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Review Article

Atrial Fibrillation Development Risk Associated with Metabolic Syndrome

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ABSTRACT

Even in the absence of antecedent myocardial infarction or congestive heart failure, atrial fibrillation (AF) is the most frequent arrhythmia seen in daily practice. There are several important predisposing factors for the initiation of AF, including growing older, being a man, being female, having high blood pressure, and having cardiac and noncardiac illnesses. Metabolic syndrome (MS) contributes to the progression of AF through its impact on the atrial substrate. MS involves metabolic risk factors that increase the likelihood of atherosclerotic cardiovascular disease and type 2 diabetes. Insulin resistance plays a significant role in MS pathophysiology, leading to glucose and lipid metabolism dysregulation, increased inflammation, and neurohormonal activation. These processes contribute to the development of hypertension, a major risk factor for AF. Atrial remodeling, including electrical and structural changes, is a common substrate for AF, and MS components further contribute to this remodeling. Hypertension, a key feature of MS, is associated with structural, contractile, and electrical remodeling in the atria, increasing the risk of AF. The renin-angiotensin-aldosterone system, implicated in hypertension regulation, also influences the pathophysiology of AF through fibrosis, ion channel alterations, oxidative stress, and inflammation. Understanding the intricate interplay between MS and AF can provide insights into therapeutic strategies for managing these conditions and reducing cardiovascular risks.

1. Introduction

Atrial fibrillation (AF), the most prevalent rhythm disorder requiring therapeutic intervention, is also linked to a higher mortality risk. In the European Union, 14 to 17 million people are anticipated to have AF by 2030; the incidence of the condition was 2.1% in men and 1.7% in women.[1] Through Indonesia, the proportion of the elderly population has increased significantly, from 7.74% in the 2000–2005 range to 28.68% in the 2045–2050 range, meaning that the incidence of AF will also rise significantly. Although the arrhythmia is not lethal in and of itself, AF-related consequences such as heart failure (HF), tachycardia-induced cardiomyopathy, and stroke increase the risk of cardiovascular and all-cause death in AF patients.[2] AF is associated with a 2- to 5-fold increase in stroke risk and 20% to 30% of all ischemic strokes. Even though the occurrence of AF is known to be higher in Europe than in Asia. The frequency in Asia has been growing due to aging populations.[3,4] MS component is linked to an increased risk of getting AF. However, not enough research has been done on the precise MS component is linked to an increased risk of getting AF. However, not enough research has been done on the precise mechanisms behind these connections. Obesity, dyslipidemia, hypertension, and insulin resistance are all signs of epidemic-level metabolic syndrome (MS). According to much research, the incidence of cardiovascular problems and the risk factor for cardiovascular morbidity, referred to as MS, has been connected to the development of AF.5 Because MS affects the atrial substrate, it is critical in evaluating disease progression and the success of therapeutic techniques like catheter ablation.[6] It is critical to assess the relationship between these two frequent disorders and to determine the processes that link them because both are associated with high cardiovascular morbidity and mortality.[7]

2. Discussion

2.1. Metabolic Syndrome Pathophysiology and Clinical Features

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Table 1 Metabolic Syndrome Diagnostic Criteria.[9]

Clinical Measure	WHO (1998)	EGIR	ATP III (2001)	AACE (2003)	IDF (2005)
Insulin resistance	IGT, IFG, T2DM, or lowered insulin sensitivity* **plus any 2 of the following**	Plasma insulin >75th percentile **plus any 2 of the following**	None, **but any 3 of the following 5 features**	IGT or IFG **plus any of the following based on clinical judgment**	None
Body weight	Men: waist-to-hip ratio >0.90; women: waist-to-hip ratio >0.85 and/or BMI >30 kg/m^2	WC ≥94 cm in men or ≥80 cm in women	WC ≥102 cm in men or ≥88 cm in women†	BMI ≥25 kg/m^2	Increased WC (population specific) **plus any 2 of the following**
Lipid	TG ≥150 mg/dL and/or HDL-C <35 mg/dL in men or <39 mg/dL in women	TG ≥150 mg/dL and/or HDL-C <39 mg/dL in men or women	TG ≥150 mg/dL HDL-C <40 mg/dL in men or <50 mg/dL in women	TG ≥150 mg/dL and HDL-C <40 mg/dL in men or <50 mg/dL in women	TG ≥150 mg/dL or on TG Rx HDL-C <40 mg/dL in men or <50 mg/dL in women or on HDL-C Rx
Blood pressure	≥140/90 mm Hg	≥140/90 mm Hg or on hypertension Rx	≥130/85 mm Hg	≥130/85 mm Hg	≥130 mm Hg systolic or ≥85 mm Hg diastolic or on hypertension Rx
Glucose	IGT, IFG, or T2DM	IGT or IFG (but not diabetes)	>110 mg/dL (includes diabetes)‡	IGT or IFG (but not diabetes)	≥100 mg/dL (includes diabetes)
Other	Microalbuminuria			Other features of insulin resistance§	

*note : T2DM indicates type 2 diabetes mellitus; WC, waist circumference; BMI, body mass index; and TG, triglycerides; European Group for Study of Insulin Resistance (EGIR); National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III); American Association of Clinical Endocrinologists (AACE); International Diabetes Foundation (IDF).

Metabolic syndrome (MS) is a collection of metabolic risk factors that, when combined, increase the probability of developing atherosclerotic cardiovascular disease (ASCVD). MS also increases the risk of type 2 diabetes. The most well-known risk factors include atherogenic dyslipidemia, high blood pressure, and high blood sugar. The metabolic syndrome, in general, causes an inflammatory and pro-thrombotic condition. MS is a major public health problem on a global scale, owing to rising urbanization, sedentary lifestyles, and excessive calorie intake. MS has been related to a five-fold increase in the likelihood of developing diabetes mellitus and a two-fold increase in the risk of cardiovascular disease during the next five to ten years. Throughout their lives, patients with MS have a 2-4 fold more significant risk of stroke and a 3-4 fold increased risk of myocardial infarction.[8] Metabolic syndrome can be diagnosed using a variety of clinical criteria, including[9]:

Metabolic syndrome (MS) is a metabolic illness such as high blood pressure, obesity, insulin resistance, and atherogenic dyslipidemia. Experts are still debating the root causes of the metabolic syndrome. According to the IDF, the two major variables driving the development of metabolic syndrome are central obesity and insulin resistance.[9,10] Other factors, including genetics, physical inactivity, aging, pro-inflammatory conditions, and hormonal changes, are also assumed to be causative, but their importance varies by ethnic group. Environmental factors such as lifestyle, calorie consumption, and inactivity play a part.[11]

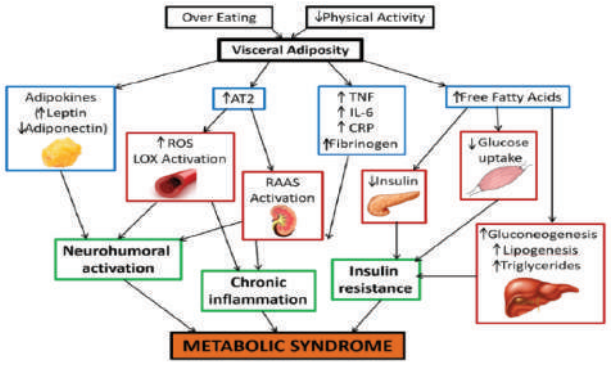

Figure 1. Pathophysiology Metabolic Syndrome AT2, angiotensin II type 2 receptor; CRP, C-reactive protein; IL-6, interleukin 6; LOX, lectin-like oxidized low-density lipoprotein; RAAS, renin- angiotensin-aldosterone system; ROS, reactive oxygen species; TNF, tumor necrosis factor.[12]

2.1.1. Insulin resistance

Insulin promotes glucose uptake in the liver and muscle while inhibiting lipolysis and gluconeogenesis in the liver. The rise in free fatty acids (FFAs) in the bloodstream caused by insulin resistance is considered to have an essential role in the pathogenesis of MS. Insulin resistance in adipose tissue impairs insulin's capacity to inhibit lipolysis, causing circulating FFA levels to increase and further reduces insulin's antilipolytic action. FFAs block the muscle from activating protein kinase, decreasing glucose uptake. They promote gluconeogenesis and lipogenesis by boosting protein kinase activity in the liver.[13] Reduced insulin production is caused by FFA's lipotoxic effects on beta cells in the pancreas. Insulin resistance plays a role in the development of hypertension due to the absence of insulin's vasodilator action. The vasoconstriction produced by FFA increased sympathetic nerve behavior and increased salt reuptake in the kidneys. Insulin resistance increases the risk of CVD by raising serum viscosity, making a prothrombotic state, and releasing pro-inflammatory cytokines from adipose tissue.[14]

Compared to subcutaneous fat, visceral fat stores significantly impact insulin resistance because visceral lipolysis increases the number of FFAs delivered to the liver through the splanchnic circulation. An increase in FFAs causes the liver to produce more apolipoprotein B, which contains triglyceride-rich, very low-density lipoprotein (LDL) and more triglyceride synthesis. Indirect effects of insulin resistance brought on by altered lipid metabolism in the liver include an increase in small dense LDL cholesterol and a decrease in HDL cholesterol. Additionally, visceral adipose tissue is thought to be more metabolically active. It produces noticeably more bioactive secretory proteins, including plasminogen activator inhibitor, which encourages a prothrombotic state, and heparin-binding epidermal growth factor-like growth factor, which promotes smooth muscle cell proliferation and vascular remodeling.[15]

2.1.2. Neurohormonal activation

The endocrine and immunological systems of adipocyte cells play a part in developing metabolic syndrome. It has been established that adipokines, substances made by visceral fat tissue, are connected to metabolic syndrome. Leptin is one form of adipokine that regulates energy balance through the hypothalamus and can activate immune cells via the Th1 pathway. Obesity will boost leptin production, and the higher the leptin level, the greater the risk for cardiovascular disease.

Adiponectin is a different kind of adipokine that works the opposite of leptin. It is anti-inflammatory and anti-atherogenic, reducing vascular reactivity, smooth muscle proliferation, and boosting plaque stability. Adiponectin levels fall, and leptin levels rise under setting of increased adipose tissue mass, reducing adiponectin's protective impact and raising the cardiovascular risk.[16]

2.1.3.. Inflammation: the final common pathway

Numerous inflammatory signaling has been found to become higher in people with MS, and inflammation plays a significant role in the pathophysiology of CVD. It is debatable whether these markers contribute to chronic inflammation or are merely bystanders to it. Tumor necrosis factor alpha (TNF-α), released from macrophages in adipose tissue., is produced more frequently when more adipose tissue is present. TNF induces fat oxidation, which increases FFA load and inhibits the release of adiponectin. It also promotes phosphorylation and deactivation of insulin receptors in adipose tissue and smooth-muscle cells. Insulin resistance and obesity, two vital elements of MS, are linked to increased blood TNF- levels. C-reactive protein (CRP) and interleukin 6. Adipocytes and immune cells produce the cytokine interleukin 6 (IL-6), which has intricate regulation mechanisms. With an increase in body fat and insulin resistance, IL-6 production rises. It affects the liver, bone marrow, and endothelium and causes the liver to produce more acute phase reactants, such as CRP. High CRP levels have been linked to the emergence of MetS, diabetes, and CVD, according to several studies. IL-6 also raises fibrinogen concentrations, resulting in a prothrombotic state. Additionally, IL-6 encourages endothelial cell production of adhesion molecules and local RAS pathway activation.[12,17]

2.2. Development of Atrial Fibrillation (Trigger and Substrate)

The precise etiology of atrial fibrillation remains unknown but is considered complex. The existence of a trigger factor and the presence of a perpetuating element (substrate) are two ideas that are widely accepted.[18] Substrates in atrial fibrillation are created due to electrical remodeling, structural remodeling, autonomic nervous system changes, and calcium handling abnormalities. All four pathways can result from a heart condition and progress to AF. The four mechanisms will then become worse due to the AF itself. The heart becomes more pop-resistant due to atrial remodeling, and AF persists.[19]

Structural heart diseases, including hypertension, coronary heart disease (CHD), valvular heart disease, cardiomyopathy, and heart failure, can cause gradual but persistent remodeling in the atria and ventricles. The proliferation and differentiation of fibroblasts into myofibroblasts, which can promote connective tissue deposition and fibrosis in the atria, are characteristics of the remodeling process in the atria due to increased wall stress. Atrial remodeling is a triggering and sustaining factor for AF because it results in electrical disruptions between muscle and conduction fibers in the atrium. The reentry circuits that sustain arrhythmias are made more accessible by this electroanatomical substrate[18,19]

The electrical remodeling procedure helps to make AF more stable in the first few days following the start. Downregulation of calcium influx (via L-type channels) and overexpression of potassium inflow are the primary biological mechanisms causing the shortening of the refractory period.[18]

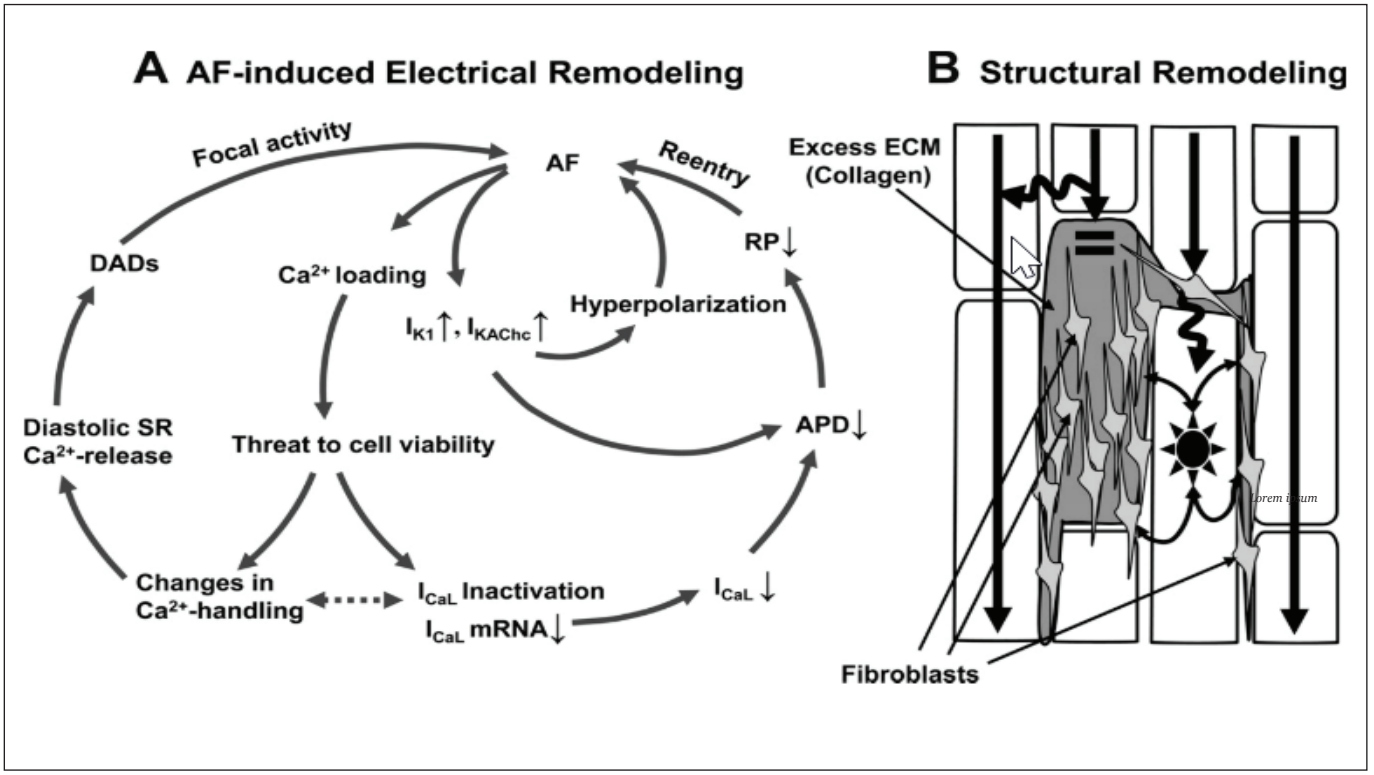

Figure 2 Electric remodeling (A) Structural remodeling (B).[18]

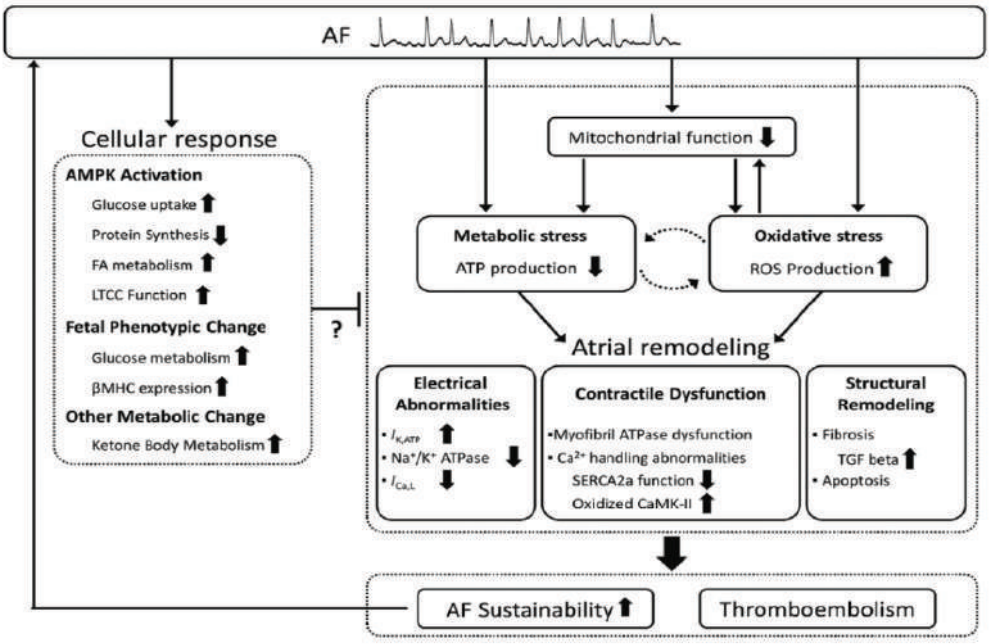

Figure 3. How metabolic syndrome and energy deprivation involvement in the pathophysiology of atrial fibrillation.[7]

2.3. Metabolic Syndrome and Atrial Fibrillation

Nearly every element of the metabolic syndrome raises the likelihood of developing atrial fibrillation, and these elements are hypothesized to do so via various pathogenic mechanisms. A delicate interplay between arrhythmia-causing triggers and defective substrates complicates the genesis of AF. As both a catalyst and a substrate, the metabolic syndrome's various elements can contribute to atrial fibrillation.[5]

Atrial remodeling can take the form of electrical remodeling, electrophysiological alterations, contractile remodeling, and structural remodeling when there is metabolic stress. When the intracellular ATP content drops, the ATP-sensitive potassium channels (IK-ATP) in the sarcolemma open. The action potential duration (APD) will be shortened, and the membrane will be hyperpolarized by an increase in IK-ATP, causing AF re-entry. 1,3-biphosphoglycerate, a glycolysis intermediate product generated by glyceraldehyde 3-phosphate dehydrogenase (GAPDH) catalysis, also activates IK-ATP. Patients with persistent atrial fibrillation experience a reduction in the IK-ATP channel subunit and IK-ATP density, which could be a protective mechanism against APD shortening, and lessen the ability of cells to contract. In patients with atrial fibrillation, AMPK activation may minimize the arrhythmogenic shortening of APD by offsetting these effects. Ca2+ transient (CaT) alterations brought on by mitochondrial energy production disruption will be mitigated by SERCA2a upregulation. The Ca2+/calmodulin kinase type-II (CaMK-II) enzyme can improve cellular Ca2+ dynamics and is an upstream regulator of Ca2+ regulatory proteins. Direct oxidation of the CaMK-II regulatory domain by mitochondrial ROS activates CaMK-II. An aberrant Ca2+ homeostasis, Ca2+ leakage in the sarcoplasmic reticulum, and the stimulation of atrial activity brought on by persistent CaMK-II activation might result in atrial fibrillation.[20,21]

2.3.1. Hypertension and Atrial Fibrillation

Hypertension, which affects 49-90% of patients with atrial fibrillation and > 2-fold increases the occurrence of atrial fibrillation, is the first feature of metabolic syndrome. From a pathophysiological standpoint, structural, contractile, and electrical remodeling are the primary factors connecting hypertension to atrial fibrillation.18 In a case–control population study, the risk of AF doubled in individuals with systolic BP of ≥150 mm Hg, compared with patients with systolic BP levels of 120 to 129 mm Hg for the follow-up period of 14 years. Compared with a reference level of 120-129 mmHg, SBP increases by category compared with AF events by odds ratio (CI 95%) were 130-139 mmHg (1.19 (0.78, 1.81));140-149 mmHg (1, 40 (0.93, 2.09)); 150-159 mmHg (2.02 (1.30, 3.15)); 160-169mmHg (1.84 (0.89, 3.80)) and ≥170 mmHg (2.27 (1.31, 3.93)).[22,23]

Long-term hypertension causes an increase in ventricular filling pressure, which causes the left atrium to enlarge and stretch the atrial myocytes. This increased ventricular filling pressure also causes the left ventricular wall to thicken gradually, resulting in left ventricular hypertrophy (LVH). By reducing atrial contractility and increasing atrial compliance, this chronic wall stretch of atria causes gradual expansion of the left atrial chamber. AF can increase left atrial enlargement in chronic high blood pressure persons with left ventricular systolic and/or diastolic dysfunction. Chronic atrial strain may potentially cause atrial morphological and electrophysiological alterations that serve as AF substrates, also increasing the risk of AF recurrence.[22]

The RAAS system, which is crucial for regulating blood pressure, also influences the pathophysiology of atrial fibrillation. According to research, angiotensin II promotes atrial fibrosis and enlargement, alterations in ion channel expression, gap junctions, calcium handling, and increased oxidative stress and inflammation. Angiotensin-II increases fibroblast proliferation and extracellular matrix protein accumulation via activating mitogen-activated protein kinase. Due to the emergence of conduction block, these modifications might result in atrial hypertrophy and fibrosis, which serve as atrial substrates for reentry. Angiotensin II caused interstitial fibrosis in the spontaneously hypertensive rat model, leading to a left atrium blockage. The L-type and T-type calcium currents (I Ca, T, I Ca, L), the rapid and slow components of the delayed rectifier potassium currents (I Ks, I Kr), and the transient outward potassium current (I too) are just a few of the ion channels that angiotensin II modulates. These changes in ion channel expression as well as altered calcium handling in atrial cardiomyocytes, can promote the development of AF.[25,26]

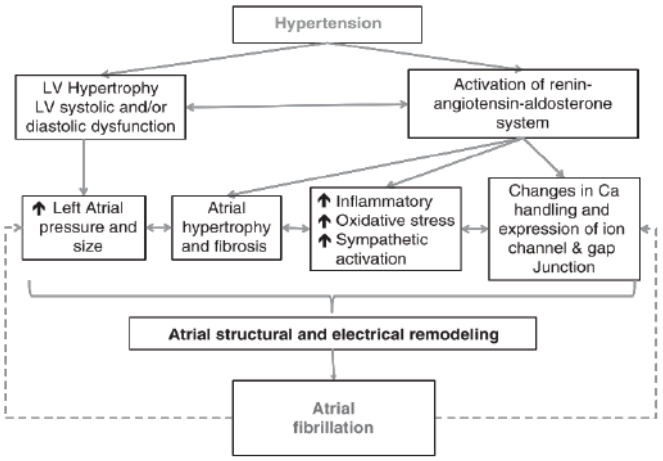

Figure 4. Mechanism of Hypertension-Induced Atrial Fibrillation

The Framingham study was the first to show a relationship between LA dilatation and high blood pressure, with systolic blood pressure having a more significant effect on LA than diastolic blood pressure. In a cohort study of initially untreated hypertensive people, baseline LV hypertrophy substantially quadrupled the risk of new-onset AF, and each 1-SD increase in LV mass increased the risk of AF by 20% (95% confidence interval [CI], 7% to 34%). The 5-year probability of persistent AF increased with LA diameter regardless of LV mass. As a result, among hypertensive people with sinus rhythm at admission and no other major risk factors, the frequency of AF new-onset rose with LV mass and age. Still, the establishment of persistent AF was more common. LV hypertrophy indicated by electrocardiography is a robust predictor of AF in the general population and hypertensive patients. Individuals with LA dilatation associated with LV diastolic dysfunction and atrial pump activity were shown to be at a greater risk of developing AF in subsequent trials.[22,27]

2.3.2. Hyperglicemia and Atrial Fibrillation

Dublin et al. concluded that compared to people without diabetes, the adjusted OR for people with treated diabetes with average Hemoglobin A1c (HbA1c) ≤7 was 1.06 (95% CI 0.74-1.51); for A1c >7 but ≤8,1.48 (1.09-2.01); for A1c >8 but ≤9, 1.46 (1.02-2.08); and for A1c >9, 1.96 (1.22–3.14).[28]

Diabetes is linked to atrial enlargement and increased levels of C-reactive protein (CRP), a marker of persistent inflammation that increases the likelihood of atrial fibrillation. Atrial dilatation can cause electrical impulses to re-enter the heart, which is a significant cause of atrial fibrillation, and high CRP levels can cause myocardial fibrosis and diastolic dysfunction. TGF-β (transforming growth factor beta) is expressed more often in diabetic rats following extended hyperglycemia exposure, which has been shown to activate profibrotic signaling pathways. Additionally, elevated levels of AGEs and AGE receptors cause connective tissue growth factor to be upregulated, which in turn causes atrial fibrosis. Finally, TGF-b signaling has been connected to the development of fibrosis via the RAAS pathway.[29]

The second idea focuses on the electrical remodeling of the atrium that occurs in diabetics. Lower Na current and larger L-type Ca current densities were seen at the cellular level in diabetic rabbit atrial, which may have retarded conduction and increased arrhythmogenicity. Different types of sympathetic and parasympathetic denervation are brought on by diabetes. Sympathetic tone anomalies produce autonomic neuropathy, left ventricular hypertrophy, heart, and blood vessel anatomy, and function alterations. The third theory, meanwhile, focuses on variations in blood glucose levels. Those with persistent hyperglycemia are less likely to develop atrial fibrillation than patients with long-term changes in glucose levels, especially those who are using insulin. In comparison to people with prediabetes, patients with long-term diabetes are also at high risk of AF occurence.[31,32]

Another factor that connects atrial fibrillation and diabetes is the remodeling of the ventricles resulting from the oxidative stress that diabetes causes. This remodeling can lead to abnormalities in microvascular flow and can happen before or shortly after the onset of AF. AF is also indirectly predicted by several clinical disorders linked to diabetes, including coronary heart disease and heart failure. Diabetes individuals were studied in the research, and even after correcting for body mass index, diabetes patients had a more typical obstructive sleep apnea more common, which can also induce atrial fibrillation.[7,33]

2.3.3. Obesity and Atrial Fibrillation

Obesity-induced hemodynamic alterations increase the likelihood of heart shape abnormalities. LV concentric remodeling then hypertrophy appears to be as common as LVH eccentric in obese individuals. This response is assisted in most fat persons by a decrease in systemic vascular resistance (SVR), which raises LV diastolic filling

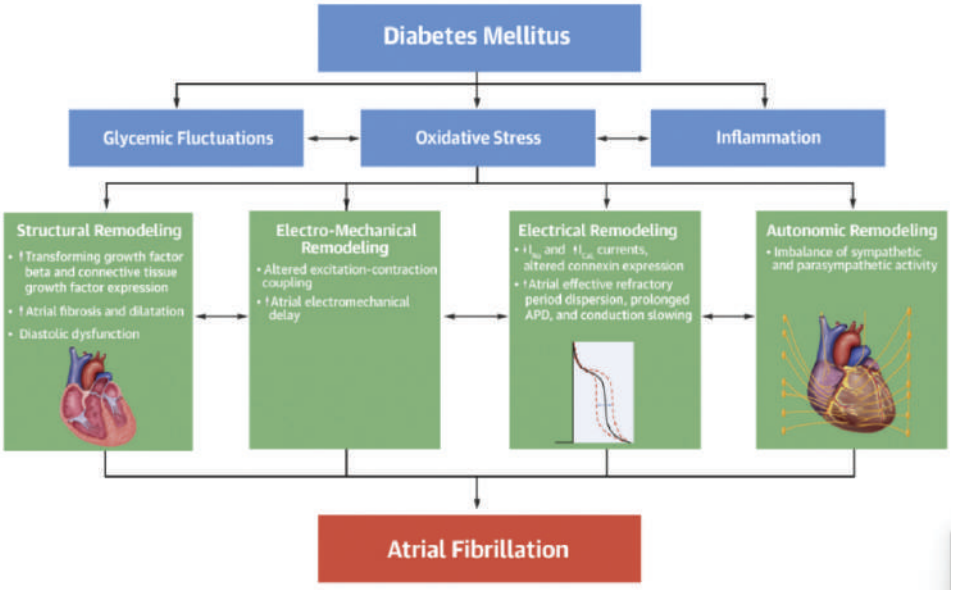

Figure 5 Pathophysiology of Diabetes and Atrial Fibrillation[30]

pressure and induces electrical and structural remodeling in the atrium.[34] From Dublin et al. compared to normal weight subjects without metabolic syndrome, increased atrial fibrillation risk was noted for overweight subjects with metabolic syndrome (OR CI 95%), 1.67 (1.16 – 2.41), obese subjects without metabolic syndrome, 1.75 (1.11 – 2.74) and obese subjects with metabolic syndrome, 1.92 (1.34 – 2.74).[35]

The role of heart fat, especially epicardial adipose tissue, in developing AF (EAT). EAT is located between the epicardial layer of the myocardium and the visceral pericardium. Contiguous fatty infiltration of the atrial myocardium, atrial fibrosis caused by paracrine adipocytokines, and fibrotic remodeling of adipose tissue in the atrial subepicardial caused by immunological or inflammatory responses are all adverse outcomes of epicardial fat. Inflammatory cytokines and chemokines may cause LA myocardial fibrosis, increasing the likelihood of the formation of micro-re-entry circuits. Growth and remodeling factors may induce LA hypertrophy and dilatation, resulting in AF. Other ways EAT and improved pericardial fat influence the development of AF are unclear. A function linked with broad innervation of the sympathetic or parasympathetic nervous systems.[34,35]

Obesity is also linked to neurohormonal activation via RAAS, which may contribute to cardiac electrical instability and left atrial enlargement that may result in atrial fibrillation. Increased sympathetic nerve activity, critical for causing renin secretion and subsequent increases in renin and/or aldosterone activity in plasma, is associated with obesity in metabolic syndrome conditions. This indirectly increases atrial fibrillation and directly raises blood pressure. In addition, obesity is linked to an imbalance of the adipokines leptin, adiponectin, and other adipokines that are independently related to heart failure, inflammation, and diabetes mellitus, all of which are linked to atrial fibrillation. Obstructive sleep apnea and other sleep disorders that raise the risk of atrial fibrillation are prevalent in obese persons. Several potential underlying causes for atrial fibrillation include hypoxemia, elevated sympathetic activity, increased afterload, pulmonary vasoconstriction, and ineffective respiratory excursions.[36,37]

According to previous studies, body mass index (BMI) influences atrial size and volume. Every 1 unit higher BMI is linked to a 7% higher chance of persistent atrial fibrillation, a 4% higher risk of intermittent atrial fibrillation, and a 1% higher risk of paroxysmal atrial fibrillation. Additionally, there is a strong relationship between BMI and the emergence of persistent atrial fibrillation. Obesity, according to a new study, shortens the left atrium and the pulmonary vein's effective refractory time, which may contribute to the development of atrial fibrillation.[33,38,39]

2.3.4. Dyslipidemia and Atrial Fibrillation

Nearly all studies demonstrate a correlation between low levels of high-density lipoprotein cholesterol (HDL-c) and the prevalence of atrial fibrillation, even though the connection between dyslipidemia and AF is still debatable. Many theories explain this correlation. Low HDL-c levels contribute to the development of atrial fibrillation because they are linked to increased left ventricular mass, diastolic dysfunction, and the advancement of heart failure. Researchers discovered that statin and anti-inflammatory medication could decrease the chance of atrial fibrillation because inflammation and oxidative stress are also linked to an increased incidence of the condition.[40,41]

Studies on the correlation between other lipid components and atrial fibrillation have found complex correlations. Some researchers found an inverse relationship between cholesterol levels and the prevalence of atrial fibrillation and an inverse relationship between LDL cholesterol levels and AF. However, other studies found no link between lipoprotein (a) and atrial fibrillation. Research on the relationship between triglyceride levels and atrial fibrillation shows different results. Some studies show an inverse relationship between triglyceride levels and atrial fibrillation, while others show no connection. These controversial research results are called the 'dyslipidemia paradox,' defined as the association of atrial fibrillation with hypotriglyceridemia and/or hypocholesterolemia and low LDL-C levels. This is generally still difficult to understand and explain because all the metabolic conditions associated with oxidative stress and inflammation are predictors of the incidence of atrial fibrillation.[42,43]

Several theories try to explain how dyslipidemia and atrial fibrillation are related. According to the first theory, triglyceride levels will rise until age 70 and then decline, while the prevalence of atrial fibrillation will continue to grow after that age. This theory relates to the growing incidence of atrial fibrillation with age. The second explanation, which also explains why triglycerides and/or LDL-c are inversely correlated with atrial fibrillation, focuses on thyroid function. The thyroid hormone boosts cholesterol synthesis by activating a protein called 5-hydroxy-3-methylglutaryl-coenzyme A reductase, but it also causes liver catabolism of cholesterol, which lowers LDL-c levels. According to a study by Asvold et al., non-HDL cholesterol levels rose concurrently with rising TSH levels even in the normal TSH range. According to the findings of this study, a low HDL-c level will be linked to a higher incidence of atrial fibrillation as people age. A survey by Folsom et al. discovered that the LDL-c level was inversely connected to the C-reactive protein level, a risk factor for atrial fibrillation. This finding supports the third explanation, which is about inflammation.[44]

2.4. Management of Metabolic Syndrome as an Atrial Fibrillation Risk Factor

As a result, throughout the last several decades, the "downstream" therapy for AF has been avoiding thromboembolic effects and rate control, restoration, and maintenance of sinus rhythm with antiarrhythmic drugs or ablative surgeries. The primary issue is still unresolved, nevertheless, because patients will continue to build substrates for AF even after therapy and will likely have a worse outcome if the risk factors are not managed, such as metabolic syndrome. The anatomic substrate, which is "upstream" of the electrical components of AF, is presently the focus of the investigation. Potentially novel pharmacological therapies for this illness, such as using non-Antiarthmic Drugs (AADs) that modify atrial substrates or target specific processes of AF, have been developed to halt arrhythmias or their recurrence. A new focus in the treatment of AF is prevention.[45]

2.4.1 Lifestyle modification

Obesity, smoking, consuming alcohol, stress, and a lack of physical activity are all risk factors for AF. A training program with more than two metabolic equivalents acquired was connected to a 10% decrease in AF for each metabolic equivalent obtained in the LEGACY (Long-Term Effect of Goal-Directed Weight Management on an Atrial Fibrillation Cohort: A 5-Year Follow-up Study) trial, underscoring the value of cardiorespiratory fitness and training programs as potent preventative measures. However, weight fluctuation > 5% partially offsets this benefit. Treatment to prevent atrial fibrillation in metabolic syndrome was lifestyle modification, especially weight normalization, and improved physical fitness.[46,47]

2.4.2. Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers

There is increasing experimental and clinical evidence that ACEI and ARB may help prevent AF through a variety of possible mechanisms, including the prevention of LA dilatation and atrial fibrosis, regression of LV hypertrophy, reduction of inflammation and oxidative stress, modulation of sympathetic nerve activity, and direct modulation of ion-channel function, all of which may work in mechanistic synergy with membrane-acting antiarrhythmics.[48]

2.4.3. Statins

Statins, HMG CoA reductase inhibitors, might be a suitable substitute. It is unclear how these medications prevent coronary artery disease in the primary and secondary preventive stages. Although there are several ways to treat dyslipidemia, numerous studies have demonstrated that statin treatment dramatically lowers the incidence of atrial fibrillation. Statins have pleiotropic actions, such as anti-inflammatory and antioxidant properties. Statin therapy was also considered reasonable for the primary prevention of postoperative AF following coronary artery surgery. The mechanism for reducing atrial fibrillation lies in the pharmacodynamics of the statins themselves, where in addition to their lipid-lowering effect, statins are also anti-oxidants, anti-ischemia, anti-inflammatory, and anti-arrhythmic.[45]

2.4.4. Antidiabetic agents

Metformin, as an AMPK inducer, has been linked to a decreased risk of atrial fibrillation in people with type 2 diabetes because AMPK activation improves Ca2+ control and atrial cardiomyocyte contraction. Metformin treatment has been shown to reduce ROS generation in an in vitro investigation and myolysis on cardiomyocytes, making it potentially helpful in treating atrial fibrillation. Other diabetes treatments, such as thiazolidinediones (rosiglitazone, pioglitazone), function by activating PPAR, which raises the expression of GLUT4 to promote insulin sensitivity. Pioglitazone inhibited electrical and structural remodeling in atrial fibrillation-affected atria in animal experiments. Thiazolidinediones lower the risk of developing atrial fibrillation in patients with diabetes. Pioglitazone reduces the likelihood of atrial fibrillation recurring following ablation in individuals with diabetes.[20]

Resveratrol, a bioactive polyphenolic molecule, is another substance thought to hold promise for treating atrial fibrillation about metabolic syndrome. Resveratrol has an antioxidant action that protects the heart. Resveratrol has been demonstrated to activate AMPK/sirtuin1 signaling, which can modify the heart's fat metabolism. Additionally, resveratrol enhances signals in a variety of ion channels, which lowers cardiomyocytes' vulnerability to atrial fibrillation and prevents electrical, contractile, and fibrosis remodeling.[49,50]

3. Conclusion

Atrial fibrillation is pathophysiologically characterized by a complicated relationship between the electrical remodeling and the anatomical substrates in the atrium that support reentry. Hypertension, central obesity, insulin resistance, and atherogenic dyslipidemia are all part of the metabolic syndrome. In addition to obesity and insulin resistance, the primary pathophysiology of the metabolic syndrome also involves neurohormonal activation and long-term inflammation. Nearly every element of the metabolic syndrome can be a risk factor for atrial fibrillation through various pathogenic mechanisms. Atrial remodeling due to metabolic dysfunction includes structural, contractile, and electrical remodeling, also known as electrophysiological alterations. Atrial fibrillation has potential causes and substrates in metabolic syndrome. Because the mechanism by which metabolic dysfunction causes atrial fibrillation is intimately related to the management of atrial fibrillation in metabolic syndrome, The incidence of atrial fibrillation in metabolic syndrome has been demonstrated to be decreased by several preventive treatments known as upstream therapy, including ACE inhibitors/ARBs, statins, and diabetic medicines like metformin and thiazolidinediones.

4. Declarations

4.1 Ethics Approval and Consent to participate
Not applicable

4.2. Consent for publication
Not applicable.

4.3 Availibility of data and materials
Data used in our study were presented in the main text.

4.4 Competing interests
Not applicable.

4.5 Funding Source
Not applicable.

4.6 Authors contributions
Idea/concept: FHA, AR Design: FHA, AR Control/supervision: AR, MSR, AFR. Data collection/processing: FHA, AR. Analysis/interpretation: FHA, AR, MSR. Literature review: FHA, AR, AFR. Writing the article: FHA, AR Critical review: FHA, AR, MSR, AFR. All authors have critically reviewed and approved the final draft and are possible for the content and similarity index of the manuscript.

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