Prevalence and risk factors of diabetes and insulin resistance in patients attending a health care centre in Kuwait, and the accuracy of a point of care device to measure glycated haemoglobin to monitor patients with diabetes.

Thesis submitted in accordance with the requirements of the University of Liverpool, Liverpool School of Tropical Medicine for the degree of Doctor in Philosophy

By

Dr Ahmad Abdulwahab Almotawa

April 2018

Liverpool School of Tropical Medicine, Pembroke Place, L3 5QA, Liverpool UK.

Telephone: +44 151 7053355, email: Luis.Cuevas@lstmed.ac.uk

Dedication

I dedicate my work to my parents and my family. A special feeling of gratitude to my late father and my loving mother, whose words of encouragement and support helped me to achieve this thesis. Special thanks to my wife Maha, my son Abdulwahab, and my daughter Sarah, they have never left my side. My gratitude to my brother Khalid, my sisters Hadeel and Fatimah, they are the best supporters.

Acknowledgement

I would like to express my truthful gratitude to my supervisor Professor Luis Cuevas for the continuous support of my PhD study, for his patience, motivation, and immense knowledge. His guidance helped me through all times of my study. I could not have imagined having a better mentor for My PhD.

I would like to thank Mr Russell Dacombe for his encouragement, and Professor Geoff Gill for his insightful comments which incentivise me to widen my research from various perspectives.

Progress Assessment Panel members; Dr Ralf Weigel and Dr Philip Jones, thank you for your guidance, and I want you to know how much I value your support.

My sincere thanks to Dr Jamila Alfaraj and Dr Aravinda Rao for providing me with an opportunity to join their team and giving me access to the clinical and laboratory facilities in Kuwait, without their valuable support, it would not be possible to conduct this research. I would also like to thank Professor Ali Sadek for helping me in analysing the data of my study.

I thank my research assistances Mr Ahmad Alnour, Mr Hussain, and last but not the least Mrs Elizabeth Mathew for her remarkable effort in the laboratory.

1. Abstract

Background

Globally, 422 million adults have type 2 diabetes mellitus (T2DM), causing 1.5 million deaths per year. Kuwait has one of the highest T2DM prevalence in the world and determining the proportion of patients and relatives who have pre-diabetes (PDM), insulin resistance (IR) and T2DM is crucial to inform preventive activities and curative services.

Study objectives:

The study describes the prevalence and risk factors of PDM, IR and T2DM, in adult patients attending a primary health care facility in Kuwait and the prevalence and risk factors of the same conditions among the patients' first-degree relatives. The study also describes the degree of glycaemic control achieved by patients with T2DM and risk factors for poor glycaemic control. Finally, we assessed the agreement of a point of care (POC) device to measure glycated haemoglobin (HbA1c) to monitor T2DM control.

Methods

We conducted cross-sectional surveys of patients and first-degree relatives attending Nuzha health care facility in Kuwait and case-control studies of participants attending Nuzha's diabetic clinic. Diabetic participants were consecutively tested by the Quo-test (POC) device to compare its agreement with a reference test.

Results

The prevalence of T2DM, IR and PDM among patients attending the clinics were 29.6% (95% CI: 25.1%-34.1%), 34.6% (95% CI: 29.1%-40.2%) and 26.0% (95% CI: 21.6%-30.4%), respectively. The proportion of patients with T2DM increased with age (AOR=5.4), with the highest prevalence occurring at 60-69 years of age. T2DM was associated with hypertension (AOR=1.95) and being a widow (AOR=6.11). IR was associated with low HDL (AOR=1.96), overweight (OR=8.25), obesity (OR=18.33) and increased waist circumference (OR= 5.5). Sugar-sweetened beverages were associated with IR.

The prevalence of T2DM, IR and PDM among first-degree relatives of T2DM patients were 29.1% (95%CI: 23.7%-34.5%), 32.8% (95%CI: 26.2%-39.4%), 20.4% (95%CI: 15.6%-25.2%). The risk factors for T2DM were similar among patients and first-degree relatives, but IR was associated with manual labour occupations (AOR=3.6).

Only 30% of T2DM patients achieved good glycaemic. Poor control was associated with high triglycerides (AOR=2.2), smoking (AOR=4.1) and the number of years since diagnosis (AOR=4).

The Quo-Test had comparable performance to the reference test, with a Coefficient of Variation of 2.1% (r2 = 935, Kappa 90% and 87% at HbA1c cut-offs of 7.0 and 9.0% respectively). The POC and the reference tests performed poorly in patients with haemoglobinopathies.

Conclusion

This study demonstrates that a high proportion of patients and first-degree relatives attending one of the main primary health care centres in Kuwait have T2DM. Many patients and relatives were unaware of their condition. There was also a very high prevalence of IR and PDM suggesting the burden of T2DM will increase further in the future. Major efforts are needed to upscale detection, and preventive programmes for IR, PDM and T2DM and the quality of T2DM management needs to improve. The POC device tested could provide timely information for the management of T2DM.

List of abbreviations

ACCORD	Action to Control Cardiovascular Risk in Diabetes
ACE	angiotensin converting enzyme
ADA	American Diabetes Association
AGEs	advanced glycation end products
AMI	acute myocardial infarction
AMPK	adenosine monophosphate protein kinase
ARBs	angiotensin receptor blocker
HbA1c	glycated haemoglobin
BMI	body mass index
BP	blood pressure
BW	body weight
CHD	coronary heart disease
CVD	cerebrovascular disease
DALY	disability-adjusted life years
DCCT	Diabetes Control and Complication Trial
DKA	diabetic ketoacidosis
DKD	diabetic kidney disease
DM	diabetes mellitus
DME	diabetic macular oedema
DN	diabetic nephropathy
DPN	diabetic polyneuropathy
DR	diabetic retinopathy
EMR	Eastern Mediterranean Region
ESRD	end-stage renal disease
ETDRS	Early Treatment Diabetic Retinopathy Study
FFA	free fatty acid
FPG	fasting plasma glucose

GCC	Gulf Cooperation Council
Hb	Haemoglobin
HCF	healthcare facility
HDL	High-density lipoprotein
HHS	hyperosmolar hyperglycaemic state
HOMA	homeostatic model assessment
HPLC	High-performance liquid chromatography
IDF	International Diabetes Federation
IFG	impaired fasting glucose
IGT	impaired glucose tolerance
IR	Insulin resistance
IRAS	Insulin Resistance Atherosclerosis Study
IRS	Insulin receptor substrate
K	Potassium
KATP	adenosine triphosphates sensitive potassium
LDL	Low-density lipoprotein
LPL	lipoprotein lipase
MENA	Middle East and North Africa
MI	myocardial infarction
MS	metabolic syndrome
NCDs	Non-communicable diseases
NGSP	National Glycohemoglobin standardization program
NGT	normal glucose tolerance
NHIS	National Health Interview Survey
NIDDK	National Institute of Diabetes and Digestive and Kidney Diseases
NPH	neutral protamine Hagedorn
OGTT	oral glucose tolerance test
OR	Odds Ratio
PCOs	polycystic ovaries
PDM	Prediabetes
PKC	protein kinase C

POC	point of care
ROS	reactive oxygen species
RR	Relative Risk
SMBG	self-monitoring blood glucose
TG	Triglyceride
UKPDS	United Kingdome Prospective Diagnostic Study
VEGF	vascular endothelial growth factor
WHO	World Health Organization
WHR	waist/hip ratio
YLDs	years lived with disability
YLLs	years of life lost due to premature death

Table of Contents

List of Tables

List of Figures

2. Literature review

Introduction

Diabetes Mellitus (DM) is a syndrome that includes a group of metabolic disorders characterised by insufficient insulin secretion, resistance to the action of insulin or both (American Diabetes, 2009).

DM is a seriously growing public health problem which has reached epidemic proportions, and its prevalence is increasing globally. In 2003, it was estimated that there were 194 million individuals with DM, with a worldwide prevalence of 5.1% (Federation, 2003). By 2015, the International Diabetes Federation (IDF) world atlas indicated that the prevalence had increased to 9.1%, with more than 415 million people living with DM around the world. Even worse, 46.5% of the individuals with DM are unware of their condition and remain undiagnosed. These individuals are likely to age prematurely and to suffer the major health consequences of poor DM management. It is estimated that one person dies every six minutes due to DM and that governments will need to spend one-ninth of their health care expenditure on DM (IDF, 2015).

Type 2 DM (T2DM) is the most common presentation of DM; Gestational DM is frequent but short-lived, followed by Type 1 DM (William T. Cefalu, 2015). T2DM is characterized by hyperglycemia resulting from a defect in the pancreas insulin secretory function and/or Insulin resistance (IR) (Gareth Williams, 2002).

IR is a condition in which the insulin target cells fail to respond to the normal actions of insulin. The pancreas produces insulin, but the cells in the body tissues become resistant to insulin and are unable to use it as efficiently, leading to high blood glucose concentration. Subsequently, β cells increase their production of insulin trying to reach proper glycemic control, causing a high blood insulin level (Chiu et al., 2007)

With the purpose of developing a programme to control the progression of DM in Kuwait, it is important to do a situation analysis of the disease in the country and to describe the leading risk factors associated with T2DM in the community.

Chapter 2 (literature review) principally sets the scene for the whole thesis as it provides an overview of the literature relating to the global and regional prevalence and risk factors of T2DM, emphasising the importance of studying T2DM in Kuwait.

Furthermore, this chapter will debate the pathogenesis of T2DM, discussing IR and β cell dysfunction. Then, it will confer the mechanism of glucose homeostasis and the key hormones regulating blood glucose concentration. This review will discuss the clinical presentation of T2DM, including acute and chronic complication.

Short and long-term monitoring methods will be included in this chapter, followed by a brief section on the management of T2DM.

Chapter 3 will discuss the methodology used in this study; the methodology is separated into five sections, describing the method of each objective including the analysis plan.

Chapter 4 presents the results of the study. The results will include the prevalence and risk factors of T2DM, prediabetes, IR in the selected population. It also contains the prevalence of IR in first degree relatives of individuals with T2DM. Furthermore, it shows the prevalence and the risk factors of poor glycaemic control in patients with T2DM attending a diabetic clinic. This is followed by a section showing the performance of a POC device against a reference test in determining the glycaemic status of people with T2DM.

Chapter 5 discusses the results of our study and compare it to other local, general, and global studies.

Finally, chapter 6 provides a brief discussion of the findings and outlines implications for health care professionals, health promotion and future research.

2.1 Importance of studying Diabetes.

Diabetes Mellitus (DM) is one of the main public health challenges, the extent of the disease demands regular population-based studies to determine the prevalence and risk factors for T2DM. Studies should also assess the trends and impact of interventions, especially in countries with a significant diabetes burden such as Kuwait. According to the NCD risk factor collaboration, the crude estimate of T2DM prevalence in Kuwait in 2004 was 14.8% in men and 14.6 in women (NCDs, 2014) It is now well recognised that countries of the Gulf Cooperation Council (GCC) are among the countries facing the greatest burden of T2DM. This has been linked mainly to the increasing and rapid urbanization and socioeconomic development in these countries, the sudden extraordinary increase in income and prosperity which resulted in substantial lifestyle changes of their populations toward sedentary life and consumption of "Western-style" fast foods (Klautzer et al., 2014).

The International Diabetes Federation (IDF) recognises that the Eastern Mediterranean Region (EMR) as a major hot-spot for T2DM (Majeed et al., 2014). With a projected 96% increase in T2DM prevalence among 20- 79 years old adults (2013 vs 2035), which is only second to the Sub-Saharan region, where the increase is expected to be as high as 110% of the 2013 baseline (World Economic Forum, 2014). However, the healthcare systems in these countries are unprepared to deal with this increasingly pressing health problem. Public health sector planners and decision makers need to be more aware of the current burden posed by T2DM and its complications. They must plan for effective primary health care strategies to prevent ` diabetes onset, early disease detection and improved management of patients with diabetes, including self-disease management and management in primary care and community settings.

In 2014, 9% of human adults had diabetes (World Health Organization, 2014), and in 2012, diabetes was the direct cause of 1.5 million deaths (Al-Mawali, 2015). Furthermore, T2DM is expected to be the 7th leading cause of death in 2030 (Mathers and Loncar, 2006).

In England, more than one in ten (11.6%) deaths of adults are diabetes-related (National Health Service, 2010), and in 2013/2014 NHS prescriptions for diabetes-related items cost was £803.1 million, consuming 9.5% of the total health care expenditure of the primary care (National Health Service, 2015). Life expectancy in people with T2DM is estimated to be reduced, and for example, people with diabetes in the UK are 34.4% more likely to die younger than other individuals without diabetes (Diabetes UK, 2016).

Data on 161,161 participants from 31 cohort studies in the Asia-Pacific region showed that patients with diabetes were 1.8 times more likely to have cardiovascular disease than patients with no diabetes (Murakami et al., 2012). Diabetic retinopathy is also a major microvascular complication of T2DM, the prevalence of diabetic retinopathy is increasing worldwide, with a higher prevalence in developing countries. A relatively recent study in China showed that 43% of patients with diabetes have retinopathy (Zheng et al., 2012). This is why T2DM is the one of the leading cause of blindness (Nentwich and Ulbig, 2015). A foot ulcer is another common microvascular complication. Data from a systemic review have shown that diabetes is second only to smoking as a cause of peripheral artery diseases which is the most important cause of limb amputation worldwide (Thiruvoipati et al., 2015).

T2DM is strongly associated with modifiable risk factors. These include obesity, sedentary lifestyle, dyslipidaemia, hypertension, smoking, and low intake of high fibres food (Wu et al., 2014). It is important to implement more comprehensive diagnostic and preventive strategies to decrease mortality and morbidity caused by T2DM (Zahra et al., 2015) especially that T2DM is now recognised as a preventable disease (Tuso, 2014).

2.2 Definition of diabetes

Diabetes mellitus is a chronic disease that occurs when the body cannot produce enough insulin or when the body cannot use insulin effectively, or both (American Diabetes, 2010). Insulin is a hormone produced by the β cells of the islets of Langerhans in the pancreas; it allows the glucose obtained from food to enter the body's cells where it is transformed into energy needed by muscles and tissues to maintain its function. A person with diabetes cannot utilize glucose properly, and glucose remains circulating in abnormally high concentrations in the blood. This condition is called hyperglycaemia and it causes severe damages to body tissues over time (Beale, 2013). This damage can lead to disabling and life-threatening health complications (Hage Hassan et al., 2014).

According to the American Association of Diabetes, the current criteria for the diagnosis of diabetes are:

- A glycated haemoglobin (HbA1c) ≥ 6.5%. The test should be performed in a laboratory using a method that is certified by the National Glycohemoglobin Standardization Program (NGSP) and standardised to the Diabetes Control and Complications Trial (DCCT) assay.

  Or
- Fasting plasma glucose ≥ 7 mmol/l (≥ 126 mg/dl). Fasting is defined as no caloric intake for at least 8 hours.

  Or
- Two-hour plasma glucose ≥ 11.1 mmol/l (≥ 200 mg/dl) during an oral glucose tolerance test (OGTT). The test should be performed as described by the World Health Organization (WHO), using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.

  Or
- In a patient with classic symptoms of hyperglycaemia or hyperglycaemic crisis, random plasma glucose ≥ 11.1 mmol/l (≥ 200 mg/dl).

In the absence of unequivocal hyperglycaemia, the result should be confirmed by repeating the test.

2.3 Types of diabetes

Hyperglycaemia may occur in a variety of situations, with different clinical presentations. In 1951 Lawrence classified diabetes into two classes (Lawrence, 1951), type 1 or juvenile diabetes with absolute insulin deficiency or type 2 with relative insulin deficiency (Table 1).

Table 1: Aetiological classification of diabetes mellitus

1) Type 1 diabetes (β cell destruction, usually leading to absolute insulin deficiency)
    a. Immune-mediated
    b. Idiopathic
2) Type 2 Diabetes (may range from predominantly insulin resistance with relative insulin deficiency to a predominantly secretory defect with insulin resistance)
3) Other specific types
    a. Genetic defects of β cell function
        1. Maturity-onset diabetes in young (MODY)
        2. Transient neonatal diabetes
        3. Permanent neonatal diabetes
        4. Mitochondrial deoxyribonucleic acid
    b. Genetic defect in insulin action
        1. Type A insulin resistance
        2. Leprechaunism
        3. Rabson-Mendenhall syndrome
        4. Lipoatrophic diabetes
    c. Disease of the exocrine pancreas
        1. Pancreatitis

2. Trauma/pancreatectomy
3. Neoplasia
4. Cystic fibrosis
5. Hemochromatosis
6. Fibrocalculous pancreatopathy

d. Endocrinopathy
1. Acromegaly
2. Cushing's syndrome
3. Glucagonoma
4. Pheochromocytoma
5. Hyperthyroidism
6. Somatostatinoma
7. Aldosteronoma

e. Drug or chemically induced
1. Vacor
2. Pentamidine
3. Nicotinic acid
4. Glucocorticoids
5. Thyroid hormone
6. Diazoxide
7. β- adrenergic agonists
8. Thiazides
9. Dilantin
10. γ-interferon

f. Infections
1. Congenital rubella
2. Cytomegalovirus

g. Uncommon forms of immune-mediated diabetes
1. "Stiff-man" syndrome
2. Anti-insulin receptor antibodies

h. Genetic syndrome

1. Klinefelter syndrome
2. Turner syndrome
3. Wolfram syndrome
4. Friedrich ataxia
5. Huntington chorea
6. Laurence-Moon Biedl syndrome
7. Myotonic dystrophy
8. Porphyria
9. Prader-Willi syndrome

4) Gestational diabetes mellitus

Source: (American Diabetes, 2013)

2.4 Pathogenesis of diabetes mellitus

The secretion of insulin is mainly modulated by the existing levels of glucose in the blood and interstitial fluid (Cerf, 2013). During the fasting period, the basal rate of insulin secretion maintains the plasma glucose levels between 4.0 and 5.5 mmol/l (70 to 100 mg/dl) (Horton, 2009). After ingestion of food, there is a sharp increase in insulin secretion in response to incretin hormones. These insulinotropic hormones are secreted by the gastrointestinal system (Kim and Egan, 2008). Failure of β cells to maintain an adequate level of insulin secretion is believed to be the primary pathway for the development of T2DM.

T2DM is a heterogeneous disorder with highly complex pathogenicity. Two factors operate in parallel with the evolution of T2DM:

1. Impaired insulin sensitivity, a condition known as insulin resistance (IR).
2. β cell defect: Insulin secretory dysfunction.

Furthermore, both insulin sensitivity and β cell action are modulated by genetic and environmental factors (Fradin and Bougnères, 2011).

2.5 Glucose homeostasis

Blood glucose values average (throughout the day) approximately 5.0 mmol/l (90 mg/dl), the maximal level after meal ingestion should not exceed 9.3 mmol/l (168 mg/dl), and glucose levels remain above 3.6 mmol/l (65 mg/dl) even after moderate starvation. This narrow glycaemic range defines normoglycaemia; which is maintained by the neurohormonal regulatory system. A decrease in blood glucose from 5.0 to 3.9 mmol/l (90 to 70 mg/dl) will suppress insulin production from the pancreas and reduce glucose uptake by the hypothalamus, where glucose sensors are located. This will trigger the sympathetic system to release counter-regulatory hormones including; glucagon, cortisol, catecholamines and growth hormones (Freckmann et al., 2007, Sprague and Arbeláez, 2011).

Plasma glucose comes from diet or as a result of the breakdown of glycogen in the liver in a process called glycogenolysis. Alternatively, it originates "gluconeogenesis" from the formation of glucose in the kidney, liver, intestine, and muscles from other glucose precursors such as alanine, lactate, and pyruvate. Some recent studies have shown that gluconeogenesis can even occur in the brain (Yip et al., 2016). Glucose under different conditions may have other fates in various tissues, but the pathways for its clearance are relatively restricted. It may be directly stored as glycogen or may undergo glycolysis in the cytoplasm producing pyruvate (Rui, 2014). Non-oxidative glycolysis carbons undergo gluconeogenesis creating glucose, and according to the different metabolic conditions, the newly formed glucose is either stored as glycogen or released back into the blood (Guo et al., 2012). Although free fatty acids are the primary fuel for the majority of organs, glucose remains the only metabolic fuel for the brain under normal physiologic conditions, that is because of the limitations of free fatty acids (FFA) transportation across the blood-brain barriers (Schönfeld and Reiser, 2013).

2.6 Key hormones influencing glucose level

Insulin, together with glucagon, is the crucial factor regulating the plasma levels of glucose, metabolism, energy production and formation of fat in the body (lipogenesis). Insulin coordinates processes related to glucose uptake, lipolysis, and gluconeogenesis, its level in plasma increase promptly after a meal, in direct response to the rise of glucose in the bloodstream (Wilcox, 2005). Skeletal muscle is the primary organ responsible for blood glucose consumption after a meal, followed by liver and adipose tissue. Moreover, Insulin facilitates vasodilatation, causing increase in blood flow to the peripheral tissues allowing for more nutrients delivery, especially to the skeletal tissues (Lambadiari et al., 2015).

2.6.1 Insulin

History of Insulin

In 1889 two German scientists, von Miring and Oskar Minkowski noted, from their studies on animals, which after total pancreatectomy animals developed severe diabetes. They theorised that there was a substance secreted by the pancreatic cells responsible for the glycaemic control. The hypothesis was later refined by others, recognising diabetes to be associated with the destruction of the islets of Langerhans. Minkowski and Zuelzer in Germany, as well as Scott in the USA and the Romanian Paulesco, attempted to isolate and administer the missing pancreatic islet substance (Karamitsos, 2011). Belgian scientist de Meyer in 1909 suggested the name “insulin”; this name has also been proposed by the British researcher Schaefer later in 1916 (De Meyts Pierre, 2014).

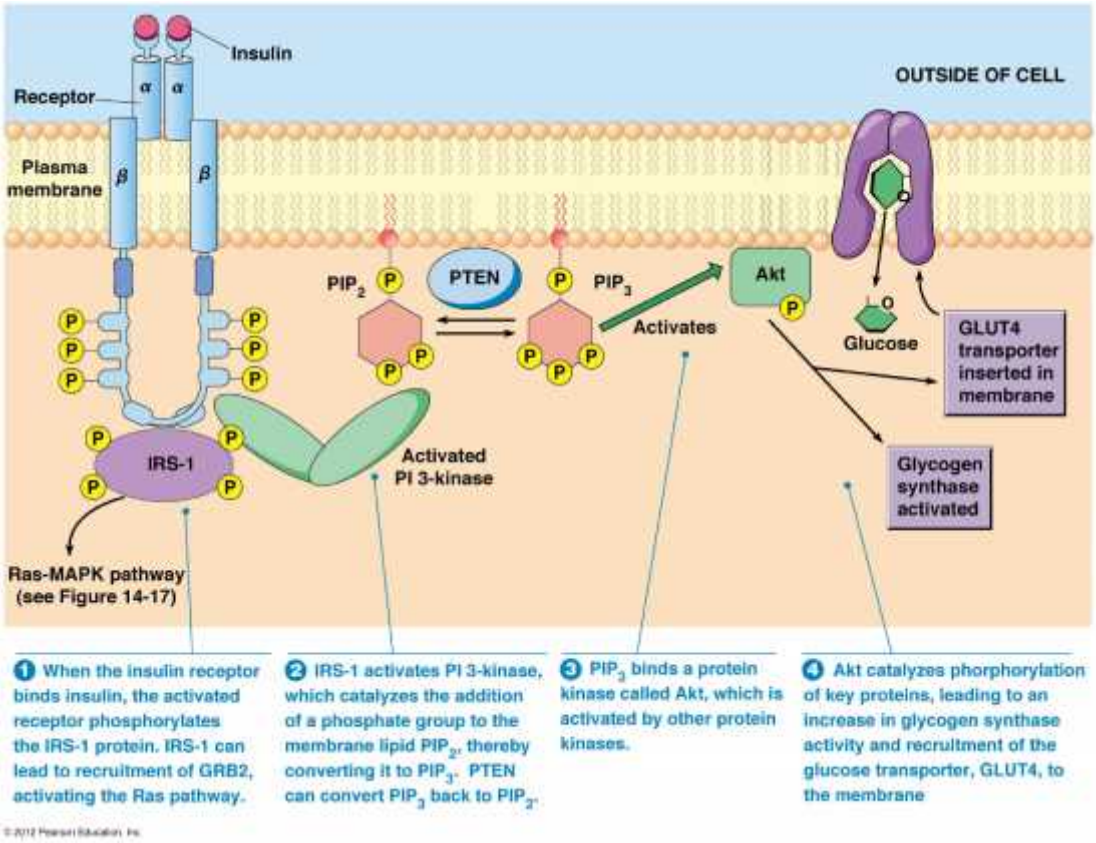
In 1921, insulin was isolated, purified and became available in a form for therapeutic administration. In May 1921, a young orthopaedic surgeon called Banting, assisted by his medical student Best, and under the supervision of McLeod, head of the physiology department at Toronto University began experiments in dogs. They infused saline extracts of pancreas intravenously to

deliberately diabetic dogs (by pancreatectomy) and observed the lowering effect of the insulin on the blood glucose (Rosenfeld, 2002). Collip, who was a biochemist, joined McLeod's experimental team in Toronto and demonstrated that this extract lowered sugar excretion in urine and established that the deficiency in insulin secretion was the cause of diabetes (Lakhtakia, 2013).

In January 1922, the first human experiments began on a 14-year-old boy with diabetes. He was clinically symptomatic; his biochemical deviations were reversed by the administration of the pancreatic isolate (Rosenfeld, 2002). In May 1922, the pancreatic extract had been named insulin, and the results of these experiments were presented to the Association of American Physicians. Eli Lilly began production of porcine insulin, enhancing purification and the production of commercial quantities in early 1923. Subsequently, Banting and McLeod were awarded the 1923 Nobel prize (Quianzon and Cheikh, 2012).

Insulin receptors signalling cascade

T2DM is increasing worldwide; a primary focus of research is understanding the signalling pathways influencing this disease. Insulin signalling regulates glucose homeostasis, lipid, and energy production, mostly via their action on the adipose tissue, liver, and skeletal muscle. Accurate control of this pathway is crucial for adaptation as the situation moves from feeding to a fasting state. Positive and negative receptor signals work at different stages of the signalling pathway, as well as the variety of protein isoform interfacing to ensure an appropriate and synchronised Insulin biological action in various tissues. Insulin controls a wide range of biological processes by acting on two closely related tyrosine kinase receptors. Activation of insulin receptors by their binding molecules starts a sequence of phosphorylation events that lead to the activation of proteins that controls metabolism and growth (Bononi et al., 2011). Insulin receptor signalling consists of several points of regulatory steps. These steps are controlled both negatively and positively, to ensure proper signal intensity and duration. Dysfunctions in these signalling pathways can lead to IR (Boucher et al., 2014).



(Pearson Education, https://goo.gl/images/Bb97nG)

Insulin action

Dysfunction of any glucose homeostasis pathway would disturb metabolic regulation and promote the development of pre-diabetes and eventually, if not corrected, to T2DM.

Defect in Insulin signalling

As mentioned before, skeletal muscle is the primary site of insulin-mediated glucose clearance and play a significant role in decreasing glucose uptake, as in states of IR. Dysfunction in the early insulin-signalling pathway leading to the reduction of glucose uptake plays a primary role in the development of IR.

A substantial body evidence supports that insulin-signalling pathway dysfunction contributes to IR in tissues like the skeletal muscle and human as general. For example, in patients with T2DM or obesity, several investigators have shown decreased phosphorylation of the insulin receptors, decreased PI3K activation and decrease IRS-1 tyrosine phosphorylation (Bandyopadhyay et al., 2005). Scientific evidence that a reduction in the insulin receptor kinase itself can add to the development of IR is increasing (Chiu and Cline, 2010). However, it is indefinite whether these changes in insulin receptor role represent a primary defect that causes IR or whether they occur secondary to hyperglycaemia or hyperinsulinemia. Even if the defect at the level of the insulin receptor can cause these physiological behaviours, whether decreased insulin receptor function can account for the insulin-resistant pathophysiology present in the general patient population is doubtful (American Diabetes, 2009).

Impaired β cell function

Some studies were conducted during the late 80s and early 90s on normoglycaemic participants with a genetic predisposition for T2DM from vulnerable ethnic groups such as African American, Mexican American, and Pacific Islands populations, demonstrating IR as the predictor and precursor for T2DM. Other studies suggested that β cell dysfunction is the primary defect in type2 diabetes (Doria et al., 2008). In 1979, DeFronzo introduced the euglycemic and hyperglycaemic clamp technique and later, this technique was used by Pimenta, to conclude that an insulin secretion defect is the major factor for T2DM (Pimenta et al., 1995, Tam et al., 2012). Furthermore, Van Haeften et.al. compared the importance of β cell dysfunction to IR, concluding that impaired β cell function has a predisposed genetic predisposition in T2DM patients (Van Haeften et al., 2000).

More recently, diabetes experts have suggested that a continuous decline in the secretion of insulin starts many years before the diagnosis of T2DM, with the

progressive dysfunction of β cells as the leading factor in the development of hyperglycaemia (Halban et al., 2014).

Mechanism of β cell dysfunction

Failure of the β cells to maintain an adequate amount of insulin secretion in response to blood glucose level is the main and final pathway in the pathogenesis of T2DM. The integrity of β cells is crucial. The islets of Langerhans are affected by several elements including obesity, consumption of saturated fat and FFA and cytokine-induced inflammation (Cerf, 2013).

Hypothetically, the β cells decompensation process can develop in five stages. These stages are based on experimental evidence and clinical observation. Stage 1 is indicated by adequate adaptation to the increase in blood glucose level, to overcome IR which is usually present in individuals with a predisposition to T2DM. At this stage, there will be an increase in β cells mass and normal or sometimes higher insulin level. Stage 2 is characterized by early signs of decompensation, β cells secretory action will start to regress, and this stage shows increase blood glucose up to 6.6 mmol/l (120 mg/dl). By the time fasting blood glucose reaches up to 6.1 mmol/l (110 mg/dl), the condition will be called prediabetes.

In Stage 3, progressive β cell dysfunction and apparent decompensation is eminent. This phase demonstrates the rise of blood glucose to a diabetes threshold. Glucose-induced Insulin secretion is entirely impaired. Other non-glucose insulin responses may still be in action but significantly compromised. Stage 4 is characterized by chronic functional decompensation with structural changes characteristics of T2DM. These consist of Amyloid deposition in the pancreas and the presence of lipid droplets; fibrosis; apoptosis; degeneration and glycogen deposits. Stage 5 is the last stage of diabetes, there will be severe loss of β cell function. Patients at this stage will depend on external insulin to survive,

otherwise, will develop fatal diabetic ketosis. This stage is typically present in type 1 diabetes (Weir and Bonner-Weir, 2004, Curran et al., 2016).

It is accepted that T2DM is a genetically predetermined failure of the β cell (DeFronzo and Abdul-Ghani, 2011). However, according to recent diabetes studies, decreased insulin receptor function, particularly in skeletal muscles, can account for the insulin-resistant pathophysiology present in the general patient population, and the hypothesis of pooled defects in insulin secretion and insulin sensitivity appear to be more accepted (Taylor, 2012). Polonsky and co-workers suggested that T2DM is a genetically programmed failure of the β cell to compensate for IR (Polonsky et al., 1996). Further, Miyazaki and co-workers and Rendell et. al. share a similar interpretation where it has been proposed that abdominal obesity, which is believed to be genetically inherited, is associated with fat deposits in pancreatic cells, muscles, and liver, can suggest the common explanation for defects in insulin secretion and insulin sensitivity (Miyazaki et al., 2002, Rendell et al., 2001).

The genes predisposing to T2DM and the metabolic syndrome are energy-saving thrifty genes that helped our ancestors to survive by storing energy in the form of fat (Genné-Bacon, 2014). This perhaps clarifies the fact of the high prevalence of T2DM among Pima Indians, Pacific Islanders, and Native Australian. Similarly, it may explain the recent massive epidemic in several developing countries like Arabian Peninsula (Acton et al., 2002, Sherif and Sumpio, 2015).

The challenging hypothesis of relative superiorities in the defective insulin secretion or IR is still a debatable issue (Cernea and Dobreanu, 2013). Highlighting the importance of IR is the fact of the frequent initial finding of hyperinsulinemia in the early stages of T2DM (Roberts et al., 2013).

Higher insulin response to glucose may be prominent during progression from normal glucose tolerance (NGT) to impaired glucose tolerance (IGT). The second phase of increased insulin secretion is noticeable in patients with prediabetes for some years before the onset of T2DM (Haffner et al., 2000, Fonseca, 2009).

Hence, it is possible to assume that both factors are equally liable for the pathogenesis of T2DM. So far, it is accepted to say that whichever comes first the other follows (Cerf, 2013). Recently, the roles of incretin, leptin, renal tubular glucose resorption and hypothalamic nuclei in homeostasis have been emphasised (DeFronzo et al., 2014).

An innovative study with the hypothesis that high caloric intake will increase the deposition of fatty liver and high content of TG in the liver, leading to decrease in hepatic insulin sensitivity, furthermore, the fat content in the pancreatic cell will increase, leading to the increase of ATP production and insensitivity to glucose. This condition will lead to the prognosis of T2DM. The study showed that low caloric intake with significant weight loss was able to cause a substantial fall in fasting plasma glucose. This was the first study to show that β cells are inhibited rather than permanently damaged in T2DM (Taylor, 2013).

2.7 Clinical and subclinical features of hyperglycaemia

In T2DM, the onset and the progress of hyperglycaemia are so slow as to remain unnoticeable. These asymptomatic patients come to attention usually by accident, as a part of the preoperative evaluation, screening campaigns and individuals having a regular annual check-up (Kasznicki, 2014). Apart from this, some patients are detected when they are under stress such as acute myocardial infarction (AMI) or stroke. These patients could become normoglycaemic once the stressful condition is over, but remain quite prone to develop diabetes in the future and should be closely monitored (Arnold et al., 2015).

2.7.1 Prediabetes

Prediabetes is defined by blood glucose concentrations higher than normal, but lower than established threshold for the diagnosis of diabetes. Prediabetes is also known as intermediate hyperglycaemia, a state in which the risk of developing diabetes is increased. The expert committee on diagnosis and classification of DM

in 1997 and 2003 recognised these intermediate group of individuals whose glucose levels, although not meeting criteria for diabetes, are however too high to be considered normal.

These persons were defined as having impaired fasting glucose (IFG) [FPG levels 5.6 mmol/l (100 mg/dl) to 6.9 mmol/l (125mg/dl)] or IGT (2-h) values in the oral glucose tolerance test (OGTT) of 7.8 mmol/l (140 mg/dl) to 11 mmol/l (199mg/dl). However, the WHO and some other diabetes organisations define the cutoff for IFG at 6.1 mmol/l (110 mg/dl) (Bansal, 2015).

Prediabetes is a high-risk state not only for developing diabetes, but also the associated cardiovascular complications. These categories of IFG and IGT should not be viewed as clinical terms, but rather as risk factors or a predictor of diabetes as well as cardiovascular disease.

Likewise, an HbA1c in the range of 5.7-6.4% also defines individuals with prediabetes and recognise a significantly higher risk for the future development of diabetes and cardiovascular disease (Matfin and Pratley, 2010).

The relationship of HbA1c to the potential for subsequent development of diabetes has also been studied in several large prospective studies which have analysed the HbA1c values in the intermediate range. These studies have demonstrated a strong, continuous association between HbA1c values and subsequent diabetes. In a systematic review of 44,203 individuals from 16 cohort studies with an average follow-up of 5.6 years, those with an HbA1c between 5.5% and 6% had a substantially increased risk of diabetes with five years' incidence ranging from 9% to 25%, while an HbA1c range of 6-6.5% had a five years' risk of developing diabetes between 25% and 50% and relative risk (RR) 20 times higher compared with an HbA1c of 5% (Zhang et al., 2010b).

In another community-based study of non-diabetes individuals of a mixed racial descent, the baseline HbA1c was a stronger predictor of subsequent diabetes and cardiovascular events than fasting glucose (Selvin et al., 2010).

Therefore, based on these data, it is reasonable to consider an HbA1c range of 5.7-6.4% as identifying individuals with prediabetes. As is the case for individuals found to have IFG and IGT, persons with an HbA1c of 5.7-6.4% should be informed of their increased risk for diabetes as when as cardiovascular disease and counselled about effective strategies to lower their risks. Accordingly, interventions should be intensive and follow-up particularly cautious for those with HbA1c above 6% who should be considered to be at very high risk for developing diabetes.

Impaired glucose tolerance (IGT)

Although IGT has become established as a category of abnormality in glucose metabolism, there remain some problems with the categorisation of individuals as IGT. Firstly, there is up to 40% variation in 2-h plasma glucose concentrations, most of which is biological. Secondly, to apply cut-off values to a continuously distributed variable with such large variability creates further difficulties. This is a problem in defining IGT as there is a narrow 2-h plasma glucose range of 3.3 mmol/l (from 7.8 to 11.1) which separates normal glucose tolerance (NGT) from T2DM (WHO and IDF, 2006). Subjects who have IGT on one occasion may not have it when tested on another day. Those who test normal, on the second test have been classified by some as having “transient IGT”, compared to those who have IGT on repeat testing “persistent IGT”. Data from Pima Indians have shown that subjects transient IGT also have increased the risk of future diabetes although it would appear to be less than that seen in those with persistent IGT. These data suggest that transient IGT at least in some populations represent an earlier stage in the progression from NGT to the more serious category of glucose intolerance (Kanat et al., 2015, Saad et al., 1988).

Aetiology and pathogenesis of IGT

Prediabetes represents an intermediate stage of glucose intolerance with the likelihood that most people who develop T2DM pass through a stage of abnormal glucose tolerance. Although there remains a debate about the underlying primary

nature of the defect, data support the view that subjects with IGT have impaired insulin action, i.e. their insulin-stimulated glucose uptake is less than those with NGT. However, these subjects, maintain plasma glucose concentrations at levels lower than those seen in manifest diabetes by compensatory hyperinsulinemia. It is only when the exhausted pancreas can no longer adequately compensate for the degree of IR that insulin deficiency arises and evident diabetes develops (Aoyama-Sasabe et al., 2016).

In a study comparing Caucasians and South Asians showed that IR was more prevalent in South Asian individuals (Bakker et al., 2013). Longitudinal data from Pima Indians confirmed that the transition from NGT to IGT is characterised by initial hyperinsulinemia and a further decrease in insulin secretion leads to the development of the full picture of T2DM (Weyer et al., 1999).

Conversion to diabetes

IGT is neither a disease nor a syndrome. It has a certain predictive ability. Subjects with IGT are at an increased risk of diabetes, the risk of conversion depends upon some other risk factors as well. The conversion rate of diabetes in individuals with glucose intolerance varies among populations. In a 10-year study, the conversion rate from IGT to diabetes was 6.8% and 6.1% from IFG, and if both were present, then the conversion to diabetes was 13.4% (Anjana et al., 2015).

2.7.2 Clinical presentation of T2DM

Clinically, patients with T2DM present with the overt disease when they are 50 years or above, but recently, studies have shown that it often occurs earlier. Recently, T2DM is becoming increasingly common in children and young adults all over the world including the Middle East (Al-Rubeaan, 2015, Wilmot and Idris, 2014). Individuals in this region have high suitability for developing vascular complications earlier and more frequently.

Markers for the diagnosis of T2DM include positive family history, obesity especially central obesity, acanthosis nigricans and polycystic ovarian syndrome (Wu et al., 2014).

The classic osmotic symptoms of polyuria, polydipsia, as well as low polyphagia, when present, are very suggestive of diabetes. However, their symptoms are more applicable to type 1 diabetes. On the other hand, fatigue, tingling of hands and feet, generalised muscle ache and pain are more often seen in T2DM. Even these symptoms usually occur after an extended and variable asymptomatic period. Other presentations could include a non-healing wound or ulcer, recurrent boils, unexplained vaginal itching, fungal infection and recurrent bacterial infection. Male patients may complain of impotence as the first symptoms. A collection of ants of places of urination is a common indicator in the rural setting. Whitish spots from dried up urine on hard surfaces or undergarments may offer another indication for glycosuria (Ramachandran, 2014, Karamanou et al., 2016).

As an example, a descriptive study of 132 T2DM patients attending a diabetes clinic in India, reported that their average age was 55.2 ± ten years, 56% were male, and 44% female. About 35% had a sedentary life, 42% were obese, 58% with central obesity, presenting complaints in these patients (Table 2) were osmotic symptoms polyuria, polydipsia, and nocturia in 39%, 37%, 37% respectively, and lethargy in 61%. Weight loss in 11%, polyphagia in 40%, progressive loss of vision in 3% delay in wound healing in 3%, paraesthesia in 17%, dyslipidaemia in 37%, hypertension in 50%, and obesity in 42%. However, 8% of the patients were asymptomatic (Borah and Goswami, 2017).

Table 2: Presenting symptoms of T2DM (overlapped symptoms)

Characteristics presenting symptoms	**n (%)**
polyuria	51 (39)
nocturia	49 (37)

polydipsia	49 (37)
polyphagia	53 (40)
lethargy	81 (61)
delay in wound healing	4 (3)
visual impairment	4 (3)
paraesthesia	22 (17)
weight loss	14 (11)
no symptoms	11 (8)
Co-morbidities	
obesity	56 (42)
dyslipidaemia	49 (37)
hypertension	66 (50)

2.8 Complication of T2DM

The disease burden of T2DM is mainly due to its wide range of complications. Diabetes consequences result from the duration and degree of hyperglycaemia and mainly affect the heart, kidney, and eye. Several prospective studies have also shown that strict control of the glucose levels prevents or postponed the complications (King et al., 1999). The broad spectrum of complications includes acute and late complications, as shown in table 3. The late "chronic" complications are mostly due to microvascular or macrovascular changes.

Table 3: Acute and chronic complications of DM

Acute metabolic complications
• diabetic ketoacidosis • hyperosmolar hyperglycaemic state (HHS) • lactic acidosis
Chronic complications
• microvascular - retinopathy - neuropathy - nephropathy

- macrovascular
  - hypertension
  - coronary heart disease (CHD)
  - cerebrovascular disease (CVD)
  - peripheral vascular disease (PVD)

Other

- cardiac
  - diabetic cardiomyopathy
- infection
  - fungal, bacterial, mycobacterial
- ocular
  - infections
  - cataract
  - glaucoma
- dermatological
  - necrobiosis lipoidca diabeticorum
  - granuloma annulare
  - diabetic scleroderma
  - diabetic bullae
- connective tissue
  - carpal tunnel syndrome
  - limited joint mobility
  - osteopenia, osteoarthritis
  - adhesive capsulitis of shoulder joint
- oral
  - periodontal disease
  - caries
  - candidiasis

2.8.1 Acute metabolic complications

Acute metabolic complications are more common with T1DM. The main acute metabolic complications are often grouped as Hyperosmolar hyperglycaemic state (HHS) and Diabetic ketoacidosis (DKA) (Gosmanov AR et al., 2015).

A better understanding of the pathogenesis of DKA, standardisation of fluid and insulin therapy and patient education has rapidly decreased the incidence of DKA and consequent mortality (Misra et al., 2013). The management of DKA depends

on some very basic principles of fluid/electrolyte balance accompanied by insulin therapy. The treatment requires replacement of fluids, potassium and sometimes sodium bicarbonate, Insulin is usually administered through intravenous infusion. Major metabolic complications of DKA include hypokalaemia, cerebral oedema, and hypoglycaemia (Gosmanov et al., 2014).

HHS is usually found in T2DM, often among older patient who has insufficient water intake due to mental limitations. In this case, the water deficit is massive, but there is minimal or no acidosis, and insulin infusion is required in quantities smaller than that administered in DKA (Pasquel and Umpierrez, 2014).

Lactic acidosis is a life-threatening condition, which can occur in any hypoperfusion state, or altered glucose metabolism. Acidosis is usually severe, and its management requires an introduction of large doses of sodium bicarbonate intravenously (Cox et al., 2012). The administration of thiamine with insulin has shown a beneficial effect in the treatment of lactic acidosis (Amrein et al., 2011).

2.8.2 Long-term complications of T2DM

The long-term complications of T2DM are responsible for serious chronic health problems. The atherosclerotic macrovascular complication such as CHD, CVD, and peripheral vascular disease are all common complications (Chait and Bornfeldt, 2009). Diabetes tissue damage occurs mainly in tissues were glucose uptake is insulin independent, and therefore, the influx of glucose in the cells is unregulated and greatly increased in the presence of hyperglycaemia. Target organ damage in diabetes occurs mainly in the retina, kidneys, peripheral nerves, cardiac arteries and blood vessels, although no organ is spared.

Overall, the vascular wall appears to be the principal site of injury regardless of the organ. Since little can be done after the development of overt complications, the emphasis has always been on preventing or delaying complications (Mather, 2013, Asif, 2014).

2.8.3 Mechanism of DM chronic complications

The role of hyperglycaemia in the development of diabetes complication and the beneficial effect of strict glycaemic control have now been well established by well-designed controlled clinical trials (Mannucci et al., 2013). Four major pathways are believed to mediate the development of complications:

1. Polyol pathway flux
2. The advanced glycation end-products (AGEs)
3. The protein kinase C (PKC) isoforms
4. The over-activation of the hexosamine pathway.

Hyperglycaemia is the preliminary catalytic agent for most steps of these pathways, which through a cascade of events exclusive to each pathway result in tissue damage. The role of oxidative stress is critical in this process, elevated extracellular glucose significantly increases the production of reactive oxygen species (ROS), and several studies support the essential role of ROS in oxidative stress (Giacco and Brownlee, 2010). In patients with diabetes, hyperglycaemia primarily, and subsequent production of ROS decrease insulin gene expression and secretion, eventually leading to the destruction and death of the tissue cells (Asmat et al., Wright et al., 2006). Major links in the oxidative stress pathway especially the stress sensitive gene expression mechanisms and other events leading to nuclear factor-kappa B (NF-κB) activation have now been fully explained, thereby, our understanding of the basis of diabetes complications has been greatly increased (Patel and Santani, 2009). Recently, a unifying innovative theory for the development of diabetes complications has been proposed that the oxidative stress is the catalyst in all the major pathways. Studying the cellular and molecular mechanisms that mediate diabetes complications has identified areas of potential therapeutic benefit (Roberts and Porter, 2013).

In general, the long-standing damaging effects of diabetes are divided into microvascular (diabetic neuropathy, retinopathy, and nephropathy) and

macrovascular complications (peripheral arterial disease, CVD, and CHD) (Collinson et al., 2004).

2.8.4 Macrovascular complications

There is an agreement that the main pathological mechanism in macrovascular disease is atherosclerosis, which contributes to the increase in the thickness of the vessels wall and narrowing of arterial lumens throughout the body.

Atherosclerosis is believed to develop from the damage of the arterial wall and the chronic inflammation in the peripheral vascular system, most prominent in the coronary arteries (Rajendran et al., 2013). As a result of endothelial inflammation and damage, oxidised lipids from low-density lipoprotein (LDL) particles aggregate in the endothelial wall of arteries (Badimon et al., 2012). A peptide hormone that causes vasoconstriction called Angiotensin II may stimulate the oxidation of the LDL particles into VLDL. Monocytes then penetrate the intima of the arteries and differentiate into macrophages, which builds up oxidised lipids to form foam cells. Once formed, foam cells excite macrophage production and attract T-lymphocytes. T-lymphocytes causes smooth muscle proliferation in the arterial walls causing collagen build-up. The final result of this process is the development of a fatty atherosclerotic lesion indicating a plaque formation (Singh et al., 2002). Rupture of this atheroma will lead to acute vascular infarction. Along with atheroma build-up, there is solid evidence that in T2DM, the ability of blood coagulation and platelet aggregation is significantly increased (Nicholaos Kakouros et al., 2011, Suslova et al., 2014).

Diminished nitric oxide production in platelets and increased formation of free radical formation, as well as abnormal calcium regulation, may endorse platelet aggregation (Vélez and García, 2015). The combination of impaired fibrinolysis and increased coagulability anticipated to further increase the risk of

cardiovascular events and vascular obstructions in patients with T2DM (Lorber, 2014).

Furthermore, hyperglycaemia appears to contribute directly to the development of cardiomyopathy, rather than solely via coronary atherosclerosis and hypertension. While the exact mechanisms by which diabetes increases the chance of atherosclerotic plaque formation are not yet completely established, the association between the two is well established (Laakso, 2010, Leon and Maddox, 2015). CHD is the most common cause of death in people with T2DM, and it is responsible for the uppermost part of health care expenditure (Zhuo et al., 2014).

Among macrovascular diabetes complications, CHD is the most common serious complication in many studies. Beginning about 70 years ago with the Framingham study (Kannel and McGee, 1979). More recent studies have revealed that the risk of developing myocardial infarction (MI) in people with diabetes is comparable to the risk in patients with no diabetes with a history of the previous cardiovascular event (Juutilainen et al., 2005). These findings led to new recommendations by the American Heart Association and ADA that diabetes mellitus should be considered as a risk equivalent to coronary artery disease as a risk factor for developing MI (Boyko and Meigs, 2011).

T2DM usually occurs as a component of metabolic syndrome, which also includes hypertension, increased ability to form blood clots, dyslipidaemia, and abdominal obesity. These other factors can also facilitate the development of CHD. Even in this situation of several co-existing risk factors, T2DM by itself acts as an independent risk factor for the development of CHD, CVD, and death (Martín-Timón et al., 2014). Among individuals with T2DM, females may be at greater risk for CHD than males, increasing the risk by three folds in males and up to 6 folds in females (Maas and Appelman, 2010, Ergul et al., 2012). Coronary heart events can be similarly predicted by the presence of microvascular disease. Likewise, diabetes is a strong independent predictor of risk of cerebrovascular disease and

stroke, as in coronary artery disease (Arboix et al., 2005). The potential for stroke-related dementia as well as mortality is notably elevated in patients with diabetes (Kalaria et al., 2016).

People with diabetes have higher mortality from CHD at all ages, and their cardiovascular mortality rate is higher for all ages matched to the general population (Lee et al., 2015c). The recognition of these associations has led to the strictest treatment of DM to attain an effective prevention of CHD. Studies in type 1 diabetes have shown that IR and uncontrolled hyperglycaemia is associated with a higher resting heart rate, which is associated with increased risk of CHD (Perciaccante et al., 2006). An innovative study showed that during 17 years of strict prospective treatment of diabetes, including lowering HbA1c, the outcome was associated with a 57% decrease in total risk of nonfatal stroke, or death from CVD, and 42% risk reduction in all CHD events (Skyler et al., 2009).

Another aim of treatment is to reduce blood lipid levels. Various studies have shown that patients with diabetes managed with anti-cholesterol agents have a reduced risk of macrovascular disease. These agents are effective in preventing CHD, and diabetes patients with a history of CHD may benefit most from this treatment (Eldor and Raz, 2009).

Studies like the UK Prospective diabetes study (UKPDS) showed that introducing metformin to the therapy reduces the risk of CHD events (Kishore et al., 2012).

Reducing blood pressure in patients with T2DM has also been associated with a reduction in the cardiovascular events and mortality (Conget and Giménez, 2009). There is an added advantage to lowering blood pressure with angiotensin receptor blockers (ARBs) or angiotensin-converting enzyme (ACE) inhibitors. Obstructing the renin-angiotensin system using either an ARBs or an ACE inhibitor decreases cardiovascular endpoints more than other antihypertensive drugs (Dézsi, 2014).

2.8.5 Microvascular complications

The microvascular complication of diabetes involves kidneys, eyes, and the nervous system, the economic and logistic burden of the individuals with diabetes, plus the societal, national and global burden of these complications. There has been much interest in the pathophysiology to (or "intending to") develop suitable pharmacologic preventive and therapeutic strategies (Kahn et al., 2014).

These complications are already present in the prediabetes stages (IFG and IGT) and metabolic syndrome and continue to damage the patients even when the hyperglycaemia has apparently subsided. Indeed, there is evidence of physiological abnormalities such as pancreatic dysfunction, C-peptide secretion, even when patients are normoglycaemic (Praveen et al., 2012).

Diabetic polyneuropathy

Neuropathy is the most frequent complication of diabetes. Diabetic neuropathy has a distal symmetric form which progresses proximally with a severe effect on quality of life which can extend to several physiological systems (Schreiber et al., 2015). The early detection and proper management of neuropathy in the patients with diabetes is crucial because effective treatment options are available which not only provide symptomatic relief but also delay the progression of the disease efficiently and around 50% of the cases may be asymptomatic and can be recognized only by specific tests, which include autonomic and sensory function testing and nerve conduction studies too. Autonomic neuropathy is also a common presentation, which can lead serious and may be life-threatening complications and their main complaints are neuropathic pain, burning sensation, tingling, decreased sensation and loss of temperature sensation (Pasnoor et al., 2013).

The definition of diabetic neuropathy is "the presence of symptoms and/or signs of peripheral nerve dysfunction in people with diabetes after the exclusion of other cases" (Raza, 2016).

The exact nature of the damage to the peripheral nerves from hyperglycaemia has not been identified, but it is likely linked to mechanisms such as oxidative stress injury from advanced glycation end products and polyol accumulation (Schreiber et al., 2015).

This definition indicates that most but not all patients with peripheral nerve dysfunction and diabetes have diabetic polyneuropathy (DPN). The prevalence of DPN ranges between 5 and 66% in people with diabetes (Hasani et al., 2013). Confirmation of the aetiology requires quantitative electrophysiology, autonomic and sensory function testing (Misra et al., 2008).

One of the largest published series reported a prevalence of DPN of 7.5 % at the time of a diagnosis of diabetes, with the prevalence increasing steadily after diagnosis. Most patients with diabetic neuropathy are asymptomatic at diagnosis, soon after, many patients manifest with a mixture of neuropathic manifestations (Hasani et al., 2013).

The most important risk factors for the development of neuropathy are the long duration and the severity of hyperglycaemia. Other factors for developing DPN include; male gender, increased height, smoking, the presence of microalbuminuria, and alcoholism (Misra et al., 2008, Rosenberg et al., 2001).

Neurological dysfunction may occur in a wide variety of organ systems and can by manifest by bladder dysfunction, constipation, diarrhoea, impotence, tachycardia, and even sudden cardiac death (Stone et al., 2005).

Diabetic retinopathy

Diabetic retinopathy is one of the leading causes of preventable blindness. Annual retinal examinations are mandatory in all patients with diabetes as it can be asymptomatic. The main motivation for screening for diabetic retinopathy is the preventing visual loss. The risk of acquiring diabetic retinopathy is affected by both severity and the duration of hyperglycaemia (Lee et al., 2015a).

The early treatment of diabetic retinopathy study (ETDRS) demonstrated that argon laser photocoagulation treatment is beneficial in reducing the risk of retinal bleeding and visual loss from clinically significant diabetic macular oedema (DME) and proliferative diabetic retinopathy (Royle P et al., 2015). Innovative technology like optical coherence tomography and novel treatment options like intravitreal steroid injections have presented new hope to the patients with diabetes with severe vision impairment (Sarao et al., 2014). National level programs should be formulated for early detection, prompt referral and appropriate treatment and lifelong follow-up of patients with sight-threatening retinal detachment as more than 90% of cases of blindness could be prevented (Wu et al., 2013).

There are several pathological mechanisms by which diabetes may lead to the development of retinopathy. Retinal complications are a result of a loss of the cellular components of retinal capillaries: the perivascular cells “pericyte”, and the blood vessel inner lining cells “endothelial cell”. In addition, there is a formation of new vessels, microaneurysms and breakdown of the blood-retinal barrier (Safi et al., 2014).

Histologically, vascular lesion in the early stages of diabetic retinopathy is characterised by the presence of saccular capillary microaneurysms, pericyte-deficient capillaries and obliterated and degenerated capillaries (Ezra et al., 2013).

Hyperglycaemia increases the glucose molecules turnover through the activation of the polyol pathway, which leads to sorbitol accumulation in cells. Sorbitol causes osmotic stress, which is the chief factor involved in the pathogenesis of the retinopathy (Brocker et al., 2012, Zhang et al., 2014). Another significant factor is the oxidative processes which play an important role in cellular injury from hyperglycaemia. Elevated glucose levels can stimulate the production of free radicals (Kawahito et al., 2009). Genetic and biochemical factors, vascular endothelial growth factor (VEGF), cytokines, chemokines, growth factors,

neuronal factors, have been claimed to play roles in the development of diabetic retinopathy. VEGF production is augmented in diabetic retinopathy, probably in response to hypoxia (Gupta et al., 2013).

Diabetic nephropathy

Diabetic nephropathy is the leading cause of End Stage Renal Disease (ESRD) in the developed world (Gross et al., 2005) and is a common microvascular complication, contributing to chronic renal failure. If not treated, patients with diabetes with microalbuminuria usually proceed to proteinuria and in a significant proportion to diabetic nephropathy. There are strong associations between glycaemic control and the risk of diabetic nephropathy (Fares et al., 2010).,

Diabetic nephropathy is diagnosed by the presence of excess protein (albumin) in the urine and is defined by the passage of more than 500 mg protein in a 24 hours urine in the presence of diabetes (Robles et al., 2015). This condition is preceded by a mild form of proteinuria or "microalbuminuria", which is defined as urine albumin of 30-299 mg/24 hours (Toto, 2004, Van Buren and Toto, 2011).

A study of 2630 patient with diabetes who attended a specialised diabetes care centre in Chennai, India over 12 years, reported that the incidence of microalbuminuria was a 44% (Viswanathan et al., 2012). In the UKPDS, the incidence was 2% per year, and after ten years of diagnosis, the prevalence increased to 25% (King et al., 1999). This progression occurred in both type 1 and T2DM. As many as 7% of patients with T2DM might already have microalbuminuria at the time of diagnosis (Roshan and Stanton, 2013).

Recently, the term Diabetic nephropathy has been replaced by diabetic kidney disease (DKD) and is now best suited only to describe the histopathological condition. The term DKD covers the clinical state produced by, the various pathologies that may combine to produce chronic kidney disease in a person with

diabetes such as DN, nephrosclerosis, atherosclerosis and interstitial nephritis (Hung et al., 2013).

Figures from the U.S. Renal Data System over the last two decades have shown a continual increase in the incidence of renal failure among patients with diabetes (Rivara and Mehrotra, 2014). Earlier it was thought that the risk of renal complications was lower among patients with T2DM than among patients with type 1 diabetes. However, the incidence of ESRD in patients with T2DM has increased dramatically, which might be due to the availability of better management options for hypertension and CHD in patients with diabetes. As a result, more patients with T2DM live longer enough for DKD and ESRD to develop ESRD (Ghaderian et al., 2015). The incidence of proteinuria and glomerulosclerosis increases because of the increased duration of diabetes, DKD increases in both T1DM and T2DM for up to 20-25 years of diabetes disease after which there is a decline in the number of patients developing renal disease (Gheith et al., 2016).

There is a greater relative risk of DKD in men than in women (RR = 1.17, 1.01–1.36). Certain racial and ethnic groups such as Asians, West Indians, Pima Indians and Hispanic Americans have a higher incidence. This may relate to their predisposing to develop diabetes more frequently and at an earlier age than other populations as well as to their lesser renal blood flow and increased vascular resistance (Ozawa et al., 2015).

Familial clustering of DKD was reported. The cumulative incidence of overt proteinuria in siblings of patients with advanced DKD is 38%, whereas out of the siblings with diabetes without DKD, only 17% had DKD (Harjutsalo et al., 2004). Hyperglycaemia is an important factor in the development and evolution of DKD, Patients who adequately control their blood glucose develop less glomerulosclerosis than patients whose diabetes is poorly controlled. Patients with diabetes should be treated to the lowest safe glucose level that can be achieved to prevent or control diabetic nephropathy.

2.9 Monitoring of Diabetes Mellitus

The DCCT and the UKPDS have confirmed that intensive treatment (maintaining HbA1c to approximately 7% or 1% above the upper limit of normal) is associated with less long-term diabetes complications provided early intervention be commenced to attain good glycaemic control and modify risk factors. However, intensive control increases the risk of severe hypoglycaemia and weight gain (Schwartz, 2013).

Diabetes complications claimed 13% of healthcare budget, and people with diabetes incurred 23 % of the healthcare expenditures in developed nations (ADA, 2013). To prevent diabetes complications, it is crucial that proper diagnosis and monitoring is carried out; first to detect response to treatment (glycaemic control) and second to detect any complications. Monitoring glycaemic control is essential to guide therapeutic interventions to achieve the best possible Blood glucose control (Parkin and Davidson, 2009).

2.9.1 Short-term monitoring system

Urine Glucose

An English physician called Matthew Dobson experimentally demonstrated in Liverpool the presence of sugar in the urine of a patient with diabetes. He boiled the urine to evaporate the fluids and examined the residues. He observed there was a crystalline substance that tasted like sugar (Karamanou et al., 2016).

Urine glucose testing has been the traditional method of monitoring glycaemic status since the discovery of insulin in 1922 until it was replaced by the introduction of home glucose monitoring.

Urine glucose reflects the mean blood glucose over the time the urine was collected. The maximum renal threshold for glucose ranges between 10 and 11.1 mmol/l (180-200 mg/dl). The kidneys do not reabsorb glucose beyond a renal

threshold of 11mmol/l (200mg/dl). The urine glucose depends on the blood glucose concentrations and urine flow. The urine glucose is the average of the blood glucose level over the time of urine accumulation (Shubrook et al., 2015). However, the renal threshold differs within and across individuals at different times. Therefore, urine glucose may not have a fixed relationship with blood glucose. For example, the renal threshold is higher in long-standing T2DM patients, who may mark hyperglycaemia without glycosuria (Osaki et al., 2016).

Ketones

Urine ketones indicate insulin deficiency and impending ketoacidosis or established ketonemia.

There are three ketones bodies: (1) acetoacetic acid; (2) acetone; and (3) β hydroxyl -butyric acid. It is important to test for these bodies as a part of routine evaluation of patients with diabetes. Ketone bodies are normally present in urine, but their concentrations are below the limit of detectability with conventional detection methods. The excretion of > 1 mmol/l of these substances indicates ketonuria (Luethi et al., 2016).

Blood Glucose

Blood, plasma or serum glucose can be analysed using the same principle as described for urine glucose. Most standard laboratories now use the enzymatic determination for blood glucose testing (Nagaraja et al., 2012). Ideal values for blood glucose control in T2DM patients are shown in table 4 (WHO and IDF, 2006).

Table 4: Ideal values for blood glucose control in T2DM patients

Plasma glucose test	Normal	Prediabetes	Diabetes
Random	< 11.1 mmol/l < 200 mg/dl	N/A	≥ 11.1 mmol/l ≥ 200 mg/dl
Fasting	< 6.1 mmol/l < 110 mg/dl	6.1 to 6.9 mmol/l 110 to 125 mg/dl	≥ 7.0 mmol/l ≥ 126 mg/dl
2 hours post-prandial	< 7.8 mmol/l < 140 mg/dl	7.8 to 11.0 mmol/l 140 to 200 mg/dl	≥ 11.1 mmol/l ≥ 200 mg/dl

Reagent Strips

Just as urine glucose can be estimated using test strips, blood glucose estimation can also be performed using test strips. A drop of blood is obtained by a finger prick. The skin can be punctured by a needle or by various finger-pricking devices comprising a lancet. The procedure is quick and virtually painless. Washing the hands in warm water, shaking the hands, and avoiding spirit which tends to harden the skin could minimise pain. The finger is pricked on its lateral aspect, which has relatively fewer nerve endings (Heinemann, 2008).

Other Methods of Non-invasive Blood Glucose Monitoring

Innovative methods to measure blood glucose include:

Near-infrared radiation spectroscopy: This method uses an external light source whose wavelength is just above the visible spectrum. The light passes through or is reflected by a body part and glucose and other blood constituents absorb a small amount of light at each wavelength. The reflected light is analysed to determine the Blood glucose level (Maruo and Yamada, 2015).

Mid/Far-infrared radiation spectroscopy: this device measures natural thermal emissions or body heat. When radiation in the mid/far-infrared, well outside the visual spectrum, passed out of the body, glucose in the blood absorbs part of it. The absorption can be spectroscopically determined by comparing measured and

predicted amounts of thermal energy at the skin surface, and the difference can be converted to a blood glucose concentration (Yoshida et al., 2013).

Radio wave impedance: When a radio wave passes through a solution that contains a non-ionic solute, such as glucose, the solute interacts with the beam to attenuate the amplitude and shift its phase of the beam. Using a conversion factor, the glucose concentration in blood can be calculated by measuring the impedance of the radio wave as it passes through the fingertip (Murthy et al., 2008).

Optical rotation of polarised light: If a beam of polarised light is passed through a fluid containing glucose, the polarisation plane rotates in proportion to the concentration of glucose in that fluid. A beam can be passed through a body compartment such as ocular aqueous humour and the amount of rotation used to calculate the glucose concentration (Purvinis et al., 2011).

2.9.2 Long-term monitoring system

Glycated haemoglobin (HbA1c) is considered the best laboratory parameter available to assess long-term metabolic control. It is a highly valuable tool in research studies and has been used widely.

Kunkel et al. found in 1955 that using electrophoresis, adult haemoglobin (Hb) could be shown to consist of fast and slow migrating components, and in 1968, Rahbar established that the fast haemoglobin component was increased in persons with uncontrolled diabetes (Sacks, 2012). The clinical relevance of HbA1c was established by Bunn, and Nathan and its kinetics were studied by Goldstein (Kahn and Fonseca, 2008).

Process of Glycation of Haemoglobin

Glycation of haemoglobin takes place by the interaction of glucose with amino-terminal valine of one or both β chains of haemoglobin A (HbA). This glycation site alters the mobility of haemoglobin in cation exchange chromatography.

Glycation also occurs at other sites of the Hb molecule. For example, at the ε-amino groups of lysine residues and even α chains. Although the glycation occurring at the latter site is extensive, it does not alter the ionic charge and hence cannot be separated from the non-glycated haemoglobin (HbA0) by cation exchange chromatography (Baeshen et al., 2014). The chemical method measures total GHb, i.e. HbA1c plus the glycated non-N-terminal sites, including an amino group of lysine residues. The initial process of glycation results in an unstable compound produced by the interaction of amine group in haemoglobin with the carbonyl group of glucose. This produces the unstable Schiff base, which is proportional to the actual glycaemia and therefore can impair the quality of GHb assessment in cation exchange chromatography where Schiff base pre-glycohemoglobin (pre-GHb) co-elutes with HbA1c (Pandey et al., 2015). It is possible to remove Schiff base by a simple process of saline incubation. This process has been used in many methods to separate pre-GHb from GHb (Nathan, 1981).

Methodology to estimate Glycation

Methods of GHb assays have primarily evolved around four core principles:

- The difference in ionic charge.
- Structural characteristics (e.g. boronic affinity methods).
- Chemical reactivity.
- Enzyme method.

Methods Based on Differences in Ionic Charge

These methods are extensively used. Cation exchange chromatography can either be undertaken on mini-columns or in a sophisticated, automated system. The pH and temperature conditions affect the results significantly; hence, the need for a sophisticated system where the conditions can be adequately controlled (Chandrashekar, 2016).

HbA1c possesses lesser charge positivity and can be washed faster from a cation exchange column than HbA0. Pre-glycohemoglobin has similar mobility in this system, and hence, it should be removed before column chromatography. Most of these systems cannot differentiate between abnormal HbS, but many advanced systems possess such ability. Foetal haemoglobin co-elutes with HbA1c, and hence, produces falsely high values, while HbS and HbC co-elute with HbA0 and thus produce falsely low values (Ryan et al., 2010).

Methods Based on Structural

One method called boronate affinity method uses a column containing m-aminophenyl-boronic acid coupled to agarose. GHb possesses more cis-diol groups, which has a stronger affinity to the m-aminophenylboronic acid and hence washed later than HbA0. This method is influenced to a lesser extent by haemoglobinopathies (Little and Roberts, 2009, Chen et al., 2016).

Clinical relevance and application of HbA1c

a) Relationship to mean blood glucose

The clinical relevance of HbA1c was established and has been re-examined extensively. A total of 507 participants from 10 international centers in the USA, Europe, and Africa, were recruited in a study to determine the relationship between HbA1c and the average glucose, after three months average glucose results were compared to the HbA1c and a close correlation of the estimated average glucose (eAG) with HbA1c was documented (Nathan et al., 2008).

In the Diabetes Control and Complications Trial (DCCT) in the USA, initial feasibility data measured HbA1c and seven-point blood glucose profiles quarterly for a 1-year period in 1439 patients with type 1 diabetes, bringing out a close linear relationship between glycaemic control and HbA1c. In this study, each 1% increase in HbA1c corresponded to an increase of average blood glucose by 2 mmol/l (35 mg/dl) (Rohlfing et al., 2002). More recently, this relationship has been confirmed (Cha and Ko, 2016).

Glycated haemoglobin cannot be used as a measure of hypoglycaemia, but in the DCCT study, the patients in the intensive group had a two to three-fold increase in hypoglycaemic episodes, and this group had a significantly lower HbA1c (DCCT, 1993).

It is clinically relevant to know that stress hyperglycaemia increases HbA1c levels. In a group of 826 critically ill patients with stress hyperglycaemia, as determined by an initial and follow-up OGTT, a significant elevation of HbA1c was observed in 45.5% of patients (Zhang et al., 2013). This may support the fact that such transient hyperglycaemia is important and could justify treatment.

Discrepancies between HbA1c and blood glucose values reported by patients are expected, as self-monitoring of blood glucose (SMBG) is not yet an accurate procedure, and many studies have shown that SMBG has failed to correlate to the glycaemic control (Karter, 2006). This brings out the importance of HbA1c as a non-manipulable and reliable parameter in assessing metabolic control as compared to SMBG or one-point blood glucose estimations.

b) Glycaemic level variations and Relationship to FBG and post-prandial blood glucose

Although the relationship between the mean blood glucose and HbA1c is well established, it is important to understand that HbA1c does not reflect the glycaemic range. A patient having a markedly high mean of glucose level may show the same HbA1c values as one with an acceptable mean of glucose level during the day because the peaks and troughs of glycaemic level during the day tend to cancel each other. Hence, blood glucose monitoring by itself, or continuous glucose monitoring, continue to retain their role.

HbA1c and blood glucose values were measured in 12,527 patients and interpreted in three FPG levels, < 5.6, 5.6-9 and > 9. A strong relationship between FPG in the range of 5.6-9.0 mmol/l and the corresponding HbA1c was

seen across different ethnic groups and geographic regions (Ramachandran et al., 2012a)

The relative contributions of fasting versus prandial hyperglycaemia toward HbA1c values have been documented. Postprandial glucose has a higher correlation with HbA1c than FPG, and the major contributor to HbA1c is the prandial glucose (Ceriello, 2010, Ketema and Kibret, 2015).

c) Anaemia and HbA1c

The commonest anaemia seen is due to iron deficiency, and there is a positive correlation between iron deficiency anaemia and HbA1c level (L. Christy et al., 2014). Any stable anaemic condition (normal retics count) does not affect the estimation directly when HPLC, boronic affinity or immunoassay or enzyme methods are used, as there is an adequate amount of haemoglobin is used to carry out the estimation.

Haemolytic anaemias will alter the result HbA1c, because of the ongoing destruction of erythrocytes or accelerated erythropoiesis during recovery increases the retics count. A study of HbA1c in haemolytic anaemia showed that HbA1c value could decide the reduced half-life of erythrocytes by correlating the dropping in HbA1c level and degree of haemolysis (Cohen et al., 2008).

Haemoglobinopathies that alter the ionic change of the Hb molecule produce unreliable results HbA1c by methods that use ionic charge to separate HbA1c from HbA0 (Nasir et al., 2010).

d) Relationship HbA1c with Complications of Diabetes

The relationship is stronger for microvascular disease than the macrovascular disease. In the DCCT, the intensive method control group maintained an average HbA1c at about 7% and conventional method control groups at about 9%. The 10% lowering of HbA1c level in the intensive group resulted in significant

reduction (about 30-44 %) of microvascular and neurological complications like retinopathy, nephropathy, and peripheral neuropathy.

The intensive control group continued to maintain benefits for 17 years of post-study follow up, as the risk of any cardiovascular disease was reduced by 42% as compared to the standard treatment group (Kitsios et al., 2011).

In the UKPDS, the mean HbA1c was about 1% lower in the intensive control group as compared to the standard control group. This resulted in 16% reduction in macrovascular disease and 25% reduction in microvascular disease. A 10-year follow-up continued to reveal reduced diabetes-related endpoints (9%, p= 0.04), microvascular disease (24%, p= 0.001) and myocardial infarction (15%, p= 0.01) in intensively treated group as compared to standard treatment group (King et al., 1999). This firmly establishes the importance of HbA1c as an important parameter in long-term studies. However, rapid and marked lowering of HbA1c in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) and the Veterans Affairs Diabetes Trial studies could have been responsible for an increase in the cardiovascular diseases (Kishore et al., 2012).

e) HbA1c Targets and Current State of Target Achievement

Glycaemic control has a well-documented relationship with vascular complications of diabetes.

Table 5: Suggested targets of HbA1c based on ADA/EASD recommendations

Diabetes category	Targets
T2DM	
• Newly discovered T2DM	6.0-6.5%
• Most T2DM	<7.0%
• Long-standing T2DM	<8.0%
• Long-standing T2DM with complication	<8.5%
Type 1 diabetes	
• On multiple dose insulin	<7.5%
• On insulin pump therapy	<7.0%

(ADA: American Diabetes Association; EASD: European Association for the Study of Diabetes).

The HbA1c targets are derived from population studies showing a threshold of 6.3-6.7% for a sudden deterioration in the retina. Various associations have recommended targets in general and in specific situations in diabetes. In general, more recent onset T2DM calls for a stricter target and long-standing T2DM requires more relaxed targets. Fortunately, achieving stricter targets is feasible in the first 5-10 years of T2DM, this also leads to greater long-term benefits as shown in the follow-up studies of DCCT and UKPDS.

In type 1 diabetes, the targets are somewhat relaxed, because, with the current standard insulin therapy, the desired targets are usually not achievable without producing unjustifiable hypoglycaemia (Martín-Timón and del Cañizo-Gómez, 2015).

The present state of metabolic control, as reflected by HbA1c values, is far from satisfactory. It is probably due to imperfect treatment tools, the patient behavioural problems and imperfect application of therapy. In most diabetes clinics, only 37% of patients with diabetes achieve an HbA1c < 7.0%. To sustain this degree of control over an extended period seems to be more difficult. Data from the USA reveal that the percentage of patients that achieved the targeted HbA1c of 7.0% in 1999-2002 was 37%, which was later improved to 57.1% in 2003-2006 (Pérez et al., 2012).

f) Use of HbA1c in the Diagnosis of Diabetes

Most studies have highlighted that OGTT is a more sensitive diagnostic method than HbA1c test. An impaired OGTT may be associated with normal HbA1c especially in anaemic patients or individuals with abnormal haemoglobin (Sacks, 2011).

The sensitivity and specificity of HbA1c in the diagnosis of diabetes have been compared with the standard OGTT. Using different HbA1c cut-off points, the best balance of sensitivity and specificity is achieved by using a threshold < 6.1% as normal, 6.1- 6.5% as IGT and > 6.5% as diabetes (John et al., 2007). When these thresholds were compared to the diagnostic accuracy of OGTT in 997 participants, the sensitivity was 57.2% and specificity 67.4% for HbA1c compared to 69.1% and 61.6%, respectively for FPG (Gomyo et al., 2004).

The Insulin Resistance Atherosclerosis Study (IRAS) of over 850 participants, compared the performance of OGTT, FPG, and HbA1c. HbA1c diagnosed 44 (5.2%), FPG 61 (7.1%), and OGTT 132 (15.4%) patients with DM (Lorenzo and Haffner, 2010).

Using HbA1c instead of a blood glucose estimation offers several advantages. Currently, the Coefficient of variation of HbA1c assays has been brought down to 2% while that of blood glucose continues to be at about 5% (NGSP, 2016). Samples for HbA1c are stable for more than a week while pre-analytical glycolysis in blood samples offers poor stability. HbA1c may also be useful for epidemiological purposes, but the cost of the test remains high at present (Bonora and Tuomilehto, 2011).

2.9.3 Point of care devices

POCs devices are increasingly used for a broad range of diagnostic tests and treatment monitoring (Rajendran and Rayman, 2014). POC testing is on-site, and the timeliness of results minimise the delay associated with traditional laboratory

procedures condcuted at centralised laboratories and reduce the need for further office visits (Bhurosy and Jeewon, 2014).

The availability of instant results by HbA1c POC devices has benefited patient care services. Comparing the standard laboratory HbA1c testing with POC devices, POC devices allow health care providers to swiftly evaluate the efficiency of diabetes treatment and boost therapy outcomes (Hermayer et al., 2015). Together, this will help the medical staff to improve patients' future HbA1c figures, specifically for T2DM patients with poor glycaemic control, by enabling timely therapeutic adjustments (Joseph, 2013).

There are very few National Glycohemoglobin Standardization Program (NGSP)-certified POC HbA1c devices. This thesis will compare the NGSP-certified Quo-test HbA1c POC device to the traditional laboratory HbA1c testing, to help guide healthcare facilities in deciding on the performance of the quo-test device in testing HbA1c in outpatient clinics.

The capability of a POC device to duplicate the laboratory HbA1c results of any given patient is the ultimate quest (Schwartz et al., 2009). Since its establishment in 1996, the NGSP has been the reference in developing guidelines and protocols for standardising HbA1c testing for both laboratory apparatuses and POC devices since 1996. The Diabetes Control and Complications Trial (DCCT) was a medical study conducted by the United States National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) (Penttilä et al., 2016). From the 1990s onwards, the findings in this study were the key to the changes that shaped the principles of management of DM (DCCT, 1993). To ensure continued precision, the NGSP requires annual device certification, during which the HbA1c device must be tested in a 40-samples compared to an NGSP secondary reference laboratory in a controlled environment. The 40 HbA1c test samples are ranged from 4% to 10%. Certificates are only issued when at least 37 of the 40 samples fall within 6% (lowered from ±15% in 2007) of the NGSP secondary reference laboratory values (NGSP, 2016). This strict evaluation test provides health care providers

confidence in the precision and accuracy of the devices in a controlled environment (John et al., 2007). The ADA endorsed the criterion set by the NGSP and strongly recommends that laboratories use only methods that have been approved by NGSP (Sacks, 2012).

Even though the NGSP has not set clear targets for precision and accuracy, it does endorse a mean bias of < 0.2 and CV < 3% (preferably < 2%) and labelling those with a mean bias of > 0.3 and a CV > 5% as less satisfactory assay methods. Alternatively, the ADA recommends a CV <4%, and ideally <3% (Whitley et al., 2015).

In this thesis, we will study the performance of a POC device called Quo-test, the NGSP-certified Quo-test device is based on structural differences (boronate affinity) rather than the ionic charge differences (e.g., cation-exchange chromatography and agar gel electrophoresis) (NGSP, 2016).

According to the NGSP guidelines, abnormal haemoglobins such as haemoglobin C (HbC), D (HbD), E (HbE), and S (HbS) causes assay interference in more than half of laboratory and POC HbA1c instruments. The Que-test, reports that it has no interference in the presence of the common Hb-variants HbS, HbC, HbD, HbE, HbJ, elevated A2 (β thalassemia) and showed no significant bias in the presence of < 8.6% Hbf in the blood sample (Lenters-Westra, 2016).

Normally, HbF levels drop to < 1% soon after birth. However, abnormal levels can remain high or increase in neonates until the end of the first month, hereditary persistence of fetal haemoglobin, thalassemia's, and patients with abnormal Hb variants. Normal haemoglobin A (HbA) is composed of two α and two β chains compared to the two α and two γ chains in HbF. This structural change decreases the ability of antigenic sites on immunoassays to recognize glycated fetal haemolobin. During HbA1c analysis, non-glycated HbF can be detected as a glycated haemolobin. Therefore, immunoassays used in patients with significantly high HbF (>10%) will have falsely low results , which may lead to inadequate clinical interventions (Nasir et al., 2010).

In addition to improving glycaemic control, introducing HbA1c POC devices is anticipated to lower health care system expenditure. The economic impact of strict glycaemic control on overall health care costs is manifested in the subsequent prevention of complications and reduction in the need for further care. For every one-percentage-point increase above HbA1c of 4.4 %, there is an increase in overall medical costs, and about 30% of the pharmacy charges are correlated to the glycaemic level (Fitch et al., 2013). Patients with strict glycaemic control (HbA1c <7.0 %) are hospitalised less frequently with pneumonia compared to those with an HbA1c ≥ 9.0% (Kornum et al., 2008).

2.10 Risk factors for diabetes mellitus

Researchers do not fully understand why some people develop prediabetes and T2DM and others do not. Specific factors increase the risk, these factors include:

2.10.1 Urbanization

The developing countries are undergoing rapid urbanisation and migration of population to urban areas. A major redistribution of the population is already occurring, and it is projected that by the year 2030, 60% of the world's population would be living in urban areas (Ferreira et al., 2010). According to the WHO estimates, in the last five decades two-fold to five-fold increase in urban population has occurred in Asia (Sherif and Sumpio, 2015).

The increase in urban population and ageing has been attributed as main determinants of the global rise in the prevalence of diabetes. Internal rural to urban migration adversely impacts lifestyle factors such as a reduction in physical activity, unhealthy changes in dietary habits, and increasing adiposity and obesity (Carrillo-Larco et al., 2016). As shown in recent studies in China, considerable changes have occurred in the lifestyle of rural populations resulting in marked increase in overweight and diabetes (Guo et al., 2014). The situation is similar in most Asian countries.

In Kuwait, the percentage of the population living in urban centres is 99% (CSB, 2005). The rise in prevalence of diabetes has been attributed to socioeconomic and behavioural changes in recent decades (Ahmed et al., 2013).

Studies from different parts of India have shown that social and economic changes occurring in rural India have produced significant changes in the occupational, dietary and activity levels. Many villagers have sought jobs in urban areas involving less manual labour. Physical activity levels have decreased with better transport facilities, Increased calorie intake with consumption of fat and carbohydrates (Hu, 2011).

The changing demography of diabetes is evident from studies in Singapore and Malaysia. A phenomenal increase in diabetes occurred in Singapore; increasing from 2% in 1975 to 4.7 in 1984, 8.6% in 1992 and 9% in 1998. Sedentary lifestyle and growing rate of obesity were strongly associated with the increasing prevalence of glucose intolerance (Lee, 2000). National initiatives taken to improve the health status of the population resulted in a decrease in the prevalence of diabetes (from 9% in 1998 to 8.2% in 2004), but the prevalence is increasing again, reaching 12.3% in 2013 (Shuyu Ng et al., 2015).

2.10.2 Racial Predisposition

A racial predisposition to diabetes has been evident from migrant Indian studies which showed that Asian populations living in different parts of the world had a higher prevalence of diabetes compared with the co-inhabitants of other races. In the UK, the prevalence of diabetes in Asian migrants is about five times higher than the native inhabitants (Montesi et al., 2016). Even internal migration within a country, resulting in prosperity and sedentary lifestyle, reveals the tendency for diabetes in the Asian races (Ramachandran et al., 2010).

Asians have a high predisposition to diabetes, but there are wide variations in the prevalence rates and age at development of diabetes in different Asian cohorts (Ramachandran et al., 2012b).

2.10.3 Genetic Risk

Both the thrifty phenotype and thrifty genotype hypotheses appear to play etiological roles in the development of diabetes in Middle East populations (Sherif and Sumpio, 2015). While the thrifty genotype hypothesis suggests a discrepancy between the ancestral genes and modem environment, the hypothesis assumes a divergence between intrauterine and adult life environments. The combination of gestational diabetes, in utero-nutritional imbalance, childhood obesity, and overnutrition in adulthood will continue to fuel the epidemic in countries undergoing rapid nutritional transitions. The genetic risk factors for T2DM are complex and still largely elusive. However, the genetic predisposition is obvious from the heritable nature of the disease. A strong familial aggregation of the disease has been noted in Asian populations. In India, nearly 75% of T2DM patients, have a first-degree family history of diabetes (Mehta et al., 2009).

2.10.4 Ageing

The increase in life expectancy and a decline in fertility are expected to result in faster ageing of the global population in the 21st century. Diseases of the elderly, such as diabetes, hypertension, CVD, CHD, and cancer will become more common (Lunenfeld and Stratton, 2013). The prevalence of diabetes increases with increasing age. In China and Japan, diabetes usually occurs in individuals between 70 and 89 years old. In India, the onset of diabetes occurs at a younger age (60-69 years). Studies have shown a much younger age at onset of diabetes compared to the western population. The DECODA study made a comparative analysis of age at diagnosis of diabetes in different races. The overall effect of age on prevalence of diabetes differed considerably between ethnic, groups even after correcting for other confounding factors such as body mass index (BMI). The association between age and diabetes was higher in the Indian population compared to all other populations studied (Qiao et al., 2003).

The age and sex-specific prevalence and the peak prevalence of diabetes were higher in the Indian and Singapore cohorts than in the Chinese and Japanese cohorts (Nakagami et al., 2003).

An early occurrence of diabetes in the population has a severe economic impact; as serious morbidity and early mortality occur in the most productive years of life, and T2DM subjects live long enough to develop the debilitating vascular complications of diabetes (Deshpande et al., 2008).

2.10.5 Anthropometric Characteristics

Although the prevalence of obesity and overweight are relatively lower in Asia compared with Western populations, the recent socio-economic transition in Asia is resulting in a parallel increase in its prevalence of obesity and diabetes. Among younger Asians, diabetes occurs at lower levels of BMI than in Western populations and small increments in weight trigger glucose intolerance in the susceptible subjects (Hu, 2011).

Analysis of the National Health Interview Survey (NHIS) in the United States (USA) from 1997 to 2008 showed that Asian Americans had significantly higher rates of diabetes than white populations. There was a significant upward trend in both groups for diabetes and BMI with age. However, Asian Americans had higher odds of developing diabetes; they are 30-50% more likely to have diabetes, despite having significantly lower BMI than the white populations (Lee et al., 2011).

An excess of body fat especially concentrated within the abdomen has a range of potentially harmful effects. It includes increased risk for diabetes, blood pressure, dyslipidaemia, IR, CHD and some forms of cancer. It has also been observed that Asian have a higher percentage of body fat, for a given BMI, when compared with the white population (Davis et al., 2013). For diabetes, obesity and specifically, abdominal obesity, is a major risk factor. In the white population, overweight is defined as a BMI ≥25 kg/m^2 and obesity as BMI ≥30 kg/m^2 (Friedl, 2009).

However, several studies have shown that overweight BMI levels in Asians range between 23 kg/m^2 and 27 kg/m^2, while obesity should be a BMI ≥ 27 kg/m^2. The risk of metabolic disease in Asian individuals increases progressively > 23 kg/m^2 (Jih et al., 2014).

The ADA and WHO have considered a BMI ≤23 kg/m^2 as the cut-off for normal in Asian populations (Misra, 2015). China has adopted standards to define overweight as a BMI > 24 kg/m^2 and obesity as a BMI > 28 kg/m^2 (Wang et al., 2006).

Abdominal obesity is defined by a waist circumference > 94 cm in men and >80 cm in women. Similarly, the cut-off for waist circumference is lower in Asian populations (World Health Organization, 2008) as several studies have highlighted the "metabolically obese" phenotype among normal weight individuals in Asian populations. Greater abdominal obesity characterises this phenotype despite a normal BMI, less muscle mass, a higher proportion of body fat and an increased tendency for IR compared with Western populations, leading to a higher predisposition for diabetes and vascular diseases (Lee et al., 2015b, Dulloo et al., 2010).

2.11 Burden of diabetes

2.11.1 Global Burden of T2DM

According to the WHO Global Burden of Disease (GBD) 2012, T2DM is one of the 15 leading disability-adjusted life years (DALYs) diseases (table 6).

In 2015, there were 5 million deaths caused by T2DM, accounting for a death every 6 seconds (IDF, 2015). This is despite the fact that the diabetes-related mortality is greatly underestimated, as diabetes is often under-reported on death certificates (Cheng et al., 2008).

The direct health care costs of T2DM in 2010 was estimated to be $ 376 million, accounting for 12% of the annual global healthcare budgets (Zhang et al., 2010a).

It is hard to measure the indirect cost of diabetes since it is affecting not only patients but also the families and the society, that is why we are expecting that the indirect costs are more likely to be much higher.

Table 6: Top 10 causes of DALYs globally 2015 (

Rank	Cause	DALYs (000s)	% DALYs	DALYs per 100,000
	All Causes	2,668,296	100.0	36331
1	Ischemic heart disease	192,056	7.2	2615
2	Lower respiratory infections	142,384	5.3	1939
3	Stroke	139.874	5.2	1905
4	Preterm birth complications	102,297	3.8	1393
5	Diarrheal diseases	84,928	3.2	1156
6	Road injuries	76,020	2.8	1035
7	COPD	72,815	2.7	991
8	Diabetes mellitus	70,667	2.6	962
9	Birth asphyxia and birth trauma	67,266	2.5	916
10	Congenital anomalies	64,825	2.4	883

Wild et al. projected the global prevalence of diabetes for all age groups in 2000 and made estimates for 2030 (reference). They obtained age- and sex-specific data on diabetes prevalence from population-based prevalence studies from a restricted number of countries. Diabetes prevalence estimates from these countries were extrapolated to the 191 WHO member states, using a combination of criteria including ethnicity, socioeconomic state, and geographical proximity. Prevalence estimates were then applied to the UN population estimates for individual countries. The estimated prevalence was 2.8% in 2000 and 4.4% in 2030 (Wild et al., 2004).

The future projections in diabetes prevalence were informed by demographic changes alone. It was assumed that other diabetes risk factor levels (e.g. obesity and decreased physical activity) would remain constant in developed countries. In comparison, in developing countries, urbanization was used as an indirect measure of the levels of risk factors, as urbanization in these countries is associated with increased prevalence of obesity, reduced physical activity, and changes in dietary habits. It was estimated that in 2013, 382 million adults had diabetes (20-79 years), and it was projected this number would increase to 592 million by 2035 with higher rates in developing countries (Guariguata et al., 2014).

In an earlier study, King et al. (1998) used age-specific diabetes prevalence estimates from the WHO's diabetes database (collected from 32 countries). They applied these data to the UN demographic estimates for the world's population to predict the global prevalence of diabetes in adults ≥ 20 years for 1995, 2000, and 2025. Similar to the study by Danaei et al., countries without prevalence estimates were extrapolated from neighbouring countries or those with similar socioeconomic and ethnic characteristics. The prevalence of diabetes worldwide was estimated to be 4% in 1995 and was projected to increase by 35% to reach 5.4% by 2025, with more than 75% of them living in developing countries. The number of adults with diabetes was predicted to increase from 135 million in 1995 to 300 million in 2025, with the majority of this increase occurring in developing countries (King et al., 1998).

2.11.2 Diabetes burden in developing countries

In the past, industrialised countries were the primary focus for non-communicable diseases (NCDs), and NCDs were known as "diseases of affluence"(Wagner and Brath, 2012). However, in the recent decades, NCDs prevalence (including T2DM) have increased globally with higher numbers and increasing rates in developing countries. It is estimated that NCDs are responsible for around 50% of the total disease burden in these countries (Boutayeb and Boutayeb, 2005). The main reason for these elevated levels is the increase in the

major risk factors (e.g. obesity, physical inactivity, smoking, and changes in diet), because of rapid urbanisation, lifestyle and nutrition changes. Increasing life expectancy has also resulted in ageing populations with increased rates of chronic diseases (Deshpande et al., 2008). It is well documented that T2DM prevalence is lowest among people who have a more active “primitive” lifestyle in developing countries, despite similarities in ethnicity and genetic characteristics (Deepa et al., 2014).

The estimates and future projections of diabetes burden in developing countries are rising progressively. Over the 30-year period from 1995 to 2025, the increase in the number of adults with diabetes in developing countries is expected to increase by 170%, from 84 to 228 million, compared to 42% increase, from 51 to 72 million, in developed countries (King et al., 1998). The biggest increase in prevalence by 2025 is expected to be in the Pacific and East Asia followed by the Middle East and North Africa, and the smallest is projected to be in Sub-Saharan Africa (Narayan KMV, 2006).

The age distribution of people with diabetes is also different in developing countries. While most diabetes cases in developed countries are older age groups, many cases in developing countries tend to occur among young and middle-aged people. There are 320.5 million people of working age (20-64 years) with diabetes and 94.2 million individuals aged 65-79 with diabetes. This implies that the health, social, and economic burdens of the disease extend to even younger ages and for a longer period of an individual’s lifespan.

There are few gender differences in the global number of people with diabetes between 2015 or 2040. There are about 15.6 million more men than women with diabetes (215 million men vs 200 million women). This difference is expected to decrease to about 15.1 million (328 million men vs 313 million women) by 2040.

Presently, there are more individuals with diabetes in urban (270 million) than rural areas (145 million). In low and middle-income countries, the number of people with diabetes in urban areas is 186 million while 127 million live in rural areas. By 2040, the worldwide difference is likely to broaden, with 478 million people living in urban areas and 164 million in rural areas (IDF, 2015).

Health organisations in most developing countries are structured primarily to confront acute and chronic communicable diseases. These services are usually not prepared to offer effective prevention and care for NCDs. As a result, disappointingly, there are now many "poor" developing countries that face a double burden, since the levels of infectious diseases (e.g. Tuberculosis, HIV/AIDS, and malaria) continue to be high, in addition to increasing levels of NCDs (Miranda et al., 2008).

2.11.3 Diabetes burden in the Eastern Mediterranean Region

In the EMR, the problem of T2DM is growing significantly, with a sharp increase in the disease prevalence in both sexes. Many countries in the region have experienced rapid and immense socioeconomic development over recent decades. These socioeconomic changes have been said to be the principal reason for the epidemiological changes in risk and disease burden in the region. The WHO has projected that around 47% of the EMR's disease burden is currently due to NCDs and this number is expected to increase to 60% by 2020 (Saidi et al., 2015).

Figure 1: Map of WHO's Eastern Mediterranean Region (http://www.iapb.org/)

The prevalence of major risk factors for NCDs is projected to be very high in EMR. According to regional WHO estimates in 2004, 14.5% of adults (≥20 years old) diabetes and 43% were overweight/obese. As with most developing countries, many EMR countries have reported a large number of T2DM cases starting in the second and third decades of age (Musaiger, 2011a).

The IDF's region of the Middle East and North Africa (MENA), which is similar to the WHO's EMR including Algeria and excluding Somalia and Djibouti, has been recognized as a major hot spot for diabetes , with the highest estimated age-adjusted prevalence of diabetes (7.4-14.2%) globally in 2015 and will continue to have the highest predicted prevalence (7.7-14.9%) by 2040 (IDF, 2015).

Most of EMRO countries have national strategies for the prevention and management of diabetes, and more than half of the countries reported having diabetes control policies. However, WHO indicated these plans are not being rationally or widely employed. The countries of the Gulf Cooperation Council (GCC) have the highest levels of diabetes within the region and are almost always among the top 10 countries with the highest diabetes prevalence in the world (Sherif and Sumpio, 2015).

2.11.4 Prevalence of diabetes in the countries of the GCC

The GCC was established in 1981 between six countries located on the coast of the Arabian Gulf given the special relations between them, their similar political systems, and common objectives. The GCC includes Saudi Arabia, Kuwait, Qatar, Oman, Bahrain and the United Arab Emirates. People of these countries have many familial inter-relations and share many similarities in environments, cultural, social and lifestyle (At-Twaijri and Al-Muhaiza, 1996).

Figure 2: Map showing the Gulf Cooperation Council countries (http://www.erutledge.com/)

The GCC countries are major suppliers of oil. According to the International Monetary Fund, Qatar was ranked to have the highest gross domestic product purchasing power parity (GDP-PPP) in the world in 2015.

Accordingly, the GCC countries have witnessed extensive social and financial developments in the recent decades, with significant changes toward sedentary lifestyles and 'Western' dietary habits and are considered a major focus for diabetes.

2.11.5 The state of Kuwait and its Health system

Historical background

The State of Kuwait is located to the Northwest of the Arabian Gulf. To the South and Southwest it shares the border with the Kingdom of Saudi Arabia and to the East with the Gulf, to the North and Northwest, it shares the borders with the Republic of Iraq (Central Statistical Bureau, 2016).

Figure 3: Map of Kuwait (http://www.worldatlas.com)

Due to the strategic location, Kuwait is considered a natural doorway to the northeast of the Arabian Peninsula which gave the country its known commercial importance.

In the 17th century, Nomadic tribes from central Arabia (Najd) settled in the Bay of Kuwait City. Kuwait is a constitutional state under the hereditary rule of the Al

Sabah family since the middle of the 18th century. The Emir is the leader of the nation and holds executive authority, appointing the prime minister and the government.

With a surface area of $(17,818)^2$ kilometres, Kuwait has six governorates: Al-Asimah, Hawalli, Al-Ahmadi, Al-Farwaniyah, Mubarak Al-Kebir, and Al-Jahrah. The total population is 3,065,850 (2011). Nationals constitute about 35.6% of the population, and more than 99% of the population live in urban areas in and around the capital (Central Statistical Bureau, 2016). The population density in urbanised areas is several times higher than the reported 172/km^2, which is calculated by dividing the total population by the country's total surface area.

The public in Kuwait enjoy a high standard of health services; sufficient hospitals, health centres and clinics staffed by skilled health workers who provide efficient and safe health care. The burden of disease and health indicators are similar to those of highly industrialised countries (World Health Organization, 2016).

The Health System in Kuwait

The Ministry of Health in Kuwait is working to provide comprehensive health care for its citizens, residents and to protect them from physical, psychological threats, including availability of health services, preventive, curative and other emergencies. The health services in Kuwait in the past matched the simplicity of life and the conditions that existed at that time, and expertise and availability of services were limited. Kuwaitis have thus relied on traditional (alternative) medicine in the treatment of diseases.

Health care has since evolved. In 1911 an American mission built the first hospital in the country, which continued to work until 1967. The Ministry of Health has since become the main provider of health services. Services are provided through three levels::

1. Primary care: offered through health centres, which includes General Medicine - Dentistry - child and maternity care, preventive medicine and school health, laboratory and radiology.
2. Secondary care: provided through six general public hospitals: Al-Amiri, Al-Adan, Al-Sabah, Mubarak Al-Kabeer, Al-Farwaniyah and Al - Jahrah.
3. A Tertiary Care: offered through specialised hospitals and medical centres (Psychiatry - Ibn Sina - communicable diseases - Physical Medicine and Rehabilitation system).

Burden of Noncommunicable diseases

Food availability is plentiful and affordable to all sections of the population. Kuwait has a widespread increase in fast food restaurants, leading to the increased eating of high-fat and high-energy foods, such as fried foods and soft drinks, mainly among youngsters, with adverse health impact. Overweight and obesity are highly prevalent risk factors with a considerably higher prevalence among Kuwaiti nationals. The Nutrition and Catering Administration is under the Department of Public Health. Much of its work focuses on hospitals. It also works on healthy diets for the general population; however, the division needs to be evaluated and strengthened to fulfil more public health aspects, especially given the high prevalence of obesity, including children and youth.

Kuwait has experienced an increase in CHD, cancer and unintentional injuries (mainly road traffic accidents). Obesity, dyslipidaemia, physical inactivity and diabetes have a high prevalence, demanding a modification from therapeutic to preventive approaches. Regarding DALYs in Kuwait, high body mass index, dietary risks, and high fasting plasma glucose are the leading risk factors in 2013 (Mokdad, 2016).

A study conducted by the Department of Food and Nutrition in the Ministry of Health showed that the prevalence of overweight was 38.9% and 28.9% for adult males and females, respectively and the prevalence of obesity was 39.2% and 53% for adult females and males, respectively (Musaiger, 2011a).

Diabetes mellitus in Kuwait

Since the discovery of oil, the lifestyle in Kuwait changed dramatically. People now lack physical activities and have adopted a western lifestyle. Governmental jobs do not include physical activities, partially due to the hot weather conditions, leading to a more sedentary life. The cultural habits in Kuwait involve food in almost every social event. This gives rise to many health problems; including metabolic syndrome, with its trilogy; diabetes, hypertension, and dyslipidaemia leading to CVDs and stroke. According to the recent statistics, T2DM has reached 23.1% of the population (Guariguata et al., 2014).

The growth of T2DM does not only burden health sector, but it also affects the economy due to its direct and indirect impact on the economy. Direct economic costs include medical treatment expenditures, acute and chronic complications, hospitalisations and excess general medical costs, which have placed a substantial financial burden on the country (Seuring et al., 2015).

Even for a wealthy country like Kuwait, the economic costs of T2DM are hard to tolerate and should motivate the government to evaluate the extent of the disease and to seek other methods to prevent the disease and disease-related conditions. (Alhyas et al., 2012, Channanath et al., 2013, Al-Hussaini and Mustafa, 2016).

Glycaemic control is an important approach for the management of people with T2DM, and according to the ADA the optimal blood glucose level to prevent T2DM complication is < 7%. A study in Kuwait reported that the proportion of individuals with T2DM with poor glycaemic control (HbA1c > 7%) is 79%. A further study also reported that the proportion of individuals with T2DM having HbA1c > 8% is 66.7% (Al-Rasheedi, 2015).

Delays in treatment intensification can lead to poor control of T2DM, and using more than one oral antidiabetic agent or adding insulin to the treatment plan if needed, should not be delayed (Khunti et al., 2013).

Point of care devices (POC) can help health staff to decide promptly to modify the strategy and to intensify treatment. At the same time, POC devices are more convenient to the patients, as they do not need to revisit the clinic to receive the results. In this study, we will evaluate the accuracy of a POC device against the reference laboratory machine.

2.12 Management of T2DM

Individuals with high risk of developing T2DM can significantly decrease the rate of diabetes onset by undertaking some interventions.

Lifestyle modification is the cornerstone of diabetes prevention (Tabák et al., 2012). Some programs have been shown to be effective (51% reduction after four years) (Salas-Salvadó et al., 2011). Three large studies of lifestyle intervention have shown a continuous decrease in the incidence of T2DM, with 43% reduction at seven years in the Finnish Diabetes Prevention Study (Hu, 2011), 51% reduction over six years in the Da Qing study (Li et al., 2008), and 34% reduction at ten years (Tuso, 2014).

People with known risks of progressing from prediabetes to T2DM or with an HbA1c 5.7-6.4%, should be advised of lifestyle changes, recommending a 7% weight loss and moderate physical activity for at least 150 minutes per week (Knowler et al., 2002).

The aim of managing patients with diabetes is to stop symptoms and to prevent the development of complications. Microvascular, macrovascular, metabolic and neurological risk reduction is accomplished through control of hyperglycaemia, anti-hypertensive drugs, cholesterol-lowering agents, smoking cessation, and physical activity (Lorber, 2014).

Ideally, blood glucose in T2DM patients should be maintained at near-normal levels pre-prandial of < 5 mmol/l (< 100 mg/dl), post-prandial of < 7.8 mmol/l (<

140 mg/dl) and HbA1c levels < 6.5% (Ceriello and Colagiuri, 2008). However, emphasis on glucose alone does not provide adequate treatment for patients with T2DM. Treatment involves multiple goals including hyperglycaemia, dyslipidaemia, and hypertension (Nyenwe et al., 2011).

T2DM care is best provided by a multidisciplinary team of healthcare professionals with proficiency in diabetes, working in association with the patient and the family. The management team should include physicians, endocrinologists, pharmacists, dieticians, social workers and psychologists (Bowen and Rothman, 2010).

2.12.1 Dietary control

Nutrition interventions must incorporate a variety of meal planning and nutrition education that the patients can easily understand and use.

These include reassessing how the goals have been accomplished and identification of future areas for self-management education. The goal of diet therapy is to maintain and prolong a healthy, productive and satisfying life.

Goals

- To improve health through optimum nutrition.
- To provide calories for reasonable body weight (BW), normal growth and development.
- To maintain glycaemic control.
- To achieve optimal blood lipid levels.
- To minimize nutrition related chronic degenerative complications.

Adapting diet therapy to the specific needs of an individual patient is most essential; however, there are few basic principles that are to be followed.

Nutrition and Body weight in T2DM

Controlling blood glucose and lipid levels along with weight loss to attain an ideal weight are the focus of treatment for overweight patients with T2DM. This identifies the fact that adjustment of fat intake, the spacing between meals, reducing the size of meals, exercise, and sensible weight loss can be effective in achieving the targeted blood glucose and lipid levels in patients with T2DM.

The primary goal for patients with T2DM should be to reach and maintain near-normal blood glucose levels. Making healthy food choices, especially controlling calorie intake can be advantageous. Current recommendations aim to promote good glycaemic control and maintain ideal body weight while reducing the risk of CAD through improved lipid profiles. People with diabetes find it harder to lose weight compared to those without the disease; it is now clear that they do not need to reach their ideal body weight to improve their metabolic status; as little as 5-10% reduction in BW is sufficient to result in clinically relevant benefits (Wing et al., 2011).

Basic principles for planning a diet for T2DM patients

- Age, sex, activity, height, BW, cultural factors.
- Type of diabetes, mode of treatment, control of diabetes.
- Aggravating factors; infections, gastrointestinal disorders, cardiovascular disorders, and pregnancy.

Based on these factors, the primary consideration is of calorie requirements, to achieve one's ideal body weight with a healthy balanced meal.

Definitions frequently used in T2DM

BMI defines obesity. BMI is calculated by the formula:

Weight in kilogram ÷ Height in meter^2

Obese persons are ten times more likely to develop T2DM, and obesity is the principal risk factor, especially when it is central obesity (higher waist circumference or higher waist to hip ratio -WHR).

Criteria for obesity

- Normal: 18.5-24.9
- Overweight: 25-29.9
- Obese: More than 30

Most people store their body fat in two distinct ways:

1. Around the middle (apple-shaped)
2. Around the hips (pear-shaped)

Being apple-shaped or so-called truncal obesity (more fat around the waist) places them in the higher risk category than the pear-shaped (carrying more fat on hips) (Martín-Timón et al., 2014).

The measures are as follows:

1. Waist-hip ratio (WHR)
    - Waist measure midpoint between the last palpable rib and the top of the iliac crest.
    - Hip measure at its maximum.
2. Waist circumference is another quick measure to determine obesity, especially in the Asian population, due to more marked central obesity.

The cut-off points of WHR:

- Men Less than 0.90
- Women Less than 0.85

Healthy cut-off points of Waist circumference

- Men 94 cm
- Women 80 cm

2.12.2 Pharmacological control

Insulin secretagogues

The recent management guidelines suggested by various professional bodies across the world advocate the initiation of treatment of T2DM with medical nutrition therapy along with metformin. However, when metformin alone is not sufficient to maintain glycaemic control the addition of an insulin secretagogue (a substance which promotes secretion) is the next available option (Moses, 2010). The use of insulin secretagogues may also be considered earlier when the patient with T2DM has difficulty in tolerating metformin or has a contraindication to metformin or in those in whom a defective β cell function is thought to be the predominant pathology (Irons and Minze, 2014).

Role of Insulin secretagogues in the management of T2DM

Defects in both insulin secretion and sensitivity are described in the pathogenesis of T2DM. Fasting glucose levels are determined by hepatic glucose output, which is controlled by insulin and glucagon concentrations in the portal circulation whereas postprandial glucose levels are dependent on the composition of the diet and insulin-mediated peripheral glucose uptake. While the maintenance of hepatic glucose output, i.e. fasting glucose requires significantly lower levels of insulin, enhancement of the peripheral glucose uptake, which is reflected as the postprandial glucose level requires much higher levels of insulin. It is, therefore, logical that the sequence of abnormal glucose metabolism starts from IGT, progresses to minimal fasting hyperglycaemia with significant postprandial

hyperglycaemia and finally to fasting hyperglycaemia with marked postprandial hyperglycaemia.

All patients with T2DM with hyperglycaemia have some deficiency in insulin secretion and the higher the degree of fasting hyperglycaemia; greater is the insulin deficiency. Therefore, insulin secretagogues which act by improving β cell function and augment insulin secretion are powerful tools in the management of T2DM (Maria Rotella et al., 2013).

Sulfonylurea

Sulfonylurea was discovered accidentally while looking for newer sulphonamides. The first sulfonylurea to be used in clinical practice was carbutamide, which became available in the 1950s. It was later withdrawn from the market due to bone marrow toxicity. First-generation sulfonylureas are no longer available. However, compounds from the subsequent generations are currently widely used in practice (e.g. glibenclamide, glipizide, and gliclazide) (Kalra et al., 2015).

Mechanism of Action of sulfonylurea

Sulfonylurea stimulates insulin secretion by binding to a specific receptor in the pancreatic β cell, which causes closure of ATP-sensitive potassium (K+) (KATP) channels, resulting in membrane depolarization, and the influx of calcium into the β cell. This increase in intracellular calcium causes contraction of the intracellular filaments responsible for the release of insulin from β cell secretory granules (Sola et al., 2015).

Metformin

Metformin has enjoyed widespread popularity since 1957 and has been widely used all over the world since that time. From 1995 onwards, particularly with the publication of UKPDS data, there has been a significant increase in the study and use of metformin. Today, there is universal acceptance that it is the

pharmacological agent of choice in the initiating treatment of T2DM (Nasri and Rafieian-Kopaei, 2014).

Mechanism of action of metformin

Metformin is lipophilic and binds to membrane phospholipids in the cell wall and mitochondria. The cellular targets are the hepatocyte and skeletal muscle cell and to a lesser extent the adipocyte. The primary enzyme target is adenosine monophosphate protein kinase or activated protein kinase (AMPK). This enzyme is a major regulator of intracellular energy production via its effects on glucose and fat metabolism (Pernicova and Korbonits, 2014).

Usefulness of Metformin in T2DM

All professional bodies presently recommend metformin as the drug of choice for control of hyperglycaemia once lifestyle measures prove inadequate. A usual dose is 500 mg once, twice or three times daily. Metformin can be added to all other oral antidiabetic agents and can be used with insulin. Failure rates with metformin as monotherapy are relatively high and approach 17% per year, but when compared to participants with HbA1c < 7 or within three months of diabetes diagnosis, the failure rate was reduced to 12%. This introducing metformin early might improve β cell function and delay complication and prolong the effectiveness of the drug (Brown et al., 2010).

Metformin is beneficial in improving lipid metabolism and reduces the triglyceride levels parallel to its glucose-lowering effect. Metformin does not cause weight gain. Some studies have shown it to be weight neutral while others have found a modest weight loss (Viollet et al., 2012).

Human Insulin

Human insulin became available for treatment in 1981, initially as semi-synthetic, and a year later as the first genetically engineered product.

Semi-synthetic human insulin or human insulin, as it was called earlier, was made by modifying porcine insulin, i.e. enzymatically replacing the B 30 alanine with threonine, thus convening pork insulin to human insulin (Pickup, 1989).

Human insulin was the first genetically engineered protein used in therapy, and this method of production is widely used.

Insulin Analogues

Using genetic engineering technique, it became possible to change amino acids at strategic locations to produce insulin analogues that have different absorption and pharmacokinetics. Thus, it is possible to have fast and short-acting or long-acting insulin analogues. The fast-acting analogues are absorbed faster; achieve a quicker peak and their level declines more rapidly as compared to short-acting human insulin. Similarly, by changing the amino acid structure or by enhancing binding to a protein (e.g. albumin); it has been possible to produce long-acting analogues that have slower and more predictable absorption and can provide stable insulin level throughout the 24 hours. Several analogues have now been marketed worldwide (Baeshen et al., 2014).

Types of Insulin

Insulin release occurs both at a continuous basal rate and short-lived large gushes, secondary to physiologic stimuli related to food intake. Thus, to replace insulin, there is need of insulin which can rise rapidly in response to a meal as well as insulin which is released into circulation continuously at a slow rate. When insulin was discovered, for many years only regular or soluble insulin was available. Later, prolonged action formulations were developed with protamine

or zinc or both, as a retarding agent, to delay absorption and extend the duration of effect.

After the 1996 introduction of human insulin, animal insulin lost its value, and hence animal insulins have been discontinued (Donner, 2015). The following types of insulin are now available:

a- Short-acting insulin
b- Analogues (short-acting, long-acting)
c- Intermediate, delayed action due to the addition of neutral protamine Hagedorn (NPH)
d- Premixed
    - short with NPH
    - Analogues premix.

Indications for Insulin therapy

The aim of insulin therapy is changing to provide physiological substitution and painless administration.

Patients with T2DM should try to change their dietary habits and increase their physical activities- If the glycaemic status is not controlled, the physician will start oral anti-diabetic drugs (OAD), the doses should be tailored gradually according to the blood glucose level. It is preferable to initiate insulin therapy if a patient with T2DM is not controlled on maximum doses of three oral drugs. It is β cell failure rather than OAD failure (Nyenwe et al., 2011).

All patients with diabetes have insulin deficiency in a relative or absolute matter. The following table shows various well-known indications of insulin.

Table 7: Indications for Insulin

- Type1 diabetes.
- T2DM not controlled with maximal doses of oral anti-diabetic agents
- Type 2 patients during periods of stress
    - Acute infection
    - Major surgery
    - Acute myocardial infarction, stroke
    - Acute fever
    - Acute emergencies, e.g. Hyperosmolar non-ketone state, diabetic ketoacidosis.
- Pregnancy with diabetes
    - Renal failure

Incretin-based therapy

Incretins are two intestinal hormones secreted in response to a meal. They were named glucose-dependent insulinotropic peptide (GIP) and glucagon-like peptide-1 (GLP-1). Both of these hormones demonstrated insulinotropic properties.

GLP-1 has a very short half-life of less than 2 minutes, and it is rapidly demolished by the protease enzyme dipeptidyl peptidase-4 (DPP-4). GIP, in turn, was found to be very weak (Holst et al., 2009).

Development of GLP-1 based treatment

To realise the therapeutic potential of GLP-1, either its half-life has to be prolonged, or the DPP-4 enzyme needs to be blocked. DPP-4 inhibitors can be classified by their molecular structures into peptidomimetic and non-peptidomimetic.

- Peptidomimetic DPP-4 inhibitors:
    - Vildagliptin
    - Saxagliptin
- Non-peptidomimetic DPP-4 inhibitors:
    - Alogliptin
    - Linagliptin
    - Sitagliptin

Gliptins have the capability of reducing HbA1c safely by 0.5 to 2%, with a prediction that each 1% HbA1c baseline increase provides 0.4 to 0.5% decrease in HbA1c results (Gupta and Kalra, 2011, Esposito et al., 2015).

Incretin mimetics or analogues

Incretin mimetics or incretin analogues were the first amongst the incretins to be used in clinical practice. They have strong effect on glycaemic control and cause significant weight loss without causing hypoglycaemia (Tasyurek et al., 2014).

- Liraglutide

  Liraglutide is the first human GLP-1 analogue and was developed by molecular engineering to increase its half-life up to 13 hours.

It effectively protects β cells and increases their sensitivity to glucose, which could explain the prolonged glycaemic control of up to 3 years achieved with Liraglutide (Mehta et al., 2017).

Sodium-glucose cotransporter 2 (SGLT-2) inhibitors

Sodium-glucose cotransporter 2 (SGLT-2) inhibitors are a novel therapeutic class of antidiabetic drugs. SGLT-2 are exclusively present in the epithelial cells of the proximal renal tubules. SGLT-2 accounts for 90% of the glucose reabsorption in the kidneys. The selective inhibition of SGLT-2 increases the excretion of glucose by inhibiting the reabsorption of glucose (Ndefo et al., 2015).

Thiazolidinedione

Thiazolidinediones are a group of antidiabetic agents that stimulate the peroxisome proliferator-activated receptors. Pioglitazone used as a monotherapy causes a 0.92% to 1.05% fall in HbA1c levels (Desouza and Shivaswamy, 2010). It is recommended to be used as a second line agent and in various combinations with sulfonylureas and metformin (Singh et al., 2014).

Alpha-glucosidase inhibitors

There are three α-glucosidase inhibitors, currently available: acarbose, miglitol and voglibose. This class of oral hypoglycaemic agents competitively inhibit enzymes in the small intestinal brush responsible for the breakdown of oligosaccharides and disaccharides into monosaccharides to make them suitable for absorption (Dabhi et al., 2013).

Acarbose

Of the three α-glucosidase inhibitors, the benefits of acarbose are best documented. Acarbose increases insulin sensitivity in individuals with T2DM and IGT (Zhuo et al., 2014).

3: Methodology

3.1 Research design (by objectives)

3.1.1 Objective 1: To determine the prevalence of T2DM and IR among a Kuwaiti adult population attending Nuzha health facility.

This was a cross-sectional survey in Kuwait conducted from October 2015 to September2016.

Setting: The study was based at Nuzha health care facility (HCF). Nuzha HCF is a governmental health centre in an urban area (Kuwait City) providing about 50,000 consultations per year. This primary health care centre provides general practice (GP) services and selected specialised clinics for a diabetes monitoring and management, hypertension and obesity.

Figure 4: Nuzha health care centre

Target Population: The target population was adult patients aged 18 years or more attending Nuzha HCF.

Inclusion/exclusion criteria: All adults attending Nuzha HCF seeking medical advice for any illness at the general clinics (with minor symptoms only) were eligible to participate, independently of the reasons why they attended the clinics. Eligible patients were enrolled prospectively until the desired sample size was achieved. We excluded pregnant women, patients with acute infections who

have a fever, patients on steroids, those unable to consent, patients who are unable to fast overnight or unwilling to return the next day to the clinic.

We used systemic sampling to choose participants, every 3rd patient starting from the first patient attending the general clinic; we enrolled three patients daily four days a week. When a patient refused to participate, we invited patients consecutively and continuously until a replacement was found. Then the 3rd patient interval was resumed.

Patients who agreed to participate and signed a consent form were interviewed to complete a questionnaire containing demographic background and medical history.

The participant was fasting for 12 hours, and when it was convenient, a phlebotomist collected one venous blood sample after the patient has completed the clinic consultation. When the participant was not fasting, we gave instructions to fast for 12 hours and to return the next day in the morning.

The catchment area population of Nuzha health care centre is about 25,000. It was expected that 20% of the adult population had T2DM. We aimed to establish the prevalence of DM in the clinic population with an error margin of ±4%, with 95% power and 5% confidence limit. The survey sample size was estimated to be 380 participants.

Laboratory procedures: Patients' blood was collected to measure Fasting Plasma Glucose (FPG), Fasting plasma insulin, HbA1c and lipid profile, including high-density lipoprotein (HDL), low-density lipoprotein (LDL), Triglycerides (TG). These tests were free for the participants. Patients were classified as having normal values, IR or T2DM according to the following parameters.

T2DM was defined as the presence of an abnormal (defined as HbA1c ≥6.5%) and an abnormal FPG (defined as ≥ 7.0 mmol/l (126 mg/dl).

Patients with IR but who are not T2DM were defined as patients with FPG < 7.0 mmol (126 mg/dl) but homeostatic model assessment (HOMA2-IR) * ≥ 2.

Patients were defined not to have T2DM or IR if the HbA1c is < 6.5 and FPG is < 7.0 mmol/l (126 mg/dl), and HOMA2-IR < 2.

* HOMA is a model constructed from the combination of several tests is based on the physiological balance between insulin secretion and glucose concentrations in blood and are therefore a reflection of the balance between glucose uptake by tissues and insulin production, the cut-off point for HOMA2-IR is 2 (Berm et al., 2014).

Laboratory tests

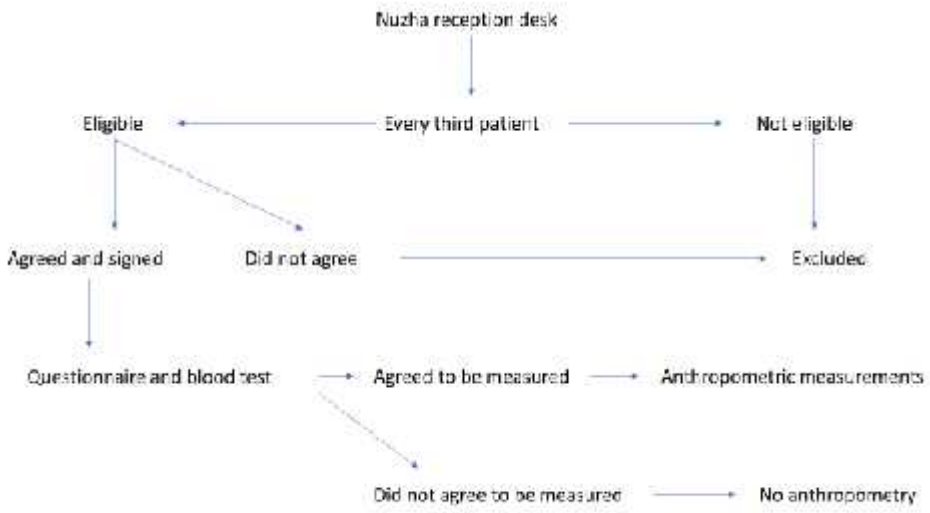
For the FPG test, we collected 2 ml blood in a grey top tube with Potassium Oxalate/Sodium Fluoride. Blood samples were centrifuged to separate the serum within 2 hours, and about 0.5 ml of the plasma were collected in an aliquot for testing using the Spectrophotometric assay (Beckman UniCel DxC 800). Specimen for these assays are stable for up to 3 days if refrigerated.

For the insulin test, we collected 5 ml blood in gold/ yellow top tube. The specimen was centrifuged promptly, and about 1ml of serum were tested for insulin level using immune-assay (Roche, Cobas e 602). Specimens for this assay are stable for 24 hours if refrigerated and for six months if frozen.

For the HbA1c test collected 1 ml blood in a lavender purple-top tube containing EDTA. This tube does not need for centrifugation, and the specimen is stable for 24 hours at room temperature. HbA1c was measured using high-performance liquid chromatography (HPLC) (Tosoh HLC- G8).

For lipid profile, the phlebotomist drew 5ml blood in a gold-top tube, centrifuge and about 2ml serum were tested using Spectrophotometric assay (Beckman UniCel DxC 600 Pro).

All patients were provided with a feedback of the results. Patients with normal results received them via phone call, or they will come personally to collect the results, as per their stated preference. Patients with abnormal results were contacted via email or phone call as per their stated preference and were invited to attend a clinic appointment to discuss their results with the diabetes clinic staff (post in Kuwait is unreliable).



3.1.2 Objective 2: To determine the risk factors for (a) T2DM and (b) IR in the same adult population.

This component was comprised of two case-control studies conducted simultaneously and was based at the same Nuzha HCF.

Cases of T2DM and IR and controls for both studies were defined using the same definitions listed above. In the case, control to determine T2DM risk factors, participants were enrolled both from patients participating in the survey (objective 1) and from known T2DM patients attending the diabetes clinic at the same centre. Cases of T2DM among patients involved in the study were identified by the time results became available and usually within 72 hours after sample collection. Patients with T2DM attending the clinic were identified among the

cases known to the service who are attending spontaneous of routine follow-up consultations. We contacted the participants identified by the survey by phone or when they came back to the clinic to inform them about their results and invite them to participate in the second part of the study.

Patients who agreed to participate and signed a consent form were interviewed to complete a questionnaire.

The second part included a more detailed questionnaire about their medical history and lifestyle; we informed them that we would take some measurements: height, weight, waist and hip circumference and BP. Patients who agree to participate were given an appointment. Cases from the survey were enrolled daily until we reached the desired sample size.

Cases with T2DM were defined as any adult who has a medical history of a diagnosis of T2DM using the same parameters described above or, at least, two consecutive FPG with abnormal values. Some of these cases may have achieved glucose homeostasis at the time of enrollment but were still considered to have T2DM.

Controls were adults who did not have T2DM nor IR patients, as defined above.

In the first case-control (risk factors for DM), study cases were adults with DM and controls were patients with normal glucose and no IR. We estimated that 20% of patients enrolled for this objective would have DM. The survey, therefore, would identify about (380x 0.2) 76 adults with DM (cases). We also expected that 10% of the survey participants would have IR (380x 0.1) resulting in 38 cases of IR and normal glucose. The remaining 266 participants were expected to be healthy controls (No DM or IR).

The main risk factors used to establish the sample size were high cholesterol level (expected to be present in 30% of the adult population), hypertension (30%) (Boodai et al., 2014). The estimated prevalence of obesity in Kuwait was 40% (Musaiger, 2011b). If we enrolled participants with a ratio of controls to cases of 1:1; to be 90% confident to have 80% chance to detect odds ratios of ≥ 2.5, the estimated sample size was 65 DM cases and 65 controls.

In the case-control study to determine the risk factors for IR, all participants were enrolled from the prevalence survey (objective 1). Cases of IR were defined according to homeostatic model assessment (HOMA2-IR). * Patient with HOMA2-IR ≥ 2 but who are not with diabetes (FPG <7 mmol/l) will be defined as cases with IR.

Controls for this case-control study were the same participants in the survey who do not have T2DM or IR.

A total of 64 controls were enrolled and32 cases, giving a ratio of 1:2 cases per control. We chose this ratio because of the expected small number of cases, as estimated that only about 10% of the survey population would have IR but no T2DM. According to the available numbers of cases and controls, this ratio would make it possible to achieve a statistical power > 80% to identify IR risk factors.

For both case-control studies, the interviewer asked the participant to fill a second questionnaire that includes a more extensive list of potential risk factors for T2DM and IR (see questionnaires in Appendix 1). The questionnaire included all known risk factors for T2DM and IR and included diet, physical activity, BMI, family history and others. A dedicated nurse measured blood pressure (BP), waist and hip circumference (cm), weight (kg), height (cm). BMI will be calculated as weight (kg)/height² (m^2).

Figure 5: Anthropometric and blood pressure measurement room

3.1.3 Objective 3: To describe the prevalence of IR among first-degree relatives of patients with T2DM.

We conducted a cross-sectional survey of relatives of patients with T2DM. The study was conducted at the same Nuzha HCF, Kuwait, from October 2015 to September 2016.

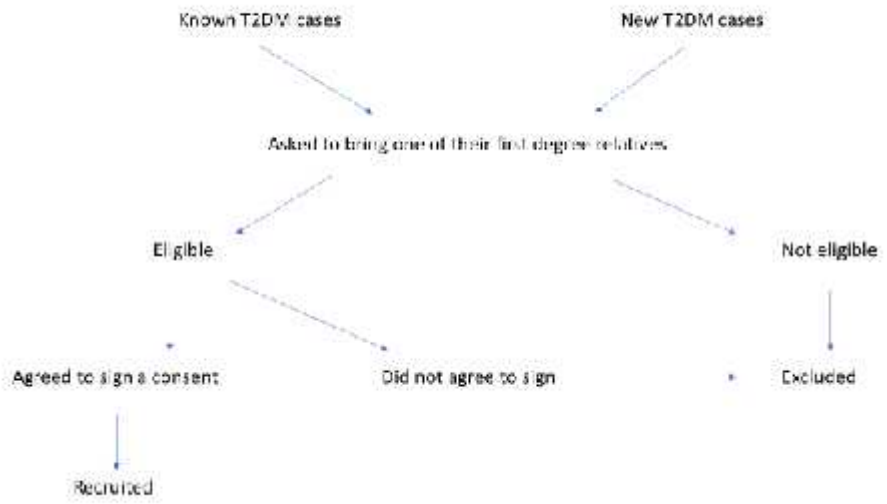
Selection of participant: we asked all known T2DM participants in objective 1 and all participants of objective 4 to invite one of their first-degree relatives to attend the clinic to participate in a study identifying the prevalence of IR in this group. When the patient agrees to invite a relative, we asked them to attend according to an appointment given and ask them to come fasting for about 12 hours. We recruited participants until the sample size was achieved.

There are 2000 diabetic patients being followed at Nuzha HCF. If each diabetic patient had about ten first degree relatives, the population size for this survey would be 20,000. The estimated prevalence of IR among the first-degree relatives

was 50%. To conduct a survey with 90% confidence level and a maximum error of ±5% the required sample size was estimated to be 270.

Eligibility were adults ≥ 18 years old, first-degree relative to a diabetes patient attending Nuzha HCF. We excluded pregnant women, relatives with known diabetes, and patients who have had a fever in the last 14 days, patients on steroids, those unable to consent, patients who are unable to fast overnight.

We asked the participant to fill the questionnaire then the phlebotomist at Nuzha HCF collected the venous blood sample.



Laboratory procedures: Relatives blood samples were collected to measure the same tests, including FPG, Fasting plasma insulin and HbA1c. To test the blood, we used the same assays mentioned in the methods section for objective one.

Figure 6: Nuzha laboratory

3.1.4 Objective 4: To establish the proportion of patients with T2DM who achieve adequate glycaemic control and risk factors for poor glycaemic control.

We conducted a cross-sectional survey study at the diabetes clinics of Nuzha HCF, Kuwait from October 2015 to September 2016. We used systematic sampling to enrol patients. Eligibility was adults > 18 years old with a previously known diagnosis of T2DM who attend a regular appointment at the diabetes clinic. We excluded pregnant women, patients with acute infections who have a fever, patients on steroids, those unable to consent.

Cases were classified as having good glucose control if their HbA1c was < 7. Cases were classified as having poor glucose control if their HbA1c was > 9.

As indicated, the clinic provides medical services for about 2000 diabetic patients. We estimated that there was a 50% chance of poor glycaemic control. To conduct a study to demonstrate this proportion with 90% confidence level and 5% confidence limits, we would require. We will need at least 240 participants.

Every third patient attending the clinic was invited, with three patients enrolled per day, four days a week. When a patient refused to participate, we invited patients consecutively until a replacement is found. Then the 3-patient interval was resumed.

Patients who agreed to participate and signed a consent form were interviewed to complete a questionnaire containing demographic background and medical history.

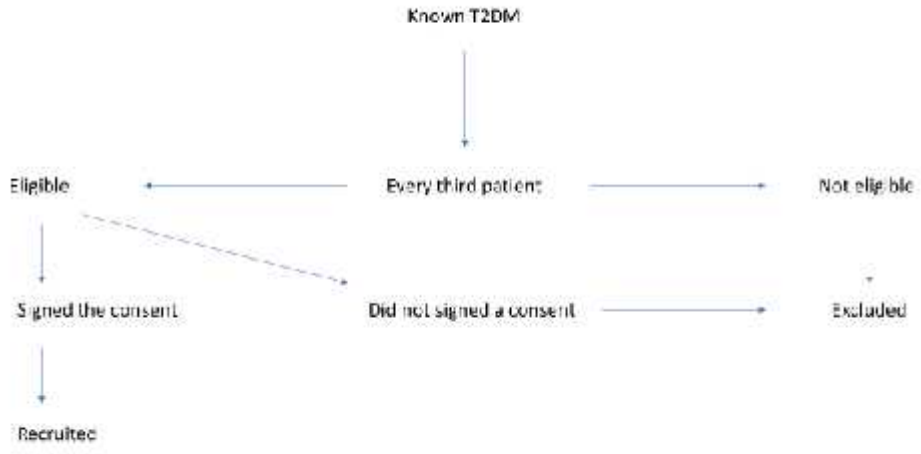


Figure 7: The main researcher filling a questionnaire

We asked the participants to fill a questionnaire with known risk factors for poor glycaemic control among T2DM patients, which included diet, physical activity, BMI, family history, adherence to treatment, understanding of diabetes and others. A dedicated nurse measured blood pressure (BP), waist and hip circumference (cm), weight (kg), height (cm). BMI was calculated as weight (kg)/height² (m^2).

The phlebotomist at Nuzha HCF collected the venous sample; we tested the blood sample for HbA1c and Lipid profile.

To test the blood, we used the same spectrophotometry assay used in objective 1.

3.1.5 Objective 5: To assess the agreement of a POC device to measure HbA1c with a reference HbA1c assay kit to monitor DM control among patients with DM and/or patients with known haemoglobinopathies.

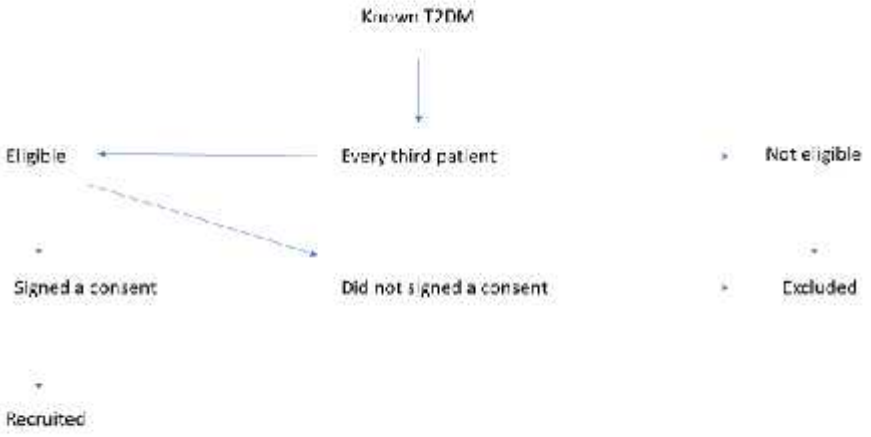
This was a cross-sectional survey in Kuwait and was conducted from October 2015 to September 2016.

Setting: The study was located in two sites according to the type of participants. At Nuzha HCF diabetes clinic, for patients not known to have abnormal haemoglobin and at the haematology clinic in Amiri hospital for patients with known to haemoglobinopathies.

Target Population: Adult patients with T2DM attending diabetes clinic in Nuzha health care facility and adult patients with abnormal haemoglobin attending haematology clinic in Amiri hospital.

Eligibility criteria for patients in the Nuzha clinic was: adults > 18 years old with a known diagnosis of T2DM who attended a regular appointment at the diabetes clinic. We excluded pregnant women, patients with acute infections and fever, patients on steroids and those unable to consent.

Eligibility criteria for patients with haemoglobinopathies were adult patients with abnormal haemoglobin attending the haematology clinic at Al-Amiri Hospital seeking medical advice. We excluded pregnant women, patients with acute infections and fever, patients on steroids and those unable to consent. Patients with haemoglobinopathies were comprised of patients with a known diagnosis of α thalassemia, β thalassemia, and sickle cell anaemia.



We asked every second eligible patient attending the haematology clinic to participate in the study when the second patient refuses to participate we invited consecutively eligible patients until we enrolled one, then we went back to every second patient systemic sampling. The plan was to recruit two patients daily.

We asked the participant to sign a consent and to fill a short questionnaire, then to take a venous blood sample and a blood finger –prick blood sample.

Eligible patients were enrolled prospectively over a period of 12 months or until the desired sample size in both settings was achieved.

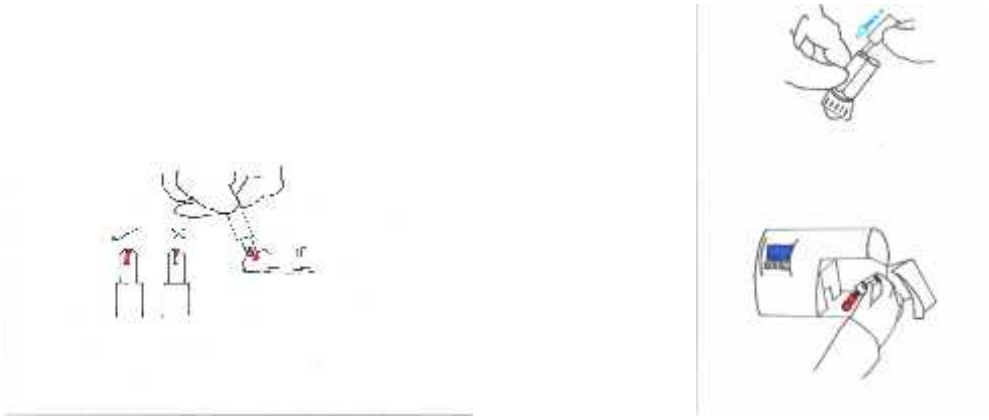
In the literature, the sensitivity of the reference A1c test (Tosoh) is between 70% and 80%. So, I used the 80% value as the comparative point., and we allowed for a 5% difference, with type I error (α) = 0.05 and type II error (β) = 0.2, the required sample size was 200 paired blood tests (200 lab reference HbA1c and 200 POC HbA1c).

Laboratory procedures

A finger-prick blood sample was collected for in-clinic HbA1c testing with the rapid one-step automatic test; Boronate affinity technique (Quo-Test) This machine provides results within about 4 minutes.

Figure 8: A participant giving finger-prick sample for HbA1c

Figure 9: Illustration of collecting blood and running the test



For the reference HbA1c test, we collected 1 ml blood in a purple top tube containing EDTA as described in previous objectives.

For Hb electrophoresis, we collected 3 ml blood in a purple top tube containing EDTA; the blood sample was tested in Amiri hospital laboratory using the Bio-Rad Variant II Haemoglobin Testing System.

4: Results

4.1 Objective 1: To determine the prevalence of T2DM and IR among adult population attending a primary health care facility in Kuwait.

Demographic characteristics of participants.

Four hundred and two subjects, 18 years or older, were interviewed for in Nuzha health care facility. Of these, 206 (51.2%) were male and 196 (48.8%) female. The mean (SD) age of the participants was 41.1 (12.92) years with a range from 19 to 91 years. About one-third (n=130, 32%) of participants were < 40 years, 222 (55.2%) between 40 and 60 and 50 (12.5%) > 60 years old, as shown in Table 8. One hundred and eighty (44.8%) participants were of Indian background, 176 (43.8%) Arabs, 31 (7.7%) from Southeast Asia, 13 (3.2%) Farsi, and two (0.5%) from other nationalities.

One hundred and sixty-four (40.8%) had higher degree education, 136 (33.8%) secondary education, 89 (22.1%) primary education and only 13 (3.2%) were uneducated. Ninety-five participants (23.6%) worked in the government sector, 55 (13.7%) in the private sector, 174 (43.3%) were labourers, 49 (12.2%) were retired, and 29 (7.2%) were not working at the time of the interview. Most participants had a partner or were married (330, 82.1%), 49 (11.9%) were single, 16 (4%) widowed, and 7 (1.7%) separated. One hundred and seven (26.6%) had hypertension, and 295 (73.4%) had normal blood pressure.

Table 8: Demographic characteristics (and blood pressure status) of participants

Demographic characteristics		**n=402 (%)**
Sex	Male	206 (51.2)
	Female	196 (48.8)
Age, Mean (SD)		41.1 (12.92)
Age group	18-29	48 (11.9)
	30-39	82 (20.4)
	40-49	116 (28.9)
	50-59	106 (26.4)
	60-69	34 (8.5)

	70+	16 (4)
Ethnicity	Arab	176 (43.8)
	Indian	180 (44.8)
	South East Asia	31 (7.7)
	Farsi	13 (3.2)
	Other	2 (0.5)
Education	No education	13 (3.2)
	Primary	89 (22.1)
	Secondary	136 (33.8)
	Higher education	164 (40.8)
Occupation	Government	95 (23.6)
	Private	55 (13.7)
	Labourer	174 (43.3)
	Not working	29 (7.2)
	Retired	49 (12.2)
Marital status	With partner	330 (82.1)
	Single	49 (12.2)
	Widowed	16 (4)
	Divorced/Separated	7 (1.7)
Smoking	No	339 (84.3)
	Ex-smoker	30 (7.5)
	yes	33 (8.2)
Hypertension	Yes	107 (26.6)
	No	295 (73.4)

Biochemical profile of participants.

Blood was obtained from all 402 participants. The mean (SD) FPG was 6.4 (2) with a range of 3.01 to 19.88 mmol/l. Two hundred ninety-nine (74.4%) had normal FPG, 38 (9.5%) participants had prediabetes range (FPG 6.1-6.99) and 65 (16.1%) had FPG ≥7. Insulin measurements were available for 401 participants and their mean (SD) Insulin was 14.8 (10.7) µU/ml with a range of 0.56 to 107.8 µU/ml (see below HOMA calculations). The mean (SD) LDL, HDL, and TG of the 402 participants were 3.9 (0.98), 1.24 (0.46) and 1.6 (0.92) mmol/l, respectively, as shown in Table 9. One hundred and fifteen (28.6%) participants had normal LDL levels, and 287 (71.4%) were with high levels. One hundred thirty-seven (34.1%) participants had normal TG levels, and 265 (65.9%) participants had high TG. HDL level was normal in 174 (43.3%) and low in 228 (56.7%), as shown in Table 9.

Two hundred twenty-five (59.5%) had HbA1c < 6%, 70 (18.5%) had HbA1c between 6 and 6.49%, and 83 (22%) had HbA1c ≥ 6.5%.

Table 9: Biochemical characteristics of participants

Variables	Results available	n (%)	Mean (SD)
FPG	402		6.4 (2)
≥7 mmol/l		65 (16.1%)	
6.1-6.99		38 (9.5%)	
<6.1		299 (74.4%)	
Insulin [µU/ml]	401		14.78 910.720
Homa2 IR	393		1.95 (1.36)
LDL mmol/l	402		3.9 (0.98)
≥ 2.6		287 (71.4%)	
< 2.6		115 (28.6%)	
HDL mmol/l	402		1.24 (0.46)
≥ 1.2		174 (43.3%)	
< 1.2		228 (56.7%)	
TG mmol/l	402		1.6 (0.92)
≥ 1.7		265 (65.9%)	
< 1.7		137 (34.1%)	
HbA1c [%]	378		6 (1.2)
≥ 6.5		83 (22%)	

6-6.49	70 (18.5%)
< 6	225 (59.5%)

* FPG = fasting plasma glucose, HOMA2 IR = homeostatic model assessment, LDL = low density lipoprotein, HDL = high density lipoprotein, TG = triglyceride, HbA1c= haemoglobin A1c.

Participants unaware of having T2DM

To identify the number of participants who did not know they had T2DM, we excluded participants with known T2DM, which left a total of 327 participants. HbA1c and FPG results of the 327 patients were cross-tabulated to identify those with FPG or HbA1c above the T2DM threshold, as shown in Table 10. Fourteen patients had missing HbA1c results.

HbA1c was < 6.5% in 279 and ≥ 6.5% in 34 participants. FPG was < 7 mmol/l in 294 and ≥ 7 mmol/l in 19 participants. Nine participants had both high HbA1c and FPG. Both tests, therefore, identified 44 patients unaware of having T2DM.

Table 10: Agreement of FPG and HbA1c among participants not known to have T2DM

		FPG mmol/l	
		< 7	≥ 7
HbA1c %	< 6.5	269 (96.4%)	10 (3.6%)
	≥ 6.5	25 (73.5%)	9 (26.5%)

Prevalence of prediabetes

We excluded 119 participants with diabetes (known and new T2DM), with data missing from fourteen cases, which left a total of 269 participants. HbA1c and FPG results of the 269 patients were cross-tabulated to identify those with FPG or HbA1c within the prediabetes range, as shown in Table 11.

Table 11: Agreement of FPG and HbA1c in participants with no diabetes

		FPG mmol/l	
		<6.1	6.1-6.99
HbA1c %	< 6	199	22
	6-6.49	32	16

HbA1c was < 6% in 221 participants and between 6 and 6.49 in 48 participants, FPG was < 6.1 mmol/l in 231and between 6.1 and 6.49 mmol/l in 38 participants. Sixteen participants had both HbA1c and FPG within the prediabetes range. Both tests, therefore, identified 70 (17.4%) participants who had prediabetes. The agreement of FPG and HbA1c is shown in Table 12.

Prevalence of T2DM and IR among participants

Seventy-five (18.6%) of the 402 participants knew they had T2DM and 44 (10.9%, 95% CI = 7.9% – 14.0%) new cases were identified by the survey, as shown in Table 12. The overall number of participants with T2DM, therefore, was 119 (29.6%, 95% CI = 25.1% to 34.1%). Table 12 describes the number of cases diagnosed by history, FPG, and HbA1c.

HOMA2 IR was calculated after exclusion of all known and newly diagnosed T2DM participants. Seven participants had insulin levels either < 2.9 or > 57.8, which are the minimum and maximum range values accepted by the HOMA2-IR formula and were excluded. Ninety-eight (34.6%) of the remaining 283 participants had HOMA2 IR ≥ 2 and 185 (65.4%) HOMA2-IR < 2. Accordingly, the prevalence of IR in individuals without T2DM was 34.6% (95% CI = 29.1% – 40.2%).

Table 12: Proportion of participants with T2DM and IR

	n = 402
	n (%)
known T2DM	75 (18.6)
New FBG ≥ 7[1]	19 (6)
New HbA1c ≥ 6.5[1]	34 (11.2)

Previously unknown T2DM	44 (13.4)
Known and new T2DM	119 (29.6)
Homa2-IR ≥ 2[2]	98 (34.6)

[1] only includes participants unaware of having T2DM

[2] only includes participants without T2DM

The age distribution of participants by sex is shown in figure 10, and the proportion of individuals with normoglycaemia, prediabetes and T2DM by age and sex are shown in the figures 11 (males) and 12 (females). Most participants were in their 30s and 50s. The proportion of participants with prediabetes started to increase in early adulthood (20-30 years) and peaked among participants in their 40s. The proportion of participants who had T2DM also started to increase among 20-30-year-old participants and peaked among participants above 40 years old, with most participants > 50 years having prediabetes or T2DM. Male participants developed T2DM from an early age, with about 10% of participants aged 18-29 having T2DM, with an increasing proportion of participants having overt T2DM and a relative decrease of prediabetes with age. Most participants > 60 had T2DM and very few prediabetes. In contrast, the proportion of women with T2DM was low at younger ages, with both T2DM and prediabetes increasing steadily with each decade of life, so that by the > 60 nearly 80% of women had either prediabetes or T2DM.

Figure 10: Age distribution by sex

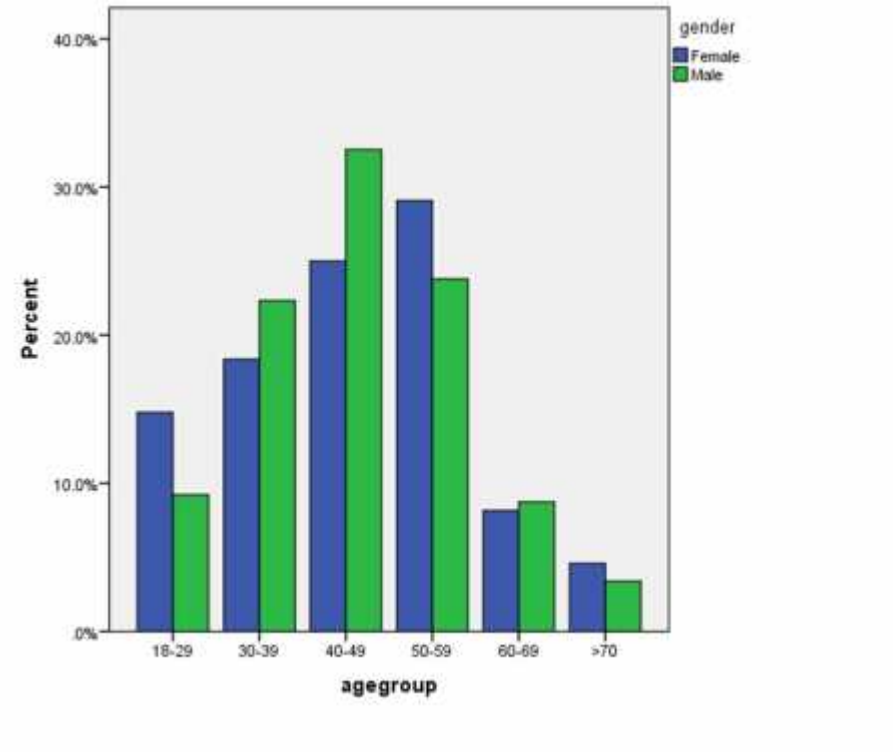


Figure 11: Glycaemic status in males, normal, prediabetes, and T2DM (HbA1c)

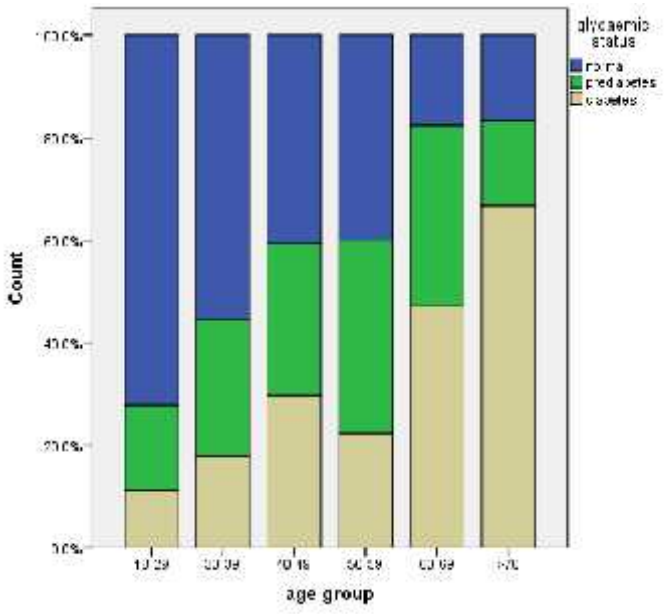
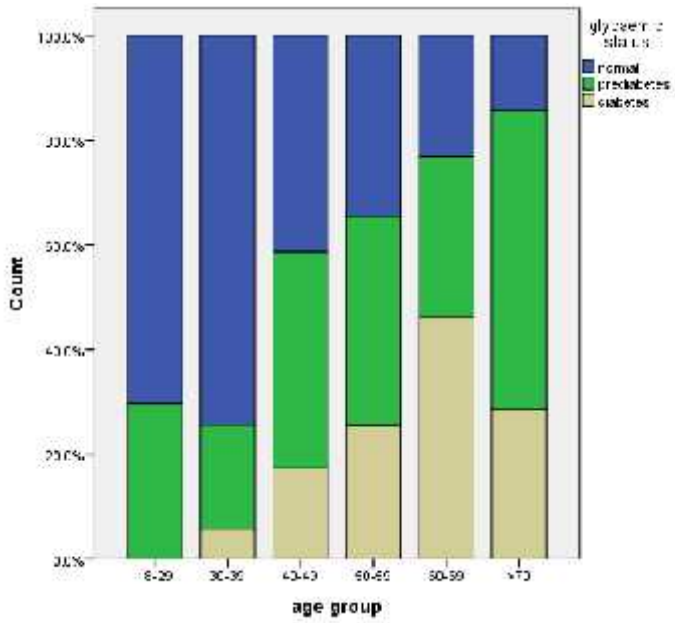


Figure 12: Glycaemic status in females, normal, prediabetes, and T2DM (HbA1c)



4.2 Objective 2: Risk factors for T2DM and IR in a clinic study population.

Comparison of participants with and without T2DM or IR

The same individuals participating in objective 1 were further interviewed to determine the risk factors for T2DM. As stated in objective 1, 185 participants did not have T2DM or IR (called normoglycaemic patients from now on), 98 had IR with normal glucose, and 119 had T2DM. Participants with T2DM were older than patients with IR or who were normoglycaemic. The mean (SD) age of normoglycaemic, IR andT2DM patients was 42.7 (12.0), 43.2 (11.1) and 51.9 (12.9) years, respectively (Chi-square 34.74, p <0.001). The proportion of participants who had IR was fairly homogeneous by age, as shown in Table 13. In contrast, the proportion of participants who had T2DM increased with age. The proportion of participants who had overt T2DM increased with each decade of life from a baseline of 8.3% among participants aged 18-29 years old to 30.2% by the time they were in their 40s and 62% among participants ≥ 60 years old.

Ninety-two (49.7%) of 185 normoglycaemic individuals were male and 93 (50.3%) female. Forty-eight (49%) of 98 participants with IR were male and 50 (51%) female, while 66 (55.5%) participants with T2DM were male and 53 (44.5%) female (Chi-Square 1.218, p= 0.544).

The country of origin of normoglycaemic, IR and T2DM participants is shown in Table 13. IR was identified more frequently among Indian (56 (31.1%) of 180) and South East Asian participants (7 (22.5%) of 31) than participants from other countries. T2DM was identified more often among Indian (55 (30.5%) of 180) and Arab participants (54 (30.6%) of 176) than participants from other countries. Indian and Arab participants therefore seemed more likely to have IR and T2DM than participants from other ethnic backgrounds, although only the higher proportion of IR was statistically significant (Chi Square= 10.618, p = 0.014).

Education was associated with the presence of IR and T2DM, although this association was not ordinal. Participants without education were more likely to have IR than participants with education (Chi Square= 4.027, p = 0.045).

In contrast participants without education were less likely to have T2DM than participants with primary or higher degree education (Chi Square= 8.374, p = 0.004).

The type of work was associated with IR and T2DM. Labourers were more likely to have IR or T2DM than private or government workers. As expected, retired participants were more likely to have T2DM (Chi Square= 17.814, p= 0.001), but this is probably due to the association of T2DM with age.

Marital status was associated with T2DM, as widows and widowers were more likely to have T2DM than single and married individuals (Chi-Square = 24.058, p < 0.001), however, this association is also likely confounded by age (see multivariate analysis below).

Smoking was associated with T2DM and smokers were more likely to have IR and T2DM than non-smokers, but this relation was not statistically significant (Chi Square =3.207, p= 0.524).

The presence of hypertension was associated with both IR and T2DM but was only significant for T2DM (OR= 3, 95% CI 1.79-5.04, p= < 0.001).

Table 13: Demographic characteristics and blood pressure status of participants with normoglycaemia, IR and T2DM

Variable		**Normal**	**IR**	**T2DM**
		n=185 (%)	**n=98 (%)**	**n=119 (%)**
Sex	Male	92 (49.7)	48 (49)	66 (55.5)
	Female	93 (50.3)	50 (51)	53 (44.5)
Age groups	18-29	29 (15.8)	15 (15.3)	4 (3.4)
	30-39	47 (25.4)	20 (20.4)	15 (12.6)
	40-49	48 (25.9)	33 (33.7)	35 (29.4)
	50-59	48 (25.9)	24 (24.5)	34 (28.6)
	60-69	10 (5.4)	5 (5.1)	19 (16)

	70+	3 (1.6)	1 (1)	12 (10)
Age mean (SD)		42.7 (11.98)	43.2 (11.07)	51.9 (12.86)
Ethnicity	Arab	91 (51.7)	31 (17.6)	54 (30.7)
	Indian	69 (38.3)	56 (31.1)	55 (30.6)
	South East Asia	17 (54.8)	7 (22.6)	7 (22.6)
	Farsi	6 (46.2)	4 (30.7)	3 (23.1)
	Other	2 (100)	0 (0)	0 (0)
Education	No education	4 (30.7)	6 (46.2)	3 (23.1)
	Primary	33 (37.1)	23 (25.8)	33 (37.1)
	Secondary	59 (43.4)	30 (22.1)	47 (34.5)
	Higher education	89 (54.2)	39 (23.8)	36 (22)
Occupation	Governmental	57 (60)	20 (21.1)	18 (18.9)
	Private	29 (52.7)	14 (25.5)	12 (21.8)
	Labourer	66 (37.9)	52 (29.9)	56 (32.2)
	Not working	16 (55.2)	4 (13.8)	9 (31)
	Retired	17 (34.7)	8 (16.3)	24 (49)
Marital status	With partner	143 (43.3)	83 (25.2)	104 (31.5)
	Single	31 (63.2)	14 (28.6)	4 (8.2)
	Widowed	4 (25)	1 (6.2)	11 (68.8)
	Separated	7 (100)	0 (0)	0 (0)
Smoking	No	158 (46.6)	86 (25.4)	95 (28)
	Ex-smoker	14 (46.7)	5 (16.6)	11 (36.7)
	Smoker	33 (39.4)	7 (21.2)	13 (39.4)
Hypertension	Yes	35 (32.7)	23 (21.5)	49 (45.8)
	No	150 (50.9)	75 (25.4)	70 (23.7)

Biochemical characteristics of normoglycaemic, IR and T2DM participants

The biochemical markers of participants with normal glucose metabolism, IR and T2DM are shown in Table 13. As expected from the definition of the categories, the mean (SD) FPG and HbA1c of normoglycaemic participants were within normal ranges [5.3 mmol/l (0.67) and 5.41% (0.47)] and were lower than in participants with IR [5.45 (0.67) mmol/l and 5.62% (0.45), $p < 0.001$ and 0.030] or T2DM [7.7 (2.9) mmol/l and 7.27% (1.5), $p < 0.001$ and <0.001].

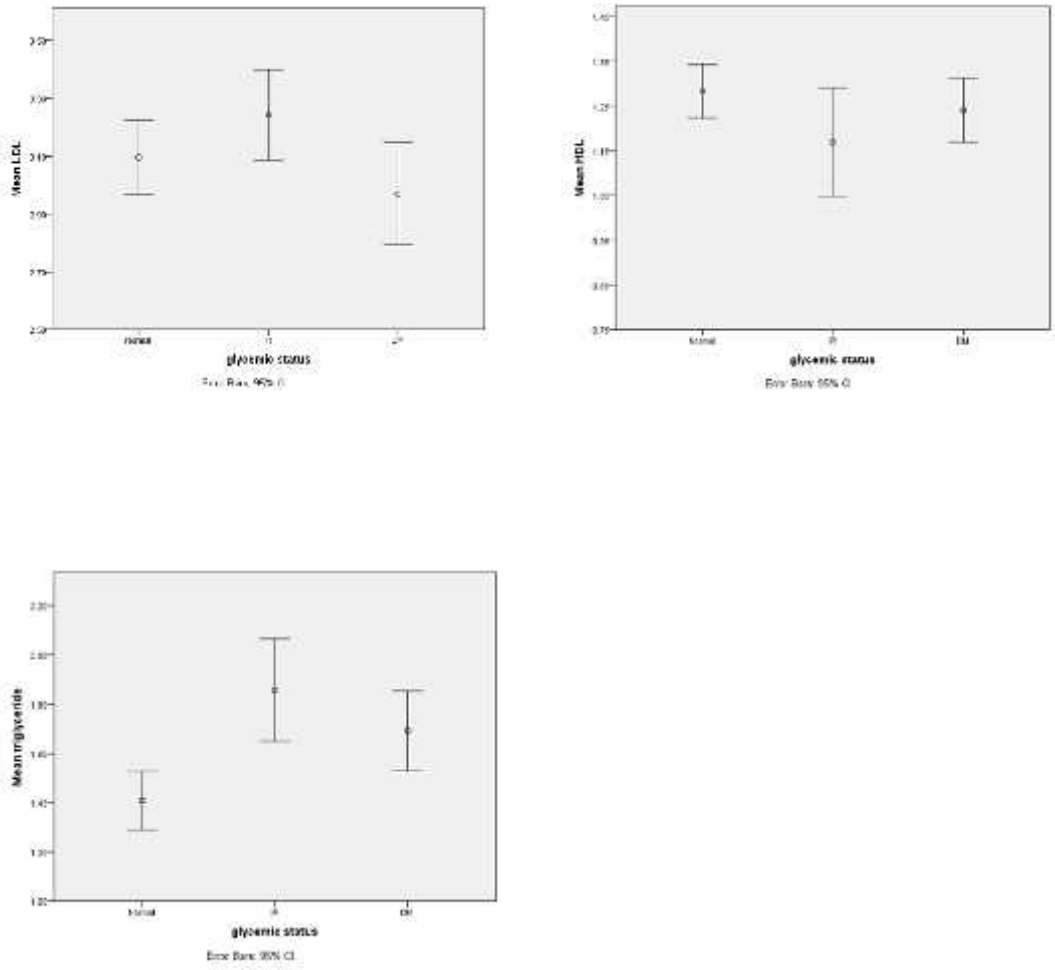
A high HDL and TG was significantly related to the presence of IR, but not to T2DM. Participants with a HDL < 1.2 mmol/l had an increased risk of IR (OR= 2.35, 95% CI 1.4-3.96, p= 0.001) and participants with TG > 1.7 mmol/l, had an increased risk of IR (OR = 2.14, 95% CI 1.28-3.57).

Table 14: Biochemical characteristics of participants with/without IR and T2DM.

Variables	Normal	Mean (SD)	IR	Mean (SD)	T2DM	Mean (SD)
FPG mmol/l		5.3 (0.67)		5.5 (0.67)		7.7 (2.9)
LDL mmol/l		3.1 (0.87)		3.24 (0.77)		2.96 (0.98)
≥ 2.6 n (%)		131 (45.6)		76 (26.5)		80 (27.9)
< 2.6 n (%)		54 (47)		22 (19.1)		39 (33.9)
HDL mmol/l		1.28 (0.41)		1.17 (0.6		1.24 (0.39)
≥ 1.2 n (%)		92 (51.7)		29 (16.3)		57 (32)
<1.2 n (%)		93 (41.5)		69 (30.8)		62 (27.7)
TG mmol/l		1.4 (0.81)		1.85 (1.03)		1.69 (0.9)
≥ 1.7 n (%)		51 (37.2)		44 (32.1)		42 (30.7)
< 1.7 n (%)		134 (50.6)		54 (20.4)		77 (29)
HbA1c %		5.4 (0.47)		5.6 (0.45)		7.3 (1.5)
Insulin µU/ml		9.25 (3.22)		23.1 (10.1)		--
Homa2 IR		1.2 (0.42)		2.97 (0.999)		--

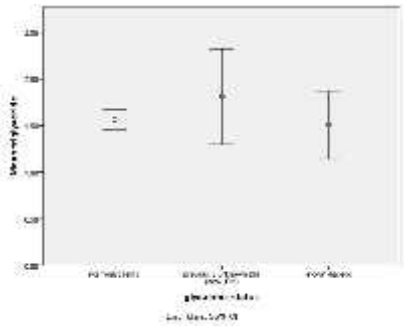
The mean (SD) of LDL, HDL, and TG in normoglycaemic participants were similar to participants with IR and T2DM, except for TG which was higher, and HDL was lower among patients with IR (p = 0.225, 0.001 and < 0.004, respectively) and T2DM (p = 0.508, 0.755 and 0.154, respectively), as shown in Figure 13.

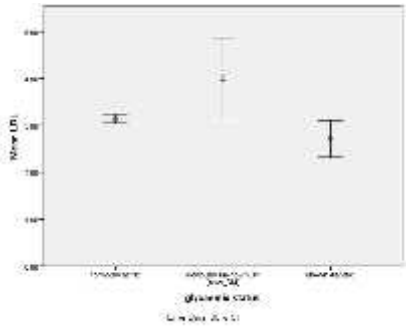
Figure 13: Mean and 95% CI (a) LDL, (b) HDL and (c) triglyceride levels in participants with normal glucose, IR and T2DM.



Comparing the levels of LDL, HDL, and TG in the normoglycaemic group vs known and newly diagnosed T2DM shows that the mean of LDL and TG is higher in newly diagnosed T2DM than in knownT2DM participants, and lower mean of HDL in newly diagnosed T2DM than in knownT2DM participants (figure 14). These results might be due to cholesterol-lowering drugs in knownT2DM individuals, knowing that clinicians tend to control the cholesterol level in T2DM patients.

Figure 14: Mean and 95% CI of LDL, HDL, and TG in normoglycaemic, newly diagnosed T2DM, and known T2DM





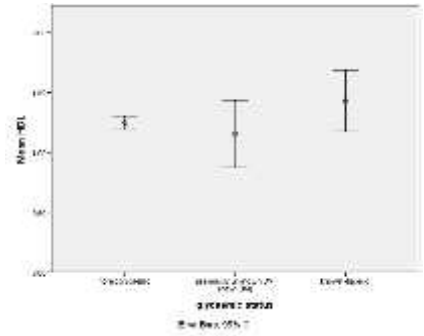


Table 15: Descriptive analysis and odds ratios for the study groups.

		Normal n=185 n (%)	IR n=98 n (%)	T2DM n=119 n (%)	(normal vs IR) OR 95%CI	P value	(normal vs T2DM) OR 95%CI	P value
Sex	Male	92 (44.7)	48 (23.3)	66 (32)	1.03 (0.63-1.68)	0.904	1.26 (0.79-2.00)	0.329
	Female	93 (47.4)	50 (25.5)	53 (27.1)	Ref		Ref	
Age groups	18-29	29 (60.4)	15 (31.3)	4 (8.3)	Ref		Ref	
	30-39	47 (57.3)	20 (24.4)	15 (18.3)	0.82 (.37-1.85)	0.638	2.31 (0.70-7.65)	0.169
	40-49	48 (41.4)	33 (28.4)	35 (30.2)	1.32 (0.62-2.85)	0.466	5.29 (1.70-16.4)	0.004
	50-59	48 (45.3)	24 (22.6)	34 (32.1)	0.97 (0.43-2.13)	0.933	5.13 (1.65-16.0)	0.005
	60-69	10 (29.4)	5 (14.7)	19 (55.9)	0.97 (0.44-2.13)	0.957	13.8 (3.77-50.3)	<0.001
	70+	3 (18.8)	1 (6.3)	12 (75)	0.64 (0.06-6.74)	0.714	29.0 (5.62-149.7)	<0.001
Age mean (SD)		42.7 (11.98)	43.2 (11.07)	51.9 (12.86)				
Ethnicity	Arab	91 (51.7)	31 (17.6)	54 (30.7)	Ref		1.44 (0.56-3.70)	0.447
	Indian	69 (38.3)	56 (31.1)	55 (30.6)	2.38 (1.39-4.08)	0.002	1.94 (0.75-5.00)	0.172
	South East Asia	17 (54.8)	7 (22.6)	7 (22.6)	1.21 (0.46-0.32)	0.702	Ref	
	Others	8 (53.3)	4(26.7)	3 (20)	1.47 (0.41-5.21)	0.553	0.91 (1.85-4.47)	0.908
Education	No education	4 (30.7)	6 (46.2)	3 (23.1)	Ref			
	Primary	33 (37.1)	23 (25.8)	33 (37.1)	0.47 (.12-1.83)	0.274	1.33 (0.28-6.43)	0.720
	Secondary	59 (43.4)	30 (22.1)	47 (34.5)	0.34 (0.09-1.29)	0.113	1.06 (0.23-4.98)	0.939
	Higher education	89 (54.2)	39 (23.8)	36 (22)	0.29 (.08-1.09)	0.068	0.54 (0.12-2.53)	0.434
Occupation	Governmental	57 (60)	20 (21.1)	18 (18.9)	1.40 (0.42-4.70)	0.582	Ref	

	Private	29 (52.7)	14 (25.5)	12 (21.8)	1.93 (0.54-6.86)	0.309	1.31 (0.56-3.09)	0.536
	Labourer	66 (37.9)	52 (29.9)	56 (32.2)	3.15 (0.99-10.0)	0.051	2.68 (1.42-5.09)	0.002
	Not working	16 (55.2)	4 (13.8)	9 (31)	Ref		1.78 (0.67-4.72)	0.245
	Retired	17 (34.7)	8 (16.3)	24 (49)	1.88 (0.47-7.49)	0.369	4.47 (1.98-10.1)	<0.001
Marital status	With partner	143 (43.3)	83 (25.2)	104 (31.5)	1.29 (0.65-2.55)	0.474	5.64 (1.93-16.5)	0.002
	Single	31 (63.2)	14 (28.6)	4 (8.2)	Ref			
	Widowed	4 (25)	1 (6.2)	11 (68.8)	0.55 (0.06-5.41)	0.611	21.3 (4.54-100)	<0.001
	Separated	7 (100)	0 (0)	0 (0)	----	0.999	--	0.999
Smoking	No	158 (46.6)	86 (25.4)	95 (28)	Ref		Ref	
	Ex-smoker	14 (46.7)	5 (16.6)	11 (36.7)	1.87 (0.63-5.54)	0.262	0.49 (0.13-1.77)	0.272
	Smoker	33 (39.4)	7 (21.2)	13 (39.4)	2.03 (0.59-6.99)	0.261	1.70 (0.54-5.33)	0.365
Hypertension	Yes	35 (32.8)	23 (21.5)	49 (45.8)	1.3 (0.73-2.38)	0.368	3.00 (1.79-5.04)	<0.001
	No	150 (50.8)	75 (25.4)	70 (23.7)	Ref		Ref	
LDL mmol/l	Mean (SD)	3.1 (0 .87)	3.24 (0.77)	2.96 (0.98)				
	≥2.6	131 (45.6)	76 (26.5)	80 (27.9)	1.42 (0.81-2.52)	0.225	1.18 (0.72-1.94)	0.508
	<2.6	54 (47)	22 (19.1)	39 (33.9)	Ref		Ref	
HDL mmol/l	Mean (SD)	1.28 (0.41)	1.17 (0.60)	1.24 (0.39)				
	≥1.2	92 (51.7)	29 (16.3)	57 (32)	Ref		Ref	
	<1.2	93 (41.5)	69 (30.8)	62 (27.7)	2.35 (1.40-3.96)	0.001	1.08 (0.68-1.71)	0.755
TG mmol/l	Mean (SD)	1.4 (0.81)	1.85 (1.03)	1.69 (0.9)				
	≥1.7	51 (37.2)	44 (32.1)	42 (30.7)	2.14 (1.28-3.57)	0.004	1.43 (0.87-2.35)	0.154
	<1.7	134 (50.6)	54 (20.4)	77 (29)	Ref			
History of T2DM in family	No	67 (44.4)	38 (25.2)	46 (30.4)				

	First degree	102 (45.5)	52 (23.2)	70 (31.3)	0.89 (.535-1.51)	0.688	1.00 (0.62-1.62)	0.999
	Second degree	14 (63.6)	5 (22.7)	3 (13.6)	0.63 (0.21-1.88)	0.408	0.31 (0.09-1.15)	0.080
	Third degree	2 (40)	3 (24.4)	0 (29.6)	2.65 (0.42-16.5)	0.298	--	0.999

Ethnicity, HDL, and TG were selected for the multivariate analysis (Normal vs. IR), of these, ethnicity and TG became non-significant, while HDL remained significant with an AOR 1.96 (95% CI 1.12-3.42) and a P value of 0.019.

Table 16: Adjusted odds ratios (normal vs IR)

		Unadjusted (normal vs. IR) OR 95%CI	P value	Adjusted (normal vs. IR) OR 95%CI	P value
Ethnicity					
	Arab	Ref			
	Indian	2.38 (1.39-4.08)	0.002		
	South East Asia	1.21 (.458-.319)	0.702		
	Others	1.47 (.413-5.21)	0.553		
HDL mmol/l					
	≥1.2	Ref			
	<1.2	2.35 (1.40-3.96)	0.001	1.96 (1.12-3.42)	0.019
TG mmol/l					
	≥1.7	2.14 (1.28-3.57)	0.004		
	<1.7	Ref			

Age group, occupation, marital status, and hypertension were selected for the multivariate analysis (Normal vs T2DM). Of these, occupation became non-significant, while the age group 60 to 69 and 70+ remained significant with an AOR of 5.40 (95% CI 1.25-23.3) and 9.59 (95% CI 1.58-58.1) respectively. Similarly, widowers remain independently related to IR with an AOR of 6.11 (95% CI 1.09-34.40, p=0.040). Hypertension also remained significant with an AOR of 1.95 (95% CI 1.9-3.49, p= 0.024).

Table 17: Adjusted odds ratio (normal vs T2DM)

		Unadjusted (normal vs. T2DM) OR 95%CI	P value	Adjusted (normal vs. T2DM) OR 95%CI	P value
Age group	18-29	Ref			
	30-39	2.31 (.700-7.65)	0.169		
	40-49	5.29 (1.70-16.4)	0.004		
	50-59	5.13 (1.65-16.0)	0.005		
	60-69	13.8 (3.77-50.3)	<0.001	5.40 (1.25-23.3)	0.024
	70+	29.0 (5.62-149.7)	<0.001	9.59 (1.58-58.1)	0.014
Occupation	Governmental	Ref			
	Private	1.31 (.556-3.09)	0.536		
	Labourer	2.68 (1.42-5.09)	0.002		
	Not working	1.78 (.673-4.72)	0.245		
	Retired	4.47 (1.98-10.1)	<0.001		
Marital status	With partner	5..64 (1.93-16.5)	0.002		
	Single	Ref			
	Widowed	21.3 (4.54-100)	<0.001	6.11 (1.09-34.4)	0.040
	Separated	--	0.999		
hypertension	Yes	3.00 (1.79-5.04)	<0.001	1.95 (1.9-3.49)	0.024
	No	Ref			

Anthropometric measurements, nutritional habits, and physical activity in a sub-sample of participants.

Only 173 individuals agreed to participate in the measurement of anthropometric characteristics.

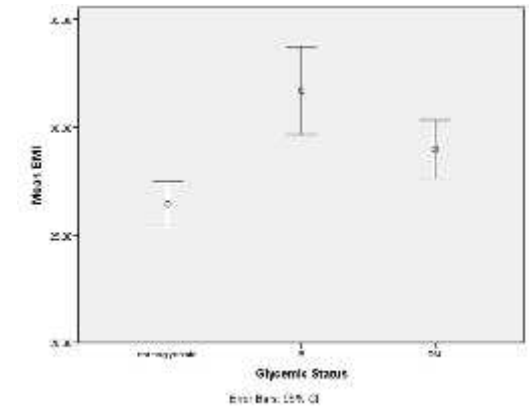
The sub-sample of 173 participants had measurements for waist and hip circumference, weight, and height and underwent further interviews to identify risk factors not documented at the initial survey interview.

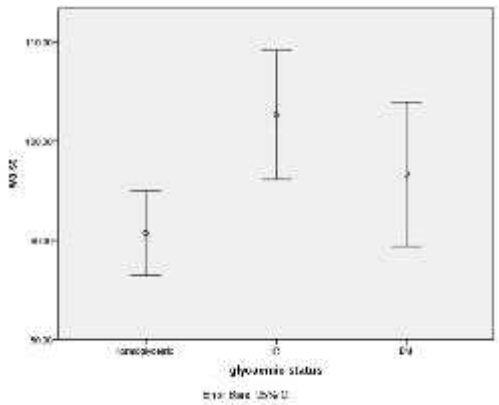
Anthropometric measurements of participants with normoglycaemia, IR and T2DM.

WHR and BMI were available for 58 (%) participants with normal glycaemia, 48 (%) with IR, and 67 (%) with T2DM, as described in Table 18. Increased waist circumference was significantly associated with IR and T2DM. Male participants with waist circumferences ≥ 94 cm were more likely to have IR (OR = 5.5, 95%CI 1.69-18.1, p= 0.005) than participants with waist circumference < 94. This risk remained unchanged when using a higher cut-off ≥ 102 (OR = 5.4, 95% CI 1.50-19.70). Waist circumference was also associated with T2DM. A waist circumference > 94 increased the Odds of having T2DM (OR = 2.18, 95% CI = 0.87-5.45). Moreover, this risk increased further when using a cut-off ≥ 102 (OR = 4, 95% CI = 1.19-13.40). Among females, a waist circumference > 80 cm was not statistically associated with IR (OR = 3.8, 95% CI = 0.39-37.10), but the risk increased substantially with a cut-off ≥ 88 cm (OR = 6.43, 95% CI = 1.21-34.20). T2DM, in turn, had a slightly different pattern, as the OR for T2DM was not increased with a waist circumference ≥ 80 (OR = 0.85, 95% CI = 0.18-3.92), but rose to 3.04 (95% CI = 0.78-11.90) with a cut-off ≥ 88 cm, as shown in Table 19. There was no association between a high WHR and IR or T2DM.

BMI was associated with both IR and T2DM. Overweight participants were more likely to have IR, and this risk increased significantly with BMI ≥ 25 and <30 (OR = 9.73, 95% CI = 2.06-45.9) and BMI ≥ 30 and < 34.9 (OR = 18.33, 95% CI = 3.46-94.96). The odds ratios increased even more with a BMI ≥ 35 (OR = 88.0, 95% CI 6.99-1108.22). This pattern was similar for T2DM as the OR increased to 1.95 (95% CI = 0.82-4.63) for overweight participants and to 2.44 (95% CI = 0.82-7.29) for BMI ≥ 30 and < 35. The odds increase significantly in participants with BMI ≥ 35 (OR 18.62, 95% CI 2.15-161.24).

Figure 15: Mean and 95% CI BMI and waist (a. female and b. male) of participants with normal glucose, IR and T2DM.





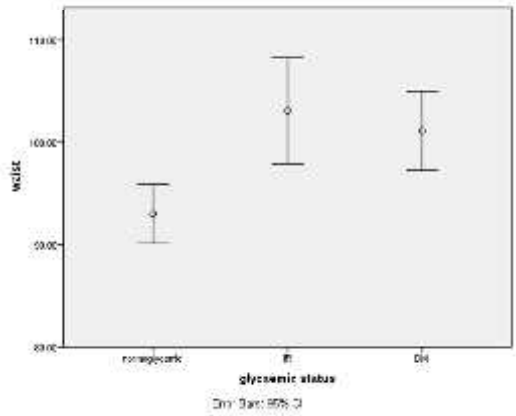


Table 18: Anthropometric measurements of participants

	Normal n=58 n (%)	IR n=48 n (%)	T2DM n=67 n (%)	(normal vs IR) OR 95%CI	P value	(normal vs T2DM) OR 95% CI	P value
WHR							
Male							
< 0.90	5 (62.5)	0 (0)	3 (738.5)	Ref		Ref	
≥ 0.90	28 (28.6)	28 (28.6)	42 (42.8)	--	0.990	2.50 (0.55-11.30)	0.234
Female							
< 0.85	5 (50)	1 (10)	4 (40)	Ref		Ref	
≥ 0.85	19 (34.5)	19 (34.5)	17 (31)	5.00 (0.53-46.90)	0.159	1.12 (0.26-4.85)	0.881
Waist (cm)							
Male							
< 94	18 (46.2)	5 (12.8)	16 (41)	Ref		Ref	
≥ 94	15(22.4)	23(34.3)	29 (43.3)	5.52 (1.69-18.10)	0.005	2.18 (0.87-5.45)	0.097
< 102	29 (39.2)	16 (21.6)	29 (39.2)	Ref			
≥ 102	4 (12.5)	12 (37.5)	16 (50)	5.44 (1.50-19.70)	0.010	4.00 (1.19-13.4)	0.025
Female							
< 80	4 (44.4)	1 (11.1)	4 (44.4)	Ref		Ref	
≥ 80	20 (35.7)	19 (33.9)	17 (30.4)	3.80 (0.39-37.10)	0.251	0.85 (0.18-3.92)	0.835
< 88	10 (35.7)	14 (50)	4 (14.3)				
≥ 88	2 (5.4)	18 (48.6)	17 (46)	6.43 (1.21-34.20)	0.029	3.04 (0.78-11.90)	0.109
BMI							
< 25	22 (40.5)	2 (5.4)	13 (35.1)	Ref		Ref	
≥ 25 to < 30	26 (32.9)	23 (29.1)	30 (38)	8.25 (2.06-46.00)	0.004	1.95 (0.82-4.63)	0.129
30-34.9	9 (24.3)	15 (40.5)	13 (35.1)	18.33 (3.46-97.08)	0.001	2.44 (0.82-7.29)	0.109
≥ 35	1 (5)	8 (40)	11 (55)	88.0 (6.99-1108.22)	0.001	18.62 (2.15-161.24)	0.008

Recall diet of participants and its association with IR and T2DM

The analysis of the dietary intake questionnaire for all participants shows that there is a higher intake of rice and full cream, and lower intake of fruit, vegetables, and proteins (Tables 19 and 20).

The only statistically significant association found was for the occasional consumption of sweets (p = 0.046), as most T2DM participants indicated they ate sweets infrequently (once per month, median rank 8, IQR 4), while normal participants consumed sweets slightly more often (once per week, with a median rank of 6 and IQR 3,25).

Table 19: Median and IQR for patients with normal glucose and T2DM

Food habits	Normal (n=58)		T2DM (n=67)			
	Median	IQR	Median	IQR	Z	p
Fruits & veg	4	2	4	3	-0.574	0.566
Fish	5	1	6	2	-1.287	0.198
Eggs	5	2.25	6	3	-1.919	0.055
Pastry	8	3.25	8	3	-0.333	0.739
Wholegrains	3.5	6	6	6	-1.412	0.158
Rice	3	0	3	0	-0.082	0.935
full cream	3	3.25	3	3	-0.360	0.719
fast food	9	1	9	1	-0.044	0.965
Sweets	6	3.25	8	4	-1.995	0.046
Meat	5	2	5	2	-0.616	0.538
sweetened drinks	9	3	8	3	-0.150	0.881

Z = Mann-Whitney Test

The comparison of medians and IQR ranks for patients with normal glucose and IR is shown in Table 20. A low proportion of participants indicated they consumed fast foods and they ate more frequently rice, whole grains and full cream milk. The only significant food associated with IR was the consumption of sweetened

drinks, with a median of 9 (IQR 3) and 7 (IQR = 4) for participants with normal glucose and IR, respectively (p= 0.036).

Table 20: Median and IQR rank for participants with normal glucose and IR.

Food habits	Normal (n=58)		IR (n=48)			
	Median	IQR	Median	IQR	Z	P
Fruits & veg	4	2	4.5	2	-0.646	0.518
Fish	5	1	6	2	-1.880	0.060
Eggs	5	2.25	6	3	-0.593	0.553
Pastry	8	3.25	7	3	-0.296	0.767
Wholegrains	3.5	6	3	6	-0.140	0.888
Rice	3	0	3	0	-0.361	0.718
full cream	3	3.25	3	3	-0.329	0.742
Fast food	9	1	8	1.75	-1.090	0.276
Sweets	6	3.25	5	5	-1.011	0.312
Meat	5	2	5	2	0.000	1.000
Sweetened drinks	9	3	7	4	-2.097	0.036

Z= Mann-Whitney Test

Physical activity was not associated with any of the glycaemic statuses. Forty-four (75.9%) of 58 normoglycaemic participants indicated they had low physical activity (<150 minutes/week), and 14 (24.1%) had good activity levels (≥ 150 minutes/ week). Thirty-eight (79.2%) of 48 participants with IR had poor levels of activity, and 10 (20.8%) indicated they had good activity. Among T2DM participants, 42 (62.7%) of 67 participants had poor and 25 (37.3%) good physical activity (Chi-Square = 4.494, p= 0.106).

One hundred seventy-two participants stated why they were inactive the week before the interview. The most frequent reason for physical inactivity was their work (Chi-Square= 18.721, p<0.001).

Prevalence of metabolic syndrome

Twenty-eight men and twenty-nine women had MS. According to the IDF criteria, MS prevalence was 32.9% (26.4% in males, and 44.6% in females). The MS rate was higher in females compared to males (Chi-Square = 4.433, p= 0.035).

4.3 Objective 3: Prevalence of IR among first-degree relatives of patients with T2DM.

This was a cross-sectional survey of relatives of patients with T2DM. All individuals with known T2DM participating in the study in objectives 1 and 4 were asked to invite one of their first-degree relatives without T2DM. If the patient had agreed to invite a relative, we provided an appointment date for the interested relative to attend fasting overnight. We recruited 275 first-degree relatives.

Demographic description

Two hundred and seventy-five first-degree relatives of patients with T2DM accepted the invitation to be screened and were interviewed. Of these, 149 (54.2%) were male and 126 (45.8%) female. Their mean (SD) age was 46.1 (12.1) years, as shown in Table 23.

Eighty-three (30.2%) relatives were < 40 years old, 161 (58.6%) between 40 and < 60 and 31 (11.3%) ≥ 60 years old. One hundred and six (38.5%) relatives were Indians, 134 (48.7%) Arabs, 25 (9.1%) from Southeast Asia, 9 (3.3%) Farsi and one (0.4%) from another ethnicity. Two (0.7%) had no education, 52 (18.9%) had primary, 135 (49.1%) secondary and 86 (31.3%) higher education. Eighty participants (29.1%) worked in the government, 51 (18.5%) in the private sector, 91 (33.1%) were labourers, 43 (12.4%) retired, and 19 (6.9%) were not working at the time of the interview.

Two hundred and twenty-nine relatives were living with a partner (83.3%), 28 (10.2%) were single, 14 (5.1%) widowed, and 4 (1.5%) had separated.

Figure 16: Age distribution of participants by gender

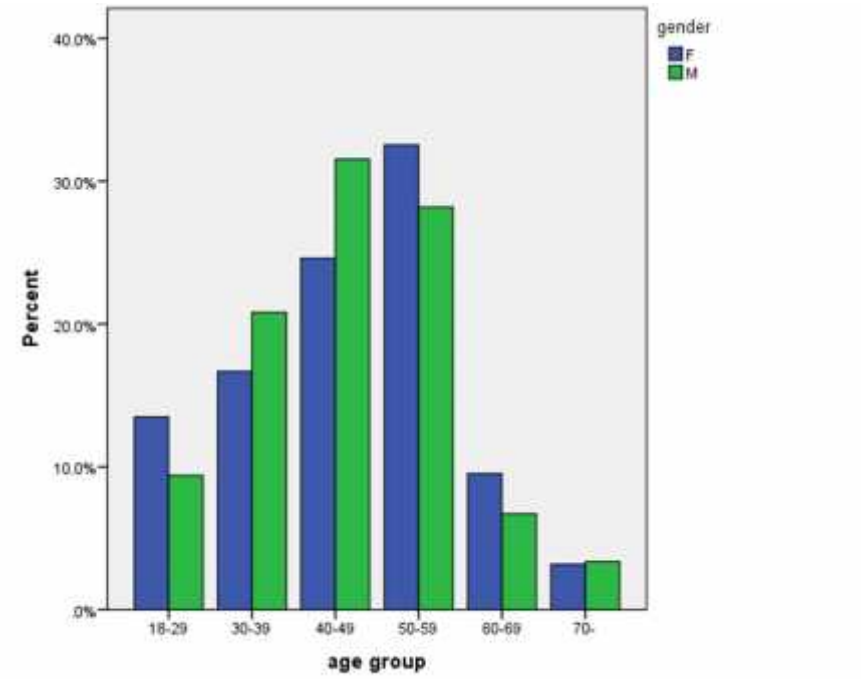


Table 21: Demographic characteristics of first-degree relatives of patients with T2DM

Demographic variable		**n=275**
		n (%)
Age	18-29	31 (11.3)
	30-39	52 (18.9)
	40-49	78 (28.4)
	50-59	83 (30.2)
	60-69	22 (8)
	70+	9 (3.3)
	Mean (SD)	46.1 (12.1)
Sex	Male	149 (54.2)
	Female	126 (45.8)
Ethnicity	Arab	134 (48.7)
	Indian	106 (38.5)
	South East Asia	25 (9.1)
	Farsi	9 (3.3)

	Other	1 (0.4)
Education	No education	2 (0.7)
	Primary	52 (18.9)
	Secondary	135 (49.1)
	Higher education	86 (31.3)
Occupation	Governmental	80 (29.1)
	Private	51 (18.5)
	Labourer	91 (33.1)
	Not working	19 (6.9)
	Retired	34 (12.4)
Marital status	With partner	229 (83.3)
	Single	28 (10.2)
	Widowed	14 (5.1)
	Divorced/Separated	4 (1.5)

Biochemical characteristics Blood tests were available for all participants (Table 22). The mean (SD) FPG was 6.1 (2.1) (mmol/l), mean (SD) Insulin 15.9 (15.7) mmol/l, mean (SD) Homa2-IR 2.05 (1.54) and the mean (SD) HbA1c 6.11% (1.3).

Table 22: Biochemical characteristics of first-degree relatives of patients with T2DM

	n =275	**Mean (SD)**	**Range**
FPG (mmol/l)		6.17 (2.1)	3.01-19.9
Insulin		15.9 (15.17)	0.56-160.4
HOMA IR2[1]		2.05 (1.54)	0.41-15.63
HbA1c %[2]		6.11 (1.3)	4.2-11.9

[1] Eight insulin results were out of the HOMA-IR calculator range.

[2] Thirteen participants had missing HbA1c results.

Prevalence of IR

After excluding 80 newly diagnosed T2DM, 131 (67.2%) relatives had a HOMA2-IR < 2 and 64 (32.8%) and HOMA2-IR ≥ 2. Accordingly, the prevalence of IR with euglycaemia among relatives was 32.8%. (Table 23), which is similar to the prevalence of IR among patients without T2DM attending the health centre (34.5%).

HbA1c was < 5.7% (normal) in 104 (39.7%), between 5.7% and 6.4% in 96 (36.6%) and ≥ 6.5% (T2DM) in 62 (23.7%) of the relatives. FPG was < 6.1 mmol/l (normal) in 184 (66.9%), between 6.1 and 6.9 mmol/l (prediabetes) in 40 (14.5%) and ≥ 7 (T2DM) in 51 (18.5%) participants.

Table 23: HOMA-IR, HbA1c and FPG of first-degree relatives of T2DM participants.

	n=275 n (%)
HOMA2-IR[1]	
< 2	131 (67.2)
≥ 2	64 (32.8)
HbA1c %[2]	
< 5.7	104 (39.7)
5.7-6.4	96 (36.6)
≥ 6.5	62 (23.7)
FPG mmol/l	
< 6.1	184 (66.9)
6.1-6.9	40 (14.5)
≥ 7	51 (18.5)

[1] Only 195 normoglycaemic participants included

[2] Results of HbA1c was available in 262 participants.

Figure 17 describes the distribution of Homa2 IR among the study participants; the distribution is unimodal, skewed to the right and the mode is between 1 and 2, with 39.3% having Homa2 IR ≥2 (including participants with newly diagnosed T2DM).

Figure 18 describes the distribution of HbA1c among participants; the distribution is also unimodal and symmetrical, with most of the values falling between 5% and 7% and 23.7% of participants having HbA1c ≥ 6.5%.

Figure 17: Homa2 IR distribution among first-degree relatives of patients with T2DM

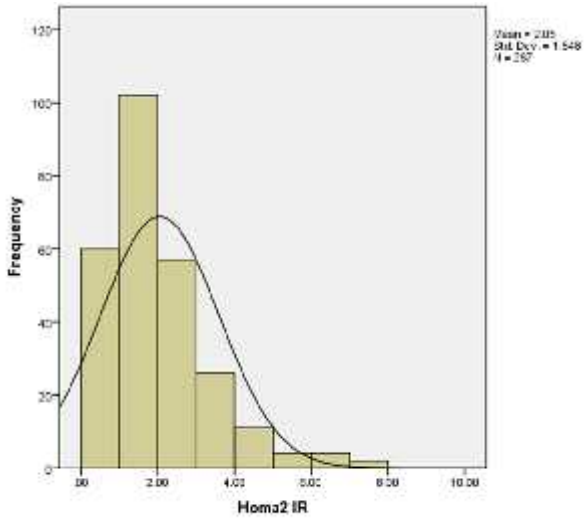


Figure 18: HbA1c distribution among first-degree relatives of patients with T2DM

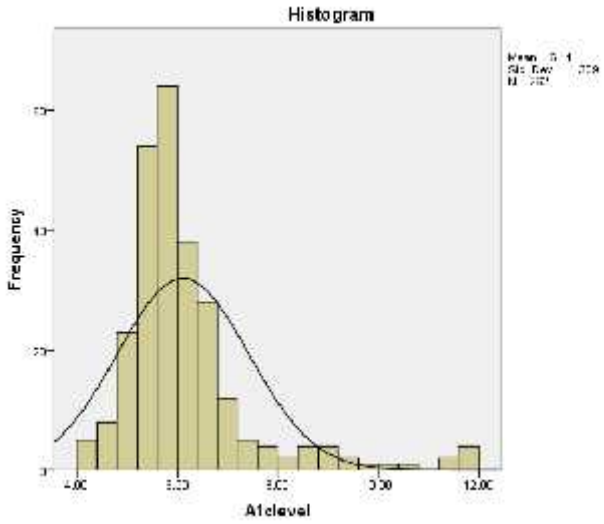
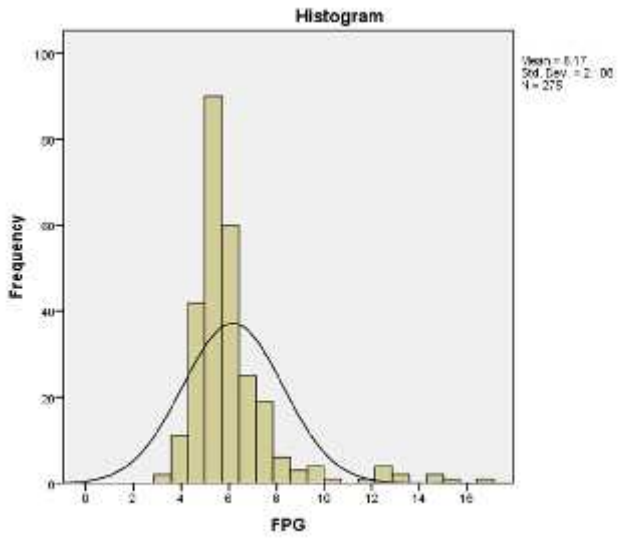


Figure 19: FPG distribution among first-degree relatives of patients with T2DM



Prevalence of T2DM among first-degree relatives

HbA1c was < 6% (normal) in 122 (46.6%) participants; between 6% and 6.4% in 78 (28.4%) and ≥ 6.5% in 62 (23.7%) participants. FPG was < 7 mmol/l in 224 (81.4%) and ≥ 7 mmol/l in 51 (19.6%) participants.

Although none of the relatives indicated they knew if they had T2DM, 33 (12%) had both high HbA1c and FPG, 29 (10.5%) had high HbA1c with normal FPG, and 18 (6.5%) had a high FPG with normal HbA1c. This cross tabulation indicates that both tests would diagnose 80 (29.1%) new T2DM patients among the 275 first degree relatives (Chi-Square=63.732, p= < 0.001). The agreement of FPG and HbA1c are shown in Table 24.

Table 24: Agreement of FPG and HbA1c among relatives of patients with T2DM.

		FPG		Total
		< 7	≥ 7	
HbA1c	< 6.5	195 (91.5%)	18 (8.5%)	213
	≥ 6.5	29 (46.8%)	33 (53.2%)	62
Total		224	51	275

FPG and HbA1c levels had a positive correlation. Figure 15 presents a scatter plot of FPG and HBA1C. Using a linear association model, R^2 values were 0.57 for the association between FPG and HBA1C.

Prevalence of prediabetes

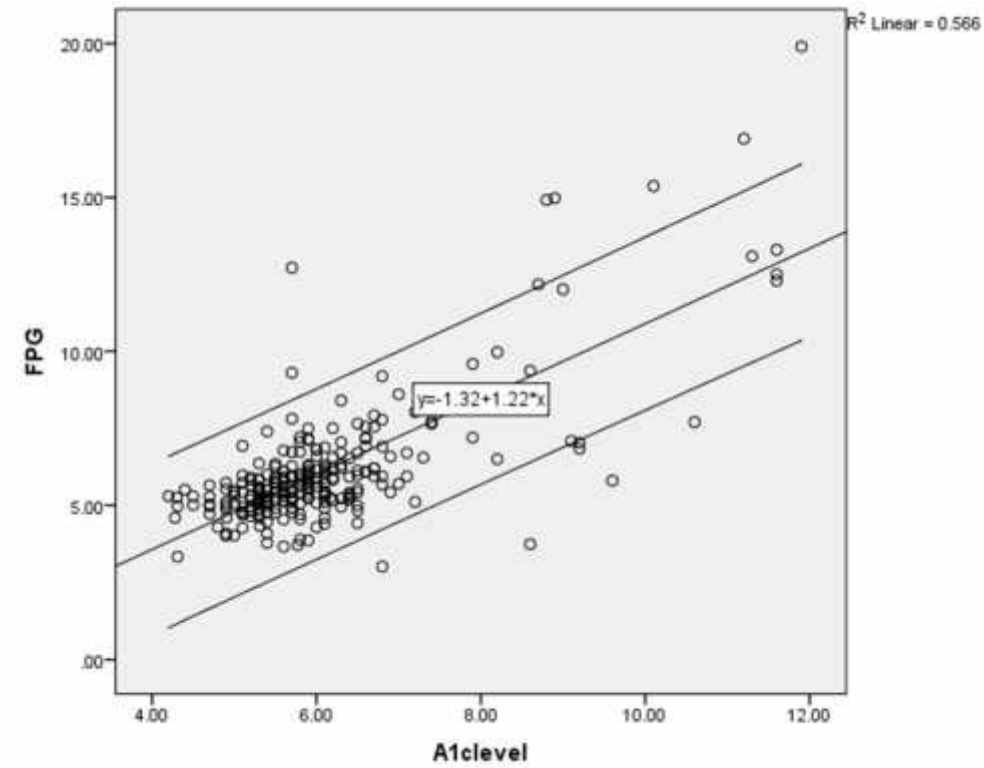
We excluded 80 participants with diabetes (known and new T2DM), with data missing from seven cases, which left a total of 188 participants. Results of HbA1c and FPG results for the 188 patients were cross-tabulated to identify those with FPG or HbA1c within the prediabetes range, as shown in Table 27.

This cross tabulation indicates that both tests would diagnose 56 (20.4%) new T2DM patients among the 275 first degree relatives (Chi-Square=17.576, p= < 0.001). The agreement of FPG and HbA1c are shown in Table 25.

Table 25: Agreement of FPG and HbA1c in participants with no diabetes

		FPG mmol/l	
		<6.1	6.1-6.99
HbA1c %	< 6	132	13
	6-6.49	28	15

Figure 20: Correlation between FPG and HbA1c (lines are the 95% CI) among first-degree relatives of patients with T2DM.



Characteristics of normoglycaemic, IR and T2DM participants

One hundred thirty-one (47.6%) relatives did not have IR, 64 (23.3%) had IR, and 80 (29.1%) had T2DM. The mean (SD) age of relatives with normal glucose, IR, and T2DM were 46.2 (12.5), 46.3 (11.5), and 51.4 (11.2), respectively (Chi-Square 138.41, p <0.026). IR was associated with female gender, as only 62 (41.6%) of 131 normoglycaemic individuals, 38 (25.5%) of 149 participants with IR, and 49 (32.9%) with T2DM were male (Chi-Square 4.784, p= 0.091).

The country of origin of normoglycaemic and IR relatives is shown in Table 28. IR was present in 25 (32%) of 106 participants from India, 25 (18.7%) of 134 Arabs, 3 (12%) of 25 South East Asians, 2 (22.2%) of 9 Persian and 1 (100%) from another ethnicity. While 36 (26.9%) Arab had T2DM, 35 (33%) of Indians, 7 (28%) from

South-east Asia, and 2 (22.2%) of Farsi had T2DM. Relatives from India were more likely to have IR than participants with other backgrounds, (Chi Square= 14.877, p = 0.062).

The type of work was also associated with IR. Relatives who were labourers were more likely to have IR and T2DM than private sector workers. IR and T2DM were present in 27 (29.7%) and 34 (37.4%) of 91 manual labourers respectively, compared to 15 (18.8%) IR and 16 (20%) T2DM of 80 governmental participants, and 13 (25.5%) IR and 10 (19.6%) T2DM of 51 participants from the private sector. (Chi square= 20.419, p = 0.009). Marital status was also statistically associated with IR, 9 (32.1%) of 28 single participants had IR, which was higher than another marital status, as shown in Table 28. Widowers were more likely to have T2DM, as 8 (57.1%) of 14 widowers had T2DM, (Chi-Square = 16.604, p = 0.011).

Education was significantly associated with T2DM, and only 16 (18.6%) of 86 participants with higher education had IR and 11 (12.8%) had T2DM, which was lower than for other education categories, as shown in table 26 (Chi Square= 32.080, p= < 0.001).

Table 26: Demographic characteristics of first-degree relatives with and without IR

Variable		Normal, n=131 n (%)	IR, n=64 n (%)	T2DM, n=80 n (%)
Sex	Male	62 (41.6)	38 (59.4)	49 (61.3)
	Female	69 (58.4)	26 (40.6)	31 (38.8)
Age groups	18-29	21 (16)	8 (12.5)	2 (2.5)
	30-39	28 (21.3)	14 (21.9)	10 (12.5)
	40-49	39 (29.7)	18 (28.1)	21 (26.3)
	50-59	33 (25.2)	20 (31.3)	30 (37.5)
	60-69	9 (6.9)	2 (3.1)	11 (13.8)
	70+	1 (0.8)	2 (3.1)	6 (7.5)

Age mean (SD)		46.2 (12.5)	46.3 (11.5)	51.4 (11.2)
Ethnicity	Arab	73 (55.7)	25 (39.1)	36 (45)
	Indian	38 (29)	33 (51.6)	35 (43.8)
	South East Asia	15 (11.5)	3 (4.7)	7 (8.8)
	Farsi	5 (3.8)	2 (3.1)	2 (2.5)
	Other	0 (0)	1 (1.6)	0 (0)
Education	No education	1 (0.8)	0 (0)	1 (1.3)
	Primary	13 (9.9)	15 (23.4)	24 (30)
	Secondary	58 (44.3)	33 (51.6)	44 (55)
	Higher education	59 (45)	16 (25)	11 (13.8)
Occupation	Governmental	49 (37.4)	15 (23.4)	16 (20)
	labourer	30 (22.9)	27 (42.2)	34 (42.5)
	private	28 (21.4)	13 (20.3)	10 (12.5)
	Not working	11 (8.4)	2 (3.1)	6 (7.5)
	Retired	13 (9.9)	10.9)	14 (17.5)
Marital status	With partner	106 (80.9)	54 (84.4)	69 (86.3)
	Single	17 (13)	9 (14.1)	2 (2.5)
	Widowed	3 (2.3)	0 (0)	1 (1.3)
	Separated	5 (3.8)	1 (1.6)	8 (10)

4.4 Objective 4: To establish the proportion of patients with T2DM who achieve adequate glycaemic control and the risk factors for poor glycaemic control.

Demographic characteristics of participants

We invited every 3rd T2DM patient attending the T2DM clinic for routine follow-up and treatment management. Two hundred thirty-six subjects were interviewed. Of these, 169 (71.6%) were male and 67 (28.4%) female. The mean (SD) age of the participants was 51.6 (10.4) years with a range from 25 to 86 years, as shown in Table 27. Only 30 (12.7%) participants were < 40 years, 159 (67.4%) between 40 and 60 and 47 (19.9%) > 60 years old. One hundred and fifty-three (64.8%) participants were of Indian background, 59 (25%) Arabs, 19 (8.1%) from Southeast Asia, and 5 (2.1%) from other nationalities.

Fifty-three (22.5%) had higher degree education, 78 (33%) secondary education, 80 (33.9%) primary education and 25 (10.6%) were uneducated. Twenty-one participants (8.9%) worked in the government sector, 27 (11.4%) in the private sector, 150 (63.6%) were labourers, 29 (12.3%) retired, and 9 (3.8%) were not working at the time of the interview. Most participants had a partner or were married (219, 92.8%), 9 (3.8%) were single, 6 (2.5%) widowed, and 2 (0.9%) separated.

Table 27: Demographic characteristics of participants

Demographic characteristics		**n=236**
		n (%)
Sex	Male	169 (71.6)
	Female	67 (28.4)
Age group	18-29	4 (1.7)
	30-39	26 (11)
	40-49	68 (28.8)
	50-59	91 (38.5)
	60-69	32 (13.6)
	70+	15 (6.3)
Age, Mean (SD) (years)		51.6 (10.4)
Ethnicity	Arab	59 (25.0)
	Indian	153 (64.8)
	South East Asia	19 (8.1)
	Other	5 (2.1)
Education	No education	25 (10.6)
	Primary	80 (33.9)
	Secondary	78 (33.0)
	Higher education	53 (22.5)
Occupation	Government	21 (8.9)
	Private	27 (11.4)
	Labourer	150 (63.6)
	Not working	9 (3.8)
	Retired	29 (12.3)
Marital status	With partner	219 (92.8)
	Single	9 (3.8)
	Widowed	6 (2.5)
	Divorced/Separated	2 (0.9)
Hypertension	Yes	152 (64.4)
	No	84 (35.6)
High cholesterol	Yes	162 (68.6)
	No	74 (31.4)
Diabetic retinopathy	Yes	16 (6.8)
	No	220 (93.2)
Diabetic nephropathy	Yes	12 (5.1)

	No	224 (94.9)
Cardiovascular disease	Yes	17 (7.2)
	No	219 (92.8)
Polycystic ovaries	Yes	5 (7.5)
	No	62 (92.5)
Gestational diabetes	Yes	11 (16.4)
	No	56 (83.6)
Smoker	No	180 (76.3)
	Ex-smoker	15 (6.3)
	Yes	41 (17.4)
Years with diabetes	Mean (SD)	8.9 (7.8)
Number of clinic visits/year	Mean (SD)	5.7 (1.2)

Biochemical characteristics of study participants

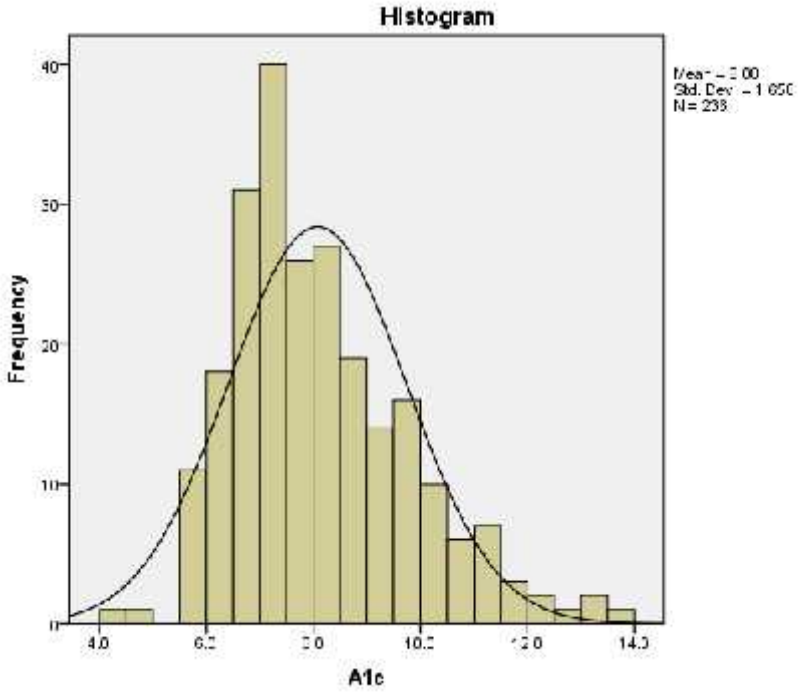
The biochemical markers of participants are shown in Table 28. Seventy-one (30.1%) of 236 participants had HbA1c ≤ 7% (considered good control), 103 (43.6%) HbA1c between 7% and 9% (called 'moderate control'), and 62 (26.3%) had HbA1c >9% and therefore had poor T2DM control. The HbA1c of participants is shown in figure 21 and Table 34, the mean (SD) HbA1c was 8.1% (1.7) with a range from 4.3% to 13.8%.

The mean (SD) LDL, HDL and TG were 2.57 (0.81), 1.04 (0.34) and 1.63 (0.83), respectively. One hundred twelve (47.5%) of 236 participants had high LDL and 48 (20.3%) normal HDL levels, and 188 (79.7%) had low HDL as shown in Table 29. Eighty-seven (36.9%) of 236 participants had high TG levels.

Table 28: Biochemical characteristics of participants

Variables	n = 236 n (%)	Mean (SD)
LDL mmol/l		2.57 (0.81)
≥ 2.6	112 (47.5)	
< 2.6	124 (52.5)	
HDL mmol/l		1.04 (0.34)
≥ 1.2	48 (20.3)	
< 1.2	188 (79.7)	
TG mmol/l		1.63 (0.83)
≥ 1.7	87 (36.9)	
< 1.7	149 (63.1)	
HbA1c [%]		8.1 (1.7)
≤ 7	71 (30.1)	
7-9	103 (43.6)	
≥9	62 (26.3)	

Figure 21: Dispersion of HbA1c level among participants



Demographic characteristics of participants by glycaemic status

The results show that only 71 (30.1%) participants had good glycaemic control, 103 (43%) with moderate control, and 62 (26.3%) with poor glycaemic control.

Forty-nine (29%) males had HbA1c ≤ 7%, 74 (43.8%) HbA1c between 7% and 9% and 46 (27.2%) > 9%. Similarly, 22 (32.8%) females had HbA1c ≤ 7%, 29 (43.3%) between 7% and 9%, and 16 (23.9) >9%. The proportion of males and females with poor glycaemic control was similar (Chi-Square= 0.442, P=0.802).

Age was not apparently associated with HbA1c percentage levels, as shown in figure 17. The mean ages (SD) of patients with good, moderate and poor glycaemic control were 51.7 (10.2), 51.2 (9.6), and 52.1 (11.7) years, respectively (Chi-Square= 8.778, P= 0.553). However, T2DM participants aged 40-60 were more likely to have good or moderate glycaemic control compared to younger and older participants as shown in figure 23.

Figure 22: A scattered diagram showing the dispersion of HbA1c according to age

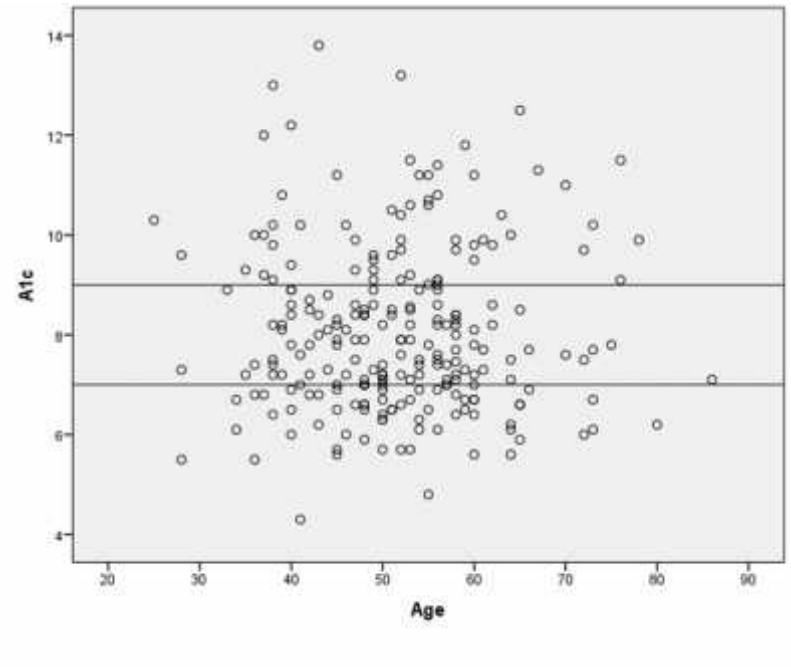
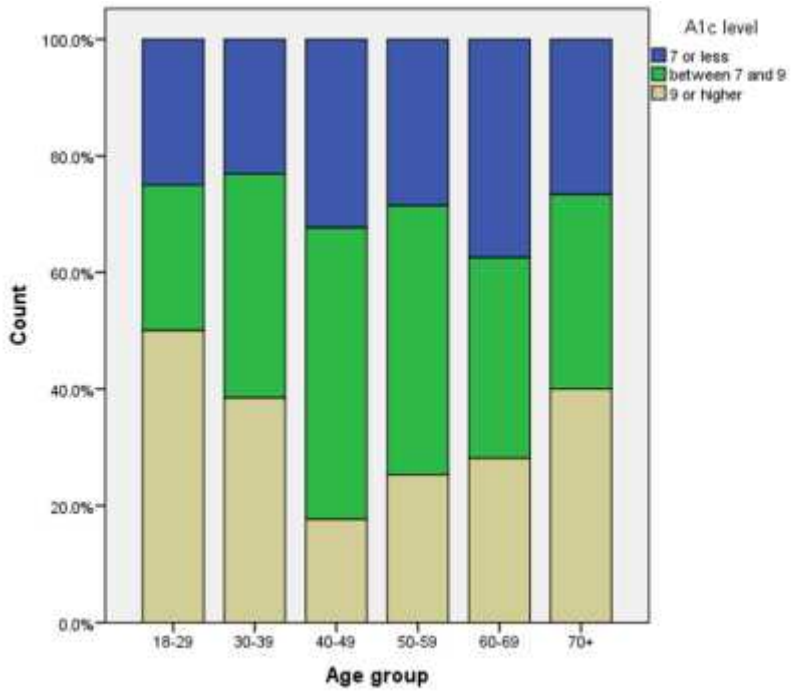


Figure 23: A stacked histogram showing the prevalence of good, moderate and poor glycaemic control in different age group



The country of origin was not associated with glycaemic control, as shown in Table 29. Good glycaemic control was attained by 47 (30.7%) of 153 participants from India, 15 (25.4%) 59 Arabs, 7 (36.8%) of 19 South East Asians and 2 (40%) of 5 participants from other countries. Conversely, poor control was attained in 41 (26.8%) Indians, 15 (25.4%) Arabs, 4 (21.1%) South East Asians and 2 (40%) participants from other countries (Chi-Square= 2.695, p= 0.846)

Similarly, glycaemic control was not associated with occupation. Although patients working in the private sector were less likely to have good glycaemic control (3 (11.1%) of 27 participants), this association was not statistically significant. Marital status was also not associated with any of the glycaemic groups (Chi-Square= 0.118, P=0.943).

Participants with poor glycaemic control were more likely to have retinopathy and nephropathy, but this association was not significant at the time of the interview (P=0.857 and P=0.718, respectively).

A medical history of CVD was associated with poor glycaemic control. Among the 17 T2DM with a medical history of CVD, 3 (17.6%) had good, 5 (29.4%) moderate and 9 (52.9%) poor control, while among the 219 participants with no history of CVD, 68 (31.1%) had good, 98 (44.7%) moderate and 53 (24.2%) poor control (Chi-Square= 6.752, P= 0.340). There was no significant association between Polycystic Ovaries syndrome and glycaemic control status (Chi-square= 4.165, P= 0.125). Similarly, a medical history of gestational diabetes and the reported level of physical activity were not associated with the glycaemic control status (P=0.672 and P= 0.921, respectively).

Smoking was associated with poor glycaemic control. Seven (17.1%) smokers had good, 17 (41.5%) moderate, and 17 (41.5%) poor glycaemic control, compared to 62 (34.4%), 79 (43.9%) and 39 (21.7%) of 180 non-smokers having good, moderate and poor control (Chi-Square= 11.203, P= 0.024). Among the 15 ex-smokers, 2 (13.3%) had good, 7 (46.7%) moderate and 6 (40%) poor control, resembling the patter of smokers.

The duration of T2DM was significantly associated with the glycaemic control status (Chi-Square= 12.067, P= 0.002). Among 90 participants with a history of T2DM for more than ten years 17 (18.9%) had good control, 40 (44.4%) moderate, and 33 (36.7%) poor control, while participants with less than 10 years of T2DM, 54 (37%) participants had good, 63 (43.2%) moderate and 29 (19.9%) poor glycaemic control.

Table 29: Demographic characteristics of participants by glycaemic control status

Variable		HbA1c ≤ 7% n (%)	7 < HbA1c < 9% n (%)	HbA1c ≥ 9% n (%)	P value
Sex	Male	49 (29)	74 (43.8)	46 (27.2)	0.802
	Female	22 (32.8)	29 (43.3)	16 (23.9)	
Age groups	18-29	1 (25.0)	2 (25.0)	2 (50.0)	
	30-39	6 (23.1)	10 (38.5)	10 (38.5)	
	40-49	22 (32.4)	34 (50.0)	12 (17.6)	
	50-59	26 (28.6)	42 (46.2)	23 (25.3)	
	60-69	12 (37.5)	11 (34.4)	9 (28.1)	
	70+	4 (26.7)	5 (33.3)	6 (40.0)	
Age mean (SD)		51.7 (10.2)	51.2 (9.6)	52.1 (11.7)	0.553
Ethnicity	Arab	15 (25.4)	29 (49.2)	15 (25.4)	
	Indian	47 (30.7)	65 (42.5)	41 (26.8)	
	South East Asia	7 (36.8)	8 (42.1)	4 (21.1)	
	Other	2 (40.0)	1 (20.0)	2 (40.0)	
Education	No education	10 (40.0)	9 (36.0)	6 (24.0)	0.465
	Primary	25 (31.3)	31 (38.7)	24 (30.0)	
	Secondary	19 (24.7)	36 (46.8)	22 (28.6)	
	Higher education	17 (32.1)	27 (50.9)	9 (17.0)	

Occupation	Governmental	7 (33.3)	8 (38.1)	6 (28.6)	0.943
	Private	3 (11.1)	16 (59.3.)	8 (29.6)	
	Labourer	48 (32)	61 (40.7)	41 (27.3)	
	Not working	2 (22.2)	4 (44.4)	3 (33.3)	
	Retired	11 (37.9)	14 (48.3)	4 (13.8)	
Marital status	With partner	67 (30.6)	95 (43.4)	57 (26.0)	0.204
	Single	1 (11.1)	4 (44.4)	4 (44.4)	
	Widowed	2 (33.3)	4 (66.7)	0 (0.0)	
	Separated	1 (50.0)	0 (0.0)	1 (50.0)	
Hypertension	Yes	45 (29.6)	66 (43.4)	41 (27.0)	0.943
	No	26 (31.3)	37 (44.6)	21 (24.1)	
High cholesterol	Yes	46 (28.4)	71 (43.8)	45 (27.8)	0.625
	No	25 (34.7)	32 (44.4)	15 (20.8)	
Diabetic retinopathy	Yes	4 (25.0)	7 (43.7)	5 (31.3)	0.857
	No	67 (30.5)	96 (43.6)	57 (25.9)	
Diabetic nephropathy	Yes	4 (33.3)	6 (50.0)	2 (16.7)	0.718
	No	67 (29.9)	97 (43.3)	60 (26.8)	
Cardiovascular disease	Yes	3 (17.6)	5 (29.4)	9 (52.9)	0.340
	No	68 (31.1)	98 (44.7)	53 (24.2)	
Polycystic ovaries	Yes	1 (20.0)	4 (80.0)	0 (0.0)	0.125

	No	21 (34.4)	24 (39.3)	16 (26.2)	
Gestational diabetes	Yes	3 (27.3)	6 (54.5)	2 (18.2)	0.672
	No	19 (34.5)	22 (40.0)	14 (25.5)	
Physical activity	< 150 min	49 (30.1)	70 (42.9)	44 (27)	0.921
	≥ 150 min	22 (30.1)	33 (45.2)	18 (24.7)	
Smoker	No	62 (34.4)	79 (43.9)	39 (21.7)	0.024
	Ex-smoker	2 (13.3)	7 (46.7)	6 (40.0)	
	Yes	7 (17.1)	17 (41.5)	17 (41.5)	
Years with diabetes	Mean (SD)	6.1 (6.4)	9.4 (7.4)	11.3 (8.9)	0.002
Number of clinic visits/year	Mean (SD)	5.7 (0.96)	5.8 (1.1)	5.4 (1.5)	

Biochemical characteristics by glycaemic control status

The biochemical markers of participants with good, moderate, and poor glycaemic control are shown in Table 30. TG was higher in participants with HbA1c ≥ 9 % (Chi-Square= 4.923, P= 0.085), with 20 (23%) participants with high level of TG having good glycaemic control, 38 (43.7%) moderate control, and 29 (33.3%) participants with high TG levels having poor control, compared to 51 (34.2%) participants with normal TG having good control, 65 (43.6%) moderate control, and 33 (22.1%) having poor control, Figure 24 shows the mean and 95% CI TG concentrations of participants with good, moderate and poor glycaemic control.

Plasma LDL and HDL levels were not associated with glycaemic control (P= 0.548 and P= 0.380, respectively).

Figure 24: Mean and 95% CI TG level among the three glycaemic control groups

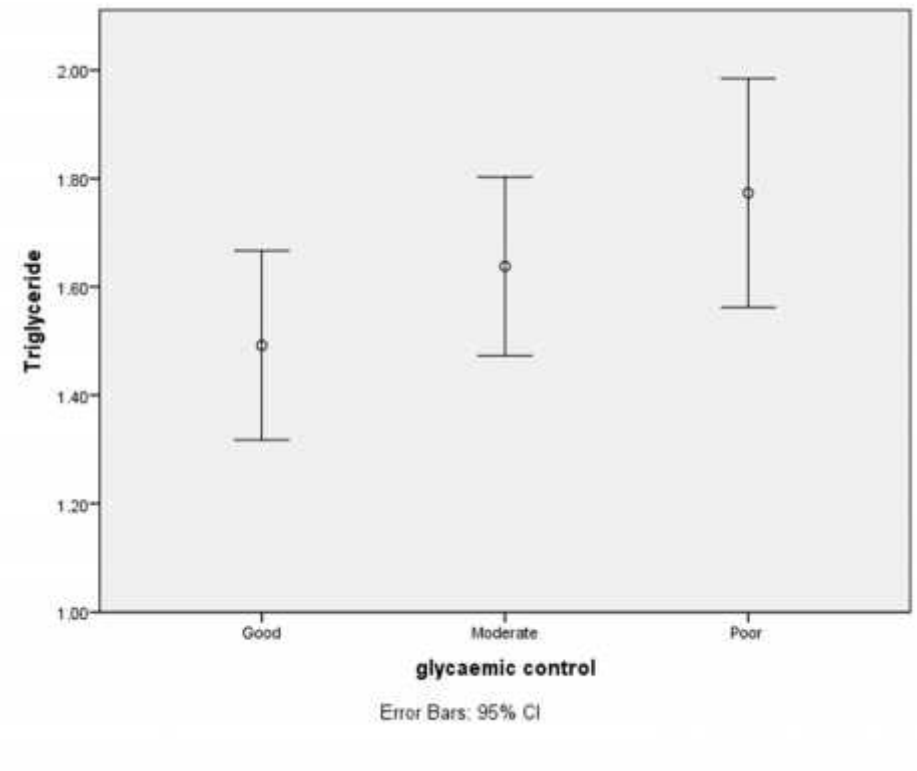


Figure 25: Mean and 95% CI of HbA1c in non-smoker, ex-smoker, and smoker groups

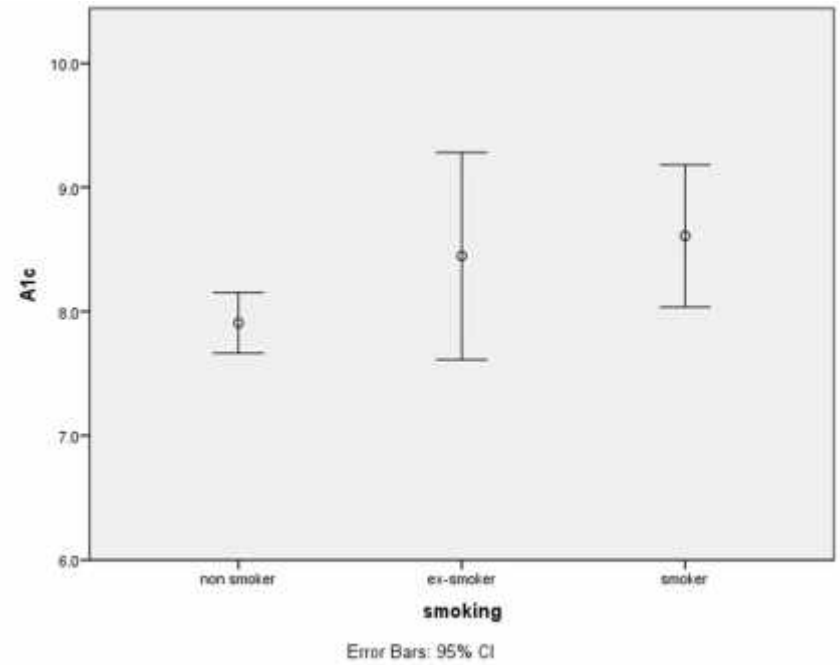


Table 30: Biochemical characteristics of participants by glycaemic control status

Variables	**HbA1c ≤ 7%**	**7 < HbA1c < 9%**	**HbA1c ≥ 9%**	**P value**
	n= 71	**n= 103**	**n= 62**	
LDL mmol/l Mean (SD)	2.58 (0.85)	2.59 (0.77)	2.51 (0.84)	
≥ 2.6 n (%)	32 (28.6)	53 (47.3)	27 (24.1)	0.548
< 2.6 n (%)	39 (31.5)	50 (40.3)	35 (28.2)	
HDL mmol/l Mean (SD)	1.05 (0.29)	1.07 (0.37)	0.97 (0.33)	
≥ 1.2 n (%)	17 (35.4)	22 (45.8)	9 (18.8)	0.380
<1.2 n (%)	54 (28.7)	81 (43.1)	53 (28.2)	
TG mmol/l Mean (SD)	1.48 (0.66)	1.64 (0.90)	1.80 (0.84)	
≥ 1.7 n (%)	20 (23.0)	38 (43.7)	29 (33.3)	0.085
< 1.7 n (%)	51 (34.2)	65 (43.6)	33 (22.2)	

Anthropometric measurement of study participants by glycaemic control status

There was no association between WHR and T2DM control, and this association was not significant in males (Chi-Square= 1.475, P=0.478) or females (Chi-Square= 1.863, P=0.394). The waist circumference was not related to HbA1c percentage levels in males (Table 31). Likewise, in female participants, the association of the waist circumference and the degree of glycaemic control was not significant (Chi-Square= 0.718, P= 0.698). Even when the cut-off was raised to 102 cm in males and 88 in females, no significant relation was detected.

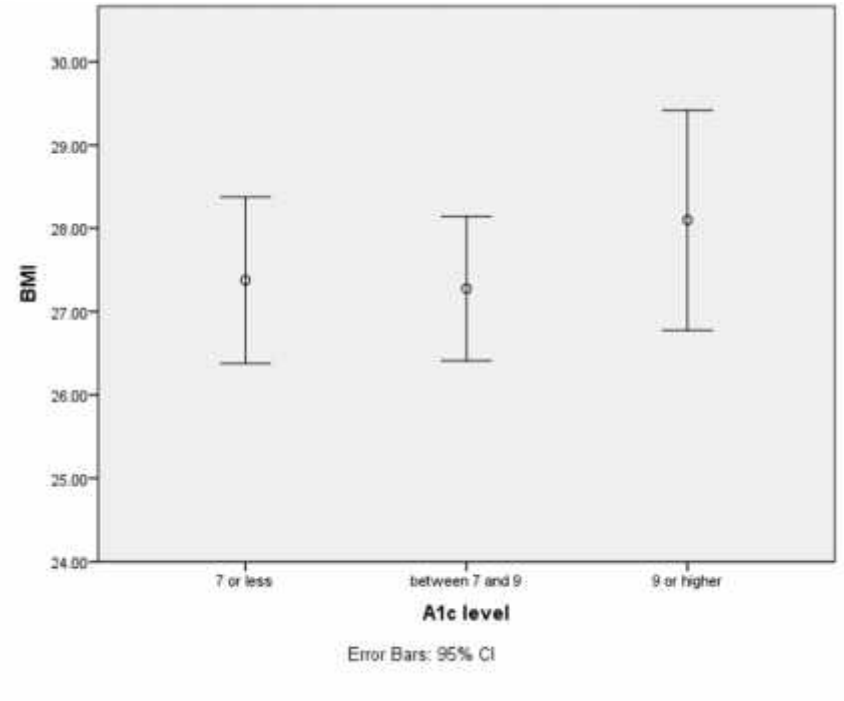
The mean BMI of participants with good, moderate, and poor glycaemic control were 27.4, 27.3, and 28.1, respectively, as shown in figure 26. BMI was higher in participants with poor glycaemic control. However, this association was not statistically significant (Chi-Square= 10.039, P= 0.437).

Table 31: Anthropometric measurements for participants according to their glycaemic status

	HbA1c ≤ 7%	**7 < HbA1c < 9%**	**HbA1c ≥ 9%**	**P value**
	n= 71	**n= 103**	**n= 62**	
WHR				
Male				
< 0.90	2 (25.0)	5 (62.5)	1 (12.5)	
≥ 0.90	47 (29.2)	69 (42.9)	45 (28)	0.478
Female				
< 0.85	3 (60.0)	1 (20.0)	1 (20.0)	
≥ 0.85	19 (30.6)	28 (45.2)	15 (24.2)	0.394
Waist (cm)				
Male				
< 94	19 (30.6)	27 (43.5)	16 (25.8)	
≥ 94	30 (28.0)	47 (43.9)	30 (28.0)	0.895
< 102	31 (27)	52 (45.2)	32 (27.8)	

≥ 102	18 (33.3)	22 (40.7)	14 (25.9)	
Female				
< 80	2 (50.0)	1 (25.0)	1 (25.0)	
≥ 80	20 (31.7)	28 (44.4)	15 (23.8)	0.698
< 88	3 (30.0)	4 (40.0)	3 (30.0)	
≥ 88	19 (33.3)	25 (43.9)	13 (22.8)	
BMI (kg/m^2)				
< 18.5	1 (100)	0 (0)	0 (0)	
18.5-24.9	18 (25.4)	36 (50.7)	17 (23.9)	
25-29.9	37 (33.6)	43 (39.1)	30 (27.3)	
30-34.9	11 (30.6)	17 (47.2)	8 (22.2)	
35-39.9	4 (30.8)	5 (38.5)	4 (30.8)	
≥40	0 (0)	2 (40)	3 (60)	0.437

Figure 26: Mean and 95%CI of BMI in the three glycaemic control



Risk factors for poor glycaemic control – Univariate and multivariate analyses.

The variables associated with poor glycaemic control are shown in table 38. These include the presence of high Triglyceride (OR 2.24, 95% CI 1.09-4.60); smoking (OR 3.86, 95% CI 1.47-10.16), and the number of years lived with T2DM (More than ten years) (OR 3.62, 95% CI 1.73-7.57), as shown in tables 32.

Table 32: Descriptive analysis and odds ratios comparing patients with good and poor glycaemic control.

	HbA1c ≤ 7%	**HbA1c ≥ 9%**	**OR 95%CI**	**P value**
	n=71 (%)	**n=62 (%)**		
Sex				
Male	49 (51.6)	46 (48.4)	1.29 (0.60-2.76)	0.510
Female	22 (57.9)	16 (42.1)	Ref	
Age groups				
18-29	1 (33.3)	2 (66.7)	Ref	
30-39	6 (37.5)	10 (62.5)	0.83 (0.06-11.27)	0.891
40-49	22 (64.7)	12 (35.3)	0.27 (0.02-3.33)	0.309
50-59	26 (53.1)	23 (46.9)	0.44 (0.04-5.20)	0.517
60-69	12 (57.1)	9 (42.9)	0.38 (0.03-4.81)	0.451
70 +	4 (40.0)	6 (60.0)	0.75 (0.50-11.31)	0.835
mean (SD) years	51.7 (10.2)	52.1 (11.7)		
Ethnicity				
Arab	15 (50.0)	15 (50.0)	Ref	
Indian	47 (53.4)	41 (46.6)	0.87 (0.38-2.00)	0.747
South East Asian	7 (63.6)	4 (36.4)	0.57 (0.14-2.37)	0.440
Others	2 (50.0)	2 (50.0)	1.00 (0.12-8.06)	1.000
Education				
No education	10 (62.5)	6 (37.5)	Ref	
Primary	25 (51.0)	24 (49.0)	1.60 (0.50-5.09)	0.426
Secondary	19 (46.3)	22 (53.7)	1.93 (0.59-6.30)	0.276

Higher education	17 (65.4)	9 (34.6)	0.88 (0.24-3.22)	0.850
Occupation				
Governmental	7 (53.8)	6 (46.2)	Ref	
Private	3 (27.3)	8 (72.7)	3.11 (0.56-17.33)	0.195
Labourer	48 (53.9)	41 (46.1)	0.99 (0.31-3.20)	0.995
Not working	2 (40.0)	3 (60.0)	1.75 (0.22-14.22)	0.601
Retired	11 (73.3)	4 (26.7)	0.42 (0.09-2.06)	0.288
Marital status				
With partner	67 (41.4)	95 (58.6)	Ref	
Single	1 (20.0)	4 (80.0)	4.70 (0.51-43.27)	0.172
Widowed	2 (33.3)	4 (66.7)	----	0.999
Separated	1 (100)	0 (0)	1.18 (0.072-19.22)	0.910
Hypertension				
Yes	45 (52.3)	41 (47.7)	1.29 (0.64-2.59)	0.482
No	26 (55.3)	21 (44.7)	Ref	
Smoker				
No	62 (61.4)	39 (38.6)	Ref	
Ex-smoker	2 (25)	6 (75)	4.77 (0.92-24.83)	0.063
Yes	7 (29.2)	17 (70.8)	3.86 (1.47-10.16)	0.007
LDL mmol/l				
Mean (SD)	2.58 (0.85)	2.51 (0.84)		
≥2.6	32 (54.2)	27 (45.8)	0.94 (0.47-1.87)	
<2.6	39 (52.7)	35 (47.3)	Ref	0.860
HDL mmol/l				
Mean (SD)	1.05 (0.29)	0.97 (0.33)		
≥1.2	17 (65.4)	9 (34.6)	0.54 (0.22-1.32)	0.175
<1.2	54 (50.5)	53 (49.5)	Ref	
TG mmol/l				
Mean (SD)	1.48 (0.66)	1.80 (0.84)		
≥1.7	20 (40.8)	29 (59.2)	2.24 (1.09-4.60)	0.028
<1.7	51 (60.7)	33 (39.3)	Ref	

Physical activity				
< 150 min	49 (52.7)	44 (47.3)	Ref	
≥ 150 min	22 (55)	18 (45)	0.91 (0.43-1.92)	0.806
Years with diabetes				
< 10	54 (65.1)	29 (34.9)	Ref	
≥ 10	17 (34)	33 (66)	3.62 (1.73-7.57)	0.001

Multiple regression (Table 33) showed that smoking (AOR 4.13, 95% CI 1.47-11.59), a high TG concentration (AOR 2.22, 1.01-4.91), and living with T2DM for more than ten years (AOR 4.03, 95% CI 1.81-9.00) were independent risk factors for poor glycaemic control.

Table 33: Adjusted odds ratios (good vs poor glycaemic control)

	Adjusted OR (95%CI)	**P value**
Smoker		
No	Ref	
Ex-smoker	2.8 (0.49-16.42)	0.244
Yes	4.13 (1.47-11.59)	0.007
TG mmol/l		
< 1.7	Ref	
≥ 1.7	2.22 (1.01-4.91)	0.048
Years with diabetes		
< 10	Ref	
≥ 10	4.03 (1.81-9.00)	0.001

Table 34: Anthropometric characteristics and odds ratios for participants with good and poor glycaemic control

	HbA1c ≤ 7% n= 71	HbA1c ≥ 9% n= 62	OR 95%CI	P value
WHR				
Male				
< 0.90	2 (66.7)	1 (33.3)	Ref	
≥ 0.90	47 (51.1)	45 (48.9)	1.92 (0.17-21.86)	0.601
Female				
< 0.85	3 (75)	1 (25)	Ref	
≥ 0.85	19 (55.9)	15 (44.1)	2.37 (0.22-25.14)	0.474
Waist (cm)				
Male				
< 94	19 (54.3)	16 (45.7)	Ref	
≥ 94	30 (50)	30 (50)	1.19 (0.52-2.74)	0.687
< 102	31 (49.2)	32 (50.8)	Ref	
≥ 102	18 (56.3)	14 (43.8)	0.75 (0.32-1.77)	0.517
Female				
< 80	2 (66.7)	1 (33.3)	Ref	
≥ 80	20 (57.1)	15 (42.9)	1.50 (0.12-18.13)	0.750
< 88	3 (50)	3 (50)	Ref	
≥ 88	19 (59.4)	13 (40.6)	0.68 (0.12-3.93)	0.671
BMI (kg/m^2)				
< 25	19 (52.8)	17 (47.2)	Ref	
≥ 25 to < 30	37 (55.2)	30 (44.8)	0.91 (0.40-2.04)	0.812
30-34.9	11 (58)	8 (42)	0.813 (0.27-2.50)	0.717
≥ 35	4 (36)	7 (64)	1.96 (0.49-7.87)	0.345

The logistic regression analysis of anthropometric variables shows no significant relation to the glycaemic control status of the study participants (Table 34).

Nutritional behaviour of participants by glycaemic control status

The food habits of the participants were analysed using Mann-Whitney's test using the same method described in objective 2 results. Food habits did not have significant associations with the glycaemic control status (Table 35).

Table 35: Median and IQR for participants with good and poor glycaemic control

Food habits	HbA1c ≤ 7% (n=71)		HbA1c ≥ 9% (n=62)		Mann Whitney's	
	Median	IQR	Median	IQR	Z	p
Fruits & veg	5	3	5	3	-0.995	0.320
Fish	6	2	6	2	-0.138	0.890
Eggs	6	1	5.5	2.25	-0.508	0.611
Pastry	8	3	8	3	-1.258	0.208
Wholegrains	8	6	8	6	0.552	0.581
Rice	3	0	3	0	-0.575	0.565
full cream	3	6	3	4	-0.749	0.454
fast food	9	1	8	1	-1.119	0.263
Sweets	6	4	7	4	-1.502	.133
Meat	5	2	5	1	-0.759	0.448
sweetened drinks	9	2	9	3	-0.367	0.714

4.5 Objective 5: Accuracy of a point-of-care device to measure HbA1c for the monitoring of HbA1c among patients with T2DM and patients with known haemoglobinopathies.

This was a cross-sectional study. The participants were the same individuals participating in objective 4 with a known diagnosis of T2DM. The HbA1c measurements of both a POC device (Quo-test, EKF DIAGNOSTICS) and the Laboratory HbA1c (Tosoh HLC G8, TOSOH BIOSCIENCE) of 217 participants were available. Tosoh HLC G8 was used as the reference standard to assess the performance of Quo-test POC.

A further smaller group of participants (n=41) were recruited from the haematology clinic of Amiri Hospital. A reference centre for patients with known haemoglobinopathies. Most of the participants in this group were known to have sickle cell anaemia. The comparison of the two tests used the same approach as for the larger group.

Demographic characteristic of participants

One hundred sixty-two (73.3%) participants were male and 59 (26.7%) female. Their mean age was 52, with only 3 (1.4%) being younger than 30 years old and 47 (21.4%) were > 60 years, as shown in Table 36.

Table 36: Demographic characteristics of participants with T2DM and no haemoglobinopathies

		n = 221
		n (%)
Gender		
	Male	162 (73.3)
	Female	59 (26.7)
Age group		
	18-29	3 (1.4)

	30-39	22 (10.0)
	40-49	65 (29.4)
	50-59	84 (38.0)
	60-69	32 (14.5)
	70+	15 (6.9)
Mean (SD) years		52 (10.3)

In another group of participants with known abnormal haemoglobin, 19 (46.3%) participants were male and 22 (53.7%) female. Their mean age was 35.7, with 34 (82.6%) being younger than 50 years old and 7 (17.4%) were > 50 years, as shown in Table 37.

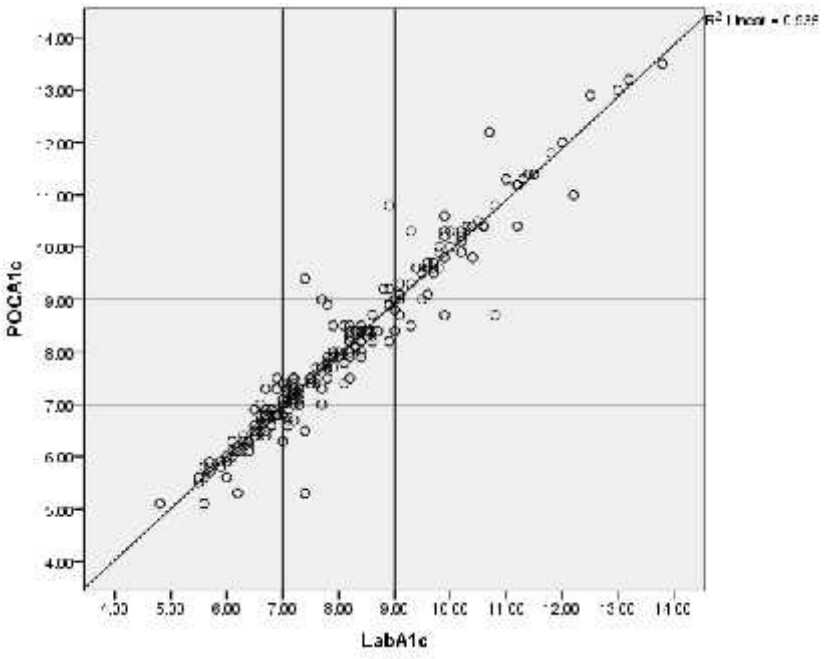
Table 37: Demographic characteristics of participants with abnormal haemoglobin

		n = 41 **n (%)**
Gender		
	Male	19 (46.3)
	Female	22 (53.7)
Age group		
	18-29	16 (39.0)
	30-39	12 (29.3)
	40-49	6 (14.6)
	50-59	3 (7.3)
	60-69	4 (9.8)
	70+	0 (0.0)
Mean (SD) years		35.7 (13.7)

The accuracy of the Quo-test in the diagnosis of the HbA1c status in individuals with T2DM.

The data in Figure 27 shows a strong positive correlation between the results of the POC device and the reference test results, the r squared = 0.935

Figure 27: Quo-test POC/Tosoh Laboratory HbA1c results



The Bland-Altman plot (Figure 28) showed that the linear regression of the difference and mean difference is - 0.063. This difference was not statistically significant (p= 0.354). This means that the difference between the two diagnostic measures is not significant and accordingly we cannot reject the null hypothesis.

Figure 28: Bland-Altman plot

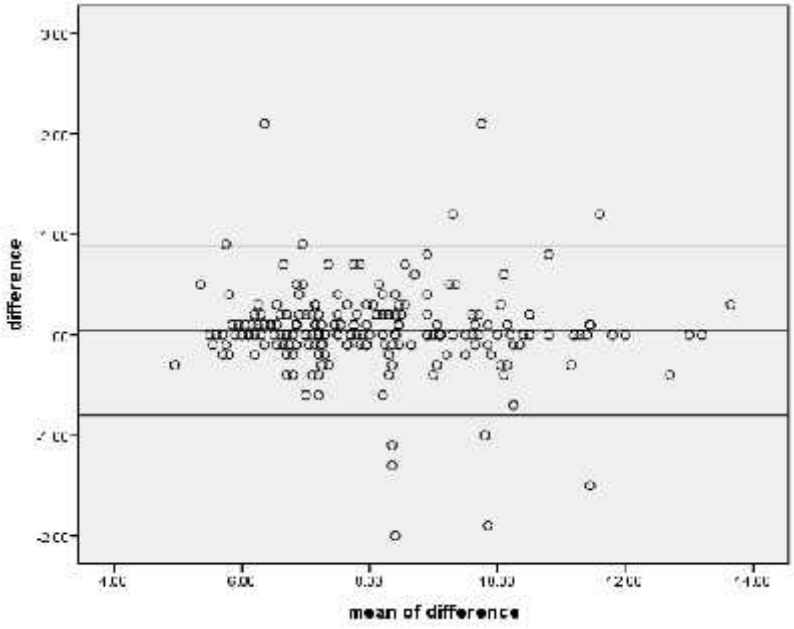


Table 38 describes the agreement between Quo-test and the Tosoh laboratory results when using a cut-off of 9%. Fifty-nine (%) had an HbA1c above 9% and 158 and HbA1c <9% when assessed by the reference laboratory test. Among the 59 participants with high HbA1c, 53 (89.8%) were classified as high by the Quo-test POC and 6 (10.2%) as having HbA1c < 9%. Among the 158 participants with HbA1c below 9%, 5 (3.2%) were classified as having an HbA1c ≥ 9% and 153 (96.8%) < 9% by the Quo-test POC device. Kappa test 0.871, P< 0.001 and prevalence and bias adjusted Kappa (PABAK) = 0.899, corresponding to strong agreement.

Table 38: Agreement between Quo-test POC HbA1c and Tosoh Laboratory HbA1c (reference) when using an HbA1c cut-off of 9%.

	Lab HbA1c		**Total**
	< 9%	**≥ 9%**	
POC HbA1c			
≥ 9**%**	5 (3.2%)	53 (89.8%)	58
< 9**%**	153 (96.8%)	6 (10.2%)	159
Total	158	59	217
Kappa = 0.871, p < 0.001			
PABAK* = 0.899			

*P_o = (b+c)/total number = (53+153)/217, Prevalence and bias adjusted Kappa (PABAK) = 2 P_o – 1 = 0.899.

Table 39 shows the agreement of the Quo-test POC and the Tosoh laboratory HbA1c results when the cut-off used is 7%. Fifty-eight (%) participants had an HbA1c <7 and 159 had values ≥ 7%. Among the 159 participants with HbA1c ≥ 7%, 151 (95%) had an HbA1c ≥ 7% by the Quo-test POC and 8 (5%) HbA1c < 7%. Among the 58 participants with HbA1c <7, 4 (6.9%) had a Quo-test POC HbA1c ≥ 7% and 54 (93.1%) < 7%. Kappa test 0.862, P< 0.001 and the prevalence and bias adjusted Kappa (PABAK) = 0.889.

Table 39: The agreement of POC HbA1c and Lab HbA1c (Kappa) when HbA1c cut-off point is 7%

	Lab HbA1c		**Total**
	< 7%	**≥ 7%**	
POC HbA1c			
≥ 7**%**	4 (6.9%)	151 (95%)	155
< 7**%**	54 (93.1%)	8 (5%)	62

Total	58	159	217

Kappa = 0.862, p < 0.001

PABAK = 0.889

The Quo-test POC and the Tosoh reference test were only able to measure HbA1c levels in only 21 out of 41 participants with abnormal haemoglobin. Both tests failed to detect HbA1c levels in patients with HbF > 30%, which is likely due to the HPLC and boronate HbA1c results not being able to provide results when HbF is > 10-15%.

Figure 29 shows the agreement of the two tests in the 16 participants with results available. There is a clear difference with the results obtained for participants with normal haemoglobin, and individuals with abnormal haemoglobin. There are noticeable differences between the two test results if compared to different levels of HbF (figure 30).

Figure 29: POC/LAB agreement plot in people with abnormal haemoglobin

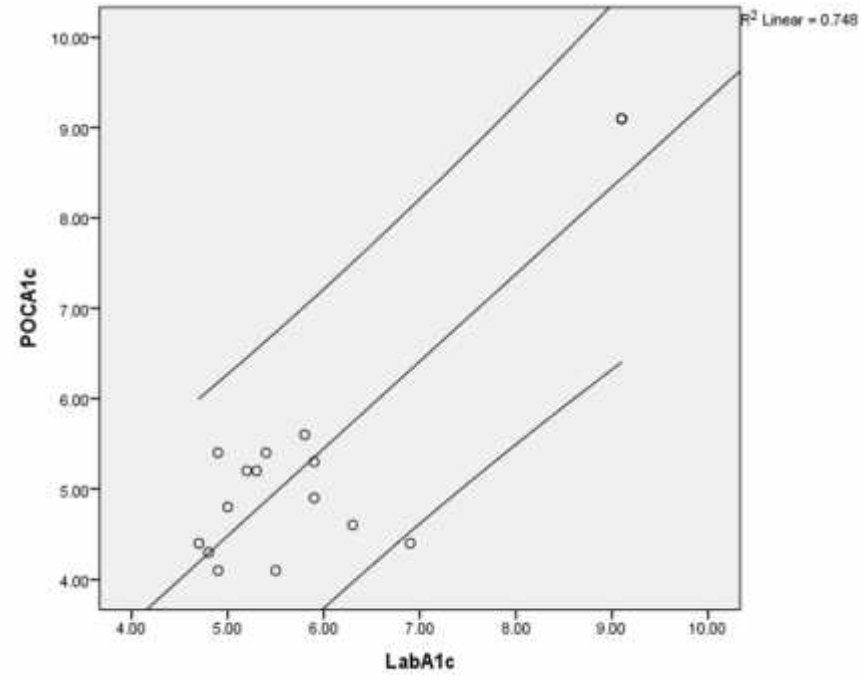
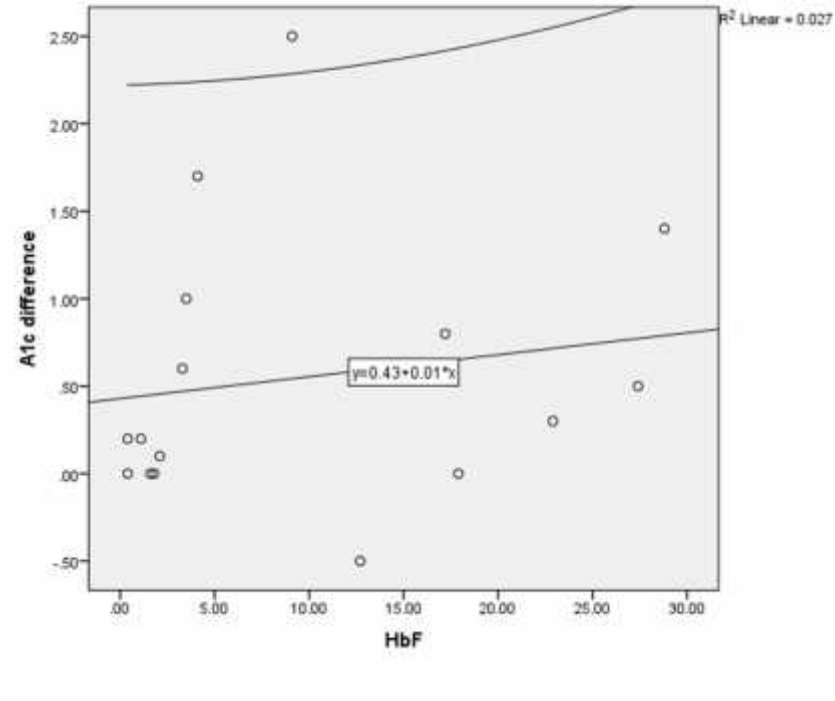


Figure 30: HbA1c difference (Lab-POC) plot according to HbF level



5: Discussion

Objectives 1 and 2

Diabetes mellitus is perhaps the most important non-communicable disease epidemic to hit the globe in the present century, with major public health implications and potential to increase the demand for health services. Kuwait and other countries in the Middle East face an especially grave problem, because the prevalence of T2DM is one of the highest in the world, despite these countries having significant differences in their economic status (Alsairafi et al., 2016). Approximately, 9.1% of adults in the EMRO region have T2DM, and 7.8% pre-diabetes (PDM) in 2015 (IDF, 2015) and Kuwait has one of the world's highest prevalence (Abuyassin and Laher, 2016) with an estimated T2DM prevalence among adults of 17.9% (Alarouj et al., 2013).

Prevalence of T2DM

The proportion of patients with T2DM in this study population was 29.6%. This percentage is much higher than the prevalence reported in national surveys, and it is likely reflecting the study setting, and the population included. Participants approaching a health care facility are usually less healthy than the general population and elderly, which it is likely to increase the prevalence of T2DM. For logistical reasons, it was not feasible to conduct a population survey for this study, as samples needed to be centrifuged and frozen within 2 hours of blood collection, and the time and resources available were limited. Despite this selection bias, our results are similar to those observed among patients attending primary care clinics in Saudi Arabia (Alqurashi et al., 2011). This cross-sectional study in Saudi Arabia reported a prevalence of T2DM of 30% among adults attending outpatient ambulatory clinics. In our study, 44 (10.9%) of 402 participants were new cases of T2DM who were unaware of their condition. This result is comparable to those reported by a cross-sectional study in a primary health care centre of the UAE (Saadi et al., 2010), where 14.6% of participants had been unaware of having T2DM. These results show the importance of

screening campaigns, and especially those targeting high-risk groups and individuals attending general ambulatory health services.

Our findings, therefore, identify T2DM as one of the leading causes of morbidity among adult populations attending health services in Kuwait. Although this high prevalence is often missed by routine health services, these metabolic changes are likely to result in a higher prevalence of the complications of T2DM and increased utilisation of services in the future.

Risk factors for T2DM

The so-called 'classical' risk factors continue to be the main factors associated with T2DM. The prevalence of obesity and hypertension and the processes of urbanisation and immigration have increased significantly during the past five decades in Kuwait. Furthermore, a sedentary lifestyle and weight gain are linked to the increasing prevalence of T2DM worldwide. All of these factors are likely to be significant contributors to the growing prevalence of T2DM in Kuwait (Serour et al., 2007, Al-Rasheedi, 2015).

Studies have shown that T2DM can be prevented by lifestyle changes that include a reduced caloric intake and increased physical activity and increased physical activity (Psaltopoulou et al., 2010). Programmes addressing sedentary and poor feeding lifestyles have been effective in reducing the progression of T2DM in individuals at high risk (Saaristo et al., 2010, Rautio et al., 2012), although the main limitation of these interventions is the lack of long-term adherence of participants (García-Pérez et al., 2013). The increasing prevalence of T2DM in Kuwait along with the higher complication and mortality rate of these patients requires an urgent assessment of how to address the risk factors that predispose individuals in Kuwait to T2DM to developed tailored interventions that are suitable for Kuwait's cultural background and climate. There is also an urgent need for healthcare providers to identify and treat modifiable risk factors, health organisations should develop and maintain programmes that focus on T2DM prevention.

T2DM is a multisystem disease. Hence, a good strategy requires the attention of other comorbidities (Munshi et al., 2016). This thesis highlights that obesity, hypertension, dyslipidaemia, and other factors are commonly associated with T2DM. In our study, the characteristics related to T2DM were hyperlipidaemia (high triglyceride) and hyper-lipoproteinemia (high LDL levels). These results resemble the results observed elsewhere in the world. For example, in an Indian study, the lipid profile of 150 patients with T2DM showed that hyperlipidaemia is significantly associated with an elevation in postprandial blood sugar (Dixit et al., 2014). Hyperlipidaemia is more frequent in patients with T2DM and is a primary contributor to the high-risk to cardiovascular disease. Epidemiologic studies have demonstrated that high concentrations of LDL and triglyceride, and low levels of HDL are major risk factors for CVD in patients with T2DM and are frequent comorbidities of T2DM (Leon and Maddox, 2015). Hypercholesterolemia is a well-recognised risk factor for atherosclerotic diseases, especially among individuals with T2DM (Stamler et al., 1993).

T2DM was once considered a disease of elderly populations. However the age at diagnosis of T2DM is decreasing, and it is now increasingly diagnosed in young adults to the extent that early onset may soon become the predominant form of the disease (Yu et al., 2016).

Our study showed that among the clinic population studies, there is an increase in the prevalence of T2DM with age, and all participants > 80 years old had T2DM. However, the burden of T2DM was also high among young adults, as a significant proportion of individuals in their 20s and 30s already had T2DM. Our study that T2DM in the age group of 18 to 29 was already detectable and this prevalence increased steadily after that. At the age of 60-69, the study population was 5.4 more likely to have T2DM, and this odd rose to 9.5 by 70 years of age.

In Kuwait, T2DM seems to start early, and public health programmes should promote effective lifestyle modifications including weight loss, implementation of

a healthy diet like the Mediterranean diet, together with an increase in the physical activity from an early age (Asif, 2014).

Impaired insulin production and its physiological effectiveness in elderly individuals versus young adults have also been reported (Du et al., 2014). Possible explanations for the reduced insulin effectiveness with ageing include hormonal changes, decreased physical activities, increased abdominal fat mass and mitochondrial dysfunction (Kalyani and Egan, 2013). Moreover, ageing is associated with chronic inflammatory cascades leading to endoplasmic reticulum stress leading to islet cell dysfunction contributing to decreasing insulin production and abnormal glucose metabolism (Park et al., 2014).

After adjusting for age, and ethnicity, our study showed that widowers were 6.1 times more likely to have T2DM than single individuals. Although age confounded this, the loss of a spouse has been associated with depressive symptoms, less physical activities, lower interest in health, increased risk of solitude and isolation from the community (Stroebe et al., 2007). Some studies have reported a higher prevalence of T2DM among widowed individuals compared to married individuals of comparable age (Cornelis et al., 2014). In 379 non-institutionalized men and women aged >70 years, T2DM was less prevalent among married participants compared to those widowed (Hiltunen, 2005). These finding can be linked to the fact that marriage provides a more stable environment, reduces loneliness and stress, and is linked to better health habits (Espinosa and Evans, 2008).

Our study shows that hypertension is also significantly associated with T2DM (OR= 1.95). T2DM and hypertension are two of the leading risk factors for atherosclerosis and its complications, including strokes and heart attacks. The Hong Kong Cardiovascular Risk Factor Prevalence Study showed that only 56% of people with hypertension are normoglycemic and only 42% of individuals with T2DM have normal blood pressure (Cheung, 2010). In the US, 30% of patients with T2DM have hypertension, and this prevalence is increased to between 50% and 80% of patients with T2DM (Landsberg and Molitch, 2004). A prospective US

cohort reported that T2DM was almost two times as likely to develop in subjects with hypertension as in subjects with normal blood pressure (Sampanis and Zamboulis, 2008). The link between these conditions is believed to be Insulin resistance. In the insulin-resistant state, there is inhibition of several insulin signalling pathways, thus contributing to vasoconstriction. Insulin inhibits the release of glucose from the liver, which in turn inhibits the release of the free fatty acids (FFAs) from adipose tissue. FFAs are believed to induce IR and increase the level of oxidative stress resulting in endothelial dysfunction and arterial intima and leading to hypertension (Cheung and Li, 2012). Intervention for the early detection of T2DM, therefore, should also screen for high blood pressure, and in turn, interventions for the detection of hypertension should check all patients with hypertension for T2DM.

Several indexes such as Waist Circumference, BMI, and WHR, are used to determine general and central obesity in clinical practice. Whereas BMI is the most commonly used parameter for evaluation of obesity, it is not the best measure to identify the body composition as well as regional body fat distribution because it is a marker of general obesity rather than central obesity (Rahman and Berenson, 2010).

The diagnosis of central (abdominal) obesity which correlates with the visceral accumulation of adipose tissue including fatty liver, and the development of subsequent metabolic abnormalities and cardiovascular morbidity is more important than BMI, especially for T2DM (Elbassuoni, 2013). Visceral fats are linked with lipolytic activity and reduce insulin activity through increasing fatty acids. Moreover, visceral fat accumulates macrophages that release inflammatory cytokines, which can impair insulin sensitivity, moreover, visceral fat is known to secretes adipokines that impair insulin sensitivity (Hardy et al., 2012).

Our study showed that males with a waist circumference ≥ 94 cm are 5.5 times more likely to have IR than participants with waist circumference < 94 cm and

males with waist circumference ≥ 102 cm are 5.4 times more likely to have IR than those with waist circumference < 102 cm. While females with waist circumference ≥ 88 cm were 6.4 times more likely to have IR than females with waist circumference < 88 cm.

Obesity is linked to many medical conditions, the most devastating of which may be T2DM. However, many obese individuals, despite being insulin resistant, do not develop T2DM. In these cases, it is likely that the pancreatic β cells of the islet of Langerhans are able to compensate the IR by releasing higher amounts of insulin to maintain normal glucose tolerance. As explained before, increased levels FFAs is the main factor causing IR, and eventually T2DM.

Physical activity improves glycaemic control and reduces the risk of CVD and mortality in patients with T2DM. Walking was the most common form of daily physical activity, with numerous studies demonstrating its beneficial effects on reducing the risk of T2DM. Furthermore, it improves glycaemic control, insulin sensitivity, and the incidence of obesity. Walking for at least 30 min per day five days a week was reduces the risk of T2DM by approximately 58% (Colberg et al., 2010, Hamasaki, 2016). Only 28.3% of T2DM had good physical activity (> 150 min/week), this is considered very low compared to 61.5% of European adults achieving the WHO physical activity recommendation (Marques et al., 2015).

Although ensuring that patients with T2DM participate in daily physical activity may be difficult, well-designed longitudinal studies that focus on daily physical activity in Kuwait should be conducted in the future.

Prevalence of IR

IR is very often a precursor of T2DM (Wilcox, 2005) and the most powerful predictor of the future development of T2DM. In addition to a high prevalence of T2DM, our study also found a high prevalence of IR.

IR prevalence is widely variable across geographical settings. European countries seem to have a lower prevalence of IR and, for example, it is estimated that 17%

of the Danish population had IR (Friedrich et al., 2012). In contrast, it has been reported that 39.1% of Americans of Hispanic descent have this condition (Qu et al., 2011). In the Middle East, an Iranian population study reported that the prevalence of IR was also high with 51% of participants having IR (Bermudez et al., 2016).

The proportion of participants with IR in our study population was 34.6%, and therefore the prevalence of IR was relatively high. This high prevalence is not unexpected, given the increasing prevalence of obesity and the increased consumption of fast foods and inactive living styles of the modern Kuwait population (Karageorgi et al., 2013).

IR was more prevalent early in life in males than females in our study. This can be explained by the results of an American study (Karakelides et al., 2010) which reported that insulin sensitivity was higher in young women. Males usually have more hepatic and visceral fat, whereas females have more subcutaneous or peripheral fat. These differences, as well as differences in sex hormones, may contribute to a higher IR in males than females (Geer and Shen, 2009).

IR is a contributor to the development of impaired glucose tolerance and T2DM. Several studies have suggested that IR exists before hyperglycaemia in nearly all T2DM patients and that hyperinsulinemia occurs before the presence of pathological abnormalities of IGT (Imamura et al., 2013, DeFronzo and Tripathy, 2009). Hyperinsulinemia and IR are harmful even in euglycemic subjects. For example, a fasting plasma insulin level of 39 μU/mL or greater is associated with a 31% increased risk of cardiovascular events in individuals without T2DM (Rubins et al., 2002). Similarly, in the Paris Prospective Study, people with no T2DM who had hyperinsulinemia were much more likely to experience atherosclerosis (Fontbonne and Eschwège, 1991). Similar to the association between hypertension and T2DM, IR is also observed in as many as 50% of individuals with high blood pressure. The oxidative stress-associated inflammation and

endothelial dysfunction of IR are both linked to an elevation of blood pressure and vascular dysfunction (Zhou et al., 2014).

These side effects might also be mediated by hypertriglyceridemia (Murguía-Romero et al., 2013) and because Insulin inhibits the hormone-sensitive lipase in the adipose tissue resulting in unrestrained lipolysis leading to an increased flux of fatty acids to the liver, which results in higher hepatic triglyceride production (Vergès, 2015).

Our study showed that the prevalence of PDM in the study population was 17.4%, a high percentage for most settings but comparable to the prevalence observed in neighbouring countries (Klautzer et al., 2014). A similar result was reported in a cross-sectional study in a primary health clinic in Saudi Arabia where the prevalence in adults was 17.6% (Turki et al., 2016). As for T2DM, the prevalence of PDM varies geographically. The WHO North America and Caribbean Region has a high prevalence of impaired glucose tolerance (15.0%), while the WHO European Region has a lower prevalence of 4.8%. The estimated global prevalence of PDM is 6.7% (IDF, 2015).

Prevalence of metabolic syndrome

The global prevalence of MS differs depending on sociodemographic factors, as well as the diagnostic criteria used. European MS prevalence has been estimated as 41% in men and 38% in women using IDF diagnostic criteria (McCracken et al., 2018). Our study showed a prevalence of 26.4% in males, and 44.6% in females.

A previous study in Kuwait showed a prevalence of 41.7% in males and 40.1% in males according to IDF criteria (Al Zenki et al., 2012).

IR and PDM risk factors

Insulin sensitivity is also determined by a critical factor, which is body fat distribution and is therefore associated with body mass (Patel and Abate, 2013, Kranendonk et al., 2015). Insulin sensitivity differs substantially even in

individuals with normal weight because of their differences in body fat distribution. Individuals whose fat distribution is more central have more IR than individuals whose fat distribution is peripheral (Al-Goblan et al., 2014, Hayashi et al., 2008).

Our results showed that 32.9% of the participants were obese. This figure is very high and is greater than in other cities. For example, 29.5% of clinic attendees in north-east European cities, 21.9% in northern Mediterranean cities, and 20.1% in north-west European cities were obese (Han et al., 2017).

Our study also found that IR was significantly associated with the presence of low HDL concentrations (OR= 1.96, 95% CI 1.12-3.42). Low levels of HDL have been associated with impaired insulin action. In population-based studies, measures of insulin action correlate negatively with HDL (D'Agostino et al., 2004). The presence of IR results in enhanced cholesterol esters transfers from HDL to triglyceride-rich lipoproteins and in reciprocal triglyceride transfer, producing triglyceride-enriched HDL. The delayed clearance of triglyceride-rich lipoproteins leads to reduced HDL concentrations (Vergès, 2015). It appears that hepatic IR reduces HDL by either decreasing HDL production or promoting a shift of HDL to non-HDL lipoproteins (Perry et al., 2014).

Moreover, our study showed that overweight participants were 8.3 times more likely to have IR. Participants with obesity class I were 18.3 times more likely to have IR, and participants with obesity class II were 88 times more liable to have IR than individuals with normal weight.

Unexpectedly, while IR was significantly associated with BMI, T2DM was not. These results echo the results of a recent cohort study in Japan, involving 3,083 adult participants over four years, which reported that a high BMI was associated with IR and that most participants with high BMI who developed T2DM had IR, but that participants with normal BMI who develop T2DM mainly through β cell dysfunction (Tatsumi et al., 2015). However, this is unlikely to be the main reason for the lack of association between BMI and IR. A major limitation of our study is

its cross-sectional design. It is likely that we missed this early stage as a high proportion of participants already had T2DM, and most of these individuals had experienced a phase of IR in the years before the study. A further explanation of the lack of association of BMI and T2DM was the poor glucose control in many cases. Individuals with poor glycaemic control often lose body mass and may become cachectic due to their metabolic derangement. Our study, therefore, needs to be followed by prospective cohort studies to test whether this lack of association is true, or an artefact of the study design used here.

Although the diet assessment in this study had many limitations, participants consuming sugar-sweetened drinks were more likely to have IR. Data from the Study on Nutrition and Cardiovascular Risk in Spain involving 7842 participants revealed that drinking sugar-sweetened beverages is positively related to IR. However, although the consumption of sweeteners has been shown to modify glucose metabolism, individuals with IR may have modified their behaviours because of their obesity and the causal association between these two factors is debatable.

Although this study component has identified some significant results, there are significant limitations to our data that require discussion to contextualise the findings.

Firstly, the study to identify risk factors used a case-control design. Case-control studies are analytical, descriptive studies, which are efficient to identify the characteristics of the participants with a higher or lower frequency among cases than controls. Although these studies are efficient to identify multiple risk factors, and to examine their likely statistical interactions, they are unable to establish causality. The risk factors identified in this thesis, therefore, may be markers of the disease, which may not be necessarily in the causal pathway (or the “cause”) of IR or T2DM. Our findings therefore merely indicate that their presence was statistically more (or less) frequent among the cases than the controls.

A further limitation of the study design was the systematic sampling. This method selects individuals by identifying every (X^{th}) number of patients attending a clinic or study setting. Although this sampling method has the advantage of being easy to implement than a random selection, it is also more prone to selection bias. For example, in a busy clinic, it is likely that waiting patients are not in a queue, that healthier individuals may be sent to the back of the queue, prioritising some population groups (e.g. elderly or very young patients and those who are frail or may have contagious illnesses). The enumerator may also subjectively recruit patients whom he/she knows are more likely to accept to participate. These potential biases, therefore, may have resulted in selection bias and increased or decreased the prevalence of the diseases we were investigating.

The study was also based in a health centre, and cases and controls were selected among patients attending the clinic. Controls are defined as individuals without the outcome of interest (in this case DM or IR), and these are usually selected among individuals from the same reference population. It is often a difficult decision whether to select cases from the same clinical setting as the cases or in another setting (e.g. in the community). In our study, we decided we would define cases at the time of the statistical analysis (by conducting several tests and identifying those who fulfilled the case definition). Controls, therefore, were patients attending the clinic and therefore had multiple reasons for attending the clinic (follow up appointments, chronic conditions). These types of controls have been shown to have poorer health than the general population (e.g. more likely to be smokers and to have poorer lifestyles) which would mask differences between cases and a healthy (general population) and thus result in ascertainment bias.

We recruited 402 participants from whom we obtained most information. However, only 173 participants agreed to be measured to obtain their anthropometric measures. This was expected given the cultural context and the norm in this population. However, the lack of anthropometric data for more than half of the population, and in particular for women reduces the power of the

study to examine the association of IR, PDM and T2DM with overweight and obesity.

The smaller sample size would increase in an increased risk of type I and II errors, which means the incorrect rejection of a true null hypothesis (a "false positive" finding), or incorrectly retaining a false null hypothesis (a "false negative" finding), respectively. Therefore, some of the associations reported as statistical significant may be spurious, and some other potential associations may have been missed due to the small sample size of the sub-set. Furthermore, the likelihood of participation is also likely to be associated with the awareness and perception of the diseases, potential fear of stigmatisation, resulting in further selection bias.

Another limitation was the limited information obtained by the physical activity and dietary questionnaire. The questions only included self-reported data and were conducted in the outpatient clinics. It is thus likely the data contains substantial recall bias, as there might be significant recalling difficulties remembering a 7-day diet, participants may try to exaggerate their physical activities exclude harmful nutritional habits and minimise portions to please or impress the interviewer.

Objective 3

Prevalence of IR in first-degree relatives of T2DM patients

As indicated in previous sections, in IR, skeletal muscles and liver tissues do not respond properly to insulin and consequently cannot easily absorb glucose from the bloodstream. Thus, the body needs higher levels of insulin to help glucose enter the cells. The β cells in the islets of Langerhans try to keep up with this increased demand for insulin by producing more. As long as the β cells can produce enough insulin to overcome the insulin resistance, blood glucose levels stay in the normal range. Over time, IR can lead to PDM and T2DM due to exhaustion of the β cells and their inability to keep pace with the body's increased need for insulin (Cerf, 2013).

Several studies outside Kuwait have reported that first-degree relatives of individuals with T2DM are more likely to have impaired mitochondrial function, with mitochondrial adenosine triphosphate (ATP) synthesis being reduced by approximately 30%. These reductions in mitochondrial function are associated with severe muscle IR (Petersen and Shulman, 2006). Our findings demonstrate that in this population with a high level of T2DM, the prevalence of IR in first-degree relatives of T2DM was also very high, reaching 32.8%. A similar high prevalence was observed in India, a country that also has a high prevalence of T2DM, were 37.8% of first-degree relatives of individuals with T2DM had IR (Kumar et al., 2005). Although this is alarmingly high, both IR and T2DM need to be considered together as Our study showed that the prevalence of PDM in first-degree relatives of individuals with T2DM was 20.4%, a recent Chinese study recruiting 1544 first-degree relatives of T2DM showed 27.4% had PDM (Zheng et al., 2016).

Our study also indicates that 29.1% of participants had an undiagnosed problem of T2DM. Our study also shows that the prevalence of PDM in first-degree relatives was 20.4%. Although IR and pre-T2DM overlap considerably, this means that 61.9% of first degree relatives had either IR/PDM or T2DM. Although some

of these relatives may have been aware of their diagnosis and were in denial, they were not receiving medications and were likely poorly controlled.

A recent Chinese study recruiting 1544 first-degree relatives of T2DM showed that 27.4% had PDM (Zheng et al., 2016). Furthermore, a further Chinese study, recruiting 2306 adults reported a prevalence of T2DM of 26.6% in first degree relatives (Hong Ma et al., 2011), and a further Chinese study showed a prevalence of undiagnosed T2DM of 30% (Zheng et al., 2016) and therefore our findings are unusual but similar to studies reported in other locations with high prevalence of T2DM.

Risk factors for IR and T2DM in first-degree relatives of T2DM

The vast majority of participants labelled as labourers (or manual workers) were professional drivers or housemaids. Our study showed that individuals in this category had a higher prevalence of IR (OR=3.6). Studies in other countries have reported that both professions are linked with a high risk of T2DM. A cross-sectional study in Iran recruiting 1903 professional drivers showed that 43% of them had preT2DM and 9.1 % had T2DM (Izadi et al., 2013). A cross-sectional study in the UAE of 599 migrant women reported that 18.6% of housemaids had PDM (Shah et al., 2017) and thus our findings are in agreement with these studies.

Our findings show that T2DM increased significantly with age among first-degree relatives is not surprising. Participants aged 60-69 had an AOR of 8.4 for having T2DM; this ratio rose to 13.5 in participants > 70 years old. These results are consistent with the literature worldwide. In the Middle East, an Iranian study reported a significant relationship between age and T2DM in individuals first degree related to T2DM patients (Adibi et al., 2007).

In conclusion, this study highlights the increasing prevalence of IR and T2DM in first degree relatives of patients with a history of T2DM, and it is imperative to screen for T2DM and IR all first-degree relatives of patients with T2DM.

Moreover, there is a high risk of T2Dm and IR among labourers (especially drivers and housemaids), specific interventions could be targeted to these high-risk groups to intervene and modify their lifestyles and risk profile.

This study component also has several limitations that are similar to those discussed in chapters 1 and 2. In addition, although the euglycemic clamp method is considered the gold standard method for assessing IR; however, because this is an invasive and labour-intensive method, and we used the HOMA2-IR as a simple, minimally invasive method that has been demonstrated as a useful tool for epidemiological studies. However, there is no data on the performance of the HOMA-IR in Kuwait. Furthermore, although we tried to select a representative sample of first degree relatives, it is possible that individuals who felt unwell or whose relatives had more severe T2DM were more likely to participate, resulting in selection bias. Furthermore, we had to ask individuals with T2DM attending the clinic to ask their relatives to come and participate in the study. This may have led to the selection of a member of the family suspected to have T2DM to take part in the study.

On the other side, our study has a strong point. Studies using insulin levels and Homa2-IR calculations are costly and uncommon in the literature outside industrialised settings. Our study is the first in Kuwait to identify the prevalence IR using Homa2-IR in a general clinic population.

Objective 4

T2DM is a complex disease with many complications and comorbidities. T2DM is a metabolic disease that concerns not just the control or treatment of high blood sugar levels but also lifestyle changes and lifelong care regarding self-management and medical care. The aim of proper T2DM management is managing hyperglycaemia, prevention and treatment of acute and chronic micro and macrovascular complications and addressing comorbid diseases such as hypertension and dyslipidemias. Ideally, glucose homeostasis should frequently be monitored, but this is often difficult in settings where the population is less aware of the importance of glucose control and not used for intensive monitoring. A patient's glycaemic control over the preceding 8 to 12 weeks can also be measured by the regular measurement of HbA1c in patients with normal haemoglobin levels. The frequency of this monitoring depends on the clinician's decision, and local treatment guidelines and a HbA1c target level of < 7.0 % is desirable (Araki et al., 2017).

The care of an individual with T2DM requires many aspects of the disease to be managed by a team of professionals so that a decrease in morbidity and mortality may be achieved. T2DM care has moved from hyperglycaemia and dyslipidemias-focused management to a wider plan. All people with T2DM should, if possible, undergo a comprehensive T2DM evaluation at initial presentation.

The lipids measured should include LDL, HDL, and triglyceride.

In individuals with T2DM, levels of HDL, LDL and triglyceride should be measured at the time of initial diagnosis, and screening is recommended annually. Testing may be done every two years if patients have low risk values (LDL < 2.6 mmol/l, HDL > 1.2 mg/dl and triglyceride < 1.7 mg/dl) (Rana et al., 2015).

Prevalence of good glycaemic control

The prevalence of good glycaemic control (defined as an HbA1c <7.0) in our study population was 30.1%. Although this may seem remarkably low, this result is

similar to studies in other settings. An Iranian study of 500 patients with T2DM revealed that only 29.4% had good glycaemic control (Yousefzadeh et al., 2015). However, these results are much lower than those found in the developed world. A study in Germany investigating changes in T2DM care indicators over the period 2008-2011 reported that 65.4% achieved good glycaemic control (Du et al., 2015).

Our findings, therefore, indicate that the degree of glucose control among patients with T2DM in a clinic population in Kuwait was poor and clinical services need to implement interventions to improve its management.

A major limitation of this finding is that the questionnaire did not include some key variables that could explain in more detail the reasons for poor control among the patients. This was due to 'poor control' being defined retrospectively, and we did not follow these patients with further interviews to gain more detail insights of the reasons for the poor control. The findings of this chapter, therefore, need to be interpreted with caution and should be complemented by further qualitative studies to develop case studies, in-depth interviews of individuals with poor control and clinical staff etc.

Participants were also selected at the time they decided to attend the clinic and thus it is likely some of them had come to the service because they perceived their T2DM was poorly controlled. If this were the case and patients with poor control attended the clinic less frequently, our findings would overrepresent the proportion of all T2DM registered in the clinic with poor control.

Risk factors for poor glycaemic control

Our study demonstrated that triglyceride is related to poor glycaemic control (OR=2.2). The mean triglyceride (SD) in participants with HbA1c ≤ 7.0 was 1.48 (0.66) mmol/l while the mean triglyceride (SD) in participants with HbA1c ≥ 7.0 was 1.80 (0.84) mmol/l. Among participants with HbA1c ≤ 7.0, 28.2% had triglyceride ≥ 1.7 mmol/l compared to 46.8% of participants with HbA1c ≥ 7.0.

These findings coincide with the results of an Ethiopian cohort study of 165 individuals with T2DM which reported a significant relationship between high triglyceride and poor glycaemic control (Mullugeta et al., 2012).

Smoking was significantly related to poor glycaemic control (OR=4.1), cigarette smoking is known to be associated with increased prevalence of T2DM (Chang, 2012). Men smoking ≥ two packs per day at baseline had 45% increase in T2DM prevalence than non-smokers individuals, and a 74 % increase in women compared to women who never smoked (Bolego et al., 2002). The effect of stopping smoking is dependent on age, the amount of tobacco use and weight changes after quitting smoking (Stein et al., 2014).

Our study showed that participants with T2DM for more than ten years were four times more likely to have poor glycaemic control than participants with and illness < ten years' duration. Similar results were reported in Sudan, where a significantly high proportion of poor glycaemic control was observed in patients with T2DM for more than two decades (OR=4) (Kamuhabwa and Charles, 2014). Furthermore, a Jordanian study showed that patients who had the disease for more than seven years were two times more likely to have poor glycaemic control (Khattab et al., 2010).

In conclusion, a high proportion of patients with T2DM attending Nuzha clinic had poor glycaemic control. Patients may benefit from better education and awareness of the disease and its complications and more frequent annual lipid profile testing, annual retinography, annual T2DM education sessions, referral to a dietitian, and physical education.

There are limitations to this study of risk factors associated with the cross-sectional model, which may interfere with causal evaluations; however, there was sufficient information to observe associations and ORs for the data.

Self-reported data usually are difficult to be independently verified. We had to take what participants say. Self-reported data can contain several potential

sources of bias. As explained in previous sections for patients attending the clinics, our questionnaire included questions about the nutritional habits and physical activities and those limitations also apply here.

Objective 5

The ADA considers glycaemic control as one of the important strategies for the management of T2DM, and HbA1c is the best measure of glycaemic levels over the previous 12 weeks. Lowering HbA1c to ≤ 7.0% has been shown to reduce macro and microvascular complications of T2DM if implemented soon after the diagnosis. The ADA recommends a goal of HbA1c < 7.0% for people with T2DM (ADA, 2016).

Despite the guidelines being available and the robustness of evidence about microvascular and macrovascular complications due to hyperglycaemia, the clinical goals for T2DM control are not usually achieved. In almost all T2DM clinics, only a fraction of individuals with T2DM achieve the therapeutic targets.

Typically, individuals with T2DM are monitored for HbA1c every three to six months (CADTH, 2014). This generally requires a visit to the laboratory, involving a nurse or phlebotomist for venepuncture, with a follow-up appointment two weeks later in the clinic to discuss the results with the treating physician once they are available from the laboratory.

As this is time-consuming, the need for employing HbA1c POC tests for T2DM monitoring is increasing. POC tests for HbA1c are more practical for the patients, the HbA1c level can be checked immediately, and the relevant prescription changes and modifications in management can be made in one visit.

Furthermore, enabling immediate treatment decisions may result in better diabetic control, improved outcomes, fewer patient visits to the clinic, and reduction of costs.

Several studies have shown that immediate feedback of results to patients, has a significant association with reductions in HbA1c levels (Plüddemann et al., 2011).

Performance of the Quo-Test against the gold standard test

We, therefore, evaluated the Quo-test POC device against the local HbA1c reference standard, a Tosoh G8 assay. The device was tested using two cutoffs (7.0% and 9.0%) as these are commonly used to determine glycaemic control status.

When the HbA1c cut-off is was 9%, the agreement was excellent, with a Kappa agreement test of 0.871 and adjusted Kappa (PABAK) = 0.899. Similar results were observed when using the HbA1c cut-off of 7.0%, as the agreement was excellent, the Kappa test was 0.862, and the adjusted Kappa (PABAK) was 0.889. To our knowledge, no one has conducted a similar study in Kuwait.

The linear correlation showed a very high positive association between the results of the POC device and the reference test results, with an $r^2 = 0.935$. A systematic review of five observational studies of devices approved by the ADA including the Bayer's A1cNow+, Bio-Rad's In2it, and Siemens' DCA Vantage showed a positive correlation between POC HbA1c testing and the laboratory reference HbA1c ($r^2 = 0.967$) (Health Quality, 2014).

The Bland- Altman plot showed no significant differences between the results of the Quo-test and the reference test in our study, with a mean difference between the quo-test and the Tosoh G8 of 6%, another similar study showed a difference of 10% between the Bio-Rad In2it and Cobas, and 5% between DCA 2000 and the Variant II (Yeo et al., 2009).

The coefficient of variation in our study was 2.1%. Although the NGSP has not set forth goals for precision and accuracy, it recommends a CV <3% (preferably <2%). Comparatively, the ADA recommends a CV <4%, and ideally <3% (Whitley et al., 2015). In conclusion, the POC device performed well within a clinic environment, and the results are available immediately. The results have the potential to improve patients' management, and further prospective studies are needed to assess this potential.

6: Recommendations

As a researcher, I wish to maximise the impact of my study convincing the policymakers that a new policy or a different approach is valuable and should be introduced in the national strategy combating the epidemic of T2DM.

According to the results of the study, the burden of T2DM in Kuwait is huge, and keeping this in mind; we need a specific strategy to prevent the disease and delay its complications.

Patients attending ambulatory services in Kuwait have a high prevalence of T2DM and its precursor stages of pre-diabetes and insulin resistance. The magnitude of these conditions has enormous public health implications and will increase health service utilization and decrease the quality of life of the country's population. It is therefore recommended that Kuwait declares T2DM prevention and control a top priority for national health programming and intervention research. Initiatives should encourage the population to adopt healthier lifestyles, including promoting awareness and encouraging physical activities and weight control. Key at-risk populations need to be prioritised. These include first degree relatives of T2DM, people > 40 years old, individuals with BMI > 25 and people with hypertension, and hyperlipidaemia. Such initiatives on preventing T2DM should be monitored and evaluated continuously.

The country should consider conducting community-based surveys at the household level, detecting undiagnosed T2DM. Research is also needed to, investigate risk factors for hyperglycaemia and high prevalence of obesity as well as the acceptability and barriers to adopting healthier lifestyles, approaches to encourage physical inactivity within Kuwait adverse weather environment. Such data could help to justify the need for the development of specific interventions, as well as national programs and guidelines to achieve significant reductions in T2DM levels in the population of Kuwait.

In individuals with T2DM, an educational program that emphasises changes towards a healthier lifestyle and proper diet regime, especially in patients with longer duration of T2DM may improve the glycaemic control. The use of an NGSP certified HbA1c POC device is more convenient for patients and healthcare providers, and provide opportunities for prompt therapy modification, and may increase the chances to improve glycaemic control.

Interventions at a macro level that go beyond personal decisions are also needed. It is likely interventions will require multi-disciplinary approaches to ensure interventions are appealing, acceptable and efficacious. Areas such as legislation and urban planning will likely have a longer-term effect than the promotion of individual diets and lifestyles alone. The country, therefore, should consider the development of legislation to reduce the location, advertising and opening hours of fast food providers; request them to reduce the size and calorie content of their foods and to increase the availability of healthier options. The Government should consider increasing the price of caloric foods and drinks, as successfully introduced in other countries. In addition, urban planning could promote the increase of sports facilities, consider unusual approaches such as developing cycling and jogging routes that are shaded and educators and employers should create opportunities for physical activity in schools and at work. If the government fails to take notice of the epidemic, the sad alternative will be to increase the number of health facilities that deal with the chronic complications of T2DM, such as amputations, blindness and early death.

Future research questions

This thesis has highlighted that DM and IR are very frequent among adults attending a major primary health care clinic in Kuwait and the characteristic associated with these conditions. We propose the following research questions for future studies in the country:

a. Conduct a systematic review of interventions that are effective for the control of IR, MS and DM in cultural and economic contexts similar to Kuwait.

b. Explore the acceptability in Kuwait of interventions known to be effective for the prevention of IR and DM in other contexts and the adaptations that are necessary to increase their adoption.

c. Conduct further studies tounderstand bettr the poor glycaemic control attained by a large proportion of patients attending the diabetic clinic and test whether quality improvement interventions lead to better control.

d. Consider the possibility of implementing large-scale population interventions to explore the efficacy of different approaches to the control of IR, DM and to reduce the risk of IR progressing to a full DM.

e. Explore whether the provision of POC rapid diagnostics for HbA1c leads to better clinical management.

f. Consider whether a repeat and representative national survey is needed to assess the full extent of the problem in Kuwait.

References

ABUYASSIN, B. & LAHER, I. 2016. Diabetes epidemic sweeping the Arab world. *World Journal of Diabetes,* 7**,** 165-174.

ACTON, K. J., RÍOS BURROWS, N., MOORE, K., QUEREC, L., GEISS, L. S. & ENGELGAU, M. M. 2002. Trends in Diabetes Prevalence Among American Indian and Alaska Native Children, Adolescents, and Young Adults. *American Journal of Public Health,* 92**,** 1485-1490.

ADA 2013. Economic Costs of Diabetes in the U.S. in 2012. *Diabetes Care,* 36**,** 1033-1046.

ADA 2016. 5. Glycemic Targets. *Diabetes Care,* 39**,** S39-S46.

ADA, A. D. A. 2015. 2. Classification and Diagnosis of Diabetes. *Diabetes Care,* 38**,** S8-S16.

ADIBI, A., JANGHORBANI, M., SHAYGANFAR, S. & AMINI, M. 2007. First-Degree Relatives of Patients with Type 2 Diabetes Mellitus and Risk of Non-Alcoholic Fatty Liver Disease. *The Review of Diabetic Studies : RDS,* 4**,** 236-241.

AHMED, F., WASLIEN, C., AL-SUMAIE, M. A., PRAKASH, P. & ALLAFI, A. 2013. Trends and risk factors of hyperglycemia and diabetes among Kuwaiti adults: National Nutrition Surveillance Data from 2002 to 2009. *BMC Public Health,* 13**,** 103-103.

AL-GOBLAN, A. S., AL-ALFI, M. A. & KHAN, M. Z. 2014. Mechanism linking diabetes mellitus and obesity. *Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy,* 7**,** 587-591.

AL-HUSSAINI, M. & MUSTAFA, S. 2016. Adolescents' knowledge and awareness of diabetes mellitus in Kuwait. *Alexandria Journal of Medicine,* 52**,** 61-66.

AL-MAWALI, A. 2015. Non-Communicable Diseases: Shining a Light on Cardiovascular Disease, Oman's Biggest Killer. *Oman Medical Journal,* 30**,** 227-228.

AL-MOOSA, S., ALLIN, S., JEMIAI, N., AL-LAWATI, J. & MOSSIALOS, E. 2006. Diabetes and urbanization in the Omani population: an analysis of national survey data. *Population Health Metrics,* 4**,** 5.

AL-RASHEEDI, A. A. 2015. Glycemic Control among Patients with Type 2 Diabetes Mellitus in Countries of Arabic Gulf. *International Journal of Health Sciences,* 9**,** 345-350.

AL-RUBEAAN, K. 2015. National surveillance for type 1, type 2 diabetes and prediabetes among children and adolescents: a population-based study (SAUDI-DM). *Journal of Epidemiology and Community Health*.

AL ZENKI, S., AL OMIRAH, H., AL HOOTI, S., AL HAMAD, N., JACKSON, R. T., RAO, A., AL JAHMAH, N., AL OBAID, I., AL GHANIM, J., AL SOMAIE, M., ZAGHLOUL, S. & AL OTHMAN, A. 2012. High prevalence of metabolic syndrome among Kuwaiti adults--a wake-up call for public health intervention. *Int J Environ Res Public Health,* 9**,** 1984-96.

ALAROUJ, M., BENNAKHI, A., ALNESEF, Y., SHARIFI, M. & ELKUM, N. 2013. Diabetes and associated cardiovascular risk factors in the State of Kuwait: the first national survey. *Int J Clin Pract,* 67**,** 89-96.

ALHYAS, L., MCKAY, A. & MAJEED, A. 2012. Prevalence of Type 2 Diabetes in the States of The Co-Operation Council for the Arab States of the Gulf: A Systematic Review. *PLOS ONE,* 7**,** e40948.

ALQURASHI, K. A., ALJABRI, K. S. & BOKHARI, S. A. 2011. Prevalence of diabetes mellitus in a Saudi community. *Annals of Saudi Medicine,* 31**,** 19-23.

ALSAIRAFI, Z. K., TAYLOR, K. M. G., SMITH, F. J. & ALATTAR, A. T. 2016. Patients' management of type 2 diabetes in Middle Eastern countries: review of studies. *Patient preference and adherence,* 10**,** 1051-1062.

AMERICAN DIABETES, A. 2013. Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care,* 36**,** S67-S74.

AMERICAN DIABETES, A. A. 2009. Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care,* 32**,** S62-S67.

AMERICAN DIABETES, A. A. 2010. Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care,* 33**,** S62-S69.

AMREIN, K., RIBITSCH, W., OTTO, R., WORM, H. C. & STAUBER, R. E. 2011. Severe lactic acidosis reversed by thiamine within 24 hours. *Critical Care,* 15**,** 457-457.

ANJANA, R. M., SHANTHI RANI, C. S., DEEPA, M., PRADEEPA, R., SUDHA, V., DIVYA NAIR, H., LAKSHMIPRIYA, N., SUBHASHINI, S., BINU, V. S., UNNIKRISHNAN, R. & MOHAN, V. 2015. Incidence of Diabetes and Prediabetes and Predictors of Progression Among Asian Indians: 10-Year Follow-up of the Chennai Urban Rural Epidemiology Study (CURES). *Diabetes Care,* 38**,** 1441-1448.

AOYAMA-SASABE, S., FUKUSHIMA, M., XIN, X., TANIGUCHI, A., NAKAI, Y., MITSUI, R., TAKAHASHI, Y., TSUJI, H., YABE, D., YASUDA, K., KUROSE, T., INAGAKI, N. & SEINO, Y. 2016. Insulin Secretory Defect and Insulin Resistance in Isolated Impaired Fasting Glucose and Isolated Impaired Glucose Tolerance. *Journal of Diabetes Research,* 2016**,** 8.

ARAKI, E., HANEDA, M., KASUGA, M., NISHIKAWA, T., KONDO, T., UEKI, K. & KADOWAKI, T. 2017. New glycemic targets for patients with diabetes from the Japan Diabetes Society. *Journal of Diabetes Investigation,* 8**,** 123-125.

ARBOIX, A., RIVAS, A., GARCÍA-EROLES, L., DE MARCOS, L., MASSONS, J. & OLIVERES, M. 2005. Cerebral infarction in diabetes: Clinical pattern, stroke subtypes, and predictors of in-hospital mortality. *BMC Neurology,* 5**,** 9-9.

ARNOLD, S. V., STOLKER, J. M., LIPSKA, K. J., JONES, P. G., SPERTUS, J. A., MCGUIRE, D. K., INZUCCHI, S. E., GOYAL, A., MADDOX, T. M., LIND, M., GUMBER, D., SHORE, S. & KOSIBOROD, M. 2015. Recognition of Incident Diabetes Mellitus During an Acute

Myocardial Infarction. *Circulation: Cardiovascular Quality and Outcomes,* 8**,** 260-267.

ASIF, M. 2014. The prevention and control the type-2 diabetes by changing lifestyle and dietary pattern. *Journal of Education and Health Promotion,* 3**,** 1.

ASMAT, U., ABAD, K. & ISMAIL, K. 2016. Diabetes mellitus and oxidative stress—A concise review. *Saudi Pharmaceutical Journal*.

AT-TWAIJRI, M. I. & AL-MUHAIZA, I. A. 1996. Hofstede's cultural dimensions in the GCC countries: An empirical investigation. *International Journal of Value-Based Management,* 9**,** 121-131.

BADIMON, L., PADRÓ, T. & VILAHUR, G. 2012. Atherosclerosis, platelets and thrombosis in acute ischaemic heart disease. *European Heart Journal. Acute Cardiovascular Care,* 1**,** 60-74.

BAESHEN, N. A., BAESHEN, M. N., SHEIKH, A., BORA, R. S., AHMED, M. M. M., RAMADAN, H. A. I., SAINI, K. S. & REDWAN, E. M. 2014. Cell factories for insulin production. *Microbial Cell Factories,* 13**,** 141.

BAKKER, L. E., SLEDDERING, M. A., SCHOONES, J. W., MEINDERS, A. E. & JAZET, I. M. 2013. Pathogenesis of type 2 diabetes in South Asians. *Eur J Endocrinol,* 169**,** R99-r114.

BANDYOPADHYAY, G. K., YU, J. G., OFRECIO, J. & OLEFSKY, J. M. 2005. Increased p85/55/50 expression and decreased phosphotidylinositol 3-kinase activity in insulin-resistant human skeletal muscle. *Diabetes,* 54**,** 2351-9.

BANSAL, N. 2015. Prediabetes diagnosis and treatment: A review. *World Journal of Diabetes,* 6**,** 296-303.

BARR, E. L. M., ZIMMET, P. Z., WELBORN, T. A., JOLLEY, D., MAGLIANO, D. J., DUNSTAN, D. W., CAMERON, A. J., DWYER, T., TAYLOR, H. R., TONKIN, A. M., WONG, T. Y., MCNEIL, J. & SHAW, J. E. 2007. Risk of Cardiovascular and All-Cause Mortality in Individuals With Diabetes Mellitus, Impaired Fasting Glucose, and Impaired Glucose Tolerance: The Australian Diabetes, Obesity, and Lifestyle Study (AusDiab). *Circulation,* 116**,** 151-157.

BEALE, E. G. 2013. Insulin Signaling And Insulin Resistance. *Journal of investigative medicine : the official publication of the American Federation for Clinical Research,* 61**,** 11-14.

BERG, J. P. 2013. HbA1c as a diagnostic tool in diabetes mellitus. *Norsk Epidemiologi,* 23**,** 5-8.

BERM, #XFA, DEZ, V., ROJAS, J., MART, #XED, NEZ, M., #XED, SOF, A., #XED, APRUZZESE, V., CH, #XE1, VEZ-CASTILLO, M., GONZALEZ, R., TORRES, Y., #XED, SALAZAR, J., BELLO, L., #XF1, EZ, R., CHAC, #XED, N, M., TOLEDO, A., CABRERA, M., MENGUAL, E., #XC1, VILA, R., PACHANO, F., #XF3, PEZ-MIRANDA, J. & #XE9 2014. Epidemiologic Behavior and Estimation of an Optimal Cut-Off Point for Homeostasis Model Assessment-2 Insulin Resistance: A Report from a Venezuelan Population. *International Scholarly Research Notices,* 2014**,** 10.

BERMUDEZ, V., SALAZAR, J., MARTÍNEZ, M. S., CHÁVEZ-CASTILLO, M., OLIVAR, L. C., CALVO, M. J., PALMAR, J., BAUTISTA, J., RAMOS, E., CABRERA, M., PACHANO, F. & ROJAS, J. 2016. Prevalence and Associated Factors of Insulin Resistance in Adults from Maracaibo City, Venezuela. *Advances in Preventive Medicine,* 2016**,** 9405105.

BHUROSY, T. & JEEWON, R. 2014. Overweight and Obesity Epidemic in Developing Countries: A Problem with Diet, Physical Activity, or Socioeconomic Status? *The Scientific World Journal,* 2014**,** 7.

BOLEGO, C., POLI, A. & PAOLETTI, R. 2002. Smoking and gender. *Cardiovascular Research,* 53**,** 568-576.

BONONI, A., AGNOLETTO, C., DE MARCHI, E., MARCHI, S., PATERGNANI, S., BONORA, M., GIORGI, C., MISSIROLI, S., POLETTI, F., RIMESSI, A. & PINTON, P. 2011. Protein Kinases and Phosphatases in the Control of Cell Fate. *Enzyme Research,* 2011**,** 26.

BONORA, E. & TUOMILEHTO, J. 2011. The Pros and Cons of Diagnosing Diabetes With A1C. *Diabetes Care,* 34**,** S184-S190.

BOODAI, S. A., CHERRY, L. M., SATTAR, N. A. & REILLY, J. J. 2014. Prevalence of cardiometabolic risk factors and metabolic syndrome in obese Kuwaiti adolescents. *Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy,* 7**,** 505-511.

BORAH, M. & GOSWAMI, R. 2017. Sociodemographic and clinical characteristics of a diabetic population at a tertiary care center in Assam, India. *Journal of Social Health and Diabetes,* 5**,** 37-42.

BOUCHER, J., KLEINRIDDERS, A. & KAHN, C. R. 2014. Insulin Receptor Signaling in Normal and Insulin-Resistant States. *Cold Spring Harbor Perspectives in Biology,* 6**,** a009191.

BOUTAYEB, A. & BOUTAYEB, S. 2005. The burden of non communicable diseases in developing countries. *International Journal for Equity in Health,* 4**,** 2-2.

BOWEN, M. E. & ROTHMAN, R. L. 2010. Multidisciplinary management of type 2 diabetes in children and adolescents. *Journal of multidisciplinary healthcare,* 3**,** 113-124.

BOYKO, E. J. & MEIGS, J. B. 2011. Does Diabetes Always Confer Coronary Heart Disease Risk Equivalent to a Prior Myocardial Infarction?: Implications for prevention. *Diabetes Care,* 34**,** 782-784.

BROCKER, C., THOMPSON, D. C. & VASILIOU, V. 2012. The role of hyperosmotic stress in inflammation and disease. *Biomolecular concepts,* 3**,** 345-364.

BROWN, J. B., CONNER, C. & NICHOLS, G. A. 2010. Secondary failure of metformin monotherapy in clinical practice. *Diabetes Care,* 33**,** 501-6.

BUCHWALD, P., CECHIN, S. R., WEAVER, J. D. & STABLER, C. L. 2015. Experimental evaluation and computational modeling of the effects of encapsulation on the time-profile of glucose-stimulated insulin release of pancreatic islets. *Biomed Eng Online,* 14**,** 28.

CADTH 2014. HbA1c Testing Frequency: A Review of the Clinical Evidence and Guidelines [Internet]. *Canadian Agency for Drugs and Technologies in Health.* Ottawa.

CARE, D. 2004. Prevention or Delay of Type 2 Diabetes. *Diabetes Care,* 27**,** s47.

CARRILLO-LARCO, R. M., BERNABÉ-ORTIZ, A., PILLAY, T. D., GILMAN, R. H., SANCHEZ, J. F., POTERICO, J. A., QUISPE, R., SMEETH, L. & MIRANDA, J. J. 2016. Obesity risk in rural, urban and rural-to-urban migrants: prospective results of the PERU MIGRANT study. *International Journal of Obesity (2005),* 40**,** 181-185.

CENTRAL STATISTICAL BUREAU 2016. Statistical Reveiw. 39 ed. Kuwait.

CERF, M. E. 2013. Beta Cell Dysfunction and Insulin Resistance. *Frontiers in Endocrinology,* 4**,** 37.

CERIELLO, A. 2010. Point: Postprandial Glucose Levels Are a Clinically Important Treatment Target. *Diabetes Care,* 33**,** 1905-1907.

CERIELLO, A. & COLAGIURI, S. 2008. International Diabetes Federation guideline for management of postmeal glucose: a review of recommendations. *Diabetic Medicine,* 25**,** 1151-1156.

CERNEA, S. & DOBREANU, M. 2013. Diabetes and beta cell function: from mechanisms to evaluation and clinical implications. *Biochemia Medica,* 23**,** 266-280.

CHA, S.-A. & KO, S.-H. 2016. Association between estimated blood glucose levels and glycated hemoglobin levels. *The Korean Journal of Internal Medicine,* 31**,** 457-460.

CHAGAS, C. E., BORGES, M. C., MARTINI, L. A. & ROGERO, M. M. 2012. Focus on vitamin D, inflammation and type 2 diabetes. *Nutrients,* 4**,** 52-67.

CHAIT, A. & BORNFELDT, K. E. 2009. Diabetes and atherosclerosis: is there a role for hyperglycemia? *Journal of Lipid Research,* 50**,** S335-S339.

CHANDRASHEKAR, V. 2016. Hb A1c Separation by High Performance Liquid Chromatography in Hemoglobinopathies. *Scientifica,* 2016**,** 4.

CHANG, S. A. 2012. Smoking and Type 2 Diabetes Mellitus. *Diabetes & Metabolism Journal,* 36**,** 399-403.

CHANNANATH, A. M., FARRAN, B., BEHBEHANI, K. & THANARAJ, T. A. 2013. State of Diabetes, Hypertension, and Comorbidity in Kuwait: Showcasing the Trends as Seen in Native Versus Expatriate Populations. *Diabetes Care,* 36**,** e75-e75.

CHEN, J., DIESBURG-STANWOOD, A., BODOR, G. & RASOULI, N. 2016. Led Astray by Hemoglobin A1c: A Case of Misdiagnosis of Diabetes by Falsely Elevated Hemoglobin A1c. *Journal of Investigative Medicine High Impact Case Reports,* 4**,** 2324709616628549.

CHENG, W. S., WINGARD, D. L., KRITZ-SILVERSTEIN, D. & BARRETT-CONNOR, E. 2008. Sensitivity and Specificity of Death Certificates for Diabetes: As Good as it Gets? *Diabetes care,* 31**,** 279-284.

CHEUNG, B. M. 2010. The hypertension-diabetes continuum. *J Cardiovasc Pharmacol,* 55**,** 333-9.

CHEUNG, B. M. & LI, C. 2012. Diabetes and hypertension: is there a common metabolic pathway? *Curr Atheroscler Rep,* 14**,** 160-6.

CHIU, H. K., TSAI, E. C., JUNEJA, R., STOEVER, J., BROOKS-WORRELL, B., GOEL, A. & PALMER, J. P. 2007. Equivalent insulin resistance in latent autoimmune diabetes in adults (LADA) and type 2 diabetic patients. *Diabetes Res Clin Pract,* 77**,** 237-44.

CHIU, S.-L. & CLINE, H. T. 2010. Insulin receptor signaling in the development of neuronal structure and function. *Neural Development,* 5**,** 1-18.

COHEN, R. M., FRANCO, R. S., KHERA, P. K., SMITH, E. P., LINDSELL, C. J., CIRAOLO, P. J., PALASCAK, M. B. & JOINER, C. H. 2008. Red cell life span heterogeneity in hematologically normal people is sufficient to alter HbA1c. *Blood,* 112**,** 4284-4291.

COLBERG, S. R., SIGAL, R. J., FERNHALL, B., REGENSTEINER, J. G., BLISSMER, B. J., RUBIN, R. R., CHASAN-TABER, L., ALBRIGHT, A. L. & BRAUN, B. 2010. Exercise and type 2 diabetes: the American College of Sports Medicine and the American Diabetes Association: joint position statement. *Diabetes Care,* 33**,** e147-67.

COLLINSON, D. J., REA, R. & DONNELLY, R. 2004. Vascular risk: diabetes. *Vasc Med,* 9**,** 307-10.

CONGET, I. & GIMÉNEZ, M. 2009. Glucose Control and Cardiovascular Disease: Is it important? No. *Diabetes Care,* 32**,** S334-S336.

CORNELIS, M. C., CHIUVE, S. E., GLYMOUR, M. M., CHANG, S.-C., TCHETGEN TCHETGEN, E. J., LIANG, L., KOENEN, K. C., RIMM, E. B., KAWACHI, I. & KUBZANSKY, L. D. 2014. Bachelors, Divorcees, and Widowers: Does Marriage Protect Men from Type 2 Diabetes? *PLoS ONE,* 9**,** e106720.

COX, K., COCCHI, M. N., SALCICCIOLI, J. D., CARNEY, E., HOWELL, M. & DONNINO, M. W. 2012. Prevalence and significance of lactic acidosis in diabetic ketoacidosis(). *Journal of critical care,* 27**,** 132-137.

CSB. 2005. General Population Census. Available: https://www.csb.gov.kw/Socan_Statistic_EN.aspx?ID=6.

CURRAN, A. M., RYAN, M. F., DRUMMOND, E., GIBNEY, E. R., GIBNEY, M. J., ROCHE, H. M. & BRENNAN, L. 2016. Uncovering Factors Related to Pancreatic Beta-Cell Function. *PLOS ONE,* 11**,** e0161350.

D'AGOSTINO, R. B., HAMMAN, R. F., KARTER, A. J., MYKKANEN, L., WAGENKNECHT, L. E. & HAFFNER, S. M. 2004. Cardiovascular Disease Risk Factors Predict the Development of Type 2 Diabetes. *The Insulin Resistance Atherosclerosis Study,* 27**,** 2234-2240.

DABHI, A. S., BHATT, N. R. & SHAH, M. J. 2013. Voglibose: An Alpha Glucosidase Inhibitor. *Journal of Clinical and Diagnostic Research : JCDR,* 7**,** 3023-3027.

DAVIS, J., JUAREZ, D. & HODGES, K. 2013. Relationship of Ethnicity and Body Mass Index with the Development of Hypertension and Hyperlipidemia. *Ethnicity & disease,* 23**,** 65-70.

DCCT 1993. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. The Diabetes Control and Complications Trial Research Group. *N Engl J Med,* 329**,** 977-86.

DE MEYTS PIERRE 2014. Jean De Meyer. *Diapedia*.

DEEPA, M., BHANSALI, A., ANJANA, R. M., PRADEEPA, R., JOSHI, S. R., JOSHI, P. P., DHANDHANIA, V. K., RAO, P. V., SUBASHINI, R., UNNIKRISHNAN, R., SHUKLA, D. K., MADHU, S. V., DAS, A. K., MOHAN, V. & KAUR, T. 2014. Knowledge and awareness of diabetes in urban and rural India: The Indian Council of Medical Research India Diabetes Study (Phase I): Indian Council of Medical Research India Diabetes 4. *Indian Journal of Endocrinology and Metabolism,* 18**,** 379-385.

DEFRONZO, R. A. & ABDUL-GHANI, M. 2011. Type 2 Diabetes Can Be Prevented With Early Pharmacological Intervention. *Diabetes Care,* 34**,** S202-S209.

DEFRONZO, R. A. & TRIPATHY, D. 2009. Skeletal Muscle Insulin Resistance Is the Primary Defect in Type 2 Diabetes. *Diabetes Care,* 32**,** S157-S163.

DEFRONZO, R. A., TRIPLITT, C. L., ABDUL-GHANI, M. & CERSOSIMO, E. 2014. Novel Agents for the Treatment of Type 2 Diabetes. *Diabetes Spectrum : A Publication of the American Diabetes Association,* 27**,** 100-112.

DESHPANDE, A. D., HARRIS-HAYES, M. & SCHOOTMAN, M. 2008. Epidemiology of Diabetes and Diabetes-Related Complications. *Physical Therapy,* 88**,** 1254-1264.

DESOUZA, C. V. & SHIVASWAMY, V. 2010. Pioglitazone in the Treatment of Type 2 Diabetes: Safety and Efficacy Review. *Clinical Medicine Insights. Endocrinology and Diabetes,* 3**,** 43-51.

DÉZSI, C. A. 2014. Differences in the Clinical Effects of Angiotensin-Converting Enzyme Inhibitors and Angiotensin Receptor Blockers: A Critical Review of the Evidence. *American Journal of Cardiovascular Drugs,* 14**,** 167-173.

DIABETES UK 2016. Diabetes UK: key facts and stats. UK.

DIXIT, A. K., DEY, R., SURESH, A., CHAUDHURI, S., PANDA, A. K., MITRA, A. & HAZRA, J. 2014. The prevalence of dyslipidemia in patients with diabetes mellitus of ayurveda Hospital. *Journal of Diabetes and Metabolic Disorders,* 13**,** 58-58.

DONNER, T. 2015. Insulin-Pharmacology. *In:* DE GROOT LJ, CHROUSOS G, DUNGAN K & ET AL. (eds.) *Therapeutic Regimens and Principles of Intensive Insulin Therapy.*

DORIA, A., PATTI, M.-E. & KAHN, C. R. 2008. The Emerging Genetic Architecture of Type 2 Diabetes. *Cell metabolism,* 8**,** 186-200.

DU, Y.-F., OU, H.-Y., BEVERLY, E. A. & CHIU, C.-J. 2014. Achieving glycemic control in elderly patients with type 2 diabetes: a critical comparison of current options. *Clinical Interventions in Aging,* 9**,** 1963-1980.

DU, Y., HEIDEMANN, C., SCHAFFRATH ROSARIO, A., BUTTERY, A., PAPROTT, R., NEUHAUSER, H., RIEDEL, T., ICKS, A. & SCHEIDT-NAVE, C. 2015. Changes in diabetes care indicators: findings from German National Health Interview and Examination Surveys 1997–1999 and 2008–2011. *BMJ Open Diabetes Research & Care,* 3.

DULLOO, A. G., JACQUET, J., SOLINAS, G., MONTANI, J. P. & SCHUTZ, Y. 2010. Body composition phenotypes in pathways to obesity and the metabolic syndrome. *Int J Obes,* 34**,** S4-S17.

ECKEL, R. H., KAHN, S. E., FERRANNINI, E., GOLDFINE, A. B., NATHAN, D. M., SCHWARTZ, M. W., SMITH, R. J. & SMITH, S. R. 2011. Obesity and type 2 diabetes: what can be unified and what needs to be individualized? *J Clin Endocrinol Metab,* 96**,** 1654-63.

ELBASSUONI, E. 2013. Better association of waist circumference with insulin resistance and some cardiovascular risk factors than body mass index. *Endocr Regul,* 47**,** 3-14.

ELDOR, R. & RAZ, I. 2009. American Diabetes Association Indications for Statins in Diabetes: Is there evidence? *Diabetes Care,* 32**,** S384-S391.

ERGUL, A., KELLY-COBBS, A., ABDALLA, M. & FAGAN, S. C. 2012. Cerebrovascular Complications of Diabetes: Focus on Stroke. *Endocrine, metabolic & immune disorders drug targets,* 12**,** 148-158.

ERIKSSON, K. F. & LINDGARDE, F. 1991. Prevention of type 2 (non-insulin-dependent) diabetes mellitus by diet and physical exercise. The 6-year Malmo feasibility study. *Diabetologia,* 34**,** 891-8.

ESPINOSA, J. & EVANS, W. N. 2008. Heightened mortality after the death of a spouse: marriage protection or marriage selection? *J Health Econ,* 27**,** 1326-42.

ESPOSITO, K., CHIODINI, P., MAIORINO, M. I., CAPUANO, A., COZZOLINO, D., PETRIZZO, M., BELLASTELLA, G. & GIUGLIANO, D. 2015. A nomogram to estimate the HbA1c response to different DPP-4 inhibitors in type 2 diabetes: a systematic review and meta-analysis of 98 trials with 24 163 patients. *BMJ Open,* 5.

EZRA, E., KEINAN, E., MANDEL, Y., BOULTON, M. E. & NAHMIAS, Y. 2013. Non-dimensional analysis of retinal microaneurysms: critical threshold for treatment. *Integrative biology : quantitative biosciences from nano to macro,* 5**,** 474-480.

FARES, J. E., KANAAN, M., CHAAYA, M. & AZAR, S. T. 2010. Fluctuations in glycosylated hemoglobin (HbA1C) as a predictor for the development of diabetic nephropathy in type 1 diabetic patients. *International Journal of Diabetes Mellitus,* 2**,** 10-14.

FEDERATION, I. D. 2003. Diabetes Atlas, second edition.

FERREIRA, F. R., CÉSAR, C. C., CAMARGOS, V. P., LIMA-COSTA, M. F. & PROIETTI, F. A. 2010. Aging and Urbanization: The Neighborhood Perception and Functional Performance of Elderly Persons in Belo Horizonte Metropolitan Area—Brazil. *Journal of Urban Health : Bulletin of the New York Academy of Medicine,* 87**,** 54-66.

FITCH, K., PYENSON, B. S. & IWASAKI, K. 2013. Medical claim cost impact of improved diabetes control for medicare and commercially insured patients with type 2 diabetes. *J Manag Care Pharm,* 19**,** 609-20, 620a-620d.

FLETCHER, B., GULANICK, M. & LAMENDOLA, C. 2002. Risk factors for type 2 diabetes mellitus. *J Cardiovasc Nurs,* 16**,** 17-23.

FONSECA, V. A. 2009. Defining and Characterizing the Progression of Type 2 Diabetes. *Diabetes Care,* 32**,** S151-S156.

FONTBONNE, A. M. & ESCHWÈGE, E. M. 1991. Insulin and Cardiovascular Disease: Paris Prospective Study. *Diabetes Care,* 14**,** 461-469.

FRADIN, D. & BOUGNÈRES, P. 2011. T2DM: Why Epigenetics? *Journal of Nutrition and Metabolism,* 2011**,** 17.

FRECKMANN, G., HAGENLOCHER, S., BAUMSTARK, A., JENDRIKE, N., GILLEN, R. C., RÖSSNER, K. & HAUG, C. 2007. Continuous Glucose Profiles in Healthy Subjects under Everyday Life Conditions and after Different Meals. *Journal of diabetes science and technology (Online),* 1**,** 695-703.

FRIEDL, C. K. E. 2009. Waist Circumference Threshold Values for Type 2 Diabetes Risk. *Journal of Diabetes Science and Technology,* 3**,** 761-769.

FRIEDRICH, N., THUESEN, B., JØRGENSEN, T., JUUL, A., SPIELHAGEN, C., WALLASCHOFKSI, H. & LINNEBERG, A. 2012. The Association Between IGF-I and Insulin Resistance: A general population study in Danish adults. *Diabetes Care,* 35**,** 768-773.

GARCÍA-PÉREZ, L.-E., ÁLVAREZ, M., DILLA, T., GIL-GUILLÉN, V. & OROZCO-BELTRÁN, D. 2013. Adherence to Therapies in Patients with Type 2 Diabetes. *Diabetes Therapy,* 4**,** 175-194.

GARETH WILLIAMS, J. C. P. 2002. *Textbook of Diabetes*, Blackwell Science.

GEER, E. B. & SHEN, W. 2009. Gender Differences in Insulin Resistance, Body Composition, and Energy Balance. *Gender medicine,* 6**,** 60-75.

GENNÉ-BACON, E. A. 2014. Thinking Evolutionarily About Obesity. *The Yale Journal of Biology and Medicine,* 87**,** 99-112.

GHADERIAN, S. B., HAYATI, F., SHAYANPOUR, S. & BELADI MOUSAVI, S. S. 2015. Diabetes and end-stage renal disease; a review article on new concepts. *Journal of Renal Injury Prevention,* 4**,** 28-33.

GHEITH, O., FAROUK, N., NAMPOORY, N., HALIM, M. A. & AL-OTAIBI, T. 2016. Diabetic kidney disease: world wide difference of prevalence and risk factors. *Journal of Nephropharmacology,* 5**,** 49-56.

GIACCO, F. & BROWNLEE, M. 2010. Oxidative stress and diabetic complications. *Circulation research,* 107**,** 1058-1070.

GOMYO, M., SAKANE, N., KAMAE, I., SATO, S., SUZUKI, K.-I., TOMINAGA, M., KAWAZU, S., YOSHINAGA, H., TSUSHITA, K., SATO, J., SATO, Y., TSUJII, S., YOSHIDA, T., SEINO, Y., USUI, T., NANJO, K., HIRATA, M., KOTANI, K., HOSOSAKO, A., KIYOHARA, Y. & KUZUYA, H. 2004. Effects of sex, age and BMI on screening tests for impaired glucose tolerance. *Diabetes Research and Clinical Practice,* 64**,** 129-136.

GORAN, M. I., BERGMAN, R. N., CRUZ, M. L. & WATANABE, R. 2002. Insulin resistance and associated compensatory responses in african-american and Hispanic children. *Diabetes Care,* 25**,** 2184-90.

GOSMANOV AR, GOSMANOVA EO & AE., K. 2015. Hyperglycemic Crises: Diabetic Ketoacidosis (DKA), And Hyperglycemic Hyperosmolar State (HHS). *In:* DE GROOT LJ, C. G., DUNGAN K, ET AL., (ed.). South Dartmouth: MDText.com.

GOSMANOV, A. R., GOSMANOVA, E. O. & DILLARD-CANNON, E. 2014. Management of adult diabetic ketoacidosis. *Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy,* 7**,** 255-264.

GOYA WANNAMETHEE, S., GERALD SHAPER, A. & WALKER, M. 2005. Overweight and obesity and weight change in middle aged men: impact on cardiovascular disease and diabetes. *Heart,* 91**,** 1220-1220.

GROSS, J. L., DE AZEVEDO, M. J., SILVEIRO, S. P., CANANI, L. H., CARAMORI, M. L. & ZELMANOVITZ, T. 2005. Diabetic Nephropathy: Diagnosis, Prevention, and Treatment. *Diabetes Care,* 28**,** 164-176.

GUARIGUATA, L., WHITING, D. R., HAMBLETON, I., BEAGLEY, J., LINNENKAMP, U. & SHAW, J. E. 2014. Global estimates of diabetes prevalence for 2013 and projections for 2035. *Diabetes Res Clin Pract,* 103**,** 137-49.

GUO, X., LI, H., XU, H., WOO, S., DONG, H., LU, F., LANGE, A. J. & WU, C. 2012. Glycolysis in the control of blood glucose homeostasis. *Acta Pharmaceutica Sinica B,* 2**,** 358-367.

GUO, X., LI, Z., GUO, L., ZHENG, L., YU, S., YANG, H., ZOU, L., ZHOU, Y., ZHANG, Y., ZHU, L., ZHANG, Y. & SUN, Y. 2014. An update on overweight and obesity in rural Northeast China: from lifestyle risk factors to cardiometabolic comorbidities. *BMC Public Health,* 14**,** 1046.

GUPTA, N., MANSOOR, S., SHARMA, A., SAPKAL, A., SHETH, J., FALATOONZADEH, P., KUPPERMANN, B. D. & KENNEY, M. C. 2013. Diabetic Retinopathy and VEGF. *The Open Ophthalmology Journal,* 7**,** 4-10.

GUPTA, V. & KALRA, S. 2011. Choosing a Gliptin. *Indian Journal of Endocrinology and Metabolism,* 15**,** 298-308.

HAFFNER, S. M., MYKKÄNEN, L., FESTA, A., BURKE, J. P. & STERN, M. P. 2000. Insulin-Resistant Prediabetic Subjects Have More Atherogenic Risk Factors Than Insulin-Sensitive Prediabetic Subjects: Implications for Preventing Coronary Heart Disease During the Prediabetic State. *Circulation,* 101**,** 975-980.

HAGE HASSAN, R., BOURRON, O. & HAJDUCH, E. 2014. Defect of insulin signal in peripheral tissues: Important role of ceramide. *World Journal of Diabetes,* 5**,** 244-257.

HALBAN, P. A., POLONSKY, K. S., BOWDEN, D. W., HAWKINS, M. A., LING, C., MATHER, K. J., POWERS, A. C., RHODES, C. J., SUSSEL, L. & WEIR, G. C. 2014. β-Cell Failure in Type 2 Diabetes: Postulated Mechanisms and Prospects for Prevention and Treatment. *Diabetes Care,* 37**,** 1751-1758.

HAMASAKI, H. 2016. Daily physical activity and type 2 diabetes: A review. *World Journal of Diabetes,* 7**,** 243-251.

HAMER, M., HACKETT, R. A., BOSTOCK, S., LAZZARINO, A. I., CARVALHO, L. A. & STEPTOE, A. 2014. Objectively assessed physical activity, adiposity, and inflammatory markers in people with type 2 diabetes. *BMJ Open Diabetes Research & Care,* 2.

HAN, T. S., CORREA, E., LEAN, M. E. J., LEE, D. M., O'NEILL, T. W., BARTFAI, G., FORTI, G., GIWERCMAN, A., KULA, K., PENDLETON, N., PUNAB, M., RUTTER, M. K., VANDERSCHUEREN, D., HUHTANIEMI, I. T., WU, F. C. W., CASANUEVA, F. F. & AND THE, E. S. G. 2017. Changes in prevalence of obesity and high waist circumference over four years across European regions: the European male ageing study (EMAS). *Endocrine,* 55**,** 456-469.

HARDY, O. T., CZECH, M. P. & CORVERA, S. 2012. What causes the insulin resistance underlying obesity? *Curr Opin Endocrinol Diabetes Obes,* 19**,** 81-7.

HARJUTSALO, V., KATOH, S., SARTI, C., TAJIMA, N. & TUOMILEHTO, J. 2004. Population-Based Assessment of Familial Clustering of Diabetic Nephropathy in Type 1 Diabetes. *Diabetes,* 53**,** 2449-2454.

HASANI, N., KHOSRAWI, S., HASHEMIPOUR, M., HAGHIGHATIYAN, M., JAVDAN, Z., TAHERI, M. H., KELISHADI, R., AMINI, M. & BAREKATEIN, R. 2013. Prevalence and related risk-factors of peripheral neuropathy in children with insulin-dependent diabetes mellitus. *Journal of Research in Medical Sciences : The Official Journal of Isfahan University of Medical Sciences,* 18**,** 132-136.

HAYASHI, T., BOYKO, E. J., MCNEELY, M. J., LEONETTI, D. L., KAHN, S. E. & FUJIMOTO, W. Y. 2008. Visceral adiposity, not abdominal subcutaneous fat area, is associated with an increase in future insulin resistance in Japanese Americans. *Diabetes,* 57**,** 1269-75.

HEALTH QUALITY, O. 2014. Point-of-Care Hemoglobin A(1c) Testing: An Evidence-Based Analysis. *Ontario Health Technology Assessment Series,* 14**,** 1-30.

HEINEMANN, L. 2008. Finger Pricking and Pain: A Never Ending Story. *Journal of diabetes science and technology (Online),* 2**,** 919-921.

HERMAYER, K. L., LOFTLEY, A. S., REDDY, S., NARLA, S. N., EPPS, N. A. & ZHU, Y. 2015. Challenges of inpatient blood glucose monitoring: standards, methods, and devices to measure blood glucose. *Curr Diab Rep,* 15**,** 10.

HILTUNEN, L. A. 2005. Are there associations between socio-economic status and known diabetes in an elderly Finnish population? *Cent Eur J Public Health,* 13**,** 187-90.

HOLST, J. J., VILSBOLL, T. & DEACON, C. F. 2009. The incretin system and its role in type 2 diabetes mellitus. *Mol Cell Endocrinol,* 297**,** 127-36.

HONG MA, YUAN GONG, YUAN-YUAN LIU, JIE SONG, HAO-MING TIAN, TAO CHEN, XING-WU RAN, HONG-LING YU, XIANG-XUN ZHANG & REN, Y. 2011. [Prevalence of diabetes and prediabetes mellitus in the first-degree relatives of patients with type 2 diabetes in Chengdu]. *Journal of Sichuan University, Medical science edition,* 42**,** 264-8.

HORTON, E. S. 2009. Defining the Role of Basal and Prandial Insulin for Optimal Glycemic Control. *Journal of the American College of Cardiology,* 53**,** S21-S27.

HU, F. B. 2011. Globalization of Diabetes: The role of diet, lifestyle, and genes. *Diabetes Care,* 34**,** 1249-1257.

HUNG, C.-C., TSAI, J.-C., KUO, H.-T., CHANG, J.-M., HWANG, S.-J. & CHEN, H.-C. 2013. Dyslipoproteinemia and Impairment of Renal Function in Diabetic Kidney Disease: An Analysis of Animal Studies, Observational Studies, and Clinical Trials. *The Review of Diabetic Studies : RDS,* 10**,** 110-120.

IDF 2014. Diabetes Atlas, 6TH EDITION. International Diabetes Federation.

IDF 2015. IDF DIABETES ATLAS - 7TH EDITION. International Diabetes Federation.

IDF/KUWAIT, I. D. F. 2014. Data by country, Kuwait.

IMAMURA, F., MUKAMAL, K. J., MEIGS, J. B., LUCHSINGER, J. A., IX, J. H., SISCOVICK, D. S. & MOZAFFARIAN, D. 2013. Risk factors for type 2 diabetes mellitus preceded by beta-cell dysfunction, insulin resistance, or both in older adults: the Cardiovascular Health Study. *Am J Epidemiol,* 177**,** 1418-29.

IRONS, B. K. & MINZE, M. G. 2014. Drug treatment of type 2 diabetes mellitus in patients for whom metformin is contraindicated. *Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy,* 7**,** 15-24.

IZADI, N., MALEK, M., AMINIAN, O. & SARAEI, M. 2013. Medical risk factors of diabetes mellitus among professional drivers. *Journal of Diabetes and Metabolic Disorders,* 12**,** 23-23.

JABER, L. A., BROWN, M. B., HAMMAD, A., NOWAK, S. N., ZHU, Q., GHAFOOR, A. & HERMAN, W. H. 2003. Epidemiology of diabetes among Arab Americans. *Diabetes Care,* 26**,** 308-13.

JIH, J., MUKHERJEA, A., VITTINGHOFF, E., NGUYEN, T. T., TSOH, J. Y., FUKUOKA, Y., BENDER, M. S., TSENG, W. & KANAYA, A. M. 2014. Using appropriate body mass index cut points for overweight and obesity among Asian Americans. *Preventive medicine,* 65**,** 1-6.

JOHN, W. G., MOSCA, A., WEYKAMP, C. & GOODALL, I. 2007. HbA(1c) Standardisation: History, Science and Politics. *The Clinical Biochemist Reviews,* 28**,** 163-168.

JOSEPH, J. I. 2013. Analysis: New point-of-care blood glucose monitoring system for the hospital demonstrates satisfactory analytical accuracy using blood from critically ill patients--an important step toward improved blood glucose control in the hospital. *J Diabetes Sci Technol,* 7**,** 1288-93.

JUUTILAINEN, A., LEHTO, S., RÖNNEMAA, T., PYÖRÄLÄ, K. & LAAKSO, M. 2005. Type 2 Diabetes as a "Coronary Heart Disease Equivalent": An 18-year prospective population-based study in Finnish subjects. *Diabetes Care,* 28**,** 2901-2907.

KAHN, R. & FONSECA, V. 2008. Translating the A1C Assay. *Diabetes Care,* 31**,** 1704-1707.

KAHN, S. E., COOPER, M. E. & DEL PRATO, S. 2014. Pathophysiology and treatment of type 2 diabetes: perspectives on the past, present, and future. *The Lancet,* 383**,** 1068-1083.

KAHN, S. E., HULL, R. L. & UTZSCHNEIDER, K. M. 2006. Mechanisms linking obesity to insulin resistance and type 2 diabetes. *Nature,* 444**,** 840-846.

KALARIA, R. N., AKINYEMI, R. & IHARA, M. 2016. Stroke injury, cognitive impairment and vascular dementia(). *Biochimica et Biophysica Acta,* 1862**,** 915-925.

KALRA, S., AAMIR, A. H., RAZA, A., DAS, A. K., AZAD KHAN, A. K., SHRESTHA, D., QURESHI, M. F., MD, F., PATHAN, M. F., JAWAD, F., BHATTARAI, J., TANDON, N., SOMASUNDARAM, N., KATULANDA, P., SAHAY, R., DHUNGEL, S., BAJAJ, S., CHOWDHURY, S., GHOSH, S., MADHU, S. V., AHMED, T. & BULUGHAPITIYA, U. 2015. Place of sulfonylureas in the management of type 2 diabetes mellitus in South Asia: A consensus statement. *Indian Journal of Endocrinology and Metabolism,* 19**,** 577-596.

KALTER-LEIBOVICI, O., CHETRIT, A., LUBIN, F., ATAMNA, A., ALPERT, G., ZIV, A., ABU-SAAD, K., MURAD, H., EILAT-ADAR, S. & GOLDBOURT, U. 2012. Adult-onset diabetes among Arabs and Jews in Israel: a population-based study. *Diabet Med,* 29**,** 748-54.

KALYANI, R. R. & EGAN, J. M. 2013. Diabetes and Altered Glucose Metabolism with Aging. *Endocrinology and metabolism clinics of North America,* 42**,** 333-347.

KAMUHABWA, A. R. & CHARLES, E. 2014. Predictors of poor glycemic control in type 2 diabetic patients attending public hospitals in Dar es Salaam. *Drug, Healthcare and Patient Safety,* 6**,** 155-165.

KANAT, M., DEFRONZO, R. A. & ABDUL-GHANI, M. A. 2015. Treatment of prediabetes. *World Journal of Diabetes,* 6**,** 1207-1222.

KANNEL, W. B. & MCGEE, D. L. 1979. Diabetes and cardiovascular disease. The Framingham study. *Jama,* 241**,** 2035-8.

KARAGEORGI, S., ALSMADI, O. & BEHBEHANI, K. 2013. A Review of Adult Obesity Prevalence, Trends, Risk Factors, and Epidemiologic Methods in Kuwait. *Journal of Obesity,* 2013**,** 378650.

KARAKELIDES, H., IRVING, B. A., SHORT, K. R., O'BRIEN, P. & NAIR, K. S. 2010. Age, Obesity, and Sex Effects on Insulin Sensitivity and Skeletal Muscle Mitochondrial Function. *Diabetes,* 59**,** 89-97.

KARAMANOU, M., PROTOGEROU, A., TSOUCALAS, G., ANDROUTSOS, G. & POULAKOU-REBELAKOU, E. 2016. Milestones in the history of diabetes mellitus: The main contributors. *World Journal of Diabetes,* 7**,** 1-7.

KARAMITSOS, D. T. 2011. The story of insulin discovery. *Diabetes Research and Clinical Practice,* 93**,** S2-S8.

KARTER, A. J. 2006. The Role of Self-monitoring of Blood Glucose in Glycemic Control. *Endocrine practice : official journal of the American College of Endocrinology and the American Association of Clinical Endocrinologists,* 12**,** 110-117.

KASZNICKI, J. 2014. Advances in the diagnosis and management of diabetic distal symmetric polyneuropathy. *Archives of Medical Science : AMS,* 10**,** 345-354.

KAWAHITO, S., KITAHATA, H. & OSHITA, S. 2009. Problems associated with glucose toxicity: Role of hyperglycemia-induced oxidative stress. *World Journal of Gastroenterology : WJG,* 15**,** 4137-4142.

KETEMA, E. B. & KIBRET, K. T. 2015. Correlation of fasting and postprandial plasma glucose with HbA1c in assessing glycemic control; systematic review and meta-analysis. *Archives of Public Health,* 73**,** 43.

KHATTAB, M., KHADER, Y. S., AL-KHAWALDEH, A. & AJLOUNI, K. 2010. Factors associated with poor glycemic control among patients with type 2 diabetes. *J Diabetes Complications,* 24**,** 84-9.

KHUNTI, K., WOLDEN, M. L., THORSTED, B. L., ANDERSEN, M. & DAVIES, M. J. 2013. Clinical Inertia in People With Type 2 Diabetes. *A retrospective cohort study of more than 80,000 people*.

KIM, W. & EGAN, J. M. 2008. The role of incretins in glucose homeostasis and diabetes treatment. *Pharmacol Rev,* 60**,** 470-512.

KING, H., AUBERT, R. E. & HERMAN, W. H. 1998. Global Burden of Diabetes, 1995–2025: Prevalence, numerical estimates, and projections. *Diabetes Care,* 21**,** 1414-1431.

KING, H., KEUKY, L., SENG, S., KHUN, T., ROGLIC, G. & PINGET, M. Diabetes and associated disorders in Cambodia: two epidemiological surveys. *The Lancet,* 366**,** 1633-1639.

KING, P., PEACOCK, I. & DONNELLY, R. 1999. The UK Prospective Diabetes Study (UKPDS): clinical and therapeutic implications for type 2 diabetes. *British Journal of Clinical Pharmacology,* 48**,** 643-648.

KISHORE, P., KIM, S. H. & CRANDALL, J. P. 2012. Glycemic Control and Cardiovascular Disease: What's a Doctor to Do? *Current Diabetes Reports,* 12**,** 255-264.

KITSIOS, K., TSAPAS, A. & KARAGIANNI, P. 2011. Glycemia and cardiovascular risk: challenging evidence based medicine. *Hippokratia,* 15**,** 199-204.

KLAUTZER, L., BECKER, J. & MATTKE, S. 2014. The curse of wealth – Middle Eastern countries need to address the rapidly rising burden of diabetes. *International Journal of Health Policy and Management,* 2**,** 109-114.

KNOWLER, W. C., BARRETT-CONNOR, E., FOWLER, S. E., HAMMAN, R. F., LACHIN, J. M., WALKER, E. A. & NATHAN, D. M. 2002. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med,* 346**,** 393-403.

KORNUM, J. B., THOMSEN, R. W., RIIS, A., LERVANG, H.-H., SCHØNHEYDER, H. C. & SØRENSEN, H. T. 2008. Diabetes, Glycemic Control, and Risk of Hospitalization With Pneumonia: A population-based case-control study. *Diabetes Care,* 31**,** 1541-1545.

KRANENDONK, M. E., VAN HERWAARDEN, J. A., STUPKOVA, T., DE JAGER, W., VINK, A., MOLL, F. L., KALKHOVEN, E. & VISSEREN, F. L. 2015. Inflammatory characteristics of distinct abdominal adipose tissue depots relate differently to metabolic risk factors for cardiovascular disease: distinct fat depots and vascular risk factors. *Atherosclerosis,* 239**,** 419-27.

KUMAR, A., TEWARI, P., SAHOO, S. S. & SRIVASTAVA, A. K. 2005. Prevalence of insulin resistance in first degree relatives of type-2 diabetes mellitus patients: A prospective study in north Indian population. *Indian J Clin Biochem,* 20**,** 10-7.

L. CHRISTY, A., A. MANJREKAR, P., P. BABU, R., HEGDE, A. & M.S, R. 2014. Influence of Iron Deficiency Anemia on Hemoglobin A1C Levels in Diabetic Individuals with Controlled Plasma Glucose Levels. *Iranian Biomedical Journal,* 18**,** 88-93.

LAAKSO, M. 2010. Cardiovascular Disease in Type 2 Diabetes From Population to Man to Mechanisms: The Kelly West Award Lecture 2008. *Diabetes Care,* 33**,** 442-449.

LAIOS, K., KARAMANOU, M., SARIDAKI, Z. & ANDROUTSOS, G. 2012. Aretaeus of Cappadocia and the first description of diabetes. *Hormones (Athens),* 11**,** 109-13.

LAKHTAKIA, R. 2013. The History of Diabetes Mellitus. *Sultan Qaboos University Medical Journal,* 13**,** 368-370.

LAMBADIARI, V., TRIANTAFYLLOU, K. & DIMITRIADIS, G. D. 2015. Insulin action in muscle and adipose tissue in type 2 diabetes: The significance of blood flow. *World Journal of Diabetes,* 6**,** 626-633.

LANDSBERG, L. & MOLITCH, M. 2004. Diabetes and hypertension: pathogenesis, prevention and treatment. *Clin Exp Hypertens,* 26**,** 621-8.

LAWRENCE, R. D. 1951. Types of Human Diabetes. *British Medical Journal,* 1**,** 373-375.

LEE, J. W. R., BRANCATI, F. L. & YEH, H.-C. 2011. Trends in the Prevalence of Type 2 Diabetes in Asians Versus Whites: Results from the United States National Health Interview Survey, 1997–2008. *Diabetes Care,* 34**,** 353-357.

LEE, R., WONG, T. Y. & SABANAYAGAM, C. 2015a. Epidemiology of diabetic retinopathy, diabetic macular edema and related vision loss. *Eye and Vision,* 2**,** 17.

LEE, S. H., HAN, K., YANG, H. K., KIM, H. S., CHO, J. H., KWON, H. S., PARK, Y. M., CHA, B. Y. & YOON, K. H. 2015b. A novel criterion for identifying metabolically obese but normal weight individuals using the product of triglycerides and glucose. *Nutrition & Diabetes,* 5**,** e149.

LEE, S. I., PATEL, M., JONES, C. M. & NARENDRAN, P. 2015c. Cardiovascular disease and type 1 diabetes: prevalence, prediction and management in an ageing population. *Therapeutic Advances in Chronic Disease,* 6**,** 347-374.

LEE, W. R. 2000. The changing demography of diabetes mellitus in Singapore. *Diabetes Res Clin Pract,* 50 Suppl 2**,** S35-9.

LENTERS-WESTRA 2016. An evaluation of the Quo-Test® performance against NGSP criteria and sigma-metric.

LEON, B. M. & MADDOX, T. M. 2015. Diabetes and cardiovascular disease: Epidemiology, biological mechanisms, treatment recommendations and future research. *World Journal of Diabetes,* 6**,** 1246-1258.

LI, G., ZHANG, P., WANG, J., GREGG, E. W., YANG, W., GONG, Q., LI, H., LI, H., JIANG, Y., AN, Y., SHUAI, Y., ZHANG, B., ZHANG, J., THOMPSON, T. J., GERZOFF, R. B., ROGLIC, G., HU, Y. & BENNETT, P. H. 2008. The long-term effect of lifestyle interventions to prevent diabetes in the China Da Qing Diabetes Prevention Study: a 20-year follow-up study. *Lancet,* 371**,** 1783-9.

LITTLE, R. R. & ROBERTS, W. L. 2009. A Review of Variant Hemoglobins Interfering with Hemoglobin A1c Measurement. *Journal of diabetes science and technology (Online),* 3**,** 446-451.

LORBER, D. 2014. Importance of cardiovascular disease risk management in patients with type 2 diabetes mellitus. *Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy,* 7**,** 169-183.

LORENZO, C. & HAFFNER, S. M. 2010. Performance Characteristics of the New Definition of Diabetes: The Insulin Resistance Atherosclerosis Study. *Diabetes Care,* 33**,** 335-337.

LUETHI, N., CIOCCARI, L., CRISMAN, M., BELLOMO, R., EASTWOOD, G. M. & MÅRTENSSON, J. 2016. Prevalence of ketosis, ketonuria, and ketoacidosis during liberal glycemic control in critically ill patients with diabetes: an observational study. *Critical Care,* 20**,** 297.

LUNENFELD, B. & STRATTON, P. 2013. The clinical consequences of an ageing world and preventive strategies. *Best practice & research. Clinical obstetrics & gynaecology,* 27**,** 643-659.

MAAS, A. & APPELMAN, Y. E. A. 2010. Gender differences in coronary heart disease. *Netherlands Heart Journal,* 18**,** 598-602.

MAJEED, A., EL-SAYED, A. A., KHOJA, T., ALSHAMSAN, R., MILLETT, C. & RAWAF, S. 2014. Diabetes in the Middle-East and North Africa: An update. *Diabetes Research and Clinical Practice,* 103**,** 218-222.

MANNUCCI, E., DICEMBRINI, I., LAURIA, A. & POZZILLI, P. 2013. Is Glucose Control Important for Prevention of Cardiovascular Disease in Diabetes? *Diabetes Care,* 36**,** S259-S263.

MARIA ROTELLA, C., PALA, L. & MANNUCCI, E. 2013. Role of Insulin in the Type 2 Diabetes Therapy: Past, Present and Future. *International Journal of Endocrinology and Metabolism,* 11**,** 137-144.

MARQUES, A., SARMENTO, H., MARTINS, J. & SABOGA NUNES, L. 2015. Prevalence of physical activity in European adults - Compliance with the World Health Organization's physical activity guidelines. *Prev Med,* 81**,** 333-8.

MARTÍN-TIMÓN, I. & DEL CAÑIZO-GÓMEZ, F. J. 2015. Mechanisms of hypoglycemia unawareness and implications in diabetic patients. *World Journal of Diabetes,* 6**,** 912-926.

MARTÍN-TIMÓN, I., SEVILLANO-COLLANTES, C., SEGURA-GALINDO, A. & DEL CAÑIZO-GÓMEZ, F. J. 2014. Type 2 diabetes and cardiovascular disease: Have all risk factors the same strength? *World Journal of Diabetes,* 5**,** 444-470.

MARUO, K. & YAMADA, Y. 2015. Near-infrared noninvasive blood glucose prediction without using multivariate analyses: introduction of imaginary spectra due to scattering change in the skin. *J Biomed Opt,* 20**,** 047003.

MATFIN, G. & PRATLEY, R. E. 2010. Advances in the treatment of prediabetes. *Therapeutic Advances in Endocrinology and Metabolism,* 1**,** 5-14.

MATHER, K. 2013. The Vascular Endothelium in Diabetes – A Therapeutic Target? *Reviews in endocrine & metabolic disorders,* 14**,** 87-99.

MATHERS, C. D. & LONCAR, D. 2006. Projections of Global Mortality and Burden of Disease from 2002 to 2030. *PLOS Medicine,* 3**,** e442.

MCCRACKEN, E., MONAGHAN, M. & SREENIVASAN, S. 2018. Pathophysiology of the metabolic syndrome. *Clinics in Dermatology,* 36**,** 14-20.

MEHTA, A., MARSO, S. P. & NEELAND, I. J. 2017. Liraglutide for weight management: a critical review of the evidence. *Obesity Science & Practice,* 3**,** 3-14.

MEHTA, S. R., KASHYAP, A. S. & DAS, S. 2009. Diabetes Mellitus in India: The Modern Scourge. *Medical Journal, Armed Forces India,* 65**,** 50-54.

MILLER, C. D., BARNES, C. S., PHILLIPS, L. S., ZIEMER, D. C., GALLINA, D. L., COOK, C. B., MARYMAN, S. D. & EL-KEBBI, I. M. 2003. Rapid A1c Availability Improves Clinical Decision-Making in an Urban Primary Care Clinic. *Diabetes Care,* 26**,** 1158-1163.

MIRANDA, J., KINRA, S., CASAS, J., DAVEY SMITH, G. & EBRAHIM, S. 2008. Non-communicable diseases in low- and middle-income countries: context, determinants and health policy. *Trop Med Int Health,* 13**,** 1225 - 1234.

MISRA, A. 2015. Ethnic-Specific Criteria for Classification of Body Mass Index: A Perspective for Asian Indians and American Diabetes Association Position Statement. *Diabetes Technology & Therapeutics,* 17**,** 667-671.

MISRA, S., OLIVER, N. S. & DORNHORST, A. 2013. Diabetic ketoacidosis: not always due to type 1 diabetes. *BMJ,* 346.

MISRA, U. K., KALITA, J. & NAIR, P. P. 2008. Diagnostic approach to peripheral neuropathy. *Annals of Indian Academy of Neurology,* 11**,** 89-97.

MIYAZAKI, Y., GLASS, L., TRIPLITT, C., WAJCBERG, E., MANDARINO, L. J. & DEFRONZO, R. A. 2002. Abdominal fat distribution and peripheral and hepatic insulin resistance in type 2 diabetes mellitus. *Am J Physiol Endocrinol Metab,* 283**,** E1135-43.

MOKDAD, A. 2016. The Global Burden of Disease: A critical resource for informed policy making in the Gulf region. *Journal of Health Specialties,* 4**,** 162-172.

MONTESI, L., CALETTI, M. T. & MARCHESINI, G. 2016. Diabetes in migrants and ethnic minorities in a changing World. *World Journal of Diabetes,* 7**,** 34-44.

MOSES, R. G. 2010. Repaglinide/metformin fixed-dose combination to improve glycemic control in patients with type 2 diabetes: an update. *Diabetes, metabolic syndrome and obesity : targets and therapy,* 3**,** 145-154.

MULLUGETA, Y., CHAWLA, R., KEBEDE, T. & WORKU, Y. 2012. Dyslipidemia Associated with Poor Glycemic Control in Type 2 Diabetes Mellitus and the Protective Effect of Metformin Supplementation. *Indian Journal of Clinical Biochemistry,* 27**,** 363-369.

MUNSHI, M. N., FLOREZ, H., HUANG, E. S., KALYANI, R. R., MUPANOMUNDA, M., PANDYA, N., SWIFT, C. S., TAVEIRA, T. H. & HAAS, L. B. 2016. Management of Diabetes in Long-term Care and Skilled Nursing Facilities: A Position Statement of the American Diabetes Association. *Diabetes Care,* 39**,** 308-318.

MURAKAMI, Y., HUXLEY, R. R., LAM, T. H., TSUKINOKI, R., FANG, X., KIM, H. C. & WOODWARD, M. 2012. Diabetes, body mass index and the excess risk of coronary heart disease, ischemic and hemorrhagic stroke in the Asia Pacific Cohort Studies Collaboration. *Prev Med,* 54**,** 38-41.

MURGUÍA-ROMERO, M., JIMÉNEZ-FLORES, J. R., SIGRIST-FLORES, S. C., ESPINOZA-CAMACHO, M. A., JIMÉNEZ-MORALES, M., PIÑA, E., MÉNDEZ-CRUZ, A. R.,

VILLALOBOS-MOLINA, R. & REAVEN, G. M. 2013. Plasma triglyceride/HDL-cholesterol ratio, insulin resistance, and cardiometabolic risk in young adults. *Journal of Lipid Research,* 54**,** 2795-2799.

MURRAY, C. J., VOS, T., LOZANO, R., NAGHAVI, M., FLAXMAN, A. D., MICHAUD, C., EZZATI, M., SHIBUYA, K., SALOMON, J. A., ABDALLA, S., ABOYANS, V., ABRAHAM, J., ACKERMAN, I., AGGARWAL, R., AHN, S. Y., ALI, M. K., ALVARADO, M., ANDERSON, H. R., ANDERSON, L. M., ANDREWS, K. G., ATKINSON, C., BADDOUR, L. M., BAHALIM, A. N., BARKER-COLLO, S., BARRERO, L. H., BARTELS, D. H., BASANEZ, M. G., BAXTER, A., BELL, M. L., BENJAMIN, E. J., BENNETT, D., BERNABE, E., BHALLA, K., BHANDARI, B., BIKBOV, B., BIN ABDULHAK, A., BIRBECK, G., BLACK, J. A., BLENCOWE, H., BLORE, J. D., BLYTH, F., BOLLIGER, I., BONAVENTURE, A., BOUFOUS, S., BOURNE, R., BOUSSINESQ, M., BRAITHWAITE, T., BRAYNE, C., BRIDGETT, L., BROOKER, S., BROOKS, P., BRUGHA, T. S., BRYAN-HANCOCK, C., BUCELLO, C., BUCHBINDER, R., BUCKLE, G., BUDKE, C. M., BURCH, M., BURNEY, P., BURSTEIN, R., CALABRIA, B., CAMPBELL, B., CANTER, C. E., CARABIN, H., CARAPETIS, J., CARMONA, L., CELLA, C., CHARLSON, F., CHEN, H., CHENG, A. T., CHOU, D., CHUGH, S. S., COFFENG, L. E., COLAN, S. D., COLQUHOUN, S., COLSON, K. E., CONDON, J., CONNOR, M. D., COOPER, L. T., CORRIERE, M., CORTINOVIS, M., DE VACCARO, K. C., COUSER, W., COWIE, B. C., CRIQUI, M. H., CROSS, M., DABHADKAR, K. C., DAHIYA, M., DAHODWALA, N., DAMSERE-DERRY, J., DANAEI, G., DAVIS, A., DE LEO, D., DEGENHARDT, L., DELLAVALLE, R., DELOSSANTOS, A., DENENBERG, J., DERRETT, S., DES JARLAIS, D. C., DHARMARATNE, S. D., et al. 2012. Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet,* 380**,** 2197-223.

MURTHY, S. S., KIRAN, V. S. R., MATHUR, S. K. & MURTHY, S. N. 2008. Noninvasive Transcutaneous Sampling of Glucose by Electroporation. *Journal of Diabetes Science and Technology,* 2**,** 250-254.

MUSAIGER, A. 2011a. Overweight and Obesity in Eastern Mediterranean Region: Prevalence and Possible Causes. *Journal of Obesity,* 2011.

MUSAIGER, A. O. 2011b. Overweight and Obesity in Eastern Mediterranean Region: Prevalence and Possible Causes. *Journal of Obesity,* 2011**,** 407237.

NAGARAJA, P., HONNUR, K., SHIVAKUMAR, A. & SHRESTHA, A. K. 2012. Development of quantitative enzymatic method and its validation for the assay of glucose in human serum. *Clinical Biochemistry,* 45**,** 139-143.

NAJJAR, S. 2001. Insulin Action: Molecular Basis of Diabetes. *eLS.* John Wiley & Sons, Ltd.

NAKAGAMI, T., QIAO, Q., CARSTENSEN, B., NHR-HANSEN, C., HU, G., TUOMILEHTO, J., BALKAU, B. & BORCH-JOHNSEN, K. 2003. Age, body mass index and Type 2 diabetes-associations modified by ethnicity. *Diabetologia,* 46**,** 1063-70.

NARAYAN KMV, Z. P., KANAYA AM, ET AL. 2006. The Pandemic and Potential Solutions. *In:* JAMISON DT, B. J., MEASHAM AR, ET AL. (ed.) *Disease Control Priorities in Developing Countries. 2nd edition.*

NASIR, N. M., THEVARAJAH, M. & YEAN, C. Y. 2010. Hemoglobin variants detected by hemoglobin A1c (HbA1c) analysis and the effects on HbA1c measurements. *International Journal of Diabetes in Developing Countries,* 30**,** 86-90.

NASRI, H. & RAFIEIAN-KOPAEI, M. 2014. Metformin: Current knowledge. *Journal of Research in Medical Sciences : The Official Journal of Isfahan University of Medical Sciences,* 19**,** 658-664.

NATHAN, D. M. 1981. Labile glycosylated hemoglobin contributes to hemoglobin A1 as measured by liquid chromatography or electrophoresis. *Clinical Chemistry,* 27**,** 1261-1263.

NATHAN, D. M., KUENEN, J., BORG, R., ZHENG, H., SCHOENFELD, D. & HEINE, R. J. 2008. Translating the A1C Assay Into Estimated Average Glucose Values. *Diabetes Care,* 31**,** 1473-1478.

NATIONAL HEALTH SERVICE 2010. NHS Atlas of Variation in Healthcare.

NATIONAL HEALTH SERVICE 2015. NHS Atlas of Variation in Healthcare.

NCDS 2014. Evolution of diabetes over time.

NDEFO, U. A., ANIDIOBI, N. O., BASHEER, E. & EATON, A. T. 2015. Empagliflozin (Jardiance): A Novel SGLT2 Inhibitor for the Treatment of Type-2 Diabetes. *Pharmacy and Therapeutics,* 40**,** 364-368.

NENTWICH, M. M. & ULBIG, M. W. 2015. Diabetic retinopathy - ocular complications of diabetes mellitus. *World Journal of Diabetes,* 6**,** 489-499.

NGSP. 2016. National Glycohemoglobin Standardization Program homepage. Available: www.ngsp.org [Accessed 4 July 2016].

NICHOLAOS KAKOUROS, RADE, J. J., ANTONIOS KOURLIOUROS & RESAR, J. R. 2011. Platelet Function in Patients with Diabetes Mellitus: From a Theoretical to a Practical Perspective. *International Journal of Endocrinology,* 2011.

NICHOLS, G. A., HILLIER, T. A. & BROWN, J. B. 2007. Progression From Newly Acquired Impaired Fasting Glusose to Type 2 Diabetes. *Diabetes Care,* 30**,** 228-233.

NYENWE, E. A., JERKINS, T. W., UMPIERREZ, G. E. & KITABCHI, A. E. 2011. Management of type 2 diabetes: evolving strategies for the treatment of patients with type 2 diabetes. *Metabolism: clinical and experimental,* 60**,** 1-23.

OLDROYD, J., BANERJEE, M., HEALD, A. & CRUICKSHANK, K. 2005. Diabetes and ethnic minorities. *Postgraduate Medical Journal,* 81**,** 486-490.

OSAKI, A., OKADA, S., SAITO, T., YAMADA, E., ONO, K., NIIJIMA, Y., HOSHI, H. & YAMADA, M. 2016. Renal threshold for glucose reabsorption predicts diabetes improvement by sodium-glucose cotransporter 2 inhibitor therapy. *Journal of Diabetes Investigation,* 7**,** 751-754.

OZA-FRANK, R. & NARAYAN, K. M. V. 2010. Overweight and Diabetes Prevalence Among US Immigrants. *American Journal of Public Health,* 100**,** 661-668.

OZAWA, G. Y., BEARSE, M. A. & ADAMS, A. J. 2015. Male–Female Differences in Diabetic Retinopathy? *Current Eye Research,* 40**,** 234-246.

PANDEY, R., DINGARI, N. C., SPEGAZZINI, N., DASARI, R. R., HOROWITZ, G. L. & BARMAN, I. 2015. Emerging trends in optical sensing of glycemic markers for diabetes monitoring. *Trends in analytical chemistry : TRAC,* 64**,** 100-108.

PARK, M. H., KIM, D. H., LEE, E. K., KIM, N. D., IM, D. S., LEE, J., YU, B. P. & CHUNG, H. Y. 2014. Age-related inflammation and insulin resistance: a review of their intricate interdependency. *Archives of Pharmacal Research,* 37**,** 1507-1514.

PARKIN, C. G. & DAVIDSON, J. A. 2009. Value of Self-Monitoring Blood Glucose Pattern Analysis in Improving Diabetes Outcomes. *Journal of diabetes science and technology (Online),* 3**,** 500-508.

PASNOOR, M., DIMACHKIE, M. M., KLUDING, P. & BAROHN, R. J. 2013. DIABETIC NEUROPATHY PART 1: OVERVIEW AND SYMMETRIC PHENOTYPES. *Neurologic clinics,* 31**,** 425-445.

PASQUEL, F. J. & UMPIERREZ, G. E. 2014. Hyperosmolar Hyperglycemic State: A Historic Review of the Clinical Presentation, Diagnosis, and Treatment. *Diabetes Care,* 37**,** 3124-3131.

PATEL, P. & ABATE, N. 2013. Body Fat Distribution and Insulin Resistance. *Nutrients,* 5**,** 2019-2027.

PATEL, S. & SANTANI, D. 2009. Role of NF-kappa B in the pathogenesis of diabetes and its associated complications. *Pharmacol Rep,* 61**,** 595-603.

PENTTILÄ, I., PENTTILÄ, K., HOLM, P., LAITINEN, H., RANTA, P., TÖRRÖNEN, J. & RAURAMAA, R. 2016. Methods, units and quality requirements for the analysis of haemoglobin A(1c) in diabetes mellitus. *World Journal of Methodology,* 6**,** 133-142.

PERCIACCANTE, A., FIORENTINI, A., PARIS, A., SERRA, P. & TUBANI, L. 2006. Circadian rhythm of the autonomic nervous system in insulin resistant subjects with normoglycemia, impaired fasting glycemia, impaired glucose tolerance, type 2 diabetes mellitus. *BMC Cardiovasc Disord,* 6**,** 19.

PÉREZ, C. M., FEBO-VÁZQUEZ, I., GUZMÁN, M., ORTIZ, A. P. & SUÁREZ, E. 2012. Are Adults Diagnosed with Diabetes achieving the American Diabetes Association Clinical Practice Recommendations? *Puerto Rico health sciences journal,* 31**,** 18-23.

PERNICOVA, I. & KORBONITS, M. 2014. Metformin--mode of action and clinical implications for diabetes and cancer. *Nat Rev Endocrinol,* 10**,** 143-56.

PERRY, R. J., SAMUEL, V. T., PETERSEN, K. F. & SHULMAN, G. I. 2014. The role of hepatic lipids in hepatic insulin resistance and type 2 diabetes. *Nature,* 510**,** 84-91.

PETERSEN, K. F. & SHULMAN, G. I. 2006. Etiology of insulin resistance. *Am J Med,* 119**,** S10-6.

PICKUP, J. 1989. Human insulin. *BMJ : British Medical Journal,* 299**,** 991-993.

PIMENTA, W., KORYTKOWSKI, M., MITRAKOU, A., JENSSEN, T., YKI-JARVINEN, H., EVRON, W., DAILEY, G. & GERICH, J. 1995. Pancreatic beta-cell dysfunction as the primary genetic lesion in NIDDM. Evidence from studies in normal glucose-tolerant individuals with a first-degree NIDDM relative. *Jama,* 273**,** 1855-61.

PLÜDDEMANN, A., PRICE, C. P., THOMPSON, M., WOLSTENHOLME, J. & HENEGHAN, C. 2011. Primary care diagnostic technology update: point-of-care testing for glycosylated haemoglobin. *British Journal of General Practice,* 61**,** 139-140.

POLONSKY, K. S., STURIS, J. & BELL, G. I. 1996. Seminars in Medicine of the Beth Israel Hospital, Boston. Non-insulin-dependent diabetes mellitus - a genetically programmed failure of the beta cell to compensate for insulin resistance. *N Engl J Med,* 334**,** 777-83.

PRAVEEN, E. P., SAHOO, J., KHURANA, M. L., KULSHRESHTHA, B., KHADGAWAT, R., GUPTA, N., DWIVEDI, S. N., KUMAR, G., PRABHAKARAN, D. & AMMINI, A. C. 2012. Insulin sensitivity and β-cell function in normoglycemic offspring of individuals with type 2 diabetes mellitus: Impact of line of inheritance. *Indian Journal of Endocrinology and Metabolism,* 16**,** 105-111.

PSALTOPOULOU, T., ILIAS, I. & ALEVIZAKI, M. 2010. The role of diet and lifestyle in primary, secondary, and tertiary diabetes prevention: a review of meta-analyses. *Rev Diabet Stud,* 7**,** 26-35.

PURVINIS, G., CAMERON, B. D. & ALTROGGE, D. M. 2011. Noninvasive Polarimetric-Based Glucose Monitoring: An in Vivo Study. *Journal of Diabetes Science and Technology,* 5**,** 380-387.

QIAO, Q., HU, G., TUOMILEHTO, J., NAKAGAMI, T., BALKAU, B., BORCH-JOHNSEN, K., RAMACHANDRAN, A., MOHAN, V., IYER, S. R., TOMINAGA, M., KIYOHARA, Y., KATO, I., OKUBO, K., NAGAI, M., SHIBAZAKI, S., YANG, Z., TONG, Z., FAN, Q., WANG, B., CHEW, S. K., TAN, B. Y., HENG, D., EMMANUEL, S., TAJIMA, N., IWAMOTO, Y., SNEHALATHA, C., VIJAY, V., KAPUR, A., DONG, Y., NAN, H., GAO, W., SHI, H. & FU, F. 2003. Age- and sex-specific prevalence of diabetes and impaired glucose regulation in 11 Asian cohorts. *Diabetes Care,* 26**,** 1770-80.

QU, H.-Q., LI, Q., RENTFRO, A. R., FISHER-HOCH, S. P. & MCCORMICK, J. B. 2011. The Definition of Insulin Resistance Using HOMA-IR for Americans of Mexican Descent Using Machine Learning. *PLoS ONE,* 6**,** e21041.

QUIANZON, C. C. & CHEIKH, I. 2012. History of insulin. *Journal of Community Hospital Internal Medicine Perspectives,* 2**,** 10.3402/jchimp.v2i2.18701.

RAHMAN, M. & BERENSON, A. B. 2010. Accuracy of current body mass index obesity classification for white, black, and Hispanic reproductive-age women. *Obstet Gynecol,* 115**,** 982-8.

RAJENDRAN, P., RENGARAJAN, T., THANGAVEL, J., NISHIGAKI, Y., SAKTHISEKARAN, D., SETHI, G. & NISHIGAKI, I. 2013. The Vascular Endothelium and Human Diseases. *International Journal of Biological Sciences,* 9**,** 1057-1069.

RAJENDRAN, R. & RAYMAN, G. 2014. Point-of-Care Blood Glucose Testing for Diabetes Care in Hospitalized Patients: An Evidence-Based Review. *Journal of Diabetes Science and Technology,* 8**,** 1081-1090.

RAMACHANDRAN, A. 2014. Know the signs and symptoms of diabetes. *The Indian Journal of Medical Research,* 140**,** 579-581.

RAMACHANDRAN, A., MA, R. C. & SNEHALATHA, C. 2010. Diabetes in Asia. *Lancet,* 375**,** 408-18.

RAMACHANDRAN, A., RIDDLE, M. C., KABALI, C. & GERSTEIN, H. C. 2012a. Relationship between A1C and fasting plasma glucose in dysglycemia or type 2 diabetes: an analysis of baseline data from the ORIGIN trial. *Diabetes Care,* 35**,** 749-53.

RAMACHANDRAN, A., SNEHALATHA, C., SHETTY, A. S. & NANDITHA, A. 2012b. Trends in prevalence of diabetes in Asian countries. *World Journal of Diabetes,* 3**,** 110-117.

RANA, J. S., LIU, J. Y., MOFFET, H. H., SOLOMON, M. D., GO, A. S., JAFFE, M. G. & KARTER, A. J. 2015. Metabolic Dyslipidemia and Risk of Coronary Heart Disease in 28,318 Adults With Diabetes Mellitus and Low-Density Lipoprotein Cholesterol <100 mg/dl. *American Journal of Cardiology,* 116**,** 1700-1704.

RAUTIO, N., JOKELAINEN, J., OKSA, H., SAARISTO, T., PELTONEN, M., PUOLIJOKI, H., TUOMILEHTO, J., VANHALA, M., MOILANEN, L., UUSITUPA, M. & KEINANEN-KIUKAANNIEMI, S. 2012. Family history of diabetes and effectiveness of lifestyle counselling on the cardio-metabolic risk profile in individuals at high risk of Type 2 diabetes: 1-year follow-up of the FIN-D2D project. *Diabet Med,* 29**,** 207-11.

RAZA, A. K. M. M. 2016. *Peripheral Neuropathies Associated With Diabetes Mellitus: A Review*.

RENDELL, M., HULTHEN, U. L., TORNQUIST, C., GROOP, L. & MATTIASSON, I. 2001. Relationship between abdominal fat compartments and glucose and lipid metabolism in early postmenopausal women. *J Clin Endocrinol Metab,* 86**,** 744-9.

RIVARA, M. B. & MEHROTRA, R. 2014. Is Early Initiation of Dialysis Harmful? *Seminars in dialysis,* 27**,** 250-252.

ROBERTS, A. C. & PORTER, K. E. 2013. Cellular and molecular mechanisms of endothelial dysfunction in diabetes. *Diab Vasc Dis Res,* 10**,** 472-82.

ROBERTS, C. K., HEVENER, A. L. & BARNARD, R. J. 2013. Metabolic Syndrome and Insulin Resistance: Underlying Causes and Modification by Exercise Training. *Comprehensive Physiology,* 3**,** 1-58.

ROBLES, N. R., VILLA, J. & HERNANDEZ GALLEGO, R. 2015. Non-Proteinuric Diabetic Nephropathy. *Journal of Clinical Medicine,* 4**,** 1761-1773.

RODRIGUEZ, B. L. 2006. Dietary Studies in the Multi-Ethnic Hawaiian Population. *Journal of the American Dietetic Association,* 106**,** 209-210.

ROHLFING, C. L., WIEDMEYER, H.-M., LITTLE, R. R., ENGLAND, J. D., TENNILL, A. & GOLDSTEIN, D. E. 2002. Defining the Relationship Between Plasma Glucose and HbA1c, analysis of glucose profiles and hbA1c in the Diabetes Control and Complication Trial. *Diabetes Care,* 25**,** 275-278.

ROSENBERG, N. R., PORTEGIES, P., DE VISSER, M. & VERMEULEN, M. 2001. Diagnostic investigation of patients with chronic polyneuropathy: evaluation of a clinical guideline. *Journal of Neurology, Neurosurgery & Psychiatry,* 71**,** 205-209.

ROSENFELD, L. 2002. Insulin: Discovery and Controversy. *Clinical Chemistry,* 48**,** 2270-2288.

ROSHAN, B. & STANTON, R. C. 2013. A story of microalbuminuria and diabetic nephropathy. *Journal of Nephropathology,* 2**,** 234-240.

ROYLE P, MISTRY H, AUGUSTE &):, E. A. 2015. *The landmark trials: Diabetic Retinopathy Study and Early Treatment Diabetic Retinopathy Study. ,* UK, NIHR Journals Library.

RUBINS, H. B., ROBINS, S. J., COLLINS, D., NELSON, D. B., ELAM, M. B., SCHAEFER, E. J., FAAS, F. H. & ANDERSON, J. W. 2002. Diabetes, plasma insulin, and cardiovascular disease: subgroup analysis from the Department of Veterans Affairs high-density lipoprotein intervention trial (VA-HIT). *Arch Intern Med,* 162**,** 2597-604.

RUDERMAN, N., CHISHOLM, D., PI-SUNYER, X. & SCHNEIDER, S. 1998. The metabolically obese, normal-weight individual revisited. *Diabetes,* 47**,** 699-713.

RUI, L. 2014. Energy Metabolism in the Liver. *Comprehensive Physiology,* 4**,** 177-197.

RYAN, K., BAIN, B. J., WORTHINGTON, D., JAMES, J., PLEWS, D., MASON, A., ROPER, D., REES, D. C., DE LA SALLE, B., STREETLY, A. & ON BEHALF OF THE BRITISH COMMITTEE FOR STANDARDS IN, H. 2010. Significant haemoglobinopathies: guidelines for screening and diagnosis. *British Journal of Haematology,* 149**,** 35-49.

SAAD, M. F., KNOWLER, W. C., PETTITT, D. J., NELSON, R. G. & BENNETT, P. H. 1988. Transient impaired glucose tolerance in Pima Indians: is it important? *BMJ : British Medical Journal,* 297**,** 1438-1441.

SAADI, H., AL-KAABI, J., BENBARKA, M., KHALILI, A., ALMAHMEED, W., NAGELKERKE, N., ABDEL-WARETH, L., AL ESSA, A., YASIN, J., AL-DABBAGH, B. & KAZAM, E. 2010. Prevalence of undiagnosed diabetes and quality of care in diabetic patients followed at primary and tertiary clinics in Abu Dhabi, United Arab Emirates. *Rev Diabet Stud,* 7**,** 293-302.

SAARISTO, T., MOILANEN, L., KORPI-HYÖVÄLTI, E., VANHALA, M., SALTEVO, J., NISKANEN, L., JOKELAINEN, J., PELTONEN, M., OKSA, H., TUOMILEHTO, J., UUSITUPA, M. & KEINÄNEN-KIUKAANNIEMI, S. 2010. Lifestyle Intervention for Prevention of Type 2 Diabetes in Primary Health Care: One-year follow-up of the Finnish National Diabetes Prevention Program (FIN-D2D). *Diabetes Care,* 33**,** 2146-2151.

SACKS, D. B. 2011. A1C Versus Glucose Testing: A Comparison. *Diabetes Care,* 34**,** 518-523.

SACKS, D. B. 2012. Measurement of Hemoglobin A(1c): A new twist on the path to harmony. *Diabetes Care,* 35**,** 2674-2680.

SAFI, S. Z., QVIST, R., KUMAR, S., BATUMALAIE, K. & ISMAIL, I. S. B. 2014. Molecular Mechanisms of Diabetic Retinopathy, General Preventive Strategies, and Novel Therapeutic Targets. *BioMed Research International,* 2014**,** 801269.

SAIDI, O., O'FLAHERTY, M., MANSOUR, N. B., AISSI, W., LASSOUED, O., CAPEWELL, S., CRITCHLEY, J. A., MALOUCHE, D., ROMDHANE, H. B. & ON BEHALF OF, E. C. F. P. F. M. P. 2015. Forecasting Tunisian type 2 diabetes prevalence to 2027: validation of a simple model. *BMC Public Health,* 15**,** 104.

SALAS-SALVADÓ, J., BULLÓ, M., BABIO, N., MARTÍNEZ-GONZÁLEZ, M. Á., IBARROLA-JURADO, N., BASORA, J., ESTRUCH, R., COVAS, M. I., CORELLA, D., ARÓS, F., RUIZ-GUTIÉRREZ, V., ROS, E. & FOR THE, P. S. I. 2011. Reduction in the Incidence of Type 2 Diabetes With the Mediterranean Diet: Results of the PREDIMED-Reus nutrition intervention randomized trial. *Diabetes Care,* 34**,** 14-19.

SAMPANIS, C. & ZAMBOULIS, C. 2008. Arterial hypertension in diabetes mellitus: from theory to clinical practice. *Hippokratia,* 12**,** 74-80.

SARAO, V., VERITTI, D., BOSCIA, F. & LANZETTA, P. 2014. Intravitreal Steroids for the Treatment of Retinal Diseases. *The Scientific World Journal,* 2014**,** 14.

SCHÖNFELD, P. & REISER, G. 2013. Why does brain metabolism not favor burning of fatty acids to provide energy? - Reflections on disadvantages of the use of free fatty acids as fuel for brain. *Journal of Cerebral Blood Flow & Metabolism,* 33**,** 1493-1499.

SCHREIBER, A. K., NONES, C. F. M., REIS, R. C., CHICHORRO, J. G. & CUNHA, J. M. 2015. Diabetic neuropathic pain: Physiopathology and treatment. *World Journal of Diabetes,* 6**,** 432-444.

SCHWARTZ, K. L., MONSUR, J., HAMMAD, A., BARTOCES, M. G. & NEALE, A. V. 2009. Comparison of Point of Care and Laboratory HbA1c Analysis: A MetroNet Study. *The Journal of the American Board of Family Medicine,* 22**,** 461-463.

SCHWARTZ, S. S. 2013. Optimizing glycemic control and minimizing the risk of hypoglycemia in patients with type 2 diabetes. *Drugs in Context,* 2013**,** 212255.

SELVIN, E., STEFFES, M. W., ZHU, H., MATSUSHITA, K., WAGENKNECHT, L., PANKOW, J., CORESH, J. & BRANCATI, F. L. 2010. Glycated hemoglobin, diabetes, and cardiovascular risk in nondiabetic adults. *N Engl J Med,* 362**,** 800-11.

SEROUR, M., ALQHENAEI, H., AL-SAQABI, S., MUSTAFA, A.-R. & BEN-NAKHI, A. 2007. Cultural factors and patients' adherence to lifestyle measures. *The British Journal of General Practice,* 57**,** 291-295.

SEURING, T., ARCHANGELIDI, O. & SUHRCKE, M. 2015. The Economic Costs of Type 2 Diabetes: A Global Systematic Review. *Pharmacoeconomics*.

SHAH, S. M., ALI, R., LONEY, T., AZIZ, F., ELBARAZI, I., AL DHAHERI, S., FAROOQI, M. H. & BLAIR, I. 2017. Prevalence of Diabetes among Migrant Women and Duration of Residence in the United Arab Emirates: A Cross Sectional Study. *PLOS ONE,* 12**,** e0169949.

SHERIF, S. & SUMPIO, B. E. 2015. Economic development and diabetes prevalence in MENA countries: Egypt and Saudi Arabia comparison. *World Journal of Diabetes,* 6**,** 304-311.

SHETTY, P. & SCHMIDHUBER, J. 2006. Introductory lecture the epidemiology and determinants of obesity in developed and developing countries. *Int J Vitam Nutr Res,* 76**,** 157-62.

SHUBROOK, J. H., BOKAIE, B. B. & ADKINS, S. E. 2015. Empagliflozin in the treatment of type 2 diabetes: evidence to date. *Drug Des Devel Ther***,** 5793-5803.

SHUYU NG, C., TOH, M. P. H. S., KO, Y. & YU-CHIA LEE, J. 2015. Direct Medical Cost of Type 2 Diabetes in Singapore. *PLOS ONE,* 10**,** e0122795.

SINGH, R. B., MENGI, S. A., XU, Y.-J., ARNEJA, A. S. & DHALLA, N. S. 2002. Pathogenesis of atherosclerosis: A multifactorial process. *Experimental & Clinical Cardiology,* 7**,** 40-53.

SINGH, V. P., BALI, A., SINGH, N. & JAGGI, A. S. 2014. Advanced Glycation End Products and Diabetic Complications. *The Korean Journal of Physiology & Pharmacology : Official Journal of the Korean Physiological Society and the Korean Society of Pharmacology,* 18**,** 1-14.

SKYLER, J. S., BERGENSTAL, R., BONOW, R. O., BUSE, J., DEEDWANIA, P., GALE, E. A. M., HOWARD, B. V., KIRKMAN, M. S., KOSIBOROD, M., REAVEN, P. & SHERWIN, R. S. 2009. Intensive Glycemic Control and the Prevention of Cardiovascular Events: Implications of the ACCORD, ADVANCE, and VA Diabetes Trials: A position statement of the American Diabetes Association and a scientific statement of the American College of Cardiology Foundation and the American Heart Association. *Diabetes Care,* 32**,** 187-192.

SOLA, D., ROSSI, L., SCHIANCA, G. P. C., MAFFIOLI, P., BIGLIOCCA, M., MELLA, R., CORLIANÒ, F., FRA, G. P., BARTOLI, E. & DEROSA, G. 2015. Sulfonylureas and their use in clinical practice. *Archives of Medical Science : AMS,* 11**,** 840-848.

SONKSEN, P. & SONKSEN, J. 2000. Insulin: understanding its action in health and disease. *British Journal of Anaesthesia,* 85**,** 69-79.

SPRAGUE, J. E. & ARBELÁEZ, A. M. 2011. Glucose Counterregulatory Responses to Hypoglycemia. *Pediatric endocrinology reviews : PER,* 9**,** 463-475.

STAMLER, J., VACCARO, O., NEATON, J. D. & WENTWORTH, D. 1993. Diabetes, other risk factors, and 12-yr cardiovascular mortality for men screened in the Multiple Risk Factor Intervention Trial. *Diabetes Care,* 16.

STEIN, J. H., ASTHANA, A., SMITH, S. S., PIPER, M. E., LOH, W.-Y., FIORE, M. C. & BAKER, T. B. 2014. Smoking Cessation and the Risk of Diabetes Mellitus and Impaired Fasting Glucose: Three-Year Outcomes after a Quit Attempt. *PLoS ONE,* 9**,** e98278.

STONE, J., CARSON, A. & SHARPE, M. 2005. Functional symptoms and signs in neurology: assessment and diagnosis. *Journal of Neurology, Neurosurgery & Psychiatry,* 76**,** i2-i12.

STROEBE, M., SCHUT, H. & STROEBE, W. 2007. Health outcomes of bereavement. *Lancet,* 370**,** 1960-73.

SUSLOVA, T. E., SITOZHEVSKII, A. V., OGURKOVA, O. N., KRAVCHENKO, E. S., KOLOGRIVOVA, I. V., ANFINOGENOVA, Y. & KARPOV, R. S. 2014. Platelet hemostasis in patients with metabolic syndrome and type 2 diabetes mellitus: cGMP- and NO-dependent mechanisms in the insulin-mediated platelet aggregation. *Frontiers in Physiology,* 5**,** 501.

TABÁK, A. G., HERDER, C., RATHMANN, W., BRUNNER, E. J. & KIVIMÄKI, M. 2012. Prediabetes: A high-risk state for developing diabetes. *Lancet,* 379**,** 2279-2290.

TAM, C. S., XIE, W., JOHNSON, W. D., CEFALU, W. T., REDMAN, L. M. & RAVUSSIN, E. 2012. Defining Insulin Resistance From Hyperinsulinemic-Euglycemic Clamps. *Diabetes Care,* 35**,** 1605-1610.

TASYUREK, H. M., ALTUNBAS, H. A., BALCI, M. K. & SANLIOGLU, S. 2014. Incretins: their physiology and application in the treatment of diabetes mellitus. *Diabetes Metab Res Rev,* 30**,** 354-71.

TATSUMI, Y., MORIMOTO, A., MIYAMATSU, N., NODA, M., OHNO, Y. & DEURA, K. 2015. Effect of body mass index on insulin secretion or sensitivity and diabetes. *Am J Prev Med,* 48**,** 128-35.

TAYLOR, R. 2012. Insulin Resistance and Type 2 Diabetes. *Diabetes,* 61**,** 778-779.

TAYLOR, R. 2013. Banting Memorial lecture 2012: reversing the twin cycles of type 2 diabetes. *Diabet Med,* 30**,** 267-75.

THARKAR, S., DEVARAJAN, A., KUMPATLA, S. & VISWANATHAN, V. 2010. The socioeconomics of diabetes from a developing country: a population based cost of illness study. *Diabetes Res Clin Pract,* 89**,** 334-40.

THIRUVOIPATI, T., KIELHORN, C. E. & ARMSTRONG, E. J. 2015. Peripheral artery disease in patients with diabetes: Epidemiology, mechanisms, and outcomes. *World Journal of Diabetes,* 6**,** 961-969.

TOTO, R. D. 2004. Microalbuminuria: Definition, Detection, and Clinical Significance. *The Journal of Clinical Hypertension,* 6**,** 2-7.

TUOMILEHTO, J., LINDSTROM, J., ERIKSSON, J. G., VALLE, T. T., HAMALAINEN, H., ILANNE-PARIKKA, P., KEINANEN-KIUKAANNIEMI, S., LAAKSO, M., LOUHERANTA, A., RASTAS, M., SALMINEN, V. & UUSITUPA, M. 2001. Prevention of type 2 diabetes mellitus by

changes in lifestyle among subjects with impaired glucose tolerance. *N Engl J Med,* 344**,** 1343-50.

TURKI, Y. M., HEGAZY, A. A. & ABAALKHAIL, B. A. 2016. Prevalence of Pre-Diabetes among Adults Attending Primary Health Care Centers, Makkah City, Saudi Arabia. *International Journal of Medical Research Professionals (IJMRP),* 2.

TUSO, P. 2014. Prediabetes and Lifestyle Modification: Time to Prevent a Preventable Disease. *The Permanente Journal,* 18**,** 88-93.

VAN BUREN, P. N. & TOTO, R. 2011. Hypertension in Diabetic Nephropathy: Epidemiology, Mechanisms, and Management. *Advances in chronic kidney disease,* 18**,** 28-41.

VAN HAEFTEN, T. W., PIMENTA, W., MITRAKOU, A., KORYTKOWSKI, M., JENSSEN, T., YKI-JARVINEN, H. & GERICH, J. E. 2000. Relative conributions of beta-cell function and tissue insulin sensitivity to fasting and postglucose-load glycemia. *Metabolism,* 49**,** 1318-25.

VÉLEZ, P. & GARCÍA, Á. 2015. Platelet proteomics in cardiovascular diseases. *Translational Proteomics,* 7**,** 15-29.

VERGÈS, B. 2015. Pathophysiology of diabetic dyslipidaemia: where are we? *Diabetologia,* 58**,** 886-899.

VIOLLET, B., GUIGAS, B., SANZ GARCIA, N., LECLERC, J., FORETZ, M. & ANDREELLI, F. 2012. Cellular and molecular mechanisms of metformin: an overview. *Clinical Science (London, England : 1979),* 122**,** 253-270.

VISWANATHAN, V., TILAK, P. & KUMPATLA, S. 2012. Risk factors associated with the development of overt nephropathy in type 2 diabetes patients: A 12 years observational study. *The Indian Journal of Medical Research,* 136**,** 46-53.

WAGNER, K.-H. & BRATH, H. 2012. A global view on the development of non communicable diseases. *Preventive Medicine,* 54, Supplement**,** S38-S41.

WANDELL, P. E., CARLSSON, A. & STEINER, K. H. 2010. Prevalence of diabetes among immigrants in the Nordic countries. *Curr Diabetes Rev,* 6**,** 126-33.

WANG, Y., MI, J., SHAN, X. Y., WANG, Q. J. & GE, K. Y. 2006. Is China facing an obesity epidemic and the consequences? The trends in obesity and chronic disease in China. *Int J Obes,* 31**,** 177-188.

WEIR, G. C. & BONNER-WEIR, S. 2004. Five stages of evolving beta-cell dysfunction during progression to diabetes. *Diabetes,* 53 Suppl 3**,** S16-21.

WEYER, C., BOGARDUS, C., MOTT, D. M. & PRATLEY, R. E. 1999. The natural history of insulin secretory dysfunction and insulin resistance in the pathogenesis of type 2 diabetes mellitus. *Journal of Clinical Investigation,* 104**,** 787-794.

WEYKAMP, C., JOHN, W. G. & MOSCA, A. 2009. A review of the challenge in measuring hemoglobin A1c. *J Diabetes Sci Technol,* 3**,** 439-45.

WHITLEY, H. P., YONG, E. V. & RASINEN, C. 2015. Selecting an A1C Point-of-Care Instrument. *Diabetes Spectrum : A Publication of the American Diabetes Association,* 28**,** 201-208.

WHO & IDF 2006. *Difinition and diagnosis of diabetes mellitus and intermediate hyperglycemia*.

WILCOX, G. 2005. Insulin and Insulin Resistance. *Clinical Biochemist Reviews,* 26**,** 19-39.

WILD, S., ROGLIC, G., GREEN, A., SICREE, R. & KING, H. 2004. Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. *Diabetes Care,* 27**,** 1047 - 1053.

WILLIAM T. CEFALU, M. E. A. 2015. Diabetes Care. *The Juornal of Clinical and Applied Research and Education.,* 38**,** S1-S90.

WILMOT, E. & IDRIS, I. 2014. Early onset type 2 diabetes: risk factors, clinical impact and management. *Therapeutic Advances in Chronic Disease,* 5**,** 234-244.

WING, R. R., LANG, W., WADDEN, T. A., SAFFORD, M., KNOWLER, W. C., BERTONI, A. G., HILL, J. O., BRANCATI, F. L., PETERS, A., WAGENKNECHT, L. & THE LOOK, A. R. G. 2011. Benefits of Modest Weight Loss in Improving Cardiovascular Risk Factors in Overweight and Obese Individuals With Type 2 Diabetes. *Diabetes Care,* 34**,** 1481-1486.

WORLD ECONOMIC FORUM 2014. Global risk, ninth edition.

WORLD HEALTH ORGANIZATION 2008. Waist circumference and waist-hip ratio. *WHO Library Cataloguing-in-Puplication Data.* Geneva: World Health Organization.

WORLD HEALTH ORGANIZATION 2014. Global status report on noncommunicable diseases.

WORLD HEALTH ORGANIZATION 2016. Kuwait, Country Cooperation Strategy.

WRIGHT, E., SCISM-BACON, J. L. & GLASS, L. C. 2006. Oxidative stress in type 2 diabetes: the role of fasting and postprandial glycaemia. *International Journal of Clinical Practice,* 60**,** 308-314.

WU, L., FERNANDEZ-LOAIZA, P., SAUMA, J., HERNANDEZ-BOGANTES, E. & MASIS, M. 2013. Classification of diabetic retinopathy and diabetic macular edema. *World Journal of Diabetes,* 4**,** 290-294.

WU, Y., DING, Y., TANAKA, Y. & ZHANG, W. 2014. Risk factors contributing to type 2 diabetes and recent advances in the treatment and prevention. *Int J Med Sci,* 11**,** 1185-200.

YEO, C.-P., TAN, C. H.-C. & JACOB, E. 2009. Haemoglobin A1c: evaluation of a new HbA1c point-of-care analyser Bio-Rad in2it in comparison with the DCA 2000 and central laboratory analysers. *Annals of Clinical Biochemistry,* 46**,** 373-376.

YIP, J., GENG, X., SHEN, J. & DING, Y. 2016. Cerebral Gluconeogenesis and Diseases. *Frontiers in Pharmacology,* 7**,** 521.

YOSHIDA, S., YOSHIDA, M., YAMAMOTO, M. & TAKEDA, J. 2013. Optical screening of diabetes mellitus using non-invasive Fourier-transform infrared spectroscopy technique for human lip. *J Pharm Biomed Anal,* 76**,** 169-76.

YOUSEFZADEH, G., SHOKOOHI, M. & NAJAFIPOUR, H. 2015. Inadequate control of diabetes and metabolic indices among diabetic patients: A population based study from the Kerman Coronary Artery Disease Risk Study (KERCADRS). *International Journal of Health Policy and Management,* 4**,** 271-277.

YU, H., XIE, L.-F., CHEN, K., YANG, G.-Y., XING, X.-Y., ZHAO, J.-J., HONG, T.-P., SHAN, Z.-Y., LI, H.-M., CHEN, B., TANG, X.-L., QI, L., YANG, J., FANG, Y., LI, T., WANG, S.-S., LIANG, X., YIN, Y.-Q. & MU, Y.-M. 2016. Initiating Characteristics of Early-onset Type 2 Diabetes Mellitus in Chinese Patients. *Chinese Medical Journal,* 129**,** 778-784.

ZAHRA, A., LEE, E. W., SUN, L. Y. & PARK, J. H. 2015. Cardiovascular disease and diabetes mortality, and their relation to socio-economical, environmental, and health behavioural factors in worldwide view. *Public Health,* 129**,** 385-95.

ZHANG, H.-Y., WU, C.-J. & LI, C.-S. 2013. Glycated hemoglobin A1C and diabetes mellitus in critically ill patients. *World Journal of Emergency Medicine,* 4**,** 201-204.

ZHANG, P., ZHANG, X., BROWN, J., VISTISEN, D., SICREE, R., SHAW, J. & NICHOLS, G. 2010a. Global healthcare expenditure on diabetes for 2010 and 2030. *Diabetes Res Clin Pract,* 87**,** 293-301.

ZHANG, P., ZHANG, Z. & KADOR, P. F. 2014. Polyol Effects on Growth Factors and MAPK Signaling in Rat Retinal Capillary Cells. *Journal of Ocular Pharmacology and Therapeutics,* 30**,** 4-11.

ZHANG, X., GREGG, E. W., WILLIAMSON, D. F., BARKER, L. E., THOMAS, W., BULLARD, K. M., IMPERATORE, G., WILLIAMS, D. E. & ALBRIGHT, A. L. 2010b. A1C Level and Future Risk of Diabetes: A Systematic Review. *Diabetes Care,* 33**,** 1665-1673.

ZHENG, S., SHI, S., REN, X., HAN, T., LI, Y., CHEN, Y., LIU, W., HOU, P. C. & HU, Y. 2016. Triglyceride glucose-waist circumference, a novel and effective predictor of diabetes in first-degree relatives of type 2 diabetes patients: cross-sectional and prospective cohort study. *Journal of Translational Medicine,* 14**,** 260.

ZHENG, Y., HE, M. & CONGDON, N. 2012. The worldwide epidemic of diabetic retinopathy. *Indian Journal of Ophthalmology,* 60**,** 428-431.

ZHOU, M.-S., WANG, A. & YU, H. 2014. Link between insulin resistance and hypertension: What is the evidence from evolutionary biology? *Diabetology & Metabolic Syndrome,* 6**,** 12.

ZHUO, X., ZHANG, P., BARKER, L., ALBRIGHT, A., THOMPSON, T. J. & GREGG, E. 2014. The Lifetime Cost of Diabetes and Its Implications for Diabetes Prevention. *Diabetes Care,* 37**,** 2557-2564.

Appendices

Prevalence of Type 2 DM and IR questionnaire (objective 1)

Patient number ☐ date ☐☐☐☐☐☐

Name of health care facility ☐ file number ☐

Name _____ Address ☐ Area

Mobile phone ☐

Demographic characteristics

Age Years [not known = 99] ☐☐ Sex (Male=1, Female=2) ☐

Marital status [Single=1, with partner/married=2, divorced/separated=3, widowed=4] ☐

Education (no education=1, primary=2, secondary=3, higher education=4) ☐

Occupation (governmental=1, private=2, employed for wages=3, out of work=4, retired=5, a homemaker=6) ☐

Medical history

Do you have diabetes? (Yes=1, No=2, don't know=3) ☐

Do you have Hypertension? (Yes=1, No=2, don't know=3) ☐

Laboratory data (if not available=999)

HbA1c level ☐

FPG level ☐

Insulin level ☐

LDL level ☐

HDL level ☐

Triglyceride level ☐

AIP ☐

DM and IR risk factors questionnaire (for objective 2)

Patient number ☐ date ☐☐☐☐☐☐

Name of health care facility ☐ file number ☐

Name _____ Address ☐

Mobile phone ☐

Patient group (DM=1, IR=2, No DM and No IR=3) ☐

Demographic characteristics

Age (Years) ☐☐ Sex (Male=1, Female=2) ☐

Marital status (Single=1, with partner/married=2, divorced/separated=3, widowed=4) ☐

Education (No education=0, primary=1, secondary=2, higher education=3, prefer not to answer=4) ☐

Occupation (governmental=1, private=2, labourer=3, not employed=4, other=5) ☐

Family history of T2DM (first degree=1, second degree=2, third degree=3, no history of T2DM=4) ☐

Ethnicity (Arab=1, South Asian=2, Indian=3, Persian=4, others=5) ☐

Anthropometric

Height (cm) ☐ Body Mass Index (BMI = kg/m^2) ☐

Weight (kg) ☐ Waist/Hip Ratio (WHR) ☐

Waist (cm) ☐ Systolic blood pressure (mmHg) ☐

Hip (cm) ☐ Diastolic blood pressure (mmHg) ☐

Life style

Smoking (Yes=1, No=2, ex-smoker=3, prefer not to answer=4) ☐

If smoker, how many cigarettes per day? (Don't know=99) ☐

Diet habits

Type of food	Per day			Per week			Per month		Never
	1 time	2 times	3 or more	1 time	2 times	3 or more	1 to 3 times	Less than once	
Vegetables/ fruits									
Fish									
Meat/Poultry									
Eggs									
Pastry									
Whole grain seeds									
Rice									
Full cream dairy products									
Fast food									
Canned/Bottled drinks containing sugar									
Do you consume olive oil?									

Physical activity

Think about all the **vigorous** activities that you did in the **last 7 days**. **Vigorous** physical activities refer to activities that take hard physical effort and make you breathe much harder than normal. Think *only* about those physical activities that you did for at least 10 minutes at a time.

3. During the **last 7 days**, on how many days did you do **vigorous** physical activities like heavy lifting, digging, aerobics, or fast bicycling?

   _____ **days per week**

   ☐ No vigorous physical activities → ***Skip to question 3***

4. How much time did you usually spend doing **vigorous** physical activities on one of those days?

_____ **hours per day**

_____ **minutes per day** Don't know/Not sure ☐

Think about all the **moderate** activities that you did in the **last 7 days**. **Moderate** activities refer to activities that take moderate physical effort and make you breathe somewhat harder than normal. Think only about those physical activities that you did for at least 10 minutes at a time.

5. During the **last 7 days**, on how many days did you do **moderate** physical activities like carrying light loads, bicycling at a regular pace, or doubles tennis? Do not include walking.

   _____ **days per week**

   ☐ No moderate physical activities

6. How much time did you usually spend doing **moderate** physical activities on one of those days?

   _____ **hours per day**

   _____ **minutes per day**

   ☐ Don't know/Not sure

Medical history

(Yes=1, No=2, don't know=3)

Have you ever been diagnosed with high blood glucose? ☐

Hypertensive? ☐

On any kind of antihypertensive medication? ☐

On any kind of Lipid lowering therapy? ☐

Have you ever been diagnosed with ischemic heart disease? ☐

History of polycystic ovaries (for females)? ☐

History of gestational diabetes (for females)? ☐

Do you have any other chronic disease? (Yes=1, No=2, don't know=3) if yes please specify)

IR in first degree relative's questionnaire (objective 3)

Patient number ☐ date ☐☐☐☐☐☐

Name of health care facility ☐ file number ☐

Name _____ Address ☐ Area

Mobile phone ☐

Patient is relative to group (DM=1, IR=2, No DM and No IR=3) ☐

Demographic characteristics

Age Years (not known=99) ☐☐ Sex (Male=1, Female=2) ☐

Marital status (Single=1, with partner/married=2, divorced/separated=3, widowed=4) ☐

Education (No education=0, primary=1, secondary=2, higher education=3, prefer not to answer=4) ☐

Occupation (governmental=1, private=2, labourer=3, not employed=4, other=5) ☐

Ethnicity (Arab=1, South Asian=2, Indian=3, Persian=4, others=5) ☐

Laboratory results

FPG level ☐

Insulin level ☐

HbA1c level ☐

Diabetic clinic questionnaire (for objective 4)

Patient number ☐ date ☐☐☐☐☐☐

Name of health care facility ☐ file number ☐

Name _____ Address ☐ Area

Mobile phone ☐

Demographic characteristics

Age Years ☐☐ Sex (Male=1, Female=2) ☐

Marital status (Single=1, with partner/married=2, divorced/separated=3, widowed=4) ☐

Education (No education=0, primary=1, secondary=2, higher education=3, prefer not to answer=4) ☐

Occupation (governmental=1, private=2, labourer=3, not employed=4, other=5) ☐

Family history of T2DM (first degree=1, second degree=2, third degree=3, no history of T2DM=4) ☐

Ethnicity (Arab=1, South Asian=2, Indian=3, Persian=4, others=5) ☐

Anthropometric

Height (cm) ☐ Body Mass Index (BMI = kg/m^2) ☐

Weight (kg) ☐ Hip (cm) ☐

Waist (cm) ☐ Systolic blood pressure (mmHg) ☐

Waist/Hip Ratio (WHR) ☐ Diastolic blood pressure (mmHg) ☐

Life style

Smoking (Yes=1, No=2, ex-smoker=3, prefer not to answer=4) ☐

If smoker, how many cigarettes per day? (Don't know) ☐

Diet habits

Type of food	Per day			Per week			Per month		Never
	1 time	2 times	3 or more	1 time	2 times	3 or more	1 to 3 times	Less than once	
Vegetables/ fruits									
Fish									
Meat/Poultry									
Eggs									
Pastry									
Whole grain seeds									
Rice									
Full cream dairy products									
Fast food									
Canned/Bottled drinks containing sugar									

Physical activity

Think about all the **vigorous** activities that you did in the **last 7 days**. **Vigorous** physical activities refer to activities that take hard physical effort and make you breathe much harder than normal. Think *only* about those physical activities that you did for at least 10 minutes at a time.

7. During the **last 7 days**, on how many days did you do **vigorous** physical activities like heavy lifting, digging, aerobics, or fast bicycling?

   _____ **days per week**

   ☐ No vigorous physical activities → ***Skip to question 3***

8. How much time did you usually spend doing **vigorous** physical activities on one of those days?

_____ **hours per day** Don't know/Not sure ☐

_____ **minutes per day**

Think about all the **moderate** activities that you did in the **last 7 days**. **Moderate** activities refer to activities that take moderate physical effort and make you breathe somewhat harder than normal. Think only about those physical activities that you did for at least 10 minutes at a time.

9. During the **last 7 days**, on how many days did you do **moderate** physical activities like carrying light loads, bicycling at a regular pace, or doubles tennis? Do not include walking.

   _____ **days per week** No moderate physical activities ☐

10. How much time did you usually spend doing **moderate** physical activities on one of those days?

    _____ **hours per day** Don't know/Not sure ☐

    _____ **minutes per day**

Medical history

Diabetic for how long? (By Years, less than 12 months=0, if don't know=999) ☐

If diabetic for more than a year, how many visits to the diabetic clinic in the last 12 months?

(If not applicable=999) ☐

Hypertensive (Yes=1, No =2, don't know=3) ☐

On any kind of antihypertensive medication? (Yes=1, No =2, don't know=3) ☐

On any kind of Lipid lowering therapy? (Yes=1, No =2, don't know= 3) ☐

Have you ever been diagnosed with diabetic eye disease? (Yes= 1, No=2, don't know=3) ☐

Have you ever been diagnosed with diabetic kidney disease? (yes=1, no =2, Don't know=3) ☐

Have you ever been diagnosed with ischemic heart disease (Yes=1, No=2, don't know=3)? ☐

History of polycystic ovaries (for females)? (Yes=1, No=2, don't know=3) ☐

Laboratory data

HbA1c by laboratory (if not available=999) ☐

The records of the last 5 lipid profile test

Test (if not available=999)	DATE M/Y	DATE M/Y	DATE M/Y	DATE M/Y	DATE M/Y
HDL					

LDL					
Triglyceride					
AIP					

Accuracy of POC test questionnaire (objective 5)

Patient number ☐ date ☐☐☐☐☐☐

Name of health care facility ☐ file number ☐

Name _____ Address ☐ Area

Mobile phone ☐

Demographic characteristics

Age Years [not known = 99] ☐☐ Sex (Male=1, Female=2) ☐

Marital status [Single=1, with partner/married=2, divorced/separated=3, widowed=4] ☐

Education (no education=0, primary=1, secondary=2, higher education=3, prefer not to answer=4) ☐

Occupation (governmental=1, private=2, labourer=3, not employed=4, other=5) ☐

Medical history

Do you have diabetes? (Yes=1, No=2, don't know=3) ☐

Do you have abnormal haemoglobin? (Yes=1, No =2, don't know=3) ☐

ONLY IF THE ANSWER IS YES, PLEASE ANAWER THE NEXT QUESTION

Type of abnormal Haemolgobin

(α thalassemias= 1,betathalassemias= 2, sickle cell=3, other=4, not available=999) ☐

Laboratory data

HbA1c level reference lab (if not available=999) ☐

HbA1c level POC device ☐

Consent Form (English)

Study Title: Prevalence and risk factors of diabetes and insulin resistance in patients attending a health care Centre in Kuwait, and the accuracy of a point of care device to measure glycated haemoglobin to monitor patients with diabetes.	
Principal Investigator: Dr. Ahmad Almotawa	**Study Site: Nuzha HCF- Kuwait**

	Please initial box
1. I confirm I have read and understood the information sheet dated 14-9-2015, Version 1.1 for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.	
2. I understand that participation in this study is voluntary and I am free to withdraw consent at any time, without giving a reason, without any penalties.	
3. I understand that data collected during the study, may be looked at by individuals from LSTM and from regulatory authorities. I give permission for these individuals to have access to my records.	
4. I hereby declare that I have not been subjected to any form of coercion in giving this consent.	
5. I agree to the data about me collected in this study being stored for further use in the future.	
6. I agree that my blood sample will be transported to Amiri hospital to be analyzed.	
7. I agree to gift this blood sample for future research purpose	
8. I agree to take part in this study.	

* **All data gathered on this form and any information you provide us for the study will be confidential and will not be communicated to anyone outside the study team.**

Signing this declaration does not affect your right to decline to take part in any future study.

Name of participant	Date	Signature
Name of person taking Consent	Date	Signature

Consent form (Arabic)

لقد وجهت لي الدعوة للمشاركة في بحث الاختبار التشخيصي الجديد لمرض السكر وأنا أدرك أنه قد لا يكون هناك أي فائدة بالنسبة لي شخصيا من هذا الاختبار، وأنني لن يتم دفع اي مبلغ نتيجة المشاركة.

لقد قرأت المعلومات السابقة، أو تمت قراءتها لي. وقد أتيحت لي الفرصة لطرح الأسئلة حول هذا الموضوع. أوافق طوعا على المشاركة في هذا البحث وأعلم أن لدي الحق في الانسحاب من البحث في أي وقت من دون أن تؤثر على الرعاية الطبية المقدمة لي.

اسم المشارك _____

توقيع المشارك _____

تاريخ يوم / شهر / سنة _____

إذا كنت لا تعرف القراءه

لقد شهدت قراءة نموذج الموافقة على المشاركين المحتملين، وكان للمشارك الفرصة لطرح الأسئلة. وأؤكد أن المشارك قد أعطى موافقته بحرية.

اسم الشاهد _____

بصمة المشارك

توقيع الشاهد _____

تاريخ يوم / شهر /سنة _____

تم تقديم نسخة من هذا النموذج (**الموافقة المسبقة**) **الي المشارك**

توقيع مساعد البحث _____

أسم الباحث _____ توقيع الباحث _____

Ethical approval (LSTM)

Dr Ahmad Almotawa
Liverpool School of Tropical Medicine
Pembroke Place
Liverpool
L3 5QA

LSTM
LIVERPOOL SCHOOL OF TROPICAL MEDICINE

Monday, 26 October 2015

Dear Dr Almotawa

Re. Research Protocol (15.024RS) Prevalence and risk factors of diabetes and insulin resistance in patients attending a health care Centre in Kuwait, and the accuracy of a point of care device to measure glycated haemoglobin to monitor patients with diabetes.

Thank you for your email of 26 October 2015 providing the necessary in-country approvals for this project. I can confirm that the protocol now has formal ethical approval from the LSTM Research Ethics Committee.

The approval is for a fixed period of three years and will therefore expire on 25 October 2018. The committee may suspend or withdraw ethical approval at any time if appropriate.

Approval is conditional upon:

- Continued adherence to all in-country ethical requirements.
- Notification of all amendments to the protocol for approval before implementation.
- Notification of when the project actually starts.
- Provision of an annual update to the Committee.
  Failure to do so could result in suspension of the study without further notice.
- Reporting of new information relevant to patient safety to the Committee
- Provision of Data Monitoring Committee reports (if applicable) to the Committee

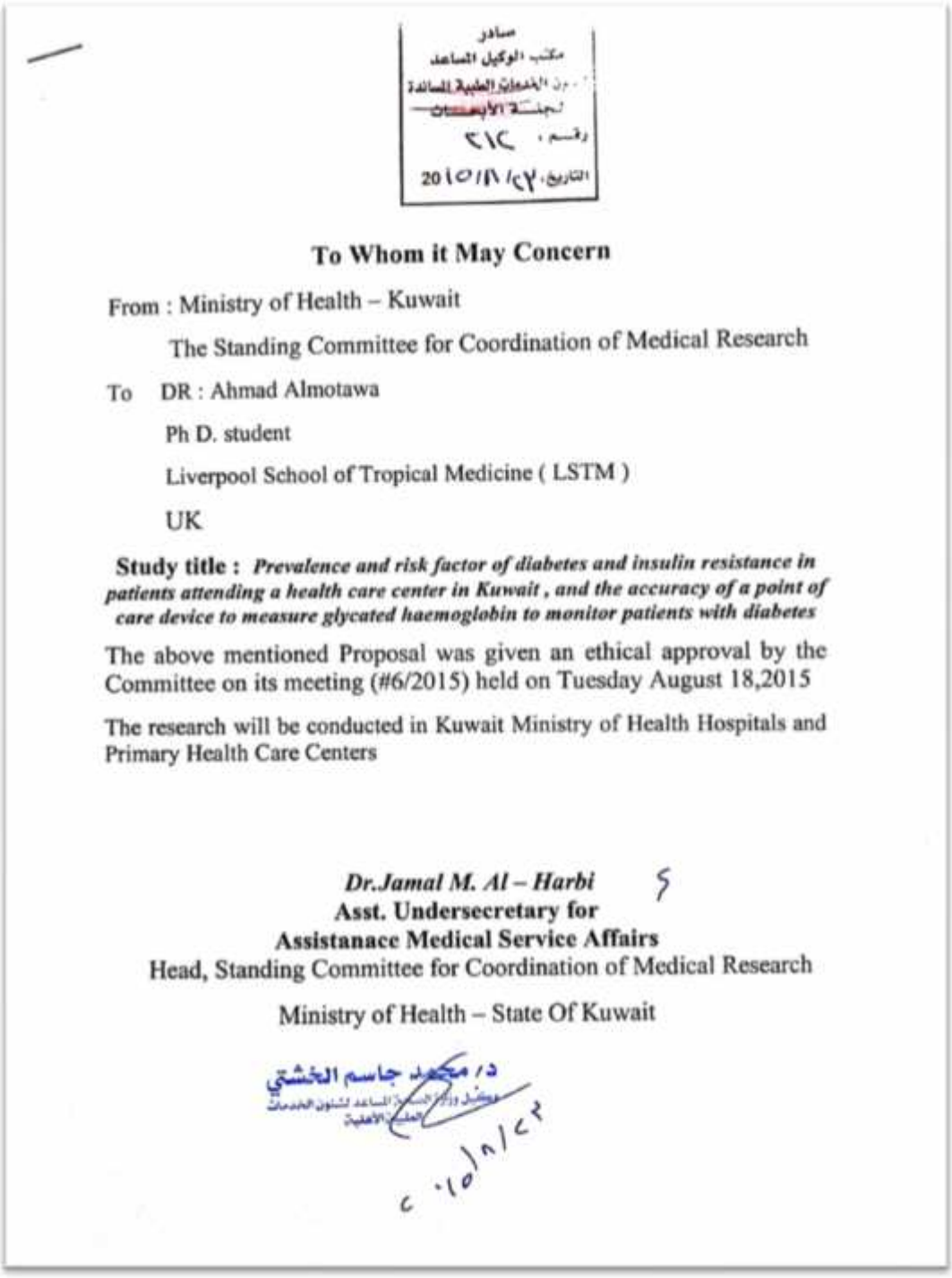
Failure to comply with these requirements is a breach of the LSTM Research Code of Conduct and will result in withdrawal of approval and may lead to disciplinary action. The Committee would also like to receive copies of the final report once the study is completed. Please quote your Ethics Reference number with all correspondence.

Yours sincerely

Angela Obasi

Dr Angela Obasi
Chair
LSTM Research Ethics Committee

Ethical approval (Kuwait)



صادر
مكتب الوكيل المساعد
لشؤون الخدمات الطبية المساندة
لجنة الأبحاث
رقم: ٢١٢
التاريخ: ٢٠١٥/١٨/٢٤

To Whom it May Concern

From : Ministry of Health – Kuwait

The Standing Committee for Coordination of Medical Research

To DR : Ahmad Almotawa

Ph D. student

Liverpool School of Tropical Medicine (LSTM)

UK

Study title : ***Prevalence and risk factor of diabetes and insulin resistance in patients attending a health care center in Kuwait , and the accuracy of a point of care device to measure glycated haemoglobin to monitor patients with diabetes***

The above mentioned Proposal was given an ethical approval by the Committee on its meeting (#6/2015) held on Tuesday August 18,2015

The research will be conducted in Kuwait Ministry of Health Hospitals and Primary Health Care Centers

Dr.Jamal M. Al – Harbi
Asst. Undersecretary for
Assistanace Medical Service Affairs
Head, Standing Committee for Coordination of Medical Research

Ministry of Health – State Of Kuwait

د/ محمد جاسم الخشتي
وكيل وزارة الصحة المساعد لشؤون الخدمات الطبية الأهلية

Ethical committee proposal

Prevalence and risk factors of diabetes and insulin resistance in patients attending a health care Centre in Kuwait, and the accuracy of a point of care device to measure glycated haemoglobin to monitor patients with diabetes.

Dr Ahmad Almotawa (LSTM)[1*]

Prof Luis E Cuevas (LSTM)[1]

Mr Russell Dacombe (LSTM)[1]

Dr Jamila Alfaraj (Nuzha HCF)[2]

Prof Geoff Gill (LSTM)[1]

Institutions

[1]Liverpool School of Tropical Medicine, Pembroke Place, L3 5QA, Liverpool UK. Telephone: +44 151 7053355, email: lcuevas@liv.ac.uk

[2]Nuzha Health care centre, Mohamad bin Labon Street, block 3, Nuzha, Kuwait. Telephone: +965 22526804, email: jmkmf@hotmail.com

[3]Al-Amiri hospital, the Gulf Street, Sharq, Kuwait. Telephone: +965 22450005.

Background and rationale

The first clear description of diabetes was made by Aretaeus of Cappadocia, a famous Greek physician of the 2nd AD century. He described the disease as a chronic disease of thirst, excessive drinking, excessive urination and short life span (Laios et al., 2012).

Although neglected for many years, today, DM is a seriously growing worldwide disease which has reached epidemic proportions. There are more than 387 million people living with DM around the world, with 43% of them being undiagnosed. It is estimated that one person dies every seven minutes due to DM and that governments will need to spend 1/9th of their health care expenditure on DM (IDF, 2014).

Diabetes Mellitus (DM) is a syndrome encompassing a group of metabolic disorders characterised by insufficient insulin secretion, resistance to the action of insulin or both (American Diabetes, 2009).

Global disease burden is continually shifting away from communicable to non-communicable diseases and from years of life lost (YLLs) to years lived with disability (YLDs).

The global burden of disease study proposed disability-adjusted life years (DALYs) as the sum of YLLs and YLDs, to measure disease burden. Global DALYs calculated from 187 countries for 291 causes in both male and female from 1990 to 2010, DALYs remained stable but significant shift has occurred in DALYs due to DM, increasing by 69%, with an obvious increase in DALYs of chronic kidney disease due to DM by 77%.(Murray et al., 2012).

Prevalence of diabetes is increasing globally; it is well recognised as major health problem. In the year 2003, it was estimated that there were 194 million with prevalence of 5.1%.(Federation, 2003)

Today, according to the International Diabetes Federation (IDF) world atlas there are more than 387 million people with diabetes in the world, with prevalence of 8.3%.(IDF, 2014)

The several studies revealed that there is an enormous economic burden of diabetes, affecting patients in Low and middle-income countries (LMICs) mostly in a direct way (Seuring et al., 2015, Tharkar et al., 2010).

Global burden

Patients with DM are categorised into four broad types: Type 1 (T1DM), Type 2 (T2DM), gestational DM (GDM) and DM due to other causes. T2DM is the most common presentation, with GDM being frequent but short lived, followed by T1DM (William T. Cefalu, 2015).

Insulin action

Insulin (from the Latin, insula meaning island) is a hormone produced by beta cells of the islets of Langerhans in the pancreas (Sonksen and Sonksen, 2000). Insulin is released mainly when the level of glucose increases in the blood stream (Buchwald et al., 2015), Activation of insulin receptors leads mechanisms that directly affect glucose uptake by protein molecules in the cell membrane that transport glucose into the cell, leading to lowering blood glucose level (Najjar, 2001).

Pathogenesis of Type 2DM

Type 2 DM is characterized by hyperglycemia resulting from a defect in the pancreas insulin secretory function and/or Insulin resistance (IR) (Gareth Williams, 2002).

Pre-diabetes and insulin resistance

Prediabetes is the medical stage in which not all of the symptoms existing to diagnose a person as diabetic, but impaired fasting glucose (IFG), which refers to

a condition in which the fasting plasma glucose (FPG) is elevated above the normal levels but is not high enough to be classified as DM (Nichols et al., 2007). IFG is strongly associated with Insulin resistance and dysglycemia, predisposing to life threatening cardiovascular diseases among other serious diseases (Barr et al., 2007).

IR is a condition in which the insulin target cells fail to respond to the normal actions of insulin. The pancreas produces insulin, but the cells in the body tissues become resistant to insulin and are unable to use it as efficiently, leading to high blood glucose level. Subsequently, Beta cells increase their production of insulin trying to reach proper glycemic control, causing a high blood insulin level (Chiu et al., 2007). Dietary fat has been strongly recognised as a stimulant of insulin resistance, and it is known that IR coexists with obesity (Eckel et al., 2011, Kahn et al., 2006).

Anthropometric characteristics

The recent socio-economic transition in the Middle East resulted in a parallel increase in the prevalence of overweight and obesity(Saadi et al., 2010). Among Arab and Mediterranean, diabetes occurs at lower level of BMI than the Western populations, and a small increase in weight can produce a state of glucose intolerance (Jaber et al., 2003, Nakagami et al., 2003). An excess of body fat, especially around the abdomen, increases the probability of developing a range of diseases. It includes diabetes, insulin resistance, hypertension, dyslipidemia, ischemic heart diseases and some forms of cancer (King et al., Rodriguez, 2006). Obesity is a major risk factor for diabetes. In white population, obesity is defined as a BMI of more than 30 kg/m^2 and overweight as a BMI of equal to or more than 25 kg/m^2. WHO consider these numbers are valid for Arab population too.

Several studies in Asian populations showed that there is a phenotype characterised by normal BMI but just like obese people are having insulin resistance, diabetes and Ischemic heart disease. This phenotype is called metabolically obese-normal weight, despite having normal BMI; those individuals

have less muscle mass and greater abdominal obesity (Ruderman et al., 1998, Ramachandran et al., 2010).

Racial/ Ethnic predisposition

There is strong evidence that there is a higher prevalence of T2DM among migrant populations in Europe, with an increase in the morbidity and mortality related to the disease compared to the native European populations(Wandell et al., 2010). London school of hygiene and tropical medicine is taking part in an interdisciplinary study on obesity and diabetes among African migrants; the study is funded by the European Union. The study aims to understand the reasons of the high prevalence of T2DM among the migrant populations. Prevalence of obesity and diabetes is greater in migrants from south Asia, Africa and the Caribbean region(Oldroyd et al., 2005).

A population-based study in Israel showed that Arabs in Israel are at 70% higher risk for adult onset T2DM and a significantly younger age of presentation with the disease than the Jewish group (Kalter-Leibovici et al., 2012). Another study was done in Los Angeles showed that Hispanic and African children are more insulin resistance than the white children(Goran et al., 2002). Similarly, a study recruiting 626 Arab American in Michigan revealed that the combined rate of glucose intolerance 32.3% for women and 49.8 for men (p= 0.0001) (Jaber et al., 2003). Recruiting 34,456 adult immigrants, the data of the national health interview survey from 1997 to 2005 analysed by Reena Oza-frank and Narayan K.M, The data showed that men and woman from Mexico, Central America and the Caribbean were more likely to be diabetic than European migrants (OR = 2 for both groups)(Oza-Frank and Narayan, 2010).

Obesity

A study in the UK followed 7176 male participants showed that diabetes increases significantly with obesity and overweight(Goya Wannamethee et al., 2005) (overweight is defined as $25 < BMI < 30$, while obesity is $BMI \geq 30$).

Complications of diabetes mellitus

In Kuwait, the prevalence of T2DM and GDM is unusually high, with an estimated crude prevalence of 17.9% of 20-79 years old adults having T2DM. As Kuwait has a relatively young population, the age-adjusted prevalence is even higher with 23.1% being affected (IDF/Kuwait, 2014).

The rapidly growing prevalence of T2DM in the developing countries is linked to the effect of urbanisation and lifestyle changes (Al-Moosa et al., 2006, Shetty and Schmidhuber, 2006).

Although T2DM is a preventable disease, it requires regular screening, early detection, lifestyle changes and proper treatment to reduce its incidence and associated morbidity and mortality (Care, 2004, Eriksson and Lindgarde, 1991, Tuomilehto et al., 2001). T2DM is associated with many factors; some of which are modifiable and others that are not. The fixed factors include, among others, age, sex and genetic susceptibility; while the modifiable include socioeconomic status, lifestyle and environmental factors, obesity (Eckel et al., 2011), a high body mass index (BMI) (Hamer et al., 2014), inflammatory markers (Chagas et al., 2012), poor dietary habits and inactivity (Fletcher et al., 2002).

With the purpose of developing a programme to control the progression of DM in Kuwait, it is important to do a situation analysis of the disease in the country and to describe the leading risk factors associated with T2DM in the community. Although it is recognised that T2DM is a major health problem in Kuwait, Kuwait does not have a DM surveillance system. Chronic hyperglycaemia is the distinctive sign of T2DM. Until recently, its diagnosis was established with the detection of elevated glucose levels in the blood (Berg, 2013).

In the late 20th century the aim was to identify patients at risk of developing signs and symptoms of acute hyperglycaemia. In 1997 however, the American Diabetes Association recommended that the diagnostic levels of plasma glucose should be

based on the risk of developing a chronic complication and accordingly the diagnostic of preference became the measurement of fasting plasma glucose (FPG), which was set to ≥ 7 mmol/L and oral glucose tolerance test threshold ≥ 11.1 mmol/L. Despite these changes, single measurements of FGP was still a poor marker of the long term glycaemic control, and it was recommended that other markers should be used to reflect the long term euglycemic state of the individual. Haemoglobin A1c (HbA1c) is a haemoglobin variant created when the glucose molecule binds to the β chain of haemoglobin A (Weykamp et al., 2009). The proportion of haemoglobin that is glycated accurately reflects the average plasma glucose concentration in the proceeding 2-3 months in most patients (Nathan et al., 2008). HbA1c, therefore, became the recommended test for the diagnosis of T2DM, with a threshold of 6.5% (ADA, 2015), and an accepted marker to monitor the degree of glucose control attained.

Until recently, HbA1c measurements required referral of the patient or transport of the sample to a reference laboratory. Point of care (POC) tests for HbA1c are nowadays available and obtaining immediate HbA1c results has the potential to improve glycaemic control by providing rapid information to the managing clinician and is more convenient to the patient (Miller et al., 2003). Some, but not all of these POC tests do not seem to have the same accuracy than tests conducted at reference centres; especially in the presence of anaemia, haemoglobinopathies, chronic renal failure and other conditions and the consideration of adopting POC HbA1c diagnostics should be proceeded by an evaluation of their performance. There is however limited evidence of the performance of the POC HbA1c devices in Kuwait suggesting that further research on the effectiveness of POC against laboratory HbA1c is needed.

Aim of the study

In this project, we propose to assess the burden and risk factors for diabetes, factors associated with poor glucose control and assessing diagnostic methods for initial diagnosis and monitoring of diabetes that are suitable for the point of care of patients.

Objectives of the study

The study will have the following objectives:

I. To determine the prevalence of Type 2 DM and IR among adult population attending a primary health care facility in Kuwait.

II. To determine the risk factors for Type 2 DM and IR in this adult population.

III. To describe the prevalence of IR among first degree relatives of patients with Type 2 DM.

IV. To establish the proportion of patients with type 2 DM who achieve adequate glycaemic control and the risk factors for poor glycaemic control.

V. To assess the accuracy of a POC device to measure A1c for the diagnosis of Type 2 DM among patients with DM and patients with known haemoglobinopathies.

Capacity building and training

- Dedicated staff will be trained on the operation and troubleshooting of POC/HbA1c.
- Sites visits may identify additional capacity building required to conduct the study to international standards.

Evaluation site

The Liverpool School of Tropical Medicine:

LSTM has about 350 academic staff and extensive expertise in developing and evaluating disease control programmes, with a first-class track record for researching health problems in resource developing countries. Over the last

decade, LSTM has led many related projects on tropical diseases, developing and mainstreaming frameworks for diagnosis, improving screening strategies and treatment and designing and testing interventions to promote gender equity. The LSTM team has conducted multi-centre projects on barriers to access diagnosis and treatment uptake. These strengthened the international evidence underlining accelerated diagnostic schemes and packages that bridge the gap between the service and the patient, increase case detection and treatment uptake. The School has extensive experience in managing large projects with substantial staff and funding.

Al Amiri hospital

The Amiri Hospital is a general hospital located in Kuwait City, and it serves an estimated 400,000 patients per year. The hospital was built in 1949 to be the first government owned hospital. The capacity of this hospital is about 400 beds. The hospital earned accreditation for complying with international health care quality standards including achieving the highest level of performance possible, improving patient outcomes, and creating an environment for continuous improvement.

The laboratory is equipped with the latest technology for accurate testing.

Nuzha HCF

Nuzha HCF is a governmental health centre in an urban area (Kuwait City) providing about 50,000 consultations per year. This primary health care centre provided general practice (GP) services and selected specialised clinics for diabetes monitoring and management, hypertension and obesity.

Study plan

This will be a prospective collaboration of two health institutions: Nuzha health centre and Al-Amiri hospital in Kuwait with technical support from the Liverpool School of Tropical Medicine (LSTM).

The study will be coordinated by Dr Ahmad Almotawa and supported by his PhD supervisors who will maintain close electronic and Skype communication. Protocol change decisions will be made in consultation with Prof Cuevas at LSTM.

The study will be independent of POC device Agent Company to ensure its objectivity.

Study design

There will be cross-sectional studies and case-control studies.

Methodology

Objective 1: To determine the prevalence of Type 2 DM and IR among a Kuwaiti adult population attending Nuzha health facility.

This will be a cross sectional survey in Kuwait and will be conducted from September 2015 to September2016.

Setting: The study will be based at Nuzha health care facility (HCF). Nuzha HCF is a governmental health centre in an urban area (Kuwait City) providing about 50,000 consultations per year. This primary health care centre provides general practice (GP) services and selected specialised clinics for diabetic monitoring and management, hypertension and obesity.

Target population: The target population will be adult patients aged 18 years or more attending Nuzha HCF.

Inclusion/exclusion criteria: All adults attending Nuzha HCF seeking medical advice for any illness at the general clinics will be eligible to participate, independently of the reasons why they attend the clinics. Eligible patients will be enrolled prospectively over a period of 12 months or until the desired sample size is achieved. We will exclude pregnant women, patients with acute infections who have fever, patients on steroids, those unable to consent, patients who fail to fast overnight or unwilling to return the next day to the clinic.

We will use systemic sampling to choose participants, every 5th patient starting from the first patient attending the general clinic, we are planning to enrol 3 patients daily 5 days a week. If a patient refuses to participate, we will invite patients consecutively, continuously until a replacement is found. Then the 5th patient interval will resume.

Patients who agree to participate will be interviewed to complete a questionnaire containing demographic background and medical history.

If the participant has been fasting for 12 hours and if it is convenient, a phlebotomist will collect one venous blood sample after the patient has completed the clinic consultation. If the participant is not fasting, we will give instructions to fast for 12 hours and to return the next day in the morning.

Laboratory procedures: Patients' blood will be collected to measure Fasting Plasma Glucose (FPG), Fasting plasma insulin, A1c and lipid profile, including high-density lipoprotein (HDL), low-density lipoprotein (LDL), Triglycerides (TG). These tests will be free for the participants. See laboratory tests below.

Patients will be classified as having normal values, IR or DM according to the following parameters.

- DM will be defined as the presence of an abnormal (defined as A1C ≥6.5%) and an abnormal FPG (defined as ≥126 mg/dl (7.0 mmol/L)).

- Patients with IR but who are not DM will be defined as patients with FPG < 125 mg/dl (6.9 mmol/L) but homeostatic model assessment 2 (HOMA)2 -IR > 2.
- Patients will be defined not to have DM or IR if the A1c is < 5.7, and FPG is < 110 mg/dl (6.1 mmol/L), and HOMA2 ≤ 2.

* HOMA 2 is a model constructed from the combination of several tests is based on the physiological balance between insulin secretion and glucose concentrations in blood and are therefore a reflection of the balance between glucose uptake by tissues and insulin production.

All patients will be provided feedback of the results. Patients with normal results will receive them via email or phone call, as per their stated preference. Patients with abnormal results will be contacted via email or phone call as per their stated preference and will be invited to attend a clinic appointment to discuss their results with the DM clinic staff (post in Kuwait it unreliable).

Objective 2: To determine the risk factors for (a) Type 2 DM and (b) IR in the same adult population.

This component will be two case control studies conducted simultaneously and will be based at the same Nuzha HCF.

Cases of DM and IR and controls for both studies will be defined using the same definitions listed above.

(a) In the case control to determine Type 2 DM risk factors, participants will be enrolled both from patients participating in the survey (objective 1) and from known DM patients attending the diabetes clinic at the same centre. Cases of DM among patients participating in the survey will be identified at

the time results become available and usually within 72 hours after sample collection. Patients with DM attending the clinic will be identified among the cases known to the service who are attending spontaneous of routine follow up consultations. We will contact the participants identified by the survey by phone or email to inform them about their results and invite them to participate in the second part of the study which will include more detailed questionnaire about their medical history and life style, we will also inform them that we will take some measurements: height, weight, waist and hip circumference and BP. Patients who agree to participate will be given an appointment. Cases from the survey will be enrolled daily until reaching the desired sample size.

Patients enrolled in the DM clinic will also be enrolled consecutively, restricting the number to two patients per day, to obtain a mixture of participants from the clinic who were aware, and the survey (who were unaware) of having DM. Cases of DM will be defined as stated above for patients attending the survey. Cases with DM will be defined as any adult who has a medical history of a diagnosis of DM using the same parameters described above or at least two consecutive FPG with abnormal values. Some of these cases may have achieved glucose homoeostasis at the time of enrolment, but will still be considered to have DM.

Controls will be adults who do not have DM nor IR patients, as defined above.

A total of N=64 controls will be enrolled for N=64 cases, giving a ratio of 1:1 cases per control, we choose that ratio because we can attain cases from the diabetic clinic to participate in this case control study.

(b) In the case control study to determine the risk factors for IR, all participants will be enrolled from the prevalence survey (objective 1). Cases of IR will be defined according to homeostatic model assessment (HOMA) 2.

Patient with HOMA2 > 2 but who are not diabetic (FPG <7 mmol/L) will be defined as cases with IR.

Controls for this case control study will be the same participants in the survey who do not have DM or IR.

A total of N=64controls will be enrolled for N=32cases, giving a ratio of 1:2 cases per control, we choose that ratio because it is we are expecting small number of cases, as we are estimating that only about 10% of our survey population would have IR but no DM, and according to the available numbers of cases and controls, this ratio would make it possible to achieve a statistical power > 80% to identify IR risk factors.

For both case control studies, the interviewer will ask the participant to fill a second questionnaire that includes a more extensive list of potential risk factors for DM and IR (see questionnaires in appendix 1). The questionnaire will include all known risk factors for TYPE 2 DM and IR and will include diet, physical activity, BMI, family history and others. A dedicated nurse will measure blood pressure (BP), waist and hip circumference (cm), weight (kg), height (cm). BMI will be calculated as weight (kg)/height^2 (m^2).

Laboratory tests

- For the FPG test, we will collect 2 ml blood in a grey-top tube with Potassium Oxalate/Sodium Fluoride. Blood samples will be centrifuged to separate the serum within 2 hours, and about 0.5 ml of the plasma will be collected in an aliquot for testing using the Spectrophotometric assay (Beckman UniCel DxC 800). Specimen for these assays are stable for up to 3 days if refrigerated.
- For the insulin test, we will collect 5 ml blood in a gold/yellow-top tube. The specimen will be centrifuged promptly, and about 1ml of serum will be tested for insulin level using immune-assay (Beckman UniCel Dxi 600).

Specimens for this assay are stable for 24 hours if refrigerated and for 6 months if frozen.

- For the A1c test we will collect 1 ml blood in a lavender (purple)-top tube containing EDTA. This tube does not need for centrifugation, and the specimen is stable for 24 hours at room temperature. A1c will be measured using high-performance liquid chromatography (Tosoh's HLC- G7).

- For lipid profile, the phlebotomist will draw 5ml blood in a gold-top tube, centrifuge and about 2ml serum will be tested using Spectrophotometric assay (Beckman UniCel DxC 600 Pro).

Objective 3: To describe the prevalence of IR among first degree relatives of patients with Type 2 DM.

We will conduct a cross sectional survey of relatives of patients with Type 2 DM study will be conducted at the same Nuzha HCF, Kuwait, from September 2015 to September 2016.

Selection of participants will be identified from patients following up at Nuzha diabetic clinic

We will ask all diabetic patients to invite at least one adult direct relative (first-degree consanguineous relative), including siblings, parents or son/daughters to participate in the study. If the patient agrees to invite a relative, we will ask them to attend according to an appointment given IR and to come fasting for about 12 hours. We will recruit participants until the sample size is achieved.

Eligibility will be adults >18 years old, first degree relative to a diabetic patient attending Nuzha HCF. We will exclude pregnant women, relatives with known diabetes, and patients who have had fever in the last 14 days, patients on steroids, those unable to consent, patients who are unable to fast overnight.

We will ask the participant to fill the questionnaire then the phlebotomist at Nuzha HCF will collect the venous blood sample.

Laboratory procedures: Relatives blood samples will be collected to measure the same tests, including Fasting Plasma Glucose (FPG), Fasting plasma insulin and A1c.

- For the FPG test, we will collect 2 ml blood in a grey-top tube with Potassium Oxalate/Sodium Fluoride. Blood samples will be centrifuged to separate the serum within 2 hours, and about 0.5 ml of the plasma will be collected in an aliquot for testing using the Spectrophotometric assay (Beckman UniCel DxC 800). Specimen for these assays are stable for up to 3 days if refrigerated.
- For the insulin test, we will collect 5 ml blood in a gold/yellow-top tube. The specimen will be centrifuged promptly, and about 1ml of serum will be tested for insulin level using immune-assay (Beckman UniCel Dxi 600). Specimens for this assay are stable for 24 hours if refrigerated and for 6 months if frozen.

For the A1c test, we will collect 1 ml blood in a lavender (purple)-top tube containing EDTA. This tube does not need for centrifugation, and the specimen is stable for 24 hours at room temperature. A1c will be measured using high-performance liquid chromatography (Tosoh's HLC- G7).

Objective 4: To establish the proportion of patients with type 2 DM who achieve adequate glycaemic control and risk factors for poor glycaemic control.

We will conduct a cross sectional survey study at the diabetic clinics of Nuzha HCF, Kuwait from September 2015 to September 2016. We will use systematic sampling to enrol patients. Eligibility will be adults > 18 years old with a previously known diagnosis of Type 2 DM who attend a regular appointment at the diabetic clinic. We will exclude pregnant women, patients with acute infections who have fever, patients on steroids, those unable to consent and those unable to fast overnight.

We will use systematic sampling to choose participants. Every 3rd patient attending the clinic will be inviting, with 3 patients enrolled per day, 5 days a week. If a patient refuses to participate, we will invite patients consecutively until a replacement is found. Then the 3-patient interval will resume.

Patients who agree to participate will be interviewed to complete a questionnaire containing demographic background and medical history.

We will ask the participants to fill a questionnaire with known risk factors for poor glycaemic control among DM patients, which will include diet, physical activity, BMI, family history, adherence to treatment, understanding of DM and others. A dedicated nurse will measure blood pressure (BP), waist and hip circumference (cm), weight (kg), height (cm). BMI will be calculated as weight (kg)/height² (m^2).

The phlebotomist at Nuzha HCF will collect the venous sample; We will test the blood sample for A1c and Lipid profile.

Laboratory procedures:

- For the A1c test, we will collect 1 ml blood in a lavender (purple)-top tube containing EDTA. This tube does not need for centrifugation, and the specimen is stable for 24 hours at room temperature. A1c will be measured using high-performance liquid chromatography (Tosoh's HLC- G8).
- For lipid profile, the phlebotomist will draw 5ml blood in a gold-top tube, centrifuge and about 2ml serum will be tested using Spectrophotometric assay (Beckman UniCel DxC 600 Pro).

Cases will be classified as having good glucose controls if A1c < 7, Controls with classified as having poor glucose control if A1c > 9.

Objective 5: To assess the accuracy of a POC device to measure A1c for the diagnosis of Type 2 DM among patients with DM and patients with known haemoglobinopathies.

This will be a cross sectional survey in Kuwait and will be conducted from September 2015 to September2016.

Setting: The study will be based at Nuzha HCF diabetic clinic and the haematology clinic (for haemoglobinopathies). This clinic is based at Al-Amiri hospital; it is a specialized clinic for patients with abnormal haemoglobin.

Target population: The target population will be the same patients participating in objective 4 study for DM. Eligibility criteria for patients with haemoglobinopathies will be adult patients with abnormal haemoglobin attending the haematology clinic at Al-Amiri hospital seeking medical advice. Patients with haemoglobinopathies will comprise patients with a known diagnosis of α thalassemia, beta-thalassemia and sickle cell anaemia.

We will ask every 2nd eligible patient attending the haematology clinic to participate in the study; we will invite consecutively eligible patients until we enrol one, then we will go back to every 2nd patient systemic sampling. We are planning to recruit 2 patients daily.

We will ask the participant to fill a short questionnaire then to take a venous blood sample and a blood finger –prick blood sample.

Eligible patients will be enrolled prospectively over a period of 12 months or until the desired sample size in both settings is achieved.

Laboratory procedures

- A finger-prick blood sample will be collected for in-clinic HbA1c testing with the rapid one-step automatic test, Boronate affinity technique (Quo-Test) This machine provides results with in about 4 minutes.

- For the reference A1c test we will collect 1 ml blood in a lavender (purple)-top tube containing EDTA as described in previous objectives.

Physicians will be blinded to POC HbA1c results and will rely on the reference HbA1c results for clinical decision making.

---

* Wallace, T. M., J. C. Levy and D. R. Matthews (2004). "Use and Abuse of HOMA Modelling." Diabetes Care 27(6): 1487-1495.

*Gayoso-Diz, P., A. Otero-Gonzalez, M. Rodriguez-Alvarez, F. Gude, C. Cadarso-Suarez, F. Garcia and A. De Francisco (2011). "IR index (HOMA-IR) levels in a general adult population: curves percentile by gender and age. The EPIRCE study." Diabetes Res Clin Pract 94: 146 - 155.

* Qu, H.-Q., Q. Li, A. R. Rentfro, S. P. Fisher-Hoch and J. B. McCormick (2011). "The Definition of Insulin Resistance Using HOMA-IR for Americans of Mexican Descent Using Machine Learning." PLoS ONE 6(6): e21041.

Sample size calculation

Objective 1: To establish prevalence of TYPE 2 DM and IR in a Kuwait

The population in Nuzha health care centre catchment area is about 25,000; it is expected that 20% of the adult population has TYPE 2 DM. We aim to establish the prevalence of DM with an error margin of +/-4%, with 95% power and 5% confidence limit, the survey sample size will be 380 participants.

Objective 2: To determine the risk factors for (a) Type 2 DM and (b) IR in the same adult population.

We will conduct 2 case control studies simultaneously; the participant will be the same participants from the first objective. We will classify the patients into

patients with diabetes, patients with insulin resistance IR and normal patients (NO DM and NO IR)

In the first cc study cases are adults with DM and controls are patients with normal glucose and no IR. We estimate that 20% of patients enrolled for objective 1 will have DM. The survey, therefore, will identify about (380x 0.2) = 76 adults with DM (cases). We also expect that 10% of participants in the survey will have with IR (380x 0.1) resulting in 38 cases of IR and normal glucose. The remaining 266 participants are expected to be normal controls (No DM or IR).

The main risk factors used to establish the sample size are high cholesterol level (expected to be present in 30% of the adult population), hypertension (30%) and obesity (40%). If we enrol participants with a ratio of controls to cases of 1:1; to be 90% confident to have 80% chance to detect odds ratios of 2.5 or more, the estimated sample size will be 65 DM cases and 65controls.

For the second case control study, again the participants are from the first objective, and cases are IR patients, control are normal patients. We are looking for risk factors with the same prevalence as stated above. With a ratio of controls to cases of 2:1, to be 90% confident to have 80% chance to detect an odds ratio of 3 or more, the calculated sample size is 35 cases and 65 controls.

Objective 3: To describe the prevalence of IR among first degree relatives of patients with Type 2 DM.

There are 2000 patients following up at Nuzha HCF, assuming that each diabetic patient has about 10 first degree relatives, the population size for this survey would be2000. The estimated prevalence of IR among the first-degree relatives is 50%. To conduct a survey with 90% confidence level and a maximum error of 5% the required sample size will be 270.

Objective 4: To establish the proportion of patients with type 2 DM who achieve adequate glycaemic control and the risk factors for poor glycaemic control.

We will conduct a descriptive survey in the diabetic clinic. The clinic provides medical services for about 2000 diabetic patients. We estimate that there is 50% chance of poor glycaemic control. To conduct a study with 90% confidence level and 5% confidence limits. We will need at least 240 participants.

Objective 5: To assess the accuracy of a POC device to measure A1c for the diagnosis of Type 2 DM among patients with DM and patients with known haemoglobinopathies.

In the literature, the sensitivity of reference A1c test (Tosoh) is between 70% and 80%.

So, I used the 80% as the comparative point, and I allowed for 10% difference, with $\alpha = 0.05$ andbeta= 0.2 the required sample size will be 200 tests in each group, (total of 400).

Study outcome

For objective 1:

The outcome is the prevalence of participants with DM, IR according to the following parameter

- DM will be defined as the presence of an abnormal (defined as A1C ≥6.5%) and an abnormal FPG (defined as ≥126 mg/dl (7.0 mmol/L)).
- Patients with IR but who are not DM will be defined as patients with FPG < 125 mg/dl (6.9 mmol/L) but homeostatic model assessment (HOMA)2-IR > 2.

For objective 2:

The outcome measure is to describe the association of Type 2 DM and IR with the following assumed risk factors: age, sex, obesity, BMI, cholesterol, triglyceride and BP.

For objective 3:

The outcome measure is the prevalence of IR among first degree relatives of people with Type 2 DM.

For objective 4:

The outcome measure will be the percentage of the diabetic patient attending Nuzha HCF with good glycaemic control and to describe the risk factors associated with the poor glycaemic control.

Good glycaemic control is when A1c < 7, and poor glycaemic control is when A1c > 9.

Patients with A1c between 7 and 9 will be considered as fairly controlled.

For objective 5:

The outcome measures are to describe the accuracy of POC device in measuring A1c, describing the precision of the POC device, comparing the means (95% CI) and difference (95% CI) against the reference laboratory results.

Study management

Study team

The study activities will be initiated by the Liverpool School of Tropical Medicine (Prof Luis Cuevas, Ahmad Almotawa and Russell Dacombe), Nuzha health centre, Al-Amiri Hospital in Kuwait.

The research will be conducted within the context of routine clinical and laboratory practise at the study sites and procedures required will be performed by those providing patients' services.

Responsibilities of study team members

Responsibility of LSTM team

- Development of the initial protocol;
- Initial site assessment visit;
- Coordination of ethical approval applications;
- Facilitate study initiation;
- Study monitoring;
- Development of standardised study forms and record keeping procedures;
- Development of standardised databases;

Responsibility of Nuzha health care centre

- Feedback of the initial protocol in collaboration with LSTM;
- Support data analysis and reporting;
- Provision of the study support staff in Kuwait.
- Facilitate the enrolment of patients at its hospital facilities.
- Record results in laboratory record book.
- Conduct two HbA1c tests, one in the Centre using POC device and the other one in the reference lab as the usual routine.
- Conduct I.V glucose and insulin level per participant.
- Conduct the study survey.

Responsibility of Al-Amiri hospital

- Feedback of the initial protocol in collaboration with LSTM;
- Support data analysis and reporting;
- Provision of the study support staff in Kuwait.
- Facilitate the enrolment of patients at its hospital facilities.
- Record results in laboratory record book.

- Conduct two HbA1c tests, one in the Centre using POC device and the other one in the reference lab as the usual routine.
- Conduct I.V glucose and insulin level per participant.
- Conduct the study survey.

Trouble shooting

Clinical and laboratory staff should approach the study coordinators, and in turn, the latter should approach the LSTM. External technical assistance can be arranged if needed.

Study site preparation

Nuzha health care centre and LSTM investigators should review the master protocol with the study team. Any changes to the master protocol would need to be approved by Prof Cuevas at LSTM.

Ethical considerations

Institutional review board (ethics committee) approvals to the protocol will be requested from the ethical committees in LSTM and Nuzha health care Centre.

Once the study is approved, the letter of approval with the names and affiliation of all the members of the ethics committees will be stored at LSTM for documentation. The consent form and patient information sheets must be available in English and Arabic. LSTM will prepare Material Transfer Agreements, as needed.

Benefits for Participants

All participants will have an HbA1c and I.V glucose level, and therefore patients will obtain an optimal glycaemic diagnosis. Within the context of a research study, patients are also likely to benefit from good medical services. No

reimbursement of patient's costs will be offered as costs for patients will be equal or less than those incurred by attending the routine diagnostic services.

Potential harms to the Participants

Within the context of the national public health services and following National Guidelines of counselling and testing. Participants will be informed they do not need to answer questions they find unpleasant or disturbing.

Training for study staff

Site assessment visits and study initiation visits will be critical to ensure that training needs are identified and addressed and do not delay the study or compromise quality. Training in standardised procedures integral to the study will be provided as necessary and may include the use of the POC device, obtaining samples of good quality and interviewing techniques. POC device will be installed and calibrated according to the manufacturer. Staff will be trained on-site on the use of the POC.

Piloting the study protocol

The study protocol will be implemented at the study sites for 3-5 days as a pilot phase; we will try to query 20 patients before collection of data to be included in the analysis. This period will familiarise staff with the procedures and identify potential for errors.

Biosafety guidelines for clinic and laboratory staff

Laboratory workers are responsible for their own safety and that of their co-workers. Transmission of the blood borne disease can only happen if the staff did not follow the local and international infection control recommendations.

Statistical analysis

For objective 1:

Patients will be classified as having normal values, IR or DM according to the following parameters.

- DM will be defined as the presence of an abnormal (defined as HbA1C ≥6.5%) and an abnormal FPG (defined as ≥126 mg/dl (7.0 mmol/L)).
- Patients with IR but who are not DM will be defined as patients with FPG < 125 mg/dl (6.9 mmol/L) but homeostatic model assessment 2 (HOMA 2)-IR > 2.
- Patients will be defined not to have DM or IR if the HbA1c is < 5.7 and FPG is < 110 mg/dl (6.1 mmol/L), and HOMA 2 ≤ 2.

Although euglycaemic clamp is the gold standard to quantify IR, we will use HOMA- IR calculation as an IR indicator, because it is much less sophisticated and practically more convenient.

The formula for calculation will be: HOMA 2 = (Insulin x glucose mmol/L) ÷ 22.5

The cut-off point for IR will be 2**.**

For objective 2

The outcome measure is to describe the association of Type 2 DM and IR with the following assumed risk factors: age, sex, obesity, BMI, cholesterol level, triglyceride level and BP.

<u>Categorization of risk factors</u>

Blood pressure (BP) will be measured for each individual in mmHg; readings will be separated into four categories:

	Diastolic	Systolic

Category 1	< 90	< 140
Category 2	< 90	≥ 140
Category 3	≥ 90	< 140
Category 4	≥ 90	≥ 140

Hypertension in this study will be defined as the presence of any of the following conditions:

If SBP ≥ 140 mmHg, or if DBP is ≥ 90, or if the patient is on antihypertensive drug.

Cholesterol levels (mmol/L) will be divided into categories (<4.3; 4.3–5; 5.1–5.8; and >5.8); cholesterol= 5 mmol/L will be considered to be high. Patient on anti-hyper cholesteric drug will be defined as high also.

Triglyceride level Normal triglycerides = < 2.0 mmol/l, Borderline High triglycerides = 2- 4 mmol/l, High triglycerides = > 4 mmol/l.

Measures of obesity will include waist circumference, body mass index [BMI; weight in kilogrammes divided by the square of the height in meters $(kg/m)^2$], and waist-to-hip ratio. Following WHO guidelines, waist circumference will be considered to be abnormal if ≥ 102 cm for men and ≥ 88 cm for women; and waist-to-hip ratio (WHR) will be considered abnormal if >0.95 cm for men and >0.85 cm for females.

Participants will be classified as overweight if BMI = 25 and <30 and obese if BMI ≥30.

The demographic variables include age, grouped into 10-year age bands between 20 and 80 years (18 and 19 will be included in the first band); sex; and marital status.

History of DM in the family, smoking, dietary habits and physical activity will also be included.

Strategy of analysis

Then multiple Logistic regression analyses will be conducted to analyse the significant factors associated with the dependent variable (Type 2 DM and IR). Independent variables were selected on the basis of the literature of diabetes risk factors.

We will conduct Univariate, and a multivariate, results will be presented as crude and adjusted odds ratios with associated 95% Confidence intervals.

For objective 3

The outcome measure is the prevalence of IR among first degree relatives of people with Type 2 DM.

We will use the same IR definition and cut-off point mentioned above in objective 1.

For objective 4

The outcome measure will be the percentage of the diabetic patient attending Nuzha HCF with good glycaemic control and to describe the risk factors associated with poor glycaemic control.

Good glycaemic control is when HbA1c < 7, and poor glycaemic control is when HbA1c > 9

We will use the same risk factors categorization and strategy of analysis used in objective 2

Strategy of analysis

Then multiple Logistic regression analyses will be conducted to analyse the significant factors associated with the dependent variable (good and poor glycaemic control).

We will conduct Univariate, and a multivariate, results will be presented as crude and adjusted odds ratios with associated 95% Confidence intervals.

For objective 5

The outcome measures are to describe the accuracy of POC device in measuring HbA1c, describing the precision of the POC device, comparing the means (95% CI) and difference (95% CI) against the reference laboratory results.

Strategy of analysis

HbA1c POC results will be compared to reference laboratory results. Pearson correlations will be calculated to compare the performance of the POC method to standard laboratory analysis; accuracy will be measured by the area under the ROC curve.

To test the null hypothesis of non-equivalence (a difference of more than 0.5 in HbA1c) between the methods, we will use the paired t test to determine whether the HbA1c value from the POC test is equivalent to the value from the laboratory test.

Matched data will be used to compare the sensitivity, specificity and the agreement between the Quo-test to the reference results.