What Do We Currently Know About Metabolic Syndrome and Atrial Fibrillation?

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ABSTRACT

Metabolic syndrome represents a cluster of atherogenic risk factors including hypertension, insulin resistance, obesity, and dyslipidemia. Considering that all of these risk factors could influence the development of atrial fibrillation, an association between atrial fibrillation and the metabolic syndrome has been suggested. Additionally, oxidative stress and inflammation have been involved in the pathogenesis of both metabolic syndrome and atrial fibrillation. The mechanisms that relate metabolic syndrome to the increased risk of atrial fibrillation occurrence are not completely understood. Metabolic syndrome and atrial fibrillation are associated with increased cardiovascular morbidity and mortality. Because atrial fibrillation is the most common arrhythmia, and along with the prevalence of metabolic syndrome constantly increasing, it would be very important to determine the relationship between these 2 entities, especially due to the fact that the risk factors of metabolic syndrome are mainly correctable. This review focused on the available evidence supporting the association between metabolic syndrome components and metabolic syndrome as a clinical entity with atrial fibrillation.

Introduction

Metabolic syndrome (MS) represents a cluster of cardiovascular (CV) and metabolic derangements (ie, increased blood pressure, abdominal obesity, insulin resistance, and dyslipidemia), which deteriorate vascular function and cause subclinical damage in a variety of organs, more than traditional risk factors individually.¹ Atrial fibrillation (AF) is certainly the most prevalent arrhythmia in everyday clinical practice, and its prevalence increases parallel to MS frequency.² Each of the MS components are related to increased risk for AF occurrence. However, the exact mechanisms of these relationships have not been studied enough. Because both of these conditions are associated with significant CV and cerebrovascular morbidity and mortality, it is important to assess the relationship between these 2 frequent conditions and to determine the mechanisms that connect them.

For the purpose of this review article, we used PubMed, Medline, OVID, and EMBASE databases and searched for the studies published from January 1990 up to March 2013 in the English language using the following keywords: "atrial fibrillation," "metabolic syndrome," "arterial hypertension," "systemic hypertension," "increased blood pressure," "obesity," "overweight," "body mass index," "diabetes," "dyslipidemia," "triglycerides," and "HDL cholesterol."

Hypertension

In the latest trials, arterial hypertension has been found in 49% to 90% of the patients with AF.³ The studies showed that hypertension increased the risk of AF almost 2-fold.⁴ In untreated or insufficiently treated patients, it could be explained by left ventricular (LV) hypertrophy, increased LV stiffness and filling pressure, reduced compliance, and coronary flow reserve.⁵ Left atrial remodeling in hypertension is based on atrial enlargement,⁶ whereas from a pathophysiological point of view, it has 3 main elements: electrical, contractile, and structural remodeling.

In the presence of increased blood pressure (BP), filling pressure increases and therefore dilates the left atrium, consequently inducing stretching of atrial myocytes that can depolarize the myocyte membrane within milliseconds and produce afterdepolarizations that induce premature supraventricular beats. In AF paroxysms, intracellular changes of calcium induce a reduction in the action potential duration. Finally, the atrium dilates and becomes an ideal substrate for the maintenance and persistence of AF.⁷ However, even in prolonged AF, electrical remodeling reverses promptly and completely once sinus rhythm is restored.

On the other hand, contractile remodeling happens quickly. The changed level of calcium usually seen in AF could be responsible for contractility loss. Impaired atrial contraction causes blood stasis, primarily affecting the left atrial appendage, and induces the formation of blood clots, which promotes thromboembolic events, particularly stroke.

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Pathological studies confirmed the existence of structural atrial remodeling that develops in a period of weeks or months and contributes to contractile dysfunction and arrhythmia.⁸ Recently a study confirmed the importance of fibrosis, gap junction remodeling, and myofibroblast proliferation in AF development.⁹

As shown in Table 1, a consistent body of evidence supports the concept that high BP is an important risk factor for AF.^{10–14} The Framingham Heart Study revealed that levels of systolic BP and duration of hypertension are predictors of left atrial remodeling,¹⁰ whereas other studies showed that wide pulse pressure is associated with increased incidence of AF.^{11,12} Conen et al, in a large cohort of 34 221 initially healthy women, revealed that systolic BP is a better predictor than diastolic BP for incident AF.¹³ Furthermore, Grundvold et al found that even upper normal BP values are long-term predictors of incident AF in initially healthy middle-aged men.¹⁴ Finally, Webb and Rothwell, in a systematic review that included 125 878 treated hypertensive patients, did not find any association between the effects on BP variability and AF.¹⁵

Activation of the renin-angiotensin-aldosterone system (RAAS) plays a key role in arterial hypertension and left ventricular hypertrophy and represents an important pathway leading to AF. Stretching of atrial myocardiocytes causes an increase in the expression of the tissue angiotensin-converting enzyme in the atria and consequently increases production of angiotensin II and aldosterone,¹⁶ which furthermore promotes myocyte hypertrophy, fibrosis, apoptosis, and vasoconstriction, ideal substrates for AF occurrence.

The sympathetic nervous system is also very important in the pathophysiology of AF in 2 ways. First, a mutual interaction between the RAAS and the sympathetic nervous system,¹⁷ and second, atrial electrophysiological properties, could be changed by autonomic tone influence.

Diabetes Mellitus and Glucose Intolerance

Large studies have shown that diabetes mellitus, poor glycemic control, and the HbA1c level are independently associated with a new onset of AF (Table 1).^{4,18–22} However, not all studies agree on the impact of diabetes or insulin resistance on AF occurrence.^{23,24} Some investigations revealed that diabetes is a significant risk factor only in women but not in men.²⁵ However, there are several hypotheses about the relationships between insulin resistance and the increased risk of AF.

First, diabetes is associated with atrial dilatation²⁶ as well as with elevated C-reactive protein level, which is a marker of chronic inflammation, consequently increasing the risk of AF.²⁷ High levels of C-reactive protein could induce myocardial fibrosis and diastolic dysfunction, whereas dilated atria could promote reentry of electrical impulses, which are the cornerstones of AF. Second, electrical remodeling of the atria, which may contribute to AF, is also present in diabetes. This involves parasympathetic denervation and heterogeneous sympathetic denervation.²⁸ An abnormal sympathetic tone in diabetes is associated with changes in cardiac and vascular structure and/or function that causes left ventricular hypertrophy, cardiac dysfunction, and autonomic neuropathy.²⁹ The third

possibility that connects diabetes and arrhythmia is fluctuation of the glucose level. Namely, hypoglycemia and variation in metabolic control, rather than chronic hyperglycemia, provoke AF in patients with insulin-dependent diabetes mellitus.³⁰ Huxley et al, in a large cohort of 13 025 participants, did not find any correlation between markers of glucose homeostasis (fasting glucose and insulin levels, HbA1c) and AF onset in subjects without diabetes or with prediabetes, which suggests that the severity of diabetes and long-term cumulative exposure to hyperglycemia could induce AF, and not hyperglycemia itself.²¹

An additional mechanism of AF origin and AF-related ventricular remodeling in diabetes could be oxidative stress, which is associated with microvascular flow abnormalities and occurs before or immediately after new-onset AF.³¹ Clinical conditions that could connect diabetes and AF are heart failure and coronary artery disease, which are well-known predictors of AF.¹⁸ Finally, the studies showed that patients with diabetes, even after adjustments for body mass index (BMI), had a higher prevalence of obstructive sleep apnea, which also may induce AF.³²

Obesity and Waist Circumference

A true mechanism that induces AF in obesity is still unknown because pathophysiological studies are missing. The studies found that a higher BMI is associated with the risk of AF recurrence in both sexes (Table 2).^{33–38}

Most of the published studies correlated BMI with AF occurrence because of unavailability of data on waist circumference.^{34–39} However, investigations that studied the impact of MS on AF incidence revealed a significant relationship between waist circumference and AF in both genders.^{40,41} Verdecchia et al reported that, besides BMI, hip circumference is also associated with AF occurrence.¹²

There are several proposed mechanisms that connect obesity and AF. Enlargement of the left atrium in obesity is a consequence of elevated plasma volume, increased preload and LV diastolic filling pressure, and represents 1 of the most studied precursors of AF due to structural and electrical remodeling of the left atrium. Previous studies showed that BMI is certainly 1 of the most important markers of atrial size and volume.^{34,42} In addition, the investigators revealed that each 1-unit increase in BMI is associated with a 7% greater risk of permanent AF, a 4% greater risk of intermittent AF, and a 1% greater risk of transitory AF.³² However, even after the adjustment for left atrial size, BMI still remained significantly associated with AF progression to permanent.³⁹ In a recently published study, Munger et al showed that the shortened effective refractory period in the left atrium and pulmonary veins are potential factors that facilitate and perpetuate AF in obese patients.⁴³

Enhanced neurohormonal activation accompanies obesity and may contribute to left atrial enlargement and electrical instability, which may result in AF development.⁴⁴ Changes in circulating RAAS have been reported in MS patients with visceral obesity. The levels of plasma renin activity and/or aldosterone, produced by human adipocytes, are at the upper limit or even elevated.⁴⁵ Leptin, adiponectin, and other adipokines are independently associated with

Table 1. The Impact of Hypertension, Diabetes, and Glucose Intolerance on AF Occurrence

Reference	Sample Size and Subjects Included in the Study	Main Findings
Hypertension		
Mitchell et al ¹⁰	5331 Framingham Heart Study participants ≥35 years, initially free from AF	Systolic and pulse pressure were important risk factors for AF occurrence.
Larstorp et al ¹¹	8810 patients with hypertension and electrocardiographic left ventricular hypertrophy	Systolic, diastolic, and pulse BP were predictors of new-onset AF.
Conen et al ¹³	34 221 women participating in the Women's Health Study	Systolic BP was a better predictor than diastolic BP for incident AF.
Verdecchia et al ¹²	30 424 patients with vascular disease or complicated diabetes who were in sinus rhythm at entry	Systolic BP and pulse pressure, left ventricular hypertrophy, and history of hypertension were predictors of AF.
Grunvold et al ¹⁴	2014 healthy men	Upper normal systolic BP was predictor of new AF.
Webb et al ¹⁵	125 878 treated hypertensive patients	Variability in BP is unrelated to risk of new-onset AF.
Diabetes mellitus and glucose intolerance		
Movahed et al ¹⁸	293 124 patients with type 2 diabetes mellitus and 552 624 nonmatched controls without diabetes but with hypertension	Diabetes is a strong independent risk factor for the occurrence of AF and atrial flutter.
Dublin et al ¹⁹	1410 subjects with newly diagnosed AF and 2203 controls	Diabetes was associated with higher risk of AF development, and risk was higher with longer duration of treated diabetes and worse glycemic control.
Huxley et al ²⁰	1 686 097 subjects with 108 703 cases of AF	Diabetes was associated with an increased risk of subsequent AF.
Huxley et al ²¹	13 025 participants were categorized as having no diabetes, prediabetes, or diabetes	Diabetes, HbA1c level, and poor glycemic control were independently associated with an increased risk of AF.
Iguchi et al ²²	52 448 elderly (median age 72 years)	The level of HbA1c, especially in patients with HbA1c >6.5%, was associated with AF occurrence.
Benjamin et al ⁴	2090 men and 2641 women, free of a history of atrial fibrillation	Diabetes was an independent determinant of AF in both sexes.
Fontes et al ²³	3023 participants without baseline AF (Framingham Offspring fifth and seventh examination cycles)	No significant association was found between insulin resistance and incident AF.
Ruigomez et al ²⁴	1035 confirmed incident cases of chronic AF and 5,000 controls	No difference in diabetes prevalence between patients with AF and control group.
Nichols et al ²⁵	17 372 patients with diabetes	Diabetes was an independent determinant of AF-only among women.
Abbreviations: AF, atrial fibrillation; BP, blood pressure.		

diabetes, obesity, inflammation, and heart failure, risk factors for the AF occurrence.⁴⁶ Obesity and MS can increase inflammation, oxidative stress, lipoapoptosis, and myocardial fibrosis, which facilitate the development of AF.²⁷

Obesity, especially when associated with MS, is also associated with increased activity of the sympathetic

nervous system,⁴⁷ which is a very important factor for inducing renin secretion. Obstructive sleep apnea and other sleep disorders (central sleep apnea/Cheyne-Stokes respiration) often seen in obese people are associated with increased risk of AF onset, as well as permanent AF, even after the adjustments for BMI.⁴⁸ There are several possible reasons: hypoxemia, increased sympathetic activation and

Table 2. The Impact of Obesity, Waist Circumference, and Dyslipidemia on AF Occurrence

Reference	Sample Size and Subjects Included in the Study	Main Findings
Obesity and waist circumference		
Verdecchia et al ¹²	30 424 patients with vascular disease or complicated diabetes who were in sinus rhythm at entry	BMI and hip circumference were independent predictors of AF occurrence.
Gami et al ³²	3542 adults without past or current AF	Obesity and obstructive sleep apnea were independent predictors of incident AF.
Wanahita et al ³³	123 249 individuals (78 602 subjects from general population and 44 647 patients who underwent cardiac surgery)	BMI and obesity were associated with increased risk of developing AF.
Wang et al ³⁴	5282 participants without baseline AF	Obesity was associated with AF occurrence. After adjustment for left atrial diameter, BMI was no longer associated with AF risk.
Guglin et al ³⁵	2518 patients with recurrent AF	Increased BMI was associated with a higher likelihood of recurrent AF and higher number of cardioversions.
Frost et al ³⁶	47 589 participants without preexisting cardiovascular or endocrine disease	Overweight and obesity are associated with an increased risk of a diagnosis of AF or flutter.
Murphy et al ⁴⁷	15 402 individuals age 45–64, from general population	BMI >30 kg/m ² was associated with increased risk of AF.
Wilhelmsen et al ³⁸	7495 men age 47–55 years from general population	BMI >30 kg/m ² and hypertension were associated with AF occurrence.
Tsang et al ³⁹	3248 patients from general population who developed paroxysmal AF (mean age 71 ± 15 years)	BMI was associated with progression from paroxysmal to permanent AF, independently of left atrial volume.
Tanner et al ⁴⁰	23 650 African American and white US adults >45 years of age	Waist circumference was associated with AF occurrence.
Chamberlain et al ⁴¹	15 094 adults age 45–64 years from the general population	Increased waist circumference was associated with AF occurrence in both sexes.
Dyslipidemia		
Watanabe et al ⁴⁹	28 449 Japanese ≥20 years of age without baseline AF	Low HDL-C was risk factor for AF.
Watanabe et al ⁵⁰	28 449 Japanese ≥20 years of age without baseline AF	Low HDL-C was associated with the development of AF in women but not in men. Neither triglycerides nor lipid ratios were associated with AF.
Haywood et al ⁵¹	423 patients with AF	HDL-C <35 mg/dl was associated with AF.
Psaty et al ⁵⁸	5201 adults ≥65 years old	High cholesterol level was associated with a reduced risk of AF.
Annoura et al ⁵²	197 patients referred due to arrhythmia	Low serum levels of triglycerides and total cholesterol, as well as reduced HDL-C level, were associated with paroxysmal AF.
Lopez et al ⁵⁷	13 969 participants from general population without baseline AF	Higher levels of LDL-C and total cholesterol were associated with a lower incidence of AF. HDL-C and triglycerides levels were not independently associated with AF incidence.

Table 2. continued

Reference	Sample Size and Subjects Included in the Study	Main Findings
Diaz-Peromingo et al ⁵⁹	202 subjects (101 patients with and 101 without AF matched by sex and age)	Total cholesterol, LDL-C, HDL-C, triglycerides, Lp(a), and the LDL/HDL and CHOL/LDL indexes were not associated with AF.
Tanner et al ⁴⁰	23 650 African American and white US adults >45 years of age	Low HDL-C level was associated with AF occurrence.
Chamberlain et al ⁴¹	15 094 adults age 45–64 years from general population	Low HDL-C level was associated with AF occurrence.
Abbreviations: AF, atrial fibrillation; BMI, body mass index; CHOL, cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; Lp, lipoprotein.		

afterload, pulmonary vasoconstriction, as well as inefficient respiratory excursions that modify the transmural pressure and volume relations and consequently induce AF.⁴⁸

Dyslipidemia

The relationship between dyslipidemia and AF is controversial. Almost all investigators agree that low high-density lipoprotein cholesterol (HDL-C) level correlates with AF occurrence (Table 2).^{40,41,49–52} There are several hypotheses that could explain this relationship. First, the low HDL-C level is associated with increased left ventricular mass, diastolic dysfunction, and heart failure development,^{53,54} possible causes of left atrium remodeling and AF occurrence. Second, inflammation and oxidative stress are at the same time related to dyslipidemia and AF onset.³¹ Researchers showed that the use of statin therapy and anti-inflammatory drugs decreased the risk of AF development,⁵⁵ whereas Watanabe et al disagreed.⁵⁶ Only Lopez et al did not confirm this relationship between low HDL level and AF occurrence.⁵⁷

The situation with other lipid fractions is more complicated. Some authors showed an inverse relationship between total cholesterol level and AF prevalence,^{52,58} others found an inverse relationship between the low-density cholesterol (LDL-C) level and AF,⁵⁰ whereas Diaz-Peromingo et al showed no association between lipoprotein (a) and AF.⁵⁹ Furthermore, Watanabe et al and Lopez et al revealed no relationship between triglyceride level and AF occurrence,^{50,57} whereas Annoura et al found lower triglycerides in patients with AF.⁵²

These controversial results are called the “dyslipidemia paradox,” which means that AF is associated with hypotriglyceridemia and/or hypocholesterolemia⁵² and even a lower level of LDL-C.⁵⁰ This is difficult to understand and explain because all of these metabolic conditions are related to oxidative stress and inflammation, which are the predictors of AF development.⁶⁰ However, there are several theories that could explain these findings. Namely, triglyceride level increases until the age of 70 years, and after this period of its lifespan, the triglyceride level decreases, whereas the prevalence of AF continuously increases with age.⁶¹ The second theory involves thyroid function, which could also explain the inverse relationship between triglycerides and/or LDL-C level and AF. On 1 hand, thyroid hormones stimulate the synthesis of cholesterol by inducing

5-hydroxy-3-methylglutaryl-coenzyme A reductase, and on the other hand they also induce the hepatic catabolism of cholesterol and decrease the LDL-C level. Asvold et al showed that non-HDL-C level increases in parallel with thyroid-stimulating hormone (TSH) level, even in the normal range of TSH.⁶² Considering the results of this study, which found that TSH level decreases in an age-dependent manner, we could easily understand the lower non-HDL-C level and higher incidence of AF in the elderly.⁶³ The third possibility that could provide an explanation for the “lipid paradox” is inflammation. Folsom et al found that the LDL-C level was inversely associated with the C-reactive protein level,⁶⁴ a well-known risk factor for AF.

Metabolic Syndrome

There are several definitions of MS, but the key features are abdominal obesity, elevated blood pressure, dyslipidemia (high triglycerides and low HDL-C), and glucose intolerance. In everyday clinical practice, as well as in clinical research, the most widely accepted definitions are those that have been proposed by the National Cholesterol Education Program–Third Adult Treatment Panel (NCEP ATP III),⁶⁵ the American Heart Association (AHA)/National Heart, Lung, and Blood Institute (NHLBI),⁶⁶ and the International Diabetes Federation (IDF).⁶⁷

The NCEP ATP III defined MS by the presence of 3 or more criteria⁶⁵: abdominal obesity (waist circumference ≥ 102 cm in men and ≥ 88 cm in women), increased fasting triglycerides (≥ 1.7 mmol/L), decreased HDL-C (< 1.0 mmol/L in men and < 1.3 mmol/L in women), high blood pressure ($\geq 130/85$ mm Hg), and the increased level of fasting glucose (≥ 6.1 mmol/L). The AHA-NHLBI definition⁶⁶ maintained the NCEP ATP III criteria,⁶⁵ except for minor changes. The cutoff value for impaired fasting glucose was reduced from 6.1 mmol/L to 5.6 mmol/L, and waist circumferences were decreased for Asians.⁶⁶ The IDF defined MS as the presence of central obesity, adjusted for different races, plus 2 other metabolic risk factors.⁶⁷ This definition favors abdominal obesity as the essential risk factor for the diagnosis of MS, unlike other definitions that consider each factor equally.

The vast majority of epidemiological and observational studies conducted in general population samples have shown that subjects with MS have a greater likelihood of AF than their non-MS counterparts (Table 3).^{40,41,49,68–78}

Table 3. The Impact of Metabolic Syndrome on AF Occurrence

Reference	Sample Size and Subjects Included in the Study	Main Findings
Metabolic syndrome		
Tanner et al ⁴⁰	23 650 African American and white US adults >45 years of age	MS is associated with an increased prevalence of AF. Each MS component except serum triglycerides was significantly associated with AF.
Chamberlain et al ⁴¹	15 094 adults age 45–64 years from general population	MS and most of its components (except triglycerides level) were associated with a higher risk of AF in both blacks and whites.
Watanabe et al ⁵⁰	28 449 Japanese patients ≥20 years of age without baseline AF	MS was associated with higher AF occurrence.
Liu et al ⁵⁸	972 hypertensive patients without left ventricular hypertrophy	MS, hypertension duration, age, and left atrial diameter correlated with AF occurrence.
Umetani et al ⁶⁹	592 consecutive hospitalized patients without obvious structural heart diseases	MS was highly associated with AF/atrial flutter in patients without structural heart diseases.
Altieri et al ⁷⁰	173 patients with MS and 600 patients with diabetes without MS	MS in this subgroup of Hispanics showed a higher incidence of AF in MS group of patients.
Nicolaou et al ⁷¹	60 patients with AF (26 with MS and 34 without MS)	MS influenced paroxysmal AF occurrence; left atrial size in MS group was increased.
Tang et al ⁷²	741 patients with AF in the absence of structural heart disease	The prevalence of MS in patients with AF in the absence of structural heart disease was high. Correlation analyses were not done.
Vyssoulis et al ⁷³	15,075 consecutive nondiabetic patients with essential hypertension	MS is directly and independently related to the AF prevalence in nondiabetic patients with essential hypertension.
Hu et al ⁷⁴	3775 hypertensive patients age 55–80 years	MS does not increase the risk for AF in elderly hypertensive patients. Aging, heart failure, and LV hypertrophy played more important roles.
Tang et al ⁷⁵	654 consecutive AF patients who underwent pulmonary vein ablation	MS is an independent predictor of AF recurrence.
Chang et al ⁷⁶	282 patients with AF who underwent catheter ablation	MS is associated with larger left atrial size and the risk for AF recurrence after the ablation of AF.
Mohanty et al ⁷⁷	1496 consecutive patients with AF undergoing first catheter ablation	MS, independently of its components, predicted higher recurrence after ablation in patients with nonparoxysmal AF.
Cai et al ⁷⁸	186 patients with paroxysmal and nonparoxysmal AF	Overweight/obesity and MS, independently of diabetes and hypertension, were predictors of late recurrence of AF.
Abbreviations: AF, atrial fibrillation; LV, left ventricular; MS, metabolic syndrome.		

Despite this relatively large body of evidence, mechanisms of this relationship still remain in the domain of hypothesis.

Vyssoulis et al, in a population of 15 075 hypertensive patients, found that MS is an independent risk for AF, even after the adjustment for traditional risk factors for AF

development.⁷³ They also found that the increasing number of MS components is associated with a progressive increase in the risk of the AF occurrence. Similar results were found in the Reasons for Geographic and Racial Differences in Stroke (REGARDS) study, which included 23 650

participants,⁴⁰ and in the Niigata Preventive Medicine study, which included 28 449 participants.⁴⁹ The Atherosclerosis Risk in Communities (ARIC) study, which was a prospective research study with a 15-year follow-up period that involved 15 094 subjects, revealed higher cumulative probabilities of incident AF with greater numbers of MS components, with a cumulative risk of 5.1% among those with 0 components and 20.4% among those with all 5 criteria.⁴¹ The AF occurrence in these studies gradually and proportionally increased from subjects with no MS risk factors to patients who fulfilled all 5 MS criteria.^{40,41,49} Interestingly, Tang et al found that AF was the most prevalent among subjects, with 2 and 3 MS criteria. The prevalence of paroxysmal AF was 9.4%, 19.4%, 26.7%, 26.7%, 12.6%, and 5.3% from 0 to 5 MS components, respectively.⁷²

The relative impact of each component of MS on AF occurrence was also studied previously. The REGARDS study showed that increased BP, decreased HDL-C level, and increased fasting glucose level had a similar relative risk for AF development (odds ratio [OR]: 1.21, 1.17, and 1.17, respectively), whereas abdominal obesity was associated with a slightly lower risk (OR: 1.14).⁴⁰ From the individual MS parameters in the ARIC study, elevated BP was associated with the highest relative risk of AF occurrence (hazard ratio [HR]: 1.95); abdominal obesity had a somewhat lower relative risk (HR: 1.40), whereas decreased HDL-C and increased fasting glucose levels were related with similar risks (HR: 1.20 and 1.16, respectively).⁴¹ Among the components of MS, according to the Niigata Preventive Medicine study, increased BP and abdominal obesity contributed the most to the increased risk of new-onset AF (HR: 1.69 and 1.64, respectively), whereas decreased HDL-C level and hyperglycemia contributed less (HR: 1.52 and 1.44, respectively).⁴⁹ In all 3 studies hypertriglyceridemia was not an independent predictor of AF development. The hazard ratios for AF developing increased across a number of the fulfilled MS components.^{40,41,49}

MS was also found to be an independent predictor of AF recurrence after catheter ablation.^{75,76} However, Mohanty et al, in their prospective study that included 1496 consecutive patients with AF who underwent their first ablation, for the first time showed that MS, but not its individual components, was associated with AF recurrence.⁷⁷ Additionally, Cai et al recently found that overweight/obesity and MS, independent of diabetes and hypertension, were associated with late AF recurrence after ablation.⁷⁸ The authors did not consider the influence of dyslipidemia on AF recurrence. These studies, unlike previous investigations, showed that the coexistence of the different MS components, and possibly their interaction, has more than an additive impact on the risk of AF development.

The possible explanations for the AF occurrence in MS are structural, functional, and electrical changes of the left atrium and the left ventricle: left ventricular hypertrophy, impaired ventricular filling (diastolic dysfunction), left atrial enlargement, and decreasing of atrial conduction velocity. We had previously shown that patients with MS have increased left ventricular mass, higher prevalence of left ventricular diastolic dysfunction, and a dilated left atrium that could possibly explain the higher prevalence of AF in this population of patients.^{79,80} However, Tang et al found

a high prevalence of MS in patients who were referred for AF catheter ablation and in the absence of structural heart disease.⁷²

The other possible mechanism that connects MS and AF is inflammation and increased oxidative stress in MS.²⁷ Considering that inflammation and oxidative stress could induce atrial remodeling,²⁷ it is reasonable to assume that these processes might also facilitate the development of AF in the context of MS. On the other hand, the same mechanism could facilitate the atherosclerosis development at the same time, which also provokes structural and electrical remodeling of the heart.⁴⁹

Therapeutic Strategies for Patients With MS and AF

Dyslipidemia in MS could be treated in several ways. Studies have shown that statins significantly reduced the risk of AF.^{81,82} The possible explanation could lie in the fact that these drugs, besides a lipid-lowering effect, also have an antioxidant, anti-ischemic, anti-inflammatory, and antiarrhythmic effect. The usage of polyunsaturated fatty acids (n-3 PUFAs) at the beginning seemed promising because they could stabilize the myocyte membrane and reduce inflammation. However, a recent meta-analysis, which included 4677 patients, revealed disappointing results considering n-3 PUFAs agents in AF prevention.⁸³

Lifestyle modification, particularly normalization of body weight, and physical fitness improvement is also a very important part in the therapeutic strategy of patients with coexisting AF and MS. Grundvold et al revealed that the overall risk of AF is significantly reduced in fit men, whereas weight gain of ≥ 10 kg from age 25 to midlife were long-term predictors of incident AF in men with lower physical fitness.⁸⁴

Considering the fact that MS is characterized by hypercoagulability,⁸⁵ we should be aware that those patients are at greater risk for cardio and cerebrovascular events,⁸⁶ especially in a hypertensive and diabetic subpopulation, which makes up a significant percentage of MS subjects. This further implicates the need for oral anticoagulant therapy prescriptions due to high CHA2DS2-VASc score.⁸⁷

Conclusion

MS and AF are common disorders, and their prevalence is constantly increasing with the growth of the elderly population and changing lifestyle. Because many MS components are also risk factors for the development of AF, an association between these 2 disorders has been proposed. Proposed mechanisms that could explain the relationship between MS and AF are: high blood pressure, activation of the RAAS, oxidative stress, low-grade inflammation, and left atrial as well as ventricular remodeling. Prevention and treatment of hypertension, obesity, and metabolic disorders may have an important role in reducing the burden of AF and related CV complications in the general population. This strategy should be based on healthy lifestyle measures including regular physical activity, weight loss, dietary changes, and appropriate pharmacologic interventions. The use of antihypertensive agents modulating the RAAS should be preferred as initial therapy in the MS setting, as well as therapy with statins.

Lifestyle changes and improvement of physical fitness also should be recommended to these patients. Finally, due to the increased prevalence of cardiac structural and functional alterations predisposing to arrhythmias, a comprehensive diagnostic evaluation encompassing an echocardiographic examination would be useful to stratify the risk for AF development in patients with MS.

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