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The Role of Different Components of Metabolic Syndrome in the Pathogenesis of Atrial Fibrillation

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ABSTRACT

Metabolic syndrome (MetS) goes by various aliases such as dysmetabolic syndrome, syndrome X, and insulin resistance syndrome. Dysmetabolic syndromes indicate factors that pose risks for the onset of cardiovascular diseases and type 2 diabetes, making it a rapidly escalating global health concern. Atrial Fibrillation (AF) disrupts the heart's electrical system, manifesting as dysrhythmias and arrhythmias with irregular heartbeats. This condition significantly amplifies worldwide mortality and morbidity rates. The principal hazard associated with metabolic syndrome is cardiovascular disease. Notably, metabolic syndrome plays a pivotal role in the genesis of AF, as numerous studies have highlighted the fundamental connection between the two. This review underscores that the distinct components of metabolic syndrome – hypertension, diabetes, obesity, and dyslipidemia – actively participate in the pathophysiology of AF development and progression through atrial remodeling, involving both structural and electrical modifications.

KEYWORDS: Metabolic Syndrome; Atrial Fibrillation; Hypertension; Obesity; Diabetes Mellitus; Dyslipidemias.

INTRODUCTION

Metabolic Syndrome (MetS) is recognized by various names like dysmetabolic syndrome, syndrome X, and insulin resistance syndrome. Dysmetabolic syndromes denote factors that pose risks for the emergence of cardiovascular diseases and type 2 diabetes, constituting a swiftly escalating global health challenge[1]. Atrial Fibrillation (AF) is a condition that disrupts the heart's electrical system, often manifesting asdysrhythmias orarrhythmias, showcasing irregular heartbeats. This condition significantly elevates global rates of mortality and morbidity. Atrial Fibrillation diminishes functional capacity, impacts quality of life, and heightens mortality due to a combination of altered hemodynamics, progressive atrial and ventricular mechanical dysfunctions, atrioventricular dyssynchrony, and thromboembolic complications[2].

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Defining criteria for MetS and AF

Metabolic syndrome is a compilation of diverse medical conditions, requiring the presence of at least three out of five specific disorders—namely high blood sugar, elevated blood pressure, increased serum triglycerides, reduced serum high-density lipoprotein, and central obesity—to qualify as metabolic syndrome. Furthermore, the definition, identification, and criteria for metabolic syndrome have been delineated by five distinct international health organizations, including the International Diabetes Federation, World Health Organization, National Cholesterol Education Programme Adult Treatment Panel III, American Association of Clinical Endocrinologists, and the European Group for the Study of Insulin Resistance[3,4].

The detection of atrial fibrillation on an electrocardiogram involves recognizing characteristic features such as the absence of P waves. This results in the disruption of electrical activity and the emergenceof irregular RR intervals on the ECG surface. These irregularities may be attributed to the erratic conduction of impulses, which affects the ventricles[5-7].

Risk factors for MetS and AF

The principal risk factors for metabolic syndrome includehypertension, low HDL cholesterol, advanced age, cigarette smoking, elevated LDL cholesterol, and a family history of premature coronary heart disease (CHD). The underlying factors that contribute to the development of cardiovascular disease (CVD) include physical inactivity, obesity, and a diet that promotes the formation of atherosclerotic plaques[8]. Conversely, risk factors for atrial fibrillation involve aging, particularly beyond 60 years, hypertension, diabetes, heart failure, coronary artery disease, alcohol consumption, obstructive sleep apnea (OSA), obesity, hyperthyroidism, chronic renal insufficiency, and a depressed ejection fraction. Diabetes mellitus is an independent risk factor for AF, accounting for 10-25% of total risk factors in AF patients. Additionally, various cardiovascular conditions, including heart valve disease, heart failure, coronary artery disease, rheumatic heart disease, congenital heart defects, and cardiomyopathy may contribute to the development[9].

Metabolic syndrome emerges as a risk factor for AF, elevating the mortality rate by 1.5 times and increasing the incidence of cardiovascular events by 2 times[10]. The factors linking AF with metabolic syndrome include oxidative stress, inflammation, insulin resistance, high plasma volume, neurohormonal activation, atrial remodeling, alterations in ion channels, atrial structure changes, cellular hypertrophy, tissue fibrosis, fibroblast activation, disrupted calcium homeostasis, heightened sympathetic activity, increased left ventricular diastolic activity, muscle mass loss, mechanical stress, atrial enlargement, spatial remodeling of gap junctions, fibrosis, and an augmented conduction system in heart activity[11].

Another study indicates a potential association between AF and metabolic syndrome. The linking factors involvestructural changes in the left atrium and left ventricle, alterations in electrical and functional properties, impaired ventricular filling (such as diastolic dysfunction), left ventricular hypertrophy, decreased atrial conduction velocity, left atrial enlargement, inflammation, increased oxidative stress, and a potential role in atherosclerosis development[12].

Numerous studies have delved into the intricate relationship between metabolic syndrome and AF, These studies have consistently demonstrated the pivotalrole of metabolic syndrome in the progression and development of atrial fibrillation. Consequently, this review aims to elucidate the pathophysiological aspects of different metabolic syndrome components in the pathogenesis and development of atrial fibrillation (Fig. 1).To this end, a comprehensive search was conducted usingGoogle Scholar, Science Direct, and PubMed, employing a multitude of keywords, including “Metabolic Syndrome”, “Atrial Fibrillation”, “Hypertension”, “Obesity”, “Diabetes”, and “Dyslipidemia”.

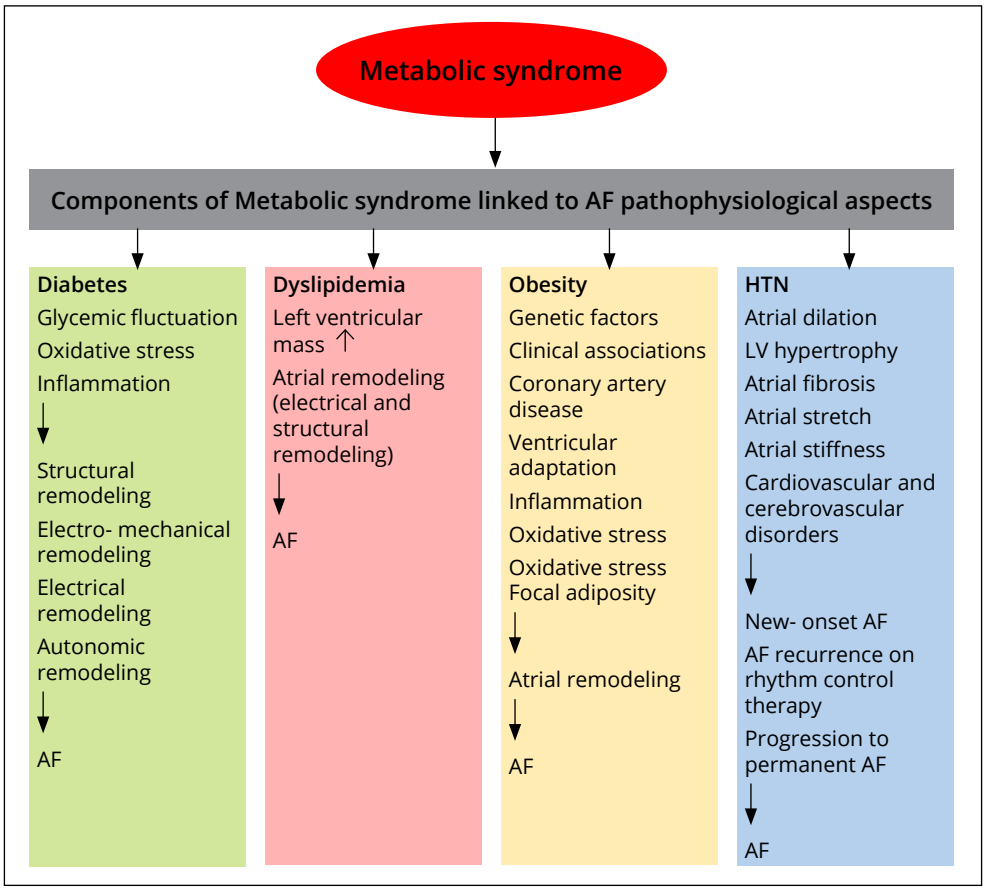

Figure 1. Pathophysiological relationship of Atrial Fibrillation with the different components, diabetes, dyslipidemia, obesity, hypertension, of metabolic syndrome
Source: Elaborated by the authors.

Dyslipidemia pathophysiological link to AF

Dyslipidemia is a condition characterized by the abnormal accumulation of lipids, such as cholesterol and fats, in the bloodstream. Lipid disorders involve elevated fasting triglyceride levels and decreased high-density lipoprotein cholesterol (HDL-C), contributing to approximately 20 to 40 percent of the risk of developing AF. Dyslipidemia is a recognized risk factor for atherosclerotic disease, stroke, coronary artery disease, and heart failure, consequently increasing the likelihood of AF development. A reduction in HDLcholesterol levels is associated with an increase in left ventricular mass, the development of heart failure, and cardiac dysfunction, which collectively serve to amplify the risk factors for AF[13]. Low plasma levels of HDL-C influence atrial fibrillation and hypertrophic cardiomyopathy. Abnormal HDL-C levels are indirectly associated with an increased risk of AF due to structural abnormalities in the atria, rather than abnormalities in lipid profiles. The inverse association between LDL-C levels and AF is attributed to the stabilizing effect of cholesterol on myocardial cell membranes, impacting ion channel density, function, and other aspects of membrane excitability[14]. Various hypotheses suggest a correlation between AF occurrence and low high-density lipoprotein cholesterol levels. It has been demonstratedthat increased left ventricular mass, heart failure development, and diastolic dysfunction are associated with low HDL-C, contributing to left atrial remodeling and the occurrence of AF[12].

The concept of metabolic maladaptation comprises three main concepts. Lipotoxicity posits that a hyperlipidemic environment leads to lipid accumulation within the heart, resulting in reactive oxygen species and apoptosis, leading to contractile dysfunction. Glucotoxicity, similar to lipotoxicity, involves chronic hyperglycemia causing reactive oxygen species formation, observed in hypertrophied hearts and hearts of patients with diabetes. Hypoglycemia, associated with elevated plasma catecholamine levels and low potassium, may unmask or enhance the effects of hypoglycemia on QT prolongation. Finally, glucolipotoxicity is the combination of these processes, possibly accelerated by hyperglycemia downregulating the

expression of fatty acid-metabolizing genes, accelerating lipid deposition and cardiac dysfunction[15]. The available evidence suggests aparallel increase in both cardiac mass and pericardial fat[16]. Triglyceride droplets, termed myocardial fat content, accumulate in cardiomyocytes, surrounded by adipose tissue layers around the heart[17,18]. Epicardial fat, an adherent layer linking the myocardium and visceral pericardium, is identified through pericardial fat, encompassing adipose tissue between the parietal and visceral pericardium, surrounding arterioles and arteries[19]. Cardiac adiposity has been demonstrated to result in higher left ventricular mass, impaired diastolic function, and suppressed septal wall thickening[20]. The higher fatty acid levels linked to the myocardial triglyceride which causes the decline in LV diastolic function[21].

Elevated fatty acid levels linked to myocardial triglycerides cause a decline in left ventricular diastolic function. Free fatty acids are produced in structural lipids and disposed of through mitochondrial oxidation, generating heat and ATP and stored as triglyceride-filled droplets. Excessive beta-oxidation of lipids results in lipid droplet accumulation, mitochondrial dysfunction, diacylglycerol (DAG), and ceramide accumulation[22]. Another study reported the accumulation of triglyceride droplets, referred to as myocardial fat content, stored within cardiomyocyte adipose tissue layers around arteries and the heart. The accumulation of these droplets has been linked to an increased risk of obesity, type 2 diabetes, and impaired glucosemetabolism, which in turn has been associated with an increase inleft ventricular mass and impaired diastolic function[23]. Myocardial degeneration, left atrial enlargement, and abnormal SA node conduction are pathogenic factors related to decreasing blood lipids and increasing age. Lipid bilayers in membranes impact the electrical stability of membrane ion channels in atrial myocytes due to abnormal lipid metabolism[24].

Obesity pathophysiological link to AF

Obesity isa risk factor for cardiovascular disease due to its association with a few conditions, including heart failure, dyslipidemia, diabetes mellitus, cardiac arrhythmias, hypertension, and coronary artery disease. In essence, obesity induces alterationsin cardiac function and structure among individuals with overweight status by promoting left and right ventricular hypertrophy while reducing peripheral resistances. Additionally, obesity has adverse effects on left atrium hypertrophy and cardiac output[25]. It is associated with a range ofcardiovascular disease pathologies, includingleft ventricular hypertrophy, obesity-related cardiomyopathy, alterations in the release of chemical mediators and adipokines, accelerated atherosclerosis, an increased prothrombotic and proinflammatory state, endothelial dysfunction, and heightened arterial stiffness. These include alterations in changes in cardiomyocyte electrical properties, fat accumulation in the myocardium, hemodynamic shifts, increased sympathetic tone with neurohormonal activation, elevated circulating catecholamines, calcification of coronary arteries, and cardiometabolic consequences[11].

The increase in abdominal mass results in reduced oxygen supply, impaired diaphragm function, an elevated number of extrasystoles, AF, sinus node arrest, and supraventricular tachyarrhythmia. These effects ultimately lead to cardiac death. Furthermore, the increasedabdominal mass also induces hypoxia, which contributes to right heart failure, pulmonary vasoconstriction, and pulmonary hypertension[26]. Adipose tissue acts as a cardiovascular disease mediator or biomarker, secreting adiponectin, an adipocytokine that enhances cardiac contractility and action potential duration, leading to left ventricular and atrial remodelling. In patients with chronic AF patients, adiponectin levels are higher than those related to collagen type 1 degradation markers, contributing to atrial structural remodeling through fibrosis and fibroblast activation[27,28].

Epicardial fat tissue modulates atrial electrophysiological and contractile properties through inflammatory cytokines, adipocytokines, and interactions between adipocytes and cardiomyocytes. In heart failure, epicardial fat has been demonstrated to exert an arrhythmogenic effect on the left atrium, prolonging action potential duration[29]. Epicardial adipose tissue is suggested to be involved in maintaining atrial fibrillation, with experiments demonstrating that epicardial adipocytes modulate atrial cardiac ionic currents, causing delayed rectifier inward and outward currents, as well as increased late sodium currents and L-type calcium currents[30].

Patients with morbid obesity have been found to exhibit high rates of sudden cardiac death (SCD) even before the onset of heart disease. The key mechanisms that leadto arrhythmia and SCD in individuals with obesity include cardiomyopathy, myocyte hypertrophy, abnormal cardiomyocyte lipid deposits, myocardial lipotoxicity induced by free

fatty acids, cardiac fibrosis, mononuclear cell infiltration, obesity-induced electrophysiological remodeling, myocardial infarction, left ventricular hypertrophy, impaired connexins, sympathetic hyperinnervation, and parasympathetic withdrawal[31]. Fatty infiltration results in the separation of myocardial bundles, disruption of their parallel orientation, and impairment of ventricular activation, ultimately leading to heterogeneous repolarization[32]. Moreover, increased intracellular lipid content can impair repolarization, reducing potassium channel protein levels, causing ventricular tachycardia, and ultimately leading to sudden cardiac death[10]. Adipocytokines derived from epicardial fat significantly contribute to delayed rectifier outward currents in cardiomyocytes, prolonged action potential duration, and facilitate triggered activity early after afterdepolarizations[28].

The risk factors for AF include, but are not limited to, conditions such as hypertension, diabetes mellitus, left ventricular hypertrophy, myocardial infarction, left ventricular diastolic dysfunction, left atrial enlargement, obstructive sleep apnea, and heart failure. These concurrent conditions demonstrate that obesity and high BMI are independent risk factors for AF. A number ofpopulation-based studies have demonstrated a correlation between high BMI and an elevated risk of AF.Five different meta-analyses have indicated that individuals with obesity are ata 49% greater risk of developing AF[33]. Lifestyle risk factors for obesity includesleep apnea, hypertension, alcohol consumption, diabetes, hyperlipidemia, and smoking. Additionally, impaired diastolic function, inflammation (CRP, IL-6, TNF-α), pericardial fat (adipokines) causing atrial stretch, atrial scar, local atrial infiltration, and paracrine effects have been proven to be reasons for atrial structural and electrical remodeling, leading to atrial fibrosis, sinus node dysfunction, conduction heterogeneity, and an increased risk, burden, persistence, and symptoms of AF[34].

Hypertension pathophysiological link to AF

Hypertension represents a notable risk factor for the onset of AF due to its higher prevalence in the population. It results in increased thickness, stiffness, and diastolic dysfunction of the left ventricles (LV). These changes in the LV contribute to the elevated left atrium (LA) pressure, augmented LA wall thickness, increased myocyte volume and fibrosis, and a decrease in LA empty fraction. These pathophysiological alterations result in left atrial enlargement and atrial cardiomyopathy, causing complex structural, contractile, and electrophysiological changes that ultimately predispose the atria to develop atrial fibrillation[35].

Hypertension has been demonstrated to induce the proliferation of cardiac fibroblasts, as well as diastolic dysfunction, and left ventricular hypertrophy. These effects lead to disruption of intra-atrial conduction velocity and leading to left atrial enlargement. The mechanical and electrical remodeling of the atria, known as atrial refractoriness, is influenced by pathways such as the activation of the renin-angiotensin-aldosterone system (RAAS). This activation leads to left ventricular hypertrophy and arterial hypertension. In the atria, stretching of atrial myocytes results in increased expression of tissue angiotensin-converting enzyme, production of angiotensin II and aldosterone, myocyte hypertrophy, apoptosis, vasoconstriction, and fibrosis, creating ideal conditions for the occurrence of AF[36].

Hypertension increases the risk of AF by twofold. Untreated or improperly treated hypertension can exacerbate left ventricular hypertrophy, increase left ventricular stiffness, reduce compliance, and compromise coronary flow reserve. From a pathophysiological standpoint, three main components—structural, electrical, and contractile remodeling—contribute to left atrial remodeling in patients with hypertension. Elevated filing pressure, in the presence of increased blood pressure, leads to left atrium dilation, inducing stretching of atrial myocytes. This scenario can result in rapid depolarization of the myocyte membrane, generating afterdepolarizations and premature supraventricular beats. AF paroxysms exhibit reduced action potential duration due to intracellular calcium changes, ultimately leading to atrial dilation and providing an ideal substrate for the development, maintenance, and persistence of AF[37-40].

A number of risk factors for hypertension contribute to the development of AF, including age, race, gender, sleep apnea, obesity, overweight, genetic predisposition, inflammation, oxidative stress, family history, and endothelial dysfunction. These factors collectively result in arterial hypertension through RAAS and sympathetic activation, left ventricular hypertrophy, diastolic dysfunction, arterial stiffness, and kidney dysfunction. Subsequently, these factors play a significant role in the

development of atrial fibrillation by causing increased atrial stretch and fibrosis, new-onset AF, AF recurrence on rhythm control therapy, and progression to permanent AF. These aspects contribute to adverse outcomes such as stroke, myocardial infarction, congestive heart failure, major bleeding, cognitive decline, and death[41].

Furthermore, diabetes represents a substantial risk factor for the development AF and other cardiovascular complications. Studies have demonstrated that diabetes increases the risk of cardiovascular diseases, including coronary artery disease and atrial fibrillation, through mechanisms such as oxidative stress, myocardial stiffness, increased nonenzymatic glycosylation, dispersion of atrial refractoriness, atrial fibrosis, and autonomic dysfunction[42]. The risk of AF is notably increased in women with diabetes, constituting a 26% higher risk than in men[43]. Hyperglycemia associated with diabetes leads to left ventricular chamber thickening, particularlyin women with obesity and severe glucose intolerance, resulting in left atrial size enlargement[44].

Another study underscored the multifaceted relationships between chronic hyperglycemia and AF. One of the identified pathways involves the activation of advanced glycation end products (AGEs), the receptor of advanced glycation end products, and the up regulation of circulating tissue growth factors (CTGF). These processes ultimately results in the structural remodeling of atrial chambers. Additionally, the Johansen study observed a higher incidence of diabetes in elderly individuals, contributing to an increased number of hospital admissions and stroke cases in the local population. The prevalence of AF is also elevated when abnormal glucose metabolism is linked to the activation of inflammation processes[45,46].

A number of risk factors associated with diabetes, including glycemic fluctuation, oxidative stress, and inflammation, contribute to structural remodeling, electro-mechanical remodeling, electrical remodeling, and autonomic remodeling. This results in increased fibrosis, an imbalance of sympathetic and parasympathetic activity, altered excitation-contraction coupling, increased atrial electromechanical delay, elevated effective refractory period dispersion, prolonged action potential duration, conduction slowing, increased dilatation, heightened expression of transforming growth factor-beta and connective tissue growth factor, and diastolic dysfunction— all contributing to the pathogenesis of atrial fibrillation[47].

CONCLUSION

In conclusion, metabolic syndrome contributes to the pathogenesis of AF through a complex interplay of factors involving hypertension, insulin resistance, dyslipidemia, obesity, inflammation, oxidative stress, and atrial remodeling. The presence of metabolic syndrome increases the likelihood developing AF and its associated complications.Regular monitoring and adjustments to the management plan may be necessary to effectively control metabolic syndrome and reduce the risk of AF.

CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest.

AUTHOR CONTRIBUTIONS

Conceptualization: Rafaqat S, Sharif S, Murad MA, Bibi F, Rafaqat S; **Methodology:** Rafaqat S, Sharif S, Murad MA, Bibi F, Rafaqat S; **Investigation:** Rafaqat S, Sharif S, Murad MA, Bibi F, Rafaqat S; **Writing – Original Draft:** Rafaqat S, Sharif S, Murad MA, Bibi F, Rafaqat S; **Writing – Review and Editing:** Rafaqat S, Sharif S, Murad MA, Bibi F, Rafaqat S; **Funding Acquisition:** Rafaqat S, Sharif S, Murad MA, Bibi F, Rafaqat S; **Resources:** Rafaqat S, Sharif S, Murad MA, Bibi F, Rafaqat S; **Supervision:** Rafaqat S, Sharif S, Murad MA, Bibi F, Rafaqat S.

DATA AVAILABILITY STATEMENT

All datasets were generated or analyzed in the current study.

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