and 1993) who were followed up for a mean of 17 years (until December 2000) (Laing at al 2003, Soedamah-Muthu et al 2006a). Ischaemic heart disease was responsible for 11% and 8% of deaths before the age of 40 years in women and men respectively and this increased to 40% and 47% after age 40 years. In addition, compared to the general population, mortality rates due to ischaemic heart disease for those with type 1 diabetes were higher in all age groups (20-70, 10 year age bands) particularly in women. Compared to a woman without type 1 diabetes, a woman with type 1 diabetes (aged 20-40 years) was reported to have a 40 times greater risk of dying from ischaemic heart disease. Both of these studies involved cohorts of individuals diagnosed before the age of 30 years and results therefore cannot be generalized to those diagnosed after that age. However a recent study from Finland compared the risk of death from CVD in 173 people with type 1 diabetes, 834 with type 2 diabetes and 1294 people with no diabetes (Juutilainen et al 2008). Those with diabetes were all diagnosed after the age of 30 years, all participants were aged 45-64 at the beginning of the study (recruited 1982- 1984) and all were free from CVD. At 18 year follow up, CVD mortality rates per 1000 patient years were 23.1 in type 1 diabetes, 35.3 in type 2 diabetes and 4.6 in those with no diabetes. In the past, although the increased incidence of CVD in type 1 diabetes has been acknowledged, there has been a tendency to focus on the prevention of microvascular disease, especially in young people. This study highlights the similar impact of type 1 and type 2 diabetes on cardiovascular outcome and the need for global risk factor reduction in both. Furthermore the Nurses' Health Study, a longitudinal study of over 116 000 women aged 30-55 years in 1976 and followed up until 2002, reported that the risk of stroke was fourfold higher in women with type 1 diabetes and twofold higher in women with type 2 diabetes compared to women without diabetes (Janghorbani et al 2007).

Several studies have demonstrated a relationship between CVD and glycaemic control. One recent observational study of over 7000 people with type 1 diabetes (followed from 2002 to 2007) receiving routine diabetes care demonstrated a progressively increasing risk for coronary heart disease and CVD with higher $HbA_{1c}$ and this was independent of traditional risk factors (blood pressure, lipid profile, BMI, smoking) (Eeg- Olofsson et al 2010). An $HbA_{1c}$ of 7.9% or less at baseline was associated with significant risk reductions of 41% for fatal/ non fatal coronary heart disease and 37% for CVD compared with a baseline $HbA_{1c}$ of 8% or over. In addition the Wisconsin Epidemiologic Study of Retinopathy has consistently reported an association between glycaemic control and CVD with recent data suggesting a relative risk of 1.20 per 1% $HbA_{1c}$ for cardiovascular mortality (Shanker et al 2007). However a recent study from the Pittsburg group suggests that glycaemic control more strongly predicts death from coronary artery disease rather than morbidity. Traditional risk factors such as diastolic blood pressure, lipid profile, renal function and a lower insulin dose were shown to be predictors of non fatal events (Conway et al 2009).

It may be that the relationship between glycaemic control and CVD is more pronounced in type 1 than type 2 diabetes. One study reported a greater hazard ratio per percentage change of $HbA_{1c}$ in type 1 diabetes (n=173) than in type 2 diabetes (n=834) over an 18 years follow up period. An increment of 1 % increased CVD mortality by 52.5% in type 1 diabetes compared to 7.5% in type 2 diabetes (Juutilainen et al 2008). As the risks of CVD did not differ according to type of diabetes non glycaemic risk factors may have a significant role in the risk of CVD in type 2 diabetes.

At completion of the DCCT in 1993, there was no significant difference in macro vascular events between the intensive and conventionally treated groups. This was not surprising considering the groups as a whole were relatively young at entry to the study. In addition event rate was low during the study which was not powered to detect cardiovascular events. However, when all major cardiovascular and peripheral vascular events were combined, there was a 41% risk reduction in those randomised to the intensive group. Conversely the observational follow up EDIC study did reveal some unforeseen findings (DCCT/EDIC 2005). During a mean follow up of 17 years, when glycaemic control was similar in both groups, there was a statistically significant reduction in cardiovascular events in those who were originally

randomized to the intensive treatment group. There were 46 cardiovascular events (defined as nonfatal or subclinical myocardial infarction or stroke, death due to CVD, angina, clinically significant obstruction on coronary angiography, the need for revascularization with angioplasty or coronary artery bypass) occurring in 31 people who were originally randomised to the intensive treatment group compared to 98 events in 52 people originally in the conventional treatment group. This represented a 42% reduction in the risk of any cardiovascular event (p=0.02) and a 57% reduction in the risk of nonfatal myocardial infarction, stroke or death from CVD (p=0.02) and these differences remained significant after adjusting for microalbuminuria or albuminuria. Every 10% reduction in $HbA_{1c}$, for example a reduction from 8.0% to 7.2%, was associated with a 20% reduction in the risk of a cardiovascular event. In addition carotid intima-media thickness, a well established index of atherosclerosis, was assessed in a subset of the EDIC study. Compared to a control population there was no significant difference in intima-media thickness at 1 year. However by 6 years, progression was greater in those with diabetes than the controls (DCCT/EDIC 2003). Also the mean progression of intima-media thickness was significantly less in the group originally randomised to the intensive group than those in the conventional group. Longer follow up of this group will reveal if this finding influences long term cardiovascular clinical outcomes. Other more predictable factors shown to influence intimal thickening were increased age, baseline systolic blood pressure, lipid profile and smoking status.

These findings provided further evidence in support of "metabolic memory" (see section 2.6.1) which was suggested in the EDIC studies assessing microvascular complications. However the study does have some limitations. The number of macrovascular events was relatively low during the study period although this may have been expected given that the mean age of the group was only 45 years. In addition some of the cardiovascular events such as revascularization are subject to the clinicians judgment and therefore at risk of bias. However these results serve to remind all health care professionals of the importance of striving for good glycaemic control as early as possible in the disease process.

Not all studies have suggested an association between glycaemic control and CVD. Two cohort studies, the Pittsburg Epidemiology of Diabetes Complications study and the EURODIAB study (Orchard et al 2003, Soedamah-Muthu et al 2004) failed to show a significant association. In

addition a smaller study from Australia involving 147 people with type 1 diabetes, followed up for 14 years, reported that baseline high density lipoprotein (HDL), serum creatinine, low density lipoprotein(LDL) and systolic blood pressure were significant predictors of coronary artery disease but glycaemic control was not (Weis et al 2001). Several studies have reported a significant association between CVD and traditional risk factors such as dyslipidaemia, renal function, blood pressure, physical activity and smoking in type 1 diabetes (Orchard et al 2003, Conway et al 2009, Bishop et al 2009, Grauslunda et al 2010). In addition insulin resistance and the metabolic syndrome have been implicated in the development of CVD in type 1 diabetes (Orchard et al 2003, Thorn et al 2009,)

Discrepant findings from epidemiological studies in relation to the association between glycaemic control and CVD may be in some way explained by differences in the study populations, particularly the presence of renal disease which is strongly associated with cardiovascular morbidity and mortality. However data from the DCCT/EDIC study do suggest that a period of good glycaemic control, in the first few years following diagnosis, has a lasting effect on cardiovascular morbidity even after adjustment for albuminuria. That combined with the effect of good control on micro vascular complications makes improvements in glycaemic control worth striving for in people with type 1 diabetes.

CVD remains a significant cause of morbidity and mortality in type 1 diabetes. Findings from the Pittsburg Epidemiology of Diabetes study suggest that whilst the incidence of some complications associated with type 1 diabetes for example renal failure and neuropathy are declining at 30 years duration, the incidence of coronary artery disease remains unchanged (Pambianco et al 2006).

## 2.4 TYPE 1 DIABETES AND MORTALITY

Several studies have shown that people with type 1 diabetes are at greater risk of death at a younger age than would be expected in the general population (Laing et al 1999a,Laing et al 1999b, Asao et al 2003, Skrivarhaug et al 2006, Secrest et al 2010a). The EURODIAB group investigated early mortality in a large cohort of young people (28,887) from 13 European countries diagnosed with type 1 diabetes (1989 – 2005) before the age of 15 years (mean duration of type 1 diabetes 7.6 years). Overall the standardised mortality ratio (SMR) was 2.0, varying from 0.0 (Iceland) - 4.7 (Bulgaria) between countries (Patterson et al 2007). Almost half

(47%) of the reported mortality was either directly due to diabetes (35%) or it was considered that diabetes may have been a contributory factor (12%). Of the deaths thought to be directly related to diabetes DKA was considered a causative factor in 57% and hypoglycaemia in 11%. Consistency in reporting of cause of death within countries can be problematic. Quality and completeness of data cannot be assured, however the authors report that the number of deaths reported, which were considered unrelated to diabetes, corresponds with that which would have been expected from national mortality rates which goes some way to validating the data. Of interest is the variability of the SMR across European countries with the lowest reported rate in Iceland (0.0) and the highest in Eastern Bulgaria (4.7) this variability could not be explained by prevalence of diabetes or national prosperity. Worryingly in this study SMR in the UK was reported to be the second highest at 4.2. A rate of 3.7 in the UK has been reported previously (Soedama-Muthu et al 2006a).

A large study from the UK compared all cause mortality over a seven year period (1992-1999), in a large cohort (7713 subjects) of people with long standing type 1 diabetes (mean duration 15 years) with an age and sex matched population without diabetes (38,518 people from the General Practice Research Database) (Soedamah et al 2006a). Annual mortality rates were 8.0 per 1000 person years in those with type 1 diabetes compared to 2.4 per 1000 person years in those without diabetes (hazard ratio 3.7) and a significantly increased mortality rate was evident in type 1 diabetes across all age bands. The predominant cause of death in those with type 1 diabetes was CVD with the risk being greater in women than in men. Subgroup analysis revealed that younger women (age at baseline less than 35 years) were at the greatest risk with an almost twelve fold increase in overall mortality compared to the control population. Similar outcomes for females with type 1 diabetes have been reported in a cohort from the USA (Secrest et al 2010a).

Several studies have investigated mortality trends in type 1 diabetes over a 20 -30 year period. A large study (17 306 subjects) in 2011 from Finland, a country with an efficient health care system and one of the highest rates of type 1 diabetes in the world, investigated 20 year mortality in type 1 diabetes according to age of diagnosis (0-14 years and 15-30 years) (Harjutsalo et al 2011). The authors report SMR's of 3.6 and 2.8 in the early onset and late onset group respectively. Further analysis revealed that at 20 years duration, in the early onset group, mortality ratios reduced significantly from 3.5 in those diagnosed between 1970-1974

to 1.9 in those diagnosed between 1985-1989, indicating an improvement in outcome for those who had been diagnosed more recently. This may have been expected due to improvements in knowledge, health care delivery and pharmacological interventions with the passage of time. However surprisingly, in the late onset group, mortality ratios at 20 years duration of diabetes increased significantly from 1.4 in those diagnosed in 1970-74 to 2.9 in those diagnosed from 1985-89. Mortality due to chronic complications did not change according to the period of diagnosis however mortality due to acute complications of diabetes increased significantly with poorer outcomes in those diagnosed more recently. There was also an increase in alcohol related deaths, at 20 years duration, in those diagnosed between 1985-1989. This increase in alcohol related deaths is also reflected in the background population. However the relationship between alcohol and acute complications of diabetes, particularly hypoglycaemia, is well recognised and this may have contributed to the increase in deaths due to acute complications of diabetes found in the late onset group. The authors also suggest the recession of the 1980's which resulted in disparities in care and cuts in preventative healthcare may have adversely affected the late onset group who in Finland are mostly managed in primary care.

Furthermore a study from the USA also reports improvements in 30 year mortality according to time period of diagnosis with those who have been diagnosed the most recently having more favourable outcomes (Secrest et al 2010a). This study included 1057 people with type 1 diabetes diagnosed before the age of 18 years; the group was divided into 3 cohorts according to year of diagnosis (1965-69, 1970-74, 1975-79). Overall mortality at 30 years was seven times higher than would have been expected in the general population. However, as reported in the Finnish study (Harjutsal et al 2011), mortality rates decreased in a stepwise manner by diabetes diagnosis cohort with a significant decrease in SMR in the cohort diagnosed in 1965-69 compared to the 1975-79 cohort (9.3 v 5.6). Individuals who were diagnosed before the age of 10 years (pre pubertal) had significantly lower mortality rates, both overall and at 30 years duration, than those who were diagnosed age 10-14 (peri pubertal) and those diagnosed after puberty (over 14 years of age).

All of the studies discussed above are consistent in reporting an excess in SMR in women with type 1 diabetes compared to men with type 1 diabetes such that the sex difference in mortality observed in the non diabetic population is eliminated (Patterson et al 2007,

Harjutsalo et al 2011, Soedamah-Muthu et al 2006a). One study reported the overall 30 year SMR for women to be nearly three times higher than for men with type 1 diabetes (13.2 v 5.5) (Secrest et al 2010a). In addition an older study from the UK reported an increase in the relative risk of death for females with type 1 diabetes than males in all age groups with a peak of 5.7 in females aged 20-29 years (Laing et al 1999b).

Not all studies have shown an improvement in mortality in type 1 diabetes over time. A study from Norway compared mortality in a cohort diagnosed between 1978-82 with a cohort diagnosed earlier (1973-77) and did not show any difference in cumulative survival (Skrivarhaug et al 2006). Both groups were followed up until the end of 2002. Similar finding are reported from Sweden (Waernbaun et al 2006). A further study compared mortality associated with type 1 diabetes in Japan and Finland and reported SMR's of 12.9 and v 3.7 respectively. However in Japan a dramatic improvement was noted when the mortality of those diagnosed between 1965-69 was compared with those diagnosed between 1975-79 (15.7 v 6.9) whereas in Finland there was no change (Asao et al 2003). The authors suggest that these findings are due to the differences in the prevalence of type 1 diabetes and health care systems in the two countries.

Recent studies have suggested that this surplus mortality may be confined only to those with renal disease. The Finnish Diabetic Nephropathy study, a large study of adults with longstanding type 1 diabetes (4201 subjects, studied between 1997-2006), reported that at seven year follow up excess mortality was related to renal status (Groop et al 2009). The presence of microalbuminuria, macroalbuminuria and end stage renal failure was associated with 2.8, 9.2 and 18.3 times higher SMR's respectively. However individuals with normoalbuminuria, independent of duration of diabetes, showed no excess in mortality compared to the general population. More recently the Pittsburgh Epidemiology of Diabetes Complications Study confirmed these findings in a 20 year follow up study of adults with longstanding type 1 diabetes (mean duration 19 years at baseline) , reporting SMR's of 6.4, 12.5 and 29.8 in microalbuminuria, overt nephropathy and end stage renal failure respectively (Orchard et al 2010). Both of these studies have demonstrated an independent graded association between the presence and severity of renal disease and mortality in type 1 diabetes. In addition both report no excess mortality in those with normal renal function. The studies do however have limitations. Both involved individuals with longstanding diabetes

which may reflect outdated diabetes management strategies and may not be generalisable to those with recently diagnosed type 1 diabetes. Nevertheless these studies will serve as valuable comparisons for future studies involving patients exposed to more current management regimens.

A recent study from the USA suggests that in the first 10 years after diagnosis acute complications are the major cause of death in people with type 1 diabetes; between 10 – 20 years duration deaths are evenly attributed to acute complications, CVD, renal or infectious causes; and after 20 years duration chronic complications account for 70% of all deaths, with CVD being the leading cause of death (Secrest et al 2010b). Again in this study there was no difference in mortality ratios for non-diabetes related deaths compared to the general population.

Mortality, especially from acute complications of type 1 diabetes, has been reported to be associated with psychosocial and socioeconomic risk factors. A case controlled study from the UK, involving patients from the Diabetes UK cohort, reported that living alone, past drug abuse and previous psychiatric referral were all significant risk factors for death from acute events but not from chronic complications of diabetes (Laing et al 2005). However not all of the acute events were diabetes related. Of the 51 deaths due to acute events, 24 (47%) were diabetes related and the rest were due to accidents or suicide/possible suicide. In addition this study only included deaths in individuals before the age of 40 years.

Mortality data reported in the recent literature is encouraging indicating that mortality associated with type 1 diabetes has declined over the last few decades. Although the majority of studies involved patients diagnosed with type 1 diabetes before the benefits of good glycaemic control were fully appreciated it is likely that this improvement is due to a combination of factors including better diabetes management, more structured organisation of care, and improvements in the detection and management of CVD .

However there is no room for complacency as mortality is still about 5-6 times higher than the general population (Harjutsal et al 2011, Secrest et al 2010a) and there is still much preventative work to be done. In addition, cause of death is often difficult to assess in diabetes as in some cases data from the death certificate may not include diabetes as a primary cause of death depending on the initial presentation and this can influence mortality data. Screening

and early identification of those at risk, followed by aggressive risk factor intervention will hopefully improve outcomes further in the future.

## 2.5 LONG TERM SURVIVORS OF TYPE 1 DIABETES

The incidence and severity of diabetes complications varies considerably. Some individuals with a long duration of diabetes are relatively free from complications whilst others of a lesser duration are more severely affected. In the UK people with type 1 diabetes of 50 and 60 years duration are awarded the Nabarro and Lawrence medals respectively. A similar system exists in the USA with the Joslin medal being awarded according to duration of type 1 diabetes. Groups of such individuals have been studied on several occasions to identify the characteristics of long term survivors and factors that may be linked to protection from serious complications. One recent cross sectional study from the USA, involving 351 Joslin 50 year medallists, reported that after a mean duration of 56 years of type 1 diabetes, 57% of the cohort had evidence of retinopathy, 13% nephropathy, 60.5% neuropathy and 48.5% CVD (Sun et al 2011). Despite evidence linking glycaemic control to complications, this study did not report a significant relationship between current $HbA_{1c}$ (mean $HbA_{1c}$ 7.3±1.0) and any complication. This observation has also been reported elsewhere (Keenan et al 2007). There are nonetheless problems in interpreting the significance of a single measure of $HbA_{1c}$. To overcome this Sun et al (2011) assessed current and longitudinal glycaemic control (over the previous 15 years) in a sub group of 73 patients (20.1%) of their cohort. They found that current $HbA_{1c}$ correlated highly with longitudinal $HbA_{1c}$ and that there was no significant relationship between longitudinal $HbA_{1c}$ and complications. Furthermore there was no correlation between either systolic or diastolic blood pressure and microvascular complications. Both systolic and diastolic blood pressure are associated with a greater risk of vascular complications. However complications were associated with significantly higher levels of inflammatory markers and higher levels of C-reactive protein were detected in those with CVD.

The UK Golden Years Study described the characteristics of 400 individuals with type 1 diabetes of greater than 50 years duration (Bain et al 2003). Physical and biochemical features of these survivors included a mean normal BMI (25.0 ± 3.7 kgm2), a mean low daily insulin dose (0.52 units / kg) and mean elevated HDL cholesterol (1.84 mmol/l). In addition parental longevity

was a key feature and this has been reported since in a study of 326 people with type 1 diabetes of greater than 50 years duration in the USA (Keenan et al 2007). Both studies report remarkably similar findings with both parents, who would have been born around the turn of the century when life expectancy was about 46 years, living beyond 70 years of age. Both studies also report the protective effects of HDL cholesterol. The UK cohort (Bain et al 2003) had a high mean HDL cholesterol (1.84±0.57 mmol/l) as a group and subgroup analysis found a tendency to a higher HDL in the USA patients without complications (1.85±0.8 v 1.67 ± 0.65 mmol/l , p = 0.06) (Keenan et al 2007). Finally Keenan et al also report that current regular physical activity was associated with a reduced risk of complications and a higher insulin dose (units / kg) was associated with an increase in risk.

Interestingly the studies above report a prevalence of retinopathy of 43-57%. This is in contrast to the previous literature suggesting that over 90% of people with type 1 diabetes will eventually develop retinopathy (Klein et al 1984). There is however a wide range in the reported prevalence of nephropathy 6.7% (Keenan et al 2007), 13% (Sun et al 2011) and 37% (Bain et al 2003) in long term survivors and this may reflect different methods of data collection. The study that reported the lowest prevalence of nephropathy (Keenan et al 2007) used self reported data whereas objective measures of albumin excretion were used in the other studies.

Long term survivors of type 1 diabetes are an interesting group to study. Most will have been diagnosed before the days of structured diabetes care. Intensive intervention and education within the first 30 years duration of diabetes would have been very rare. Only the Golden Years study documented the current insulin regimen. At the time of assessment only 17% were on an intensive insulin regimen (three or more insulin injections per day) and 10% were using a once daily insulin regimen (Bain et al 2003). In addition only 56% of the cohort reported regular contact with diabetes services and over one third reported only intermittent contact (gaps in attendance greater than 5 years). Furthermore 64% of the group were current or ex smokers. Nevertheless the majority survived without major complications therefore other factors such as genetics may be implicated and parental longevity could support this.

## 2.6 THE DIABETES CONTROL AND COMPLICATIONS TRIAL AND OBSERVATIONAL FOLLOW-UP STUDY

The Diabetes Control and Complications Trial (DCCT) was a landmark study which has influenced the management of type 1 diabetes since its publication in 1993 (DCCT 1993). This was a prospective, multicentre, randomised controlled clinical study, involving 1441 people with type 1 diabetes (aged 13-39 years). Recruitment was from 1983-1989, at which time all were free from major diabetic complications. Of the whole group 726 had no retinopathy (primary prevention group) and 715 had mild retinopathy (secondary prevention group). The aim of the study was to determine if intensive insulin treatment, with the goal of maintaining blood glucose levels close to the normal range, could prevent or delay the onset or progression of complications. Participants were randomised to receive either intensive insulin treatment, involving CSII or multiple daily injections (three or more injections per day) or conventional treatment with one or two insulin injections per day. Those randomised to intensive treatment were asked to monitor capillary blood glucose 3-4 times daily and alter insulin dose according to the results also taking into account carbohydrate intake and anticipated activity. In addition this group were reviewed in clinic on a monthly basis with frequent telephone contact in between clinic visits to advise on changes to treatment. The group randomised to conventional insulin treatment were asked to monitor capillary blood glucose or urine glucose on a daily basis and were reviewed in clinic every three months. Glycaemic control improved within the first 6 months in the intensive group and this improvement was maintained over the study period (mean of 6.5 years). After baseline there was a statistically significant difference in $HbA_{1c}$ between the intensive and conventional groups and this was maintained thorough the study period (7.4% versus 9.1% at the end of the study). At the end of the study in the primary prevention group, intensive insulin treatment reduced the risk for the development of retinopathy by 75% compared to conventional treatment and in the secondary prevention group intensive treatment slowed the progression of retinopathy by 54% and reduced the development of proliferative retinopathy or severe non proliferative retinopathy by 47%. In addition intensive treatment reduced the occurrence of clinically significant renal damage (urinary albumin excretion ≥ 300 mg / 24 hours) by 54% and clinical neuropathy by 60%. When all major cardiovascular and peripheral vascular events were combined there was a non significant risk reduction (p=0.06).

Achievement of tight glycaemic targets is not without risk. In the DCCT episodes of severe hypoglycaemia were 2-3 times more common in the intensive group than the conventional group. In addition, as may have been expected, weight gain was significantly greater in those randomised to the intensive treatment group and despite a reduction in risk this may not be acceptable to some individuals in routine clinical care. Participants in the DCCT were relatively young therefore It may not be surprising that there was no significant affect on macrovascular events.

The DCCT provided evidence that improvements in glycaemic control are associated with prevention and severity of progression of micro vascular complications in type 1 diabetes and indicated glycaemic control targets. However achievement of such targets can be difficult in routine diabetes care. The DCCT was resource intensive and impractical for most healthcare economies, particularly in current times of financial austerity. However this landmark study has served as an impetus to all involved in the care of people with type 1 diabetes to strive to achieve optimal diabetes control whilst minimising the risk of hypoglycaemia. For many people with type 1 diabetes this is a difficult balance to accomplish. Many people with type 1 diabetes are fearful of hypoglycaemia, particularly during the night or in public places, and choose to run blood glucose at a higher level to avoid this. In addition health care professionals are also wary of hypoglycaemia, especially considering its implications in 'dead in bed' syndrome and driving and employment issues (Tanenberg et al 2010). This may lead to acceptance of suboptimal control and exposure to an increased risk of complications. Achieving optimal glycaemic control for individual patients is a skilful process involving the application of skills and knowledge to practice and most importantly working collaboratively with people with diabetes to develop working relationships and gain trust. This requires protected time particularly in the first months after diagnosis. However, this may be a worthwhile investment as a few studies have suggested that $HbA_{1c}$ within the first 6-12 months of starting insulin is predictive of future glycaemic control. Thereafter, individual $HbA_{1c}$ remains stable over time, a so called 'tracking' or 'streaming' effect (Jorde and Sundsfjord 2000, Edge et al 2010).

The DCCT highlighted the importance of support and frequent contact with health care professionals in maintaining glycaemic control. Improvements in communication systems for example email conversations and text messaging may make this easier for some groups of people with diabetes. In the UK it is mainly diabetes specialist nurses who provide this ongoing

support. In the years following the DCCT there was a steady rise in the number of diabetes specialist nurses. However more recently, in a financially challenged health service, there are now frequent reports of specialist nurse posts not being replaced which may impact on diabetes care in the future.

### 2.6.1 Epidemiology of diabetes interventions and complications study - 'metabolic memory'

On completion of the DCCT in 1993, the care of all participants was transferred back to their own physicians and intensive insulin treatment was offered to those previously randomised to the conventional group. Of the original cohort 96% agreed to be followed up in a prospective longitudinal observational study, the Epidemiology of Diabetes Interventions and Complications study (EDIC). At 4 years post DCCT the difference in $HbA_{1c}$ had reduced to 0.3% (7.9 versus 8.2%), in the intensive versus conventional group and by 5 years there was no significant difference in mean $HbA_{1c}$ (8.1 versus 8.2%) (DCCT/EDIC 2002) and glycaemic control remained similar in both groups 10 years after completion of the DCCT (7.9% versus 7.8%) (DCCT/EDIC 2005). However the benefits of a period of intensive diabetes management and hence good glycaemic control were maintained. Four years following completion of the DCCT frequencies of progression of retinopathy, microalbuminuria and albuminuria were significantly lower in the group who were originally randomised to intensive management compared to the conventional group (DCCT 2000). However, in terms of retinopathy, by 10 years the differences between the 2 groups, although still present, appeared to be declining (DCCT 2008). Furthermore eight years after completion of the DCCT, prior intensive therapy reduced the signs and symptoms of neuropathy, as assessed by the Michigan Neuropathy Screening Instrument (43% versus 51% in the routine group) (Martin et al 2006). This beneficial effect of a 6.5 years period of intensive therapy on the micro vascular complications associated with type 1 diabetes has been termed 'metabolic memory'. There are several possible explanations for this effect. One such theory is that as chronic complications are related to chronic rather than acute hyperglycaemia and develop over the course of some years it takes time for improvements in glycaemic control to counteract the effects of previous prolonged hyperglycaemia. There may be some support for this from the DCCT where glycaemic control between the 2 groups was significantly different by 6 months following randomisation. However a difference in the cumulative incidence of micro vascular disease was not evident for a further 3-4 years (DCCT 2002).

The important clinical message is that glycaemic control in the early stages of the condition is important as it affects long term outcome and any improvement in $HbA_{1c}$ is beneficial even if ideal targets are not reached.

## 2.7 SUMMARY

Type 1 diabetes is associated with considerable morbidity and mortality from both micro vascular and macro vascular complications. Although longitudinal studies indicate that morbidity and mortality outcomes are improving, excess mortality, compared with the background population, remains evident. Most of this morbidity and mortality, as reported in the 1970's, is still due to renal and CVD. The chronic complications of type 1 diabetes can have detrimental effects not only on physical wellbeing but also on psychological well being and quality of life. The effects can be are far reaching and include ability to work which may have financial implications effecting not only the individual with diabetes but also their families.

The past few decades have seen several important developments in diabetes care including structured diabetes management, specialist centres and screening programmes for microvascular complications. However uptake of such programmes remains suboptimal and this may be due to fear or poor awareness of the complications associated with diabetes. Also clinical trials have recognised the effectiveness of, for example, ACE inhibitors in delaying the progression of microalbuminuria. Treatment with such agents is now an established part of diabetes care.

It is clear from the DCCT and EDIC studies that a major risk factor in the development of micro vascular complications is poor glycaemic control and that this is also associated with poor macro vascular outcomes. However the EDIC study also demonstrates that the goal of long term near normal glycaemic control is elusive to most people with type 1 diabetes, even those who have been involved in an intensive education programme and had prolonged support from health care professionals. Once intensive support is withdrawn, glycaemic control begins to deteriorate thus showing that intensive insulin management in itself does not maintain improvements in glycaemic control. Conversely 2 years following completion of the DCCT, 75% of those originally randomized to the conventional group were receiving intensive insulin treatment and by 5 years $HbA_{1c}$ had improved compared to exit from the DCCT (8.2% versus 9.1%). This demonstrates that intensive insulin treatment even without intensive education and support can improve glycaemic control in some people. This must of course be viewed in

the context of heath care professionals being more focused on glycaemic control following publication of the DCCT. However it is apparent that to improve and maintain glycaemic control intensive insulin treatment needs to be accompanied by education and ongoing support which is often difficult to attain in routine diabetes care. Motivation on the part of the person with diabetes is also essential. Motivation is often at its best following initial diagnosis when education and support are greatest. It may be that this is the time to strive for good control, particularly as recent reports have indicated that $HbA_{1c}$ in the early years following diagnosis (6 – 24 months) may predict long term control (Edge et al 2010, Chemtob et al 2011). Furthermore the DCCT highlighted that any improvement in control is beneficial even if targets are not reached and this can be utilized to motivate those with very poor control to reach stepwise realistic goals. However evidence gained from intervention studies needs to be put into practice and this requires a knowledgeable multidisciplinary diabetes team who are highly skilled to work in partnership with people with type 1 diabetes.

The majority of the epidemiological data relating to morbidity and mortality in type 1 diabetes highlights the importance of global risk factor reduction to improve outcomes. As the DCCT was designed to assess the effects of intensive insulin treatment on the complications of diabetes other risk factors such as blood pressure and lipid profile were not properly assessed. The benefits of global risk factor reduction in type 2 diabetes have been demonstrated in the Steno-2 diabetes study (Gaede et al 2003) and it is reasonable to believe that such benefits can also be achieved in type 1 diabetes. The next chapter will focus on risk factor reduction in type 1 diabetes.

## 2.8 REFERENCES


Abbott CA, Malik RA, Van Ross ERE, Kulkarni J, Boulton AJM. Prevalence and characteristics of painful diabetic neuropathy in a large community-based diabetic population in the U.K. Diabetes Care 2011; 34: 2220–2224

ACE Inhibitors in Diabetic Nephropathy Trialist Group. Should all patients with type 1 diabetes mellitus and microalbuminuria receive angiotensin-converting enzyme inhibitors?: A meta-analysis of individual patient data. Annals of Internal Medicine 2001;134:370-379

Adolescent type 1 Diabetes cardio-renal Intervention Trial Research Group. Adolescent type 1 Diabetes cardio-renal Intervention Trial (AdDIT). BioMed Central Pediatrics 2009, 9:79-99

Albers JW, Herman WH, Pop-Busui R, Feldman EL, Martin CL, Cleary PA. Effect of prior intensive insulin treatment during the diabetes control and complications trial (DCCT) on peripheral neuropathy in type 1 diabetes during the Epidemiology of Diabetes Interventions and Complications (EDIC) study. Diabetes Care 2010; 33: 1090–1096

Arun CS, Stoddart J, Mackin P, Macleod JM, New JP, Marshall SM. Significance of microalbuminuria in long-duration type 1 diabetes. Diabetes Care 2003; 26:2144–2149

Asao K, Sarti C, Forsen T, Hyttinen V, Nishimura R, Matsushima M, Reunanen A et al. Long-term mortality in nationwide cohorts of childhood-onset type 1 diabetes in Japan and Finland. Diabetes Care 2003; 26:2037–2042

Bain SC, Gill GV, Dyer PH, Jones AF, Murphy M, Jones KE, Smyth C, Barnett AH. Characteristics of Type 1 diabetes of over 50 years duration (the Golden Years Cohort). Diabetic Medicine 2003; 20: 808-811

Benbow S, Wallymahmed ME, MacFarlane I. Diabetic peripheral neuropathy and quality of life. Quarterly Journal of Medicine 1998; 733-737

Bilous R, Chaturvedi N, Sjølie AK, Fuller J, Klein R, Orchard T, et al. Effect of candesartan on microalbuminuria and albumin excretion rate in diabetes: Three randomized trials. Annals of Internal Medicine 2009;151:11-20

Bishop FK, Maahs DM, Snell-Bergeon JK, Ogden LG, Kinney GL, Rewers M. Lifestyle risk factors for atherosclerosis in adults with type 1 diabetes. Diabetes and Vascular Disease Research 2009; 6: 269-275

Boulton AJM, Gries FA, Jervell JA: Guidelines for the diagnosis and outpatient management diabetic peripheral neuropathy. Diabetic Medicine 1998; 15:508 –514

Boulton JM, Malik RA, Arezzo JC, Sosenko JM. Diabetic Somatic Neuropathies. Diabetes Care 2004; 27: 1458-1486

Boulton AJM, Vinik AI, Arezzo JC, Bril V, Feldman EL, Freeman R, et al. Diabetic Neuropathies: A Statement by the American Diabetes Association. Diabetes Care 2005a; 28: 956-962

Boulton AJM, Vileikyte L, Ragnarson-Tennvall G, Apelqvist J. The global burden of diabetic foot disease. Lancet 2005b; 366: 1719–1724

Chaturvedi N, Sjolie AK, Stephenson JM, Abrahamian H, Keipes M, Castellarin A, et al. Effect of lisinopril on progression of retinopathy in normotensive people with type 1 diabetes. Lancet 1998; 351: 28-31

Chaturvedi N, Bandinelli S, Mangili R, Penno G, Rottiers RE, Fuller JH. Microalbuminuria in type 1 diabetes: Rates, risk factors and glycemic threshold. Kidney International, 2001; 60: 219–227

Chaturvedi N, Porta M, Klein R, Orchard T, Fuller J, Parving HH. Eff ect of candesartan on prevention (DIRECT-Prevent 1) and progression (DIRECT-Protect 1) of retinopathy in type 1 diabetes: randomised, placebo-controlled trials. Lancet 2008; 372: 1394–1402

Chemtob CM, Hochhauser CJ, Shemesh E, Schmeidler J, Rapaport R. Does poor early metabolic control predict subsequent poor control in young children with Type 1 diabetes: An exploratory study. Journal of Diabetes 2011; 3: 153–157

Cobas RA, Santos B, da Silva PCB, Neves R, Gomes MB. Progression to microalbuminuria in patients with type 1 diabetes: a seven-year prospective study. Diabetology & Metabolic Syndrome 2011, 3:21-37

Conway B, Costacou T, Orchard T. Is glycaemia or insulin dose the stronger risk factor for coronary artery disease in type 1 diabetes? Diabetes & Vascular Disease Research 2009; 6: 223– 230

Daousi C, MacFarlane IA, Woodward A, Nurmikko TJ, Bundred PE, Benbow SJ. Chronic painful peripheral neuropathy in an urban community: a controlled comparison of people with and without diabetes. Diabetic Medicine 2004; 21: 976–982

Daousi C, Benbow SJ, Woodward A, MacFarlane IA. The natural history of chronic painful peripheral neuropathy in a community diabetes population. Diabetic Medicine 2006; 23: 1021–1024

de Boer IH, Rue TC, Cleary PA, Lachin JM, Molitch ME, Steffes MW, et al. Long-term renal outcomes of patients with type 1 diabetes mellitus and microalbuminuria: An analysis of the diabetes control and complications trial/epidemiology of diabetes interventions and complications cohort. Archive Internal Medicine 2011; 171:412-420

Deckert T, Poulson JE, Larsen M. Prognosis of diabetics with diabetes onset before the age of thirtyone. Diabetologia 1978; 14: 363-370

Department of Health. National Service Framework for Diabetes: Standards. London; 2010

Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. The New England Journal of Medicine 1993; 329: 977-986

Diabetes Control and Complications Trial Research Group. The effect of intensive diabetes therapy on the development and progression of neuropathy. Annals of Internal Medicine 1995a; 122: 561-568

Diabetes Control And Complications (DCCT) Research Group. Effect of intensive therapy on the development and progression of diabetic nephropathy in the Diabetes Control and Complications Trial. Kidney International 1995b; 47: 1703-1720

Diabetes Control and Complications Trial/ Epidemiology of Diabetes Interventions and Complications Research Group. Retinopathy and nephropathy in patients with type 1 diabetes four years after a trial of intensive therapy. New England Journal of Medicine 2000; 342:381-389

Diabetes Control and Complications Trial/ Epidemiology of Diabetes Interventions and Complications Research Group. Effect of intensive therapy on the microvascular complications of type 1 diabetes mellitus. Journal of American Medical Association 2002; 287:2563-2569

Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Research Group. Intensive diabetes therapy and carotid intima–media thickness in type 1 diabetes mellitus. New England Journal Medicine 2003; 348: 2294-303

Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Study Research Group. Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. New England Journal of Medicine 2005; 353: 2643-2653

Diabetes Control and Complications Trial/ Epidemiology of Diabetes Interventions and Complications Research Group. Prolonged effect of intensive therapy on the risk of retinopathy complications in patients with type 1 diabetes mellitus: 10 years after the diabetes control and complications trial. Archives of Ophthalmology 2008; 126: 1707-1715

Dyck PJ, Albers JW, Andersen H, Arezzo JC, Biessels G, Bril V, et al. Diabetic polyneuropathies: update on research definition, diagnostic criteria and estimation of severity. Diabetes/Metabolism Research and Reviews 2011; 27: 620-628

Edge JA, James T, Shine B. Persistent individual tracking within overall improvement in HbA1c in a UK paediatric diabetes clinic over 15 years. Diabetic Medicine 2010; 27, 1284–1288

Eeg-Olofsson K, Cederholm J,Nilsson PM, Zethelius B, Svensson A. Gudbjornsdottir S, et al. Glycemic Control and Cardiovascular Disease in 7,454 Patients With Type 1 Diabetes: An observational study from the Swedish National Register (NDR). Diabetes Care 2010; 33: 1640-1646

Epidemiology of Diabetes Interventions and Complications (EDIC) Study. Sustained effect of intensive treatment of type 1 diabetes mellitus on development and progression of diabetic nephropathy. Journal of American Medical Association 2003; 290: 2158-2167

ESRD Incidence Study Group. Divergent trends in the incidence of end-stage renal disease due to Type 1 and Type 2 diabetes in Europe, Canada and Australia during 1998–2002. Diabetic Medicine 2006; 23: 1364–1369

EUCLID study group. Randomised placebo-controlled trial of lisinopril in normotensive patients with insulin-dependent diabetes and normoalbuminuria or microalbuminuria. Lancet 1997; 349: 1787–92

Feldman EL, Stevens MJ, Thomas PK, Brown MB, Canal N Greene DA. A practical two step quantitative clinical and electrophysiological assessment for the diagnosis and staging of diabetic neuropathy. Diabetes Care 1994; 17:1281-1289

Gaede P, Vedel P, Larsen N, Jensen GV, Parving HH, Pedersen O. Multifactoral intervention and cardiovascular disease in patients with type 2 diabetes. New England Journal of Medicine 2003; 348:383-393

Galer BS, Gianas A, Jensen MP. Painful diabetic polyneuropathy: epidemiology, pain description, and quality of life. Diabetes Research and Clinical Practice 2000; 47: 123–128

Giacco F, Brownlee M. Pathogenesis of Microvascular complications. In Holt RIG, Cockram CS, Flyvberg A, Goldstein BJ (eds). Textbook of Diabetes. London: Wiley-Blackwell 2010

Gill GV, Daousi C, Barnett AH, Bain SC. Chronic kidney disease in long duration type 1 diabetes lasting more than 50 years. Current Medical Research and Opinion 2009; 25: 395-400.

Giorgino F, Laviola L, Perin PC, Solnica B, Fuller J, Chaturvedi N. Factors associated with progression to macroalbuminuria in microalbuminuric Type 1 diabetic patients: the EURODIAB Prospective Complications Study. Diabetologia 2004; 47:1020–1028

Grauslunda J, Jørgensenb TMM, Nybob M, Green A, Rasmussenb LM, Sjøliea AK. Risk factors for mortality and ischemic heart disease in patients with long-term type 1 diabetes. Journal of Diabetes and Its Complications 2010; 24: 223–228

Groop P, Thomas MC, Moran JL, Wade J, Thorn LM, Makinen V, et al. The presence and severity of chronic kidney disease predicts all-cause mortality in type 1 diabetes. Diabetes 2009; 58:1651–1658

Hammes HP, Kerner W, Hofer S, Kordonouri O, Raile K, Holl RW. Diabetic retinopathy in type 1 diabetes—a contemporary analysis of 8,784 patients. Diabetologia 2011; 54:1977–1984

Harjutsalo V, Forsblom C, Groop P. Time trends in mortality in patients with type 1 diabetes: nationwide population based cohort study. British Medical Journal 2011; 343: 1-11

Holt RIG, Cockram CS, Flyvberg A, Goldstein BJ (eds). Textbook of Diabetes. London: Wiley-Blackwell 2010

Hovind P, Rossing P, Tarnow L, Smidt UM, Parving H. Remission and regression in the nephropathy of type 1 diabetes when blood pressure is controlled aggressively. Kidney International 2001; 60: 277–283

Hovind P, Tarnow L, Rossing K, Rossing P, Eising S, Larsen N, et al. Decreasing incidence of severe diabetic microangiopathy in type 1 diabetes. Diabetes Care 2003; 26:1258–1264

Hovind P, Tarnow L, Rossing P, Jensen BR, Graae M, Torp I, et al. Predictors for the development of microalbuminuria and macroalbuminuria in patients with type 1 diabetes: Inception cohort study. BMJ, doi:10.1136/bmj.38070.450891.FE (published 19 April 2004)

Janghorbani M, Hu FB, Wilett WC, Li TY, Manson JE, Logroscino G, et al. Prospective study of type 1 and type 2 diabetes and risk of stroke subtypes: The Nurses' Health Study. Diabetes Care 2007; 30: 1730-1735

Jorde R, Sundsfjord J. Intra-individual variability and longitudinal changes in glycaemic control in patients with type 1 diabetes mellitus. Diabetic Medicine 2000; 17: 451-456

Juutilainen A, Lehto S, Ronnemaa T, Pyorala K , Laakso M. Similarity of the impact of type 1 and type 2 diabetes on cardiovascular mortality in middle-aged subjects. Diabetes Care 2008; 31:714–719

Keenan HA, Costacou T, Sun JK, Doria A, Cavellerano J, Coney J, et al. Clinical factors associated with resistance to microvascular complications in diabetic patients of extreme disease duration: The 50-year medalist study. Diabetes Care 2007; 30: 1995-1997

Klein R, Klein BE, Moss SE, Davis MD, DeMets DL. The Wisconsin epidemiologic study of diabetic retinopathy II: Prevalence and risk of diabetic retinopathy when age at diagnosis is less than 30 years. Archive Ophthalmology 1984; 10: 520-526

Klein R, Knudtson MD, Lee KE, Gangnon R, Klein BE. The Wisconsin Epidemiologic Study of Diabetic Retinopathy XXII: The twenty-five-year progression of retinopathy in persons with type 1 diabetes. Ophthalmology 2008; 115: 1859–1868

Krishnan S, Nash F, Baker N, Fowler D, Rayman G. Reduction in diabetic amputations over 11 years in a defined U.K population: Benefits of multidisciplinary team work and continuous prospective audit. Diabetes Care 2008; 31:99–101

Kubin M, Tossavainen P, Hannula V, Lahti S, Hautala N, Falck A. Prevalence of retinopathy in Finnish children and adolescents with type 1 diabetes: a cross-sectional population-based retrospective study. Archives of Disease in Childhood 2011; 96: 963–968

Kytö JP, Harjutsalo V, Forsblom C, Hietala K, Summanen PA, Groop P. Decline in the cumulative incidence of severe diabetic retinopathy in patients with type 1 diabetes. Diabetes Care 2011; 34:2005–2007

Laing SP, Swerdlow AJ, Slater SD, Botha JL, Burdent AC, Waugh NR, et al. The British Diabetic association Cohort Study, II: cause-specific mortality in patients with insulin-treated diabetes mellitus. Diabetic Medicine 1999a; 16: 466-471

Laing SP, Swerdlow AJ, Slater SD, Botha JL, Burdent AC, Waugh NR, et al. The British Diabetic Association Cohort Study, I: all-cause mortality in patients with insulin-treated diabetes mellitus. Diabetic Medicine 1999b; 16: 459-465

Laing SP, Swerdlow AJ, Slater SD, Burden AC, Morris A, Waugh NR, et al. Mortality from heart disease in a cohort of 23,000 parients with insulin-treated diabetes. Diabetologia 2003; 46: 760-765

Laing SP, Jones ME, Swerdlow AJ, Burden AC, Gatling W. Psychosocial and socioeconomic risk factors for premature death in young people with type 1 diabetes. Diabetes Care 2005; 28: 1618–1623

Luckie R, Leese G, McAlpine R, MacEwen CJ, Baines PS, Morris AD, et al. Fear of visual loss in patients with diabetes: results of the Prevalence of Diabetic Eye Disease in Tayside, Scotland (P-DETS) study. Diabetes Medicine 2007; 24, 1086–1092

Marcovecchio ML, Dalton RN, Schwarze CP, Prevost AT, Neil HAW, Acerini CL, et al. Ambulatory blood pressure measurements are related to albumin excretion and are predictive for risk of microalbuminuria in young people with type 1 diabetes. Diabetologia 2009; 52:1173–1181

Martin CL, Albers J, Herman WH, Cleary P, Waberski B, Greene DA. Neuropathy among the diabetes control and complications trial cohort 8 years after trial completion. Diabetes Care 2006; 29:340–344

Microalbuminuria Collaborative Group. Predictors of the development of microalbuminuria in patients with type 1 diabetes mellitus: A seven year prospective study. Diabetic Medicine 1999; 16, 918-925

National Diabetes Audit Executive Summary 2009-2010. The NHS Information Centre 2011

Orchard TJ, Olsen JC, Erbey JR, Williams K, Forrest KY, Kinder LS, et al. Insulin resistance-related factors, but not glycemia, predict coronary artery disease in type 1 diabetes. Diabetes Care 2003; 26:1374-1379

Orchard TJ, Secrest AM, Miller RG, Costacou T. In the absence of renal disease, 20 year mortality risk in type 1 diabetes is comparable to that of the general population: a report from the Pittsburgh Epidemiology of Diabetes Complications Study. Diabetologia 2010; 53:2312–2319

Pambianco G, Costacou T, Ellis D, Becker DJ, Klein R, Orchard TJ. The 30 year natural history of type 1 diabetes complications: The Pittsburgh Epidemiology of Diabetes Complications Study Experience. Diabetes 2006; 55: 1463-1469

Patterson CC, Dahlquist G, Harjutsalo V, Joner G, Feltbower RG, Svensson J, et al. Early mortality in EURODIAB population-based cohorts of type 1 diabetes diagnosed in childhood since 1989. Diabetologia 2007; 50:2439–2442

Perkins BA, Ficociello LH, Silva KH, Finkelstein DM, Warram JH, Krolewski AS. Regression of Microalbuminuria in Type 1 Diabetes. The New England Journal of Medicine 2003; 348: 2285-2293

Pop-Busui R, Low A, Waberski BH, Martin CL, Albers JW, Feldman EL, et al. Effects of prior intensive insulin therapy on cardiac autonomic nervous system function in type 1 diabetes mellitus : The Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Study (DCCT/EDIC). Circulation 2009; 119:2886-2893

Poulsen PL, Hansen KW, Mogensen CE. Ambulatory blood pressure in the transition from normo- to microalbuminuria. A longitudinal study in IDDM patients. Diabetes 1994; 43:1248–1253

Raile K, Galler A, Hofer S, Herbst A, Dunstheimer D, Busch P, et al. Diabetic nephropathy in 27,805 children, adolescents, and adults with type 1 diabetes: Effect of diabetes duration, a1c, hypertension, dyslipidemia, diabetes. Diabetes Care 2007; 30:2523–2528

Royal College of Ophthalmologists. Preferred Practice Guidance: Diabetic Retinopathy Screening (DRS) and the Ophthalmology Clinic set up in England. The Royal College of Ophthalmologists 2010

Sahakyan K, Klein BEK, Lee KE,Myers CE, Klein R. The 25-year cumulative incidence of lower extremity amputations in people with type 1 diabetes. Diabetes Care 2011; 34: 649- 651

Secrest AM, Becker DJ, Kelsey SF; LaPorte RE, Orchard J. All-cause mortality trends in a large population-based cohort with long-standing childhood-onset type 1 diabetes: The Allegheny County type 1 Diabetes Registry. Diabetes Care 2010a; 33: 2573-2579

Secrest AM, Becker DJ, Kelsey SF; LaPorte RE, Orchard J. Cause-specific mortality trends in a large population-based cohort with long-standing childhood. Diabetes 2010b; 59: 3216-3222

Shankar A, Klein R, Klein BE, Moss SE. Association between glycosylated haemoglobin level and cardiovascular and all-cause mortality in type 1 diabetes. American Journal of Epidemiology 2007; 166: 393-402

Skrivarhaug T, Bangstad TJ, Stene LC, Sandvik L, Hanssen KF, Joner G. Long-term mortality in a nationwide cohort of childhood-onset type 1 diabetic patients in Norway. Diabetologia 2006; 49: 298–305

Soedamah-Muthu SS, Chaturvedi N, Toeller M, Ferriss B, Reboldi P, Michel G, et al. Risk factors for coronary heart disease in type 1 diabetic patients in Europe. Diabetes care 2004; 27: 530-537

Soedamah-Muthu SS, Fuller JH, Mulnier HE, Raleigh VS, Lawrenson RA, Colhoun HM. All-cause mortality rates in patients with type 1 diabetes mellitus compared with non-diabetic population from the UK general practice research database, 1992-1999. Diabetologia 2006a; 49: 660-666

Soedamah-Muthu SS, Fuller JH, Mulnier HE, Raleigh VS, Lawrenson RA, Colhoun HM. High risk of cardiovascular disease in patients with type 1 diabetes in the UK: A cohort study using the General Practice Research Database. Diabetes Care 2006b; 29: 798-804

Stewart JH, Mccredie MR, Williams SM, Jager KJ, Trpeski L, Mcdonald SP, et al. Trends in incidence of treated end-stage renal disease, overall and by primary renal disease, in persons aged 20–64 years in Europe, Canada and the Asia-Pacific region, 1998–2002. Nephrology 2007; 12, 520–527

Sun JK, Keenan HA, Cavallerano JD, Asztalos BF, Schaeffer EJ, Sell DR et al. Protection from retinopathy and other complications in patients with type 1 diabetes of extreme duration: The Joslin 50 year Medalist study. Diabetes Care 2011; 34: 968-974

Tanenberg RJ, Newton, CA, Drake AJ. Confirmation of hypoglycemia in the "dead-in-bed" syndrome, ascaptured by a retrospective continuous glucose monitoring system. Endocrinology Practical 2010; 16: 244-248

Tesfaye S, Stevens LK, Stephenson JM, Fuller JH, Plater M, Ionescu-Tirgoviste C, et al. Prevalence of diabetic peripheral neuropathy and its relation to glycaemic control and potential risk factors: the EURODIAB IDDM Complications Study. Diabetologia 1996; 39: 1377–1384

Tesfaye S, Chaturvedi N, Eaton SEM, Ward JD, Manes C. Vascular risk factors and diabetic neuropathy. New England Journal of Medicine 2005; 352: 341-350

Tesfaye S, Boulton AJM, Dyck PJ, Freeman R, Horowitz M, Kempler P, et al. Diabetic neuropathies: update on definitions, diagnostic criteria, estimation of severity, and treatment. Diabetes Care 2010; 33: 2285-2293

Thorn LM, Forsblom C, Waden J, Saraheimo M, Tolonen N, Hietala K, et al. Metabolic syndrome as a risk factor for cardiovascular disease, mortality, and progression of diabetic nephropathy in type 1 diabetes. Diabetse Care 2009; 32: 950-952

Van Acker K, Bouhassira D, De Bacquer D, Weiss S, Matthys K, Raemen H. Prevalence and impact of quality on life of peripheral neuropathy with or without neuropathic pain in type 1 and type 2 diabetic patients attending outpatients clinics. Diabetes and Metabolism 2009; 35: 206-213

Vileikyte L, Peyrot M, Gonzalez JS, Rubin RR, Garrow AP, Stickings D, et al. Predictors of depressive symptoms in persons with diabetic peripheral neuropathy: a longitudinal study. Diabetologia 2009; 52:1265–1273

Waernbaum I, Blohmé G, Östman J, Sundkvist G, Eriksson JW, Arnqvist HJ. Excess mortality in incident cases of diabetes mellitus aged 15 to 34 years at diagnosis: a population-based study (DISS) in Sweden. Diabetologia 2006; 49: 653–659

Weis U, Turner B, Gibney J, Watts GF, Burke V, Shaw KM, et al. Long-term predictors of coronary artery disease and mortality in type 1 diabetes. Quarterly Journal of Medicine 2001; 94: 523-630

Young MJ, Boulton AJM, Macload AF, Williams DRR, Sonksen PH. A multicentre study of the prevalence of diabetic peripheral neuropathy in the United Kingdom hospital clinic population. Diabetologia 1993; 36: 150-154

Ziegler D. Diabetic peripheral neuropathy In Holt RIG, Cockram CS, Flyvberg A, Goldstein BJ (eds). Textbook of Diabetes. London: Wiley-Blackwell; 2010

# CHAPTER 3

# REDUCING RISK AND IMPROVING OUTCOME IN TYPE 1 DIABETES

# CHAPTER 3

# REDUCING RISK AND IMPROVING OUTCOME IN TYPE 1 DIABETES

## 3.1 INTRODUCTION

Risk factors for the development of vascular complications in type 1 diabetes can be divided into those that are modifiable (hypertension, dyslipidaemia, poor glycaemic control and current smoking status) and those that are non-modifiable, for example age, duration of diabetes, race and family history. Modifiable risk factors may be adjusted by lifestyle changes and pharmacological interventions, which should be appropriately utilized to achieve risk factor targets. Non modifiable risk factors should be considered when making a clinical decision regarding a particular risk factor for example a first degree family history of premature cardiovascular death may influence the decision to treat dyslipidaemia in a young person with type 1 diabetes. This chapter will focus on risk factor reduction in type 1 diabetes.

## 3.2 RISK FACTOR TARGETS AND GUIDELINES IN TYPE 1 DIABETES

There are currently two UK based published guidelines for the management of vascular risk in type 1 diabetes, the National Institute for Clinical Excellence (NICE 2004) and the Joint British Societies (2005).

### 3.2.1 National Institute for Clinical Excellence targets

NICE guidance (2004) for the management of type 1 diabetes in children, young people and adults advocate the following targets **(Table 3.1)**:

| | |
|---|---|
| $HbA_{1c}$ | < 7.5% or ≤ 6.5% in those at increased arterial risk |
| BP | 135/85 mmHg or<br>130/80 mmHg in those with an abnormal albumin excretion rate or 2 or more features of the metabolic syndrome |
| Lipids | A standard dose of a statin should be recommended for:<br>• adults in the highest risk (those with abnormal albumin excretion or 2 or more features of the metabolic syndrome)<br>• adults in the moderately high risk groups (increasing age over 35 years, family history of premature heart disease, ethnic group with high risk or those with more severe abnormalities of blood lipids or blood pressure) |

### 3.2.2 Joint British Societies targets

The Joint British Societies Guidelines (2005) on prevention of cardiovascular disease in clinical practices recommend the following targets **(Table 3.2 )** :

| | |
|---|---|
| $HbA_{1c}$ | < 6.5% |
| BP | < 130/80 mmHg |
| Lipids | A statin is recommended for :<br>• All those aged 40 years or more<br>• People aged 18 – 39 who have at least one of the following:<br>o Retinopathy<br>o Nephropathy including persistent microalbuminuria<br>o Poor glycaemic control ($HbA_{1c}$ > 9%)<br>o Elevated blood pressure requiring anti hypertensive therapy<br>o Raised total cholesterol ≥ 6.0mmol/l<br>o Features of the metabolic syndrome<br>o Family history of premature CVD in a first degree relative |

### 3.2.3 European Diabetes Policy Group targets

Prior to 2004 when this thesis was started the above guidelines had not been published. At that time the only guidelines and targets available were those defined by the European Diabetes Policy Group (1999). The targets at that time were (**Table 3.3**):

| | |
|---|---|
| $HbA_{1c}$ | <7.5% |
| BP | No microalbuminuria <135/85 mmHg<br>Microalbuminuria < 130/80 mmHg |
| Lipids | Total cholesterol <4.8 mmol/l<br>LDL cholesterol <3.0 mmol/l<br>HDL cholesterol >1.2 mmol/l<br>Triglycerides <1.7 mmol/l |

## 3.3 GLYCAEMIC CONTROL

Since the introduction of insulin therapy the main cause of morbidity and mortality in type 1 diabetes is micro vascular and macro vascular disease. Poor glycaemic control is a major risk factor for the development of long term microvascular complications (DCCT 1993). Whilst the DCCT was a landmark study providing clear evidence that, compared to conventional therapy, intensive insulin treatment leading to an improvement in glycaemic control delayed the onset and progression of micro vascular complications other studies had previously reported a relationship between glycaemic control and micro vascular complications (Pirart 1978, Dahl-Jorgensen et al 1986, Dahl-Jorgenson et al 1992, Feldt-Rasussen at al 1991, Kroc Collaborative Study Group 1984).

One very early study from Belgium involving 4400 patients with type 1 and type 2 diabetes (2795 who were followed up for 25 years) reported that poor glycaemic control and duration of diabetes were related to a higher incidence and prevalence of microvascular complications (Pirart 1978). Glycaemic control was assessed by home urine testing initially with Benedicts solution and later with strip reagents when available (verified by 24 hour urine collections for glucose estimation in 'suspect cases') and annual blood glucose. The degree of glycaemic control was considered to be good, fair or poor according to the degree of glycosuria on a

serial basis. A preliminary analysis in 1955 (before the introduction of oral hypoglycaemic agents) involving 1145 patients estimated that about 25% of the group had type 1 diabetes and that micro vascular disease , peripheral artery disease but not coronary disease correlated with poor glycaemic control. The peak incidence of complications was reported to be 15- 20 years following diagnosis. Interestingly treatment strategies which included normalizing body weight, encouraging physical activity, low calorie diets including 'slow acting carbohydrate' and use of the 'lowest possible efficient dose' of insulin or oral hypoglycaemic agents (when they became available) to avoid hypoglycaemia are still the basis of treatment today. In addition this study, which started in 1947, emphasized patient education and personal responsibility for diabetes control. Although the method of assessing glycaemic control was somewhat crude, the message was clear: good glycaemic control was associated with better outcomes. This study did not seek to inform on how to improve glycaemic control but to confirm the relationship between glyceamic control and complications. Later studies went on to compare the effects of different treatment regimens in achieving good control.

One such study from the 1980's, the Oslo Study investigated the effects of 3 different treatment regimens, continuous subcutaneous insulin infusion (CSII), multiple daily injections (5-6 injections per day) and conventional treatment (2 injections per day) on glyceamic control (Hba1)and micro vascular complications in 45 adults with type 1 diabetes (Dahl -Jorgensen et al 1986). After 2 years, CSII or multiple daily injections resulted in significantly better glycaemic control than conventional treatment and glycaemic control was slightly but not significantly better in those randomized to CSII compared with multiple daily injections. However CSII was associated with several episodes of diabetic ketoacidosis and subcutaneous abscesses probably related to the technology and consumables available at the time. This cohort were followed up 7 years after the study started when 10 patients were using CSII, 2 twice daily insulin and 33 multiple daily injections (Dahl-Jorgensen et al 1992). Hba1 in the group as a whole had improved from 11.2% at baseline to 9.5% at 7 years which may have reflected changes in diabetes care in general. Intention to treat analysis revealed those who were originally randomized to the CSII or multiple injection interventions still had better glycaemic control than those originally in the conventional group and that a mean Hba1 of greater than 10% was associated with a substantial progression of urinary albumin excretion.

The Stockholm Diabetes Intervention Study also reported an improvement in glycaemic control and reduction in the progression of micro vascular complications in patients randomized to

intensive insulin treatment (Reichard et al 1991). This study randomized 96 adults with longstanding type 1 diabetes to intensive or conventional insulin treatment for 5 years. Intensive insulin treatment resulted in a significantly greater improvement in Hba1 than conventional treatment and a delay in the occurrence or progression of micro vascular complications. A one unit increase in $HbA_{1c}$ was associated with a 2-3.5 fold increased risk of deterioration of microvascular complications. However as with the DCCT, intensive treatment was associated with more frequent serious hypoglycaemia and greater weight gain. Again this cohort was followed up at 7.5 years by which time over 60% of the original conventional treatment group were taking at least 3 injections per day (Reichard et al 1993). Glycaemic control continued to be better in the group originally randomized to intensive treatment than those in the conventional group and the progression of complications was also significantly delayed. A similar picture emerged at 10 year follow up (Reichard et al 1996). In relation to glycaemic control these results differ from the DCCT, as in the Stockholm group a difference in $HbA_{1c}$ was still evident between groups after 10 years despite a return to routine care, and the reason for this is unclear. It may reflect differences in routine care in the cohorts, or possibly intensity of ongoing education and support following completion of the studies.

Whilst the DCCT and the studies discussed above have clearly demonstrated that good glyceamic control reduces the risk of long term microvascular complications they did not really inform on how to do this in routine clinical practice. The most commonly used insulin regimens in type 1 diabetes are twice daily often premixed insulin, multiple daily injections (basal bolus) and continuous insulin infusion (CSII). No particular insulin regimen will meet the needs of every person with type 1 diabetes therefore insulin regimens need be adapted according to individual need considering such factors as individual choice, willingness to give multiple injections, lifestyle and social circumstances. In addition an individual may need to change insulin regimens at various stages according to the specific situation, for example during pregnancy, according to cognitive function or social dependence.

### 3.3.1 Insulin regimens and type 1 diabetes - twice daily insulin

Many people with type 1 diabetes manage blood glucose levels with 2 injections of insulin per day, before breakfast and before evening meal. In the past soluble and isophane insulin have been independently 'free mixed' in the same syringe. Free mixing allows the person with diabetes some flexibility to alter the amount of soluble and/or isophane insulin according to

the current blood glucose, physical activity and carbohydrate consumption. However it does require a degree of dexterity and skill in the mixing process. Since the introduction of biphasic insulin in the late 1950's many people with type 1 diabetes have opted for twice daily injections of premixed insulin. In the past there has been a variety of premixed insulin available ranging from 10%:90% – 50%:50% (soluble to isophane insulin). However more recently many of these combinations have been withdrawn mainly on a commercial basis due to lack of use. In the UK currently the only premixed insulins available are; 25:75, 30:70, 50:50, of which 30:70 mixes are the most commonly used. For many people premixed insulins are easier to use as they eliminate mixing errors thereby helping to maximize the consistency of the insulin dose.

Recently there has been some debate on the use of biphasic analogue insulin as opposed to biphasic human insulin and whilst there are a number of clinical trials in type 2 diabetes, data in type 1 diabetes is limited. One open label, randomized controlled trial involving 294 people with type 1 and type 2 diabetes (104 type 1), already using twice daily insulin, compared the efficiency and safety of biphasic insulin aspart 30 (Novomix 30) with an equivalent formulation of biphasic human insulin (Boehm et al 2002). After 12 weeks there was no difference in $HbA_{1c}$ however postprandial control was significantly improved in those randomized to analogue insulin. In addition there was a tendency to less episodes of minor nocturnal hypoglycaemia in the analogue group but this was not statistically significant. The authors report that subgroup analyses for type 1 and type 2 diabetes were in agreement with the overall analysis. In another randomized three way crossover study 50 adults with type 1 diabetes received an injection of biphasic analogue insulin immediately before a standardized breakfast or biphasic human insulin immediately or 30 minutes before breakfast on three separate occasions (Hermansen et al 2002). Postprandial blood glucose control was significantly better with biphasic analogue insulin than human insulin regardless of the timing of human insulin.

In addition improvements in postprandial control with a biphasic insulin analogue compared to multiple daily injections have been reported by other groups (Mortensen et al 2006, Chen et al 2006). One multinational, randomized, open label parallel study involving 167 adolescents with type 1 diabetes compared pre meal biphasic analogue insulin plus NPH at bedtime with a human insulin regimen consisting of biphasic insulin at breakfast plus soluble insulin at lunch and dinner time plus NPH at night (Mortensen et al 2006). After 4 months there was no significant difference in $HbA_{1c}$ between the groups although there was a non significant

improvement in postprandial hyperglycaemia. In addition BMI increased significantly in both groups but the increase was significantly less in the analogue insulin group. Similarly Chen et al (2006) compared pre- meal biphasic insulin aspart 30 (with an option of also injecting NPH at bedtime) with multiple injection therapy using human insulin before meals and bedtime NPH in a 24 week crossover study. At the end of the study $HbA_{1c}$ improved significantly with both regimens but there was a greater improvement during the biphasic analogue insulin phase. This was however, mainly driven by the 50% of participants who opted to inject bedtime NPH in addition to pre-meal biphasic analogue insulin. In this study biphasic analogue insulin was associated with a significant reduction in postprandial blood glucose after evening meal but not after breakfast or lunch.

Over the years, mainly due to the results of the DCCT, there has been a gradual move away from twice daily insulin regimens to multiple injection regimens in type 1 diabetes. However there is still a place for twice daily insulin regimens in the management of type 1 diabetes, particularly for those who are unwilling or unable to give more than two injections per day. This may include those who require supervision to give insulin injections, and people with a very regular lifestyle who may not desire the flexibility afforded by multiple daily injections. Finally a compromise between frequently of injections and flexibility may be found in twice daily 'free mixing' insulin regimens which are still used by some people with type 1 diabetes.

### 3.3.2 Multiple daily insulin regimens

The basic theory behind multiple daily injection regimens is that they mimic physiological insulin secretion and may therefore help to improve glycaemic control. Multiple daily injections became popular in the mid 1980's around the time that pen injectors became commercially available. Although initial studies indicated that multiple daily injections were associated with greater flexibility of lifestyle, greater psychological wellbeing and satisfaction with the pen injector there was no real evidence for improvements in glycaemic control when compared to twice daily insulin injections (Small et al 1988, Murray et al 1988, Houtzagers et al 1989). Indeed one retrospective study suggested that multiple daily injections were associated with a significant deterioration in glycaemic control in female but not male patients with type 1 diabetes (Hardy et al 1991). However most of these studies involved small numbers of patients and were of relatively short duration. A retrospective audit of 145 people with type 1 diabetes

who changed from twice daily to multiple daily injections in a routine diabetic clinic reported a small but significant improvement in glycaemic control (as assessed by fructosamine) and a significant reduction in insulin dose after 3 months of multiple daily injections (Baxter and Wright 1993). The main impetus for changing to multiple daily injections in this group was flexibility of lifestyle rather than to specifically improve glycaemic control. Multiple daily injections were associated with a high level of acceptance with only 5 (3%) patients returning to twice daily injections and there was no increased incidence of reported hypoglycemia. In addition a few uncontrolled studies of short duration involving small numbers of people with type 1 diabetes have demonstrated statistically insignificant improvements in glycaemic control associated with multiple daily injections (Jefferson et al 1985, McCaughey et al 1986). More recently a 7 year observational study of 35 male patients with type 1 diabetes using multiple daily injections in a routine clinical setting demonstrated long term improvements in glycaemic control (Perez- Mendez et al 2007). All had an $HbA_{1c}$ of 9.0% or more at baseline which reduced gradually to a mean of 6.8% at 7 year follow up by which time 33% of the group had reached a target of less than 6.2% without an increase in mild or moderate hypoglycaemia. Regardless of effect on glycaemic control flexibility of lifestyle and patient satisfaction are important in a chronic condition such as type 1 diabetes and should not be disregarded. Conversely in some individuals twice daily injections may be more acceptable simply due to the number of injections required and insulin regimens should be tailored to meet individual needs.

As with other insulin regimens, recently the debate around multiple daily injection regimens has turned to the type of insulin used, more specifically analogue versus unmodified human insulin. The rationale for the use of insulin analogues rather than unmodified human insulin in multiple daily insulin regimens is that analogue insulin provides a more physiological mealtime profile resulting in a reduction in postprandial blood glucose and nocturnal hypoglycaemia (Anderson et al 1997, Garg et al 2010). A recent randomized cross over study involving 56 patients from five centres in the UK compared multiple daily injections using unmodified human insulin at mealtimes and once or twice daily NPH with an insulin analogue regimen (meal time and basal insulin analogues) (Ashwell et al 2006). Home blood glucose monitoring was encouraged (pre meal and pre bed). All involved were asked to record a daily fasting blood glucose plus an 8 point profile in the week before review, all were reviewed in clinic on a 2 weekly basis (or more frequently if needed) and insulin dose was titrated using a target driven

algorithm. Glycaemic control ($HbA_{1c}$) was significantly lower and nocturnal hypoglycaemia significantly reduced with the insulin analogue regimen. After 16 weeks $HbA_{1c}$ was 0.5% lower with the insulin analogue regimen than with human insulin regimen. This reduction was thought to be due to a reduction in pre breakfast blood glucose (mean 1.5 mmol/l) and a 1.9mmol/l lower mean 24 hour home blood glucose monitoring level. This study was of relatively short duration and involved only a small group of people with type 1 diabetes therefore it is difficult to generalize the results. In addition it was resource intensive involving clinic reviews on a two weekly basis and is therefore not transferable to a routine clinic situation. Several other studies comparing analogue and human insulin have reported a reduction in nocturnal hypoglycaemia but no effect on glycaemic control in type 1 diabetes (Vague et al 2003, Murphy et al 2003).

In current economic times, considering the available evidence and the cost of analogue insulin, it may be that the use of analogue insulin should be confined to those with specific problems, for example nocturnal hypoglycaemia. In England in 2007, £286 million of the drugs budget was spent on insulin of which £234 million was accounted for by analogue insulin (Gale 2010). Between 2001- 2007, information from the Health Information Network , which includes data from approximately 300 practice in the UK, reported that in type 1 diabetes the mean cost of diabetes specific prescribing increased from £331 to £573 per person per year (after adjustment for inflation). Conversely, during the same time period, there was no change in $Hba_{1c}$ (8.8% verus 8.7%) (Currie et al 2010).

Despite the initial lack of evidence and following the publication of the DCCT, multiple daily injection regimens have become commonplace in the management of type 1 diabetes. However frequent injections alone are unlikely to result in a sustained improvement in glycaemic control, but need to be part of a comprehensive education programme including self management skills such as estimation of carbohydrate intake, alteration of insulin dose and access to health care professionals.

### 3.3.3 Continuous Subcutaneous Insulin Infusion

Insulin pumps have been discussed previously in Chapter 1 section 1.6.2

### 3.3.4 Metformin as an adjunct in type 1 diabetes

Metformin is a biguanide agent which is first line therapy in the management of type 2 diabetes. It can used as monotherapy or in combination with other oral hypoglycaemic agents or insulin. Metformin exerts its glucose lowering effect by reducing hepatic glucose production and increasing glucose uptake in muscle thus improving insulin sensitivity. In type 2 diabetes metformin is associated with less weight gain compared to other oral hypoglycaemic agents (UKPDS 1998a). In addition, in the United Kingdom Prospective Diabetes Study, metformin was associated with a reduction in the rate of myocardial infarction in people with diabetes and this was sustained at 10 years after the end of the study (Holman et al 2008). As the effect of metformin is not dependent on residual β-cell activity it has been used more recently as an adjunct agent in type 1 diabetes.

In a randomized double blind cross over study, 15 overweight adults with type 1 diabetes were randomized to either metformin (gradually increased to 850mg three times daily as tolerated) or placebo for 2 separate 16 week study periods separated by a 4 week wash out period (Khan 2006). Glyceamic control was significantly better and insulin dose significantly lower during the metformin treatment period but there was no change in body weight. Beneficial effects of metformin on insulin dose, body weight and quality of life in adults with type 1 diabetes have been reported by others (Moon et al 2007, Jacobson et al 2009). However these beneficial effects have not been associated with improvements in glycaemic control and this may be due to the short duration of the study periods. One study also included a retrospective review of 30 people with type 1 diabetes treated with metformin for at least 4 months (Moon et al 2007). Although there was an initial significant improvement in glycaemic control after 3 months of metformin treatment (-0.8% compared with baseline) this effect diminished with time. Nevertheless $HbA_{1c}$ remained significantly improved compared to baseline in those who continued with metformin for 19-25 months (-0.4% compared to baseline). However of the 30 patients included in the retrospective review only 8 patients were still taking metformin after 2 years. The authors do not elaborate on the reasons for this but it may have been due to gastrointerstinal side effects or a perceived lack of benefit of metformin. A recent large randomised placebo controlled study involving 100 people with poorly controlled type 1 diabetes, from the Steno Diabetes centre in Denmark, reported that after 12 months of treatment metformin did not have a significant effect on glyceamic control however there

were significant reductions in insulin dose and body weight in those randomised to metformin ( Lund et al 2008).

Metformin has also been used as an adjunct to insulin in adolescents with type 1 diabetes (Sarnblad et al 2003, Hamilton et al 2003). Both randomised double blind placebo controlled studies report significant improvements in glycaemic control in those randomised to metformin. Hamilton et al report that this improvement in glyceamic control was achieved with a lower insulin dose however this was not the case in the Sarnblad study. In addition a significant improvement in insulin sensitivity was reported by Sarnblad et al but not by Hamilton et al. There were no differences in gastrointestinal side effects in those randomised to metformin compared to the placebo group.

A recent systematic review and meta analysis of the randomised trials of metformin in type 1 diabetes concluded that metformin is associated with a reduction in insulin dose, a small reduction in body weight but that there is no clear evidence of an improvement in glyceamic control (Vella et al 2010).

Metformin is an inexpensive and generally safe medication which may be useful in some mainly overweight people with type 1 diabetes. However it is not licensed for use in type 1 diabetes and people with diabetes should be made aware of this.

### 3.4 TYPE 1 DIABETES - DYSLIPIDAEMIA AND HYPERTENSION

Dyslipidaemia and hypertension are risk factors for the development of CVD. In the UK there are several published targets and guidelines for the management of cardiovascular risk in people with type 1 diabetes (NICE 2004, Joint British Societies 2005). However these targets are often difficult to achieve in a routine diabetic clinic. A recent study from the UK, involving 1282 people with type 1 diabetes (mean age 46 years, mean duration of diabetes 21 years) attending three secondary care trusts audited achievement of cardiovascular risk factor targets as defined by the Joint British Societies 2005 (BP<130/80, $HbA_{1c}$ < 6.5%, total cholesterol > 4mmol/l) (Syed et al 2007). A minimum cardiovascular data set, defined as documentation of total cholesterol, BP, smoking history and $HbA_{1c}$, was available in 72% of patients, of whom only 0.7% achieved all 4 targets. Glycaemic control was documented in 93% of records reviewed with only 7% achieving an $HbA_{1c}$ of less than 6.5% and 26% achieving an $HbA_{1c}$ of less than 7.5%. In addition BP was documented in 93% of all records and only 36% achieved a

target of 130/80 or less. Forty percent of participants were taking anti hypertensive medication, of whom 68% had a BP above target. Total cholesterol was documented in 94% with 32% achieving a target level. In the Joint Society Guidelines routine statin therapy is recommended for all people with type 1 diabetes over the age of 40 years however in this study only 57% of those in this age group were prescribed a statin. Smoking status was documented in 84% of cases of whom 24% reported being current smokers. This study highlights that even with clear guidelines in specialist centres management of cardiovascular risk factors is suboptimal. Similar results have been reported in other European countries and in the USA (Waden et al 2005a, Schwab et al 2006, Eeg- Olofsson et al 2007). However a few studies do suggest that risk factors are being managed more effectively over the past decade, mainly due to the increased use of lipid lowering and anti hypertensive agents nevertheless achievement of treatment targets is still unsatisfactory (Eeg- Olofsson et al 2007, Coppell et al 2006). This may be more apparent in men than in women. A recent study, involving 1153 people with type 1 diabetes (DCCT/EDIC cohort), found that women reported significantly less use of statins, aspirin and anti hypertensive agents when compared to men, even after adjusting for lipid profile and blood pressure (Larkin et al 2010).

### 3.4.1 Statins in the management of diabetes

Whilst the role of statins in type 2 diabetes in primary and secondary prevention of cardiovascaular disease is now well established the case is not quite so clear for type 1 diabetes. The Scandinavian Simvastatin Survival Study ("4S") was the first study to indicate that lowering cholesterol reduced the risk of coronary heart disease in people with diabetes (Pyorala et al 1997). This study involved 4444 participants with a raised cholesterol and a previous history of myocardial infarction or angina randomised to either placebo or simvastatin (initially 20mg daily but titrated to 40mg according to response) and followed up for a median of 5.4 years. Subgroup analysis revealed that in the 202 people with diabetes simvastatin was associated with a 55% reduction in the risk of a fatal or non fatal coronary heart disease event (p=0.002) compared with a 32% reduction in a major event in subjects without diabetes. The study concluded that the benefit of cholesterol lowering in people with diabetes may be greater than in those without diabetes because people with diabetes have a higher absolute risk of atherosclerotic events. Another randomised double blind secondary prevention study, the Cholesterol and Recurrent Events Trial (CARE), included 586 people with type 2 diabetes

(with 'average' total cholesterol levels, mean 5.4 mmol/l) randomised to pravastatin or placebo for a 5 year study period (Goldberg et al 1998). Pravastatin resulted in a 25% reduction in the risk of death due to coronary heart disease, non fatal myocardial infarction, bypass surgery or angioplasty.

Primary prevention of CVD in people with type 2 diabetes has been assessed in the Collaborative Atorvastatin Diabetes Study (Colhoun et al 2004). This UK based, multi centre double blind placebo controlled study, assessed the effect of Atorvastatin 10mg on cardiovascular events in 2838 adults with type 2 diabetes and at least one other risk factor for the development of CVD (retinopathy, albuminuria, current smoking or hypertension). The study was stopped 2 years earlier than expected when interim analysis revealed significant benefits in those who were randomised to atorvastatin. After a median follow up of 3.9 years atorvastatin was associated with a 1.2 mmol/l reduction in LDL and a 37% reduction in the risk of a major cardiovascular event compared to placebo. Acute coronary events were reduced by 36% and the risk of stroke reduced by 48%. These benefits were irrespective of LDL cholesterol or triglycerides at baseline. In addition the Heart Protection Study included 5963 people with diabetes (aged 40 – 80 years, 615 type 1) and a total cholesterol of at least 3.5mmol/l in a randomized double blind controlled study of intervention with simvastatin 40mg (Heart Protection Collaborative group 2003). After a mean follow up of 4.8 years, in the group randomised to simvastatin, LDL cholesterol was reduced by a mean of 0.9 mmol/l and this was associated with significant reductions in coronary mortality (20%), first non fatal myocardial infarction (37%), stroke (24%) and revascularization (17%) compared to placebo. When considered together there was a 22% reduction in the first occurrence of a major vascular event in the group randomised to simvastatin and this was even greater (33%) amongst those who did not have any diagnosed coronary or other arterial disease at baseline. These effects were seen regardless of type of diabetes, duration or baseline lipid profile. In the subgroup with type 1 diabetes (615 subjects) treatment with simvastatin was associated with a 24% reduction in events however this was statistically non significant probably due to the small numbers involved. A recent meta- analysis of 14 randomised studies of statin therapy in 18,686 people with diabetes (1466 type 1 diabetes) reported a significant 21% reduction in major vascular events per mmol/l reduction in LDL cholesterol which was not related to if there was a prior history of vascular disease (Cholesterol Treatment Trialists (CTT) Collaborators 2008). The risk reduction was similar regardless of type of diabetes.

However the use of statins in type 1 diabetes is still an area of debate. People with type 1 diabetes do have an increased risk of CVD however diabetes is usually diagnosed at an earlier age when the absolute incidence is very small therefore when to start statin treatment is unclear. In addition there are concerns about the long term effects of statin therapy and the use of statins in women of childbearing age. A statement from the Association of British Clinical Diabetologists endorses an individual 'tailored' approach to statin treatment in diabetes. In type 1 diabetes routine treatment is advised in those over 50 years of age and people over 40 years of age with complications. In the 18 – 39 years age group, were evidence of benefit is unclear, individual assessment is recommended taking into account complications, duration of diabetes, other risk factors, glycaemic control and family history (Feher and Winocour 2007).

## 3.5 SMOKING AND DIABETES

Smoking is a well established risk factor for vascular disease in type 1 diabetes and has been shown to be associated with the development and progression of microalbuminuria and retinopathy (Microalbuminuria Collaborative Study Group UK 1993, Karamanos et al 2000, Rossing et al 2002, Nilsson et al 2004). A recent study from the USA compared self reported smoking habits of 582 adults with type 1 diabetes to 724 control subjects and reported that significantly more adults with type 1 diabetes reported current smoking than control subjects (Bishop et al 2009). In addition smoking was significantly associated with coronary artery calcification in the whole cohort (those with and without diabetes) and type 1 diabetes was reported to be an independent risk factor for the development of coronary artery calcification. Another large study from Sweden examined trends in smoking habits in adults with type 1 diabetes between 1996 (6740 adults with type 1 diabetes) and 2001 (11,513 adults with type 1 diabetes). The percentage of smokers varied between 11.7 and 15% with no significant trend over time (14.5% smokers in 1996, 15% in 1997, 11.7% in 1998, 13.5% in 1999 and 14.5% in 2001) (Nilsson et al 2004). Smoking was particularly high in females aged less than 30 years (12-16%) compared to males of the same age (7-10%) and in the 30-59 years age group (13-17%, males and females combined). Smokers were reported to have significantly worse glycaemic control and greater frequencies of microalbuminuria than non smokers. In addition smokers had a significantly lower BMI which may account for the high levels of smoking noted in young women as smoking may have an effect on appetite. Although there was no difference

in blood pressure between smokers and non smokers significantly more smokers were taking anti hypertensive and lipid lowering agents than non smokers. This may indicate previously diagnosed hypertension or dyslipidaemia or alternatively may be a reflection of the greater frequency of microalbuminuria in the smokers.

Self reported smoking habits in children and young people with type 1 diabetes have also been investigated. A large study involving 27,561 children and young people, from 267 centres in Austria and Germany, reported an increasing rate of self reported smoking according to age band. In those aged less than 11 years 0.1% reported current smoking compared to 5% in the 11–15 age group and 28.4% in the 15-20 age group (Hofer et al 2009). Glycaemic control, diastolic blood pressure and lipid profile was significantly worse in those who smoked. An increase in self reported smoking according to age in youth with type 1 diabetes has been reported by another group (Reynolds et al 2011). This paper reported the prevalence of smoking in a large group of children and young people (2887 subjects) aged between 10 – 22 years, to be 2.7% in those aged 10-14 years, 17.1% in the 15-19 years age band and 34% in those aged 20 years or over. Of concern in this study is that over 50 % of those with type 1 diabetes reported having never been asked about smoking habits and only 47% reported having ever been counseled about smoking. As most adult smokers report starting to smoke in the teenage years anti smoking advice is crucial in this age group as they have much to gain.

There are few randomised controlled studies on smoking cessation in diabetes and most involve people with type 2 diabetes. One controlled interventional study, involving people with type 2 diabetes attending primary care health centres in Sweden, compared anti smoking intervention (a group programme of eight weekly motivational interviewing sessions or telephone support at 6 and 12 months) with once only written smoking cessation advice sent in the post (Persson and Hjalmarson 2006). At 12 months follow up 20% of the interventional group reported having stopped smoking compared to 7% of the control group ($p<0.01$). In addition those in the intervention group who had attended the group motivational interviewing sessions reported a 40% smoking cessation rate compared to 14% of those who declined the group sessions but accepted the telephone support ($p<0.01$). Although not specifically designed as an anti smoking intervention significantly more people with newly diagnosed type 2 diabetes who were randomised to the group intervention arm of the UK based Diabetes Education and Self Management for ongoing and Newly Diagnosed (DESMOND) programme gave up smoking than those in the routine group (Davies et al 2008). This

programme involves advice and learner based activities aimed at reducing overall personal risk through lifestyle changes.

The majority of prevalence and interventional studies have relied on self reported smoking status which could be inaccurate as participants may underestimate the number of cigarettes smoked or deny smoking at all. A few older studies have measured urinary cotinine, a nicotine metabolite, to objectively assess prevalence of smoking of in type 1 diabetes. One such study assessed smoking habits using a structured interview and urinary cotinine measurement in 99 young people with type 1 diabetes attending a routine diabetes clinic in UK (Masson et al 1992). Forty eight percent of the group had a raised urinary cotinine, indicating active smoking, however only 31% admitted to being current smokers. This is important information as if stop smoking strategies are to be directed appropriately an honest smoking history needs to be obtained. The same group reassessed smoking habits in the same clinic nine years later again using direct questioning and urinary cotinine (MacFarlane et al 2001). There was a non significant reduction in the number of smokers in the second study (31% versus 28%). However whilst in the first study 17 subjects denied smoking but had an unequivocally raised urinary cotinine level indicating active smoking ('covert' smokers), in the second study only 3 subjects were considered to be covert smokers. Corrected data indicated a significant reduction in smoking (48% versus 30%, $p<0.02$) and that young people with diabetes (mean age 23 year) were more comfortable with giving an accurate smoking history. A few studies have assessed the effectiveness of anti smoking counseling in people with type 1 diabetes. In one early study, 60 young adults with type 1 diabetes, who wanted to stop smoking, received standard anti smoking advice and were reviewed six months later (Ardron et al 1988). Many claimed to have cut down or stopped smoking but urinary cotinine concentrations did not confirm this. In fact, only one person had stopped smoking and this was following a myocardial infarction. However some adults with type 1 diabetes do manage to stop smoking. In a six year follow up study, involving 100 people with type 1 diabetes aged less than 45 years (53 smokers and 47 non smoking controls), twelve (27%) of the 45 smokers who could be traced had stopped smoking but this was often after the development of microvascular complications (Sinha et al 1997). In addition microvascular complications (retinopathy and increased urinary albumin excretion) were more common and more severe in the smokers. Alarmingly three of the non smokers (7%) had started smoking during the 6 year follow up period. In another uncontrolled study 93 current smokers with diabetes (80% type 1) were given anti smoking counseling by a doctor.

This advice was reinforced by a specialist nurse and accompanied by literature regarding methods of stopping smoking (Ismail et al 2000). Smoking habits were assessed by direct questioning and urinary cotinine measurements at the start of the study and then again at a mean of 10 and 20 months at routine clinic appointments. At 10 months 3 patients reported they had stopped smoking and they remained stopped at 20 months, this was verified by urinary cotinine.

Many people with diabetes do want to stop smoking and have tried to stop on several occasions only to relapse to the smoking habit. People with diabetes may feel restricted by treatment regimens and may also fear weight gain which may influence their motivation to stop smoking. Nevertheless, over time, some do give up smoking therefore anti smoking advice should be an integral element of risk factor reduction in people with type 1 diabetes and this should include advice on nicotine replacement and other pharmacotherapeutic aids. However a survey from the UK involving 100 people with diabetes (96% type 2) attending a routine diabetic clinic revealed poor awareness of aids to stop smoking thereby demonstrating the need for health care professionals to raise this awareness (Gill et al 2005) .

### 3.6 PHYSICAL ACTIVITY

The benefits of physical activity in the prevention and treatment of CVD in adults in the general population are well accepted (Thompson et al 2003). Regular physical activity in people with type 1 diabetes has been associated with improvements in cardiovascular risk factors and quality of life (Lehmann et al 1997, Zoppini et al 2003) and people with diabetes are encouraged to participate in regular physical activity as part of their treatment regimen. However despite this evidence and advice over 60% of people with type 1 diabetes do not regularly take part in physical activity (Thomas et al 2004, Plotnikoff et al 2006).

Whilst in type 2 diabetes physical activity has been associated with reduced morbidity and mortality and improvements in glycaemic control (Smith et al 2007, Sigal et al 2007) in type 1 diabetes the benefits on glycaemic control are not quite so clear.

Children and young people with type 1 diabetes have been shown to have reduced cardio respiratory fitness compared to healthy controls (Williams et al 2011, Komatsu et al 2005, Nadeau et al 2010). In two of these studies cardio respiratory fitness was measured by peak

oxygen consumption using a cycle ergometer or a motorized treadmill and both reported reduced aerobic capacity compared to the control group (Komatsu at al 2005, Nadeau et al 2010). In addition despite normal body weight (and no other features of the metabolic syndrome) young people with type 1 diabetes had greater insulin resistance (hyperinsulinaemic-euglycaemic clamp), reduced vascular reactivity, evidence of diastolic dysfunction and evidence of left ventricular hypertrophy (Nadeau et al 2010). Although this study involved only small numbers (12 in each group) the results are worrying as despite a short duration of diabetes, reasonable glyceamic control for an adolescent group ($HbA_{1c}$ 8.6%), normal weight, waist to hip ratio and lipid prolife, compared to a carefully matched control group (usual physical activity, BMI, pubertal stage, age and gender), adolescents with type 1 diabetes displayed risk factors which may adversely influence future cardiovascular outcomes.
A further study assessed cardio respiratory fitness in a larger group of children (aged 5-14 years) with type 1 diabetes and compared results with an age, sex and anthropometric matched group (Williams et al 2011). In this study cardio respiratory fitness was assessed using a step test (Queens College Step Test) which is a sub maximal test of aerobic capacity. In agreement with previous studies, children with diabetes were shown to have reduced fitness levels compared to matched controls. In addition this study reported that female sex and poorer glycaemic control were associated with reduced fitness. All three of these studies, despite using different methods of assessing aerobic capacity, report consistent results.

It could be speculated that the reduced aerobic fitness noted in children with type 1 diabetes, especially females, reflects a general reduction in participation in physical activity. Children with type 1 diabetes may be discouraged, by parents and teachers, from taking part in physical activity due to lack of knowledge of type 1 diabetes and fear of hypoglycaemia. In addition it is generally accepted that teenage girls are less likely to engage in physical activity than their male peers. However in these studies most participants were still at school where some physical activity is generally part of the curriculum and more importantly controls were matched for current involvement in physical activity in two of the studies. A few older studies have also demonstrated reduced aerobic capacity in adults with type 1 diabetes when compared to control populations (Wanke et al 1992, Niranjan et al 1997).

The effect of physical activity on glycaemic control in type 1 diabetes is not clear. Several mainly self reported questionnaire studies, involving children and adolescents, have assessed the relationship between glycaemic control and physical activity in type 1 diabetes with conflicting results. One recent large international study, involving 2093 young people with diabetes aged 11-18 years from 19 countries, assessed physical activity using measures developed by the Health Behaviors in School Children WHO project (Aman et al 2009). Physical activity was not associated with glycaemic control, BMI or hypoglycaemia. However poorer glycaemic control was associated with more reported time spent on a computer and less time spent doing homework. It is possible that this may reflect personality factors, for example those who are more conscientious are more likely to focus on school work and personal health issues which may contribute towards good glycaemic control. However in the absence of a relationship between physical activity and glycaemic control it is difficult to conclude that sedentary time spend on a computer replaces what would have otherwise been time spend being physically active. In addition older participants and females reported significantly less physical activity. However the questionnaire used in this study defined physically active days as those days when participants engaged in at least 1 hour of physical activity.

Another large study involving 19143 children and young people with type 1 diabetes (age 3 to 20 years) defined regular physical activity as at least 30 minutes of activity (excluding school based sport) on at least one day per week (Herbst et al 2006). Glycaemic control was reported to be better in adolescents reporting this level of activity compared to those who did not report any physical activity. In addition participants were grouped according to frequency of regular physical activity. $HbA_{1c}$ was significantly higher in those who reported less frequent regular physical activity and this was evident across all age groups and in both sexes. However a cross sectional case control study from Italy reported that adolescents who participated in moderate or vigorous physical activity for 60 minutes or more at least once a week were more likely to have a $HbA_{1c}$ less than 8.5% (Valerio et al 2007). This study also reported that children and adolescents with type 1 diabetes reported taking part in significantly less physical activity than an age and sex matched control group. This may support the view that children with diabetes are not encouraged to participate in sporting activities. Furthermore females with type 1 diabetes and their counterparts without diabetes were involved in significantly less frequent physical activity than their male peers and girls with diabetes took part in significantly

less physical activity than girls without diabetes. There was no significant difference in reported activity between boys with diabetes and male control subjects.

The studies discussed above have involved children or adolescents with type 1 diabetes and studies in adults are sparse. A cross sectional self reported questionnaire study from the Finnish Diabetic Nephropathy cohort (1030 adults with type 1 diabetes, mean age 38 years, mean duration of diabetes 22 years) reported that leisure time physical activity was associated with poor glycaemic control in women but not in men (Waden et al 2005b). In addition an earlier study assessed self reported physical activity in 221 adults with type 1 diabetes using the Baecke questionnaire which considers physical activity in 3 areas: work, leisure time and sport (Ligtenberg et al 1999). Women were reported to be involved in significantly more physical activity than men mainly due to leisure time activity. However there was no correlation between different levels of physical activity and glycaemic control although more active participants used a significantly lower daily insulin dose than those who were less active. However this may represent a planned reduction in insulin to avoid hypoglycaemia.

Self reported physical activity questionnaires do have limitations. They rely on recall which is often difficult, and even more so when the response is by proxy, for example a parent answering for a child. They also vary in cognitive demands and interpretation can often be variable especially when terms are ill defined and ambiguous, for example "moderate exercise". In addition they are open to social desirability bias especially in health care settings where respondents may want to please those who are involved in their care. Careful reliability and validity studies can help deal with some of these issues.

Interventional studies can provide more objective data but are more difficult to conduct in studies involving large patient populations. A recent small randomized controlled interventional study assessed the effect of a 20 week supervised programme of combined strength and aerobic training in 16 adolescents with type 1 diabetes on glycaemic control, quality of life and physical fitness (D'hooge et al 2011). At the end of the study period there was no improvement in glycaemic control in either group although there was a significant reduction in insulin dose in the intervention group. In addition physical fitness as assessed by a functional sit-to-stand test and a six minute walk test improved significantly in the intervention group. However there was no significant improvement in peak oxygen uptake. Failure to detect an improvement in glycaemic control in the intervention group may have been due to

the frequent episodes of hypoglycaemia reported by this group. However, there was no deterioration in glyceamic control. Overall there was no improvement in health related quality of life in either group, though there was a trend towards an improvement in perceived general health, emotional functioning and vitality in the intervention group. A previous study assessed quality of life using the Diabetes Quality of Life-Short Form, a well validated questionnaire, reported that physical activity was associated with greater psychological well-being (Aman et al 2009). Greater quality of life associated with physical activity has been reported by others (Wiesinger et al 2001).

An intensive intervention study in a controlled environment (a two week diabetes summer camp) resulted in a significant improvement in glycaemic control in 20 adolescents with type 1 diabetes ($HbA_{1c}$ 8.3% versus 7.9%) (Ruzic et al 2008). The programme involved 4 hours of supervised low intensity activity per day along with supervision of calorie intake, blood glucose monitoring and insulin dosage. However benefits were unsustainable. Two months after the camp finished $HbA_{1c}$ returned to baseline values confirming the difficulties of maintaining high levels of physical activity and glyaemic control in everyday life.

A few older studies, involving small numbers of adults with type 1 diabetes, have failed to report significant improvements in glycaemic control following exercise interventions (Lehmann et al 1997, Laaksonen et al 2000). A more recent study comparing the effects of a 12 week programme of resistance training versus aerobic training in 13 adults with type 1 diabetes reported a significant deterioration in glycaemic control in those randomized to aerobic training ($HbA_{1c}$ 8.7% versus 9.8%) (Ramalho et al 2006). The authors suggest that this deterioration in control may be related to the frequent episodes of hypoglycaemia reported by this group, again highlighting the difficulties faced by people with type 1 diabetes in trying to maintain blood glucose control during and after exercise. Improvements in glycaemic control in adults with type 1 diabetes have been demonstrated following a randomised controlled cross over study of intensive lifestyle intervention including dietary advice, exercise intervention and frequent contact with health care professionals (Perry et al 1997). However there was an improvement in glycaemic control in both groups in the run in period between recruitment and randomization. The programme involved a number of interventions therefore it is difficult to attribute the beneficial effect to any specific one.

The studies reviewed in this section are diverse and therefore can be difficult to interpret and compare. Many studies are based on self reported questionnaires which as previously discussed have limitations. The studies vary in their definition of what constitutes being physically active and interventional studies are often multifaceted, including for example education and physical activity, thereby making it difficult to separate one aspect of the intervention from another. However the literature does highlight the complexities of type 1 diabetes and the issues that need to be considered when trying to maintain a balance of good blood glucose control and managing physical activity, for example carbohydrate intake, insulin dose and regular blood glucose testing. Intensive intervention programmes such as the summer camp for children (Ruzic et al 2007) and the lifestyle intervention programme for adults (Perry et al 1997) may lead to improvements in glyceamic control in the short term but it is difficult to maintain the same degree of motivation and support from health care professional in the real world. In addition several of the studies discussed above allude to fear of hypoglycaemia as being an obstacle to regular physical activity (Ligtanberg et al 1999, Ramalho et al 2006, D'hooge et al 2011). A recent study, involving 100 people with type 1 diabetes, reported that fear of hypoglycaemia was the strongest barrier to regular physical activity followed by work commitments, concern about loss of control over diabetes and a low fitness level (Brazeau et al 2008). Further analysis revealed that greater knowledge about the pharmacokinetics of insulin and using appropriate management strategies to avoid activity related hypoglycaemia was associated with fewer barriers. It is possible that, to avoid activity induced hypoglycaema, people with type 1 diabetes over consume carbohydrate before, during and after exercise whilst simultaneously reducing insulin. There is clearly a need for structured education programmes for people with type 1 diabetes to include the management of physical activity and this need to be re-enforced on a regular basis. However whilst some studies have reported frequent hypoglycaemia related to physical activity (Barnardini et al 2004, Lehmann et al 1997), others have not (Guelfi et al 2005, Ruzic et al 2008).

Regular physical activity may be associated with reduced mortality in people with type 1 diabetes. A prospective 7 year follow up study of 548 people with type 1 diabetes from Pittsburg reported that after adjusting for age, BMI, smoking and complications, sedentary males were three times more likely to die than active males (Moy et al 1993). In addition increased physical activity has been show to have beneficial effects on traditional cardiovascular risk factors; lipid profile, systolic and diastolic blood pressure and body weight in

adolescent and adults with type 1 diabetes (Lehmann et al 1997, Laaksonen et al 2000, Idzior-Walus et al 2001, Herbst et al 2007, Aouadi et al 2011). Furthermore increased physical activity has been shown to have beneficial effects on endothelial dysfunction, an early manifestation of vascular disease in children and adolescents with type 1 diabetes (Trigona et al 2010, Seeger et al 2011). CVD is major cause of death in people with type 1 diabetes therefore physical activity should be encouraged in children, adolescents and adults with diabetes from diagnosis. This is especially important for females with diabetes, who not only lose their gender protection from CVD but also tend to be less fit and less physically active than men. Initiatives such as workplace physical activity and exercise on prescription schemes need to be more accessible. Recent data on the effects of physical activity on adults with type 1 diabetes is sparse and resources need to be directed to this area.

## 3.7 NURSE LED INTERVENTION AND DIABETES CARE

There are surprisingly few randomised controlled studies of the effects of nurse-led intervention on glycaemic control and CV risk factor reduction in people with diabetes and most have involved patients with type 2 diabetes. One older study, from Canada, involving 46 adults with insulin requiring diabetes, investigated the effects of adding regular telephone contact (to routine diabetes care) on glycaemic control (Thompson et al 1999). At the end of the 6 months study period there was a significant improvement in glycaemic control in the intervention group but not in the control group. However results cannot be generalised as the study involved only small numbers (23 subjects in each group) and was of short duration. In addition the study was resource intensive as each patient had an average of 3 calls per week, each call lasting approximately 15 minutes and this would be difficult to maintain for a total clinic caseload on a long term basis. Also each patient was provided with insulin and blood glucose monitoring equipment free of cost which may have influenced motivation to take part in the study and behaviour during the study. Automated telephone calls have been used in a study from the USA. In this study 272 people with type 1 and type 2 diabetes were randomised to receive routine care or routine care plus automated telephone disease management which included optional health promotion messages. Responses were reviewed by a diabetes nurse educator and telephone follow up was initiated according to clinical need. At the end of the 12 months period there was no significant improvement in glycaemic control in the group as a whole. However sub-group analysis revealed significant improvements in glycaemic control in

those with a baseline $HbA_{1c}$ of 8% or over (Piette et al 2001). Again this study has resource implications along with the cost of purchasing an automated telephone disease management system.

A further uncontrolled study, from the UK, involved 43 adults with diabetes (14 type 1 diabetes). All patients had an initial assessment followed by at least one follow up appointment and then clinic appointments or telephone contact according to individual need. After 6 months of individualised specialist nurse intervention 63% of patients achieved a final $HbA_{1c}$ of less than 7.0% (DCCT aligned 7.8%) or an improvement in $HbA_{1c}$ of at least 1% (Yong et al 1997). Interestingly glycaemic control improved in significantly more patients with type 2 diabetes than those with type 1 diabetes (74 versus 41%, $p < 0.03$).

A recent Cochrane report including 6 randomised controlled trials involving 1382 people with type 1 or type 2 diabetes followed up for 6-12 months concluded that intervention from diabetes specialist nurses was effective in improving glycaemic control at least in the short term (Loveman et al 2009).

More recently the focus of nurse led intervention has moved to include not only glycaemic control but also the management of hypertension and dyslipidaemia. This is largely due to evidence from studies such as the United Kingdom Prospective Diabetes study (UKPDS 1998b) demonstrating that control of blood pressure is associated with a reduction in the risk of micro and macro vascular complications in type 2 diabetes. Once again studies have involved mainly people with type 2 diabetes. A recent community based study, from Canada, randomised 227 patients with type 2 diabetes to either usual care or nurse / pharmacist intervention (McLean et al 2008). Patients in the intervention arm were reviewed on a 6 weekly basis for 6 months and each intervention involved education on the importance of blood pressure targets, a review of medication and discussion on compliance with medication. At the end of the study period systolic blood pressure decreased in both groups without a change in the use of anti hypertensive medication. However the reduction in the intervention group was significantly greater than in the control group (-10.0mmHg versus -5.0 mmHg, p=0.008. This was even more pronounced in those with a baseline systolic blood pressure above 160 mmHg. It was speculated that the improvements in systolic blood pressure observed may have been due to an improvement in adherence with medication and lifestyle factors. An uncontrolled study,

from the UK, investigated the effects of protocol driven pharmacist intervention on cardiovascular risk reduction in patients with type 2 diabetes (McGowan et al 2008). After a mean of 4 visits pharmacist led intervention led to a significant mean reduction in systolic and diastolic blood pressure of 23 mmHg and 10 mmHg respectively and this was maintained at 6 months following discharge from the clinic. This improvement in blood pressure was associated with an increase in the use of anti-hypertensive agents. The mean number of antihypertensive agents per patient increased from 2.82±1.05 at baseline to 3.67±1.12 at discharge from the clinic. There was also a significant reduction in total cholesterol attributed to an increased use of lipid lowering agents. However in this study the pharmacist discussed each case with the consultant responsible for the patients care which has time and resource implications. In addition patients did not have immediate access to changes to medication as changes were implemented following written communication with the patients general practitioner.

A few randomised controlled studies in the UK have investigated the effects of nurse led intervention on glycaemic control or cardiovascular risk factors in patients with type 2 diabetes in primary care settings and findings have been inconsistent. One study from Nottingham, involving 42 practices and 1534 patients with type 2 diabetes, reported no difference in systolic or diastolic blood pressure or the proportion of patients reaching target BP levels between patients randomised to nurse led algorithm driven care and those randomised to usual care (Bebb et al 2007). A further 2 year study, involving 1486 patients (from 21 inner city practices) with type 2 diabetes of South Asian origin, reported significant improvements in diastolic blood pressure in those patients randomised to nurse led protocol driven care (Bellary et al 2008). However there were no differences in systolic blood pressure, total cholesterol or $HbA_{1c}$ between groups. In this study the practice nurses delivering care were supported by community diabetes specialist nurses. However another randomised controlled study, involving a similar South Asian population (401 participants), reported significant improvements in systolic and diastolic blood pressure and total cholesterol but not $HbA_{1c}$, in the nurse-led, protocol driven intervention group at the end of the 12 months study period (O'Hare et al 2004). In this study the clinics were staffed by community based diabetes specialist nurse with the support of link workers.

A recent randomised controlled study from the USA investigated the effects of nurse led intervention (12 months) on blood pressure, glycaemic control and LDL cholesterol in 556

people with established diabetes (type not specified) (Ishani et al 2011). Significantly more patients achieved target blood pressure, $HbA_{1c}$, and LDL cholesterol in the nurse led intervention group than in the routine group. Nurse led intervention was driven by a treatment algorithm and included lifestyle modification, the setting of personal goals, home blood pressure and blood glucose monitoring and frequent contact. It is difficult to assess if any single one of these intervention had a greater effect than others on the achievement of cardiovascular risk targets. Again improvements were associated with greater use of anti-hypertensive, lipid lowering and diabetes medications and the use of these agents was significantly more in the patients randomised to the nurse led intervention group.

In addition some uncontrolled studies, from secondary care settings, involving mainly patients with type 2 diabetes have reported significant improvements in systolic and diastolic blood pressure, glycaemic control and lipid profile following protocol driven nurse- led intervention (Woodward et al 2006, Singh et al 2007, Mugarza et al 2008). In these studies improvements in blood pressure were associated with an increase in the use of antihypertensive agents. Interestingly all were staffed by experienced diabetes specialist nurses and reported an improvement in $HbA_{1c}$, although glycaemic control was not a specific component of the clinic protocol. A randomised controlled study of the effects of protocol driven diabetes specialist nurse-led care on hypertension and hyperlipidaemia reported that targets were achieved more frequently in the nurse led group for hyperlipidaemia but the same was not true for hypertension (New at al 2003).

There are several possible explanations for the inconsistencies reported in these studies. The study populations may differ with some studies including populations of mainly South Asian origin, where cultural needs may be different. Some of the studies have been based in primary care and others in secondary care and the clinics have been staffed by practice nurse in some studies and by diabetes specialist nurses in others. Diabetes specialist nurses may have more intensively developed skills in the management of glycaemic control and those working in secondary care may have easy access to consultant medical staff to discuss management issues. However, in the past, practice nurse have been more involved in cardiovascular risk factor management and most are supported by GPs within the surgery. In addition the protocols used in the studies may have varied according to local practice.

## 3.8 SUMMARY

Insulin replacement treatment has prolonged the life of people with type 1 diabetes. However, over time chronic complications have influenced both quality of life and life expectancy.
The DCCT, a landmark study, established the importance of good glycaemic control in preventing or delaying the onset and progression of micro vascular complications in type 1 diabetes. However, many people with type 1 diabetes continue to have chronic poor glycaemic control and there are many obstacles to improving glyceamic control. Such barriers include; difficulties with physiological insulin replacement regimens, patient motivation and personal and professional support (Zinman 1997). In addition there is some evidence for an association between lower socioeconomic status and psychological factors such as lack of motivation, emotional distress, depression and eating disorders and poor glycaemic control (DeVries et al 2004). A change of insulin regimen or type of insulin may help some individuals to achieve and maintain good glycaemic control. However type 1 diabetes is complex and psychological or behavioral interventions may be indicated. There is however need for a cohesive message and open / ongoing communication between the person with diabetes and the diabetes team.

The DCCT suggested glycaemic targets which, in routine practice, are difficult to achieve without an increase in the incidence of hypoglycaemia. Severe hypoglycaemia is in itself a risk for the individual with type 1 diabetes. It has been implicated in 'dead in bed' syndrome and recurrent severe hypoglycaemia is associated with cognitive dysfunction. For the individual with type 1 diabetes each day is a balancing act involving careful consideration of insulin dose, activity and carbohydrate intake. Current insulin regimens encourage flexible insulin dosing according to carbohydrate intake which carries the burden of frequent blood glucose monitoring and insulin to carbohydrate ratio calculations. All of this with no guarantee of good glycaemic control and the avoidance of complications. For many people with type 1 diabetes this is too much too take on and insulin injection regimens need to be tailored to meet individual need. The ultimate aim is to achieve optimal glycaemic control for a particular individual bearing in mind that any improvement in glycaemic control is worthwhile
Lifestyle interventions including encouraging a healthy diet, maintaining a healthy body weight, participation in regular physical activity and abstinence from smoking can have a beneficial effect on glycaemic control and cardiovascular risk factors and should be encouraged at every

available opportunity. In addition referral to and working in collaboration with other agencies such as community based weigh loss programmes and exercise on prescription initiatives should be an integral part of diabetes care. However lifestyle changes are often difficult to maintain.

In addition to glycaemic control other risk factors such as blood pressure and lipid profile, traditionally associated with macro vascular disease, have been associated with the progression of micro vascular complications particularly renal disease and retinopathy. In recent years, in type 1 diabetes, the focus has moved to include global risk factor management (BP, lipids, BMI, lifestyle issues) in an attempt to reduce the threat of both micro and macro vascular disease. However, in the absence of evidence from randomised controlled trials, the use of statins in type 1 diabetes, particularly in young people, remains controversial with most health care professionals taking a targeted approach. Results are awaited from the Adolescent type 1 Diabetes cardio-renal Intervention Trial (AdDIT 2009). This study involves 500 high risk (raised albumin excretion) adolescents (aged 11-16 years) with type 1 diabetes randomised to either a statin, an ACE inhibitor, both a statin and an ACE inhibitor or placebo for a period of 3-4 years. Outcome measures include albumin excretion, CV risk factors (BP, lipids, smoking status) and quality of life.

Risk factor targets for the prevention of vascular disease are available however several studies have demonstrated that, even in specialist centres, these targets are difficult to achieve. In many people with type 1 diabetes dylipidaemia and hypertension are either not treated or sub optimally managed leaving these people at increased risk of both micro and macro vascular complications.

This chapter has reviewed the risk factors associated with the development of vascular complications in type 1 diabetes. The next chapter will assess achievement of risk factor targets in a routine diabetes clinic at Aintree University Hospitals in North Liverpool.

## 3.9 REFERENCES


Adolescent type 1 Diabetes cardio-renal Intervention Trial Research Group. Adolescent type 1 Diabetes cardio-renal Intervention Trial (AdDIT). BioMed Central Pediatrics 2009, 9:79-99

Aman J, Skinner TC, de Beaufort CE, Swift PGF, Aanstoot HJ, Cameron F. Associations between physical activity,sedentary behavior, and glycemic control in a large cohort of adolescents with type 1 diabetes: the Hvidoere Study Group on Childhood Diabetes. Pediatric Diabetes 2009: 10: 234–239

Anderson J H, Brunelle RL, Koivisto VA, Pfutzner A, Trautmann ME, Vignati L, et al. Reduction of postprandial hyperglycemia and frequency of hypoglycemia in IDDM patients on insulin-analog treatment. Diabetes 1997; 46, 265-270

Aouadi R, Khalifa R, Aouidet A, Ben Mansour A, Ben Rayana M, Mdini F et al. Aerobic training programs and glycaemic control in diabetic children in relation to exercise frequency. Journal of Sports Medical and Physical Fitness 2011; 51: 393-400

Ardon M, MacFarlane IA, Robinson C. Anti-smoking asvice for young diabetic smokers: Is it a waste of breath? Diabetic Medicine 1988; 5: 667-670

Ashwell SG, Amiel SA, Bilous RW, Dashora U, Heller SR, Hepburn DA, et al. Improved glycaemic control with insulin glargine plus insulin lispro: a multicentre, randomized, cross-over trial in people with Type 1 diabetes. Diabetic Medicine 2006; 23: 285–292

Baxter MA, Wright AD. Audit of the change from twice daily to basal-bolus insulin regimens in insulin- dependent diabetes. Journal of Diabetes and its Complications 1993; 7:34-38

Bebb C, Kendrick D, Coupland C, Madeley R, Stewart J, Brown K, et al. A cluster randomised controlled trial of the effect of a treatment algorithm for hypertension in patients with type 2 diabetes. British Journal of General Practice 2007; 57: 136–143

Bellary S, O'Hare JP, Raymond NT, Gumber A, Mughal S, Szczepura A, et al. Enhanced diabetes care to patients of south Asian ethnic origin (the United Kingdom Asian Diabetes Study): a cluster randomised controlled trial. Lancet 2008; 371: 1769–76

Bernardini AL, Vanelli M, Chiari G, Iovane B, Gelmetti C, Vitale R, et al. Adherence to physical activity in young people with Type 1 diabetes. Acta BioMedica Ateneo Parmense 2004; 75: 153-157

Bishop FK, Maahs DM, Snell-Bergeon JK, Ogden LG, Kinney GL, Rewers M. Lifestyle risk factors for atherosclerosis in adults with type 1 diabetes. Diabetes & Vascular Disease Research 2009; 6: 269–275

Boehm BO, Home PD, Behrend C, Kamp NM, Lindholm A. Premixed insulin aspart 30 vs. premixed human insulin 30/70 twice daily: A randomized trial in Type 1 and Type 2 diabetic patients. Diabetic Medicine 2002; 19, 393–399

Brazeau AS, Rabasa-Lhoret R, Strychar I, Mircescu H. Barriers to physical activity among patients with type 1 diabetes. Diabetes Care 2008; 31:2108–2109

Chen JW, Lauritzen T, Bojesen A. Christiansen JS. Multiple mealtime administration of biphasic insulin aspart 30 versus traditional basal-bolus human insulin treatment in patients with type 1 diabetes. Diabetes, Obesity and Metabolism 2006; 8: 682–689

Cholesterol Treatment Trialists' (CTT) Collaborators. Efficacy of cholesterol-lowering therapy in 18, 686 people with diabetes in 14 randomised trials of statins: A meta-analysis. Lancet 2008; 371: 117–25

Colhoun HM, Betteridge DJ, Durrington PN, Hitman GA, Neil HAW, Livingstone SJ, et al. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial. Lancet 2004; 364: 685–96

Coppell KJ, Anderson K, Williams S, Manning P, Mann J. Evaluation of diabetes care in the Otago region using a diabetes register, 1998-2003. Diabetes Research and Clinical Practice 2006; 345-352

Currie CJ, Gale EAM, Poole CD. Original Article: Health Economics Estimation of primary care treatment costs and treatment efficacy for people with Type 1 and Type 2 diabetes in the United Kingdom from 1997 to 2007. Diabetic Medicine 2010; 27, 938–948

Dahl-Jorgensen K, Brinchmann-Hansen O, Hanssen KF, Ganes T, Kierulf P, Smeland E, et al. Effect of near normoglycaemia for two years on progression of early diabetic retinopathy, nephropathy, and neuropathy: the Oslo study. British Medical Journal 1986; 293: 1195-1199

Dahl-Jørgensen K, Bjøro T, Kierulf P, Sandvik L, Bangstad HJ, Hanssen KF. Long-term glycemic control and kidney function in insulin dependent diabetes mellitus. Kidney International 1992; 41: 92 0—923

Davies MJ, Heller S, Skinner TC, Campbell MJ, Carey ME, Cradock S, et al. Effectiveness of the diabetes education and self management for ongoing and newly diagnosed (DESMOND) programme for people with newly diagnosed type 2 diabetes: cluster randomised controlled trial. British Medical Journal 2008; 336: 491-495

DeVries JH, Snoek FJ, Heine RJ. Persistent poor glycaemic control in adult Type 1 diabetes. A closer look at the problem. Diabetic Medicine 2004; 21, 1263–1268

D'hooge R, Hellinckx T, Van Laethem C, De Schepper J, Van Aken S, Dewolf D, et al. Influence of combined aerobic and resistance training on metabolic control, cardiovascular fitness and quality of life in adolescents with type 1 diabetes: a randomized controlled trial. Clinical Rehabilitation 2011; 25: 349–359

Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. The New England Journal of Medicine 1993; 329: 977-986

Eeg-Olofsson K, Cederholm J,Nilsson PM, Gudbjornsdottir S, Eliasson B. Glycaemic and risk factor control in type 1 diabetes: Results from 13,612 patients in a national diabetes register. Diabetes Care 2007; 30: 496-502

European Diabetes Policy Group. A desktop guide to type 1 (insulin dependent) diabetes mellitus. Diabetic Medicine 1999; 16:253-256

Feher MD, Winocour PH. ABCD position statement on lipid modifying drug therapy in diabetes. Practical Diabetes International 2007; 24: 458-462

Feldt-Rasussen, B, Mathiesen ER, Jensen T, Lauritzen T, Deckert T. Effect of improved metabolic control on loss of kidney function in type 1 (insulin dependent) diabetic patients: An update of the Steno studies. Diabetologia 1991; 34:164-170

Gale EAM. Diabetes in the UK: time for a reality check? Diabetes Medicine 2010;27: 973-976

Garg S, Moser E, Dain M, Rodionova A. Clinical Experience with Insulin Glargine in Type 1 Diabetes. Diabetes Technology & Therapeutics 2010; 12: 835-846

Gill GV, Morgan C, MacFarlane IA. Awareness and use of smoking cessation treatments among diabetic patients. Diabetic Medicine 2005; 22: 658–660

Goldberg RB, Mellies MJ, Sacks FM, Moyé LA, Howard B, Howard JW, et al. cardiovascular events and their reduction with pravastatin in diabetic and glucose-intolerant myocardial infarction survivors with average cholesterol levels : subgroup analyses in the cholesterol and recurrent events (CARE) trial. Circulation 1998, 98:2513-2519

Guelfi KJ, Jones TW, Fournier PA. Intermittent high-intensity exercise does not increase the risk of early postexercise hypoglycaemia in individuals with type 1 diabetes. Diabetes Care 2005; 28: 416- 418

Hamilton J, Cummings E, Zdravkovic V, Finegood D, Daneman D. Metformin as an adjunct therapy in adolescents with type 1 diabetes and insulin resistance: A randomised controlled trial. Diabetes Care 2003; 26:138–143

Hardy KJ, Jones KE, Gill GV. Deterioration in blood glucose control in females with diabetes changed to a basal-bolus regimen using a pen-injector. Diabetic Medicine 1991; 8: 69-71

Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol-lowering with simvastatin in 5963 people with diabetes: A randomised placebo-controlled trial. Lancet 2003; 361: 2005-2016

Herbst A, Bachran R, Kapellen T, Holl RW. Effects of regular physical activity on control of glycemia in pediatric patients with type 1 diabetes mellitus. Archives of Pediatrics & Adolescent Medicine 2006; 160:573-577

Herbst A, Kordonouri O, Schwab KO, Schmidt F, Holl RW. Impact of physical activity on cardiovascular risk factors in children with type 1 diabetes: A multicenter study of 23,251 patients. Diabetes Care 2007; 30: 2098-2100

Hermansen K, Vaaler S, Madsbad S, Dalgaard M, Zander M, Begtrup K, et al. Postprandial glycemic control with biphasic insulin aspart in patients with type 1 diabetes. Metabolism 2002; 51: 896-900

Hofer SE, Rosenbauer J, Grulich-Henn J, Naeke A, Fröhlich-Reiterer E, Holl RW. Smoking and Metabolic Control in Adolescents with Type 1 Diabetes. Journal of Pediatric 2009; 154:20-23

Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HAW. 10-Year follow-up of intensive glucose control in type 2 diabetes. New England Journal of Medicine 2008;359:1577-1589

Houtzagers CMG, Bemtzen PA, van der Stap H, van Maarschalkerweerd WWA, Heine RJ, van der Veen EA et al. Multiple daily insulin injections improve self-confidence. Diabetic Medicine 1989; 6: 512-519

Idzior-Walus B, Mattock MB, Solnica B, Stevens L, Fuller JH and the EURODIAB IDDM Complications Study Group. Factors associated with plasma lipids and lipoproteins in Type 1diabetes mellitus: the EURODIAB IDDM Complications Study. Diabetic Medicine 2001; 18:786-796

Ishani A, Greer N, Taylor BC, ;Kubes L, Cole P, Atwood M, et al. Effect of nurse case management compared with usual care on controlling cardiovascular risk factors in patients with diabetes: A randomised controlled trial. Diabetes Care 2011; 34: 1689-1694

Ismail AA, Wallymahmed ME, Gill GV, MacFarlane IA. Failure to reduce to nicotine addiction in young adults with diabetes. Diabetic Medicine 2000; 17: 330-331

Jacobsen IB, Henriksen JE, Beck-Nielsen H. The effect of metformin in overweight patients with type 1 diabetes and poor metabolic control. Basic & Clinical Pharmacology & Toxicology 2009; 105: 145–149

Jefferson IG, Marteau TM, Smith MA, Baum JD. A multiple injection regimen using an insulin pen and pre-filled cartridged soluble human insulin in adolescent with diabetes. Diabetic Medicine 1985; 2: 493-495

Joint British Societies. JBS 2: Joint British Societies Guidelines on prevention of cardiovascular disease in clinical practice. Heart 2005; 91 suppl v: v1-52

Karamanos B, Porta M, Songini M, Metelko Z, Kerenyi Z, Tamas G, et al. Different risk factors of microangiopathy in patients with Type I diabetes mellitus of short versus long duration. The EURODIAB IDDM Complications Study. Diabetologia 2000; 43: 348-355

Khan ASA, McLoughney CR, Ahmed AB. The effect of metformin on blood glucose control in overweight patients with Type 1 diabetes. Diabetic Medicine 2006; 23: 1079–1084

Komatsu WR, Gabbay MAL, Castro ML, Saraiva GL, Chacra AR, Neto TLB, et al. Aerobic exercise capacity in normal adolescents and those with type 1 diabetes mellitus. Pediatric Diabetes 2005: 6: 145–149

KROC collaborative study Group. Blood Glucose control and the eveolution of diabetic retinopathy and albuminuria: a preliminary multicenter trial. New England Journal Medicine 1984 ;311:365-72

Laaksonen DE, Atalay M, Niskanen LK, Mustonen J, Sen CK, Lakka TA et al. Aerobic exercise and the lipid profile in type 1 diabetic men a randomised controlled trial. Medicine and Science in Sports and Exercise 2000: 1541-1548

Larkin ME, Backlund JY, Cleary P, Bayless M, Schaefer B, Canady J. Original Article: Organisation and Delivery of Care: Disparity in management of diabetes and coronary heart disease risk factors by sex in DCCT/EDIC. Diabetes Medicine 2010; 27: 451–458

Lehmann R, Kaplan V, Bingisser R, et al. Impact of physical activity on cardiovascular risk factors in IDDM. Diabetes Care 1997; 20:1603-1611

Ligtenberg PC, Blans M, Hoekstra JBL et al. No effect of long term physical activity on the glycaemic control in type 1 diabetes patients: a cross-sectional study. Netherlands Journal of Medicine 1999; 55:59-63

Loveman E, Royle P, Waugh N. Specialist nurses in diabetes mellitus (Review). Cochrane Collaboration 2009.

Lund SS, Tarnow L, Astrup AS, Hovind P, Jacobsen PK, Alibegovic AC, et al. Effect of adjunct metformin treatment in patients with type-1 diabetes and persistent inadequate glycaemic control. A randomized study. Public Library of Science ONE 2008; 3: 3363-3373

MacFarlane I, Gill GV, Grove T, Wallymahmed M. Trends in smoking habits of young adults with diabetes. Postgraduate Medicine 2001; 77: 461-463

McCaughey ES, Betts PR, Rowe DJ. Improved diabetic control in adolescents using the Penject syringe for multiple insulin injections. Diabetic Medicine 1986; 3: 234-236

McGowan N, Cockburn A, Strachan MW, Padfield PL, Mcknight JA. Initial and sustained cardiovascular risk reduction in a pharmacist-led diabetes cardiovascular risk clinic. British Journal of Diabetes & Vascular Disease 2008; 8: 34-38

McLean DL, McAlister FA, Johnson JA, King KM, Makowsky MJ, Jones CA. et al. A randomized trial of the effect of community pharmacist and nurse care on improving blood pressure management in patients with diabetes mellitus : Study of cardiovascular risk intervention by pharmacists–hypertension (SCRIP-HTN). Archive Internal Medicine 2008; 168:2355-2361

Masson EA, MacFarlane IA, Priestley CJ, Wallymahmed ME, Flavell HJ. Failure to prevent nicotine addition in young people with diabetes. Archives of Disease in Childhood 1992; 67: 100-102

Microalbuminuria Collaborative Study Group UK: Risk factors for development of microalbuminuria in insulin dependent diabetic patients: A cohort study. British Medical Journal 1993; 306:1235–1239

Moon RJ, Bascombe LA, Holt RIG. The addition of metformin in type 1 diabetes improves insulin sensitivity, diabetic control, body composition and patient wellbeing. Diabetes, Obesity and Metabolism 2007; 9: 143–145

Mortensen H, Kocovab M, Tengc LY, Keidingd J, Brucknere I, Philotheouf A. Biphasic insulin aspart vs. human insulin in adolescents with type 1 diabetes on multiple daily insulin injections. Pediatric Diabetes 2006; 7: 4–10

Moy CS, Songer TJ, LaPorte RE, Dorman JS, Kriska AM, Orchard TJ, et al. Insulin-dependent diabetes mellitus, physical activity and death. American Journal of Epidemiology 1993; 137: 74-81

Mugarza JA, Wilding JP, Woodward A, Hayden K, Gill GV. Achieving blood pressure control in patients with type 2 diabetes and diabetic renal disease by a nurse-led protocol based clinic. British Journal of Diabetes & Vascular Disease 2008; 8: 279-284

Murphy NP, Keane SM, Ong KK, Ford-Adams M, Edge JA, Acerini CL. Randomized cross-over trial of insulin glargine plus lispro or nph insulin plus regular human insulin in adolescents with type 1 diabetes on intensive insulin regimens. Diabetes Care 2003; 26:799–804

Murray DP, Keenan P, Gayer E, Saimon P, Tomkin GH, Drury MI et al. A randomised trial of the efficacy and acceptability of a pen injector. Diabetic Medicine 1988; 5: 750-754

Nadeau KJ, Regensteiner JG, Bauer TA, Brown MS, Dorosz JL, Hul A, et al. Insulin resistance in adolescents with type 1 diabetes and its relationship to cardiovascular function. Journal Clinical Endocrinology and Metabolism 2010; 95: 513–521

National Institute for Clinical Excellence. Type 1 Diabetes In Adults: National clinical guideline for diagnosis and management in primary and secondary care. NICE 2004

New JP, Mason JM, Freemantle N, Teasdale S, Wong LM, Bruce NJ, et al. Treat and control hypertension and hyperlipidemia in diabetes (SPLINT): A randomised controlled trial. Diabetes Care 2003; 26:2250–2255

Nilsson PM, Gudbjörnsdottir S, Eliasson B, Cederholm J. Smoking is associated with increased HbA1c values and microalbuminuria in patients with diabetes — data from the National Diabetes Register in Sweden. Diabetes and Metabolism 2004; 30: 261-268

Niranjan V, McBrayer DG, Ramirez LC, Raskin P, Hsia CCW. Glycemic control and cardiopulmonary function in patients with insulin-dependent diabetes mellitus. American Journal of Medicine 1997;103:504–513

O'Hare JP, Raymond NT, Mughal S,Dodd L, Hanif W, Ahmad Y, et al. Evaluation of delivery of enhanced diabetes care to patients of South Asian ethnicity: the United Kingdom Asian Diabetes Study (UKADS). Diabetic Medicine 2004; 21, 1357–1365

Perez -Mendez LF, Alvarez-Garcia E, Alvarez-Vazquez P, Hervas E, Casteras A, Fajar L, et al. Long-term improvement of metabolic control without increased risk of hypoglycaemia by intensive insulin regimen in type 1 diabetes patients treated in a regular clinical setting. Experimental and Clinical Endocrinology & Diabetes 2007; 115: 182-186

Perry TL, Mann JI, Lewis-Barned NJ, Duncan AW, Waldron MA, Thompson C. Lifestyle intervention in people with insulin-dependent diabetes mellitus (IDDM). European Journal of Clinical Nutrition 1997; 51:757-763

Persson L, Hjalmarson A. Smoking cessation in patients with diabetes mellitus: Results from a controlled study of an intervention programme in primary healthcare in Sweden. Scandinavian Journal of Primary Health Care, 2006; 24: 75-80

Piette JD, Weinberger M, Kraemer FB, Mcphee SJ. Impact of automated calls with nurse follow-up on diabetes treatment outcomes in a department of veterans affairs health care system: A randomised controlled trial. Diabetes Care 2001; 24:202–208

Pirart J. Diabetes mellitus and its degenarative complications: A prospective study of 4,400 patients observed between 1947 and 1973. Diabetes Care 1978; 1: 168-186

Plotnikoff RC, Taylor LM, Wilson PM, Courney KS, Sigal RJ, Birkett N, et al. Factors associated with physical activity in Canadian adults with diabetes. Medicine & Science in Sports & Exercise 2006; 38: 1526-1534

Pyorala K, Pedersen TR, Kjekshus J, Faergeman O, Olsson AG, Thorgeirsson G, etal. Cholesterol lowering with Simvastatin improves prognosis of diabetic patients with coronary heart disease: A subgroup analysis of the Scandinavian Simvastatin Survival Study. Diabetes Care 1997; 20:614-620

Ramalho AC, Lima MdL, Nunes F et al. The effect of resistance versus aerobic training on metabolic control in patients with type-1 diabetes mellitus. Diabetes Research and Clinical Practice 2006; 72:271-276

Reichard P, Berglunds B, Britz A, Cars I, Nilssont BY, Rosenqvists U. Intensified conventional insulin treatment retards the microvascular complications of insulin-dependent diabetes mellitus (IDDM) : the Stockholm Diabetes Intervention Study (SDIS) after 5 years. Journal of Internal Medicine 1991: 230: 101-108

Reichard, P, Nilsson B, Rosenqvist U. The effects of long term intensified insulin treatment on the development of microvascular complications of diabetes mellitus. The New England Journal of Medicine 1993; 329: 340-349

Reichard P, Pihl M, Rosenqvist U, Sule J. Complications in IDDM are caused by elevated blood glucose level: The Stockholm Diabetes Intervention Study (SDIS) at 10-year follow up. Diabetologia 1996 39: 1483–1488

Reynolds K, Liese AD, Anderson AM, Dabelea D, Standiford D, Daniels SR, et al. Prevalence of tobacco use and association between cardiometabolic risk factors and cigarette smoking in youth with type 1 or type 2 diabetes mellitus. Journal of Pediatric 2011; 158:594-601

Rossing P, Hougaard P, Parving HH. Risk factors for development of incipient and overt diabetic nephropathy in type 1 diabetic patients: Ten years prospective observational study. Diabetes Care 2002; 25:859– 864

Ruzic L, Sporis G, Matkovic BR. High volume-low intensity exercise camp and glycemic control in diabetic children. Journal of Paediatrics and Child Health 2008; 44: 122–128

Sarnblad S, Kroon M, Aman J. Metformin as additional therapy in adolescents with poorly controlled type 1 diabetes: randomised placebo-controlled trial with aspects on insulin sensitivity. European Journal of Endocrinology 2003; 149: 323–329

Schwab KO, Doerfer J, Hecker W , Grulich-henn J, Wiemann D, Kordonouri O, Beyer P, Holl RW. Spectrum and prevalence of atherogenic risk factors in 27,358 children, adolescents, and young adults with Type 1 diabetes. Cross-sectional data from the German diabetes documentation and quality management system (DPV). Diabetes Care 2006: 29:218–225

Seeger JPH, Thijssen DHJ, Noordam K, Cranen MEC, Hopman MTE, van der Sanden MWG. Exercise training improves physical fitness and vascular function in children with type 1 diabetes. Diabetes, Obesity and Metabolism 2011; 13: 382–384

Sigal RJ, Kenny GP, Boule MG, Wells GA, Prud'homme D, Fortier M. Effects of aerobic training, resistance training, or both on glycemic control in type 2 diabetes a randomized trial. Annals of Internal Medicine 2007;147:357-369

Singh PK, Beach P, Iqbal N, Buch HN, Singh BM. Nurse-led management of uncontrolled hypertension in those with diabetes and high vascular risk: The outcomes of the Wolverhampton protocol. Practical Diabetes International 2007; 24: 92–96

Sinha RN, Patrick AW, Richarson L, Wallymahmed M, MacFarlane, IA. A 6 year follow-up study of smoking habits and microvascular complications in young adults with type 1 diabetes. Postgraduate Medicine 1997; 73: 1-3

Small M, MacRury S, Boal A, Paterson KR, MacCuish AC. Comparison of conventional twice daily subcutaneous insulin administration and a multiple regimen (using the NovoPen) in insulin-dependent diabetes mellitus. Diabetes Research 1988; 8: 85-89

Smith TC, Wingard DL, Smith B, Kritz-Silverstein D, Barrett-Connor E. Walking decreased risk of cardiovascular disease mortality in older adults with diabetes. Journal of Clinical Epidemiology 2007; 60: 309-317

Syed A, Hussain S, Nightingale P, De P, Charlton MH, Gangopadhyay K, et al. Cardiovascular risk factors and their management in 1282 adult people with type 1 diabetes. Current Medical Research and Opinion. 2007; 23-2921-2927

Thomas N, Alder E, Leese GP. Barriers to physical activity in patients with diabetes. Postgraduate Medicine 2004; 80: 287-291

Thompson DM, Kozak SE, Sheps S. Insulin adjustment by a diabetes nurse educator improves glucose control in insulin-requiring diabetic patients: a randomized trial. Canadian Medical Association Journal 1999; 161: 959-962

Thompson PD, Buchner D, Piña IL, Balady GJ, Williams MA, Marcus BH, et al. Exercise and physical activity in the prevention and treatment of atherosclerotic cardiovascular disease: A statement from the council on clinical cardiology (Subcommittee on Exercise, Rehabilitation, and Prevention) and the Council on Nutrition, Physical Activity, and Metabolism (Subcommittee on Physical Activity). Circulation. 2003;107:3109-3116

Trigona B, Aggoun Y, Maggio A, Martin XE, Marchand LM, Beghetti M, et al. Preclinical noninvasive markers of atherosclerosis in children and adolescents with type 1 diabetes are influenced by physical activity. Journal of Pediatric 2010; 157:533-539

UK Prospective Diabetes Study (UKPDS) Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). Lancet 1998a; 352: 854–65

UK Prospective Diabetes Study Group. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38b. British Medical Journal 1998; 317:703–713

Vague P, Selam J, Skeie S, De Leeuw I, Elte JWF, Haahr H, et al. Insulin detemir is associated with more predictable glycemic control and reduced risk of hypoglycemia than NPH insulin in patients with type 1 diabetes on a basal-bolus regimen with premeal insulin aspart. Diabetes Care 2003; 26:590–596

Valerio G, Spagnuolo MI, Lombardi F, Spadaro R, Siano M, Franzese A. Physical activity and sports participation in children and adolescents with type 1 diabetes mellitus. Nutrition, Metabolism & Cardiovascular Diseases 2007; 17, 376-382

Vella S, Buetow L, Royle P, Livingstone S, Colhoun HM, Petrie JR. The use of metformin in type 1 diabetes: A systematic review of efficacy. Diabetologia 2010; 53:809–820

Waden RP, Kinney GL, Maahs DM, Snell-Bergeon J, Hokanson JH, Garg SK, et al. Awareness and treatment of dyslipidemia in young adults with type 1 diabetes. Diabetes Care 2005a; 28: 1051-1056

Waden J, Tikkanen H, Forsblom C et al. Leisure time physical activity is associated with poor glycaemic control in type 1 diabetic woman. Diabetes Care 2005b; 28:777-782

Wanke T, Formanek D, Auinger M, Zwick H, Irsigler K. Pulmonary gas exchange and oxygen uptake during exercise in patients with type 1 diabetes mellitus. Diabetic Medicine 1992; 9: 252-257

Wiesinger GF, Piener J, Quittan M, Fuchsiager-Mayri G, Crevenna R, Nuhr MJ. Health related quality of life in patients with long-standing insulin dependent (type 1) diabetes mellitus: benefits of regular physical training. Wiener Klinische Wochenschrift 2001; 113: 670-675

Williams BK, Guelfi KJ, Jones TW, Davis EA, et al. Lower cardiorespiratory fitness in children with Type 1 diabetes. Diabetic Medicine 2011; 28: 1005–1007

Woodward A, Wallymahmed M, Wilding J, Gill G. Successful cardiovascular risk reduction in Type 2 diabetes by nurse-led care using an open clinical algorithm. Diabetic Medicine 2006; 23, 780–787

Yong A, Power E, Gill G. Improving glycaemic control of insulin-treated diabetic patients – A structured audit of specialist nurse intervention. Journal of Clinical Nursing 2002; 11: 773–776

Zinman B. Translating the Diabetes Control and Complications Trial (DCCT) into clinical practice: overcoming the barriers. Diabetologia 1997; 40: 88–90

Zoppini, G, Carlini M, Muggeo M. Self reported exercise and quality of life in young type 1 diabetic subjects. Diabetes, Nutrition & Metabolism 2003; 16:77-80

# CHAPTER 4

# GLYCAEMIC CONTROL AND VASCULAR RISK FACTORS IN PEOPLE WITH TYPE 1 DIABETES

# CHAPTER 4

# GLYCAEMIC CONTROL AND VASCULAR RISK FACTORS IN PEOPLE WITH TYPE 1 DIABETES

This chapter includes two audit papers. The initial study is an audit of the achievement of glycaemic and cardiovascular risk factor targets in a population of 218 individuals with type 1 diabetes. The aim of this study was to assess 'the size of the problem' locally prior to a review of services. The second study is a reassessment of glycaemic and cardiovascular risk factors in the same cohort 3.5 years after the initial audit. Results of the 2 audits are compared

## 4.1 STUDY ONE: A BASELINE EVALUATION OF GLYCAEMIC CONTROL AND VASCULAR RISK IN TYPE 1 DIABETES

## 4.2 INTRODUCTION

Type 1 diabetes is a common cause of chronic disease in young people and accounts for approximately 10% of all diabetes worldwide (Zimmet et al 2001). It results from autoimmune beta cell destruction causing insulin deficiency and must be treated with insulin injections to maintain life. Life expectancy is reduced with acute metabolic complications being the single greatest cause of death in patients under the age of 30 years (Laing et al 1999a. Laing et al 1999b). Renal and cardiovascular diseases (CVD) account for the majority of deaths after the age of 30 years (Laing et al 1999b, Dorman et al 1984, Laing et al 2003). Excess mortality due to cardiovascular and cerebrovascular disease, compared to the general population, has been reported in people with type 1 diabetes of all ages (Laing et al 1996b, Orchard et al 1990). Targets for glycaemic control and the management of blood pressure, lipids, obesity and smoking have been defined for type 1 diabetes, based on current evidence, to reduce micro- and macrovascular complications (DCCT Research Group 1993, Orchard et al 1990, European Diabetes Policy Group 1999). However, good glycaemic control is often difficult to attain in a routine diabetic clinic (Saunders et al al 2004). To determine the degree to which glycaemic, lipid and blood pressure targets are currently being achieved the case records of 218 patients with type 1 diabetes attending a hospital based diabetes service were audited.

## 4.3 AIM OF THE STUDY

The aim of the study was to assess the achievement of vascular risk factor targets in people with type 1 diabetes attending a routine hospital based diabetic clinic. Targets were those defined by the European Diabetes Policy Group (1999) (table 4.1) which closely resemble the National Institute for Clinical Excellence Draft Guidelines (2004a).

**Table 4.1** European Diabetes Policy Group targets for type 1 diabetes (1999)

| | |
|---|---|
| $HbA_{1c}$ | ≤7.5% |
| BP | No microalbuminuria <135/85 mmHg<br>Microalbuminuria < 130/80 mmHg |
| Lipids | Total cholesterol <4.8 mmol/l<br>LDL cholesterol <3.0 mmol/l<br>HDL cholesterol >1.2 mmol/l<br>Triglycerides <1.7 mmol/l |

## 4.4 PATIENTS AND METHODS

North Liverpool has a population of approximately 380 000 and is served by three primary care trusts. Specialist diabetes care is provided by a multidisciplinary team based at the Diabetes Centre, Aintree Hospitals. The centre has a caseload of more than 5000 patients per annum including approximately 1000 patients with type 1 diabetes, many with multiple vascular complications. Patients with type 1 diabetes, across the catchment area, have traditionally been managed in secondary care. Type 1 diabetes was defined as any patient requiring insulin from the onset or within one year of diagnosis.

The case notes of 218 consecutive patients with type 1 diabetes who attended a consultant led routine diabetic clinic between September 2003 and February 2004 were audited. The clinic is staffed by a diabetes specialist nurse, a dietitian, a consultant and a specialist registrar (who discusses each patient with the consultant). The patients attending this particular clinic have mostly type 1 diabetes and the great majority are young or middle aged. Patients are seen at least annually but more frequently for specific issues, e.g. diabetes control problems and

vascular complications. Multiple daily injections are encouraged and non-attenders are sent further appointments or are contacted by telephone to encourage clinic attendance.

The following information from that visit was recorded: age, sex, duration of diabetes, insulin regimen and dose, weight, blood pressure, $HbA_{1c}$, lipid profile, and albumin: creatinine ratio (ACR). The presence of micro- and macrovascular complications, other endocrine conditions and additional medication (particularly antihypertensive and lipid lowering agents) were also noted. The method of $HbA_{1c}$ assay during the study period was high pressure liquid chromatography (HPLC), and was aligned to the Diabetes Control and Complications Trial (DCCT 1993). The $HbA_{1c}$ result was available to the doctor at the clinic visit but the lipid and ACR results were not.

## 4.5 STATISTICS

Unpaired t-tests were used to compare $HbA_{1c}$ results between patients on twice daily insulin and those on multiple injection regimens. Pearson's correlation was used to examine the relationship between $HbA_{1c}$ and total cholesterol. P values $<0.05$ were considered significant. Results are expressed as mean ± standard deviation and range or actual numbers and percentage as appropriate.

## 4.6 RESULTS

Of the 218 patients studied, 109 (50%) were male, mean age was 34 years (range 16–72 years), and mean duration of diabetes was 14 years (range 0.5–40 years). Thirty-seven patients (17%) had documented background retinopathy and 51 patients (23%) had retinopathy requiring laser treatment. Thirty four patients (16%) had microalbuminuria (defined as a raised ACR in two out of the last three specimens recorded, male >2.5mg/mmol, female >3.5mg/mmol), 16 (7%) proteinuria (defined as ACR >300mg/mmol and albumin dipstick positive, in the absence of urinary tract infection), one patient was receiving renal dialysis and one patient had had a kidney transplant. Thirty-eight (17%) patients had documented symptomatic neuropathy (two gastroparesis) (table 4.2).

**Table 4.2** Characteristics of 218 patients with type 1 diabetes

| Characteristics of 218 patients with type 1 diabetes. | | |
|---|---|---|
| Sex (M:F) | 109:109 | |
| Age (years) | 34±11.9 | (16–72) |
| Duration of diabetes (years) | 14±9.0 | (0.5–40) |
| Retinopathy | 88 | (40%) |
| Microalbuminuria | 34 | (16%) |
| Proteinuria | 18 | (8.2%) |
| Symptomatic neuropathy | 38 | (17%) |
| $HbA_{1c}$ (%) | 9.7±1.9 | (6.5–16.6) |
| Total cholesterol (mmol/L) | 5.1±1.1 | (2.7–10.4) |
| LDL cholesterol (mmol/L) | 2.9±0.9 | (0.9–6.0) |
| HDL cholesterol (mmol/L) | 1.5±0.4 | (0.8–3.3) |
| Triglycerides (mmol/L) | 1.6±2.2 | (0.4–28) |
| SBP (mmHg) | 113±18.5 | (40–169) |
| DBP (mmHg) | 64±10.0 | (30–101) |
| BMI | 26.2±4.5 | (14.8–42) |

Results are expressed as mean ± SD (range) or actual number (percentage) as appropriate

### 4.6.1 Glycaemic control

All except three patients had an $HbA_{1c}$ recorded at the visit audited, mean $HbA_{1c}$ was 9.7% (range 6.5–16.6%), only 17 (8%) patients had an $HbA_{1c}$ at or below target (7.5%) and 126 (59%) patients had an $HbA_{1c}$ greater than 9% ( table 4.3). The mean daily dose of insulin was 61units (range 16–130units). There was no significant difference in $HbA_{1c}$ in those patients using twice daily insulin injections (n=89) and those on multiple insulin injections (n=126), (9.8% *vs* 9.6%).

### 4.6.2 Lipid control

In all, 205 (94%) patients had a lipid profile (non-fasting) recorded at that visit. Forty-one (19%) patients were taking lipid lowering treatment (35 patients a statin, five patients a fibrate and one patient both). Of the 205 patients, 112 (55%) had a total cholesterol above target (>4.8mmol/L) of which 83 patients were not taking lipid lowering medication. Low density lipoprotein (LDL) cholesterol was available in 150 patients, mean 2.9mmol/L (range 0.9–6.0mmol/L) and 63 (42%) were above target (>3.0mmol/L). High density lipoprotein (HDL) cholesterol was available in 201 patients, mean 1.5mmol/L (range 0.8–3.3mmol/L) and 55 (27%) were below target (<1.2mmol/L). Triglycerides were available in 199 patients, mean 1.6mmol/L (range 0.4–28mmol/L), and 43 (22%) were above target (>1.7mmol/L) (see table 4.3) Lipid lowering medication was recommended by letter to the patient's general practitioner in eight cases following the clinic visit. There was a positive correlation between total cholesterol and $HbA_{1c}$ ($r=0.24$, $p<0.01$).

### 4.6.3 Blood pressure

In total, 213 (98%) patients had blood pressure recorded at that visit. Mean systolic blood pressure (SBP) was 113mmHg (range 40–169) and mean diastolic blood pressure (DBP) was 64mmHg (range 30–101) (table 4.2.) Fifty-two (24%) patients were taking antihypertensive therapy. Twenty-eight (13%) patients had an SBP higher than target (>135mmHg) and 13 of these were not taking any antihypertensive medication. DBP was raised above target (>85mmHg) in eight patients (4%) and two of these were not on any antihypertensive medication (table 4.2). In seven patients both SBP and DBP were higher than target and two of these patients were not taking any antihypertensive medication. Anithypertensive agents (angiotensin-converting enzyme [ACE] inhibitors) were recommended by letter to the patient's general practitioner in three cases.

### 4.6.4 Microalbuminuria

Urine ACR was available in 213 (98%) patients. Thirty-four patients (16%) had raised ACRs (male >2.5mg/mmol, female >3.5mg/mmol in two out of the last three specimens), of which 21 patients were taking ACE inhibitors. Of the 34 patients with raised ACRs, nine (26%) patients had an SBP greater than 130mmHg and two (6%) patients had a DBP greater than 80mmHg (table 4.3). In addition, five patients had an ACR which was raised for the first time, four patients had non diabetic related renal disease, 16 patients had proteinuria (ACR >300mg/mmoL and dipstick proteinuria), and one patient had a renal transplant. ACE inhibitors were recommended by letter to the patient's general practitioner in two cases, after the visit, to treat the microalbuminuria.

### 4.6.5 Other data

Weight and BMI were documented in 210 (96%) patients. Mean weight was 76kg (range 36–113kg) and mean BMI was 26.2 (range 14.8–42). Self reported smoking status was recorded in only 90 (41%) patients of whom 58 had never smoked, 22 were current smokers and 10 were ex-smokers.

**Table 4.3** Results of an audit of risk factor targets in type 1 diabetes

| Variable | | Number of patients (%) |
|---|---|---|
| $HbA_{1c}$ (n=215) | | |
| | ≤7.5% | 17 (7.9) |
| | 7.6-8.0% | 23 (10.7) |
| | 8.1%-9.0% | 49 (22.8) |
| | >9.1% | 126 (58.6) |
| **Lipids** | | |
| Total cholesterol (n=205) | >4.8 mmol/l | 112 (54.6) |
| HDL cholesterol (n=201) | <1.2 mmol/l | 55 (27.4) |
| LDL cholesterol (n=150) | >3.0 mmol/l | 63 (42) |
| Triglycerides (n=199) | >1.7 mmol/l | 43 (21.6) |
| **Blood pressure** – all patients (n=213) | | |
| SBP | >135mmHg | 28 (13.1) |
| DBP | >85mmHg | 8 (3.8) |
| **Blood pressure** – all patients with microalbuminuria (n=34) | | |
| SBP | >130mmHg | 9 (26.5) |
| DBP | >80mmHg | 2 (5.9) |

Results are expressed as number of patients (percentage)

## 4.7 DISCUSSION

This study demonstrates that vascular risk factor targets are frequently not being achieved in a large number of patients with type 1 diabetes. It is disappointing, in a clinic staffed by a multidisciplinary team dedicated to the management of type 1 diabetes, that the majority of patients had an $HbA_{1c}$ greater than 9%. The mean $HbA_{1c}$ of the whole group was 9.7% which is not dissimilar to the conventional treatment arm of the Diabetes Control and Complications Trial (9.1%) (DCCT Research Group 1993). Patients, particularly those with a high $HbA_{1c}$, are offered a choice of insulin regimens in the clinic and the majority of patients (60%) had opted for multiple four times daily injections. However, there was no difference in glycaemic control between those patients taking twice daily insulin and those taking multiple injection regimens. This indicates that multiple injections alone often do not result in tight glycaemic control. Other treatment strategies such as continuous subcutaneous insulin infusion and intensive education programmes such as Dose Adjustment for Normal Eating (DAFNE) may lead to improvements in glycaemic control in some patients (Pickup at al 2002, DAFNE Study Group 2002). However, for the majority of patients with type 1 diabetes (and health care professionals) improving glycaemic control remains a challenge. It is encouraging that almost all of the patients had a lipid profile recorded but disappointing that many were not acted upon. One reason may be that lipid results were not available at the clinic visit. Comments on abnormal lipid profiles were made in several of the clinic letters to the patient's general practitioner. Five patients were referred to the dietitian for lipid lowering advice and a recommendation to start lipid lowering medication was made in eight cases. However, in the majority of the patients an adverse lipid profile was associated with high $HbA_{1c}$ levels and appropriate referrals were subsequently made to the specialist nurses to attempt to improve glycaemic control (27 patients). A relationship between poor glycaemic control and adverse lipid profile has been reported, with improvements in lipid profile following optimization of glycaemic control (Perez et al 1997, Perez et al 2000). Insulin dose was altered in 22 patients and insulin regimens changed in 25 patients. Lipid lowering medication had been recommended in five patients at previous visits who subsequently decided against pharmacological intervention (lipid profiles remained adverse in all five patients). Three of these patients were young women who were considering a pregnancy in the near future. The use of lipid lowering agents in women of childbearing age should be considered carefully and

should be accompanied by appropriate counseling on the avoidance of pregnancy.

Microalbuminuria is a risk factor for the development of proteinuria with approximately 20–24% of patients progressing to overt nephropathy over a five- to nine-year period (Tabaei et al 2001, Almdal et al 1994). ACE inhibitors have been shown to be renoprotective in type 1 diabetes delaying the progress from microalbuminuria to proteinuria in many patients (EUCLID Study Group 1997, Lovell 2004). In this audit, 34 (16%) patients had microalbuminuria of which 13 (38%) were not taking an ACE inhibitor. Again in several cases this was highlighted in clinic letters to general practitioners and there was reference to 'try to improve diabetic control and discuss with the patient next time'.

Hypertension is a risk factor for the development of CVD and is also associated with progressive renal damage. Thirty-six (17%) patients had either an SBP or a DBP above target and 15 of these (42%) were not taking any antihypertensive medication. It should be noted that this was a single attendance audit and that blood pressure was raised for the first time in several of these patients. Some were asked to consult their general practitioner for further blood pressure measurements before a diagnosis of hypertension was made.

Disappointingly, smoking status was recorded in only 90 (41%) of the patients. Of these patients only 22 (24%) were current smokers. These data were self-reported and must therefore be interpreted with care.

It is encouraging that the great majority of patients (94–98%) had $HbA_{1c}$, lipid profile, ACR and blood pressure recorded at the clinic visit, although it is of concern that abnormal results were not appropriately acted on in some cases. However, in many, these 'off target' results were noted for the first time. The time taken (several days) for lipid and ACR results to come back may be one reason why results are not acted upon. If results were available at the clinic visit then treatment plans could be discussed with the patient and medication started accordingly. In a further audit of these patients (computerized laboratory records), we looked at serial microalbuminuria levels over the last three attendances and found that persistent abnormal results had not been acted on in 13 patients.

It should be acknowledged that this audit only included those patients who attended for routine follow-up clinic and it may be that those patients who fail to attend for follow-up appointments have worse glycaemic and lipid profiles.

The risk of death due to macrovascular complications in type 2 diabetes has long been recognised and, following publication of the United Kingdom Prospective Diabetes Study

(UKPDS Group 1998a, UKPDS Group 1998b), greater efforts have been made to reduce the risk mainly through achievement of blood pressure targets. Much of this intervention has been through nurse led clinics (New et al 2003, Denver et al 2003). Attention should also be given to patients with type 1 diabetes. Many of the risk factors for the development of micro- and macrovascular complications in type 1 diabetes are modifiable with lifestyle and pharmacological interventions. To reduce these complications patients at risk must be identified, particularly those with dyslipidaemia. As a result of this audit a treat to target nurse led risk factor reduction clinic is has been implemented. It is likely that significant improvements in lipid profiles can be made by increased use of lipid lowering drugs.

## 4.8 STUDY TWO: GLYCAEMIC CONTROL AND VASCULAR RISK FACTORS OVER TIME IN TYPE 1 DIABETES

## 4.9 INTRODUCTION

Type 1 diabetes is a common cause of chronic disease in young people and has serious long term micro and macro vascular complications. Life expectancy is reduced with CVD and renal disease being the main causes of mortality. (Laing et al 1999b, Pambianco et al 2006, Soedamah-Muthu et al 2006). The Diabetes Control and Complications Trial firmly established that good glycaemic control can reduce the risk of micro vascular complications (DCCT Research Group 1993). In addition the observational follow up study, the Epidemiology of Diabetes Interventions and Complications Study, demonstrated that a period of good glycaemic control had long term benefits on the risk of cardiovascular events (DCCT/EDIC Research Group 2005). In recent years targets for glycaemic control, blood pressure and lipid profile in patients with type 1 diabetes have been defined (European Diabetes Policy Group 1999, National Institute for Clinical Excellence 2004b, Joint British Societies 2005). However, in routine diabetes follow up clinics, these targets can be difficult to achieve and there is little recent data on achievement of targets.

In a previous study of this clinic population in 2003-2004 a large number of patients with type 1 diabetes failed to meet the European Diabetes Policy Group (EDPG) targets despite being managed in a clinic staffed by a multidisciplinary team experienced in the management of type 1 diabetes (Wallymahmed et al 2005). Since the initial study attempts have been made to improve glycaemic control ($HbA_{1c}$), blood pressure (BP) levels and lipid profiles in these patients. In this current study, a mean of 3.5 years later, the degree to which the latest cardiovascular risk targets are currently being met is determined (National Institute for Clinical Excellence 2004b, Joint British Societies 2005). Data from this current study (2006 – 2007) is compared with that of the original study.

## 4.10 AIMS OF THE STUDY

The aims of the study were to assess the achievement of current cardiovascular risk factor targets in a cohort of patients with type 1 diabetes attending the Diabetes Centre at Aintree University Hospitals, Liverpool. $HbA_{1c}$, BP and lipid profiles during a 12 months period (summer

2006 – summer 2007) were compared with data from a previous study in 2003-2004, a mean of 3.5 years earlier.

At the time of the initial study the National Institute for Clinical Excellence (NICE 2004b) and the Joint British Societies (Joint British Societies 2005) guidelines had not been published. Targets were those defined by the EDPG 1998 : $HbA_{1c}$ < 7.5%, total cholesterol < 4.8 mmol/L, LDL < 3.0 mmol/L, HDL >1.2 mmol/L, Triglycerides <1.7 mmol/L. Blood pressure targets were <135/85 for patients with normal albumin excretion and < 130/80 for those with abnormal albumin excretion.

In this follow up study the following current targets were used: $HbA_{1c}$ < 7.5 % (7), BP< 130/80, total cholesterol < 4 mmol/l and LDL < 2.0 mmol/l (8) (table 4.4).

**Table 4.4** Targets for risk factor reduction in type 1 diabetes

| | |
|---|---|
| Glycaemic Control ($HbA_{1c}$)* | < 7.5% |
| Blood Pressure** | <130/80 |
| Total Cholesterol ** | <4.0 mmol/l |
| LDL** | < 2.0 mmol/l |

* NICE (2004b), ** JBS (2005)

## 4.11 PATIENTS AND METHODS

The Diabetes Centre at Aintree University Hospitals serves 3 primary care trusts with a total population of about 380, 000. In recent years there has been a trend towards more diabetes care in the community with interested GP's and practice nursing managing patients with stable type 2 diabetes. However patients with type 1 diabetes continue to receive most of their diabetes management in secondary care. The frequency of attendance at the Diabetes Centre varies depending on management problems identified and patient preference. The majority of patients attend at least twice a year.

The clinic is staffed by a consultant physician, a specialist medical registrar, a diabetes specialist nurse, a nurse consultant and a dietitian. Diabetes care includes encouraging multiple daily

insulin injections, regular home blood glucose monitoring, regular exercise, healthy eating and encouragement to achieve ideal body weight (BMI < 25). In recent years metformin tablets have been recommended to overweight patients with poor glycaemic control. All staff, except the dietitian, have been unchanged since the last study.

The diabetes clinic records of the 218 patients with type 1 diabetes reported in the original 2003 / 2004 study were examined. Data were available from 184 of these patients who attended the Diabetes Centre during the 12 months period in 2006 / 2007. The following information was recorded from the clinic visit: age, sex, duration of diabetes, insulin dose and regimen, weight, BMI, blood pressure, glycated haemoglobin ($HbA_{1c}$), non fasting lipid profile and early morning urine albumin: creatinine ratio (ACR). In addition the presence of micro and macro vascular complications was also recorded. Microalbuminuria was defined as an ACR >2.5mg / mmol in men and > 3.5 mg / mmol in woman in two out of the last three specimens. Macro proteinuria was defined as an ACR > 300mg / mmol and dipstick proteinuria.

## 4.12 STATISTICS

Paired t-tests and McNemar Test were used, as appropriate, to compare the data from the first study with the current study. Pearson's correlation was used to examine the relationship between $HbA_{1c}$ and cholesterol. Unpaired t-tests were used to compare $HbA_{1c}$ levels between patients on twice daily insulin and those on multiple insulin injection regimens. P values < 0.05 were considered significant.

## 4.13 RESULTS

The mean follow up time between the 2 studies was 3.5 years. Of the 218 patients from the original study repeat data was available on 184 (84.4%) patients. Four patients were known to have moved away from the area, 2 patients had been discharged from the Diabetes Centre and 28 patients had failed to attend despite appointments being sent. No patient was known to have died during the follow up period.

The characteristics of the 184 patients who had data available from both studies are shown in table 4.5. Ninety one (49.5%) were male. In 2006 – 2007 mean age was 37.3 years (range 20 -

76 years), and mean duration of diabetes 18.4 years (range 4 – 42 years). There was a small but significant increase in BMI from 26.1 ± 4.4 to 26.5 ± 4.6 ($p< 0.05$) between the 2 study periods.

### 4.13.1 Microvascular complications

In the second study 113 (61.4%) patients had documented retinopathy, (63 background and 50 retinopathy requiring laser therapy), compared to 75 (40.8%), (33 background and 42 requiring laser), in the first study ($p< 0.01$) ( table 4.5). In addition there were significantly more patients with documented micro and macro albuminuria in the second study than in the first study (53 (28.8%) v 41 (22.3%), $p <0.01$). In the first study 26 (14.1%) patients had microalbuminuria, 14 (7.6%) had macro proteinuria and 1 patient was receiving renal dialysis. Of these patients 29 (70.7%) were taking an ACE inhibitor. In the second study 38 (20.7%) patients had microalbuminuria, 12 (6.5%) had macro proteinuria and 3 (1.6%) patients were receiving renal dialysis. Of these patients 39 (73.6%) were currently taking an ACE inhibitor. One patient, who was involved in both studies, had previously had a renal transplant. There were more patients with documented symptomatic neuropathy in the second study than in the first (41 (22.3%) v 31 (16.8%), $p <0.05$).

### 4.13.2 Macrovascular complications

During the follow up period an additional 5 patients were diagnosed as having ischaemic heart disease (4 angina and 1 myocardial infarction), 1 patient developed symptomatic peripheral vascular disease and 1 patient had a cerebrovascular event. These patients were aged between 40 and 54 years (table 4.5).

**Table 4.5** Characteristics of 184 patients with type 1 diabetes studied

| Variable | 1st Study (2003 – 2004) n=184 | 2nd Study (2006-2007) n=184 | p |
|---|---|---|---|
| Sex (M:F) | 91:93 | 91:93 | |
| Age (years) | 33.8 ± 11.8 | 37.3 ± 11.8 | p<0.01 |
| Duration of Diabetes (years) | 14.9 ±8.7 | 18.4 ± 8.6 | p<0.01 |
| Retinopathy | 75 (40.8%) | 113 (61.4%) | p<0.01 |
| Nephropathy :<br>Microalbuminuria<br>Macro proteinuria | 41 (22.3%)<br>26 (14.1%)<br>15 (8.2%) | 53 (28.8%)<br>38 (20.7%)<br>15 (8.2%) | p<0.01 |
| Symptomatic Neuropathy | 31 (16.8%) | 41 (22.3%) | p<0.05 |
| Symptomatic Ischaemic Heart Disease | 7 (3.8%) | 12 (6.5) | ns |
| Peripheral Vascular Disease | 2 (1.1%) | 3 (1.6%) | ns |
| Cerebrovascular Vascular Disease | 5 (2.7%) | 6 (3.3%) | ns |

Results are expressed as mean ± SD or actual number (percentage) as appropriate

### 4.13.3 Glycaemic control

Glycaemic control ($HbA_{1c}$) improved significantly between the 2 study periods (9.6 ± 1.9 % v 9.1 ± 1.7%, p< 0.01) (table 4.6) . In addition more patients (31 (16.8%)v 16 (8.7%), p<0.01) achieved an $HbA_{1c}$ <7.5%. Eighty one (44%) patients had an $HbA_{1c}$ of greater than 9% in this current study compared with 103 (56%) in the previous study (p<0.01). More patients were now using multiple injection regimens than in the first study (125 v 108). However, similar to the first study there was no significant difference in glycaemic control between patients taking twice daily insulin and those on multiple daily injections ( 9.2% ± 1.7 v 9.0% ± 1.8).

### 4.13.4 Metformin

There were significantly more patients taking metformin tablets in the second study than in the first (41 (22.3%) v 3 (1.6%) patients, p<0.01). In the second study $HbA_{1c}$, (9.6 ± 1.6 % v 9.0 ± 1.7 %, p < 0.05), SBP (121 ± 17 mmHg v 111 ± 18 mmHg, p < 0.01), DBP (67 ± 10 mmHg v 64 ±10 mmHg, p < 0.05) and BMI (29 ± 4.2 v 25 ±4.0, p < 0.01) were significantly higher in the patients taking metformin than those who were not.

Of the 3 patients who were taking metformin tablets in the first study only 1 patient was still taking metformin at the time of the second study. In the 40 patients who had started on metformin since the first study there was a small increase in BMI (29.1 ± 4.1 v 29.8 ± 4.3, p =0.05) and a slight improvement in $HbA_{1c}$, however this was not statistically significant. We do not have any data on the duration of metformin therapy.

### 4.13.5 Serum Lipid Profile

There were significant improvements in both total cholesterol and low density lipoprotein (LDL) cholesterol between the first and second studies (5.0 ±1.0 mmol/L v 4.4 ± 1.1 mmol/L p <0.01, 2.8 ± 0.8 mmol/l v 2.3 ± 0.8mmol/l, p<0.01). However HDL fell significantly from 1.5 ± 0.4 mmol/l to 1.4 ± 0.4 mmol/l, p <0.05 between the two audit periods. There was no significant change in triglyceride (table 4.6).

In the first study 31 (16.8%) patients were taking lipid lowering agents (26 statins, 4 fibrates, 1 patient both). This increased significantly to 108 (58.7%) (102 statins, 2 fibrates, 1 both, 4 ezetimibe) in the current study. Despite this increase in the use of lipid lowering medication, 112 (60.9%) still had a total cholesterol above target (4 mmol/l) and 93 (50.5%) patients had an LDL cholesterol above target (2 mmol/l). However lipid lowering medication was started or a recommendation was made to increase the dose in 51 (27.7%) patients following the clinic visit during the second study. There was a positive correlation between glyceamic control and total cholesterol (r=0.04, p<0.01).

### 4.13.6 Blood pressure

Both systolic (113 ± 19 mmHg v 122 ± 17 mmHg, p <0.01) and diastolic blood pressure (65 ± 10 mmHg v 67 ± 9 mmHg, p< <0.01) increased significantly between the 2 study periods. In the first study 38 (20.7%) patients said they were taking at least one anti-hypertensive agent and this increased to 63 (34.2%) patients in the second study (p<0.01) (table 4.6). Fifty three

(28.8%) patients had a systolic and 15 (8.2%) patients had a diastolic blood pressure above target compared to 33 (17.9%) and 11 (6.0%) respectively in the first study. A recommendation to start or increase the dose of anti-hypertensive medication was made in 24 (13%) at or following the clinic visit in the second study.

**Table 4.6** Changes in vascular risk factor targets in 184 patients with Type 1 diabetes over a 3.5 year time period.

| Variable | 1st Study (2003 – 2004) n=184 | 2nd Study (2006-2007) n=184 | P |
|---|---|---|---|
| $HbA_{1c}$ (%) | 9.6 ± 1.9 | 9.1 ± 1.7 | p< 0.01 |
| Total cholesterol (mmol/l) | 5.0 ± 1.0 | 4.4 ± 1.1 | p< 0.01 |
| LDL cholesterol (mmol/l) | 2.8 ± 0.8 | 2.3 ± 0.8 | p< 0.01 |
| HDL cholesterol (mmol/l) | 1.5 ± 0.4 | 1.4 ± 0.4 | P<0.05 |
| Triglycerides (mmol/l) | 1.4 ± 1.2 | 1.3 ± 1.5 | ns |
| SBP (mmHg) | 113 ± 19 | 122 ± 17 | p< 0.01 |
| DBP (mmHg) | 65 ± 10 | 67 ± 9 | p< 0.01 |
| BMI | 26.1 ± 4.4 | 26.5 ± 4.6 | p<0.05 |
| Number of patients taking lipid lowering agents | 31 (16.8%) | 108 (58.7%) | p<0.01 |
| Number of patients taking anti-hypertensives | 38 (20.7%) | 63 (34.2%) | p<0.01 |
| Number of patients taking antiplatelet therapy | 16 (8.7%) | 47 (25.5%) | |
| Number of patients taking metformin | 3 (1.6%) | 41 (22.3%) | p<0.01 |

Results are expressed as mean ± SD (range) or actual number (percentage) as appropriate

## 4.14 DISCUSSION

This follow up study (mean 3.5 years) is of value as it examines the effects of routine diabetes care and involves a large number of patients with type 1 diabetes. It has demonstrated improvements in glycaemic control and lipid profile in a cohort of young adult / middle aged patients with type 1 diabetes of long duration (mean 18.4 years). As expected the prevalence and progression of micro vascular complications (retinopathy, microalbuminuria and symptomatic neuropathy) increased during the study period. However relatively few patients developed symptomatic macrovascular disease and all of these were over 40 years of age.

Although there was an overall improvement in glycaemic control only 17% of patients achieved an $HbA_{1c}$ at or below target and 44% had an $HbA_{1c}$ over 9%. This is despite being managed by a team experienced in the management of type 1 diabetes. A recent cross sectional study from Sweden, involving over 9000 patients with type 1 diabetes, reported an improvement in glycaemic control over a seven year period. In common with this study the authors report that only a small number of patients (21%) achieved target $HbA_{1c}$ levels (Eeg-Olofsson et al 2007). Other studies, involving patients with type 1 and type 2 diabetes, report 37- 49% of patients reaching target $HbA_{1c}$ levels (Jacobs et al 1997, Resnick et al 2006).

In this current study (2006-2007) more patients were taking multiple daily insulin injections than in the previous study (2003-2004). However there was no significant difference in glycaemic control between patients taking twice daily insulin and those on multiple daily injections. Similar findings have been reported previously (Jacobs et al 1997) and this may be due to bias, because patients with chronic poor control are often encouraged to have multiple daily injections. Also some patients with reasonable glycaemic control do not wish to change from twice daily to multiple injections.

There has been a considerable increase in the number of patients (1.6% v 22.3%) taking metformin tablets between the 2 study periods. Patients with a high BMI and poor glycaemic control were targeted for metformin therapy. However despite lifestyle and dietetic advice and an increase in the use of metformin tablets there was a small but significant increase in BMI between the 2 study periods. This is likely to be a population trend and an increase in weight and BMI have been reported in previous longitudinal studies (Coppell et al 2006, Eeg-Olofsson et al 2007). This follow up study demonstrates that improving glycaemic control remains a

challenge for the majority of patients with type 1 diabetes and additional treatment strategies need to be considered. In response to this finding a multidisciplinary 'in house' intensive education programme (4 steps programme) for patients with type 1 diabetes has been introduced. This programme consists of weekly group education sessions over a four week period and concentrates on calculating insulin dose according to carbohydrate intake. There is also a plan to introduce an insulin pump service over the next 12 months. These initiatives will be reviewed in the future.

It is encouraging that total cholesterol and LDL cholesterol improved significantly between the 2 studies but disappointing that despite a tripling in the use of lipid lowering agents, lipid profile remains off target in the majority of patients. There may be several explanations for this. The JBS2 targets (total cholesterol < 4 mmol/l, LDL < 2 mmol/l) are still not widely accepted within the local primary care trusts who are encouraging targets of <5 mmol/l for total cholesterol and <3 mmol/l for LDL cholesterol. This may affect the prescribing of lipid lowering agents for patients with lipid profiles between the 2 targets. Poor compliance may also be an issue. Anecdotally, an increase in the number of patients complaining of feeling generally unwell whilst taking statins has been noted. In the future there may be greater use of alternative lipid lowering agents such as ezetimibe. It is encouraging that adverse lipid profiles prompted action in 51 patients in whom a recommendation was made to start or increase the dose of lipid lowering medication at their last clinic visit in 2006/2007. Unfortunately there was a small but significant decrease in HDL cholesterol between the study periods and it is possible that this is due to the increased use of stains. However mean HDL cholesterol was reasonably high in both studies.

It is of concern that both systolic and diastolic blood pressure increased significantly between the 2 study periods especially as the number of patients who reported taking anti-hypertensive medication had increased during this time. This is in contrast to an earlier study that reported a marginal increase in systolic BP but a significant decrease in diastolic BP in a cohort of over 4000 patients with type 1 diabetes over a seven year period (Eeg-Olofsson et al 2007). Poor compliance with medication may account for the increase in BP seen in our patients as may increasing age and BMI. Blood pressure targets are difficult to achieve in patients with type 1 and type 2 diabetes (Joseph et al 2003, Zgibor et al 2005). Two recent studies from Sweden and USA, using the same BP target as this study, report achievement of BP targets in 61% and 40%

of patients respectively (Resnick et al 2006, Eeg-Olosson et al 2007). It is encouraging that blood pressure readings outside of target levels prompted action (starting or altering anti hypertensive therapy) in 24 patients at their last 2006/7 attendance. It is possible that in a few patients blood pressure was raised for the first time or that 'white coat' hypertension has previously been identified. It would then be good practice to repeat the readings on several occasions before starting anti hypertensive therapy.

It should be acknowledged that this follow up study included only the 184 patients who attended for routine follow up at the Diabetes Centre. It may be that those who failed to attend over the 3.5 years period have worse glycaemic control, lipid and BP profiles.

## 4.15 CONCLUSION

This study has demonstrated that in a routine clinic setting attention to cardiovascular risk factor targets can result in improvements in glycaemic control and lipid profile. However blood pressure control remains a challenge. Compliance with and appropriate increases in anti hypertensive medication needs to be emphasised to patients. Overall a large proportion of patients with type 1 diabetes continue to have glycaemic and cardiovascular risk factors above target and additional strategies need to be considered.

## 4.16 REFERENCES


Almdal T, Norgaard K, Feldt-Rasmussen B, et al. The predictive value of microalbuminuria in IDDM. A five year follow up study. Diabetes Care 1994; 17: 120–125

Coppell KJ, Anderson K, Williams S, Manning P, Mann J. Evaluation of diabetes care in the Otago region using a diabetes register, 1998-2003. Diabetes Research and Clinical Practice 2006; 71: 345-352

DAFNE Study Group. Training in flexible, intensive insulin management to enable dietary freedom in people with type 1 diabetes: dose adjustment for normal eating (DAFNE) randomised controlled trial. British Medical Journal 2002; 325: 746–749

Denver EA, Woolfson RG, Barnard M, et al. Management of uncontrolled hypertension in a nurse-led clinic compared with conventional care for patients with type 2 diabetes. Diabetes Care 2003; 26: 2256–2260

Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long term complications in insulin dependent diabetes mellitus. New England Journal of Medicine 1993;329: 977–986

Diabetes Control and Complications Trial / Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Study Research Group. Intensive diabetes treatment and cardiovascular disease in patients with Type 1 diabetes. New England Journal of Medicine 2005; 353:2643-53

Dorman TJ, Laporte RE, Kuller LH,et al. The Pittsburgh insulin dependent diabetes mellitus (IDDM) morbidity and mortality study. Diabetes 1984; 133: 271–276. 5.

Eeg-Olofsson K, Cederholm J, Nilsson PM, Gudbjornsdottir S, Eliasson B. Glycemic and risk factor control in Type 1 diabetes. Diabetes Care 2007; 30:496-502

EUCLID Study Group. Randomised placebo-controlled trial of lisinopril in normotensive patients with insulin dependent diabetes and normoalbuminuria or microalbuminuria. Lancet 1997; 349:1787–1792.

European Diabetes Policy Group. A desktop guide to type 1 (insulin dependent) diabetes mellitus. Diabetic Medicine 1999; 16:253-256

Jacobs ML, Elte JWF, van Ouwerkerk BM, Janssens ENW, Schop C, Knoop JA et al . Effect of BMI, insulin dose and number of injections on glycaemic control in insulin-using diabetic patients. Netherlands Journal of Medicine 1997; 50: 153-159

Joint British Societies. JBS 2: Joint British Societies Guidelines on prevention of cardiovascular disease in clinical practice. Heart 2005; 91 suppl v: v1-52

Joseph F, Younis N, Sowery J, Soran H, Stanaway S, Bowen-Jones D. Blood pressure control in diabetes: are we achieving the guideline target? Practical Diabetes International 2003; 20:276-282

Laing SP, Swerdlow AJ, Slater SD, et al. The British Diabetic Association Cohort Study, I: all cause mortality in patients with insulin treated diabetes mellitus. Diabetic Medicine 1999a; 16:459–465

Laing SP, Swerdlow AJ, Slater SD, Botha JL, Burden AC, Waugh NR. The British Diabetic Association Cohort Study, II: cause-specific mortality in patients with insulin treated diabetes mellitus. Diabetic Medicine 1999b; 16:466-471

Laing SP, Swerdlow AJ, Carpenter LM, et al. Mortality from cerebrovascular disease in a cohort of 23 000 patients with insulin treated diabetes. Stroke 2003; 34: 418–421

Lovell HG. Angiotensin converting enzymes in normotensive diabetic patients with microalbuminuria (Cochrane Review). In The Cochrane Library, Issue 2. Chichester: John Wiley & Sons, 2004

National Institute for Clinical Excellence. Type 1 diabetes: management of Type 1 diabetes in adults in primary and secondary care (Draft Version 1.6). National Institute for Clinical Excellence, 2004a

National Institute for Clinical Excellence. Type 1 diabetes: National clinical guidance for diagnosis and management in primary care. National Institute for Clinical Excellence. 2004b

New JP, Mason JM, Freemantle N, etal. Specialist nurse-led intervention to treat and control hypertension and hyperlipidaemia in diabetes (SPLINT): a randomised controlled trial. Diabetes Care 2003; 26:2250–2255

Orchard TJ, Dorman JS, Maser RE, et al. Factors associated with avoidance of severe complications after 25yr of IDDM. Pittsburgh Epidemiology of Diabetes Complications Study I. Diabetes Care 1990; 13: 741–747

Pambianco G, Costacou T, Ellis D, Becker DJ, Klein R, Orchard TJ. The Pittsburgh epidemiology of diabetes complications study experience. Diabetes 2006; 55:1463-1469

Pickup J, Mattock M, Kerry S. Glycaemic control with continuous subcutaneous insulin infusion compared with intensive insulin injections in patients with type 1 diabetes: meta analysis of randomised controlled trials. British Medical Journal 2002; 324: 705–708

Perez A, Caixas A, Carreras G, et al. Lipoprotein compositional abnormalities in type 1 diabetes: Effect of improved glycaemic control. Diabetes Research and Clinical Practice 1997; 36: 83–90

Perez A, Wagner AM, Carreras G, et al. Prevalence and phenotypic distribution of dyslipidemia in type 1 diabetes mellitus. Archives Internal Medicine 2000; 160: 2756–2762

Resnick HE, Bardsley J, Foster GL, Ratner RE. Achievement of American Diabetes Association clinical practice recommendations among U.S. adults with diabetes, 1999-2002. Diabetes Care 2006; 29: 531-537

Saunders S, Wallymahmed ME, MacFarlane IA. The glycaemic control achieved in a younger adult type1 diabetes clinic. Quarterly Journal of Medicine 2004; 97: 575–580

Soedamah- Muthu SS, Fuller JH, Mulnier HE, Raleigh VS, Lawrenson RA, Colhoun HM. All-cause mortality rates in patients with type 1 diabetes mellitus compared with a non-diabetic population from the UK general research database, 1992-1999. Diabetologia 2006; 49:660-666

Tabaei BP, Al Kassab AS, Ilag LL, *et al.*Does microalbiminuria predict diabetic nephropathy? Diabetes Care 2001; 24: 1560–1566

United Kingdom Prospective Diabetes Study (UKPDS) Group. Intensive blood glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type2 diabetes (UKPDS 33). Lancet 1998a;352: 837–85.

United Kingdom ProspectiveDiabetes Study (UKPDS) Group. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes (UKPDS 38). British Medical Journal 1998b: 317:703–713

Wallymahmed ME, Pinkney J, Saunders S, MacFarlane IA. Vascular risk factors in patients with type 1 diabetes. Practical Diabetes International 2005; 22:81-85

Zimmet P, Alberti KGMM, Shaw J. Global and societal implications of the diabetes epidemic. Nature 2001;414: 782–787

Zgibor JC, Wilson RR, Orchard TJ Has control f hypercholesterolemia and hypertension in type 1 diabetes improved over time? Diabetes Care 2005; 28:521-526

# CHAPTER 5

# PHYSICAL FITNESS AND GLYCAEMIC CONTROL IN TYPE 1 DIABETES

# CHAPTER 5

# PHYSICAL FITNESS AND GLYCAEMIC CONTROL IN TYPE 1 DIABETES

Chapter 5 includes 2 studies of physical fitness and glycaemic control in people with type 1 diabetes. The first study is an assessment of the relationship between aerobic capacity and glycaemic control. The results of this first study demonstrated that people with type 1 diabetes who have good aerobic capacity have poorer glycaemic control. This prompted further investigation into the possible reasons for this. The second study investigated how people with type 1 diabetes manage blood glucose levels during physical activity.

## 5.1 INTRODUCTION

Regular physical activity has been associated with improvements in cardiovascular risk factors and quality of life in patients with type 1 diabetes (Lehmann et al 1997, Zoppini et al 2003). As part of their treatment regimen people with diabetes should be encouraged to exercise on a regular basis and Diabetes UK recommends participation in regular, moderate intensity physical activity for at least 30 minutes, five times per week (Diabetes UK Position Statement 2006). Several studies have emphasised the importance of increased physical activity in the prevention of type 2 diabetes and suggest a causative role for physical inactivity in the development of type 2 diabetes (Tuomilehto et al 2001, Diabetes Prevention Programme Research Group 2002). In addition a meta analysis of the effects of exercise on glycaemic control in established type 2 diabetes, (involving 14 controlled trials, 11 randomised), reported that exercise reduced $HbA_{1c}$ by approximately 0.66% (Boule et al 2001). A further randomised controlled study, involving 70 previously inactive people with type 2 diabetes, reported significant improvements in weekly time spent participating in physical activity, glycaemic control and systolic blood pressure following exercise consultation (Kirk et al 2003).

However the effects of physical activity on metabolic control in type 1 diabetes are not clear. A few studies, mainly in young people, have demonstrated a beneficial effect of increased physical activity on glycaemic control (Mosher et al 1998, Zoppini et al 2003), whilst other interventional studies have failed to demonstrate significant improvements (Lehmann et al 1997, Laaksonen et al 2000). Indeed one recent study demonstrated a deterioration in control following a 12 week aerobic exercise programme (Ramalho et al 2006).

Self reported activity questionnaires have also been used to assess the relationship between glycaemic control and physical activity in type 1 diabetes, again with conflicting results. One such study assessed self reported physical activity, using the Baecke questionnaire, in 221 patients with type 1 diabetes (Ligtenberg et al 1999). No correlation was observed between different levels of physical activity and glycaemic control. However, more recently, low levels of leisure time activity have been shown to be associated with poor glycaemic control in women with type 1 diabetes, but not in men (Waden et al 2005). Also a study, involving a large number of children and young people with type 1 diabetes, found that self reported regular physical activity was associated with better glyceamic control (Herbst et al 2006).

Participation in physical exercise can increase the risk of hypoglycaemia (Tuominen et al 1995, Hernandez et al 2000, Rabasa-Lhoret et al 2001, Guelfi et al 2005), which can occur up to 24 hours after physical activity. Conversely physical activity of short duration, particularly anaerobic activity, can lead to an increased counter-regulatory response resulting in hyperglycaemia (Gallen 2005, Riddell and Perkins 2006). Guidance on the management of physical activity in type 1 diabetes is often general and adopts a trial and error approach (Diabetes UK 2006b) and advice from health care professionals may not always be consistent.

At Aintree Hospitals the policy has been to encourage physical activity in people with diabetes (type 1 and type 2) on the assumption that physical fitness will increase, long term cardiovascular risk will be reduced and metabolic control is likely to improve. It is firmly established that poor metabolic control increases the risk of microvascular complications (DCCT Research Group 1993). Therefore it is clearly important to determine the relationship between glycaemic control, cardiovascular risk factors and physical fitness, and to establish how people with type 1 diabetes manage physical activity and in particular potential hypoglycaemia.

The aim of the first study reported in this chapter was to assess the relationship between aerobic capacity and strength with diabetic control, lipid profile and body composition in people with type 1 diabetes. The second study assesses the relationship between diabetic control ($HbA_{1c}$) and the following: self reported vigorous physical activity, aerobic capacity and hypoglycaemic avoidance behaviour in people with type 1 diabetes.

## 5.2 STUDY ONE: AEROBIC FITNESS AND HAND GRIP STRENGTH IN TYPE 1 DIABETES: RELATIONSHIP TO GLYCAEMIC CONTROL AND BODY COMPOSITION

## 5.3 PATIENTS AND METHODS

Over a 6 months period in 2005, patients with type 1 diabetes attending a hospital clinic were randomly asked, by a research nurse, to participate in the study. Fifteen to twenty people with type 1 diabetes attended each clinic and approximately 6 patients per clinic were able to be studied. Those with significant cardiac or respiratory disorders and those on beta blockers were excluded. Patients had been encouraged to participate in daily physical activity (20 – 30 minutes per day) as routine advice in previous consultations. Four patients declined to take part in the study all due to time constraints on the day of attendance. Data is reported on 141 patients who agreed to participate in the study. The study was approved by the Sefton Local Research Ethics Committee and written informed consent was obtained from each patient.

The following clinical information was recorded: age, sex, duration of diabetes, complications of diabetes, current medication, $HbA_{1c}$, total cholesterol, LDL, HDL, body mass index (BMI), weight and blood pressure. The method of $HbA_{1c}$ assay during the study period was high pressure liquid chromatography (HPLC), and was aligned to the Diabetes Control and Complications Trial (DCCT 1993).

Aerobic capacity, (a measure of the body's maximal ability to take in, transport and use oxygen) was assessed by a multistage sub maximal test using a 20 cm step, The Chester step test (Stevens and Sykes 1996, Sykes and Roberts 2004). The subject is asked to step on and off a low step at a rate set by a music beat tape (initially 15 steps per minute) and the rate is increased every 2 minutes (20, 25, 30, 35 steps per minute). The heart rate is monitored continuously throughout the test. The test is terminated when the subjects heart rate reaches 80% of their maximal heart rate or when the subject says he/she can not go on any further or when all 5 levels are completed. Aerobic capacity (ml $O_2$/kg/min) is then calculated using a computer programme. This test has been shown to be a reliable and valid test for the estimation of aerobic capacity when compared to maximal oxygen uptake ($VO_2$ max) measured during a treadmill test (Sykes and Roberts 2004). It has previously been used to predict $VO_2$ max in patients with respiratory disorders (Lau et al 2005a, Lau et al 2005b).

Body composition was determined by bioelectrical impedance analysis (Tanita BF 350) and hand grip strength was, measured using a handheld dynamometer (Takei).

## 5.4 STATISTICAL ANALYSIS

Independent t tests were used to examine differences between males and females and relationships between variables were calculated using Spearman's correlation test (SPSS version 12). P values <0.05 were considered significant.

## 5.5 RESULTS

### 5.5.1 Demographic details:

Seventy eight patients were male. Mean age was 37 ± 11.2 years (range 16-70) and mean duration of diabetes was 16 ± 8.5 years (range 0.5 – 39 years). Mean $HbA_{1c}$ was 9.6% ± 1.6 and only 11(8%) patients had an $HbA_{1c} \leq 7.5\%$. Mean BMI was 27.1 ± 4.5 and 30 (21%) patients had a BMI ≥ 30 $kg/m^2$. Mean total cholesterol was 5.4 ± 0.9 mmol/l, mean fat mass was 27% and lean mass 73%. Twenty seven patients (20%) had microalbuminuria or proteinuria, 20 (14%) symptomatic neuropathy and 65 (46%) retinopathy. Forty seven patients (33%) were taking twice daily insulin injections and 94 (67%) were taking multiple daily injections. Thirty eight (27%) patients were taking lipid lowering agents and 33 (23%) antihypertensive agents.

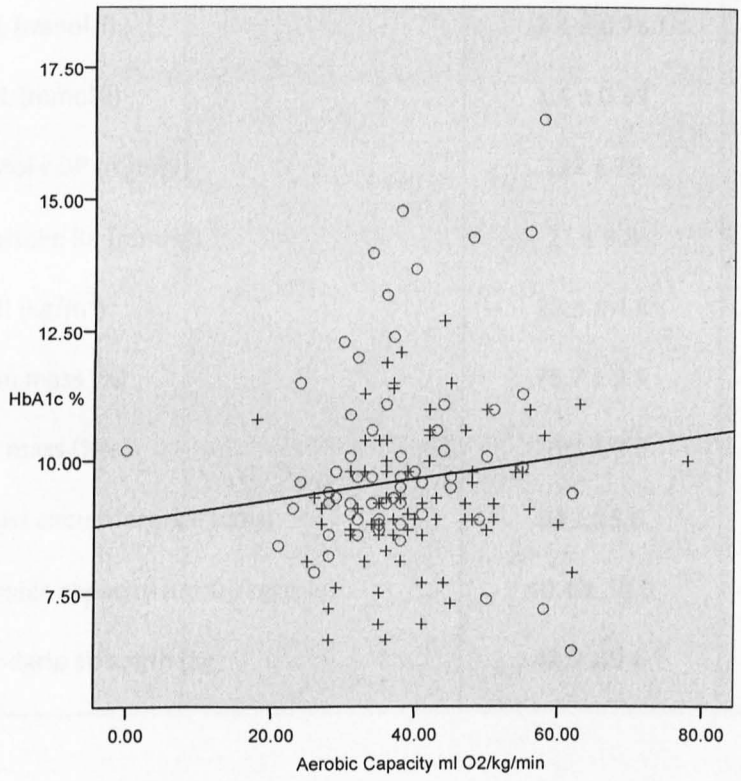
### 5.5.2 Other data

Metabolic control was significantly poorer in females than males (mean $HbA_{1c}$ 10.1% v 9.2%, p< 0.004) and female patients had significantly more fat mass and less lean mass than male patients (32% v 23.1%, p < 0.001, 69% v 76% p<0.001). However waist circumference was significantly lower in females than males (85.7 cms v 94 cms, p<0.002). Handgrip strength was greater in males than females (p<0.001) but there was no significant differences in aerobic capacity (table 5.1).

In the group as a whole aerobic capacity correlated positively with $HbA_{1c}$ (r = 0.17, p < 0.05) (figure 5.1), lean body mass (r = 0.26, p< 0.01) and handgrip strength (r = 0.27, p< 0.01) and negatively with age (r = -0.32, p< 0.001), duration of diabetes (r = -0.27, p <0.001), BMI (r = -0.17, p<0.05) and fat mass (r = -0.33, p< 0.01). Handgrip strength correlated positively with

aerobic capacity (r = 0.27, p<0.01) and lean mass (r = 0.28, p<0.01) and negatively with $HbA_{1c}$ (r = -0.24, p < 0.01) and fat mass (r = - 0.32 p < 0.01). In addition $HbA_{1c}$ correlated positively with total cholesterol (r = 0.34, p < 0.01) and fat mass (r = 0.22, p< 0.05) and negatively with lean mass (r = -0.24, p < 0.01).

**Figure 5.1** The correlation between glycated haemoglobin ($HbA_{1c}$) and aerobic capacity (r =0.17, P<0.05) in 141 patients with type 1 diabetes




Key: male(+), female (o), the solid diagonal line indicates the fit line for total

**Table 5.1** Comparison of male and female patients with type 1 diabetes

| | Male (n=78) | Female (n=63) | p |
|---|---|---|---|
| $HbA_{1c}$ (%) | 9.2 ± 1.3 | 10.1 ± 1.9 | <0.004 |
| Total cholesterol (mmol/l) | 5.4 ± 0.9 | 5.6 ± 0.9 | ns |
| LDL (mmol/l) | 3.1 ± 0.76 | 3.1 ± 0.78 | ns |
| HDL (mmol/l) | 1.4 ± 0.39 | 1.6 ± 0.44 | <0.002 |
| Systolic BP (mmHg) | 122 ± 19 | 118 ± 19 | ns |
| Diastolic BP (mmHg) | 71 ± 9.8 | 65 ± 10 | <0.001 |
| BMI ($kg/m^2$) | 26.9 ± 4.4 | 27.3 ± 4.7 | ns |
| Lean mass (%) | 75.7 ± 9.9 | 68.8 ± 8.7 | <0.001 |
| Fat mass (%) | 23.1 ± 7.9 | 31.9 ± 8.0 | <0.001 |
| Waist circumference (cms) | 94 ± 15.6 | 85.7 ± 13 | <0.02 |
| Aerobic capacity (ml $O_2$/kg/min) | 40.4 ± 10.0 | 37.4 ± 11 | ns |
| Handgrip strength (kg) | 42.9 ± 9.6 | 26.5 ± 7.1 | <0.001 |

Results expressed as mean ± standard deviation

## 5.6 DISCUSSION

There are a paucity of data on fitness and strength in type 1 diabetes. This study is valuable because of the large number (n=141) of unselected patients. The majority of the patients were overweight (BMI > 25 kg/m$^2$) and 20% were obese (BMI > 30 kg/m$^2$). The mean $HbA_{1c}$ level in the group as a whole was 9.6% similar to the mean $HbA_{1c}$ level from this clinic population reported in 2004 (Saunders et al 2004). Diabetic control was significantly poorer in females than males. There was no correlation between aerobic capacity and total cholesterol but 27% of patients were taking lipid lowering agents. Previous studies have shown that aerobic training in men with type 1 diabetes results in significant improvements in lipid profile and aerobic capacity (Laaksonen et al 2000). Another study reported similar positive effects on lipid profile (Lehmann et al 1997). In addition a cross sectional study reported a significantly positive relationship between self reported physical activity and HDL cholesterol and a negative relationship between physical activity and total cholesterol : HDL ratio in men with type 1 diabetes but not in woman (Idzior-Walus et al 2001).

In this study those with good aerobic capacity had poorer diabetic control. There is little recent information on the effects of exercise on glycaemic control in adult patients with type 1 diabetes. A few studies, with small numbers of patients, have demonstrated small but statistically insignificant improvements in glycaemic control following exercise interventions (Lehmann et al 1997, Laaksonen et al 2000). One randomised controlled cross over study did demonstrated an improvement in glycaemic control with a comprehensive programme of lifestyle interventions including dietary advice, an exercise programme and regular contact with health care professionals. However even with this degree of contact only half of the subjects reported complying with the exercise programme for at least 50% of the time and it is impossible to attribute the improvement in glycaemic control to any specific aspect of the programme, especially as glycaemic control improved in both groups in the period from recruitment to randomisation (Perry et al 1997). Studies in children and young people have also shown inconsistent results with some reporting a beneficial effect of physical activity on glycaemic control (Bernardini et al 2004) and others failing to demonstrate such a relationship (Raile et al 1999, Roberts et al 2002).

Participation in physical exercise can increase the risk of hypoglycaemia (Hernandez et al 2000, Rabasa-Lhoret et al 2001) and the risk may be greater with moderate than intermittent high intensity exercise (Guelfi et al 2005). It is possible that adults with type 1 diabetes who exercise

on a regular basis choose to maintain high blood sugars during exercise to avoid hypoglycaemia and this may account for the positive correlation between $HbA_{1c}$ and aerobic capacity found in this study. Prior experience of hypoglycaemia either during exercise or in the recovery period might be an influence. Guidance on the management of physical activity in type 1 diabetes is often general and adopts a trial and error approach and advice from health care professional may not always be consistent. Alternatively it is possible that some of the patients included in the study had physically active jobs which may influence fitness and strength but not necessarily diabetic control or there may be genetic factors which independently influence glycaemic control or physical fitness.

Encouraging regular physical activity and promoting the maintenance of a healthy body weight is a routine part of diabetes management therefore it is important to clarify the relationship between diabetic control and physical fitness. Surprisingly in this study patients with good aerobic capacity had poorer diabetic control. However this was an observational study and therefore results should be interpreted with care. The management of physical activity needs to be an integral element of any education programme for people with diabetes. Further investigation into how people with type 1 diabetes manage exercise is required, particularly if glycaemic control is compromised.

## 5.7 STUDY TWO: DOES HYPOGLYCAEMIC AVOIDANCE BEHAVIOUR CONTRIBUTE TO INCREASED $HBA_{1c}$ LEVELS IN PHYSICALLY ACTIVE PEOPLE WITH TYPE 1 DIABETES?

## 5.8 PATIENTS AND METHODS

Over a 6 months period in 2005, 53 patients with type 1 diabetes attending a routine hospital diabetic clinic were randomly asked, by a research nurse, to participate in the study. Those with significant cardiac or respiratory disorders and those taking beta blockers were excluded. Three patients declined to take part in the study all due to time constraints on the day. We report data on 50, of the previous 141 patients, who agreed to participate in the study. The study was approved by the Sefton Local Research Ethics Committee and written informed consent was obtained from each patient.

The following clinical information was recorded: age, sex, duration of diabetes, complications of diabetes, current medication, $HbA_{1c}$, BMI, weight, lipid profile and blood pressure. The method of $HbA_{1c}$ assay during the study period was high pressure liquid chromatography (HPLC), and was aligned to the Diabetes Control and Complications Trial (DCCT 1993).

Aerobic capacity was assessed by a multistage sub maximal test using a 20 cm step, The Chester step Test (Stevens and Sykes 1996, Sykes and Roberts 2004). The subject is asked to step on and off a low step at a rate set by a music beat tape (initially 15 steps per minute) and the rate is increased every 2 minutes (20, 25, 30, 35 steps per minute). The heart rate is monitored continuously throughout the test. The test is terminated when the subjects' heart rate reaches 80% of their maximal heart rate or when the subject says he/she can not go on any further or when all 5 levels are completed. Aerobic capacity (ml $O_2$/kg/min) is then calculated using a computer programme. This test has been shown to be a reliable and valid test for the estimation of aerobic capacity when compared to maximal oxygen uptake ($VO_2$ max) measured during a treadmill test (Sykes and Roberts 2004). It has previously been used to predict $VO_2$ max in patients with respiratory disorders (Lau et al 2005a, Lau et al 2005b).
Self reported physical activity, frequency of hypoglycaemia and hypoglycaemic avoidance behaviour was assessed using a simple 'in-house' questionnaire. The questionnaire asks patients to state how much time they spend undertaking specific physical activities per week e.g. sport, gym sessions. It then asks for yes / no responses to a number of questions enquiring

about the management of physical activity, frequency of hypoglycaemia, blood glucose monitoring and desired blood glucose levels prior to physical activity.
An example question is: When you undertake physical activity do you: increase your insulin, decrease your insulin, leave insulin dose the same, eat / drink more, do nothing.
Regular vigorous physical activity was defined, on an arbitrary basis, as participation in aerobic activities (i.e. sport or gym sessions) for more than 1 hour per week.

## 5.9 STATISTICAL ANALYSIS

Independent t tests or chi-square (as appropriate) were used to examine differences between groups. Relationships between variables were calculated using Spearman's correlation test (SPSS version 12). P values <0.05 were considered significant.

## 5.10 RESULTS

Fifty patients (30 male) with type 1 diabetes attending a routine diabetic clinic in North Liverpool were recruited to the study. Mean age was 36 years ± 9.2 years (range 18-52), mean duration of diabetes was 18 ± 8.8 years (range 4 -40), mean $HbA_{1c}$ was 9.1 ± 1.3% (range 6.2-12.4), mean BMI was 27 ± 3.8 (range 20-37), mean aerobic capacity 39.6 ± 9.3 ml $O_2$/kg/min (range 23 – 78), mean systolic blood pressure 120 ± 11.4 mmHg (range 98 -148), mean diastolic BP was 66 ± 8.0 (range 49-83), mean total cholesterol was 4.9 ± 0.9 mmol/l (range 2.5-6.6), mean LDL was 2.6 ± 0.8 mmol/l (range 1.1-4.2), mean HDL 1.5 ± 0.5 mmol/l (range 0.7-3.2). Three (6%) patients had symptomatic neuropathy, 25 (50%) had documented retinopathy and 15 (30%) had microalbuminuria or proteinuria. Mean insulin dose was 68 ± 21 units per day (range 24 -120), 12 (24 %) were taking twice daily insulin injection, 38 (76 %) multiple daily injections, 16 (32%) anti-hypertensive medication and 30 (60%) lipid lowering medication.

Thirty patients (60%) patients reported participating in regular vigorous physical activity and glycaemic control ($HbA_{1c}$) was significantly worse in this group compare to those who did not participate in vigorous activity on a regular basis (9.5 ± 1.35 v 8.5 ± 1.2 %, $p < 0.02$) (see table 5.2). There was a trend towards higher aerobic capacity in the vigorous activity group although this was not statistically significant (41.3 ± 9.7 v 37.2 ± 8.3 ml $O_2$/kg/min). A positive correlation

between aerobic capacity and $HbA_{1c}$ did not achieve statistical significance ($r = 0.25$, $p < 0.07$). There were no significant differences in BMI, blood pressure, lipid profile, daily insulin dose and duration of diabetes in those patients who reported regular vigorous activity and those who did not (see table 5.2) .

Thirty nine of the patients studied reported taking some action to prevent hypoglycaemia during physical activity, six reported taking no action and five did not respond to the question (one of whom reported regular vigorous activity). Of the vigorous group 25/30 (83%) reported taking hypoglycaemic avoidance action compared with 14/20 (70%) of the inactive group. The majority of the 39 patients who reported taking some action managed physical activity by eating more (30 patients, (77%), three (7.5%) patients reduced their insulin dose, five (13%) patients ate more and reduced insulin dose and one (2.5%) patient increased her insulin and ate more. There was no difference in $HbA_{1c}$ in the group as a whole between those who reported taking some action to prevent hypoglycaemia and those who did not (9.1% v 9.2%).

In the vigorous activity group, 23 (77%) reported occasional hypoglycaemia during exercise and 26 (86%) reported occasional hypoglycaemia after exercise. No one reported disabling hypoglycaemia requiring help from others after exercise. In the group who were not vigorously active, 16 (80%) reported occasional hypoglycaemia during exercise and 16 (80%) reported occasional hypoglycaemia after exercise.

Significantly more patients in the vigorously active group reported that they tried to achieve higher than usual blood glucose levels during exercise than in the group who were not vigorously active (8 v 0, $p< 0.03$). The $HbA_{1c}$ was worse in these 8 patients than in the group as a whole (9.9% v 8.8%, $p< 0.05$). However within the vigorously active group there was no significant difference in $HbA_{1c}$ between those who reported deliberately aiming for higher than usual blood glucose levels during exercise and those who did not (9.9% v 9.3%). Four patients in each group did not answer the question.

**Table 5.2** Demographic details of patients with type 1 diabetes who participate in vigorous physical activity (VPA) versus those who do not participate in vigorous physical activity (No VPA)

| Variable | VPA (n=30) | No VPA (n=20) | p |
|---|---|---|---|
| Age (yrs) | 37 (9.9) | 34.6 (8.1) | ns |
| Duration of diabetes (yrs) | 17.2 ( 8.4) | 19.2 (9.5) | ns |
| $HbA_{1c}$ (%) | 9.5 (1.35) | 8.5 (1.2) | p<0.02 |
| Insulin dose (units per day) | 66.6 (22) | 71.7 (19) | ns |
| Body mass index | 26.8 (3.7) | 27.1 (4.2) | ns |
| Lipid lowering agents | 19 (63%) | 11 (55%) | ns |
| Anti hypertensives agents | 9 (30%) | 7(35%) | ns |
| Aerobic capacity (ml $O_2$/kg/min) | 41.3 (9.7) | 37.2 (8.3) | ns |
| Systolic BP (mmHg) | 119 (13) | 122 (9) | ns |
| Diastolic BP (mmHg) | 67 (9) | 67 (7) | ns |
| Total cholesterol (mmol/l) | 4.9 (0.9) | 5.0 (1.0) | ns |
| LDL- Cholesterol (mmol/l) | 2.7 (0.8) | 2.5 (0.8) | ns |
| HDL-Cholesterol (mmol/l) | 1.6 (0.4) | 1.5 (0.6) | ns |
| Active management of blood glucose during activity (number) | 25 (83%) | 14 (70%) | ns |
| Maintain BG above normal levels to avoid hypoglycaemia (number) | 8 | 0 | p<0.03 |

Results shown as mean (SD) or actual numbers (%)

## 5.11 DISCUSSION

In this study patients who reported taking regular vigorous physical activity had poorer glycaemic control than those who did not. There was a non significant trend to higher aerobic capacity in the physically active group. However numbers of patients in this study were small and in a larger study of type 1 patients from this clinic a significant positive correlation between aerobic capacity and $HbA_{1c}$ was reported (Wallymahmed et al 2007). There may be several reasons for higher $HbA_{1c}$ levels in the active group. The majority of patients reported that they aimed to avoid hypoglycaemia by eating more carbohydrate prior to physical activity. Previous experience of hypoglycaemic events related to physical activity may be an influencing factor. Most of the patients in this study (in both active and less active groups) reported occasional hypoglycaemia either during or after exercise but no one reported severe disabling exercise related hypoglycaemia. Many people who participate in physical activity do so to maintain a healthy body weight or to loose weight. However because most of the patients in this study actively manage physical activity by eating additional carbohydrate and not reducing insulin doses this may actually promote weight gain. Also some of the vigorously active patients aimed for blood glucose levels higher than normal during and after exercise. Finally exercise, particularly anaerobic exercise, can induce an acute rise in blood glucose in type 1 diabetes (Gallen 2005, Riddell and Perkins 2006). It is acknowledged that the questionnaire used to assess the management of physical activity in this study was designed by the authors and not validated. This is a preliminary study and therefore results must be interpreted with care.

For many years' encouraging physical activity and promoting weight loss has been included in routine consultations in the Diabetes centre. Regular blood glucose monitoring and a reduction in insulin dose is also encouraged rather than eating more carbohydrate during planned exercise, particularly in those patients who are trying to loose weight. However the results of this survey suggest that this advice has not been effective. This may be because concern of hypoglycaemia automatically leads to increased carbohydrate intake by many individuals. . Fear of hypoglycaemia has been reported to be a barrier to physical activity (Brazeau et al 2008). In addition the same study reported that that greater knowledge about the pharmacokinetics of insulin and using appropriate management strategies to avoid activity related hypoglycaemia was associated with fewer barriers. It may be that the perceived risk of

hypoglycaemia is greater than the actual risk which leads to overcompensation. In addition hypoglycaemia in public places, such as a gym, may lead to embarrassment and distress reinforcing the need to avoid and therefore overcompensate. Furthermore, it is possible that health care professionals, in an attempt to maximise patient safety, may overemphasise the risk of activity related hypoglycaemia.

Alternatively fear of markedly elevated blood glucose levels and possible ketoacidosis may mitigate against a reduction in insulin dose. It is possible that advice for the management of physical exercise in patients with type 1 diabetes by health care professionals in the clinic setting is inconsistent and may confuse patients. This may contribute to the elevated $HbA_{1c}$ levels in patients who are particularly physically active.

For most people with type 1 diabetes the management of physical activity involves a considerable amount of trial and error until personal experience informs a practical solution. It is difficult to produce management advice which would be effective for all individuals particularly as the presence of diabetes related complications and / or other medical conditions also require consideration. Guidelines available for people with type 1 diabetes tend to be general and advocate consulting with health care professionals for specific advice. However health care professionals themselves may be ill prepared to provide such advice as there is little specific training and practical information available for guidance. These issues may lead to reluctance to participate in physical activity in people with type 1 diabetes.

Guidelines have been published emphasising the importance of insulin reduction as well as sensible carbohydrate supplements during and after exercise (Riddell and Perkins 2006, American Diabetes Association 2004) but few of the patients in this study reduced their insulin doses. In conclusion it is important that health care professionals should receive training in the management of exercise in type 1 diabetes and patients should be given both verbal and written advice. Also patients should be carefully counselled about possible effects of excess carbohydrate on glycaemic control and body weight.

## 5.12 REFERENCES

American Diabetes Association. Physical activity / exercise and diabetes. Diabetes Care 2004; 27(suppl 1): S58-S62

Bernardini AL, Vanelli M, Chiari G, Iovane B, Gelmetti C, Vitale R et al. Adherence to physical activity in young people with type 1 diabetes. Acta Bio Medica Atenei Parmensis 2004; 75:153-157

Boule N, Haddad E, Kenny G, Wells G, Sigal R. Effects of exercise on glycaemic control body mass in Type 2 diabetes: A meta-analysis of controlled clinical trials. Journal of the American Medical Association 2001; 286:1218-1227

Brazeau A, Rabasa-Lhoret R, Strychar I, Mircescu H. Barriers to physical activity among patients with type 1 diabetes. Diabetes Care 31:2108–2109, 2008

Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin dependent diabetes mellitus. New England Journal of Medicine 1993; 329: 977-986

Diabetes Prevention Programme Research Group. Reduction in the incidence of Type 2 diabetes with lifestyle intervention and metformin. New England Journal of Medicine 2002; 346:393-403

Diabetes UK. Position Statement 2006. Physical Activity www.diabetes.org.uk

Gallen I. The management of insulin treated diabetes and sport. Practical Diabetes International 2005; 22:307-312

Guelfi KJ, Jones TW, Fournier PA. The decline in blood glucose levels is less with intermittent high intensity compared with moderate exercise in individuals with type 1 diabetes. Diabetes Care 2005; 28:1289-1294

Herbst A, Bachran R, Kapellen T et al. Effects of regular physical activity on control of glycemia in pediatric patients with type 1 diabetes mellitus. Archives of Pediatrics & Adolescent Medicine 2006; 160:573-577

Hernandez JM, Moccia T, Fluckey JD, Ulbrecht JS, Farrell PA. Fluid snacks to help persons with type 1 diabetes avoid late onset post exercise hypoglycaemia. Medicine & Science in Sports & Exercise 2000; 32:904-910

Idzior-Walus B, Mattock MB, Solnica B, Stevens L, Fuller JH and the EURODIAB IDDM Complications Study Group. Factors associated with plasma lipids and lipoproteins in Type 1 diabetes mellitus: the EURODIAB IDDM Complications Study. Diabetic Medicine 2001; 18:786-796

Kirk A, Mutrie N, MacIntyre P, Fisher M. Increasing physical activity in people with type 2 diabetes. Diabetes Care 2003; 26:1186-1192

Laaksonen DE, Atalay M, Niskanen LK, Mustonen J, Sen CK, Lakka TA et al. Aerobic exercise and the lipid profile in type 1 diabetic men a randomised controlled trial. Medicine and Science in Sports and Exercise 2000; 32:1541-1548

Lau HM, Lee EW, Wong CN, Ng GY, Jones AY, Hui DS. The impact of severe acute respiratory syndrome on the physical profile and quality of life. Archives of Physical Medicine and Rehabilitation 2005a; 86:1134- 1140

Lau HM, Ng GY, Jones AY, Lee EW, Siu EH, Hui DS. A randomised controlled trial of the effectiveness of an exercise training programme in patients recovering from severe acute respiratory syndrome. Australian Journal of Physiotherapy 2005b; 51: 213-219

Lehmann R, Kaplan V, Bingisser R, Bloch KA, Spinas GA. Impact of physical activity on cardiovascular risk factors in IDDM. Diabetes Care 1997; 20:1603-1611

Ligtenberg PC, Blans M, Hoekstra JBL, van der Tweel I, Erkelens DW. No effect of long term physical activity on the glycaemic control in type 1 diabetes patients: a cross-sectional study. The Netherlands Journal of Medicine 1999; 55:59-63

Mosher PE, Nash MS, Perry AC et al. Aerobic circuit exercise training: effect on adolescents with well controlled insulin-dependent diabetes mellitus. Archives of Physical Medicine and Rehabilitation 1998; 79:652-657

Perry TL, Mann JI, Lewis-Barned NJ, Duncan AW, Waldron MA, Thompson C. Lifestyle intervention in people with insulin-dependent diabetes mellitus (IDDM). European Journal of Clinical Nutrition 1997; 51:757-763

Rabasa-Lhoret R, Bourque J, Ducros F, Chiasson JL. Guidelines for premeal insulin dose reduction for postprandial exercise of different intensities and durations in type 1 diabetic subjects treated intensively with a basal bolus insulin regimen (ultralente-lispro). Diabetes Care 2001: 24:625-630

Raile K, Kapellen T, Schweiger A, Hunkert F, Nietzschmann U, Dost A et al. Physical activity and competitive sport in children and adolescents with type 1 diabetes (Letter). Diabetes Care 1999; 22:1904

Ramalho AC, Lima MdL, Nunes F et al. The effect of resistance versus aerobic training on metabolic control in patients with type-1 diabetes mellitus. Diabetes Research and Clinical Practice 2006; 72:271-276

Riddell MC, Perkins BA. Type 1 diabetes and vigorous exercise: Applications of exercise physiology to patient management. Canadian Journal of Diabetes 2006; 30:63-71

Roberts L, Jones TW, Fournier PA. Exercise training and glycemic control in adolescents with poorly controlled type 1 diabetes mellitus. Journal of Pediatric Endocrinology 2002; 15:621-627

Saunders SA, Wallymahmed ME, Macfarlane IA Glycaemic control in a type 1 diabetes clinic for younger adults. Quarterly Journal of Medicine 2004: 97: 575-580.

Stevens N, Sykes K. Aerobic fitness testing: an update. Journal of Occupational Health 1996; 48:436-438

Sykes K, Roberts A. The Chester step test – a simple yet effective tool for the prediction of aerobic capacity. Physiotherapy 2004; 90:183-188

Tuominen JA, Karonen SL, Melamies L, Bolli G, Koivisto VA. Exercise induced hypoglycaemia in IDDM patients treated with a short acting insulin analogue. Diabetologia 1995:38:106-111

Tuomilehto J, Lindstrom J, Eriksson J et al. Prevention of Type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. New England Journal of Medicine 2001; 344:1343-1350

Waden J, Tikkanen H, Forsblom C, Fagerudd J, Pettersson-Fernholm K, Lakka T. Leisure time physical activity is associated with poor glycaemic control in type 1 diabetic woman. Diabetes Care 2005; 28:777-782

Wallymahmed ME, Morgan C, Gill GV et al. Aerobic fitness and hand grip strength in type 1 diabetes: relationship to metabolic control and body composition. Diabetic Medicine 2007; 24:1296-1299

Zoppini, G, Carlini M, Muggeo M. Self reported exercise and quality of life in young type 1 diabetic subjects. Diabetes Nutrition and Metabolism 2003; 16:77-80

# CHAPTER 6

# NURSE – LED OR DOCTOR LED CARDIOVASCULAR RISK FACTOR MANAGEMENT IN TYPE 1 DIABETES: A RANDOMISED CONTROLLED TRIAL EVALUATION

# CHAPTER 6

# NURSE – LED OR DOCTOR LED CARDIOVASCULAR RISK FACTOR MANAGEMENT IN TYPE 1 DIABETES: A RANDOMISED CONTROLLED TRIAL EVALUATION

## 6.1 INTRODUCTION

Type 1 diabetes is a common cause of chronic disease in young people and accounts for approximately 10% of all people with diabetes worldwide. Poorly controlled diabetes can cause distressing symptoms and severely impair an individuals quality of life. Life expectancy is reduced with the main causes of mortality being renal and cardiovascular disease (CVD) (Laing et al 1999, Pambianco et al 2006, Soedamah-Muthu et al 2006). It is well established that good glycaemic control can reduce the risk of micro vascular complications (DCCT Research Group 1993) and may reduce the risk of cardiovascular events (DCCT/EDIC Study Research Group 2005). In the past there has been a tendency to focus on the prevention of microvascular complications in people with type 1 diabetes, especially in young people. However, it is clear that type 1 diabetes is associated with an increased risk of CVD (Laing et al 2003, Soedamah-Muthu et al 2006, Skrivarhaug et al 2006) and clinical management should therefore focus on global risk factor reduction.

Targets for glycaemic control, blood pressure and lipid profile in patients with type 1 diabetes have been defined in recent years (European Diabetes Policy Group 1999, National Institute for Clinical Excellence 2004, Joint British Societies 2005). However, as demonstrated in previous audits at Aintree Hospital (Wallymahmed et al 2005, Wallymahmed et al 2008, Saunders et al 2004, Saunders et al 2009) these targets can be difficult to achieve in a routine diabetic clinic.

Several studies have demonstrated that nurse led intervention can have beneficial effects on the achievement of cardiovascular (CV) risk factor targets in patients with type 2 diabetes (New et al 2003, Denver et al 2003, Woodward et al 2006). However, there are little data in type 1 diabetes. Therefore, a randomised controlled study, in people with Type 1 diabetes comparing the effects on CV risk targets in patients attending a nurse led CV risk factor intervention clinic with patients receiving routine diabetes care was conducted.

## 6.2 PATIENTS AND METHODS

Eighty one patients with type 1 diabetes attending the Diabetes Centre at Aintree University Hospitals, Liverpool were studied. Recruitment was over an 18 months period

(2005-2006). Inclusion criteria were aged > 18years, type 1 diabetes for at least 5 years, $HbA_{1c} \geq 8\%$ plus at least one other risk factor for the development of CV disease; for example, blood pressure or lipid profile above the European Diabetes Policy Group (EDPG) targets (European Diabetes Policy Group 1999). Eighty six patients were asked to participate in the study and 5 declined mainly due to work related issues. The EDPG targets were used because in 2004, when the study started, the National Institute for Clinical Excellence (NICE 2004) and the Joint British Societies (Joint British Societies 2005) guidelines had not been published. Targets were those defined by the EDPG 1998: $HbA_{1c} <$ 7.5%, total cholesterol < 4.8 mmol/L, LDL < 3.0 mmol/L, HDL >1.2 mmol/L, Triglycerides <1.7 mmol/L. Blood pressure targets were <135/85 mmHg for patients with normal albumin excretion and < 130/80 mmHg for those with abnormal albumin excretion.

Patients were randomised (computer generated blind envelope system) to either routine care or nurse led CV risk intervention. Routine care involved review by doctors (consultant and specialist registrars) in a diabetes clinic with follow up and referral to the multidisciplinary team (diabetes specialist nurse, dietitian) for diabetes control problems only. Recommendations regarding initiation or changes to lipid lowering or anti hypertensive medication were made via letter to the patients General Practitioner (GP). Usual follow up is at 6 -12 monthly intervals.

Nurse led CV risk intervention was carried out by a single diabetes nurse consultant in an out-patient clinic separate from the routine diabetes clinics. The management was protocol driven on a 'treat to target' basis. Management included lifestyle advice including increasing daily activity, healthy eating, information and advice on injection technique and pharmacological interventions (glycaemic control, hypertension, lipids) as required. Patients were reviewed monthly for the first 6 months and then on a 6 monthly basis for 2 years. Patients randomised to the nurse led group were also reviewed in the routine diabetic clinic on an annual basis. Changes to medication were made by a letter to the GP with a copy to the patient.

Characteristics of the patients studied are shown in table 6.1. Microalbuminuria was defined as an ACR >2.5mg / mmol in men and > 3.5 mg / mmol in woman in two out of the last three specimens. Macro proteinuria was defined as an ACR > 300mg / mmol and dipstick proteinuria.

The following biochemical measurements were recorded at baseline, 6 months (nurse led group only) 12 months and 24 months: $HbA_{1c}$, non-fasting serum total cholesterol, high density lipoprotein (HDL) cholesterol, low density lipoprotein (LDL) cholesterol, serum

creatinine and urinary albumin : creatinine ratio (ACR). The method of $HbA_{1c}$ assay during the study period was high pressure liquid chromatography (HPLC), and was aligned to the Diabetes Control and Complications Trial (DCCT 1993). Weight, Body mass index (BMI) and systolic and diastolic blood pressure were also recorded. Blood pressure was measured according to the European Society of Hypertension recommendations (O'Brien et al 2003). The mean of 3 consecutive measurements taken at 2 minute intervals was recorded.

In addition throughout the study, in the nurse led group, serum creatinine and potassium were measured before starting, 7-10 days after starting and following every dose titration of ACE inhibitors or angiotensin 2 receptor antagonists. Liver function tests were measured prior to starting statins and monitored 3 months later.

The study was approved by the Sefton Local Ethics Committee and written consent was obtained from each patient.

## 6.3 STATISTICAL ANALYSIS

Repeated measure ANOVA was used to assess within group differences over time. Independent t tests or chi-square (as appropriate) were used to examine differences between groups. P values $< 0.05$ were considered significant.
Using $HbA_{1c}$ as the primary outcome, a 1% reduction in $HbA_{1c}$ (power 80%, significance at 5%) required 35 patients in each group.

## 6.4 RESULTS

The baseline data showed that the groups were well matched (see table 6.1). Seventy eight (96.2%) of the original 81 patients completed the 2 year study period. Three patients (1 in the nurse led CVR group and 2 in the routine group) failed to attend despite being sent several appointments and were discharged back to general practice. All 3 ( 2 female, mean age 31 years, mean duration of diabetes 20 years) were lost to follow between the 12 – 24 month follow up period. Non attendance rates during the study were 22% in the nurse led group and 26% in the routine group. Throughout the study period 32 (78%) patients in the routine group were referred to the diabetes nurse service for poor glycaemic control.

**Table 6.1** Baseline characteristics of 81 patients with type 1 diabetes studied

| Variable | Nurse led group (n= 40) | Routine Group (n=41) | p |
|---|---|---|---|
| Sex M:F | 21:19 | 24:17 | ns |
| Age (yrs) | 34.9±8.8 | 34.4±10.2 | ns |
| Duration of diabetes (yrs) | 15.8±7.4 | 14.7±8.3 | ns |
| $HbA_{1c}$ (%) | 10.1±1.4 | 9.9±1.4 | ns |
| Weight (kg) | 81.5±16.2 | 81.3±15.6 | ns |
| BMI | 27.8±4.1 | 27.5±5.4 | ns |
| Total cholesterol (mmol/l) | 5.8±0.9 | 5.9±0.9 | ns |
| LDL cholesterol (mmol/l) | 3.4±0.9 | 3.3±.06 | ns |
| HDL cholesterol (mmol/l) | 1.5±0.3 | 1.6±0.5 | ns |
| Systolic BP (mmHg) | 127±22 | 119±17 | ns |
| Diastolic BP (mmHg) | 71±13 | 69±10 | ns |
| Retinopathy | 17 (42.5%) | 19 (46%) | ns |
| Nephropathy:<br>Microalbuminuria<br>Macroalbuminuria | 10 (25%)<br>7<br>3 | 8 (19.5%)<br>5<br>3 | |
| Symptomatic neuropathy | 6 (15%) | 8 (19.5%) | ns |
| Documented ischeamic heart disease | 2 (5%) | 2(5%) | ns |
| Number of patients taking anti-hypertensive agents<br>1 agent<br>2 agents<br>3 agents | 12(30%)<br>8<br>3<br>1 | 9(22%)<br>4<br>4<br>1 | |
| Number of patients taking lipid lowering agents<br>Statins<br>Fibrates | 16(40%)<br>16<br>0 | 9(22%)<br>7<br>2 | ns |
| Insulin regimen | | | |
| Twice daily injections | 13 | 15 | ns |
| Multiple daily injections | 27 | 26 | ns |

Results are reported as mean ± SD or actual numbers (%) as appropriate

### 6.4.1 Glyceamic control

In the nurse led CVR group there was a significant improvement in mean $HbA_{1c}$ between baseline and 6 months (10.1 ±1.4 v 9.2±1.2 %), p<0.001) and this improvement was maintained throughout the 2 year study period (baseline v 24 months, 10.1±1.4 v 9.2±1.6%, p <0.001) (see table 6.2). There were no statistically significant changes in $HbA_{1c}$ throughout the study period in the group randomised to routine care (see table 6.2). At the end of the study period, 6 (15.5%) patients in the nurse led group and 5 (13%) patients in the routine group achieved an $HbA_{1c} \leq 7.5\%$.

Between group (nurse v routine) analysis revealed no significant differences in $HbA_{1c}$ at any of the assessment points throughout the study.

### 6.4.2 Serum lipid profile

There were significant improvements in both total cholesterol and low density lipoprotein (LDL) in both groups over the study period (see table 6.2). In the nurse led group mean total cholesterol improved from 5.8±0.9 mmol/l at baseline to 4.5±0.9 mmol/l at 6 months (p<0.001) and this improvement was maintained at 2 years (4.3±1.1 mmol/l, p< 0.001 compared to baseline). Mean LDL decreased significantly from 3.4±0.9 mmol/l at baseline to 2.4±0.8 mmol/l at 6 months (p<0.001) and again this improvement was maintained at 2 years (2.2±0.9 mmol/l, p<0.001 compared to baseline).

In the routine group total cholesterol improved significantly from 5.9±0.9mmol/l at baseline to 5.2±1.0 mmol/l at 12 months and this improvement was maintained at 2 years (5.0±0.9 mmol/l, p <0.001 compared to baseline), LDL improved significantly from 3.3±0.6 mmol/l at baseline to 2.9±0.8 mmol/l at 12 months (p< 0.001) and was maintained at 2 years (2.6±0.8 mmol/l, p<0.001 compared to baseline).

Unfortunately high density lipoprotein (HDL) fell significantly in both groups throughout the study period (baseline v 2 years, nurse led group 1.5±0.3 v1.3±0.2 mmol/l, p <0.001, routine group 1.6±0.5 v 1.4±0.5 mmol/l, p<0.001).

At the end of the study period more patients in both groups achieved a target cholesterol of < 4.8 mmol/l compared to baseline: 31 (79.5%) v 4 (10%) patients in the nurse led group and 18 (46%) v 2 (5.1%) patients in the routine group. There were more patients in both groups taking lipid lowering medication than at baseline: nurse led group 16 (40%) v 37 (95%), p <0.001; routine group 9 (22%) v 24 (61.5%), p<0.001.

Between group analysis (nurse v routine group) revealed significant differences in total cholesterol ($p < 0.01$), LDL cholesterol ($p < 0.01$) and HDL cholesterol ($p < 0.05$) at 12 months. At 24 months these differences were maintained in total cholesterol ($p < 0.01$) and LDL ($p < 0.05$) cholesterol.

### 6.4.3 Blood pressure

In the nurse led group there were statistically significant improvements in systolic blood pressure over the study period. Systolic BP fell significantly from baseline to 6 months (127±22 v 116±12 mmHg, $p < 0.001$). This improvement was maintained at 12 months (6 months v 12 months, 116±12 v 115±13 mmHg, ns) but there was then a significant increase in SBP between 12 and 24 months (115±13 v 120±15 mmHg, $p < 0.05$). However systolic BP remained significantly improved at the end of the study than at entry to the study (127±22 v 120±15.mmHg, $p < 0.05$). Diastolic blood pressure improved significantly from baseline to 6 months (71±13 v 67±9 mmHg, $p<0.02$) and this improvement was maintained at 12 months (65±9 mmHg, $p<0.02$ compared with baseline). However by 2 years there was no significant difference between baseline and 2 year diastolic blood pressure (71±13 v 68±7 mmHg, $p = 0.157$).

There were no significant changes in either systolic or diastolic blood pressure in patients in the routine group over the study period. At the end of the study, there were more patients in both groups taking anti hypertensive medication: nurse group 12 (30%) v 18(46%), $p < 0.001$; routine group 9 (22%) v 11(28.2%), p=ns. In the nurse led group at the end of the study more patients achieved target systolic and diastolic blood pressure than at baseline: systolic blood pressure 32 (82%) v 27 (67.5%) patients, diastolic blood pressure 39 (100%) v 36 (90%). Whereas in the routine group less patients were at target systolic blood pressure at the end of the study than at baseline: 29 (74%) v 35 (85%) patients, although the majority achieved diastolic blood pressure targets at both baseline and completion of the study (95% v 100%).

Between group analysis (nurse v routine group) revealed a significant difference in systolic blood pressure ($p < 0.01$) at 12 months however this was not maintained at 24 months.

There were no significant changes in BMI, weight or daily insulin dose in either group throughout the study period.

| Variable | Baseline | | 6 months (nurse led group only) | 12 months | | 24 months | |
|---|---|---|---|---|---|---|---|
| | Nurse (n=40) | Routine (n=41) | Nurse (n=40) | Nurse (n=40) | Routine (n=41) | Nurse (n=39) | Routine (n=39) |
| $HbA_{1c}$ (%) | 10.1±1.4 | 9.9±1.4 | 9.2±1.2[a] | 9.3±1.4[c] | 9.7±1.3 | 9.2±1.6[b] | 9.4±1.5 |
| Weight (kg) | 81.5±16.2 | 81.3±15.7 | 81.2±14 | 80.5±14.9 | 81.5±16 | 81±15.2 | 81.8±15.7 |
| BMI | 27.8±4.1 | 27.6±5.4 | 27.8±3.6 | 27.6±4.3 | 27.5±5.6 | 27.6±4.2 | 27.5±5.2 |
| Total cholesterol (mmol/l) | 5.8±0.9 | 5.9±0.9 | 4.5±0.9[a] | 4.3±1.0[c] | 5.2±1.0[c*] | 4.3±1.1[b] | 5.0±0.9 [b*] |
| LDL cholesterol (mmol/l) | 3.4±0.9 | 3.3±0.6 | 2.4±0.8[a] | 2.2±0.8[c] | 2.9±0.8[c*] | 2.2±0.9[b] | 2.6±0.8 [b**] |
| HDL cholesterol (mmol/l) | 1.5±0.3 | 1.6±0.5 | 1.4±0.3 | 1.3±0.3[c] | 1.5±0.4[**] | 1.3±0.2[b] | 1.4±0.5[b] |
| Systolic BP (mmHg) | 127±22 | 119±17 | 116±12[a] | 115±13[c] | 124±14[*] | 120±15 [d,e] | 124±16 |
| Diastolic BP (mmHg) | 71±13 | 69±10 | 67±9[f] | 65±9 [g] | 69±9 | 68±7 | 70±8 |
| Lipid lowering medication | 16 (40%) | 9 (22%) | 32 (80%) | 35 (87%) | 21 (51%) [g*] | 37 (95%)[b] | 24 (61.5%)[b*] |
| Anti-hypertensive medication | 12(30%) | 9 (22%) | 15 (37.5%) | 17(42%) | 11 (27%)** | 18 (46%)[b] | 11 (28%)[**] |

**Table 6.2** The effects of nurse led intervention versus routine clinic care on vascular risk factors in patients with type 1 diabetes

Results expressed as mean ± SD or actual number (%) as appropriate

[a] = p≤0.001 baseline v 6 months

[b] = p≤0.001 baseline v 24 months

[c] = p≤0.001 baseline v 12 months

[d] = p≤ 0.05 12 months v 24 months

[e] = p≤0.05 baseline v 24 months

[f] = p≤ 0.05 baseline v 6 months

[g] = p≤ 0.05 baseline v 12 months

[*] = p ≤ 0.01 between nurse and routine group

[**] = p≤ 0.05 between nurse and routine group

## 6.5 DISCUSSION

Cardiovascular disease is a major cause of death in type 1 diabetes and dyslipidaemia and hypertension are associated with increased CV risk in adults with diabetes (Soedamah-Muthu et al 2004). In the past the major focus, especially in young people with diabetes, has been on the prevention of micro-vascular complications. However, cross sectional studies of children and young adults with diabetes have shown that abnormalities of lipid profile and hypertension are not uncommon and few patients are treated with lipid lowering and anti-hypertensive agents (Schwab et al 2006, Margeirsdottir et al 2008, Edge et al 2008). The benefits of global risk factor reduction in type 2 diabetes have been demonstrated in the Steno 2 diabetes study (Gaede et al 2003) and it reasonable to believe that such benefits can also be achieved in type 1 diabetes. However, achievement of risk factor targets is often difficult to achieve in a routine diabetic clinic.

In this study, at baseline, the major problems were poor glycaemic control and dyslipidaemia; 92.5% of patient had total cholesterol above target. Nurse-led CV risk intervention resulted in significant improvements in glycaemic control (mean reduction in $HbA_{1c}$ 0.9%), without weight gain or an increase in daily insulin dose, which were maintained over the 2 year study period. The education and healthy lifestyle / eating advice given to the patients in the nurse led clinic may contribute to improving glycaemic control without increasing insulin doses.

There were improvements in lipid profiles in both groups accompanied by an increase in the use of statins and this was significantly more in the nurse led CV risk group. Improvements in glycaemic control may have contributed to lipid profile improvements in the nurse led group. There are however concerns about the use of lipid lowering agents particularly in woman of childbearing age and more recently anecdotally, an increase in the number of patients complaining of feeling generally unwell whilst taking statins, has been noted. This study involved predominantly young adults (mean age 34.6 years) some of which were women of childbearing age. The use of statins in young women with diabetes is often a difficult clinical decision which should be made on an individual patient basis and must involve careful counselling about pregnancy planning and contraception. None of the women in this study were planning a pregnancy and there were no unplanned pregnancies during the study. However, all women were counselled prior to medication being started.

It is encouraging that there was a small but significant improvement in systolic blood pressure in the nurse-led CV risk group which was maintained over the study period but

disappointing that that the initial improvements seen in diastolic blood pressure at 6 and 12 months were not maintained at 2 years despite an increase in anti-hypertensive medications. This differs from recent evidence from a nurse-led CVR factor clinic for patients with type 2 diabetes attending the same centre which demonstrated that optimal blood pressure control was maintained over a 7 year follow up period (Woodward et al 2010). Compliance with medication in this current study may be an influencing factor, but there were no specific reports of adverse effects associated with anti- hypertensive agents in the nurse-led group. Hypertension and dylipidaemia are often without symptoms and taking medication may have no noticeable beneficial effects therefore patient education is crucial to maximise compliance. However, more patients in the nurse led group achieved target blood pressure levels at the end of the study than at entry to the study. In the routine group initiation or changes to lipid lowering and anti hypertensive medication were communicated to the patients GP by letter and it is possible that some recommendations may not have been actioned.

During the course of this study it became apparent that many patients were not aware of the increased risk of cardiovascular disease associated with type 1 diabetes. In addition the majority did not know what the target cholesterol and blood pressure levels were. Most however were well aware of the microvascular complications associated with type 1 diabetes. This may be due to type 1 diabetes being diagnosed at an early age when the risk of cardiovascular disease is minimal. Nevertheless people with type 1 diabetes should be made aware of the macrovascular risks associated with type 1 diabetes. Education and discussions about the micro and macrovascular complications of type 1 diabetes and risk factors should be integral elements of diabetes management. The challenge is how to do this without creating excess anxiety and also to ensure that advice is relevant to an individual at that time.

This study has demonstrated that nurse-led CV risk intervention can have a beneficial effect on glycaemic and CV risk factor targets (blood pressure, lipids and $HbA_{1c}$). However the clinic was run by a single senior diabetes nurse and it cannot be assumed that the results are generalisable. It may be that agreeing to take part in the study was a motivating factor in itself. In addition frequent contact with a health care professional can have a positive effect on glyceamic control although improvements were maintained over a 2 year period. Improvements in lipids and BP may be due to a protocol driven approach which may be favoured by nurses (Davidson 2009). However over the 2 year period there were approximately six to eight extra clinic visits per patient which incurred a cost. It could be

argued that, in the absence of this study, the majority of these patients would have been referred to the diabetes specialist nurse service anyway. In the routine group 78% of patients were referred to the diabetes specialist nurse service during the study period but this was for management of glycaemic control only.

Non attendance rates were relatively high in the nurse led clinic (22%) and consultant routine care clinic (26%) and even higher in the patients in the routine group referred to the diabetes nursing service for glycaemic control problems (40%). This is in contrast to a similar clinic in the same centre involving patients with type 2 diabetes where the non attendance rate was just 4% (Woodward et al 2006). The reasons for this are unclear although age and working status may be contributing factors. The patients in this current study were much younger than the patients in the type 2 study (34±9 v 63±9 years) and the majority were in paid employment. Several patients did report problems with getting time off work to come to clinic. Work commitments have been cited as a reason for non attendance at diabetes clinics in other studies (Archibald and Gill 1992, Lawson et al 2005). This has implications for the provision of services at times more accessible to patients, for example after 5pm and at weekends and we may need to consider this in the future. In addition at Aintree Hospital there is a local policy of not routinely discharging people who do not attend. Generally an individual who fails to attend a clinic appointment will be sent at least one additional appointment. After this, failure to attend will be reviewed on an individual patient basis, by the consultant involved in the patients care. Non attendance at clinic can lead to an increase in general waiting times for clinic appointments due to re-appointment of non attenders. In addition there is considerable financial burden to the Trust due to loss of income. It is possible, that if patients are aware that they will be sent another appointment if they fail to attend, that this may in some way make them less likely to attend if they have other pressing commitments. Non attendance rates at diabetes clinics of approximately 20% have been reported previously (Gill and Owens 1998).

In conclusion a nurse led global approach to glycaemic and CV risk factor management is more beneficial in achieving risk factor targets ($HbA_{1c}$, lipid, blood pressure) than a standard diabetes clinic system. This is probably due initially to an increase in contact (monthly appointments for 6 months), an increase in the prescribing of lipid lowering and anti hypertensive agents and possibly greater compliance with medication. The focus of nurse led intervention should shift to concentrating on global CV risk management rather than glycaemic control alone.

## 6.6 REFERENCES


Archibald LK, Gill GV. Diabetic clinic defaulters- who are they and why do they default? Practical Diabetes 1992; 9: 13-14

Davidson MB. How our current medical care system fails people with diabetes . Diabetes Care 2009;32:370-372

Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin dependent diabetes mellitus. New England Journal of Medicine 1993; 329: 977-986

Diabetes Control and Complications Trial / Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Study Research Group. Intensive diabetes treatment and cardiovascular disease in patients with Type 1 diabetes. New England Journal of Medicine 2005; 353:2643-53

Denver EA, Barnard M, Woolfson RG, Earle KA. Management of uncontrolled hypertension in a nurse-led clinic compared with conventional care for patients with type 2 diabetes. Diabetes Care 2003; 26:2256-2260

Edge JA, James T, Shine B. Longitudinal screening of serum lipids in children and adolescents with type 1 diabetes in a UK clinic population. Diabetic Medicine 2008; 25:942-948

European Diabetes Policy Group. A desktop guide to type 1 (insulin dependent) diabetes mellitus. Diabetic Medicine 1999; 16:253-256

Gaede P, Vedel P, Larsen N, Jensen GV, Parving HH, Pedersen O. Multifactoral intervention and cardiovascular disease in patients with type 2 diabetes. New England Journal of Medicine 2003; 348:383-393

Gill G, Owens L. Attendance failures in diabetes clinic. Practical Diabetes International 1998; 15: 141-142

Joint British Societies. JBS 2: Joint British Societies Guidelines on prevention of cardiovascular disease in clinical practice. Heart 2005; 91 suppl v: v1-52

Laing SP, Swerdlow AJ, Slater SD, Botha JL, Burden AC, Waugh NR. The British Diabetic Association Cohort Study, II: cause-specific mortality in patients with insulin treated diabetes mellitus. Diabetic Medicine 1999; 16:466-471

Laing SP, Swerdlow AJ, Slater SD, Burden AC, Morris A, Waugh NR, Gatling W, Bingley PJ, Patterson P. Mortality from heart disease in a cohort of 23,000 patients with insulin-treated diabetes. Diabetologia 2003; 46: 760-765

Lawson VL, Lyne PL, Harvey JN, Bundy C. Understanding why people with type 1 diabetes do not attend for specialist advice: a qualitative analysis of the views of people with insulin-dependent diabetes who do not attend diabetes clinic. Journal of Health Psychology 2005; 10: 409-423

Margeirsdottir HD, Larsen JR, Brunborg C, Overby NC, Dahl-Jorgensen K. High prevalence of cardiovascular risk factors in children and adolescents with type 1 diabetes: a population based study. Diabetologia 2008; 51:554-561

National Institute for Clinical Excellence. Type 1 diabetes: National clinical guidance for diagnosis and management in primary care. London: National Institute for Clinical Excellence. 2004

New JP, Mason JM, Freemantle N, Teasdale S, Wong L, Bruce NJ, Burns JA, Gibson JM . Specialist nurse-led intervention to treat and control hypertension and hyperlipidemia in diabetes (SPLINT). Diabetes Care 2003; 26:2250-2255

O'Brien E, Asmar R, Beilin L, Imai Y, Mallion JM, Mancia G et al. European Society of Hypertension recommendations for conventional, ambulatory and home blood pressure measurement. Journal of Hypertension 2003;21:821-848

Pambianco G, Costacou T, Ellis D, Becker DJ, Klein R, Orchard TJ. The 30 year natural history of type 1 diabetes complications. The Pittsburgh epidemiology of diabetes complications study experience. Diabetes 2006; 55:1463-1469

Saunders SA, Wallymahmed ME, Macfarlane IA Glycaemic control in a type 1 diabetes clinic for younger adults. Quarterly Journal of Medicine 2004; 97: 575-580

Saunders SA. Wallymahmed M, MacFarlane IA Improvements in glycaemic control and cardiovascular risk factors in a cohort of patient with type 1 diabetes over a 5 year period. Quarterly Journal of Medicine 2009;102:29-34

Schwab KO, Doerfer J, Hecker W, Grulich-Henn J, Wiemann D, Kordonouri O, Beyer P, Holl RW. Spectrum and prevalence of atherogenic risk factors in 27,358 children, adolescents, and young people with type 1 diabetes. Diabetes Care 2006;29:218-225

Skrivarhaug T, Bangstad HJ, Stene LC, Sandvik L, Hanssen KF, Joner G. Long-term mortality in a nationwide cohort of childhood-onset type 1 diabetic patients in Norway. Diabetologia 2006; 49:298-305

Soedamah-Muthu SS, Chaturvedi N, Toeller M, Ferriss B, Reboldi P, Michel G . Risk factors for coronary heart disease in type 1 diabetic patients in Europe: the EURODIAB Prospective Complications Study. Diabetes Care 2004; 27:530-537

Soedamah- Muthu SS, Fuller JH, Mulnier HE, Raleigh VS, Lawrenson RA, Colhoun HM. All-cause mortality rates in patients with type 1 diabetes mellitus compared with a non-diabetic population from the UK general research database, 1992-1999. Diabetologia 2006; 49:660-666

Wallymahmed ME, Pinkney J, Saunders S, MacFarlane IA. Vascular risk factors in patients with type 1 diabetes. Practical Diabetes International 2005; 22:81-85

Wallymahmed ME, Morgan C, Gill GV, Osman-Hicks V, Chamberlain P. MacFarlane IA. Changes in cardiovascular risk factors in a type 1 diabetes population: a 3.5 year study. Practical Diabetes International 2008; 25:223-227

Woodward A. Wallymahmed M. Wilding J. Gill G. Successful cardiovascular risk reduction in type 2 diabetes by nurse-led care using an open clinical algorithm. Diabetic Medicine 2006; 23: 780-787

Woodward A, Wallymahmed M, Wilding JP, Gill GV. Nurse-led clinics for strict hypertension control are effective long-term:- a seven year follow-up study. Diabetic Medicine 2010; 27:933-937.

# CHAPTER 7

# GLYCAEMIC STREAMING IN TYPE 1 DIABETES – IMPLICATIONS FOR INTERVENTION?

# CHAPTER 7

# GLYCAEMIC STREAMING IN TYPE 1 DIABETES – IMPLICATIONS FOR INTERVENTION?

## 7.1 INTRODUCTION

It is common clinical experience, that glycated haemoglobin ($HbA_{1c}$) levels in individuals with type 1 diabetes tend to remain remarkably stable over time, and that intervention to improve control often has little or only transient effect. This phenomenon is sometimes known as glycaemic "streaming" or "tracking". There is a very limited supporting literature, but it has been reported from both adult and paediatric type 1 populations (Jorde et al 2000, Edge et al 2010).

Considerable effort and resources are expended on trying to lower $HbA_{1c}$ levels above agreed targets, in order to reduce the future complications associated with persistent hyperglycaemia (DCCT 1993). In this study the issue of glycaemic streaming in a large group of people with type 1 diabetes followed for a 5 year period has been revisited. The aim was to confirm and characterise $HbA_{1c}$ tracking particularly in groups with different levels of long term glycaemic control; and also to investigate the relationship with insulin regimens and doses and frequency of clinic attendance.

## 7.2 PATIENTS AND METHODS

The study looked at retrospective data over a five-year period between 2003 and 2007 taken from a database of type 1 patients attending consultant clinics at the Walton Diabetes Centre, Aintree University Hospitals. Patients aged between 25 and 60 years, with diabetes duration between 2 and 40 years were selected for inclusion if they had attended a clinic for a minimum of four appointments between 2003 and 2007. Patients who were not seen in the start or end years of 2003 and 2007 were excluded, as were women who were either pregnant or receiving pre-pregnancy care during this period. One hundred and eighty one (181) patients were finally available for the study. Clinical information was obtained from patient records.

During the study period, all members of the diabetes care team were committed to optimising glycaemic control in people with type 1 diabetes. This included structured patient education, movement from twice daily to multiple daily injection regimens if indicated, dose adjustment by patients or diabetes specialist nurses, and addition of

metformin to insulin in some cases. During the period of study, continuous subcutaneous insulin infusion (CSCII, "insulin pumps") was not available to patients. An 'in house' structured dietary carbohydrate counting education programme was introduced during the last 4 months of the study.

Age, gender, body mass index (BMI), duration of diabetes, $HbA_{1c}$, insulin doses and frequency of insulin injections were recorded. Other information extracted included the presence of microvascular and macrovascular disease and hospital diabetic clinic attendances.

A minimum of 4 $HbA_{1c}$ measurements over the five-year period were recorded. This included a baseline $HbA_{1c}$ measured in 2003 and a closing measurement in 2007. Additionally, over the 5-year period, a mean of all individual $HbA_{1c}$ measurements was calculated (5-year mean). The method of $HbA_{1c}$ assay during the study period was high pressure liquid chromatography (HPLC), and was aligned to the Diabetes Control and Complications Trial (DCCT 1993).

## 7.3 STATISTICAL ANALYSIS

Data were recorded onto a proforma for each patient, and transferred to a Microsoft Office EXCEL worksheet 97-2003. Student's paired and unpaired t-tests (or Mann-Whitney U-test) as appropriate were used to compare quantitative data. Proportionate data were compared using a Chi-square or Fisher's exact test. Statistically significance was taken at $p < 0.05$. Statistical analysis was performed using the Statistical Package for Social Sciences (Version 18.0).

The study was approved and registered by the Aintree University Hospital Clinical Standards and Audit Group.

## 7.4 RESULTS

### 7.4.1 Group characteristics:

Baseline characteristics of the total group of 181 people with type 1 diabetes are shown in table 7.1. Mean (±/SD) age was 41 ± 8 years and duration of diabetes 19 ± 9 years. There were 58% male and mean $HbA_{1c}$ was 9.0 ± 1.6%. A significant burden of complications was present (see table 7.1)

**Table 7.1** Baseline data on total group of patients with type 1 diabetes (n = 181)

| | |
|---|---|
| Age (y) | 41 ± 8 |
| Duration diabetes (y) | 19 ± 9 |
| Gender ratio (M:F) | 105:76 (58%: 42%) |
| $HbA_{1c}$ (%) | 9.0 ± 1.6 |
| BMI ($Kg/m^2$) | 26.6 ± 4.2 |
| Retinopathy | 81 (45%) |
| Nephropathy | 18 (10%) |
| Microalbuminuria | 34 (19%) |
| Macroangiopathy | 23 (13%) |

Results are reported as mean ± SD or actual numbers (%) as appropriate

Macroangiopathy = coronary artery disease, cerebrovascular disease or peripheral vascular disease

### 7.4.2 $HbA_{1c}$ and BMI changes with time

During the 5 year study period (2003 to 2007), there was a small but significant fall in mean $HbA_{1c}$ for the whole group (9.0 ± 1.6 to 8.7 ± 1.5%, p = 0.003, see table 7.2). This was accompanied by a significant increase in BMI from 26.7 ± 4.3 to 27.5 ± 5.0 (p = 0.002). During the observation period there was no significant change in total insulin dose (0.76 ± 0.26 units/kg to 0.77 ± 0.38 units/kg). When the $HbA_{1c}$ and BMI drifts were analysed by sex, an interesting pattern emerged. The glycaemic improvement (accompanied by a BMI increase) was mostly accounted for by the male sub-population (8.9 to 8.6% $HbA_{1c}$, and 26.1 to 26.8 BMI). These were both statistically significant, whereas the similar drift in females ($HbA_{1c}$ 9.1 to 8.9%, and BMI 27.4 to 28.2) was not significant. Interestingly, though the males showed glycaemic improvement, their insulin dose did not alter significantly, whereas in the females (with no significant glycaemic change), insulin dose fell significantly.

**Table 7.2** Changes in $HbA_{1c}$ and BMI levels for the whole group (and by gender) over 5 years of follow-up

| | 0 years | 5 years | Significance |
|---|---|---|---|
| **Total group** (n = 181) | | | |
| $HbA_{1c}$ (%) | 9.0 ± 1.6 | 8.7 ± 1.5 | p = 0.003 |
| BMI ($Kg/m^2$) | 26.7 ± 4.3 | 27.5 ± 5.0 | p = 0.002 |
| Insulin dose (u/kg)* | 0.76 ± 0.26 | 0.77 ± 0.38 | NS |
| **Males (n = 105)** | | | |
| $HbA_{1c}$ (%) | 8.9 ± 1.6 | 8.6 ± 1.4 | p = 0.005 |
| BMI ($Kg/m^2$) | 26.1 ± 3.6 | 26.8 ± 3.8 | p = <0.001 |
| Insulin dose (u/kg)* | 0.75 ± 0.27 | 0.79 ± 0.37 | p = 0.34 |
| **Females ( n =76)** | | | |
| $HbA_{1c}$ (%) | 9.1 ± 1.6 | 8.9 ± 1.6 | p NS |
| BMI ($Kg/m^2$) | 27.4 ± 4.8 | 28.2 ± 6.0 | p NS |
| Insulin dose (u/kg)* | 0.77 ± 0.24 | 0.73 ± 0.19 | p = 0.003 |

Results are reported as mean ± SD

* Data was incomplete for insulin doses in some patients. Figures given are for n = 142 at 0 years and n = 109 at 5 years. For males n = 80 at 0 years, and n = 65 at 5 years. For females n = 62 at 0 years, and n = 44 at 5 years

### 7.4.3 Comparison of patients with "acceptable" and "poor" control

Patients were divided into 2 groups according to baseline $HbA_{1c}$, A baseline $HbA_{1c}$ <8.0% was considered to be "acceptable" control (Group 1), and those with a baseline $HbA_{1c}$ >8.0% were considered to have "inadequate" control (Group 2). There were no significant differences between these groups of patients in terms of age, diabetes duration, and BMI. There was a small but significant difference in gender ratio, with more males in Group 1. Retinopathy and microalbuminuria were significantly more common in Group 2 patients. There was also a trend for other complications to be more common in this group, but this did not reach significance (see table 7.3). Over the 5 years, Group 2 patients were seen more frequently but missed more clinic appointments than those in Group 1.

**Table 7.3** Comparison of baseline data on Group 1 patients ($HbA_{1c}$ <8.0%) and Group 2 patients ($HbA_{1c}$ >8.0%)

| | **Group 1** $HbA_{1c}$ <8.0% ( n = 32) | **Group 2** $HbA_{1c}$ >8% ( n = 149) | **Significance** |
|---|---|---|---|
| Age (y) | 42 ± 9 | 41 ± 8 | NS |
| Duration (y) | 20 ± 9 | 18 ± 9 | NS |
| Gender (M:F) | 24:8 (75%:25%) | 81:68 (54%:46%) | p = 0.03 |
| BMI | 26.2 ± 3.2 | 26.7 ± 4.4 (n = 138) | NS |
| Retinopathy<br>Nephropathy<br>Microalbuminuria<br>Macroangiopathy | 7 (22%)<br>2 ( 6%)<br>1/30 (3%)<br>1 (3%) | 76 (51%)<br>16 (11%)<br>33/133 (25%)<br>22 (15%) | p = 0.003<br>NS<br>p = 0.01<br>NS |
| Mean yearly clinic visits per patient | 9 ± 3 | 11 ± 4 | p = 0.008 |
| *DNA rate in 5-year period | 22 / 316 (7%) | 380/2076 (18%) | p <0.0001 |

Results are reported as mean ± SD or actual numbers (%) as appropriate

BMI levels were compared with the Mann Whitney U test, and complication rates by Fisher's Exact test.

"$HbA_{1c}$ <8.0%" means 8.0% or less

"$HbA_{1c}$ >8.0%" means 8.1% or more

DNA = did not attend clinic appointment

*DNA rate = number of appointments missed over the 5 year study period as a percentage of the number of appointments offered

Table 7.4 examines trends over the 5 years of observation for the 2 groups. It can be seen that $HbA_{1c}$ remained remarkably static – thus in Group 1 the baseline, 5 year, and overall mean $HbA_{1c}$ levels were 7.3%, 7.2% and 7.3% respectively (not significantly different). BMI increased slightly but significantly, but there was no difference over the 5 years in insulin dose or numbers of injections per day. For Group 2, the HbA1c levels again remained close, though there was a significant drop from 9.4% at baseline to 9.0% at 5 years, and the overall 5 year mean was also slightly significantly different from either figure at 9.2%. As

with Group 1, there was a small but significant rise in BMI, but no difference over the 5 years in insulin dose, although there was a significant increase in the number of patients using multiple insulin injections.

**Table 7.4.** Five year changes in $HbA_{1c}$, BMI, insulin dose and regimen for Group 1 (baseline $HbA_{1c}$ <8.0%) and Group 2 (baseline $HbA_{1c}$ >8.0%) patients

| | 0 years | 5 years | Significance |
|---|---|---|---|
| **GROUP 1 (n = 32)** | | | |
| HbA1c (%) | 7.3 ± 0.6 | 7.2 ± 08 | NS |
| Mean 5 year $HbA_{1c}$ (%) | | 7.3 ± 0.6 | NS (v. 0 and 5 years) |
| BMI ($Kg/m^2$) | 26.2 ± 3.2 | 27.4 ± 3.5 | p = 0.003 |
| Insulin dose (u/kg)* | 0.82 ± 0.33 | 0.83 ± 0.19 | NS |
| Multiple insulin injections | 18 (56%) | 21 (66%) | NS |
| **GROUP 2 (n = 149)** | | | |
| $HbA_{1c}$ (%) | 9.4 ± 1.4 | 9.0 ± 1.4 | p = 0.002 |
| Mean 5 year $HbA_{1c}$ (%) | | 9.2 ± 1.2 | p = 0.03 and p = 0.008 (v. 0 and 5 years) |
| BMI ($Kg/m^2$) | 26.7 ± 4.4 | 27.4 ± 5.2 | p = 0.002 |
| Insulin dose (u/kg)* | 0.75 ± 0.24 | 0.76 ± 0.25 | NS |
| Multiple insulin injections | 89 (60%) | 113 (76%) | p = 0.004 |

Results are reported as mean ± SD or actual numbers (%) as appropriate

**Note:**

Data was incomplete for insulin doses in some patients. Figures given are for n = 28 (Group 1) and n = 72 (Group 2)*

Fishers Exact test was used to compare the usage of 4 times daily insulin.

Definitions of "$HbA_{1c}$ <8.0%" and "$HbA_{1c}$ >8.0%" are as in Table 7.3

## 7.5 DISCUSSION

This 5 year sequential data on glycaemic control in a large number of people with type 1 diabetes took place in an era of accepted commitment to optimised glycaemia. During the 5 year study period a number of clinical / educational care pathways were introduced to target poor glycaemic control for example a structured pathway for patients changing from twice daily to multiple daily injections. The purpose of these pathways was to maximise consistency and provide structure. It is likely that some of the patients included in this study would have been involved in such pathways as they became a routine part of diabetes care in the centre. However, despite major input from the diabetes team, only a slight population improvement in $HbA_{1c}$ occurred (9.0 ± 1.6 to 8.7 ± 1.5%, p = 0.003), and this reflected improvement amongst males but not females. When comparing well ($HbA_{1c}$ <8.0%) and poorly ($HbA_{1c}$ >8.0%) controlled patients, the well-controlled group had essentially identical control throughout the 5 year period of observation. The poorly-controlled group showed a small but significant $HbA_{1c}$ improvement (9.4 ± 1.4 to 9.0 ± 1.4%, p = 0.002).

The data suggests that over time, individual $HbA_{1c}$ levels do remain remarkably "streamed" or "tracked"(Jorde et al 2000, Edge et al 2010), though small improvements can occur in specific sub-groups – notably males and those with poor baseline control. Interestingly, though improved glycaemia in these sub-groups was associated with small but significant rises in BMI (a well-known phenomenon), there was not a similar rise in mean insulin dose. Perhaps unsurprisingly, poor control was associated with more non-attendance at clinic visits.

Though it is empirically plausible that it may be easier to lower high $HbA_{1c}$ levels, than those already at or near target levels, the gender difference we observed in glycaemic streaming is less easy to explain. However, some studies have suggested that mean glycaemia in female type 1 patients may be higher than male counterparts (Pound et al 1996), and that females (particularly young females), may be more resistant to attempts to intensify insulin treatment (Hardy et al 1991). This may relate to under-treatment with insulin amongst females (Morris et al 1997), sometimes known as "insulin omission" or "insulin restriction" (Goebel-Fabbri et al 2011) – a phenomenon which may relate to weight control (Peveler et al 2005).

Only a few other studies have assessed in detail glycaemic streaming in type 1 diabetes. In 2000, Jorde and Sundsfjord assessed 272 adult type 1 patients between 1992 and 1997. Though overall glycaemic trends were not assessed, they found a close correlation between

first and last $HbA_{1c}$. Also, major clinical events such as heart disease and laser treatment for retinopathy, had a small but non-significant lowering effect on $HbA_{1c}$; but intensification of insulin treatment did not. An interesting finding was that in recently-diagnosed patients, the mean $HbA_{1c}$ between 3 to 12 months post-insulin initiation, was a strong predictor of the 5 year $HbA_{1c}$.

A second study was by Edge et al (2010) and concerned 362 paediatric type 1 patients (age 0-18 years) observed between 2001 and 2009. A mean population improvement in $HbA_{1c}$ was found, as with the study reported here (9.23 ± 1.5 to 8.1 ± 1.3%, $p < 0.0001$). However, within this improvement, marked individual "tracking" was found, and poor control at 6 months post-diagnosis rarely improved in subsequent years. In addition a recent paediatric study has shown that $HbA_{1c}$ at 12 months post-diagnosis was "highly predictive" of future control up to 4 years later (Viswanathan et al 2011). However, a further study involving 277 children and young people with type 1 diabetes, reported that glyceamic control in the second year following diagnosis (but not the first 12 months) was a strong predictor of future glycaemic control (Chemtob et al 2011).

The above studies differ from the study reported here as they included mainly children and focus on the relationship between glycaemic control in the first year following diagnosis and subsequent $HbA_{1c}$. This study involved adults (mean age 41±8 years, range 25- 60 years) with a longer mean duration of diabetes (19±9 years, range 2-40 years) and therefore focused on glycaemic control further into the disease process. Glycaemic control in the first 12 months following diagnosis was not available. Nevertheless, despite small improvements in glyceamic control in the group as a whole, over a 5 year period a "streaming" effect was observed.

The findings of the above studies and the study reported here have important implications for the care of people with type 1 diabetes. It may be that interventions, to improve glycaemic control, in the first 12 months after diagnosis reap the greatest benefit and therefore resources should be diverted to intensive clinical and educational intervention in the first 12 – 18 months. This does, however, need to be balanced against the risk of educational overload. It is possible that motivation is greatest in the months following diagnosis and that patients are more receptive to advice and health education messages.

Attempts to improve established poor glycaemic control currently consume large amounts of medical and nursing time and resources, but the returns for these efforts are small. It may be that efforts should be diverted to potentially more rewarding aspects of type 1 diabetes care – for example, lipid control, optimisation of blood pressure, smoking

cessation, and intensive micro-albuminuria management (Wallymahmed et al 2008, Saunders et al 2009).

Intensification of glucose control should perhaps be prioritised to the first 12 months after diagnosis, as the evidence suggests that good control achieved in this period will continue long-term.

## 7.6 REFERENCES


Diabetes Control and Complications Trial (DCCT) Research Group. The effect of intensive treatment of diabetes on the development of and progression of long-term complications in insulin-dependent diabetes mellitus. New England Journal of Medicine 1993; 329: 977-986

Chemtob CM, Hochhauser CJ, Shemesh E, Schmeidler J, Rapaport R. Does poor early metabolic control predict subsequent poor control in young children with Type 1 diabetes: An exploratory study. Journal of Diabetes 2011; 3: 153–157

Edge JA, James T, Shine B. Persistent individual tracking within overall improvement in $HbA_{1c}$ in a UK paediatric diabetes clinic over 15 years. Diabetic Medicine 2010; 27: 1284-1288

Goebel-Fabbri AE, Franks DL, Anderson BJ et al. Improvement and emergence of insulin restriction in women with type 1 diabetes. Diabetes Care 2011; 34: 545-550

Hardy KJ, Jones KE, Gill GV. Deterioration in blood glucose control in females with diabetes changed to a basal-bolus regimen using a pen-injector. Diabetic Medicine 1991; 8: 69-71

Jorde R, Sundsfjord J. Intra-individual variability and longitudinal changes in glycaemic control in patients with type 1 diabetes mellitus. Diabetic Medicine 2000; 17: 451-456

Morris AD, Boyle DIR, McMahon AD, Greene SA, MacDonald TM, Newton RW. Adherence to insulin treatment, glycaemic control, and ketoacidosis in insulin-dependent diabetes mellitus. Lancet 1997; 350: 1505–1510

Peveler RC, Bryden KS, Neil HAW, Fairburn CG, Mayou RA, Dunger DB. The relationship of disordered eating habits and attitudes to clinical outcomes in young adult females with type 1 diabetes. Diabetes Care 2005; 28:84–88.

Pound N, Sturrock NDC, Jeffcoate WJ. Age related changes in glycated haemoglobin in patients with insulin-dependent diabetes mellitus. Diabetic Medicine 1996; 13: 510-513

Saunders SA, Wallymahmed M, MacFarlane IA. Improvements in glycaemic control and cardiovascular risk factors in a cohort of patients with type 1 diabetes over a 5 year period. Quarterly Journal of Medicine 2009; 102: 29-34

Viswanathan V, Sneeringer MR, Miller A, Eugster EA, DiMeglio LA. The utility of haemoglobin A1c at diagnosis for prediction of future glycaemic control in children with type 1 diabetes. Diabetes Research and Clinical Practice 2011; 92: 65-68

Wallymahmed ME, Morgan C, Gill GV, Osman-Hicks V, Chamberlain P. MacFarlane IA. Changes in cardiovascular risk factors in a type 1 diabetes population: a 3.5 year study. Practical Diabetes International 2008; 25:223-227

# CHAPTER 8

# LIMITATIONS AND FUTURE DIRECTIONS

# CHAPTER 8

# LIMITATIONS AND FUTURE DIRECTIONS

## 8.1 STRENGTHS AND WEAKNESSES OF THE STUDIES

### 8.1.1 Glycaemic control and vascular risk factors in type 1 diabetes

The initial audit involved a large number of people with type 1 diabetes (218 participants) who represent over 20% of the total Diabetes Centre type 1 population. All were involved in real life routine diabetes care which included access to the multidisciplinary diabetes team as clinically appropriate. In addition all had access to patient initiated advice from a diabetes specialist nurses and dietitian. The case note audit was carried out by one researcher (a diabetes nurse consultant) therefore limiting the risk of errors of interpretation of the data. However the data retrieved was dependent on documentation from the clinical staff involved in the patients clinic attendance and it is possible that some data for example smoking status was discussed but not documented. In addition the audit focused on one consultant led clinic. It may have been useful to audit an additional type 1 population attending another consultants clinic and compare results. However there is no reason to believe that there are differences in practices and the clinic audited has the largest population of people with type 1 diabetes in the centre.

Although glycaemic targets remained the same between the two audit periods, blood pressure and lipid targets changed therefore the audit standards differed between the 2 audits. Also apart from albumin : creatinine ratios where serial results were reviewed, both audits were snap shot audits and it was not possible to assess individual trends, which may have influenced clinical management. For example a patient with chronic poor glycaemic control may have been reviewed by a diabetes specialist nurse on several occasions with no significant improvement in glyceamic control. Therefore it may not have been considered clinically appropriate to refer again. However the audits did reveal that in routine care improvements in glycaemia and cardiovascular risk factors are possible although many patients fail to achieve such targets.

### 8.1.2 Physical fitness and glycaemic control in type 1 diabetes

There are few data on fitness and aerobic capacity in type 1 diabetes. The first study on physical fitness is valuable because it involves a large number (141) of unselected people with type 1 diabetes. However it is an observational study and results should therefore be interpreted with care. The Chester Step test is an objective measure of aerobic capacity (as opposed to a self reported questionnaire), is simple to use and can be conducted in a routine clinic setting. Nevertheless it does not directly measure peak maximal oxygen uptake.

The results of the second study of physical fitness, investigating how people with type 1 diabetes manage physical activity, should also be interpreted with care. This study involved only a small number of participants (50) and the definition of vigorous activity (at least 1 hour of aerobic activity per week) was made on an arbitrary basis. In addition the physical activity questionnaire was developed 'in-house' (see appendix 1) and the psychometric properties of the questionnaire were not assessed. Furthermore self reported questionnaires do have limitations and these have been discussed previously (section 3.6). However the questionnaire was simple, consisting mainly of tick box responses and there were no reported problems with interpretation of the questions.

Aside from these limitations it is clear that management advice for people with type 1 diabetes during physical activity is suboptimal. General guidelines may be insufficient and individual advice is indicated. Since these studies have been completed we have introduced two intensive education programmes for people with type 1 diabetes. A four week group education programme ('the 4 steps programme') and a pathway for people requesting individual advice. Both involve a diabetes specialist nurse and a dietitian with a focus on flexible insulin dosing according to carbohydrate intake and physical activity. The management of physical activity is included in these pathways.

### 8.1.3 Randomised controlled study

The major strengths of the study of nurse led intervention were that it was a randomised controlled design and it included only patients with type 1 diabetes. The majority of previous studies of nurse led intervention have not been controlled and have included mainly people with type 2 diabetes. The baseline characteristics of the group were similar therefore adding

strength to the outcome data. However, compared to the total clinic population of people with type 1 diabetes, the number of participants in group was relatively small.

Whilst previous studies of nurse led intervention have been of a relatively short duration (6-12 months), data was available for 2 years in this study. However re-examination of the patients involved in this study may be worthwhile to assess the long term effects of a period of nurse led intervention. The effects of structured nurse-led intervention on long term glycaemic control (4 years post intervention), in 80 people with type 2 diabetes from rural Africa, has been investigated (Price et al 2011). Significant improvements in $HbA_{1c}$ were evident in the first 18 months (10.8±4.0% versus 7.5±2.0%, baseline versus 18 months, $p<0.001$) after which $HbA_{1c}$ began to deteriorate. However at 48 months $HbA_{1c}$ was still significantly better than at baseline (10.8±4.0% versus 9.7±4.0, $p=0.015$). The authors suggest that the deterioration in glycaemic control was due to both educational 'wear off' and the natural history of type 2 diabetes. Deterioration in $HbA_{1c}$ in patients randomised to the intensive treatment arm of the DCCT was evident after completion of the study.

Although the study, of nurse-led intervention, reported in this thesis was initially resource intensive (monthly appointments for the first 6 months of the study), patients were then reviewed on a 6 monthly basis which is the same frequency as in the routine clinic. Therefore although consideration has to be given to resources in the initial stages, on a long term basis there were no additional resource implications and this may favour the long term viability of the clinic.

Encouraging lifestyle change and self management strategies were integral elements of nurse led intervention as it can influence not only glycaemic control but also lipid profile and blood pressure. In addition nurse led intervention included a comprehensive review of injection technique, injection sites, timing of insulin injections, pen needle size and compliance with insulin injections. Anecdotally there were several reports of poor compliance with insulin often due to uncertainty on how to manage insulin injections in specific situations, for example how to adapt long acting insulin according to social situations. Another contributory factor may have been poor management of hypoglycaemia, overcompensating or the use of chocolate, which were reported. All of these issues may influence overall glycaemic control. Patients were encouraged to monitor blood glucose levels in a systematic manner, alter insulin doses according to blood glucose patterns and contact the diabetes specialist nurse running the clinic

for advice as required. There were no formal arrangements for the diabetes specialist nurse to contact the patient between clinic visits. Being involved in a study may have encouraged patients to make telephone contact in between clinic visits however we did not collect data on the frequency of telephone contact.

Agreeing to take part in a study may have been a motivating factor in itself, encouraging a greater focus on lifestyle changes and compliance with blood glucose monitoring and medication. It is well known that the behaviour of individuals who are involved in a study can change due to the novelty effect of being in a study, this is known as the 'Hawthorne effect' (Gale 2004). However as this study was of 2 years duration the novelty effect may have started to decline. Recruitment to a clinical trial which involves a single screening visit has been shown to have a beneficial effect on glucose control between screening and randomisation, independent of any therapeutic interventions, (Gale et al 2007). In this study, involving 3 trials and 429 people with type 1 diabetes, $HbA_{1c}$ changed by a mean of -0.13% in the time between screening and randomisation (median time from screening to randomisation 28 days). In those patients who waited more than 28 days between screening and randomisation the mean change in $HbA_{1c}$ was greater (-0.24%). This may reflect an increase in motivation leading to altered behaviour as a result of information given during the screening visit. It is also possible that the behaviour of health care professionals involved in clinical studies is altered. This may be influenced by a desire for positive results or more consultation time being available enabling health care professionals to provide more individualised clinical care and education. In the study reported in this thesis patients who agreed to take part in the study were randomised on the day. In those randomised to the nurse led group, 40 minutes was allocated to the first visit, and then follow up appointments were of 30 minutes duration. Standard appointments times (new patient or follow up) in nurse led clinics in the diabetes centre at the time of the study were 30 minutes.

The clinic was run by a single senior diabetes nurse, experienced in the management of type 1 diabetes (especially glycaemic control) and it cannot be assumed that the results can be generalised. In addition the management of hypertension and dyslipidaemia, which were not previously the remit of the diabetes specialist nurse, was protocol driven which provided a more structured approach to treatment changes and may have aided the achievement of targets. Diabetes specialist nurses are skilled in the management of glycaemic control, some

have experience of cardiovascular risk management and many have knowledge of associated auto immune endocrine conditions. However they do not have comprehensive medical knowledge and experience and are not able to deal with other presenting medical conditions. Advice to contact general practitioners about emerging health problems can be given however this may not meet the patients expectations.

The switching of focus to global risk factor reduction from soley glycaemic control may have been a positive influence of nurse led intervention. In the past the central element of nurse led intervention has been glycaemic control and it is possible that patients with chronic poor glycaemic control grow weary of advice ("educational fatigue") and referral especially if they feel they are giving their best efforts. This may be evident in the high non attendance rate noted in those in the routine group who were subsequently referred to the diabetes specialist nurse team. Changing the emphasis to other risk factors such as lipid control may enable them to concentrate on positive lifestyle changes affecting several risk factors.

### 8.1.4 Glycaemic streaming in type 1 diabetes

The retrospective glycaemic streaming study involved a large group of people (181) with type 1 diabetes attending for routine diabetes follow up at one large specialist centre were serial $HbA_{1c}$ data was available. It is well accepted that glycaemic control is complex and influenced by many factors such as motivation, compliance and social support (Fukunishi et al 1998, van Dam et al 2005) which were not assessed in this study. In addition this study involved only those who continued to attend for follow up and results cannot be generalised to non-attenders. However results do support the commonly held view that those who frequently fail to attend have the poorest control but this may simply be due to having more appointments to attend. In addition the results add strength to the limit information on glycaemic streaming in type 1 diabetes.

## 8.2 TYPE 1 DIABETES – FUTURE RESEARCH AND DIRECTIONS

The focus of this thesis has been the achievement of glycaemic and cardiovascular risk factor targets in people with type 1 diabetes. The studies included demonstrate that type 1 diabetes is a complex condition requiring at least lifelong insulin replacement and that for many patients, even with intensive intervention, target $HbA_{1c}$, blood pressure and lipid levels are difficult to achieve. There are of course many wide ranging barriers to achieving these targets, including access to health care, motivation, economic and social factors. Many of these barriers are beyond the immediate remit of the diabetes team.

### 8.2.1 Who should care for people with type 1 diabetes – doctor or nurse?

It is well accepted that cardiovascular and renal disease are the major cause of premature death in people with type 1 diabetes. Targets for glycaemic control, blood pressure and lipid profile in people with type 1 diabetes have been defined in recent years. However, as demonstrated in this thesis, in "real life" clinic situations achievement of these targets is difficult.

The randomised controlled study conducted as part of this thesis demonstrated that, in the nurse-led group, improvements in glycaemic control and other cardiovascular risk factors in people with type 1 diabetes can be achieved. However it may be that these improvements are simply a consequence of more frequent contact, with the same health care professional. This frequent contact may have increased the intensity of the intervention resulting in for example greater patient motivation and compliance with treatment regimens. A more effective way of comparing nurse and doctor led care would be to conduct a randomised controlled study of intervention of the same frequency and intensity. Such a study could include external observation (by an independent observer) of clinical consultations which may help indentify elements / behaviours of nurse or doctor led intervention which may influence specific outcomes, for example different consultation styles or structure of the consultation.

### 8.2.2 Patient factors influencing the achievement of vascular risk targets

A diagnosis of type 1 diabetes requires changes in life style, lifelong medical care and adherence to an often complicated treatment regimen to reduce the risk of long term complications. Effective self care depends on the person with diabetes performing a series of

self care behaviours which include insulin injections (often several times daily), monitoring of blood glucose levels and dietary considerations. Many people with type 1 diabetes manage to successfully integrate the demands of the condition into their daily lives to achieve target blood glucose levels however for others this is not the case. Identification of the personal and social factors associated with self management skills could lead to early identification of those who require more intensive support and resources could be directed to these individuals. This could include factors associated with compliance and non compliance in individuals with type 1 diabetes.

### 8.2.3 The effects of physical activity on glycaemic control in type 1 diabetes

A review of the current literature and the results of the studies included in this thesis leads to an uncertainly of the effects of physical activity on glycaemic control in adults with type 1 diabetes. There is an urgent need for randomised controlled studies investigating the effects of structured programmes of physical activity on glycaemic control including the direct measurement of peak maximal oxygen uptake. Such studies also need to investigate methods of managing blood glucose levels in preparation for physical activity, during activity and after physical activity (when the risk of hypoglycaemia is often greatest). The utilisation of continuous blood glucose monitoring systems would be a useful tool in such studies. However studies such as these are resource intensive and expensive to conduct. On a local level a randomised controlled study investigating the effects of structured individualised patient education on time spent being physically activity, physical fitness, glycaemic control, frequency of hypoglycaemia and cardiovascular risk factors in a group of sedentary people with type 1 diabetes could help identify if education influences these factors. Education of health care professionals in the management of physical activity in type 1 diabetes would be a central element of such a study. Therefore it would be useful to assess both the current knowledge of health care professionals in this area and the advice currently given to patients regarding the management of exercise before conducting the study.

### 8.2.4 Should type 1 diabetes be managed in primary care?

The current health care climate favours a move towards the management of both type 1 and type 2 diabetes in primary care. In north Liverpool this would represent a large change as traditionally type 1 diabetes has been managed, by specialist teams, in secondary care.

However practice nurses and GP's do have the advantage of being able to view the person with type 1 diabetes within the context of the family and social setting and this may have some advantages. In addition they are ideally placed to assess compliance with medication at least as defined by prescription requests. Although a request for a prescription does not necessary mean that the medication is collected from the pharmacy and taken as prescribed. Further research is required into the factors associated with compliance and non compliance in type 1 diabetes. This requires open, honest and non-judgemental dialogue with people with type 1 diabetes. If reasons for non compliance are established then resources may be directed to improve compliance. However designing robust methods of assessing compliance is difficult and future research may focus on this area.

Perhaps the way forward for the management type 1 diabetes is for specialist teams to work with primary care colleagues in community based 'satellite' clinics. This would facilitate the development and transfer of skills and knowledge in type 1 management enabling primary care colleagues to manage initially non complicated type 1 diabetes. Wherever diabetes care is delivered there is a need for ongoing audit of glyceamic control, achievement of cardiovascular risk factors, ideal body weight and smoking status followed by a re-evaluation of services.

## 8.3 CONCLUSION

Type 1 diabetes is a complex condition requiring lifelong insulin replacement and contact with health services. However the burden of day to day management falls to the person with diabetes. Health care systems should adapt to deliver optimum care for people with type 1 diabetes ensuring that clinical advice, screening, education and support are available according to clinical need. Nurse led clinics have become common place in both primary and secondary care and non medical prescribing has aided further development. However nurse led services are not without their limitations as most nurses do not have the breath of medical knowledge that their medical colleagues possess. Nevertheless available evidence suggests that, at least in type 2 diabetes, specialist nurses are effective in managing glycaemic control and cardiovascular risk factors. This thesis supports a role for nurse led intervention in type 1 diabetes. It may be that routine diabetes care should become the responsibility of specialist nurses freeing medical staff to manage only the most complex of patients. There is, however, a need for longer term (4-5 years duration) studies of nurse led intervention in both primary and secondary care.

Self management of type 1 diabetes requires constant vigilance. Health care professionals should work in partnership with people with type 1 diabetes involving them in care planning, setting and reviewing individual goals. This may necessitate a change in consultation style and culture which may initially be more time consuming. In addition people with diabetes now have greater expectations from health care. These expectations should be accompanied by greater self responsibility explicit from diagnosis.

Engaging patients in pathways of care can be problematic, especially in those with chronic poor control. The assessment of motivation to change before embarking on intervention may be useful as may 'contracted' care pathways. Such pathways involve patients agreeing to a contract of care including willingness to attend appointments, setting and working towards individual objectives. If either party do not meet the requirement of the contract it is terminated. This would however require not only a change in culture but also training of staff involved and careful explanation to patients. Nevertheless when resources are scarce and non attendance rates high services need to be reviewed.

Services should be guided by current research evidence. Emerging evidence indicates that once glycaemic control is established a streaming effect occurs. A concerted effort to achieve target glycaemic control within the first year following diagnosis is indicated and this requires redirection of resources. A system utilising a care pathway contract, which includes assessment of motivation, may be indicated in the management of established poor glycaemic control.

Since the start of the work reported this thesis, the role of the diabetes specialist nurse has changed considerably in many areas. Diabetes nurses, like medical staff, have developed sub specialties for example renal, weight management, cardiovascular risk and insulin pump clinics. Patients attending all of these sub specialty clinics also require attention to global risk factor reduction. The current economic climate has made it more difficult for some patients to take time away from work to attend clinic appointments and appointments need to be multifunctional addressing all risk factors in a step wise approach. A great deal of this management can be pathway and protocol driven. Protocol driven care is generally favoured by nurses. Many specialist nurses are now independent non medical prescribers widening their scope of practice and responsibility and putting them in an ideal position to lead protocol driven care.

## 8.4 REFERENCES

Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Study Research Group. Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. The New England Journal of Medicine 2005; 353: 2643-2653

Fukunishi I, Horikawa N, Yamazaki T, Shirasaka K. Perception and utilization of social support in diabetic control. Diabetes Research and Clinical Practice 1998; 41: 207-211

Gale EAM. The Hawthorne studies: a fable for our times? Quarterly Journal of Medicine 2004;97:439-449

Gale, EAM, Beattie SD, Hu J, Koivisto V, Tan MH. Recruitment to a clinical trial improves glycemic control in patients with diabetes. Diabetes care 2007; 30:2989-2992

Price C, Shandu D, Dedicoat M, Wilkinson D, Gill GV. Long-term glycaemic outcome of structured nurse-led diabetes care in rural Africa. Quarterly Journal of Medicine 2011; 104: 571-574.

Van Dam HA, Van der Horst FG, Knoops L, Ryckman RM, Crebolder HFJM, Van der Borne BHW. Social support in diabetes: A systematic review of controlled intervention studies. Patient Education and Counselling 2005; 59: 1-12.

# APPENDICES

## APPENDIX 1 - EXERCISE QUESTIONNAIRE

We are interested in understanding how people with type 1 diabetes manage physical activity and insulin injections and we would be grateful if you could complete this questionnaire. Please answer each question and write any comments related to the question in the space provided

Patients Name:

Hospital Number:

HbA1c:

1) What is your current occupation and what physical activity does your job entail?

2) How much time do you spend undertaking the following physical activities **per week**?

| | Walking (Specify) | Housework | Sport | Gym | Other |
|---|---|---|---|---|---|
| Hours | ..... | ..... | ..... | ..... | ..... |

3) When you undertake **Extra** physical activity (E. G. Gym/football etc...) do you? **(Please Tick)**

| | **Yes** | **No** |
|---|---|---|
| Increase Insulin | | |
| Decrease Insulin | | |
| Leave Insulin dose the same | | |
| Eat/Drink more | | |
| Do nothing | | |

4) If you eat/drink more with extra activity?

What do you eat/drink?

When do you eat/drink more?

5) Do you check your sugars? **(Please Tick)**

| | **Always** | **Occasionally** | **Never** |
|---|---|---|---|
| Before exercise | | | |
| After exercise | | | |
| During exercise | | | |

6) If after exercise, how long after?

7) During exercise, what blood sugars levels do you aim for? **(Please Tick)**

| | Please Tick |
|---|---|
| Above usual levels | |
| Usual levels | |
| Don't worry about them | |

8) If above usual why do you do this?

9) Do you try and take more or less exercise because you have diabetes? **(Please Tick)**

| | Please Tick |
|---|---|
| More | |
| Less | |
| About the same | |

| **Why do you do this?** |
|---|
| |

10) What are your reasons for taking exercise? **(Please Tick)**

| | Please Tick |
|---|---|
| Enjoyment | |
| Keep fit and healthy | |
| Reduce weight | |
| All of the above | |

| Please add any further comments below |
|---|
| |

11) How often do you experience hypoglycaemia (a blood sugar less than 4 mmol/L) during exercise? **(Please Tick)**

| | Please Tick |
|---|---|
| Never | |
| Occasionally | |
| A lot | |

12) How often do you experience hypoglycaemia (blood sugar < 4 mmol/L) after exercise? **(Please Tick)**

| | Please Tick |
|---|---|
| Never | |
| Occasionally | |
| A lot | |

13) Have you ever had a bad hypo during or after exercise requiring assistance from someone else? **(Please tick)**

| | Please Tick |
|---|---|
| Yes | |
| No | |

13) We would be grateful for any comments you have about managing diabetes and exercise.

## APPENDIX 2 - CONSENT FORM

### MANAGEMENT OF RISK FACTORS IN TYPE 1 DIABETES

Name of Researcher: Maureen Wallymahmed – Nurse Consultant – Diabetes

Name.....

1. I confirm that I have read and understand the information sheet dated..... (Version 2) for the above study and have had the opportunity to ask questions. ( )

2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. ( )

3. I understand that sections of my medical notes may be looked at by members of medical and nursing staff involved in this study. I give my permission for these individuals to have access to my records ( )

4. I agree to take part in the above study ( )

Name of Patient..... Date.....

Signature.....

Name of person taking consent ..... Date.....

Signature.....

Researcher..... Date.....

Signature.....

1 copy for the patient, 1 copy for the researcher, 1 copy to be kept with the hospital notes

## APPENDIX 3 - PATIENT INFORMATION SHEET

### MANAGEMENT OF RISK FACTORS IN TYPE 1 DIABETES

The Diabetes Team at University Hospital Aintree is conducting a study looking at the management of "risk factors" e.g. inactivity, high blood sugars, high blood pressure and high blood fats for developing complications of diabetes.

You are being invited to take part in this study. Before you decide it is important for you to understand why this research is being done and what it will involve. Please take the time to read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether you wish to take part.

**What is the purpose of the study?**

People with diabetes are at risk of developing problems with their eyes, limbs and kidneys. We know that the chances of developing these problems can be reduced if patients follow healthy lifestyles and keep active and if blood sugar, blood pressure and blood fats (cholesterol) are well controlled.
We are not sure if patients who are at risk of developing complications are best looked after in a clinic run by specially trained nurses or in the normal diabetic clinic. The purpose of this study is to identify patients who may be at risk of developing these problems and then to investigate which is the best way to care for them

**Do I have to take part?**

It is up to you whether or not you to take part. If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form. If you decide to take part you are still free to withdraw at any time and without giving a reason. A decision not to take part, or to withdraw at any time, will not effect the standard of care you receive.

**What will happen if I take part?**

If you decide to take part you will be asked to attend the Diabetes Centre at Walton Hospital for an assessment. We will try to arrange this for a day you are attending the clinic for your normal check up.
We will ask you some questions about your medical and family history. We will also measure your blood pressure, height, weight, waist and hips and ask you to stand on a machine (similar to weighing scales)
to measure the amount of fat you have in your body. We will then take a small amount of blood from your arm (about 2-4 teaspoons) for routine blood tests. The whole visit should take no more than 30 minutes.

Following this initial assessment patients who may be at risk of developing complications will be contacted by letter or phone. If you agree to take part in the study you will be allocated (on a random basis) to attend <u>either</u> a clinic run by a specially trained nurse or to continue attending the Diabetes Centre as normal.

If you are in the group who attends the nurse led clinic you will be seen on a monthly basis (for up to 6 months) to control your blood sugars, blood pressure and blood fats. You will then be seen on a 6 monthly basis to make sure these things are still well controlled. In addition you will still be seen on a yearly basis by your medical consultant. This may involve several extra visits to the Diabetes Centre initially but then should only be on a twice yearly basis for a period of 2 years. Every year we will measure your fitness level, weight, hips, waist and body fat.

If you are in the group who continues to attend the Diabetes Centre as normal every year (for 2 years) we will measure your fitness level , weight, waist, hips and body fat. As far as possible we will try to do this when you are due to attend for your routine clinic appointment.

**What are the possible disadvantages and risks of taking part?**

You may experience some slight discomfort when the blood sample is being taken, as you would in the routine diabetic clinic.

**What if something goes wrong?**
If you are harmed by taking part in this research project, there are no special compensation arrangements. If you are harmed due to someone's negligence, then you may have grounds for legal action but you may have to pay for it. Regardless of this, if you wish to complain about any aspect of the way you have been approached or treated during the course of the study the normal National Health Service complaint mechanism should be available for you.

**Will my taking part in this study be confidential?**

All information collected about you during the course of this study will be kept strictly confidential. If any changes to your treatment are made your General Practitioner will be informed by letter in the usual way.

If you agree to take part in this study you will be given a copy of this information sheet and a consent form to sign.

South Sefton Research Ethics Committee reviewed this study

If you need any further information please contact: Maureen Wallymahmed, Nurse Consultant – Diabetes on 0151-529-3012

Thank you for agreeing to help in this study