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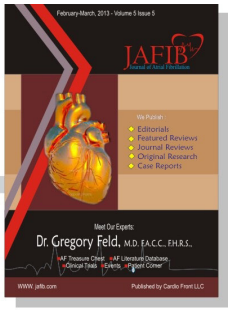

Impact of Metabolic Syndrome on Ablation-Outcome in Patients with Atrial Fibrillation: A Systematic Review

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Abstract

Metabolic syndrome (MS), a pro-inflammatory state with hypertension, diabetes, dyslipidemia and obesity is presumed to be a close associate of atrial fibrillation (AF). However, the exact mechanism by which MS facilitates perpetuation of AF is yet to be fully understood. Moreover, the impact of the components of MS as well as MS as a group, on ablation-outcome in AF is not clearly elucidated until now. This review has compiled the results from major studies that have looked into those risk factors and defined their significance in influencing ablation-outcome in AF. It has also overviewed the impact of life-style changes that might improve the success rate of AF-ablation by effectively addressing the different constituents of MS.

Introduction

Catheter ablation has evolved in recent years as one of the major therapeutic options for atrial fibrillation (AF), the commonest cardiac arrhythmia in clinical practice around the globe. Several ablation strategies are currently available, each with its merits and limitations, the later being primarily attributed to the complex pathophysiology of this multi-factorial disorder. Although AF itself is not a life-threatening condition, it greatly increases the risk of stroke, heart failure and all-cause mortality.[1] Additionally, it seriously impairs quality of life (QoL). Therefore, restoration and maintenance of sinus rhythm, prevention of thromboembolic complications and improvement in QoL are the three main long-term outcome-measures of AF ablation. A number of factors influence ablation-outcome; one of those is metabolic syndrome (MS), a pro-inflammatory condition with a conglomeration of risk factors such as obesity, dyslipidemia, glucose intolerance, and hypertension.

Various organizations including World Health Organization (WHO) and Adult Treatment panel III (ATP III) have defined MS differently because of a lack of consensus on which components are

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fundamentally essential for the diagnosis. WHO defines insulin-resistance as a required component for diagnosis of MS, although ATP III differs in considering it as a prerequisite for diagnosis.[2] All of the definitions nonetheless include the four major measures, e.g. hypertension, elevated glucose level, obesity and dyslipidemia, to characterize MS.

Recent studies have not only documented a close association between MS and AF, but also have demonstrated MS to be an independent predictor of AF recurrence after catheter ablation.[3, 4]

This review examines major evidences on the correlation of different components of MS and MS as a composite model with long-term outcome in AF ablation. Additionally, it also overviews the impact of life-style changes that might improve the success rate of AF-ablation by effectively addressing different risk-factors of MS.

Association of Different Components of MS with AF

Diabetes and Glycemic Derangement

Diabetes and AF often coexist. Inflammation and oxidative stress are implicated in both of these conditions, which indicate a causal link between the two.

Results from previous studies are contradictory in

Table 1 | **Studies Evaluating Association of Diabetes with Atrial Fibrillation**

First Author	Year Published	Study Design	Sample Size	Conclusion
Benjamin (5)	1994	Cohort study (Framingham Heart Study)	4731	Significant association of diabetes with risk for AF in both sexes (OR, 1.4 for men and 1.6 for women)
Ostgren (10)	2004	Cross-sectional observational study	No DM=597 DM=318	Age and sex-adjusted OR for AF were 3.3 (95% CI 1.6–6.7) in combined hypertension and DM and 2.0 (0.9–4.7) in DM only.
Movahed (7)	2004	Case-control	No DM= 552,624 DM= 293,124	Diabetes independently associated with AF with an OR of 2.13, (95% CI: 2.10 to 2.16; p <0.0001) and flutter (OR 2.20, CI: 2.15 to 2.26; p <0.0001)
Aksnes (9)	2008	Prospective, randomized clinical trial (VALUE)	No DM=7874 New-onset DM=1252 DM at baseline=4634	Patients with new-onset DM had a significantly higher event rate of new-onset AF with a hazard ratio of 1.49 (1.14 to 1.94, p _ 0.0031) and more persistent AF (hazard ratio 1.87, 1.28 to 2.74, p _ 0.0014) compared with patients without DM
Nichols (6)	2009	Observational-cohort	No DM=7159 DM= 10,213	Diabetics without AF at baseline developed AF at a rate of 9.1 per 1000 person-years (95% CI 8.6-9.7) compared with a rate of 6.6 (95% CI 6.2-7.1) among non-diabetic patients
Dublin (8)	2010	Case-control	No AF= 2,203 AF= 1,410	Adjusted OR for AF was 1.40 (95% CI 1.15-1.71) for people with treated diabetes compared to those without diabetes. Among those with treated diabetes, the risk of developing AF was 3% higher for each additional year of diabetes duration (95% CI 1-6%)
Ruigomez (13)	2005	Observational	PAF=525	No major association between DM and PAF (OR 0.9, 95% CI 0.6–1.4)
Smith (14)	2010	Prospective cohort study	30,447	DM was not significantly associated with AF in either men(HR 1.1, 95% CI = 0.84–1.59) or women (1.4, 95% CI = 0.95–2.05)
Fontes (11)	2012	Cohort study (Framingham Heart Study)	3023	Insulin resistance was not significantly associated with incident AF (hazard ratio comparing top quartile to other 3 quartiles of homeostatic model assessment index 1.18, 95% confidence interval 0.84 to 1.65, p= 0.34).

depicting a clear association between diabetes or elevated blood glucose and AF Many demonstrated a definite relation between the two,[5-10] while others did not find any[11-16] (Table 1).

Although the pathophysiologic link between diabetes and AF is yet to be clearly elucidated, studies that demonstrated an association credited it to inflammation promoting myocardial fibrosis and diastolic dysfunction, left atrial enlargement leading to development and propagation of re-entrant circuits, coronary microvascular disease with ischemia, metabolic stress, cardiac autonomic neuropathy, cardiomyopathy, and many systemic infections associated with diabetes that cause electrolyte abnormalities leading to irritability of the myocardium and triggering of AF.[6,7,8,9]

Studies that did not detect any significant link between AF and diabetes speculated the following explanations; 1) younger age of the study population with modest prevalence of cardiovascular risk factors, 2) components of MS might be needing to act in concert rather than diabetes alone to predispose to AF, 3) the association of diabetes with AF being not independent of the effect of obesity, ischemic heart disease, hypertension and congestive heart failure and 4) lower prevalence of diabetes in the study population.[11, 15, 16]

In addition to its association with AF incidence, diabetes is a well-known independent predictor of stroke in AF patients.[17-19] It is a prothrombotic state that favors left atrial thrombus formation.[19] It not only increases the prevalence of stroke in AF patients, but also heightens the risk of fatal strokes in patients with diabetes than those without.[18] There are indications that in diabetics there may be hypercoagulability of blood, decreased fibrinolytic activity and altered platelet function that might contribute toward thrombi formation. Additionally, diabetic cardiomyopathy might lead to cardiac dysfunction resulting in stasis of blood and thrombus formation.[18]

Inconsistent findings have been reported by earlier studies regarding the relationship between diabetes and patient-reported QoL.[20] Some correlational research have demonstrated worse life quality in diabetics and positive improvement in QoL with better glycemic control, whereas others did not find any association.[20,21,22] Forleo et al, in a pilot randomized study have shown catheter ablation of AF in comparison with anti-arrhythmic drugs, to be associated with better improvement in QoL among diabetics (42% in AAD group vs. 80% in catheter ablation group off AAD, remained arrhythmia free at 1-year follow up; p=0.001).[23]

Given the rising prevalence of diabetes and emerging evidence on its potential role in development of AF, larger prospective randomized studies are required to establish the causal link between both. As it is a treatable and controllable morbidity, its effective management would plausibly not only curtail the incidence of AF but also reduce the risk of AF-related strokes, improve QoL and enhance the success rate of catheter ablation in AF.

Hypertension

Hypertension with consequent left ventricular hypertrophy and atrial remodeling is known to be associated with increased incidence of AF.[24, 25, 26] To make matter worse, AF combined with hypertension increases the risk of stroke almost 8-fold .[26]

Framingham Heart study reported hypertension to be an independent predictor of AF (OR, 1.5 for men and 1.4 for women),[5] which was supported by few other studies published later.[27]

Wokhlu et al identified hypertension to be a univariate predictor of ablation efficacy in AF, but the same was not observed in a multivariate model.[28] We did not detect significant association between hypertension and arrhythmia-recurrence after catheter ablation, in a large prospective study.[22] Plausibly, hypertension does not act alone in AF, but in alliance with other risk factors such as obesity and diabetes etc.

In a recently published study conducted by Pokushalov et al, blood pressure control via renal artery denervation added to PVI in patients with drug-resistant AF and hypertension, was reported to have a positive impact on AF recurrence. At 1-year follow-up, 69% of PVI plus renal artery ablation group were AF-free whereas in PVI-only group 29% were arrhythmia-free off AAD (p= 0.033). They reasonably provided two explanations to be potentially responsible for this observation; 1) optimized blood pressure control in drug-resistant hypertension might have a substantial

role at the substrate level of the atria in preventing AF recurrence, 2) ablation of afferent renal nervous input decreases central sympathetic output , which might attenuate autonomic triggers of AF in addition to improved blood pressure control and offer the potential for an antiarrhythmic effect superior to medications.[29]

A deeper look at the association of hypertension and AF reveals another angle. In two recently published articles, Sanders et al and Ramirez et al have concluded that restoration of normal sinus rhythm after successful catheter ablation improves blood pressure control in AF patients.[24, 27] There are few assumptions that explain the possible mechanism behind blood pressure reduction with restoration of sinus rhythm; 1) irregular ventricular response in AF results in increased sympathetic activity that promotes hypertension, 2) AF is known to be associated with activation of rennin-angiotensin-aldosterone axis, 3) endothelial dysfunction and impaired endothelial-dependent vasodilatation are recognized associates of AF and 4) decreased bio-availability of nitric oxide at rest and during exercise in AF patients. All these factors can conceivably elevate blood pressure in AF and on the other hand, elimination of these factors by restoration and maintenance of sinus rhythm can lead to reduction in blood pressure.

To summarize, hypertension is a potential risk factor of AF and AF-related stroke that can be easily altered by effective treatment. Therefore, aggressive and timely steps to control blood-pressure would possibly arrest the cascade of atrial substrate modifications that will facilitate better ablation-outcome in AF.

Obesity

Obesity is not only the fastest growing health problem in United States; it is also associated with increased cardiovascular risk and could be responsible for nearly 60% of the increase in the incidence of AF.[30] Although obesity can be defined by several factors such as body mass index (BMI), weight, waist circumference and waist-to-hip ratio, in all of the below-mentioned studies, it was measured by BMI.

Dublin et al, in an independent study, identified BMI to be having a stronger association with sustained AF (duration ≥ 6months) than transitory (duration < 8 days) or intermittent AF (duration ≥ 8 days or recurrent) [risk was higher by 7% (95% CI, 3%-11%), 4% (95% CI, 1%-6%) and 1% (95% CI,−1% to +4%) respectively per unit BMI increment compared with those with normal BMI]. They attributed the obesity-AF association to be partially mediated by diabetes and minimally by other cardiovascular risk factors.[31]

Wang et al reported a 4% increase in AF risk per 1-unit increase in BMI in both men (95% confidence interval [CI], 1%-7%; P=.02) and in women (95% CI, 1%-7%; P=.009). Adjusted hazard ratios for AF recurrence associated with obesity were 1.52 (95% CI, 1.09-2.13; P=.02) and 1.46 (95% CI, 1.03- 2.07; P=.03) for men and women, respectively, compared with individuals with normal BMI. They hypothesized the excess AF risk to be mediated by left atrial dilatation.[32]

Tedrow et al, in the Women's Health Study, observed association of BMI with short and long-term increase in AF risk (4.7% increase in risk of incident AF for each kg/m2 increase in BMI), in apparently healthy females.[33]

Furthermore, obesity was demonstrated to be associated with increase in the risk of developing AF by 49% compared to non-obese individuals (relative risk 1.49, 95% CI 1.36-1.64), in a meta-analysis published in 2008.[34]

Interestingly, although obesity is evidently a prominent risk factor for developing AF, it does not seem to negatively influence the outcome of AF-ablation. Comparable long-term success of catheter ablation between obese and non-obese AF population has been reported by several earlier studies including one by our group [Mohanty et al; 69% normal BMI, 63% high BMI, log-rank P =0 .109, Cha et al; 75%, 72%, and 70% for the lean, overweight, and obese patients; p= 0.41 and Letsas et al; 34.9% for normal weight, 46.2% for overweight, and 46.2% for obese patients; p= 0.258].[30,35,36] Obese AF patients tend to have a higher prevalence of non-pulmonary vein (non-PV) triggers and in our study; we speculated that the success rate could have been lower in the obese population, if the non-PV triggers were not targeted for ablation.[30]

Additionally, Ardestani et al have demonstrated that obesity does not adversely affect either overall survival in AF or all cause mortality [Rate of death from any cause was higher in the normal BMI group (5.8 per 100 patient-years) than in the overweight and obese groups (3.9 and 3.7, respectively)].[37] In accordance with the prior study, Badheka et al observed lower all-cause and cardiovascular (CV) mortality as compared with the normal weight patients [All-cause mortality: over-weight, HR 0.64; 95% CI, 0.48-0.84; P=0.001 and obese HR 0.80; 95% CI, 0.68-0.93; P=0.005; CV mortality: overweight, HR 0.40; 95% CI, 0.26-0.60; P =0.001 and obese patients, HR 0.77; 95% CI, 0.62-0.95; P=0.01].[38]

The pathophysiology behind the paradoxical relationship between obesity and AF is unclear yet. Nonetheless, we have demonstrated not only comparable outcomes in terms of recurrence between obese and non-obese, but also a better improvement in QoL in high BMI than in the normal BMI cohort.[30] In a prior study, Wokhlu et al[39] reported a less robust QoL improvement in patients with a higher baseline score and in agreement with that we saw insignificant change in QoL in the normal-BMI cohort, which had a higher pre-ablation QoL score. In contrast, high-BMI group had a lower baseline score and it changed significantly after AF ablation.[30]

Although comparable or favorable outcomes of catheter ablation seem to be associated with increased body weight in AF, this observation does not underestimate the importance of purposeful weight reduction as constellation of data incriminate obesity in myriad of cardiovascular diseases.

Dyslipidemia

Dyslipidemia is defined as high-density lipoprotein (HDL) < 40 mg/dl (1 mmol/L) in men and < 50 mg/dl (1.3 mmol/L) in women and serum triglycerides ≥ 150 mg/dl (1.7 mmol/L).[22] It has been suggested to increase the risk of AF.

Tang et al did not find any of the components of dyslipidemia to be independent predictors of AF [HR 0.85 (95% CI 0.63–1.15, p= 0.294) and HR 0.98 (95% CI 0.71–1.36, p= 0.918) for high triglycerides (≥ 1.69 mmol/L) and low HDL (<1.03 mmol/L in male, <1.29 mmol/L in female) respectively].[4] A report published by Chang et al stated comparable results (HR 1.00, 95% CI 1.00–1.003, p= 0.48 for high triglycerides and HR 0.99, 95% CI 0.99–1.04, p= 0.40 for low HDL in men).[40] In a large prospective study conducted by our group, dyslipidemia was not found to be an independent predictor of AF recurrence (HR 1.13, p= 0.141).[22]

Watanabe et al, in an observational cohort study conducted in Japan, examined the association of dyslipidemia with AF in 28,449 subjects who did not have AF at baseline. During a follow-up of 4.5±2.7 years, 265 (0.9%) individuals developed AF. In multivariate analysis, they observed low HDL to be associated with new-onset AF more strongly in women (HR 2.86; 95% CI: 1.49–5.50) than in men (HR, 1.35; 95% CI: 0.77–2.38). They attributed this observation to inflammation, oxidative stress and structural cardiac abnormalities consequent of reduced level of HDL. Difference in electrophysiological properties in men and women was hypothesized to be accountable for the observed gender-related difference. Furthermore, they reported an inverse relationship between LDL level and AF risk; a seemingly dyslipidemia paradox (risk of AF increased as LDL cholesterol decreased in women (HR, 1.08 per 10-mg/dl decline; 95% CI: 1.02–1.14 per 10-mg/dl decline; P=0.01) and men (HR, 1.06 per 10-mg/dl decline; 95% CI: 1.02–1.11 per 10-mg/dl decline; P=0.007). Clinical and subclinical hyperthyroidism resulting from low LDL cholesterol was speculated to be a potential cause for high AF risk.[41]

The above results strongly suggest that the underlying mechanism defining the variable association of dyslipidemia and AF is yet to be fully elucidated. Therefore, further studies are needed to clarify the mechanistic link, if any, between the two. Understanding the mechanism would immensely help the electrophysiologists in patient selection and risk-stratification for AF ablation.

Association of MS as a Composite Model with AF

Impact of MS on AF Recurrence Following Catheter Ablation:

Although the individual components of MS dem-

onstrate conflicting association with AF, a significant correlation of MS as a group of cardiovascular risk factors with increased risk of AF recurrence is well evident from many prior studies.[22, 4, 40, 42, 43]

In 2009, Chang et al, reported MS, as a composite model, to be an independent predictor of AF recurrence (HR 2.56, 95% CI 0.20–0.79, p= 0.008). They also evaluated the contribution of the metabolic components to recurrent AF and found no association with any except for high BMI.[41] A similar result was reported by Tang et al in the same year (association of MS with AF recurrence, HR =1.64, 95% CI 1.07–2.49, P=0.022).[4]

In 2011, in an original study conducted by Cai et al, MS was again demonstrated to be an independent predictor of AF recurrence (OR=4.41, 95% CI 1.56–12.46, P=0.005). High BMI was the only metabolic component found to be correlated with ablation-outcome ((OR=4.71, 95% CI 1.71–12.98, P=0.003).[42]

Later in 2012, we published the results from a prospective study on 1496 consecutive AF patients undergoing first catheter ablation, where we reported MS, as a disease complex, to be a strong predictor of AF recurrence after first catheter ablation (HR 1.28, p= 0.021).[22] In accordance with the above studies, we also did not observe any substantial association between MS components and AF recurrence except for high BMI. Berkowitsch et al demonstrated a similar association of MS with ablation outcome in AF (HR1.49, 95% CI1.15–1.97, p=0.003).[43]

The above studies have demonstrated one important finding; ablation fails more commonly when MS is associated with AF.[44] Non-PV triggers are potential source of recurrence as shown by Di Biase et al[45] and those are frequently observed in MS.[22] Therefore, the role of targeting non-PV triggers in achieving long-term success cannot be overemphasized.

Impact of MS on Stroke Risk

MS not only has its impact on ablation outcome in AF, but also is an important risk factor for ischemic stroke, by itself.

Boden-Albala et al reported a gender and race-specific influence of MS on stroke incidence (risk of stroke, HR=1.5; 95% CI, 1.1 to 2.2; risk of vascular events HR=1.6; 95% CI, 1.3 to 2.0; risk of stroke among women, HR=2.0; 95% CI, 1.3 to 3.1; among men HR=1.1; 95% CI, 0.6 to 1.9 and among Hispanics HR=2.0; 95% CI, 1.2 to 3.4).[46] In another study, Ashtari et al observed a similar association between MS and ischemic stroke.[47] Possible explanation for gender-related difference in stroke risk are; more vascular risk-factors in women than men and a greater impact of MS among post-menopausal women.[46]

AF is known to cause a 5-fold increase in the risk of ischemic stroke.[48] With the rising prevalence of MS and AF, risk of stroke remains a lingering concern and should be identified early and addressed effectively with anticoagulants and treatment of MS components.

Impact of MS on QoL in AF

Both MS and AF seriously impair QoL. In a recently published study, our group has reported an interesting finding regarding the association between MS, QoL improvement and AF ablation. In our study population, patients with MS had significantly lower baseline scores on all SF-36 (Medical Outcome Survey) Health Survey subscales. At 1 year follow-up, both mental component summary ($\Delta 5.7 \pm 2.5$, $p < 0.001$) and physical component summary ($\Delta 9.1 \pm 3.7$, $p < 0.001$) scores improved in those with MS, whereas only mental component summary scores ($\Delta 4.6 \pm 2.8$, $p = 0.036$) were improved in those without MS.[22] It is already known that patients with lower baseline QoL scores report a more robust improvement in their QoL score following interventions.[39] Our result was in agreement with that observation.

From the information available so far, one can prudently conclude that the components of MS, rather than acting alone, act in concert in causing LA enlargement and disturbances of the intra-atrial conduction velocity and atrial refractoriness that increase the genesis of ectopic triggers, in AF.[22, 40] Therefore, a strong association between MS as a complex and AF are depicted clearly whereas independent components of the syndrome majorly fail to do so.

The unique designation of metabolic syndrome identifies patients with higher metabolic risks

for AF among other cardiovascular diseases and warrants for aggressive strategies for treatment of the component parameters before catheter ablation. That would certainly result in robust risk-factor reduction in this population and enhance the success rate of AF-ablation.

Impact of Life-Style Changes on Ablation Outcome in Patients with MS:

MS is becoming a world-wide epidemic as a result of the increased prevalence of obesity and sedentary life style.

In a meta-analysis conducted by Yamaoka et al, life style modification such as dietary interventions and moderate-intensity exercise was found to be effective in reducing the values for all components of MS except HDL. The values were -11.5 mg/dl (95% CI -22.4 to -0.6) for fasting blood glucose, -2.7 cm (95% CI -4.6 to -0.9) for waist circumference, -6.4 mmHg (95% CI -9.7 to -3.2) for systolic BP, -3.3 mmHg (95% CI -5.2 to -1.4) for diastolic BP, and -12.0 mg/dl: 95% CI -22.2 to -1.7) for triglycerides. The reduced mean values were not significant for HDL (1.3 mg/dl; 95% CI -0.6 to 3.1).[49]

The impact of life style changes such as alcohol consumption, exercise and smoking on AF is yet to be understood clearly with studies reporting inconsistent results.[50]

However, the evidences gathered so far strongly suggest that long-term life style modifications reduce the prevalence of MS and thus should be considered as a useful supplemental tool to control MS effectively which might lead to more ablation success in AF.

Conclusions

From the day MS was identified as a prominent risk factor for AF, the debate is ongoing if the 'whole syndrome' is a stronger predictor of increased AF risk and arrhythmia recurrence, than its parts. In seeking answer to this question, this review has compiled evidences from major studies that have attempted in recent years to address it in one way or another. These results, on the whole, suggest that MS predicts higher AF recurrence following ablation and MS as a composite model, is a better predictor of ablation-outcome in AF than its individual components. However, inconsistency between different studies makes it short of being conclusive evidence. Therefore, further studies are needed to establish the mechanistic link between the two conditions. In the mean time, physicians should continue emphasizing on improving lifestyle for their patients, which would help in curtailing the prevalence of obesity, the driving force for other components of MS.

Disclosures

- Dr. Luigi Di Biase is a consultant for Hansen Medical and Biosense Webster.
- Dr. Andrea Natale received speaker honorariums from Boston Scientific, Biosense Webster, St. Jude Medical, Medtronic and Life Watch and research grant from St. Jude Medical
- The remaining authors have no disclosures to report.

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