**Obesity and Atrial Fibrillation: Making inroads through fat**

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**Total file word count:** 5550 (including references, legends and table text)

**Main manuscript word count:** 4362 (including references, excluding table text)

**Abstract word count:** 150

**Total figures and tables:** 6

**Abstract**

The global prevalence of obesity has reached epidemic proportions, paralleled by a rise in cases of atrial fibrillation (AF). Data from epidemiological cohorts supports the role of obesity as an independent risk factor for AF. Increasing evidence indicates that obesity may contribute to te AF substrate through a number of pathways including by altering epicardial adipose tissue biology, inflammatory pathways, structural cardiac remodelling and inducing atrial fibrosis. Due to changes in pharmacokinetics and pharmacodynamics, specific therapeutic considerations are required to guide management of patients with AF including anticoagulation and rhythm control. Also, weight loss in patients with AF has been associated with reduced progression from paroxysmal to persistent AF and indeed regression from persistent to proximal AF. However, the role of dietary intervention in AF control remains to be fully elucidated and hard prospective outcome data to support weight loss is required in AF to determine its role as part of a comprehensive risk factor management strategy for AF in obese patients..

**Key words:** atrial fibrillation, obesity, cardiac risk factors, fat

**List of abbreviations**

|  |  |
| --- | --- |
| **AF** | Atrial fibrillation |
| **BMI** | Body-mass index |
| **CVD** | Cardiovascular disease |
| **DCCV** | Direct current cardioversion |
| **EAT** | Epicardial adipose tissue |
| **LA** | Left atrium/atrial |
| **LV** | Left ventricle/ventricular |
| **LVH** | Left ventricular hypertrophy |

**Acknowledgements**

None to declare

**Conflicts of interest**

Dr Javed and Dr Gupta have nothing to disclose

Dr. Lip reports consultancy and speaker fees from Bayer, Bayer/Janssen, BMS/Pfizer, Biotronik, Medtronic, Boehringer Ingelheim, Microlife, Roche, and Daiichi-Sankyo outside the submitted work. No fees received personally.

1. **Introduction**

Obesity is a major public health challenge affecting around 650 million people around the world(1). Its global prevalence has been rising at an alarming rate(1). Defined as a BMI greater than 30 kg/m2, obesity has profound consequences for both patients and healthcare systems but most concerning are the rising rates of cardiovascular and metabolic diseases which together conspire to drive morbidity and mortality in obese individuals(2). Paralleling this rise in obesity, the prevalence of atrial fibrillation (AF), already the commonest sustained arrythmia in adults, is expected to rise three-fold in the next three decades(3). Though a number of factors underlie this rising prevalence of AF, a mounting body of evidence indicates that obesity is a major contributor to the development of the AF substrate(4).

The pathophysiological mechanisms sustaining this AF-obesity association have not yet been completely elucidated but the relationship appears multifactorial. From a therapeutic perspective, this relationship represents a new avenue to AF management where modifying the consequences of obesity can fundamentally alter its role in arrhythmogenesis. Here, we provide a critical narrative overview of the AF-obesity relationship and explore the prognostic and therapeutic considerations for AF in obesity.

1. **Epidemiology of AF in Obesity**

Data from early epidemiological cohorts have found a multitude of risk factors for the development of AF(5-9). More recently, there is growing appreciation that obesity may be an independent risk factor for the development of AF(7). Early evidence for this association emerged from patients undergoing cardiac surgery, where a high body-mass index (BMI) was reported as a key predisposing factor for incident post-operative AF(9). Longer term data from the Framingham cohort and the Women’s Health Study demonstrated that rises in BMI parallel a considerable increase in AF risk(7, 9, 10). Most interestingly, short-term weight gain to BMI >25 kg/m2 was a substantial risk for developing AF while individuals who lost weight to a BMI <30 kg/m2 were found to have a reduced risk of AF(7).

Lim et al found that overweight and obese Korean subjects had a greater risk of new-onset AF compared to subjects with a normal BMI(11). Deng et al examined post-ablation AF recurrence in a cohort of Chinese patients with AF. They reported a U-shaped relationship where both underweight (HR 1.85, 95%CI 1.12-3.08) and obese (HR 1.78, 95%CI 1.17-2.72) subjects had an increased the risk of AF recurrence. In general, a BMI >26.36 kg/m2 was associated with an approximately 50% greater AF risk(12).

In a meta-analysis of 51 studies (n = 600 000) that evaluated the impact of obesity on AF, every 5-point increase in BMI was associated with an additional ~20-30%increase in incident AF, a 10% risk of post-operative AF and a 13% risk of post-ablation AF(4). Taken together, these studies suggest that the relationship between AF and obesity is both complex and dynamic.

Analysis of the data from other cohorts has provided further evidence of the AF obesity relationship (Table 1). This relationship appears to be independent of gender, age, diabetes and hypertension and also persists regardless of the presence of sleep apnoea, a common potentially confounding condition in obese individuals(13-16), suggesting that obesity contributes to AF through direct in addition to indirect pathways It has been suggested that the relationship between AF and obesity is such that obesity represents the second highest population-attributable risk factor for AF after hypertension(17). Indeed, the ARIC study estimates that almost one-fifth of incident AF can be attributable to a BMI >25 kg/m2 (17).

Although deducing a causal link based entirely on epidemiological studies is difficult, taken together these studies indicate that the relationship between obesity and AF is persistent, graded and seems to transcend age, conventional cardiovascular risk factors and geographical and racial boundaries.

1. **Pathophysiology of AF in obesity**

***3.1 Haemodynamic changes in obesity***

Obesity is related to a plethora of haemodynamic derangements that induce changes in cardiac morphology and physiology driving their risk of AF development and maintenance(18, 19). Increased adiposity is associated with an increase total and central blood volume in help perfuse excess tissue(18). This results in greater stroke volume and cardiac output(20). The unfortunate consequences of a rise in cardiac output is left ventricular enlargement which is associated with eccentric or concentric remodelling. As left ventricular filling pressure rises, increased left ventricular wall stress ensues, which may lead to diastolic dysfunction. With time, if left ventricular wall pressures fail to keep pace with ventricular hypertrophy systolic dysfunction may develop(18-20). This left ventricular dysfunction may result in left atrial enlargement associated with rising left atrial pressures and volumes, spurring a consequent rise in pulmonary venous and capillary pressures(18, 21).

These alterations in cardiac morphology do not occur in isolation. Indeed, obesity is associated with myriad neurohumoral and metabolic derangements (figure 1) which also drive changes in cardiac structure and function. These include an increased insulin resistance, activation of renin-angiotensin-aldosterone system, autonomic dysfunction and hypertension (18, 19). Additionally, obesity associated sleep disorders such as hypoventilation and sleep apnoea also help drive rises in pulmonary vascular pressures and, a dysfunctional autonomic response due to disordered cycles of hypoxia, acidosis and arousal from sleep increase the risk of abnormal cardiac impulse formation(22). In summary, these derangements in cardiac, and in particular left atrial, structure and function nurture a state that promotes and sustains AF formation.

***3.2 Epicardial adipose tissue and AF***

In recent years, there has been burgeoning interest in the role of pericardial and epicardial adipose tissue in relation to cardiovascular risk.  Epicardial adipose tissue (EAT) is located between the visceral pericardium and the epicardial layer of myocardium(23). Pericardial adipose tissue or pericardial fat is located beyond the parietal pericardium(24). Initially thought to be simply a maker of obesity, we now know that these fat depots boast an extensive biological arsenal, serving paracrine and autocrine function(23, 24).

There does not appear to be a distinct boundary between the myocardium and the EAT overlying it and both are supplied by the coronary vessels, providing a channel for paracrine and vasocrine signalling(25). As early as 1933, a post-mortem demonstrated that as many as 98% of obese individuals have excessive EAT(26).

Data from the Framingham cohort suggest that each standard deviation in pericardial fat volume was associated with a 28% rise in AF prevalence(27). Al Chekakie reported that pericardial fat volume was associated with paroxysmal AF (OR 1.11; 95% CI 1.01-1.23) and persistent AF (OR: 1.18; 95% CI 1.05 to 1.33), and this ainssociation was independent of age, hypertension, sex, left atrial enlargement, valvular heart disease, left ventricular ejection fraction, diabetes mellitus, and body mass index(28). These data are supported by a meta-analysis demonstrating that every standard deviation increase in epicardial fat volume was associated with a 2.6-fold higher odds of AF (OR 2.61; 95% CI 1.89-3.60) (29). Beyond predicting AF, multiple studies have demonstrated poor post-ablation outcomes in patients with higher pericardial fat volumes(27, 30).

The question around how epicardial and pericardial fat promotes AF is more complex. Although a definite paracrine mechanism remains unproven, it is evident that epicardial fat is metabolically active(23).  Thus, epicardial fat may induce atrial fibrosis through the paracrine action of adipocytokines, fatty infiltration into myocardial tissue and fibrotic remodeling of adipose tissue in the atrial epicardium as a consequence of inflammation (Figure 2)(31, 32). Evidence from experimental studies suggests that adipocytes may module the electrophysiology of atrial myocytes(32, 33).

***3.3 Atrial remodelling***

LA dilatation and dysfunction are established features of obesity associated cardiomyopathy. In animal models, these LA changes were associated with decreased conduction velocity, heterogeneity of conduction and a greater AF inducibility(34, 35). LA enlargement was present in the vast majority of obese individuals in several post-mortem studies(18).

Epidemiological evidence comes from the MONIKA/KORA (monitoring of trends and determinations in cardiovascular disease/cooperative research in the region of Augsburg) cohort where obesity was found to be a stronger predictor of LA enlargement, despite after adjusting for age and sex(36). Indeed, 21 year longitudinal data from the Olmstead Country cohort further found that BMI and LA volume incrementally predicted AF risk, even after taking height into account(14).

Obese patients have higher left atrial volume and pressure with lower left atrial strain associated with shorter refractoriness in the LA and the pulmonary veins(35). These findings suggest that the LA enlargement could potentially contribute to explaining this obesity-AF relationship.

***3.4 Inflammation***

Obesity is characterised by a systemic pro-inflammatory state(37). This is further exacerbated by the presence of obstructive sleep apnoea and obesity hypoventilation where the cycles of hypoxia exacerbate inflammation(22). There is extensive evidence that inflammation is linked to AF. The circulating levels of a number of inflammatory markers are higher in patients with AF(38). Figure 3 illustrates various inflammation-associated mechanisms that may precipitate arrhythmogenesis is AF.

In addition to the systemic inflammation, there has been increasing interest on the role of the contiguous pericardial and epicardial fat in contributing to local inflammation(39). Chen et al reported that patients undergoing valve surgery with a history of persistent AF, had a greater number of CD45+ cells (a pan-leukocyte marker) in their atrial myocardium compared to patients without AF(40). Furthermore, the chronic systemic inflammation in obesity appears to influence the biology of epicardial fat (in particular the perivascular adipose tissue that surrounds arteries), promoting the expression of a more pro-inflammatory profile(41). In addition to its role in facilitating energetic and lipid metabolism, epicardial fat boasts an extensive arsenal of biologically active molecules, such as inflammatory mediators and adipocytokines, that have been shown to mediate the effect of fat on neighbouring tissues. Several adipokines expressed by EAT are known to be involved in the formation of the AF substrate. This includes inflammatory cytokines, growth factor, or matrix metalloproteinases (MMPs). Thus, one explanation for the relationship between EAT abundance and AF could be that EAT-secreted adipokines contribute to structural remodelling of the atrial myocardium, such as fibrosis. Additionally, EAT contains abundant ganglionated plexi. Activation of the autonomic nerves in the ganglionated plexi may facilitate the maintenance of AF(42).

***3.5 Fibrosis***

In addition to inflammation, fibrosis has been shown to induce an arrhythmogenic substrate by inducing new micro re-entry circuits, electrical heterogeneity, regions of local conduction block, and alterations in atrial refractory periods(43).

One of the pathogenic effects of epicardial fat is induction of fibrosis via paracrine pathways, likely mediated via proinflammatory factors such as activin A and matrix metalloproteinases(31). For example, in a sheep model, Abed et al studied various neurohormonal and metabolic factors (34). They reported a significant increase in LA volume, transforming growth factor, platelet-derived growth factor, LA fibrosis, left atrial inflammation, and myocardial lipidosis(34). It has been suggested that the role of fibrosis in inducing and sustaining AF in humans may be similar. However, these insights are limited by using animal models which have been fed diets not reflective of modern lifestyle.

***3.6 Other risk factors***

Animal models have demonstrated enhanced atrial myocardial dilatation, mycote hypertrophy, slowing and heterogeneic conduction velocity and a number of other structural and functional derangements in patients with hypertension(44, 45). These factors have also been associated with AF. Both obesity and hypertension are associated with dysautonomia, increased circulating blood volume and renin-angiotensin system activation leading to abnormal atrial stretch and automacity, in turn increasing vulnerability to AF(46). It follows that optimising hypertension in obese patients may also help ameliorate these changes.

Obstructive sleep apnoea in the context of obesity contributes to hypertension, a pro-inflammatory state, cyclical sympathetic activation, greater atrial electromechanical delay and left atrial stretch induced dilatation(46). Again, these factors have been thought to contribute to the AF substrate.

In addition to hypertension, diabetes mellitus is a known independent risk factor for AF. Diabetes is associated inflammation, insulin resistance, structural, autonomic changes, atrial myocardial conduction slowing and greater dispersion which may influence atrial arrhythmogenicity and contribute to local AF triggers(46). Better glycaemic control in patients with obesity undergoing weight loss therefore may also impact the contribution of diabetes to AF.

***3.6* AF in the context of the obesity paradox**

Despite the multiple mechanisms responsible for the formation and sustenance of the AF substrate in obesity, recent studies have counterintuitively reported that there may be a paradoxical difference in mortality(47, 48). Prevalent AF is, in fact, associated with a lower risk of all-cause mortality in overweight subjects compared to lean subjects.

In their meta-analysis of direct oral anticoagulant (DOAC) trials, Proietti et al reported an obesity paradox for cardiovascular death and all-cause death in the subgroup analyses of randomized trial cohorts(49).  A significant obesity paradox was found, with both overweight and obese patients reporting a lower risk for stroke/systemic embolic event (OR 0.75; 95% CI 0.66–0.84 and OR, 0.62; 95% CI, 0.54–0.70, respectively). Interestingly this association was only found in secondary analysis of trial data and observational cohorts failed to show this relationship. Those studies that failed to show an obesity paradox were those with the longest follow-up duration. Moreover, most trial cohorts only considered BMI at baseline did not examine the time-dependent changes nor factors that can attenuate and modify BMI, including physical activity and cardiorespiratory fitness. However, it is not yet clear whether this obesity paradox is an actual phenomenon and a number of explanations may exist for these observed differences in mortality (figure 4)(26, 49). Given the proven benefit of weight loss and risk factor control in AF, it would be disingenuous to avoid aggressive risk management strategies in AF.

1. **Management issues specific to AF in obesity**

In light of the established role of obesity in the formation and sustenance of the AF substrate, it follows that the management of obesity and its associated cardiometabolic consequences is essential to helping manage AF in obese individuals.

***5.1 Anticoagulation for AF in obesity***

Obesity can alter the pharmacodynamics and pharmacokinetics of various drugs(50, 51). Anticoagulation is one of the pillars of AF management to control thromboembolic risk. Guidance from the European Society of Cardiology Working Group on Thrombosis has highlighted limited clinical data and risk of suboptimal anticoagulation in severe obesity(52). For direct oral anticoagulants (DOACs), there is a paucity of long-term clinical outcome data to support their use in obesity(51-53). Evidence appears conflicting: where one review found lower antithrombotic effect of DOACs in obesity, data from the AMADEUS trial found that in elderly patients, obesity was related to good quality anticoagulation control(54, 55).

***5.2 Rhythm control***

One of the most commonly performed procedures in AF patients is direct current cardioversion (DCCV). Obese patients have been found to have a lower success rate with DCCV(56). However, it is likely that this effect is due to a reduced energy delivery to the heart as result of adiposity. Indeed, when higher energies were used the success rate of DCCV was consequently greater in these patients(57).

While obese and normal BMI individuals have similar complication rates when undergoing catheter ablation, obese patients undergoing catheter ablation for AF have higher radiation exposure and longer procedural time (58). Furthermore, Shoemaker et al have reported that morbid obesity was associated with a higher burden of complications following AF ablation(59).

In a similar manner to oral anticoagulants, the pharmacokinetics and pharmacodynamics of antiarrythmic agents can be altered by body composition. For example, amiodarone is very lipophilic and can accumulate in adipose tissue leading to reduced clearance in overweight individuals(60). However, no clear guidance exists about dose adjustment in obesity. Meanwhile, digoxin requires no dosing changes as its distribution and clearance are largely unaffected by obesity(61). Overall, there is little guidance on dose adjustment of antiarrythmic agents in obesity.

***5.3 Weight loss in obesity***

A number of studies have investigated the impact of weight loss on AF in the context of obesity (Table 2). Weight loss may be achieved through bariatric surgery, caloric reduction through diet with or without physical activity. No trial has specifically explored a drug-based approach to weight loss in AF to our knowledge. (62, 63)Jamaly et al have reported that bariatric surgery was associated with a reduced risk of AF in a cohort of Swedish patients with obesity(62). In contrast, the Look Ahead study randomised 5067 subjects with diabetes to an intensive lifestyle intervention group or standard diabetes education group(63). The intervention group underwent modest weight loss through caloric reduction and weight loss.; however, the intervention did not affect AF incidence during the mean follow up period of 9 years(63). Taken together, these findings suggest that weight loss may be associated with a lower AF incidence but this effect may only manifest with dramatic weight loss.

In those with established AF, weight loss is associated with a reduction in AF severity and burden in an incremental manner, improving both symptoms and recurrence free survival(64-66).

Weight reduction may promotes better outcomes through its direct effects on cardiac structure and function, and indirectly through its impact on other cardiovascular risk factors such as hypertension, diabetes and obesity hypoventilation(18, 19, 32). Studies have demonstrated that weight reduction promotes with decreases in LA volumes, LV wall thickness, and improvements in LV diastolic function(65-67).

Most recently, the REVERSE-AF study reported that every 1 kg/m2decline in body mass index was associated with a 54% reduction in progression from paroxysmal to persistent AF and a 71% increase in regression from persistent to paroxysmal AF suggesting that the underlying substrate for AF can be reversed through a combination of weight loss and risk factor control(68). In summary, weight loss in established AF ameliorates a number of risk factors that are fundamental to developing and sustaining the substrate for AF in obese individuals(64, 65, 67-69). However, further studies are needed to determine whether weight reduction strategies in patients with AF can lower long-term risk of adverse clinical outcomes, such as mortality, stroke, and hospitalization due to heart failure.

5. Future directions

GIven the role of EAT in determining local biology, it represents an emergent therapeutic target. Patients with diabetes treated with a glucagon-like peptide 1 agonist in tandem with metformin had almost 40% reduction in EAT volume(70). These data have not been correlated to hard clinical outcomes and further work in this cohort should help shape AF management in this patient cohort.

Most promisingly, coronary perivascular adipose tissue imaging through routine CT angiograms have been used as a surrogate marker of coronary inflammation and vascular disease(71). The technique relies on using an algorithmically-derived fat attenuation index (FAI) from CT coronary angiograms to demonstrate the degree of lipid-accumulation in mature adipocytes surrounding coronary vessels. This FAI has been validated extensively and shown to be increased in patients with coronary artery disease (CAD) compared to healthy subjects(71). A similar technique for AF may help identify EAT that is particularly inflamed and most likely to be pathogenic.

Evidence is accumulating for a comprehensive risk factor management approach that combines weight loss with other traditional risk factor approaches including diabetic and hypertensive control(68). The role of dietary intervention in AF control remains to be fully elucidated and the evidence base for weight management in determining hard cardiovascular outcomes requires further prospective evaluation.

**6. Conclusion**

The rising global tide of obesity is paralleled by the rise in cases of atrial fibrillation. A mounting body of evidence indicates that AF and obesity are inextricably linked, driven by complex pathophysiological mechanisms. Given the mortality, morbidity and financial costs associated with both AF and obesity, this AF-obesity epidemic has clear implications for both health care and healthcare systems. Traditionally, the management of AF is built on three pillars: anticoagulation, rhythm control, and rate control. Emerging data indicate that risk factor control, in particular through weight loss may represent a major new approach to altering the AF substrate in obese individuals. In order to establish this fourth pillar in the management of AF further long term randomised clinical studies are required with particular emphasis on hard outcomes.

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**Figure legends**

*Figure 1: Local and systemic effects of obesity that drive cardiovascular disease (FFA: free fatty acids, NO: nitric oxide, RAAS: renin-angiotensin-aldosterone system)*

*Figure 2: Potential mechanisms for the arrhythmogenesis in patients with abundant epicardial adipose tissue*

*Figure 3: Possible explanations for the obesity paradox in AF.*