A Narrative Review on Prediabetes or Diabetes and Atrial Fibrillation: From Molecular Mechanisms to Clinical Practice

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Abstract

Based on glucose levels, people fall into three groups, normal individuals, prediabetic patients, and diabetic mellitus (DM) patients. Prediabetes (pre-DM) is an intermediate condition that exists between normal glucose levels and DM. Atrial fibrillation (AF), one of the most prevalent cardiac arrhythmias in medical practice, contributes to a considerable morbidity and mortality rate. In this review, we looked at the clinical symptoms, pathological alterations, molecular mechanisms, and associated risk factors of pre-DM, type 2 DM (T2DM), and AF. In clinical practice, pre-DM can increase the prevalence of AF. In the hyperglycemic state, oxidative stress, inflammation, and endoplasmic reticulum stress can cause alterations in atrial cell or cardiac fibroblast function through tumor necrosis factor-α/nuclear factor-κB (NF-κB)/transforming growth factor-β, mitogen-activated protein kinase-matrix metalloproteinase-9 and PARP-1 is poly (ADP-ribose) polymerase 1. IκB kinase-α/NF-κB pathways, and further cause atria undergo structural, electrical, and neural remodeling which lead to the occurrence and persistence of AF. In addition, pre-DM and T2DM may worsen as a result of obesity, obstructive sleep apnea, and arterial hypertension. Furthermore, clinical researches have demonstrated that lifestyle interventions and/or pharmacotherapy in pre-DM patients can effectively delay the progresssion of pre-DM to T2DM. Individualized glycemic management and AF management should be provided to AF patients with pre-DM or DM.

Keywords: Atrial fibrillation, diabetes, obesity, prediabetes

Introduction

Atrial fibrillation (AF), the most common form of cardiac arrhythmia, affects millions of patients worldwide. In AF, atrial cardiomyocytes contract erratically and unusually fast, which can cause symptoms including irregular heartbeat, palpitations, lightheadedness, breathe hard, and exhaustion.[1] Besides, the incidence of AF is increased by the presence of all risk factors and disorders (obesity, metabolic syndrome [MS], diabetic mellitus [DM], arterial hypertension, and obstructive sleep apnea [OSA]).[2] For population aging and rising incidence of underlying risk factors such as obesity, increased sedentary behavior, and a poor diet, the societal burden of type 2 DM (T2DM) has increased in recent years.[3] Pre-DM is a transitional stage between T2DM and normoglycemia that comprises impaired fasting glucose (IFG) and impaired glucose tolerance (IGT).[4] Poor glucose control exacerbates cardiac remodeling and leads to abnormalities in metabolic status, resulting in abnormal electrophysiological changes. In this review, we outlined the interactions and underlying mechanisms between various glycemic states and AF, along with the therapeutic management of AF patients with poor glucose control [Figure 1].

Epidemiology

Epidemiology of prediabetic mellitus and diabetic mellitus

Pre-DM, which includes two states, typically described as

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glycemic levels above normal but under DM thresholds, is a state predisposes to DM. According to the World Health Organization standard, IGT is defined as a postload plasma glucose of 7.8–11.0 mmol/L, or both, based on a 2-hour oral glucose tolerance test (OGTT); IFG is defined as fasting plasma glucose (FPG) of 6.1–6.9 mmol/L (without IGT).[5] Approximately 5%–10% of individuals with pre-DM develop diabetes annually, while conversion rates vary depending on population traits and the criteria of pre-DM.[6] The progression of blood glucose abnormalities to DM includes an asymptomatic period consisting of pre-DM and preclinical latent DM, of which pre-DM can last approximately 8.5–10.3 years.[7] The 20-year cumulative incidence of DM among participants in a Chinese DM preventive trial who had an IGT determined by repeated OGTTs was considerably higher (>90%).[8] According to another research from the Guangzhou Heart Study, among people in Guangzhou, China, who were over 35 years old, the prevalence of elevated blood glucose (EBG) level was comparatively high.[9] The overall study population had a 29.9% prevalence of EBG. In addition, a number of studies have shown that both lifestyle changes and medication-based therapies can lower the risk of developing DM among prediabetic people. Interestingly, patients with AF of over 5 years' duration have a higher prevalence of glucose metabolism abnormalities, including DM, IFG, and IGT, compared with patients without AF.[10] Pre-DM may also convert back to normal glycemia. In England, there are 55%–80% of people with IFG at baseline had normal fasting glucose levels at the 10-year follow-up in an observational population-based study of the natural course of DM.[6]

Epidemiology of atrial fibrillation patients with prediabetic mellitus or diabetic mellitus

As the most prevalent cardiac arrhythmia, AF is highly correlated with morbidity, mortality, and health-care utilization.[1] To be precise, DM or pre-DM has been linked to higher symptom burden, lower life quality, higher rates of hospitalization, and mortality, and could increase the likelihood of developing AF.[11,12] The incidence of AF is further elevated by the rising prevalence of all risk factors and illnesses (DM, arterial hypertension, obesity, MS, and OSA). The relative risk (RR) of all-cause mortality and cardiovascular (CV) disease onset in prediabetic individuals was 39% higher in comparison to the control group according to an umbrella review of a meta-analysis published in 2021.[13] Another meta-analysis by Aune *et al*.[14] that included 32 cohort studies suggested that DM and prediabetes raised the risk of AF by 20% and 28% and each 20 mg/dL increase in glycemia increased the RR of AF by 12%. Prediabetes have a positive association with the risk of CV death as well as other CV events, including AF. The summary hazard ratios for pre-DM and risk of CV mortality ranged from 1.2 to 1.3. The above report from Guangzhou not only points out the current status of EBG in the study population but also analyzes the relationship between EBG and CV disease. The odds ratio (OR) for the occurrence of AF was higher in residents receiving EBG than those not receiving EBG (1.94, 95% confidence interval [CI]: 1.40–2.70, $P < 0.001$) and this correlation was more significant among women (OR = 1.80, 95% CI: 1.12–2.91, with a statistically significant difference ($P = 0.016$).[9] As early as 2010, according to research by Chao *et al*. both atria of patients with IFG and DM exhibited considerably longer total activation times.[15] They also suggested that impaired glucose metabolism was linked to greater recurrence following catheter ablation, longer intra-atrial conduction time, and decreased atrial voltage. Consistent with these results, a crossover study found more intra- and inter-atrial electromechanical delay (EMD) in patients with

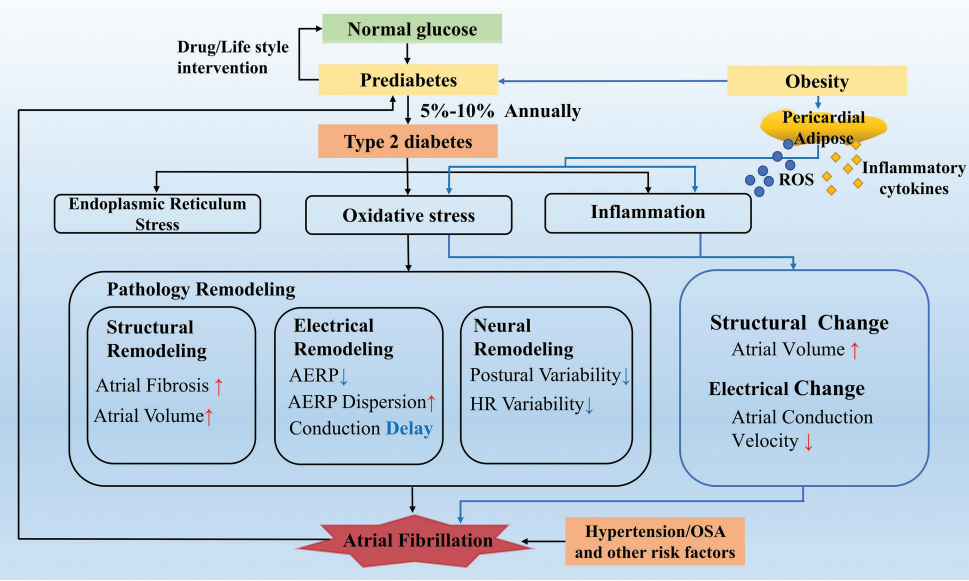

Figure 1: Prediabetes or diabetes and atrial fibrillation. ROS=Reactive oxygen species, AERP=Atrial effective refractory period, OSA=Obstructive sleep apnea, HR=Heart rate

IFG versus normal participants (median [interquartile range], 34.0 [17.0] vs. 17.0 [4.0], $P < 0.001$ and 15.0 [8.5] vs. 7.5 [2.0], $P < 0.001$). Significant prolongation of inter- and intra-atrial conduction times and a marked reduction in passive left atrial (LA) emptying can be observed in patients with IFG compared with controls.[16] They also discovered that the LA size and glycemia level were both reliable and independent predictors of the development of EMD. Therefore, they conclude that EMD may be one of the pathogenic variables contributing to the development of AF. Thus, early diagnosis and intervention for IFG have important implications in preventing atrial structural changes and the progression of AF. Another similar clinical study included 59 patients with pre-DM, defined by the investigators as individuals with reduced glucose tolerance or IFG according to the American Diabetes Association criteria, and 43 healthy controls revealed that alterations in LA mechanical function and conduction time existed before the onset of DM, LAEMD may serve as a possible indicator of the onset of AF.[17] A clinical investigation in an Asian population demonstrated that patients with impaired glucose metabolism had a higher incidence of recurrence of AF after catheter ablation compared with patients with normal glucose levels. The magnitude of the LA is an important predictor of recurrent AF after catheter ablation. This team also pointed out that the recurrence of AF after catheter ablation was associated with a decreased LA voltage and an increased duration of total LA activation.[18] A cohort study involving 44,451 nonvalvular AF patients from the Clalit Health Services electronic medical record database showed that pre-DM glucose was linked to a 19% increased risk of stroke compared to normoglycemia.[19] In addition, glycemic categorization status and stroke risk have varying degrees of correlation, with prediabetic individuals at intermediate risk levels between the diabetic and normoglycemic groups. However, in the study by Huxley *et al*.,[20] the investigators defined pre-DM as a history of DM with a FPG of 100–125 mg/dL or Hemoglobin A1c of 5.7%–6.4%, no DM medication and no physician diagnosis. Of the 13,025 patients included in the cohort, 51.4% had pre-DM, and among them, the prevalence of AF was 5.14/1,000 person-years, which was moderate level compared with patients with diagnosed DM (9.02/1,000 person-years) and those without DM (4.51/1,000 person-years). In contrast to the findings of several studies mentioned above, they did not find any evidence of an elevated risk of AF in patients with pre-DM than nondiabetic patients in any race or sex group (all P values for interaction >0.05). This suggests that the harmful effect of DM on AF only manifests after long-term exposure to DM.

Pathology

Structural remodeling

Atrial remodeling encompasses alterations of the structure and geometry of the atria, modification of atrial electrical and contractile properties, and changes in the amount and makeup of the extracellular matrix (ECM).[21,22] Structural remodeling plays an essential role in the onset of diabetes-associated AF. The researchers demonstrated that intra-atrial conduction disturbances increase the likelihood of atrial arrhythmogenicity by constructing an animal model of diabetes.[23] Atrial enlargement and fibrosis are the two main pathological changes that develop in the atria of patients with DM.[24,25] Atrial fibrosis is characterized by increased collagen deposition, which results in reduced atrial conduction velocities and fragmentation of propagating wavefronts, making atrial fibrosis one of the most important mechanisms contributing to AF.[26] In animal models of T2DM induced by a high-fat diet and streptozocin, significant extended interstitial fibrosis and increased cross-sectional areas of atrial cardiomyocytes can be observed, and it has been shown that the extent of atrial fibrosis increases with the dose of the inducing drug.[27] There is a correlation between LA interstitial fibrosis and interatrial electrical conduction delay, which may be the basis for the onset of AF in diabetic atria.[28] Atrial fibrosis can occur in patients with T2DM, and increased levels of collagen synthesis and increased collagen I expression in cardiac fibroblasts from the atria of these patients.[29] Furthermore, changes in LA size can be observed in DM patients. DM was shown to independently related to the prevalence of LA enlargement (LAE) (OR = 1.71; 95% CI = 1.19–2.43; $P < 0.01$) in the overall population, and the same significant results were also found in gender-specific subgroups.[30] However, pre-DM did not independently predict LAE in a population-based cohort study with a population from northeastern China.[31]

Electrical remodeling

The main characteristics of atrial electrical remodeling include decreased atrial effective refractory period (AERP), increased AERP dispersion, loss of frequency adaptation, and conduction delay. Diabetic rat can exhibit multiple electrophysiologic abnormalities such as delayed atrial conduction, heterogeneous conduction, and prolonged action potential duration (APD).[23] The morphology of the atrial action potential (AP) will change when the expression or regulation of ion channels is altered, which may underlie atrial electrical remodeling.[32] It can be observed in db/db mice models that increased susceptibility is associated with reduced atrial conduction velocity, prolonged APD, and increased heterogeneity of right and LA repolarization.[33] In db/db mice model, K^+ currents reduce in atria, including transient outward current (I_{to}) and I_{Kur}. The reduction of repolarizing K^+ currents I_{to} and I_{kur} could cause prolongation of APD, which could be involved in impaired atrial conduction in db/db mice and increase the occurrence of early after depolarizations, which can serve as a trigger for AF initiation.[34] Previous work showed that the atrial AP was also prolonged in Akita mice, however, the reason was associated with reductions in I_{Kur} other than changes in I_{to}.[35] In atrial myocytes of diet-induced obesity and T2DM mouse models, the expression of Kv4.2/4.3, which mediates I_{to}, was found to be reduced. Furthermore, reduced Kv4.2 expression is also shown in cardiac-specific insulin receptor

knockout mice.[36] Polina *et al*. drew another conclusion that no differences exist in AP maximum upstroke velocity, atrial I_{Na} amplitude, and activation kinetics in db/db mice.[35] In db/db mice, inactivation of I_{Na} homeostasis allows for a more positive potential, leading to increased I_{Na} window currents, which may cause prolonged APD or impair atrial conduction.[37,38] Increased AF susceptibility in diabetic patients was also associated with increased expression of the gap junction protein connexin-43 and decreased expression of connexin-40.[39] All of these results suggest that atrial ion channel remodeling may vary in patients with T2DM.

Neural remodeling

Diabetic neuropathy is the most common complication of DM, occurring in about 90% of DM patients.[40] Pre-DM has been found to be associated with parasympathetic dysfunction, such as decreased heart rate variability reduced postural variability in heart rate, and worsening of sympathetic and parasympathetic function tests.[41] The unbalanced activation of the sympathetic and parasympathetic nervous systems may be a factor in the onset of AF. Otake *et al*.[42] used streptozotocin-induced diabetic rats to demonstrate that neural remodeling may play a key role in increased susceptibility to diabetic AF. Sympathetic nerve stimulation (SNS) significantly increased the incidence of AF in DM rats. SNS shortened the AERP and increased the heterogeneity of the AERP in DM rats compared to controls.

Molecular Mechanisms

Structural and electrical remodeling of the atria is induced in DM by a variety of molecular mechanisms, including increased inflammation, oxidative stress, connexin remodeling, and mitochondrial stress.

Oxidative stress and inflammation

In the context of DM, fluctuations in glycemia levels induce an increase in reactive oxygen species (ROS) production.[43] It is well-accepted that oxidative stress and inflammation both contribute significantly to the development of AF. According to a review by Zhang *et al*., diabetic hyperglycemia can cause systemic oxidative stress in tissue and organs by potential mechanisms including autoxidation of reducing sugars, nonenzymatic protein glycosylation, increased activity of polyol pathways, activation of protein kinase C (PKC) and reduced activities of antioxidant systems.[44] ROS is the most representative one of oxidative species, including superoxide and hydrogen peroxide, and it is closely associated with the oxidative stress involved in AF.[45] In addition, it has also been reported that ROS can be involved in the electrical and structural remodeling of the atria.[46] In glucose-stimulated cardiac fibroblasts, the NOXs regulatory subunit Ras-related C3 botulinum toxin substrate 1 (Rac-1) activity is increased. NOX, as one of the major sources of ROS is activated, and subsequently ROS production is increased and its downstream mitogen-activated protein kinase signaling pathways are activated and induced by increased matrix metalloproteinase-9 expression. Through these mechanisms, cardiac fibroblast proliferation increases and atrial fibrosis increases, resulting in DM-related AF.[47] Fu *et al*.[48] used diabetic rabbit model to validate the role played by the tumor necrosis factor-α (TNF-α)/nuclear factor-κB (NF-κB)/transforming growth factor-β (TGF-β) pathway in diabetic AF. This study showed that the expression of NF-κB p65 was upregulated in atrial myocytes in DM, and the increased expression of proteins downstream to NF-κB p65, such as TNF-α and TGF-β, led to atrial remodeling. Moreover, NF-κB regulates the transcription of target genes for inflammatory factors, which are responsible for the development and progression of AF.[49] A number of inflammatory factors, such as the nucleotide-binding oligomerization domain-like receptor thermal protein domain associated protein 3 (NLRP3) inflammasome, one of the mediators of atrial remodeling, can be enhanced in transcription after NF-κB enters the nucleus. In the context of DM, NF-κB expression is increased in cardiomyocytes, which is associated with high circulating blood glucose concentrations. Meanwhile, it has been found that PKC-β subtypes can be abnormally activated in diabetic complications.[50] PKC-β acts as the upstream mediator of the TNF-α/NF-κB/TGF-β pathyway.[51] It has been well established in various diabetic animal models that diacylglycerol specifically activates PKC-β in the high glucose state, thus stimulating IκB and NF-κB activation, and it has been demonstrated that DM-induced NF-κB activation causes atrial remodeling in rats through activation of PKC-β caused atrial remodeling in rats. PKC-β is widely distributed in cardiac myocytes, and overexpression can lead to myocardial hypertrophy, fibrosis, and decreased contractility.[52] The activation of PKC-β caused structural remodelings such as atrial hypertrophy, increased interstitial fibrosis, and electrical remodeling in the high glucose state, so it can be inferred that in the context of DM or pre-DM, overexpression of PKC-β is responsible for structural remodeling and electrical remodeling of the atria and promotes the development of AF.[52] Previous studies have also found that the activation of PKC can decrease I_{to}, I_k, and I_{kl} and increase Na^+–Ca^{2+} exchanger current (NCX), leading to a net reduction in outward current, thereby leading to AP prolongation.[53]

DM also could affect insulin resistance (IR) and lipid metabolism, promote structural remodeling, and alter the expression of inflammation-related proteins in mouse atrial tissue through mediating poly (ADP-ribose) polymerase 1 (PAPR-1)/IκB kinase-α (Ikk-α)/NF-κB pathway. They discovered that DM mice had considerably higher levels of NF-κB and NLRP3 expression.[54] PAPR-1/Ikk-α belongs to the upstream pathway of NF-κB. The group of ribozymes known as PARP-1 is involved in the repair of DNA damage, mediates apoptosis, controls gene transcription, and has the ability to control NF-κB and other inflammatory signal transduction pathways.[55] It is also closely linked to the pathogenesis of tumors, inflammatory injury, and cardiac fibrosis.[56]

Advanced glycosylation end products-receptor of advanced glycosylation end products axis

Crosstalk between advanced glycosylation end

products (AGEs) and their receptors (RAGE) and the dipeptidyl peptidase-4-enteric insulin system is implicated in the pathogenesis of many diabetic complications, including atrial remodeling, retinopathy, nephropathy, and atherosclerosis.[57] AGEs are mainly derived from the nonenzymatic glycation of proteins and lipids, a process that normally occurs during aging but is significantly accelerated in the presence of DM. RAGE is the specific receptor of AGEs, the interaction between AGEs and RAGE plays an important role in the initiation and propagation of inflammatory responses and oxidative stress.[58] Kato *et al*.[23] emphasized the putative role of the AGE-RAGE axis in DM-induced atrial fibrosis. They reported that atrial centrilobular fibrosis and RAGE expression level was significantly elevated in streptozotocin-induced diabetic rats. After receiving treatment with AGEs inhibitors, fibrosis in this model was partially reversed, pointing to a causal association between AGEs level, atrial fibrosis, and AF. The binding of AGEs to RAGE increases the expression of inflammatory mediators (i.e. NF-κB), which in turn leads to tissue remodeling and injury.[59] Notably, AGEs-mediated elevated NF-κB levels increase RAGE expression, leading to further elevation of ROS, creating a vicious cycle that exacerbates oxidative stress and inflammation, thereby promoting disease progression. Patients with permanent AF demonstrated increased expression of AGEs and soluble RAGE, it positively correlated with atrial dimensions, indicating a role for the AGEs-RAGE axis in the arrhythmogenic structural atrial remodeling of AF patients.[60] Begieneman *et al*.,[58] who compared AGEs levels in the left appendage (a hotspot for AF triggers) in patients with AF and controls, found an increase in N(ε)-carboxymethyl lysine, which was consistent with a significant increase in the number of inflammatory cells. Although the exact mechanisms by which the AGEs-RAGE axis promotes atrial fibrosis is unclear, it may arise from the interaction of AGEs with molecules in the basement membrane of the ECM. In summary, both basic research and clinical studies have strongly suggested that AGEs-RAGE axis can play an important role in the process of AF and it could be a new therapeutic target for atrial structural remodeling and AF.

The phenomenon of metabolic memory refers to the fact that sustained exposure to high glucose can cause chronic abnormalities of the vessels, kidneys, and heart, which are not easily reversed even by subsequent relatively good glycemic control.[61] In DM patients, long-term poor glycemic control or even transient episodes of hyperglycemia could make epigenetic changes in several cellular progenitors, stem cells, monocytes, and immune cells involved in endogenous vascular repair, resulting in deterioration of the capacity of the endocytic vascular repair system. Hyperglycemia induces posttranslational histone modifications and aberrant action of DNA methyltransferases, as well as altering the levels of many miRNAs in endothelial, vascular smooth muscle, cardiomyocytes, retinal, and renal cells. These cells may experience impaired function and contribute to CV and non-CV complications in DM.[61] However, through searching, we found that there is no relevant research on the mechanism of metabolic memory and the occurrence of AF under the diabetic context. It has been suggested that the phenomenon of metabolic memory is explained partly by persistent activation of the AGEs-RAGE axis in the diabetic vasculature, kidneys, and heart.[62] Besides, sustained activation of the AGEs-RAGE axis can result in vascular inflammation and endothelial dysfunction, the formation of foam cells, and a decrease in the number and function of endothelial progenitor cells.[63] Further studies are needed to investigate how the metabolic memory phenomenon exerts a clinical impact on diabetes-related arrhythmias and the underlying mechanisms.

Endoplasmic reticulum stress

Endoplasmic reticulum stress (ERS), is a pathological condition that can be driven by a variety of cellular conditions, such as inadequate or excessive nutrient supply, disturbed Ca^{2+} levels or redox balance, inflammation, and hypoxia.[64] Meanwhile, there is a growing recognition that ERS and the unfolded protein response are associated with the onset and progression of metabolic diseases such as DM.[65] In one of our previous studies, we constructed an animal model of hyperglycemia and used 75-kD glucose-regulated protein (GRP75) as an initiation site to demonstrate that calcium is transferred from the ER to the mitochondria through the inositol-triphosphate receptor type 1 (IP3R1)-GRP75-voltage dependent anion channel complex, a process that may play a role in mitochondrial calcium overload and subsequent cardiomyocyte death in a model of T2DM.[66] Based on this work, in another study, it was demonstrated that inhibition of mitofusin-2, a mitochondrial dynamin-related GTPase involved in mitochondrial Ca^{2+} regulation, attenuates mitochondrial oxidative stress and Ca^{2+} overload, increases mitochondrial membrane potential and mitochondrial oxygen consumption, further protects cardiomyocytes from ERS -induced apoptosis in the presence of high glucose.[67]

In the above-mentioned studies on molecular mechanisms and pathological changes, researchers have been able to achieve a simulated hyperglycemic state, *in vivo* or *in vitro*, by culturing cells with high glucose medium or by drug-induced elevation of blood glucose in experimental animals. Whereas in pre-DM, glycemia tends not to reach the same levels as DM, and it is a reversible intermediate state, whether oxidative stress, inflammation, and mitochondrial dysfunction occur in the same pattern and in a dose-intensity relationship at relatively low glucose concentrations has not been investigated. Furthermore, how to stimulate pre-DM blood glucose levels and fluctuations in animal models and cellular experiments in pre-DM has not been investigated. To some extent, these limit the fundamental research on pre-DM.

Relationship between Other Risk Factors and Atrial Fibrillation

One of the most widely used AF risk scores, CHARGE-AF, states that to predict incident AF, risk factors (such as age,

race, height, weight, smoking status, blood pressure [BP], use of antihypertensive medication, diagnosis of DM, and history of myocardial infarction or heart failure) must be considered both modifiable and nonmodifiable.[2] In this part, we mainly discuss modifiable risk factors and how they induce AF.

Hypertension and atrial fibrillation

The relationship between BP and the incidence of AF is now well-established. Increased BP in general increase the incidence of AF because of left ventricular hypertrophy (LVH) and LA dilatation, accelerating the development of AF. The development of AF is partly brought on by arterial hypertension and LVH, which cause sympathetic overactivity and an excessive adrenergic response to stressful stimuli.[68] LVH causes an increase in filling pressure, in which case the atria undergo fibroblast proliferation, increased deposition of connective tissue, fibrosis, and other pathological changes that worsen the burden of arrhythmias.[69] The interaction between LVH and the renin–angiotensin–aldosterone system described above results in atrial remodeling characterized by connective tissue deposition, fibrosis, intercellular matrix accumulation, and inflammatory changes, and although the mechanisms involved are different, the cardiac pathological changes caused in hypertension are similar to those in T2DM. It has also been proven in large animal models that hypertension causes AF mainly by inducing LAE and impaired function, increased conduction slowing and heterogeneity, and interstitial fibrosis. In addition, similar to in T2DM, alterations in the atria, especially the LA internal diameter, are factors in the development and maintenance of AF due to hypertension.[70]

Obesity or metabolic syndrome and atrial fibrillation

There are several definitions of MS, but the key features are abdominal obesity, elevated BP, dyslipidemia (high triglycerides [TGs] and low high-density lipoprotein-C [HDL-C]), and glucose intolerance.[71] We have discussed the relationship between hypertension or glucose abnormalities and AF in the above section. Obesity is a worldwide public health problem and is independently associated with AF. In the Framingham cohort study, for each unit increase in body mass index (BMI), there was a 4%–5% increase in the risk of AF.[70] Obesity is associated with body fat accumulation and remarkable weight gain that can lead to the development and prevalence of chronic diseases including dyslipidemia, IR, and T2DM.[72] In animal models, it can be observed that obesity can lead to increased atrial fibrosis, resulting in slowed conduction, increased conduction heterogeneity, and increased atrial fibrosis, which is similar to the pathological and electrophysiological changes that occur in the cardiac in T2DM.[73] Specifically, obesity can affect the depolarization of sodium channels, the voltage-gated L-type Ca^{2+} channels and delayed rectifier K^+ currents, reduced cardiac sodium and calcium channel currents (I_{Na}, $I_{Ca\text{-}L}$), prolonged APD, and increased potassium channels (Kv1.5) and potassium currents (I_{Kur}).[74,75] In pathology, structural and electrophysiological changes such as atrial fibrosis, increased LA volume, and slowed LA conduction velocity were also observed in obese rat and rabbit models.[73,76] Obesity causes an increase in epicardial adipose tissue (EAT), which contributes to an increase of inflammatory cytokines and ROS released from EAT, resulting in inflammation, oxidative stress, and endothelial dysfunction. It has been proved that in the context of obesity, the increase in pericardial adipose volume associated with LAE is related to the increased risk of AF.[77] Meanwhile, the amount of pericardial adipose can predict the success of AF ablation procedures; reducing pericardial fat through weight loss can reduce the burden of AF.[78] According to a clinical trial from Sweden in a population with overweight T2DM patients (BMI 25.0–29.9 kg/m^2), weight decreased by 25% after bariatric surgery, and AF events reduced by 41% over a 4.5-year follow-up period.[79] In addition to bariatric surgery, dietary interventions like the removal of saturated free fat acid (FFA) or the addition of unsaturated FFA coupled with increased physical activity (PA) may also help to reduce the risk of arrhythmias. However, AF risk did not alter throughout follow-up (mean 9 years) in individuals with T2DM from a randomized US trial who lost weight with an intensive lifestyle intervention (including calorie restriction and increased PA) compared with usual treatment. Although this finding warrants further exploration, it suggests that the presence of T2DM may inhibit the independent benefit of weight loss on AF outcomes.[80] Overall, intensive weight loss is beneficial for a wide range of people who are overweight or obese, depending on BMI. As a risk factor, the relationship between blood lipids and AF has had different results according to different clinical studies. Observational studies have shown that high levels of total cholesterol (TC), low-density lipoprotein-C (LDL-C), and HDL-C are associated with an increased risk of AF in Japanese, while in addition to HDL-C and TG, higher levels of TC and LDL-C have been found to be associated with an increased risk of AF in Chinese.[81] In another review, Elliott *et al*. considered LDL-cholesterol to be a significant cause of atherosclerotic disease and can raise the risk of AF. However, in some studies, elevated HDL-cholesterol levels were associated with a lower incidence of AF.[2,82] There is also a paradox in statin therapy for dyslipidemia. Some researchers suggested that statins may reduce the risk of AF by inhibiting the inflammatory response.[83] Nonetheless, there are also several meta-analyses of clinical studies showed that statin therapy was no significant effect in reducing AF events.[84,85]

Obstructive sleep apnea and atrial fibrillation

The prevalence of OSA has been reported to be 3%–49% in the general population, while this rate is as high as 21%–74% in patients with AF.[86] OSA is an independent risk factor for AF in patients without other underlying cardiac disorders.[87] OSA induces intermittent hypoxia, negative intrathoracic pressure swings, increased venous return, and hypoxic pulmonary vasoconstriction.[86] Atrial fibrosis with connexin downregulation and electrophysiological abnormalities may result from chronic recurrence and abruptly negative changes in intrathoracic pressure. These conditions may also cause structural and functional atrial remodeling.[88] The chronic OSA animal models exhibit reduced conduction velocity, atrial

fibrosis, oxidative stress, and left ventricular dysfunction, while these physiological changes increase the susceptibility to AF.[89] Several small-scale retrospective trials have demonstrated that continuous positive airway pressure (CPAP) therapy reduces the burden of AF.[90] Moreover, in a cohort including 10,132 patients with combined OSA in AF, patients treated with CPAP were less likely to progress to permanent AF than those not treated with CPAP.[91] However, no studies have addressed whether strategies to reduce OSA are effective in the primary prevention of AF.[2] In summary, future management strategies for AF should take any concomitant sleep-breathing disorders into consideration.

Intervention and Treatment for Pre-Diabetic Mellitus Patients

According to a meta-analysis, lifestyle interventions including regular and nutritional dietary advice, PA and guidance on weight loss are an effective, safe, and cost-effective measure to reduce the risk of T2DM in patients diagnosed with pre-DM.[92] PA could enhance β cell function and improve insulin sensitivity in prediabetic patients.[93] Reducing sedentary lifestyles and moderately increasing PA are important parts of the management of DM and pre-DM, and whether PA can reduce the incidence of AF associated with LAE in diabetic patients deserves further investigation.[94] Besides PA, dietary improvements such as reducing the consumption of sugary drinks play are crucial in preventing the development of pre-DM into DM.[95] Moreover, the progression of pre-DM to DM could also be prevented by anti-diabetic drugs or anti-obesity drugs including metformin, thiazolidinediones, α-glucosidase inhibitors, incretins, sodium-glucose and cotransporter (SGLT) 2 inhibitors and the preventive effect is associated with reduced risks of AF in the hyperglycemic context.[96,97] It is reported that twice-daily oral metformin 850 mg can reduce the chance of IGT developing into T2DM.[98] In the group using metformin, a total of 7.8% pre-DM patients developed DM, whilst in the placebo group, a total of 11.0% pre-DM patients subsequently developed DM. According to the European Heart Rhythm Association guidelines, there are four steps in the management of arrhythmia patients with abnormal blood glucose: Setting glycemic goals, managing risk factors and CV disease, screening for arrhythmias, and treating arrhythmias and stroke prevention. Patients with arrhythmias associated with DM should receive individualized goals for glycemic control. Age, life expectancy, individual risk factors, and patient preferences should be considered. In the management of risk factors, emphasis should be placed on the management of hypertension, hyperlipidemia, obesity, and OSA to reduce the risk of arrhythmias. As mentioned earlier, DM is a well-known risk factor for stroke in patients with AF. Every DM patient with AF should undergo stroke risk assessment and should be treated with oral anticoagulants if CHA_2DS_2-VASc (congestive heart failure, hypertension, age ≥75 years, diabetes, stroke, vascular disease, age 65–74 years and sex category [female]) scores ≥1.[99,100]

Besides these strategies for clinical management, several researches have further investigated the mechanism of the effect of therapeutic agents. By lowering intracellular ROS, activating adenosine 5'-phosphate-activated protein kinase, enhancing calcium homeostasis, decreasing inflammation, upregulating connexin-43 gap junction expression, and restoring small conductance calcium-activated potassium channel currents, metformin prevents both structural and electrical remodeling of the left atrium.[101] Pioglitazone reduces TGF-β1 protein expression in atrial myocytes, reduces mitochondrial ROS production, decreases serum oxidative and inflammatory markers (8-hydroxy-2'-deoxyguanosine and high-sensitivity C-reactive protein) and LA (NF-κB) expression through the peroxisome proliferator-activated receptor (PPAR)-γ/PPAR-γ coactivator-1α signaling pathway, and exerts a therapeutic effect on diabetes-induced structural and electrophysiological remodeling of the atria in a diabetic model rabbit. There are also medicines that have huge clinical potential for the treatment of DM-related AF but still not have been used on a large scale in the clinic, such as apocynin, a nicotinamide adenine dinucleotide-oxidase inhibitor, reduced mitochondrial oxidative stress, thereby reducing atrial electrical remodeling and AF inducibility.[47,102] Ruboxistaurin has been demonstrated that can reduce the protein expression levels of PKC-β and NF-κB which are involved in the process of DM-related atrial remodeling and clinical combinations.[52] There is still significant potential for research about the underlying mechanisms involved in the therapeutic effects of hypoglycemic agents in AF patients with glucose abnormalities.

Conclusion

Pre-DM is an intermediate state between normal glycemia and DM, and it can also increase the incidence of AF. Basic research on the molecular mechanisms of pre-DM and AF is limited by the preparation of animal models and simulation of *ex vivo* environments. Pre-DM can progress to T2DM, and when DM is present, structural remodeling such as atrial enlargement fibrosis, as well as electrical and neural remodeling, can be observed in experimental animals and/or humans. The above pathological changes are mainly driven by molecular mechanisms such as oxidative stress, inflammation, activation of AGEs-RAGE axis, and ERS. Oxidative stress and activation of the AGEs-RAGE axis are closely related to the metabolic memory phenomenon, and the impact of that phenomenon in diabetic AF should be further explored. Conditions, such as hypertension, obesity, hyperlipidemia, and MS as risk factors for AF, can also cause atrial enlargement, atrial fibrosis, and atrial electrical remodeling, leading to the development and progression of AF. The inclusion of pre-DM and DM in the risk management category of AF is essential in reducing AF-related embolic events. For the treatment of pre-DM, lifestyle interventions are the cornerstone, and in cases where lifestyle interventions are not effective, the use of metformin, thiazolidinediones, α-glucosidase inhibitors, incretins, SGLT 2 inhibitors are also beneficial for patients.

Author contributions

Xuyao Han conducted literature searches, wrote the first draft of the manuscript and illustrated this paper with Ying Liu. Tong Liu, Gary Tse and Guangping Li provided supervision and project administration of the study. Each co-author contributed to either the delivery of the study or helped to devise the protocol. All authors have given final approval for the current version to be published.

Ethical statement

Ethical statement is not applicable for this article.

Data availability statement

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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Conflicts of interest

There are no conflicts of interest.

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