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INVITED REVIEW

Adiposity-associated atrial fibrillation: molecular determinants, mechanisms, and clinical significance

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Abstract

Obesity is an important contributing factor to the pathophysiology of atrial fibrillation (AF) and its complications by causing systemic changes, such as altered haemodynamic, increased sympathetic tone, and low-grade chronic inflammatory state. In addition, adipose tissue is a metabolically active organ that comprises various types of fat deposits with discrete composition and localization that show distinct functions. Fatty tissue differentially affects the evolution of AF, with highly secretory active visceral fat surrounding the heart generally having a more potent influence than the rather inert subcutaneous fat. A variety of proinflammatory, profibrotic, and vasoconstrictive mediators are secreted by adipose tissue, particularly originating from cardiac fat, that promote atrial remodelling and increase the susceptibility to AF. In this review, we address the role of obesity-related factors and in particular specific adipose tissue depots in driving AF risk. We discuss the distinct effects of key secreted adipokines from different adipose tissue depots and their participation in cardiac remodelling. The possible mechanistic basis and molecular determinants of adiposity-related AF are discussed, and finally, we highlight important gaps in current knowledge, areas requiring future investigation, and implications for clinical management.

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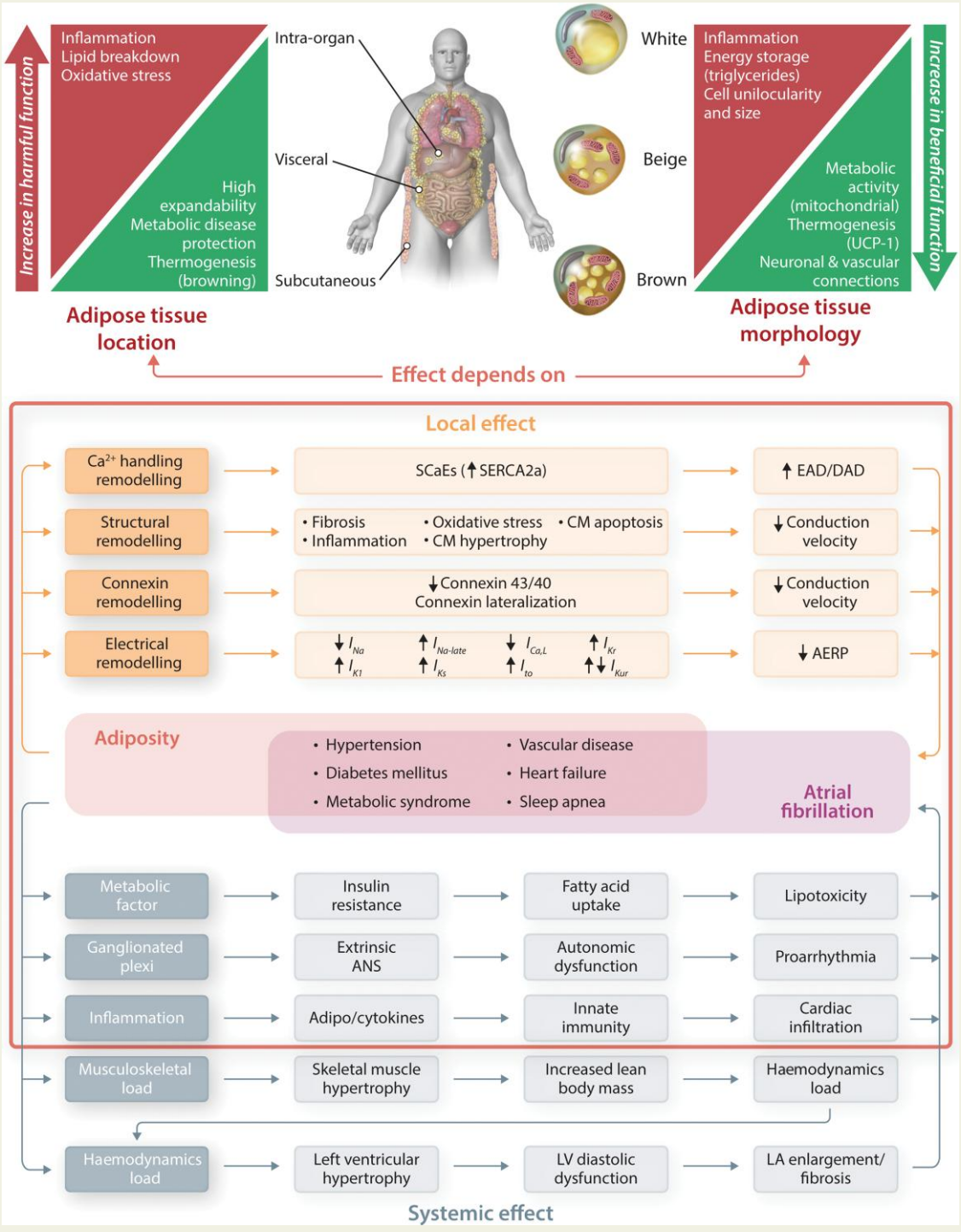
Graphical Abstract



Cellular, localization, and functional heterogeneity of adipose tissue.

CM, cardiomyocyte; see *Tables 1* and *2*.

Visceral and subcutaneous adipose tissue are two main human fat depots that represent different metabolically and proinflammatory profile (upper left panel). Adipocytes are divided into different cell types with distinct morphological and functional characteristics, including white, beige, and brown adipocytes (upper right panel). Pink adipocytes are not discussed in this review, since they mainly occur in pregnancy.

Adiposity together with accompanying obesity-related comorbidities (metabolic syndrome, diabetes, hypertension, heart failure, sleep apnoea) promote atrial fibrillation through systemic effects (bottom left) via haemodynamic, metabolic, neurohormonal, and proinflammatory factors, and through local effects promoting a proarrhythmic atrial cardiomyopathy involving Ca^{2+} handling, structural, connexin, and electrical remodelling (bottom right).

Depending on location and morphology, adipose tissue might contribute to proarrhythmia by causing local and systemic effects (red frame).

Keywords Adipokines • Atrial fibrillation • Epicardial adipose tissue • Obesity • NLRP3 inflammasome • Subcutaneous adipose tissue • Visceral adipose tissue

1. Introduction

Overweight and obesity are defined as abnormal or excessive fat accumulation that presents a risk to health.[1] A body mass index (BMI) over 25 kg/m^2 indicates overweight, whereas BMI over 30 kg/m^2 indicates obesity.[1] The prevalence of overweight/obesity has reached global epidemic status.[1] Nearly half of the world population is estimated to be overweight or obese, and for the first time in human history, the number of obese people exceeds those who are underweight.[1] The recent scientific statement of the American Heart Association[2] positions excess visceral adiposity as a crucial and independent driver of atrial fibrillation (AF).

This review assesses how specific adipose tissue depots, specifically those located around the heart, may contribute causally to AF. We describe the key culprit adipocytokines secreted by distinct fat depots and outline candidate molecular mechanisms and newly discovered metabolic pathways by which these factors, as well as obesity in general, can promote the evolution of an AF-vulnerable arrhythmogenic substrate. Finally, we highlight important gaps in current knowledge and provide perspectives for future exploration of the complex relationship between obesity and AF, as needed to improve clinical management of the arrhythmia.

2. The composition of different fat depots

Mammals, including humans, possess two principal types of fat: white adipose tissue (WAT) and brown adipose tissue (BAT), each with specific cell compositions and secretory effects (*Table 1*).[3] Moreover, brown adipocytes appearing in WAT form the third type of adipose tissue called brite, beige, or brown-in-white.

WAT is the predominant form of total body fat. Its primary functions are to store energy for times of higher energy demand and to secrete molecules that regulate food intake and energy turnover.[3] White adipocytes are large and unilocular, possessing one large fat droplet that stores energy in the form of triglycerides, and few mitochondria.[3] WAT is classified as either subcutaneous adipose tissue (SAT) or visceral adipose tissue (VAT), with VAT located in the intra-abdominal or omental region, and in and around organs such as the heart and vasculature (Figure *1*).[3] Adipocytes in VAT and SAT arise from different progenitors and exhibit distinct gene expression patterns and functions already in childhood.[21] VAT is associated with a high abundance of infiltrating macrophages and a proinflammatory secretome, whereas SAT is typically seen as relatively inert or even beneficial (*Graphical Abstract*).[22] Moreover, abdominal VAT can release its secretory products (e.g. adipokines) into both the systemic circulation and the portal vein, thereby directly worsening or protecting liver function.[23] The individual VAT: SAT ratio is higher in the elderly compared with young individuals and lower in females compared with males, and is further determined by genetic background, nutritional health, and the energy homeostasis of the specific depots.[3]

BAT makes up 4% of total body fat. It is located mainly in supraclavicular areas, and to a lesser extent in para-aortic, para-vertebral, and supra-renal regions (Figure *1*).[3] Its abundance, composition, and endocrine function are highly plastic, depending on nutritional status, sex, age, and adiposity.[3] It is higher in the female population and decreases with age.[3] BAT exhibits distinct transcriptome, proteome, and secretome signatures compared with WAT and accordingly plays a different physiological role, storing energy to a lesser degree and functioning primarily as a thermoregulatory organ.[3] Brown-like adipocytes are smaller, multilocular, and possess a higher number of mitochondria than white adipocytes (*Graphical Abstract*).[24] High expression of uncoupling protein-1 separates oxidative phosphorylation from ATP production, promoting the oxidation of fatty acids for heat production, although additional independent mechanisms may also contribute.[25] BAT is classically considered as a thermoregulatory fat depot in newborns only and is only characterized in adult mammals, including humans, just over a decade ago.[26] Intriguingly, white shifting of brown adipocytes within cardiac fat correlates with dilatation of the left atrium (LA), a strong predictor of AF.[27]

A third type of fat can evolve when batches of brown-like adipocytes accumulate in WAT (*Table 1*).[24] This may occur through inducible 'browning' of white adipocytes towards the so-called beige, brite, or brown-in-white phenotype in response to cold, β-adrenoceptor stimulation, exercise, or various other endocrine stimuli.[6]

3. Adipose tissue remodelling in obesity

Obesity causes immune-cell recruitment and infiltration and inflammation of adipose tissue and other organs, with accumulation and activation of M1-macrophages, neutrophils, CD4$^+$ T-helper cells, and CD8$^+$ T cells, while the contribution of M2-macrophages, CD4$^+$ regulatory T cells, regulatory B cells, and eosinophils decreases.[28] The contribution of other players, such as natural killer cells and innate lymphoid cells, is just beginning to be explored. Immune-cell recruitment is triggered by chemokines secreted from hypertrophic adipocytes, most notably the monocyte chemoattractant protein-1 (MCP-1),[29] which is considered a particular feature of WAT. Recent work employing a wider panel of subset markers to characterize resident macrophages in SAT and VAT from lean and obese human donors, unexpectedly revealed that total macrophage numbers increased with obesity only in SAT, but not in VAT and that M2-macrophages were actually highly prevalent in lean VAT but diminished with obesity.[30] Conversely, macrophage expansion in SAT depends largely on increased M2-macrophages, while in VAT, the subset of macrophages that increased numerically with obesity display mixed M1/M2 markers.[31] Hence, the classical view that obesity exacerbates the proinflammatory nature of VAT, while SAT is rather inert, is increasingly challenged and requires further in-depth investigations.

In the lean state, SAT is characterized by a smaller cell size but an increased number of adipocytes as well as differential adipokine secretion compared with VAT (Figure *2*). During obesity, VAT adipocytes commence an adipogenic programme encompassing hyperplasia of

Table 1 Key features of white and brown adipose tissue

	White adipose tissue	Brown adipose tissue
Macrophages' markers[4]	**CD14$^-$, CD16$^+$**, CD11c$^+$, **CD36$^+$**, CD64$^+$, CD86$^+$, HLA-DR$^+$, TL4$^+$, CCR2$^+$	**CD14$^+$, CD16$^-$**, CD68$^+$, **CD163$^+$**, CD204$^+$, CD206$^+$, CD11b+, CD301+
Immune cells[5]	CD8+ T-lymphocytes, T-helper type 1 cells	Eosinophils, T-regulatory cells, T-helper Type 2 cells
Triggers[5]	IFNy, LPS, TNF-α, MCP-1, IL-6, IL-1	IL-4, IL-10, IL-13, TGF-β
	Chemerin GDF8(myostatin)[a] Endothelin1 Ceramides RBP-4 CX3CL1 (fractalkine) Saturated fatty acids ↑ Dendritic cells and macrophage activation ↑ Proinflammatory status ↓ Adipogenesis ↓ Thermogenesis ↓ Metabolic activity	GDF15[a] Follistatin[a] CXCL14 SLIT2-C UCP-1 FGF21 L-PGDS ↑ Thermogenesis gene expression ↑ Anti-inflammatory status ↑ Macrophage M2 activation ↑ Metabolic activity
Pharmacological interventions that increase particular fat depot	Anti-diabetic drugs (insulin)[6] Anti-hypertensive drugs (beta-blockers)[7] Anti-psychotic drugs (atypical)[8] Anti-depressants (serotonin agents)[9] Glucocorticoids[10b]	Anti-diabetic drugs (GLP-1R agonists, DPP-4 inhibitors, SGLT2 inhibitors)[6] Lipid-lowering drugs[6] Anti-obesity drugs (naltrexone + bupropion, phentermine + topiramate)[6]
Lifestyle interventions that increase particular fat depot	Nutritional changes (vitamin D overconsumption)[11] Sleep loss[12] Alcohol overconsumption[13c] Cannabinoids overdose[14d] Prolonged daily light exposure[15]	Nutritional changes (vitamin A, fish oil overconsumption)[6] Increased physical activity[6] Bariatric surgery[6] Cold exposure[6] BAT transplantation[6]

Bolded markers are those distinguishing anti-inflammatory (CD14$^+$ CD16$^-$ CD36^{low}CD163$^+$) from pro-inflammatory macrophages (CD14$^+$ CD16$^+$ CD36^{high} CD163$^-$).[4]
CXCL, chemokine (C–X–C motif) ligand; DPP-4, dipeptidyl peptidase-4; FGF21, fibroblast growth factor 21; GDF, growth and differentiation factor; GLP-1R, glucagon-like peptide-1 receptor; IFNy, interferon y; IL, interleukin; L-PGDS, lipocalin prostaglandin D synthase; LPS, lipopolysaccharide; MCP-1, monocyte chemoattractant protein-1; RBP-4, retinol-Binding Protein 4; SGLT2, sodium-glucose cotransporter 2; SLIT-C, C-terminal fragment of SLIT2 protein; TGF-β; transforming growth factor beta; TLR, Toll-like receptor; TNF-α, tumour necrosis factor alpha; UCP-1, uncoupling protein 1.
[a]TGF-β superfamily.
[b]Species-specific effect on adipose tissue.[16] In rodents, glucocorticoid treatment decreases activity of BAT, whereas in humans, it acutely increases UCP-1 expression,[17] which decreases with chronic (after 48 h) glucocorticoid treatment.[18]
[c]Chronic alcohol consumption led to a reduction in adipose tissue mass.[19]
[d]Cannabidiol promotes brown-like phenotype.[20]

adipocyte precursors and hypertrophy of mature adipocytes, while subcutaneous adipocytes preferentially undergo hypertrophy.[32] Weight gain triggers cell growth of VAT (vs. SAT) adipocytes more rapidly, along with a reduction in adiponectin expression in VAT. As obesity progresses, extracellular matrix rigidity, composition, and remodelling impact adipose tissue expandability by physically limiting adipocyte hypertrophy and hyperplasia. Once the maximal capacity to store lipids is reached, lipids begin to accumulate as increased ectopic fat, defined by excess adipose tissue in locations not classically associated with adipose tissue storage including viscera, heart, and vasculature,[33] and promote insulin resistance, apoptosis, and inflammation.[23] This process is modulated by genetic and environmental factors, and for VAT is further restricted by the available space in the abdominal cavity.[23]

Noteworthy, ectopic accumulation of the fat could be referred not only to the apparent obesity but also ectopic fat accumulation in seemingly lean or slightly overweight patients. These 'metabolically unhealthy' individuals are characterized by lower SAT mass, higher VAT mass, adipocyte hypertrophy, a proinflammatory adipose tissue phenotype, and an impaired fat storage capacity of adipose tissue, which may result in ectopic fat deposition (more lipid accumulation in the heart), thereby contributing to the development of cardiometabolic AF risk factors.[34]

On the other hand, the so-called obesity paradox describes individuals with excess bodyweight and an elevated BMI who are yet 'metabolically healthy'.[34] They are characterized by more abdominal SAT and lower VAT mass, smaller adipocytes and less macrophage infiltration and inflammation in (visceral) adipose tissue, less fat accumulation in organs, and exhibit a lower risk of cardiovascular diseases.[34] This may be a transient state, prior to the progression of overt metabolic derangement and the manifestation of cardiovascular diseases.[34]

The aforementioned data indicate that the key factor driving cardiometabolic health seems to be the VAT compartment, with a low VAT content being associated with a more favourable cardiometabolic risk profile, independently of BMI.[34] Of note, the AF-promoting effect of obesity may not be due to adiposity *per se*,[35] but may rather be mediated by the increase in lean body mass caused by overweight.[35] The idea that obesity promotes AF by increasing lean body mass requires proof and validation in detailed pathophysiological studies. Because BMI does not differentiate between visceral, ectopic, or subcutaneous fat mass,[2] waist circumference might provide a better estimate of the relative abundance of visceral fat.[1] Previous work showed that waist circumference correlates much more strongly with visceral fat than BMI and that the addition of waist circumference to BMI explains an additional 11 and 16% of the

Table 2 Available clinical studies with plausible mechanistic data about the obesity-induced remodelling in AF (A) and experimental evidence for the association between adiposity and AF (B)

Reference	Study population/animal model	Results
(A) Clinical data		
Schram-Serban *et al.*[48]	Patients without baseline AF undergoing cardiac surgery; obese ($n = 106$, 74% men, 64 ± 9.6 years, BMI 33 ± 2.9 kg/m^2) and non-obese ($n = 106$, 78% men, 62 ± 12 years, BMI 25 ± 2.4 kg/m^2)	• Obese (vs. non-obese) patients had ↑incidence of post-operative AF and LA conduction disturbances
Munger *et al.*[49]	AF patients undergoing catheter ablation; obese ($n = 44$, 75% men, 57 ± 8.8 years, BMI 35 ± 4.3 kg/m^2) and non-obese ($n = 19$, 58% men, 55 ± 13 years, BMI 24 ± 1.7 kg/m^2)	• Obese (vs. non-obese) patients had ↑LA pressure, volume, and mechanical dysfunction, ↓ERP
Fang *et al.*[50]	Patients with AF; obese ($n = 14$, 50% men, 63 ± 7.0 years, BMI 32 ± 1.6 kg/m^2) and non-obese ($n = 15$, 53% men, 64 ± 7.3 years, BMI 23 ± 1.5 kg/m^2)	• Obese (vs. non-obese) patients had ↑LA levels of cadherin-11 and α-SMA • Additional experimental data: see part B of this table
Haemers *et al.*[51]	AF patients undergoing cardiac surgery ($n = 92$, 68% men, 68 ± 10 years, BMI 27 ± 5.9 kg/m^2)	• Patients with permanent (vs. paroxysmal) AF had ↑fibro-fatty infiltration in RA • Additional experimental data: see part B of this table
Nalliah *et al.*[52]	AF patients undergoing cardiac surgery ($n = 19$, 78% men, 64 ± 4.0 years, BMI 30 ± 7.0 kg/m^2)	• Patients with high (vs. low) anterior RA EAT had ↓conduction velocity, ↑electrogram fractionation, ↑RA fibrosis, connexin 40 lateralization • Additional experimental data: see part B of this table
(B) Experimental data		
Mahajan *et al.*[53]	Sheep with DIO ± weight loss; lean controls	• DIO associated with ↑AF inducibility, ↑LA inflammation, fibrosis and pressure, ↓ERP, ↓conduction velocity • 30% weight loss reversed aforementioned changes
Scott *et al.*[54]	Sheep ± DIO Mice ± DIO; WT vs. NLRP3$^{-/-}$	• DIO associated with ↑AF inducibility, ↑RA inflammation including NLRP3-inflammasome activation, and fibrosis, ↓ERP, ↑Kv1.5 levels, and Ca^{2+}-handling remodelling • NLRP3 deletion prevented DOI-induced ↓ERP, ↑RA fibrosis, and Ca^{2+}-handling remodelling
Haemers *et al.*[51]	Sheep ± RAP-induced AF	• RAP-induced AF along with fibro-fatty infiltration in LA
Mahajan *et al.*[55]	Sheep ± DIO	• DIO associated with ↑AF inducibility, ↑LA pressure, fibro-fatty infiltration, and conduction heterogeneity
Abed *et al.*[56]	Sheep ± DIO	• DIO associated with ↑AF inducibility, ↑LA inflammation, fibro-fatty infiltration, and conduction heterogeneity
Otsuka *et al.*[57]	Dogs ± DIO	• DIO associated with ↑AF inducibility, ↑LA fibrosis, lipidosis and pressure, ↓ERP
Okumura *et al.*[58]	Pigs ± DIO	• DIO associated with ↑AF inducibility, ↓ERP
Lin *et al.*[59]	Rabbit LA myocytes ± human adipocytes or adipocyte-conditioned media	• Abdominal/epicardial adipocyte secretome-induced ↑APD • Epicardial adipocyte secretome-induced depolarization of resting membrane potential, ↑$I_{Na\text{-}late}$,↑$I_{Ca.L}$, ↑I_{to}, ↓I_{Kr}, and ↓I_{K1}
Martinez-Mateu *et al.*[60]	Guinea pigs ± DIO	• DIO associated with ↑AF inducibility, ↓APD, ↑spontaneous beating rate, ↑I_{Kr}, ↑I_{Ks}, ↑I_{K1}, ↓$I_{Ca.L}$ and ↓I_{Kur}
Bernasochi *et al.*[61]	Young vs. old rodents ± DIO ± 17β-estradiol	• DIO associated with ↑AF inducibility, ↑pericardial adipose tissue volume, ↑aromatase expression in pericardial adipose tissue • 17β-estradiol associated with ↑AF inducibility and duration
Hohl *et al.*[62]	Rats ± DIO	• DIO associated with ↑AF inducibility, ↑LA fibrosis, lipidosis and dimension, ↑conduction heterogeneity
McCauley *et al.*[63]	Rats ± DIO	• DIO associated with ↑AF inducibility via autonomic imbalance
Fang *et al.*[50]	Mice ± DIO; WT vs. ± cadherin-11$^{-/-}$	• DIO associated with ↑AF inducibility, ↑LA fibrosis, inflammation and dimension, ↓connexin 40 and 43 expression via ↑cadherin-11 expression
McCauley *et al.*[64]	Mice ± DIO	• DIO associated with ↑AF inducibility, ↑LA fibrosis and oxidative stress, ↓I_{Na}, ↓$I_{Ca,L}$, ↑I_{Kur}
Nalliah *et al.*[52]	HiPSC-CM ± sheep EAT HL-1 cells ± mouse pericardial or inguinal adipose tissue	• Cardiac adipose tissue secretome associated with ↓spontaneous beating rate, ↑extracellular field potential duration, ↓conduction velocity, ↑activation time

Continued

Table 2 ***Continued***

Reference	Study population/animal model	Results
Shuai *et al.*[65]	Mice ± DIO; WT vs. ± $MD1^{-/-}$	• DIO associated with ↑AF inducibility, ↑LA fibrosis and inflammation, metabolic changes via ↓MD1 expression
Kondo *et al.*[66]	Mice ± DIO; WT vs. ± $IL\text{-}10^{-/-}$ IL-10 supplementation	• DIO associated with ↑AF inducibility, ↑LA fibrosis, inflammation and lipidosis, ↑pericardial adipose tissue volume, ↑systemic inflammation via ↓serum IL-10 levels
Zhang *et al.*[67]	Mice ± DIO ± 4-phenylbutyric acid (antioxidant)	• DIO associated with ↑AF inducibility, ↑LA fibrosis, and oxidative stress
Zhang *et al.*[68]	Mice ± DIO	• DIO associated with ↑sinoatrial node recovery time, ↓ERP, ↑Kv1.5, and Kv4.2/3 levels
Fu *et al.*[69]	Mice ± DIO	• DIO associated with ↑AF inducibility, ↑LA fibrosis and diameter
Feng *et al.*[70]	Mice ± DIO WT vs. ± $Nampt^{-/-}$	• DIO associated with ↑AF inducibility • Nampt/NAD axis associated with ↓DIO-induced AF
Ornelas-Loredo *et al.*[71]	Mice ± DIO ± flecainide or sotalol	• DIO associated with ↑AF inducibility • Flecainide (vs. sotalol) associated with ↓DIO-induced AF
Maria *et al.*[72]	Mice ± DIO	• DIO associated with ↑AF inducibility via ↑insulin signalling
Fukui *et al.*[73]	Mice ± DIO; WT vs. ± $leptin^{-/-}$	• DIO associated with ↑AF inducibility, ↑interatrial conduction time, ↑LA fibrosis via ↑leptin signalling

Abbreviations: α-SMA, alpha smooth muscle actin; AF, atrial fibrillation; APD, action potential duration; BMI, body mass index; DIO, diet induced obesity; EAT, epicardial adipose tissue; ERP, effective refractory period; hiPSC-CMs, human-induced pluripotent stem cell-derived cardiomyocytes; IL, interleukin; $I_{Ca,L}$, L-type Ca_{2+}-current; I_{Kur}, ultra-rapid delayed rectifier K_+-current; I_{Kr}, delayed rectifier K_+-current; I_{K1}, inward rectifier K_+-current; I_{Na}, Na_+-current; $I_{Na\text{-}late}$, late Na_+-current; I_{to}, transient outward K_+-current; LA, left atrium; MD-1; myeloid differentiation; NAD, nicotinamide adenine dinucleotide; Nampt, nicotinamide phosphoribosyltransferase; NLRP3, nucleotide-binding domain, leucine-rich-containing family, pyrin domains-containing-3; RA, right atrium; RAP, rapid atrial pacing; WT, wildtype; ↑ indicates increase in function or expression; ↓ indicates reduction in function or expression.

variation in visceral fat in men and women, respectively.[36] This measure could complement BMI in body fat monitoring, and improve health.[1]

4. Current conceptual model of AF

AF is the most common sustained arrhythmia and is associated with an increased cardiovascular mortality.[37] The progressive nature of AF has been attributed to worsening of the underlying atrial cardiomyopathy due to cumulative effects of genetics, chronic cardiovascular diseases and risk factors, as well as atrial remodelling induced by AF itself.[38]

Mechanistically, the genesis of AF generally requires a trigger and a vulnerable substrate (Figure 3).[39,40] The ectopic (triggered) activity is often the result of Ca^{2+}-handling abnormalities leading to abnormal automaticity (spontaneous depolarization of the membrane potential during diastole), or early and delayed afterdepolarizations.[41] Early afterdepolarizations are promoted by excessive prolongation of repolarization, providing time for L-type Ca^{2+}-currents to recover from inactivation and contribute additional depolarizing inward current, whereas delayed afterdepolarizations are promoted by spontaneous Ca^{2+} releases from the intracellular stores of the sarcoplasmic reticulum through ryanodine receptor channels.[39] The vulnerable substrate is characterized by short effective refractory period (ERP), typically due to ion-channel remodelling, and slow, heterogeneous conduction velocity resulting from structural remodelling, or remodelling of gap junctions responsible for electrical cell-to-cell coupling and voltage-gated Na^+ channels governing cellular excitability.[39] In the presence of an ectopic trigger leading to unidirectional block, short ERP and slow heterogeneous conduction promote the occurrence of re-entry, the primary AF-maintaining mechanism.[39] Finally, atrial dilatation is a common component of atrial structural remodelling that provides a larger substrate for the maintenance of re-entry.[39] The numerous AF-promoting risk factors and wide variety of mechanisms underlying AF create a highly heterogeneous condition that negatively affects the success of most AF therapies, suggesting a need for tailored therapy targeting nodal points of a specific phenotype.[39]

5. Clinical evidence and potential mechanisms linking obesity and AF

A recent meta-analysis associated obesity with a >50% increased risk of new-onset AF.[42] While mere overweight, in the absence of additional parameters of metabolic syndrome, does not increase the risk of incident AF, obesity with BMI in excess of 30 kg/m^2 is *per se* sufficient to promote AF onset[43] and progression from paroxysmal to persistent forms.[44] Another meta-analysis of 51 studies including 626 603 patients showed a significant, 10–29% increase in the risk of incident, postoperative, and post-ablation AF, for every 5 kg/m^2 increase in BMI, suggesting a linear association between obesity and AF risk.[45]

Recent studies show that AF may share some genetic loci and susceptibility genes with obesity and BMI. A Mendelian Randomization study showed that a genetic predisposition to childhood obesity is associated with an increased risk of developing AF in adult age.[46] Another Mendelian Randomization study of >50 000 European individuals without AF at baseline discovered that a genetic score comprising 39 single-nucleotide polymorphisms identified by genome-wide association studies to be associated with increased BMI was significantly linked to a higher risk of incident AF, even after adjustment for traditional AF risk factors including hypertension, diabetes mellitus, coronary artery disease, and heart failure.[47] These data point to a causal relationship between obesity and AF.

The mechanistic basis of the clinical association between AF and obesity remains incompletely understood, but numerous factors have been implicated in proarrhythmic atrial remodelling (*Table 2*; Figure 3). Among others, several adipokines and other bioactive molecules have

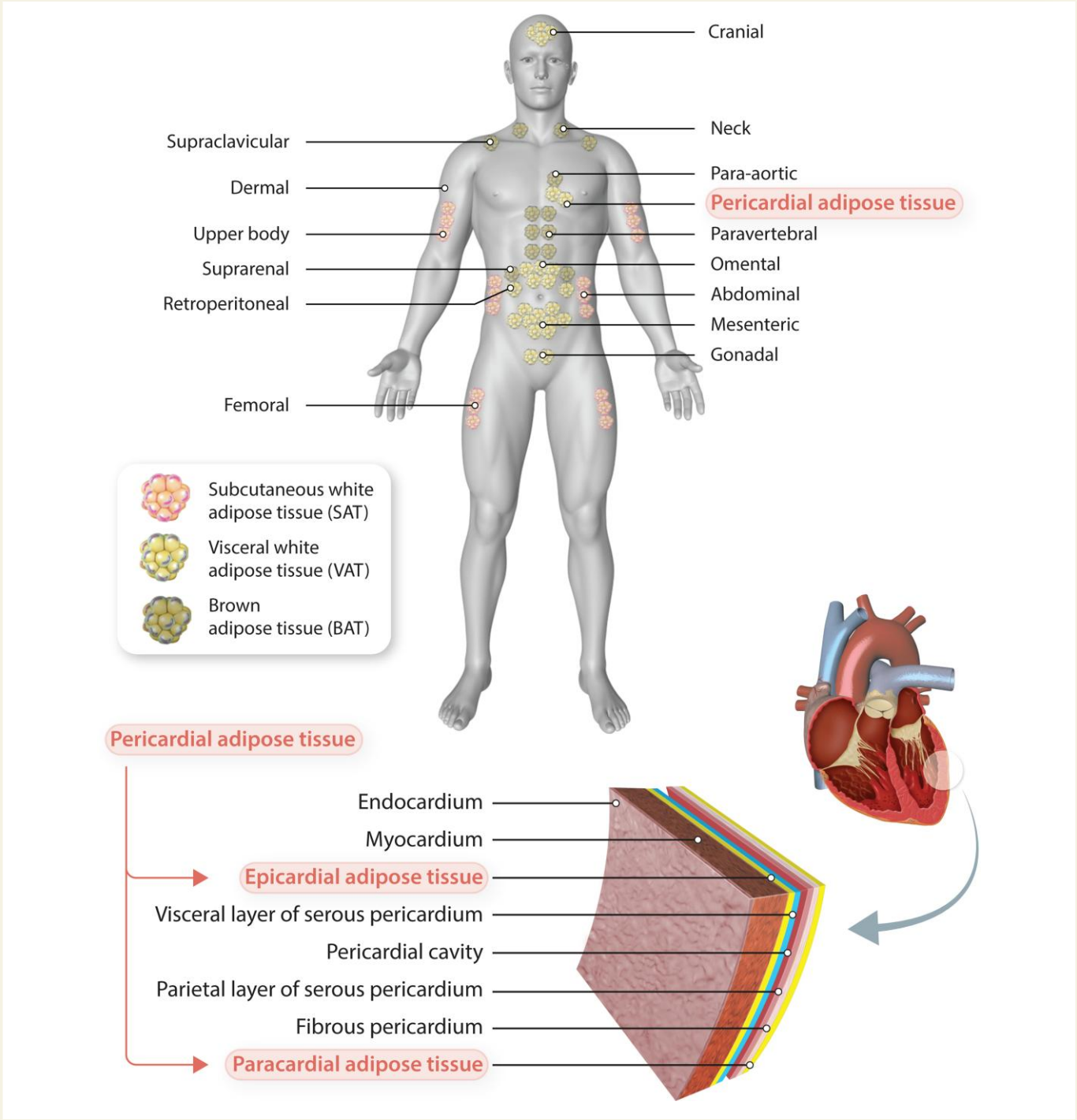


Figure 1 Types and localization of adipose tissue depots. In humans, BAT is localized mainly around the shoulders and ribs. Visceral WAT surrounds intra-abdominal organs, whereas subcutaneous WAT spreads throughout the body beneath the skin. Pericardial adipose tissue, a subtype of VAT, comprises both the epicardial and paracardial adipose tissue layers. Epicardial fat lies between the visceral pericardium and myocardium, whereas paracardial fat is located external to the fibrous pericardium.

been implicated in paracrine fat–heart communication (see Section 7) contributing to proarrhythmic atrial structural, electrical, and Ca^{2+}-handling remodelling. Among patients with AF, those with concomitant obesity exhibit shorter ERPs in both LA and around the pulmonary veins, as well as higher LA pressures and volumes, compared with AF patients with normal BMI.[49] The heart is particularly vulnerable to functional changes and end-organ damage induced by obesity and the associated metabolic risk factors hyperglycaemia, dyslipidaemia, and insulin resistance. The increased systemic blood volume that accompanies adipose tissue expansion to ensure adequate perfusion of the excess tissue, increases cardiac output and ventricular wall stress, and causes hypertrophy.[74] The resultant diastolic and systolic dysfunction

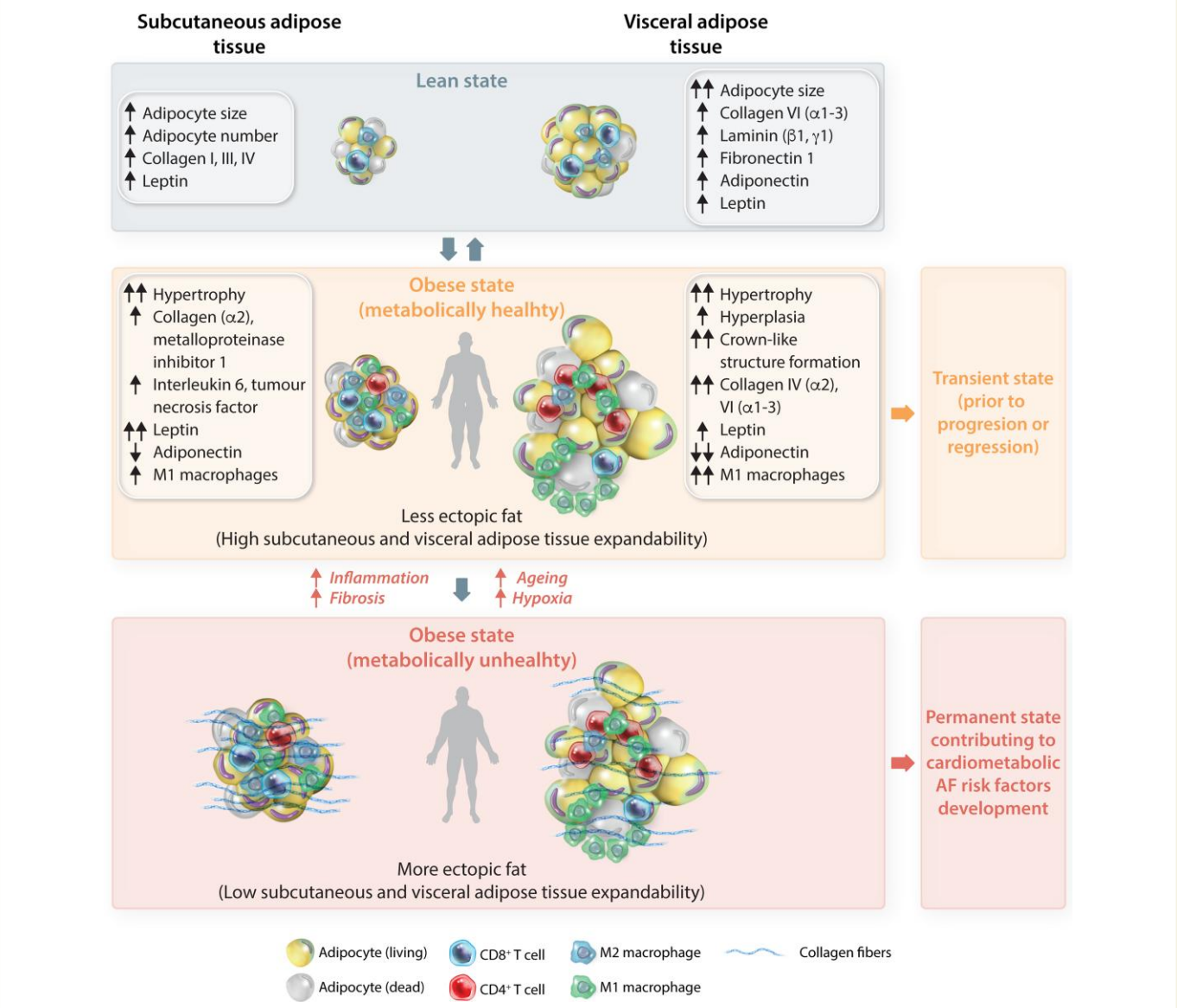


Figure 2 Schematic representation of the cellular dynamics of adipose tissue depots associated with obesity. In lean state (grey), VAT is characterized by large adipocytes, whereas SAT is characterized by a larger number of adipocytes, with VAT and SAT differing in their content of fibrotic factors and adipokines. During obesity, VAT is characterized by hyperplasia of adipocyte precursors and hypertrophy of mature adipocytes, while SAT adipocytes preferentially undergo hypertrophy. Weight gain triggers cell growth of VAT (vs. SAT) adipocytes, along with a reduction in adiponectin expression in VAT. This state is typical for 'metabolically healthy' individuals with high expandability of SAT and VAT, resulting in a low degree of ectopic fat storage (yellow). This state can regress or progress. As obesity progresses, extracellular matrix rigidity, composition, and remodelling alter adipose tissue expandability by physically limiting adipocyte hypertrophy and hyperplasia. Once the capacity to store lipids is reached, lipids begin to accumulate at ectopic sites. This process is modulated by genetic and environmental factors, and for VAT is further restricted by the available space in the abdominal cavity. This obese state describes 'metabolically unhealthy' individuals with low expandability of SAT and VAT resulting in a high rate of ectopic fat storage (red) that promotes insulin resistance, apoptosis and inflammation in places of residence (heart, liver, pancreas), thereby contributing to the development of cardiometabolic risk factors for AF.

promotes LA enlargement and a rise in pulmonary venous pressures.[74] This adaptive remodelling, together with concurrent neurohumoral activation, activation of profibrotic signalling pathways (via regulation of matrix metalloproteases, activin A, angiopoietins, and growth factors), and a sustained inflammatory state (mediated in part by intereleukin (IL)-6/8/1β, tumour necrosis factor alpha, MCP-1), may create a vulnerable substrate for AF promotion (Figure *3*).

6. Association between cardiac fat and promotion of AF

While some studies demonstrate significant correlations between visceral[75] or subcutaneous[76] adiposity and LA enlargement, others do not.[77] Lee *et al.*[78] found that pericardial and intrathoracic, but not abdominal VAT, were associated with incident AF after adjustment for

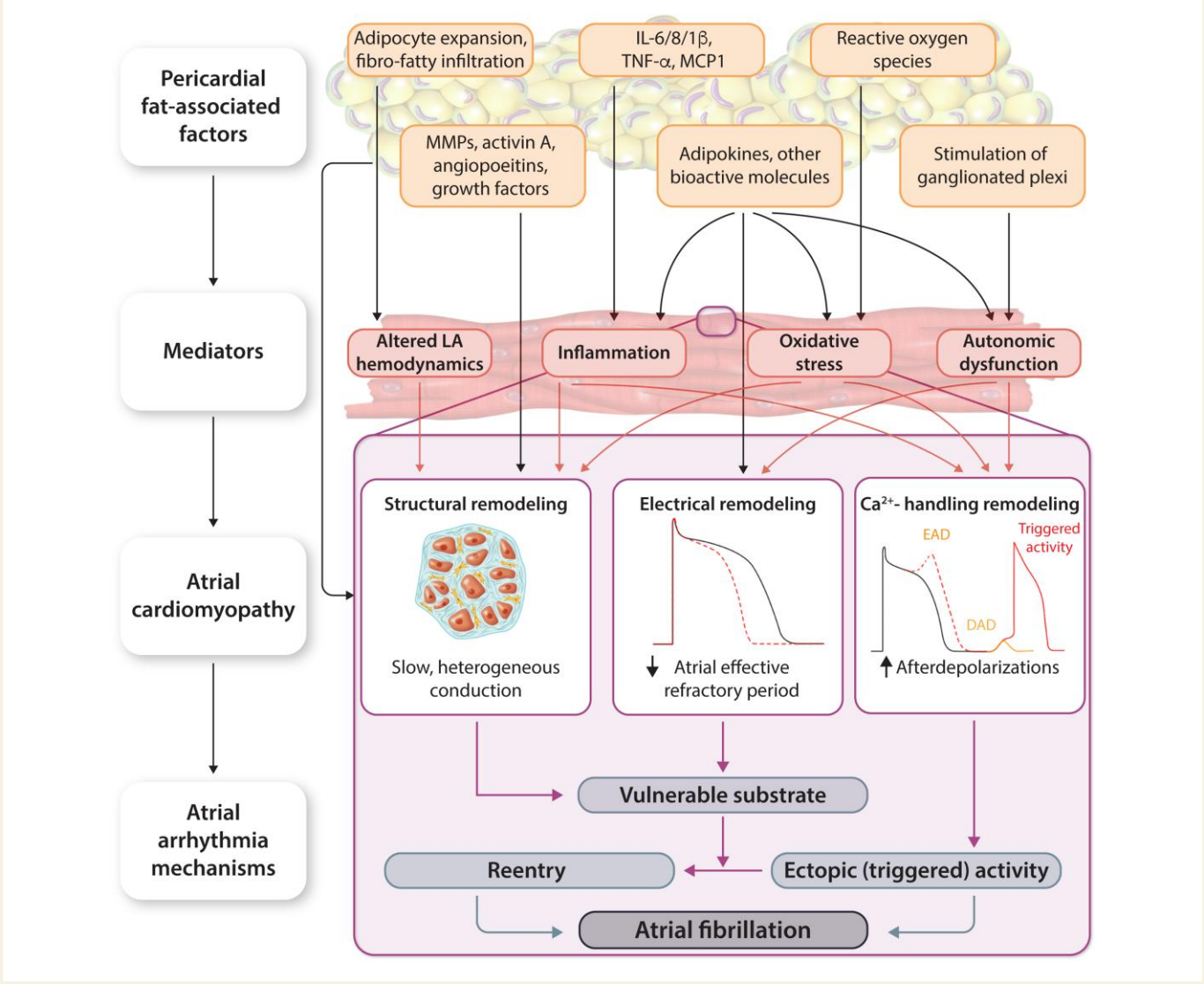


Figure 3 Role of pericardial fat in AF promotion. DAD, delayed afterdepolarization; EAD, early afterdepolarization; see *Table 1*. Pericardial fat-associated factors (adipocyte expansion/infiltration, inflammatory signalling molecules, growth factors, adipokines, reactive oxygen species, and stimulation of ganglionated plexi) stimulate the development of an atrial cardiomyopathy via a wide range of mediators (inflammation, oxidative stress, mechanical, and autonomic dysfunction). The obesity-induced atrial cardiomyopathy includes a vulnerable substrate, consisting of re-entry-promoting structural, connexin, and electrical remodelling, as well as Ca^{2+}-handling remodelling leading to triggered activity via early and delayed afterdepolarizations. Together, these arrhythmia mechanisms promote the initiation and maintenance of AF. IL, interleukin; MCP1, monocyte chemoattractant protein-1; TNF-α, tumour necrosis factor alpha.

age and sex, but no longer after adjustment for BMI. The same group had previously reported an association of pericardial, but not intrathoracic or abdominal, VAT with prevalent AF even after adjustment for other risk factors, including BMI.[79] The causal role of specialized cardiac VAT depots in AF evolution is the focus of current research, given the accumulating epidemiological evidence consistently correlating cardiac fat with AF type, duration, and recurrence rates after ablation.

6.1 Composition and distribution of cardiac fat depots

Perivascular and cardiac fat are present in humans and other mammals to varying extents and expand in obesity roughly proportional with increases in abdominal VAT, and thus do not reflect ectopic fat deposition, but rather the expansion of normal anatomical structures. This process is modifiable, since weight loss due to dietary restriction or bariatric surgery also reduces the amount of fat around the heart.[80] The nomenclature defining the distinct cardiac fat depots is inconsistent, with many terms often used interchangeably. In addition, studies of cardiac fat abundance and its relation to AF do not consistently clarify the specific anatomical and phenotypic nature of the fat under investigation, making the interpretation of how the different cardiac fat depots specifically contribute to AF difficult.

In general, pericardial adipose tissue refers to the VAT deposit over the heart and includes a combination of epicardial adipose tissue (EAT) and paracardial adipose tissue. Paracardial fat designates the total amount of fat on the external surface of the parietal pericardium, while EAT describes the fat located between the myocardium and visceral

pericardium, which also penetrates the pericardial sac and has direct contact with the coronary arteries (Figure 1).[23] Paracardial fat and EAT arise from different embryonic progenitors, and thus represent distinct types of fat.[23] EAT originates from splanchnopleuric mesoderm, while paracardial fat is derived from the primitive thoracic mesenchyme.[81] Furthermore, embryonic epicardial cells can be reprogrammed towards adipocytes contributing to fibro-fatty infiltration of the subepicardium of diseased atria.[23] Moreover, epicardial progenitor cells can differentiate into myofibroblasts or adipocytes by atrial natriuretic peptides[82] and angiotensin-II,[83] respectively. This process is mostly absent in the normal adult heart but can be reactivated after myocardial infarction or severe injury.[23]

Incrementally greater pericardial fat volumes within the pericardial sac are determined by computed tomography (CT) in patients with paroxysmal and persistent forms of AF, and predict the long-term recurrence rate of AF after ablation.[84] Of note, although the total EAT volume surrounding the heart is increased in patients with either AF or coronary artery disease, in AF patients EAT accumulation (within the pericardial sac) predominantly occurs around the atria, while ventricle-dominant EAT accumulation is observed primarily in those with coronary artery disease.[85] This spatially distinct EAT accumulation (between the visceral pericardium and myocardium) has just been validated in a canine model of AF and concomitant obesity.[57]

The vast majority of data relating cardiac fat to AF, however, come from studies on EAT. This anatomically and metabolically distinct adipose tissue exhibits increased fatty acid synthesis and a unique inflammation-associated transcriptome. Specific transcriptomic signatures can be attributed to peri-atrial, peri-ventricular, and peri-coronary EAT, implying that each cardiac subdepot displays a unique quality of interaction with adjacent myocardial structures.[86] EAT taken from the peri-ventricular area overexpressed genes implicated in Notch/p53, inflammation, ABC transporters, and glutathione metabolism. It could explain the higher sensitivity of peri-ventricular EAT to 'browning'.[23] EAT taken from peri-coronary site overexpressed genes implicated in proliferation, O–N glycan biosynthesis, and sphingolipid metabolism.[86] The peri-atrial fat can be distinguished from other localizations by expressing genes implicated in oxidative phosphorylation, muscle contraction, and calcium signalling.[86] Peri-ventricular and peri-atrial EAT mainly release proteins related to metabolism, cell growth, transport, and immune response.[87] Furthermore, some proteins are found only in peri-atrial EAT including hormone-sensitive lipase and neutrophil proteins.[87] These results might suggest a higher association between peri-atrial EAT and AF as the neutrophil to lymphocyte ratio has been proved to be a predictor of AF.[88] Also, different patterns of adipokines[89] and parasympathetic innervation[87] are observed between distinct regions of EAT. The higher acetylcholinesterase activity in peri-atrial EAT points to greater atrial parasympathetic innervation.[87]

6.2 Relationship between EAT and AF

In the healthy state, EAT has a rather cardioprotective phenotype, can buffer against fatty acid toxicity, provide mechanical protection, dampen inflammatory cytokines and oxidative stress, and support thermogenesis.[90] In obesity, altered transcription patterns and increased EAT thickness, particularly near the posterior LA and the atrioventricular groove,[23] cause a phenotypical switch with detrimental paracrine consequences to the heart.[90]

Strong and graded associations have been identified between increasing EAT volume and AF severity, incidence of post-operative AF and the recurrence rates of AF after cardioversion and ablation.[91] EAT accumulation (within the pericardial sac) coincides anatomically with regions of low voltage, reduced conduction velocity and electrocardiogram abnormalities, and these indices of atrial electrical and structural remodelling correlate strongly with EAT volume.[92] EAT (within the pericardial sac) has also been localized to regions with the highest dominant frequency.[93] Few possible explanations for these findings can be proposed (Figure 3).

6.2.1 Autonomic dysfunction

The intrinsic cardiac ganglionated plexi are embedded in the EAT and interact with the extrinsic sympathetic and parasympathetic nervous system.[94] They represent the integrative centre of the autonomic nervous system within the heart and fine-tune cardiac electrophysiology. An increasing volume/thickness of EAT might modify the activity and sensitivity of ganglionated plexi by different mechanisms involving endocrine inflammatory mechanisms[95] and lipotoxicity.[96] Additionally, autonomic nervous system activation might change the endocrine activity of EAT in a feedback system.[96] Several animal studies suggest the involvement of ganglionated plexi in the arrhythmogenic effects of risk factors commonly accompanying obesity in AF patients, e.g. sleep apnoea.[97] Although ablation of the ganglionated plexi has shown promising results in several AF animal models, the data regarding catheter- or surgical-guided ganglionated plexi ablation as an adjunct approach to pulmonary vein isolation in patients with AF have been inconsistent.[98] Thus, future mechanistic clinical and animal studies are required to dissect the precise interaction between EAT and the autonomic nervous system and to identify potential approaches to modulate interactions between EAT and the ganglionated plexi.

6.2.2 Inflammation and fibrosis

EAT from patients with AF exhibits strong inflammatory properties, showing higher 18-fluorodeoxyglucose- positron emission tomography (PET) signal intensity than EAT from patients without AF, or from SAT and thoracic VAT obtained from either group of patients.[99] Another key feature of EAT is its highly intrusive nature. Although fatty intrusion into myocardial tissue occurs physiologically, fibro-fatty infiltration of atrial myocardium was recently linked with gap-junction remodelling and impaired impulse conduction.[52] This may represent part of a feed-forward cycle, with a population of rate-responsive adipocytes within the atria undergoing transcriptional adaptation to high atrial rate and established AF.[100]

6.2.3 Lipotoxity

Cardiac VAT exhibits a relatively high lipolytic capacity, which principally governs the release of free fatty acids from triglyceride stores. Recent work highlights fatty acids as potential triggers of atrial inflammation, oxidative stress and AF.[54] Clinically, fat depot expansion leads to an increase in circulating non-esterified fatty acids, and AF patients show higher fasting serum fatty free acid levels than controls.[101] Patients with AF also show higher atrial expression of fatty acid-binding protein 3, which directs free fatty acid uptake and intracellular transport, together with autophagy-related genes.[102] Elevated saturated fatty acids moreover distinguish patients with incident and recurrent AF from those who do not (re)develop AF,[103] indicating a role in both onset and progression of AF. A direct causal link between free fatty acids and clinical AF has not yet been demonstrated; however, experimental studies have shown that certain fatty free acid species, such as stearic acid, may disrupt T-tubular structure and remodel membrane ion currents in cardiac myocytes.[104] In the contexts of myocardial infarction

and sudden cardiac death, the release of free fatty acids from triglyceride stores has been suggested to trigger proarrhythmic metabolic changes that drive ventricular arrhythmias.[105] However, whether EAT in or around the atria is the primary source of these fatty acids requires further study.

7. Paracrine communication along the fat–heart axis

Adipocytokines are the major mode of signal transmission between adipose and myocardial compartments.[23] The available data on potential contribution of selected adipokines to AF promotion are summarized in Supplementary material online, *Table S1*. Many adipokines relevant for AF pathophysiology are encapsulated in extracellular vesicles, a key component of the adipocyte secretome.[106] These small exosomes arise from the budding of intracellular endosomal membranes and contain distinct cargoes of mediators.[106] Extracellular vesicles derived from EAT of AF patients harbour greater amounts of proinflammatory and profibrotic cytokines and micro-RNAs than EAT from control patients.[107] These cytokines from EAT of AF patients induce sustained re-entry in monolayers of human-induced pluripotent stem cell (hiPSC)-derived cardiac cells, while EAT-derived extracellular vesicles from control patients had no effect.[107]

7.1 Adipokines with a potential protective role in the evolution of AF

Adiponectin exerts marked insulinomimetic[108] and anti-inflammatory actions, in part by promoting M2-macrophage phenotype transition.[109] Human EAT and omental VAT show a lower abundance of adiponectin than SAT,[110] consistent with a less benign phenotype, and adiponectin levels correlate inversely with LA size in obesity.[111] Adiponectin may blunt interstitial fibrosis and cardiomyocyte hypertrophy, apoptosis, and capillary loss.[112] It regulates cardiomyocyte Ca^{2+} homeostasis by altering sarco/endoplasmic reticulum Ca^{2+} adenosine triphosphatase-2a and phospholamban expression.[113] In dogs, bolus microinjection of adiponectin into the major ganglionated plexi suppressed rapid atrial pacing-evoked neural activity, proinflammatory signalling and macrophage activation, and prevented the abbreviation of the atrial ERP.[114] The human data consistently report larger EAT along with increased circulating levels of adiponectin in patients with AF, pointing to a compensatory increase of adiponectin in patients with AF to counteract cardiac remodelling and inflammation.

Omentin (intelectin-1) is a cardioprotective adipokine linked with metabolic control and insulin sensitivity. Omentin is highly expressed in stromal vascular cells including preadipocytes, and to lesser extent in adipocytes of VAT, including EAT, and its abundance is low in SAT.[115] Omentin is reduced in both EAT and serum from patients with AF and this appears to correlate with the extent of atrial remodelling, with the lowest levels being observed in patients with permanent AF. Mechanistically, omentin appears to activate AMP-activated protein kinase signalling and suppress mitogenic kinases to prevent myocardial hypertrophy.[116]

Vaspin, also known as Serpin A12, belongs to serine protease inhibitor (serpin) family and is generally considered to be anti-inflammatory and to possess insulin-sensitizing and anorexigenic effects.[117] Vaspin abundance is higher in paracardial fat compared with EAT or SAT, irrespective of rhythm status, with the presence of AF raising vaspin levels in EAT and SAT, while in paracardial fat, its increase is modest.

7.2 Adipocytokines with an inconclusive role in AF development

Resistin (adipocyte-secreted factor or inflammatory zone 3), belongs to the cysteine-rich secretory protein family. Adipocytes are the major source of secreted resistin in rodents; in humans, however, resistin is released mainly by macrophages.[118] Resistin impairs cardiac glucose uptake and insulin resistance[119] and induces Ca^{2+}-handling remodelling, oxido-inflammatory stress,[120] hypertrophy, and fibrosis.[121] Clinically, increased plasma or EAT resistin levels have been reported to predict AF risk, particularly of new-onset AF after surgery. However, evidence for a direct proarrhythmic action of resistin is lacking. In isolated human atrial trabeculae, acute application of resistin causes positive inotropic and lusitropic effects, but does not increase the rate of spontaneous contractions.[122]

Visfatin (pre-B cell-colony enhancing factor-1 or nicotinamide phosphoribosyltransferase) is released from adipocytes, circulating monocytes, and adipose tissue macrophages.[123] Recent evidence also indicates its expression in cardiomyocytes,[124] but VAT depots including EAT are the major source of circulating visfatin.[125] Visfatin promotes cardiac inflammation,[126] metabolic derangement,[123] hypertrophy, and fibrosis,[124] which may explain the association between high plasma visfatin and post-operative AF as well recurrent AF. However, mice with genetic deletion of visfastin are more susceptible to high-fat diet (HFD)-induced AF, through impaired cardiomyocyte Ca^{2+}-handling.[70] Clearly, further research is required to define the precise role of visfatin in AF pathophysiology.

Apelin is an insulin-sensitive hormone that is overproduced in obesity,[127] supports white adipocyte browning[128] and suppresses inflammatory and fibrotic atrial remodelling.[129] At the cellular level, apelin counteracts angiotensin-II-induced derangement of autophagy and connexin 43 expression.[130] Apelin abundance is lower in right atrial appendages from AF patients compared with sinus rhythm controls and circulating levels correlate inversely with AF burden. Low plasma apelin strongly predicts both post-operative AF and AF recurrences in patients undergoing pulmonary vein isolation or electrical cardioversion. However, apelin stimulates the sarcolemmal Na^+/H^+ exchanger, leading to intracellular alkalinization with subsequent sensitization of cardiac myofilaments to Ca^{2+}, rendering apelin one of the most potent positive inotropic stimuli.[131] Moreover, it shortens the atrial action potential (AP) and refractoriness by modulating multiple ionic channels,[132] dysregulates cellular contractility,[133] and can augment cardiomyocyte Na^+-currents.[134] This suggests that the clinical association between apelin levels and AF may be more complex and requires further study and validation.

Leptin is the prototypical adipocyte-secreted adipokine, although it is also released from cardiomyocytes.[135] Its primary physiological function is to suppress appetite and enhance energy expenditure, thereby regulating body weight.[136] Studies correlating the circulating leptin levels with AF have yielded conflicting results. Similarly, data on the systemic and cellular consequences of elevated leptin levels are also inconsistent. Leptin enhances the production of profibrotic[73] and proinflammatory[137] factors and stimulates prohypertrophic signalling pathways.[138] Yet, leptin can also attenuate cardiac contraction,[139] support cardiac metabolism by increasing glucose and fatty acid uptake,[140] and counteract lipotoxic cardiomyopathy.[141] In isoprenaline-challenged LA rabbit cardiomyocytes, acute leptin exposure ameliorated Ca^{2+}-handling abnormalities and reduced the incidence of delayed afterdepolarizations, along with an increase in Na^+-current and decreases in ultra-rapid delayed-rectifier K^+ and Na^+/Ca^{2+} exchanger currents.[142]

The discrepancies between clinical observations and basic research findings might be explained by differences in cardiac expression of adipokines' receptors between humans and animals. However, to the best of our knowledge, there are no systematic data assessing these interspecies differences.

8. Molecular basis of the association between adiposity and AF

Many experimental studies corroborate the clinical association between weight gain and the development of a proarrhythmic atrial substrate (*Table 2*). Obesity is linked to conduction abnormalities and both spontaneous and inducible AF. In sheep subjected to an high-fat diet (HFD), weight gain is paralleled by progressive LA enlargement and fibrosis together with increased fibro-fatty infiltration.[51,53,55,56] Similar findings were obtained in a canine model, where HFD augments the vulnerability to AF, in close association with the upregulation of profibrotic genes and fibro-fatty infiltration originating from EAT.[57]

The murine HFD model has proven useful for identifying the molecular determinants of obesity-driven atrial remodelling underlying AF.[50, 61,64–66] Atria of HFD-fed mice exhibit increased expression of cadherin-11, a fibroblast-activating factor that promotes atrial fibrosis, which is also upregulated in obese patients with concomitant AF.[50] Reduced expression of Myeloid differentiation 1, a negative regulator of the toll-like receptor 4 pathway that is causally involved in obesity-associated cardiac remodelling, oxidative stress and impaired autophagy, was also noted in HFD-fed mice.[65]

Besides HFD-induced structural remodelling, obese mice also display functional remodelling of various ion currents that support AF inducibility.[59,64] McCauley *et al.*[64] found a strong reduction in protein levels of the Na^+-channel subunit $Na_v1.5$ concomitant with reduced peak-Na^{+-}current in atrial cardiomyocytes of HFD-fed mice. These findings are consistent with reports in both AF patients[143] and animal models of AF,[144] in which reduced Na^+-current was associated with slowed atrial conduction.[144] Abnormal Na^+-current can potentially be attributed to increased expression of protein kinase C isoforms α and δ,[64] which show atrial upregulation in HFD-fed mice and are known to regulate both the expression and function of $Na_v1.5$.[145] Protein kinase Cδ is activated by dietary fat and phosphorylates $Na_v1.5$, thereby reducing Na^+-current.[145] The HFD-related shortening of the AP could be a result of an upregulation of the ultra-rapid delayed-rectifier K^+-current, which is conducted through Kv1.5 channels, as both were increased in HFD-fed mice.[64] Conversely, the protein levels of $Ca_v1.2$ and the corresponding L-type Ca^{2+}-currents were downregulated in HFD-fed mice, also potentially contributing to AP shortening. Thus, HFD-induced ion-channel remodelling could contribute to obesity-mediated AF arrhythmogenesis by shortening of atrial refractoriness along with conduction slowing, thereby promoting AF-maintaining re-entry.

The nucleotide-binding domain, leucine-rich-containing family, pyrin domains-containing-3 (NLRP3)-inflammasome, a multimeric signalling structure responsible for maturation of IL-1β and IL-18, has been recently implicated in obesity-driven AF initiation and progression. Yao *et al.*[146] provided the first evidence for NLRP3-inflammasome expression in human, canine, and murine atrial cardiomyocytes, and established the causal link to AF. NLRP3-inflammasome activity is also higher in atrial samples of patients who go on to develop post-operative AF after cardiac surgery.[147] NLRP3-inflammasome activity rises with increases in BMI of patients and in HFD-fed mice compared with controls,[90] mainly through an accelerated 'triggering' of the NLRP3-system (assembly of the inflammasome complex with subsequent release of the proinflammatory mediators (caspase-1 and IL-1β). Mechanistically, the NLRP3-inflammasome promotes abnormal diastolic ryanodine receptor type-2-mediated sarcoplasmic reticulum Ca^{2+} release, which might cause AF-inducing triggered activity, and upregulates ultra-rapid delayed-rectifier K^+-currents in cardiomyocytes of HFD-fed mice, thereby reducing atrial AP duration and refractoriness, which promote AF-maintaining re-entry,[54] consistent with previous findings in obese sheep.[64] NLRP3-inflammasome activity is augmented by leptin and visfastin, but suppressed by adiponectin, apelin, omentin, and vaspin (Supplementary material online, *Table S2*). However, the upstream mechanisms driving obesity-associated NLRP3-inflammasome activation are unknown and require elucidation in future work.

9. Reversibility of obesity-induced AF and remodelling

Significant weight loss achieved by bariatric surgery reduced the risk of new-onset AF by 29% in both prospective matched cohort Swedish Obese Study (mean weight loss ∼18%)[148] and retrospective Bariatric surgery to aLleviate OCcurrence of Atrial Fibrillation Hospitalization-(BLOC-AF) study during 5.5- and 19-year follow-up, respectively.[149] In addition, bariatric surgery of obese patients strongly reduced the recurrence rate of AF after ablation during a mean follow-up of 29 months.[150] Similarly, weight reduction (median weight loss, 17%) achieved by a structured weight-management programme (low-calorie diet and low-intensity exercise) reduced the burden of symptoms, as well as the number and burden of AF episodes during 12-month follow-up.[151] In the 5-year follow-up Long-Term Effect of Goal-Directed Weight Management in an Atrial Fibrillation Cohort: A Long-Term Follow-Up Study (LEGACY) study, weight loss of >10% led to a six-fold greater probability of arrhythmia-free survival compared with patients with modest or no weight change.[152] In a sub-analysis of the same study cohort (regReSsive Effect of weight-loss and risk factor modification on AF, REVERSE-AF trial), weight loss by >10% was associated with a conversion of persistent to paroxysmal AF in 88% of patients.[153] Although weight loss following bariatric surgery and dietary interventions clearly support a causal link between obesity and AF, the precise molecular mechanisms by which weight loss reduces the susceptibility to AF and whether there are differences in the type of fat that is lost following different surgical, pharmacological, or dietary approaches remain unclear. The improvement in LA mechanical function observed in patients who underwent bariatric surgery[151,154] and usual (diet) weight loss interventions[152] point to reverse atrial molecular remodelling as the potential mechanism, a hypothesis that needs direct verification in experimental and clinical AF paradigms.

Recently, in an HFD-induced obesity sheep model, the reversibility of HFD-induced atrial remodelling by weight loss was clearly demonstrated. Atrial ERPs in obese sheep were shorter compared with lean controls, but this shortening could be reversed with a 30% weight reduction. Similar observations were made for the conduction velocity, which was normalized with weight reduction. Histological assessment revealed increased infiltration of epicardial fat and interstitial fibrosis in obese animals, which could be partially reversed with 30% weight loss. The area occupied by interstitial fibrosis was 7.5 ± 2.4 and 5.5 ± 1.5%, whereas

Table 3 Knowledge gaps and future directions

Knowledge gap	Future directions
Does pericardial fat reduction prevent AF?	Controlled clinical trials targeting pericardial fat
What is the effect of different weight loss interventions on particular fat depots (subcutaneous vs. visceral) and the related changes in atrial arrhythmogenesis?	Characterization of changes in specific fat depots in clinical intervention trials comparing different surgical, pharmacological, or dietary weight loss approaches
What biomarkers typify adipose-related AF?	Controlled clinical trials of obese vs. non-obese patients with incident AF and simultaneous biomarker assessment
Is there a causal link between obesity and AF that can be revealed by genetic determinants? Do obesity and AF share common genetic determinants?	Controlled clinical trials using Mendelian Randomization techniques to link obesity to AF risk
What is the exact role of different fat depots and pericardial fat subdepots in AF pathogenesis?	Transgenic animal model with global or adipose tissue-specific deletion and cell culture-based studies
Does adipose graft transposition procedure prevent AF?	Animal model-based adipose graft transposition procedure
What is the impact of white-to-brown differentiation on AF vulnerability?	Animal model-based white-to-brown global differentiation
Which cell types contribute to NLRP3-inflammasome-mediated AF risk?	Animal model and cell culture-based studies
How to improve the quantification of pericardial fat subdepots?	Imaging techniques with advanced 3D reconstruction and analysis function
What are the mechanisms responsible for ectopic fat formation?	Animal model-based obesity with gradual increases in ectopic fat formation

AF, atrial fibrillation; NLRP3, nucleotide-binding domain, leucine-rich-containing family, pyrin domains-containing-3.

the area infiltrated by epicardial fat was 9.3 ± 1.1 and 6.4 ± 1.1%, in the obese and 30% weight loss groups, respectively.[53]

10. Limitations in translating animal model findings to man

Mechanistic investigations of obesity-induced AF are typically conducted in HFD animal models. However, pure obesity models do not adequately reproduce the dynamics of an evolving disease state, varied nutrition, and pharmacological interventions in humans.[155]

Rodent strains show large variations in their level of resistance to obesity and its metabolic sequelae; this is further affected by age-dependent variations in body fat content, composition, and endocrine function.[156] In addition, the typical HFD compositions containing on average 40–60% fat may not appropriately recapitulate the general human obesogenic Western diet that contains 30–40% dietary fat and is more complex than the formulated rodent HFDs. Prolonged overnight fasts and a nocturnal lifestyle also impact mouse metabolism, leading to altered insulin-stimulated glucose utilization.[157] Changes in pericardial fat and fat infiltration in an obese mouse model induced by at least 20-week HFD are also not as prominent as in humans. Other obese mouse models with genetic modification (mainly targeting the leptin and its receptor)[158] usually exhibit severe obesity and may exhibit ectopic fat depots. Finally, inflammatory responses to the HFD may mask other local and systemic effects of obesity and other potential contributors.

Large-animal models of obesity recapitulate key features of human obesity and are instrumental in studying the precise consequences of obesity for human health and disease.[159] In addition, techniques for genetic manipulation of large animals are also emerging.[159] However, large-animal models are very complex and require highly specialized equipment and facilities for experimentation and monitoring.[159] In addition, the animals have a long-life cycle and their cellular and molecular signatures in the heart are not well characterized.[159] Even when animals (for example, sheep) are kept obese for nearly 20% of their usual lifespan to mirror long-standing human obesity, the degree of substrate development may still not correlate with what is seen in clinical settings.[53] Moreover, the optimal duration to create obesity/metabolic syndrome in large animals has not yet been standardized.[159] Finally, sex and age affect the response to the obesogenic diet, with young and male animals being more sensitive to obesity-related comorbidities.[159] Future research focusing on humans is, therefore, essential to unravel the key determinants of the obesity–AF axis.

11. Gaps in current knowledge and future perspectives

Since cardiac fat appears to have a more pronounced impact on AF burden than systemic obesity, cardiac fat-targeted interventions could constitute new options to manage AF. Key critical issues that need addressing in future work are summarized in *Table 3*. Controlled clinical trials targeting pericardial adipose tissue on or around the atria and fatty deposits in the form of fibro-fatty intrusion of EAT deep into the atrial myocardium are required to validate the role of cardiac fat in AF pathophysiology. Studies targeting VAT and SAT are also warranted to assess the contribution of particular fat depots to both weight and AF burden, and the response to reduction. Research comparing obese vs. non-obese patients with incident AF and simultaneous biomarker assessment could help to identify and validate novel biomarkers of adiposity-related AF. Future studies linking genetics and genomics to obesity and AF risk are clearly warranted.

Fine-tuning of transgenic models, such as conditional global knockouts, or atrial vs. adipose tissue-specific deletion of culprit molecules including adipokines may help to delineate the direction and temporal nature of communication between atria and different body fat depots. One approach to dissect the crosstalk between distinct adipose tissue depots and the heart is adipose graft transposition, whereby autologous, vascularized pericardial fat is surgically placed over the myocardial scar.[160] Direct evaluation of adipose graft (SAT or BAT) transposition procedure on AF-prone atrial myocardium is clearly warranted. Since

hiPSC-derived cardiomyocytes are being increasingly used as models of heart disease,[161] testing the potential proarrhythmic effects of individual adipocyte components on hiPSC-derived cardiomyocyte function might provide valuable insights into atrial cardiomyocyte–adipocyte interactions and their consequences for AF susceptibility.[161] Conditionally immortalized human atrial cardiomyocytes constitute another novel source for *in vitro* AF models to study the causal link between obesity and AF.[162] The beneficial effect of white-to-brown differentiation on cardiovascular risk needs further investigation in animal models undergoing cold temperature or increased physical activity exposition to assess the consequences for AF susceptibility. The discovery that obesity and enhanced activity of NLRP3-inflammasome are associated with both increased risk and severity of AF opens new avenues of research on underlying mechanisms and potential therapeutic interventions against AF.

Robust quantification of cardiac fat depots and cardiac inflammation remains challenging. Echocardiography quantifies EAT thickness on the ventricular free wall, but 3D volumetric assessment requires CT or cardiac magnetic resonance.[163] The latter allows concurrent quantification of EAT and LA volumes,[164] but its application is challenging in obese subjects.[163] Concurrent metaiodobenzylguanidine scintigraphy and 18-fluorodeoxyglucose-PET/CT gives additional insight into sympathetic and inflammatory activities for improved individual risk prediction. An emerging approach to identify patients with high EAT volume is also provided by near-infrared spectroscopy.[165] The constellation of innovative machine learning methods including artificial intelligence, *in vivo/ex vivo* imaging, and biopsy characterization may facilitate a comprehensive mapping of changes predictive of AF development and the substrate response to intervention, potentially enabling personalised risk projection and identification of innovative treatment options.[166] Finally, additional research to understand the biology of cardiac adipose tissue, in particular, the mechanisms responsible for ectopic fat formation and its consequences for AF promotion is required in order to develop novel atrial fat-targeting anti-AF approaches.

12. Conclusion and outlook

Although substantial clinical and epidemiological evidence potentially link different adipose tissue depots with AF, the underlying mechanisms remain poorly understood. Thus, extensive studies are needed to dissect the exact role of different subdepots of pericardial fat and other adipose tissue sources such as VAT and SAT in AF pathogenesis. Genetic studies could be also instrumental to uncover the precise mechanisms linking pericardial fat remodelling to AF promotion. Improved imaging-based cardiac fat quantification should allow a better stratification of AF patients ultimately leading to novel therapeutic approaches.

Supplementary material

Supplementary material is available at *Cardiovascular Research* online.

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