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Biomarkers of diabetes: role in the pathogenesis of atrial fibrillation

S. RAFAQAT[1], I. RADOMAN VUJAČIĆ[2], S. GLUSCEVIC[3], S. SHARIF[1], A. KLISIC[4,5]

[1]Department of Zoology (Molecular Physiology), Lahore College for Women University, Lahore, Pakistan
[2]Department of Internal Medicine, Faculty of Medicine, University of Montenegro, Clinical Center of Montenegro, Podgorica, Montenegro
[3]Department for Neurology, Clinical Center of Montenegro, Podgorica, Montenegro
[4]Faculty of Medicine, University of Montenegro, Podgorica, Montenegro
[5]Center for Laboratory Diagnostics, Primary Health Care Center, Podgorica, Montenegro

Abstract. – The prevalence of both atrial fibrillation (AF) and diabetes is increasing day by day and commonly co-exist with a longer duration of diabetes and poor control, putting the individual at higher risk of AF. This review article presented some traditional and novel biomarkers related to AF in patients with diabetes mellitus. The literature review employed several databases, including Google Scholar, PubMed, and Science Direct. The investigation was finished on October 30, 2023. Many terms are utilized, including "AF", "Biomarkers", "Diabetes Mellitus", and "Pathogenesis". There are numerous biomarkers of diabetes, but this review article reports only leptin, adiponectin, glycated hemoglobin, ceramide, ferritin, fibrinogen, hematological indices, interleukin-18, thrombospondin 1, acylcarnitine, plasminogen activator inhibitor-1 and triglycerides and high-density lipoprotein cholesterol, since those biomarkers play a significant role in the pathogenesis of AF. However, no data was found, including fructosamine, glycated albumin, 1,5 anhydroglucitol, fetuin-A, α-hydroxybutyrate, mannose-binding lectin serine peptidase, transferrin, IL-1 receptor antagonist in AF. Understanding the interplay between diabetes and AF through the measurement of relevant biomarkers can contribute to better risk assessment, early detection, and the development of targeted therapeutic strategies for individuals at risk or already affected by these conditions.

Key Words:
Atrial fibrillation, Biomarkers, Diabetes mellitus, Pathogenesis.

Introduction

Diabetes mellitus (DM) is one of the biggest global public health issues and has a significant negative impact on both socioeconomic progress and public health worldwide. Although incidence has begun to decline in some nations, diabetes prevalence has scaled over the past few decades in the majority of other advanced and developing worlds[1]. Just under half a billion people are living with diabetes worldwide, and the number is predicted to increase by 25% in 2030 and 51% in 2045[2]. However, the most prevalent arrhythmia is atrial fibrillation (AF), and incidence rates are increasing quickly globally. In China, the prevalence of AF is 0.65%, while the global prevalence of AF (age-adjusted) is 0.60% for men and 0.37% for women. As the world's population ages, it is expected that the number of people with AF will continue increasing[3].

The prevalence of both atrial fibrillation and diabetes is increasing day by day. These two conditions commonly coexist, and the risk of developing AF increases with a longer duration of diabetes and poor control of blood sugar[4]. The new-onset AF (NAF) is gradually increasing worldwide because of the DM and comorbidity with AF[5,6]. Moreover, Nichols et al[7] reported the prevalence of AF was significantly greater among patients with diabetes (3.6 *vs.* 2.5%, $p<0.0001$). Prevalence increased with age in both groups but was significantly exaggerated among diabetic patients[7].

Two significant, closely connected, and chronic cardiovascular diseases with concurrently increasing prevalence rates are AF and DM. Although the pathogenic processes behind the co-occurrence of AF and DM remain unclear, it is now known that DM triggers the development of AF. The clinical progression of established AF is further impacted by DM, which is similarly

Corresponding Author: Aleksandra Klisic, MD, Ph.D; e-mail: aleksandranklisic@gmail.com

linked to a marked increase in the risk of stroke, AF recurrence, and cardiovascular mortality. Research on how DM affects AF management and prognosis is sufficient[8].

Prediabetes is a serious condition that is expected to impact 482 million people worldwide by the year 2040. To lower the risk of developing diabetes and its complications, accurate methods for identifying prediabetes will be required[9]. The term "biomarker," a portmanteau of "biological marker," refers to a large subclass of medical signs, or objective indicators of health status seen from the outside of the patient, which can be quantified precisely and consistently. Medical symptoms, on the other hand, are only those markers of health or illness that patients themselves may perceive[10]. Due to the increased prevalence of diabetes in AF subjects, this article will highlight the major biomarkers of diabetes in the pathogenesis of AF.

Biomarkers

There are numerous biomarkers of diabetes[9] but this review article reports only leptin, adiponectin, glycated hemoglobin (HbA1c), ceramide, ferritin, fibrinogen, hematological indices, interleukin (IL)-18, thrombospondin 1 (TSP-1), acyl-carnitine, plasminogen activator inhibitor-1 (PAI-1), triglycerides (TG) and high-density lipoprotein cholesterol (HDL-C) in the pathogenesis of AF as explained in Figure 1.

To review the literature, various databases, including Google Scholar, PubMed, and Science Direct, were employed. The search was completed on October 30, 2023. There are several keywords that were used, including "Atrial Fibrillation", "Biomarkers", "Diabetes Mellitus", and "Pathogenesis". Only clinical investigations in the English language were considered. Despite supporting more literature, we did not set a time limit. The relevant references of articles were explored.

The relationship between diabetes and AF is complex and multifactorial. Biomarkers play a crucial role in understanding the pathogenesis and identifying potential links between these two conditions. Diabetes is associated with chronic inflammation and increased oxidative stress, which can contribute to the development and progression of AF. Diabetes has been linked to atrial structural remodeling, including fibrosis, which can create a substrate for AF. There are numerous

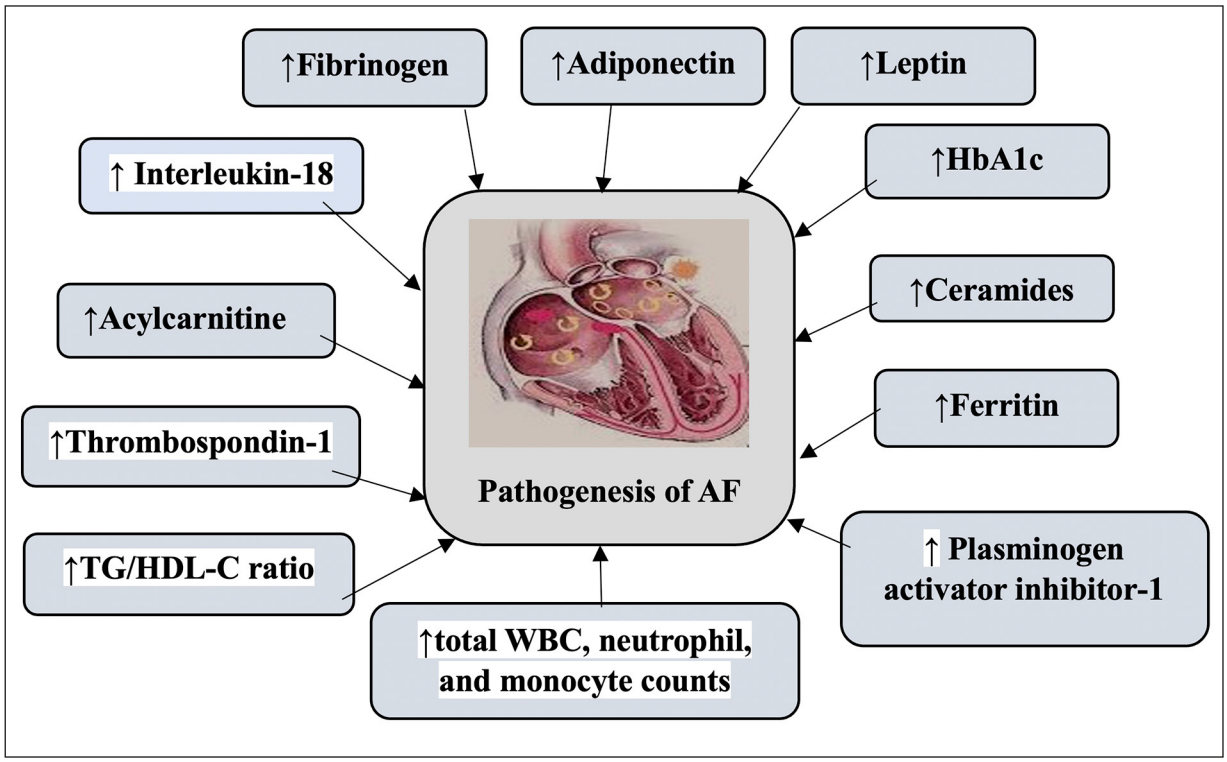

Figure 1. Summary of circulating levels of major biomarkers of diabetes in atrial fibrillation.

biomarkers of diabetes, but this article will report only a few major biomarkers of diabetes in the pathogenesis of AF, as explained in Table I. The pathophysiological aspects of leptin in AF are elucidated in Figure 2. In the same way, Figure 3 explains the pathophysiological aspects of major biomarkers of diabetes in AF.

Leptin

Leptin, an adipocyte-derived hormone, serves as a crucial regulator of food intake and energy balance. The leptin molecule has a size of 16 kDa and is composed of 167 amino acids, which includes a 21 amino acid secretory signal sequence[11,12]. Its tertiary structure resembles that of a globular protein. Insufficient levels of leptin resistance can lead to significant issues such as obesity, diabetes, and infertility in humans. Initially recognized for its anti-obesity role, the comprehension of leptin's biological functions has expanded to encompass a wide range of effects on reproduction, hematopoiesis, angiogenesis, blood pressure, bone mass, lymphoid organ homeostasis, and T lymphocyte systems[13]. The intricate biological effects of leptin are orchestrated through its receptors, which are expressed both centrally and peripherally. Belonging to the class I cytokine receptor superfamily, the leptin receptor has at least five isoforms, primarily due to alternate splicing. The longest isoform is capable of complete signal transduction, while the shorter forms may act as binding proteins, facilitating the transport of leptin across the blood-brain barrier[13].

A different investigation explored the idea that leptin signaling plays a role in atrial fibrosis and AF induced by angiotensin II (AngII). Fukui et al[14] marked the initial confirmation that leptin signalling is crucial for the progression of atrial fibrosis and AF triggered by AngII[14]. Being overweight is a significant risk element for AF[15]. Leptin, a crucial adipokine, raises questions about whether it directly influences the electrophysiological traits of atrial myocytes. Leptin directs the electrophysiological traits and calcium balance in the left atrium. Its ability to mitigate the impact of isoproterenol-induced arrhythmogenesis suggests a potentially beneficial role in the pathophysiology of atrial arrhythmogenesis[15].

Rafaqat et al[16] detailed the pathophysiological implications of leptin in AF, including increased fibrosis, increased inflammation, promotion of cardiac remodelling resulting from impaired cardiac metabolism, vascular dysfunction, ventricular hypertrophy, elevated myocardial workload and cardiac hypertrophy. Adiposity is a significant factor in the development of AF, and proteins associated with it are released differently in males and females. Another study[17] examined leptin to understand its gender-specific impact on mechanisms linked to the progression of AF. The primary discovery of this study highlights the sex-dependent behaviour of leptin about the burden of AF. The relationship of this adipokine with oxidative stress, inflammatory markers, and indirect indicators of autonomic activity may contribute to the explanation of mechanisms involved in the perpetuation of AF[17].

The adiponectin-to-leptin (A/L) ratio has been recognized as a possible surrogate marker for metabolic disorders. However, it is unclear whether serum A/L ratio is linked to heart rate variability in individuals with paroxysmal AF. It was suggested that the A/L ratio, as well as the individual levels of adiponectin and leptin, are correlated with cardiac autonomic function in patients with new-onset paroxysmal AF[18]. Nevertheless, given the acknowledged limitations of HRV analysis during the onset of paroxysmal AF, further investigation is warranted to determine the potential utility of these adipokine levels in identifying and assessing new-onset paroxysmal AF[18].

An increased body mass index (BMI) is a notable risk factor for AF[19]. The adipokines leptin and adiponectin are linked to BMI, but their specific connection with the onset of AF is not fully understood. This association was investigated in a substantial cohort of postmenopausal women[19]. The study revealed that levels of leptin and adiponectin are not significantly associated with AF[19].

Adiponectin

The loose connective tissue known as adipose tissue, or "fat", is made up of lipid-filled cells called adipocytes that are encased in a matrix of collagen fibres, blood arteries, fibroblasts, and immune cells[20]. It is believed that low adiponectin levels are a major factor in the emergence of type 2 diabetes mellitus (T2DM), obesity, and cardiovascular disease. Adiponectin is a key physiological regulator of insulin sensitivity, glucose and lipid metabolism, as well as cardiovascular homeostasis, according to research in both human and animal models[21]. Similarly, Rafaqat et al[16] explained the pathophysiological role of adiponectin in AF including involvement in cardiac remodel-

Table I. Summary of studies which reported the major biomarkers of diabetes in atrial fibrillation.

First author	Biomarker of diabetes	Main finding of major biomarkers of diabetes in the pathogenesis of AF
Fukui et al[14]	Leptin	Leptin signalling is crucial for the progression of atrial fibrosis and atrial fibrillation triggered by angiotensin II.
Lin et al[15]	Leptin	Leptin directs the electrophysiological traits and calcium balance in the left atrium. Its ability to mitigate the impact of isoproterenol-induced arrhythmogenesis suggests a potentially beneficial role in the pathophysiology of atrial arrhythmogenesis.
Lopez-Canoa et al[17]	Leptin	The sex-dependent behaviour of leptin about the burden of AF is highlighted. The association leptin with oxidative stress, inflammatory markers, and indirect indicators of autonomic activity may contribute to the explanation of mechanisms involved in the perpetuation of AF.
Ermakov et al[19]	Leptin	Serum levels of leptin and adiponectin are not significantly associated with AF.
Rafaqat et al[16]	Adiponectin	Pathophysiological role of adiponectin in AF including involvement in cardiac remodeling, atrial remodeling and autonomic dysfunction and inflammation.
Macheret et al[22]	Adiponectin	Adiponectin levels are independently associated with a higher risk of AF in older persons, despite its known cardiometabolic advantages.
Guo et al[23]	Adiponectin	Higher baseline levels of circulating adiponectin may be a risk factor for the emergence of new-onset AF.
Zhu et al[24]	Adiponectin	Higher serum adiponectin levels were not connected with an increased risk of AF in men or individuals ≥65 years old, but they were independently associated with higher risk in women and participants <65 years old.
Kim et al[25]	Adiponectin	After catheter ablation for PAF, high circulating adiponectin is independently linked to AF recurrence, especially in people <65 years old.
Hernández-Romero et al[26]	Adiponectin	In anticoagulated women with AF, adiponectin is proposed as an independent predictive biomarker for cardiovascular events.
Qi et al[28]	HbA1c	HbA1c could be used as a possible biomarker to predict the development of AF.
Zhao et al[29]	HbA1c	It is necessary to conduct additional prospective studies with larger sample size to examine the relationship between HbA1c levels and the risk of POAF.
Kuang et al[30]	HbA1c	In non-valvular AF patients, HbA1c may be significant in determining the risk for the prothrombotic condition.
Wei et al[31]	HbA1c	Reduced contractile performance of the left atrial appendage may be reflected by higher HbAlc level, which is linked to a diminished LAAV.
Fangel et al[32]	HbA1c	Increasing levels of HbA1c were linked to higher risk of thromboembolism in patients with incident AF and T2DM. However, among patients with T2DM duration of <10 years, no connection was discovered.
Narayan et al[33]	HbA1c	HbA1c levels do not independently predict the risk of AF during off-pump CABG despite controlling for confounders.
Kinoshita et al[34]	HbA1c	Preoperative HbA1c levels was independent predictor of the development of AF following isolated off-pump CABG.
Iguchi et al[35]	HbA1c	The presence of AF was correlated with HbA1c in patients with HbA1c levels <6.5%.
Chan et al[36]	HbA1c	The relationship between HbA1c levels and the risk of IS/SE and significant bleeding in AF patients using or not taking oral anticoagulants was observed.
Abbaszadeh et al[37]	HbA1c	The development of POAF could not be predicted by the HbA1c levels.
Jensen et al[40]	Ceramides	Ceramides are involved in the processes of oxidative stress, inflammation, and atrial remodelling. Additionally, apoptosis is facilitated by ceramides, and animal studies indicate that apoptosis in the presence of fibrosis may contribute to the pathophysiology features of AF.
Signori et al[41]	Ceramides	Higher coffee consumption was linked to higher levels of Cer(d18:1/24:0) and a decreased incidence of AF. The risk of AF was negatively correlated with Cer(d18:1/24:0).
Mikkelsen et al[44]	Ferritin	Higher ferritin concentrations are linked to a higher incidence of AF in the general population.
Sokal et al[47]	Ferritin	Serum ferritin levels may be a useful tool for determining the effectiveness of AF treatment.
Lip et al[49]	Fibrinogen	Increases in plasma fibrinogen and fibrin D-dimer levels are linked to AF. These markers are present at intermediate levels in PAF patients, which is consistent with their intermediate risk of thromboembolism.

Table continued

Table I. ***(Continued).*** Summary of studies which reported the major biomarkers of diabetes in atrial fibrillation.

First author	Biomarker of diabetes	Main finding of major biomarkers of diabetes in the pathogenesis of AF
Lip et al[50]	Fibrinogen	Persistent AF had elevated levels of VWF and plasma fibrinogen.
Mukamal et al[51]	Fibrinogen	Even after controlling for their relationship to the risk of cardiovascular disease, higher levels of fibrinogen and lower levels of albumin were linked to a higher risk of AF.
Carter et al[52]	α-fibrinogen	Thr312Ala polymorphism may give rise to an increased susceptibility for embolization of intra-atrial clot.
Tilly et al[54]	Fibrinogen	Fibrinogen and the incidence of AF were not significantly associated.
Tóth et al[55]	Fibrinogen	When compared to non-AF controls, none of the studied hemostasis or fibrinolysis parameters indicated intracardiac changes in AF patients.
Rienstra et al[57]	WBC	Higher WBC count was linked to incident AF throughout a 5-year follow-up in a community-based population.
Suzuki et al[58]	NLR, monocytes	Residents in the Fukushima Prefecture evacuation zone had higher NLR and monocyte counts, which may indicate that inflammation and psychological stress played a significant role in mediating the development of AF following the earthquake.
Tran et al[59]	WBC	Observed the relationship between WBC at hospital admission, changes in WBC while in the hospital, and the emergence of new-onset AF while being treated for an ACS.
Misialek et al[60]	WBC, neutrophils, monocytes	Higher total WBC, neutrophil, and monocyte counts all increased the probability of developing AF, whereas lymphocyte count had the opposite relationship.
Jacob et al[61]	WBC	The development of PNAF was not linked to the perioperative WBC response or any of its constituent parts.
Lamm et al[62]	WBC	Postoperative WBC count independently predicts the emergence of postoperative AF with a more severe increase.
Bazoukis et al[64]	NLR	Larger prospective trials could test the efficacy of straightforward and low-cost hematological markers like NLR in predicting AF recurrence in patients receiving catheter ablation.
Özbek et al[65]	RDW	Additional research was required to determine the prognostic value of RDW and epicardial fat in POAF.
Luan et al[67]	IL-18	IL-18 levels in patients with AF were increased.
Wang et al[68]	IL-18	IL-18 rs187238, rs360719, and rs549908 were linked to a lower incidence of AF in the patient population.
Liu et al[69]	IL-18	The severity and recurrence of AF following cryoablation may be connected to the levels of IL-18 which were higher in left atrial blood than peripheral blood.
Liao et al[71]	TSP-1	TSP-1 is a potential novel indicator of atrial arrhythmias during AMI.
Yang et al[72]	TSP-1	Elevated TSP-1, TGF-β, and MMP-9 expression as well as elevated atrial fibrosis in AF patients.
Smith et al[75]	Acylcarnitine	Link between altered acylcarnitine metabolism and the incidence of AF in a general population for the first time, regardless of conventional AF risk variables.
Ruiz-Canela et al[76]	Acylcarnitine	Elevated long-chain acylcarnitines were linked to a greater risk of incident HF and AF in people with high cardiovascular risk. A combination of MedDiet and extra virgin olive oil may lessen the incidence of AF brought on by long-chain acylcarnitines.
Aitken-Buck et al[77]	Acylcarnitines	Circulating acylcarnitines can cause arrhythmic contractions when exposed directly to the atrial myocardium, indicating that dysregulated acylcarnitine levels may play a role in the pathophysiology of AF.
Mulder et al[80]	PAI-1	Community-based cohort, PAI-1 and TPA levels were not associated with incident AF.
Li et al[81]	PAI-1	PAI-1 may be a new therapeutic biomarker for AF, and the p53/PAI-1 signaling axis may contribute to the pathophysiological processes of the disease.
Pretorius et al[82]	PAI-1	Following cardiac bypass, the development of AF is independently predicted by an increased preoperative or postoperative PAI-1 antigen concentration.

Table continued

Table I. ***(Continued).*** Summary of studies which reported the major biomarkers of diabetes in atrial fibrillation.

First author	Biomarker of diabetes	Main finding of major biomarkers of diabetes in the pathogenesis of AF
Li et al[86]	LDL-C and HDL-C	Patients with AF had lower blood lipid levels than healthy controls, particularly lower LDL-C and HDL-C levels. Hypolipoproteinemia may make a patient more susceptible to AF development.
Alonso et al[88]	HDL-C and TG	HDL-C and TG, but not total cholesterol or LDL-C were linked to an increased risk of AF.
Ding et al[89]	Low HDL-C and ApoA-I and high TG/HDL-C ratio	Low ApoA-I and HDL-C, as well as high TG/HDL-C ratio, were related to a higher risk of AF over a follow-up of almost 35 years.
Okin et al[90]	HDL-C	The risk of new AF is highly correlated with lower HDL-C levels while receiving therapy.

HbA1c – Glycated hemoglobin; VWF – Von Willebrand factor; WBC – White blood cells; NLR – Neutrophil-to-lymphocyte ratio; RDW – Red cell distribution width; IL-18 – Interleukine-18; TSP-1 – Thrombospondin 1; PAI-1 – Plasminogen activator inhibitor-1; TG – Triglycerides; HDL-C – High-density lipoprotein cholesterol; AF – Atrial fibrillation; POAF – Postoperative atrial fibrillation; CABG – Coronary artery bypass grafting; T2DM – Type 2 diabetes mellitus; LAAV – Left atrial appendage flow velocity; IS-SE – Ischemic stroke/systemic thromboembolism; AMI – Acute myocardial infarction; TPA – Tissue plasminogen activator; TGF-β – Transforming growth factor-β; MMP-9 – Matrix metalloproteinase-9; ApoA-I – Apolipoprotein A-I.

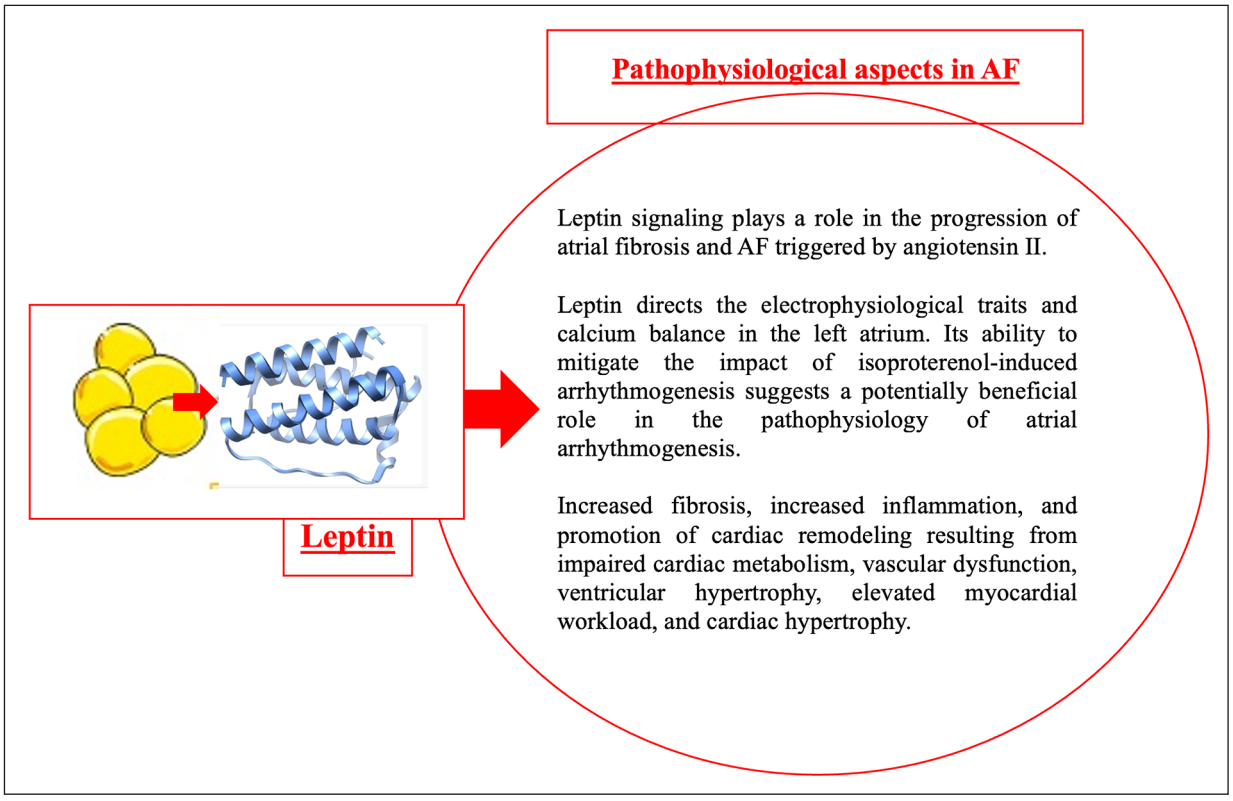

Figure 2. Major pathophysiological aspects of leptin in atrial fibrillation.

ing, atrial remodeling and autonomic dysfunction and inflammation.

Another study results[22] show that higher levels of this adipokine are independently associated with a higher risk of AF in older individuals, despite its known cardiometabolic advantages. Further research is required to identify whether adiponectin is a sign of dysfunctional counter-regulatory networks or whether this hormone actively problems individuals as they get older[22]. Particularly in cohort studies[23] with longer follow-up periods, higher baseline levels of circulat-

ing adiponectin may be a separate risk factor for the emergence of new-onset AF during follow-up.

Zhu et al[24] reported that higher serum adiponectin levels were not associated with an increased risk of AF in men or individuals ≥65 years old, but they were independently linked to a higher risk in women and participants under the age of 65. In the same way, Kim et al[25] explained that after catheter ablation for PAF, high circulating adiponectin is independently linked to AF recurrence, especially in individuals under age 65. In anticoagulated female patients with AF, adiponectin is proposed as an independent predictive biomarker for cardiovascular events. Another study's findings[26] highlight the significance of AF as a risk factor for atherosclerotic vascular injury.

Hemoglobin A1c

Although recent research suggested a link between HbA1c (i.e., an indicator of long-term glycemic status levels)[27] and the incidence of AF, the conclusions are not consistent[28]. More information is required, although elevated HbA1c levels may be linked to an increased risk of AF. HbA1c concentrations could be used as a possible biomarker to predict the development of AF[28].

Furthermore, AF or postoperative AF (POAF) in coronary artery bypass grafting (CABG) patients and HbA1c are still controversial topics of discussion. HbA1c levels and the risk of AF or POAF may or may not be correlated in a dose-response manner. According to the findings of Zhao et al[29], having DM, not having DM, or having an

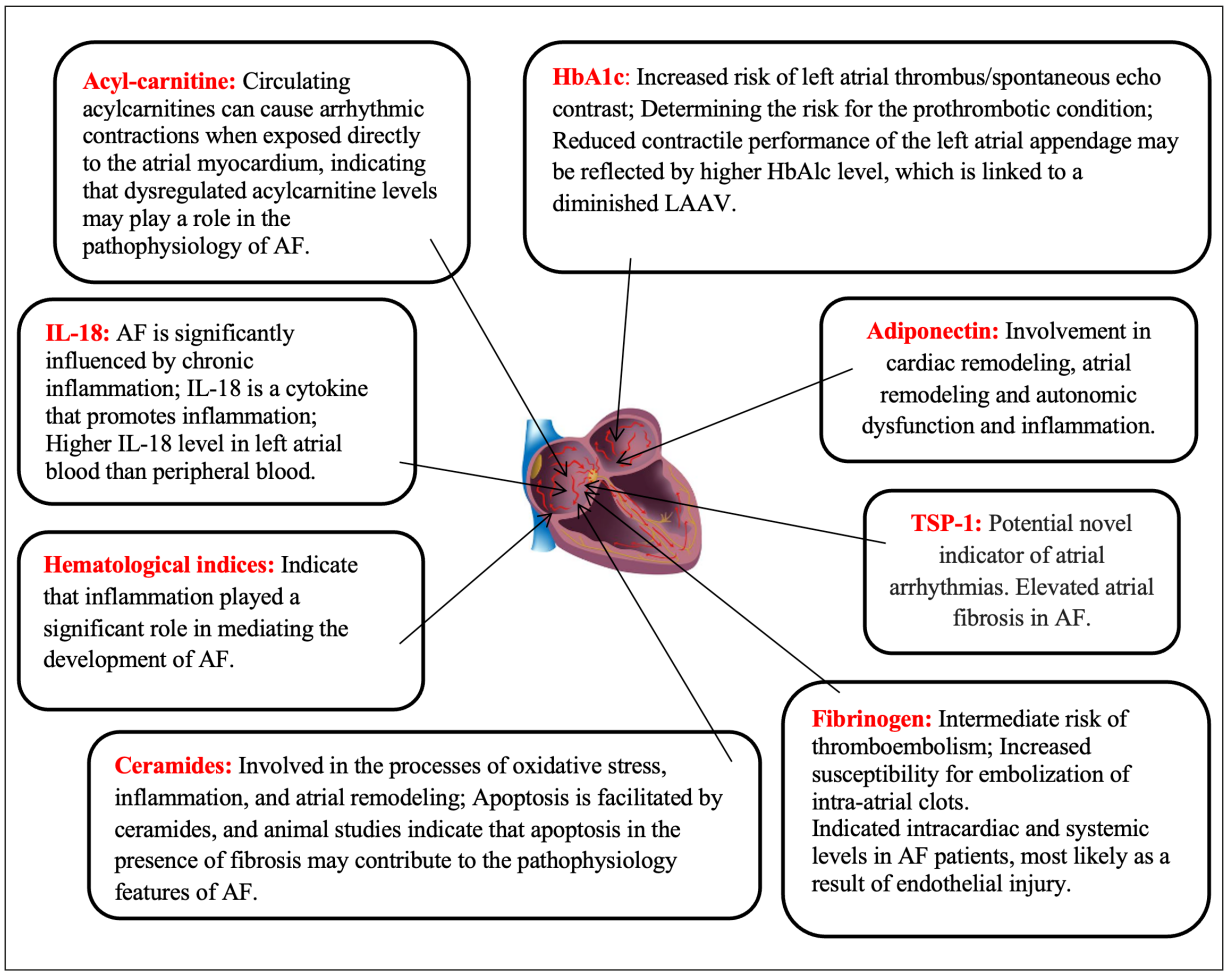

Figure 3. The pathophysiological aspects of biomarkers of diabetes in atrial fibrillation.

unknown form of diabetes, all of these increased the likelihood of having AF. HbA1c and POAF did not, however, appear to be related in individuals following CABG. It is necessary to conduct additional prospective studies with larger population sizes to examine the relationship between blood HbA1c levels and the risk of POAF[29]. Also, in individuals with non-valvular AF, it is important to assess the association between HbA1c and the risk of left atrial thrombus/spontaneous echo contrast (LAT/SEC). Elevated HbA1c in non-valvular AF patients demonstrated a markedly elevated risk for LAT/SEC. In non-valvular AF patients, HbA1c may be significant in determining the risk for the prothrombotic condition[30].

Thromboembolic events and cardiovascular disease risk are both enhanced by high HbA1c levels. The goal of the study was to investigate if HbAlc and left atrial appendage flow velocity (LAAV) are related in non-valvular AF patients. Reduced contractile performance of the left atrial appendage may be reflected by an elevated HbAlc level, which is linked to a diminished LAAV[31]. Patients with AF who have DM have an elevated risk of stroke, and variations in glycemic status may have an impact on this risk. The authors[32] observed the relationship between individuals with AF and T2DM and their glycemic status as measured by HbA1c. Increasing levels of HbA1c were linked to a higher risk of thromboembolism in patients with incident AF and T2DM. However, among patients with T2DM duration of fewer than 10 years, no connection was discovered[32].

DM is linked to increased mortality and poorer postoperative results in patients undergoing coronary artery bypass graft (CABG), and higher HbA1c levels have repeatedly been linked to poor post-operative results. However, it is still unknown how HbA1c affects the development of AF. HbA1c levels do not independently predict the risk of AF during off-pump CABG despite controlling for confounders[33].

Although postoperative AF has not been significantly linked to DM, it is known to be a risk factor for mortality and morbidity after CABG[34]. Even while a recent study suggested a possible connection between preoperative HbA1c level and the risk of postoperative AF, this association has not been sufficiently explored. Kinoshita et al[34] investigated to determine whether isolated off-pump CABG was associated with AF and preoperative HbA1c. Independently, preoperative HbA1c predicts the development of AF following isolated off-pump CABG[34].

Moreover, Iguchi et al[35] determined if the prevalence of AF and HbA1c levels among Japanese individuals in Kurashiki-city are related. Two examinations of residents over 40 were conducted in 2006 and 2007. Higher HbA1c (OR, 1.18; 95% CI, 1.09-1.28; $p<0.001$) was the factor related to AF after adjusting for age, gender, vascular risk factors, cardiac disease, and estimated glomerular filtration rate. Particularly in patients with HbA1c levels <6.5%, the presence of AF appears to be correlated with HbA1c[35].

There are not many studies, particularly looking at the relationship between HbA1c levels and the risk of ischemic stroke/systemic thromboembolism (IS/SE) in people with AF. Chan et al[36] observed the relationship between HbA1c levels and the risk of IS/SE and significant bleeding in AF patients using or not taking oral anticoagulants (OACs). Additionally, in various HbA1c categories, the efficiency and safety of warfarin with direct oral anticoagulants (DOACs) were contrasted. OACs may lessen these relationships. For AF patients, IS/SE risk dramatically increased once HbA1c levels approached 6.5%. In general, HbA1c categories, and DOACs were safer and more effective than warfarin[36]. Therefore, for eligible AF patients, more aggressive glycemic control to attain an HbA1c level of 6.5% may be explored in addition to DOAC prescriptions as necessary. This approach should be evaluated in future prospective trials[28]. In contrast, Abbaszadeh et al[37] reported that the development of POAF could not be predicted by the serum HbA1c level.

Ceramide

In terms of structure, ceramides are described as having a sphingoid base, commonly sphingosine with 18 carbons (d18), connected to a fatty acyl chain with a range of lengths (14 to 26 carbons), with mammalian cells having the most frequent length of 16 carbons[38]. The name "ceramides" comes from the unique amide group and waxy properties of the molecules (the Latin word "cer" means "wax"). Because of their high hydrophobicity and low water solubility, these molecules are mainly found in biological membranes. Ceramides are extremely prevalent in the upper layer of our skin, the epidermis, where they make up between 30 and 40 percent of it and act as a permeability barrier[39].

Ceramides have a variety of biological functions that could affect the pathophysiology as-

pects of AF. It is unknown if the length of the saturated fatty acid carried by ceramide or the precursors of their sphingomyelin is related to the risk of AF[40]. It was suggested that different ceramide and sphingomyelin species have different correlations with the incidence of AF depending on the fatty acid. Ceramides and sphingomyelins containing palmitic acid were linked to an increased risk of AF, but those containing very long-chain saturated fatty acids were linked to a decreased risk of AF[40]. Ceramides are lipids with a sphingoid backbone and one N-acylated fatty acid. Ceramides are involved in the processes of oxidative stress, inflammation, and atrial remodelling[40]. Additionally, apoptosis is facilitated by ceramides, and animal studies indicate that apoptosis in the presence of fibrosis may contribute to the pathophysiology features of AF[40].

Sphingolipids called ceramides function in biological processes as second messengers and structural lipids[40]. Major cardiovascular events like AF are predicted by circulating ceramides, which are affected by diet and food[41]. In conclusion, higher coffee consumption was linked to higher levels of Cer(d18:1/24:0) and a decreased incidence of AF. The risk of AF was negatively correlated with Cer(d18:1/24:0)[41].

Ferritin

Although a mitochondrial form of ferritin has recently been discovered and nuclear localization and functions have been hypothesized, ferritin is primarily found in the cytosol of most tissues[42]. Ferritin is crucial for the storage of intracellular iron and has been extensively reviewed in recent years. Ferritin is a 24-subunit protein made up of two different subunit kinds known as H and L[42]. The clinician can use ferritin to assess common disease states such as iron deficiency anemia as well as acquired and genetic iron overload diseases like hereditary hemochromatosis and prolonged transfusion therapy. Serum ferritin is undoubtedly the most helpful marker in the majority of populations and is typically included in a panel of many blood tests that are frequently ordered to identify and treat these diseases, albeit there are significant limitations[42].

The results of the current study revealed that serum ferritin and iron levels have an impact on the QT interval in several medical disorders, potentially causing the development of lethal cardiac arrhythmias[43]. As a biomarker of iron overload, moderately elevated plasma ferritin has been linked to a greater incidence of heart failure (HF) and cardiovascular death. However, it is unknown if moderately elevated plasma ferritin is associated with a higher incidence of AF in the general population. In the general population, higher ferritin concentrations are linked to a higher incidence of AF[44].

Anemia and iron deficiency seem to be extremely common in people with AF[45]. Additionally, women with AF may experience worse symptoms and results if they have anemia or iron deficiency[45]. Although further research is needed to validate these preliminary findings, the scant information available to date suggests that symptomatic patients with AF may benefit from investigating and treating anemia and iron deficiency. Future research is necessary to validate the incidence of anemia and iron deficit in other groups with AF, characterize relationships with outcomes better, and ultimately decide whether treating anemia and iron deficiency is a unique management strategy for individuals with AF[45].

Among arrhythmia diseases, AF is the most prevalent. Studies[46,47] on animals and casual observations have connected low iron levels to AF. However, it is still unclear how iron status and AF are related causally. Wang et al[46] aimed to determine if systemic iron status was causally connected to AF by using Mendelian randomization analysis, which has been widely used to evaluate the causal effect. Authors have reported the findings which have demonstrated a direct relationship between a higher iron status caused by genetics and an elevated risk of AF. New concepts for the clinical prevention and management of AF were offered by these results[46].

The pathophysiology of cardiac arrhythmia involves intricate pathways that are responsible for the development and maintenance of AF. Atrial tissue undergoes significant arrhythmic remodeling as a result of inflammation[47]. The current study aims to evaluate the applicability of ferritin and high-sensitivity CRP as AF biomarkers and their utility in determining the effectiveness of cryoablation. The authors reported findings that imply that measuring ferritin serum levels may be a useful tool for determining the effectiveness of AF treatment[47].

Fibrinogen

The primary plasma protein coagulation factor is fibrinogen. Its lower levels are related to a high-

er risk of bleeding since primary and secondary hemostasis are impaired in such circumstances. This traditional positive acute-phase reactant protein is a good predictor of coronary heart disease events[48]. In the same way, authors reported the results that have supported the idea that increases in plasma fibrinogen and fibrin D-dimer levels are linked to AF. These markers are present at intermediate levels in PAF patients, which is consistent with their intermediate risk of thromboembolism[49].

Patients with persistent AF had elevated levels of von Willebrand factor (VWF) and plasma fibrinogen[50]. Individuals with persistent AF who were not taking warfarin also had higher plasma D-dimer levels, which may indicate that these patients have enhanced intravascular thrombogenesis[50]. Warfarin treatment appears to be successful in reducing excessive fibrin turnover, consistent with the antithrombotic properties of warfarin, as seen by the normalization of circulating fibrin D-dimer levels following warfarin administration. These findings point to three potential thrombotic indicators that could be used to evaluate AF patients who are at high risk for thrombogenesis. D-dimer also deserves consideration as a way to measure how well warfarin reduces thrombotic risk in these patients[50]. Even after controlling for their relationship to the risk of cardiovascular disease, higher levels of fibrinogen and lower levels of albumin were linked to a higher risk of AF. These results back up the theory that inflammation plays a role in the genesis of AF[51].

The α-fibrinogen Thr312Ala polymorphism occurs close to several sites important for factor XIIIa–-dependent cross-linking, which raises the possibility that it affects fibrin clot stability. The Thr312Ala polymorphism may give rise to an increased susceptibility for embolization of intra-atrial clots, and these findings could have important implications for identifying subjects most at risk of developing thromboembolic complications[52].

When individuals with paroxysmal and persistent AF are compared to matched patients with persistent AF or controls in sinus rhythm, there are significant variations in the prothrombotic condition. Despite the restoration of atrial systole, cardioversion of persistent AF did not significantly change markers of hypercoagulability even after 3 months of sinus rhythm maintenance[53]. In contraction, Tilly et al[54] reported that fibrinogen and the incidence of AF were not significantly associated, according to their meta-analysis (HR 1.04, 95% CI 0.99-1.08). Fibrinogen had a negligible correlation with the incidence of AF when the more thorough adjustments were included (HR 1.05, 95% CI 1.00-1.10)[54]. When compared to non-AF controls, none of the studied hemostasis or fibrinolysis parameters indicated intracardiac changes in AF patients. Elevated FVIII and VWF levels are seen at both the intracardiac and systemic levels in AF patients, most likely as a result of endothelial injury[55].

Hematological Indices

Throughout at least part of their lifespan, white blood cells (WBC), a diverse collection of nucleated cells, can be present in circulation. Their average blood concentration ranges from 4,000 to 10,000 microliters. They are crucial to phagocytosis, immunity, and thus, the fight against infection[56].

Inflammatory indicators have been linked to AF in several studies. Counting WBC is a frequently used and accessible indicator of systemic inflammation. Authors[57] observed whether smoking, myocardial infarction, and HF were factors that mediate the link between elevated WBC count and incidence of AF. Participants in the Original Cohort of the Framingham Heart Study were assessed. To investigate the relationship between WBC count and incidence of AF over a 5-year follow-up period, Cox proportional hazard regression analysis was used. After accounting for smoking, prior myocardial infarctions, interim myocardial infarctions, and heart failure, the authors discovered no meaningful differences. In conclusion, increasing WBC was linked to incident AF throughout a 5-year follow-up in a community-based population. Authors have given findings that offer more proof that systemic inflammation and AF are related[57].

The increase in AF prevalence among residents of Fukushima Prefecture's evacuation zone following the Great East Japan Earthquake[58]. The authors used an observational cross-sectional design to examine the relationship between the prevalence of AF and WBC following the earthquake. Residents in the Fukushima Prefecture evacuation zone had higher neutrophil-to-lymphocyte ratio (NLR) and monocyte counts on average, which may indicate that inflammation and psychological stress played a significant role in mediating the development of AF following the earthquake[58].

There is not much data connecting high WBC, a sign of inflammation, to the emergence of AF

following an acute coronary syndrome (ACS). Therefore, authors have observed the relationship between WBC at hospital admission, changes in WBC while in the hospital, and the emergence of new-onset AF while being treated for an ACS[59]. Further research should be done to determine whether an increase in the WBC during hospitalization for an ACS is a simple predictor of new-onset AF in these patients[59].

While AF is a result of inflammation, the relationship between WBC and AF has not been adequately studied in large cohorts with prolonged follow-up. Higher total WBC, neutrophil, and monocyte counts all increased the probability of developing AF, whereas lymphocyte count had the opposite relationship[60]. Further research is necessary to develop preventative measures for AF because systemic inflammation may be the cause of this connection[60].

The most frequent adverse event following heart surgery is postoperative new-onset atrial fibrillation (PNAF)[61]. Numerous studies have been done on the inflammatory response as a potential underlying mechanism. WBC has been proven to be the only constant inflammatory parameter linked to PNAF in limited trials[61]. In a larger study population, this investigation sought to ascertain the relationship between perioperative WBC response and PNAF. The development of PNAF was not linked to the perioperative WBC response or any of its constituent parts[61].

The most typical postoperative rhythm problem after cardiac surgery is AF, which can develop in up to 50% of patients. The best methods for preventing AF following cardiac surgery are not developed yet, and its cause is still not fully understood. Research is currently being done to determine how inflammation and oxidative stress affect electrical remodeling, and recent studies have shown that CRP levels are higher in AF. The authors[62] look into the relationship between the development of postoperative AF following cardiac surgery and the postoperative WBC as a marker of inflammation. An increased postoperative WBC count, a classic indicator of inflammation, was linked to cardiac surgery. Postoperative WBC count independently predicts the emergence of postoperative AF with a more severe rise[62]. These findings add to the body of evidence indicating a connection between postoperative AF and the inflammatory response[62].

One of the most serious and frequent consequences following cardiovascular surgery, new postoperative AF is responsible for both early and late morbidities. The complete blood count (CBC) is a crucial blood test used frequently in clinical practice to examine cardiovascular disorders. Before surgery, hematological indices may be used to estimate the risk of POAF. In individuals receiving solitary CABG, valvular surgery, or combined treatments, these simple diagnostics must be considered[63].

Simple hematologic markers like NLR and red cell distribution width (RDW) have been used to forecast unfavorable outcomes in a variety of therapeutic contexts. Whether RDW and NLR can predict AF recurrence in individuals undergoing AF ablation was the goal of the investigation of Bazoukis et al[64]. Larger prospective trials could test the efficacy of straightforward and low-cost hematological markers like NLR in predicting AF recurrence in patients receiving catheter ablation[64].

Despite medical advancements, postoperative AF is a common complication following heart surgery that poses a challenge for cardiac surgeons. Numerous investigations have been made to aspect at different factors and determine which patients are most likely to develop POAF. RDW and epicardial adipose tissue (EAT) volume were examined as potential indicators of POAF in the investigation[65]. Even though patients who developed AF after surgery had high EAT volumes, age was the only variable that consistently predicted POAF in multivariate analysis. Additional research was required to determine the prognostic value of RDW and epicardial fat in POAF[65].

Interleukin-18

Interleukin-18 (IL-18) has a heterodimer structure, a molecular weight of 22.3 kDa, and is produced by macrophages, dendritic cells, epithelial cells, chondrocytes, osteoblasts, Kupffer cells, keratinocytes, astrocytes, renal tubular epithelial cells[66]. AF is taken on by and is maintained by inflammation. A key player in the inflammatory cascade is the pleiotropic proinflammatory cytokine IL-18. The authors hypothesized that AF patients have higher circulating IL-18 levels. Luan et al[67] study showed that IL-18 levels in patients with AF were increased. Compared to other inflammatory indicators that were known to be elevated in AF, IL-18 may be more effective[67].

Approximately 1% to 2% of the general population suffers from AF. The development of AF is significantly influenced by chronic inflammation, and IL-18 is a cytokine that promotes inflamma-

tion[68]. Wang et al[68] were interested to evaluate the relationship between IL-18 single nucleotide polymorphisms (SNPs) and the risk of AF. In AF patients compared to controls, the left ventricular ejection percentage was lower, and the left atrial diameter was larger, according to the presented results[68]. Even after correcting for several confounding variables, IL-18 SNPs were linked to a lower risk of AF. Particularly, the rs549908 GT genotype and G allele, as well as the rs360719 AG genotype and G allele, were linked to a lower incidence of AF. In conclusion, results show that IL-18 rs187238, rs360719, and rs549908 were linked to a lower incidence of AF in the patient population[68]. Moreover, the severity of AF and recurrence of AF following cryoablation may be connected to the levels of IL-18, which were higher in left atrial blood than peripheral blood[69].

Thrombospondin 1

TSPs are a group of matricellular proteins that can be released by a variety of cell types. The TSP family, which consists of five members (TSP1–5), has been separated into two subgroups, subgroup A and subgroup B, based on structural differences[70]. TSP-1 and TSP-2, which are both trimeric and structurally identical and belong to subgroup A, are joined by TSP-3, TSP-4, and TSP-5, which are pentameric and smaller than those in subgroup A[70].

Acute myocardial infarction (AMI) patients may experience AF, atrial flutter, atrial tachycardia, and many premature atrial beats as a result of atrial remodeling, the primary developmental cause of atrial arrhythmias. Although it has been demonstrated that TSP-1 is crucial for inflammatory and fibrotic processes, its function in atrial arrhythmias is not well understood. The authors[71] aimed to learn about TSP-1's function in AMI patients who have atrial arrhythmias. As a result, the authors concluded that TSP-1 is a potential novel indicator of atrial arrhythmias during AMI[71].

Another study[72] provided data indicating elevated TSP-1, transforming growth factor-β (TGF-β), and matrix metalloproteinase-9 (MMP-9) expression, as well as elevated atrial fibrosis in AF patients. Another interesting finding from this study[72] was that atrial fibrosis in people with AF was positively linked with serum levels of TSP-1, TGF- β, and MMP-9. In individuals with AF, the TSP-1/TGF-β/MMP-9 axis expressed more frequently, which led to atrial fibrosis[72].

Acylcarnitine

Esters of l-carnitine with fatty acids make up acylcarnitines. They belong to a sizable class of metabolites called non-protein amino acids. The Human Metabolome Database claims that the human body may contain more than 1,200 fatty acids[73,74]. The most prevalent cardiac arrhythmia is AF, yet its pathophysiology is not fully understood. Discovering new metabolic pathways implicated in the progression of the disease may be assisted by the use of metabolomics. The authors[75] demonstrated links between altered acylcarnitine metabolism and the incidence of AF in a general population for the first time, regardless of conventional AF risk variables. These findings[75] draw attention to metabolic changes that occur several years before the diagnosis of AF and may shed light on the pathophysiology of the condition. Future research is required to confirm our findings in a different cohort and to determine whether the link between acylcarnitines and AF is causal[75].

Furthermore, HF and AF development frequently include a fatty acid metabolic imbalance in mitochondria[76]. The authors[76] investigated the relationship between plasma acylcarnitine levels and the risk of developing HF or AF, as well as the potential moderating effects of the Mediterranean diet (MedDiet). Elevated long-chain acylcarnitines were linked to a greater risk of incident HF and AF in people with high cardiovascular risk. A combination of MedDiet and extra virgin olive oil may lessen the incidence of AF brought on by long-chain acylcarnitines[76].

In AF, remodeling of myocardial metabolism is well-established. It is unclear if the circulating metabolome of AF patients has changed as a result of this remodeling[77]. The purpose of this investigation was to identify blood metabolites that were dysregulated in AF and to assess whether any prospective circulating metabolites might be involved in arrhythmogenesis[77]. The metabolites dysregulated in persistent AF have been identified by these exploratory analyses as being fat intermediates, or acylcarnitines[77]. Furthermore, circulating acylcarnitines can cause arrhythmic contractions when exposed directly to the atrial myocardium, indicating that dysregulated acylcarnitine levels may play a role in the pathophysiology of AF[77].

Plasminogen Activator Inhibitor-1

Endothelial cells produce tissue-type plasminogen activator (TPA), which activates the fibrinolytic

proenzyme plasminogen. The fibrinolytic process is inhibited by PAI-1, a substance that blocks the action of TPA. Both are thrombosis and atherosclerosis risk factors as well as indicators of fibrinolysis[78,79]. The relationship between incident AF and TPA, PAI-1, and higher risk for stroke has not been shown. In this community-based cohort, PAI-1 and TPA levels were not associated with incident AF[80].

PAI-1 may, therefore, be a new therapeutic biomarker for AF, and the p53/PAI-1 signaling axis may contribute to the pathophysiological processes of the disease[81]. Moreover, following cardiac bypass, the development of AF is independently predicted by an increased preoperative or postoperative PAI-1 antigen concentration. Research is required to ascertain whether medications that lower PAI-1 concentrations also lower the risk of postoperative AF[82].

Triglycerides and High-Density Lipoprotein Cholesterol

Triglycerides (triacylglycerol or triacylglyceride) allow the bidirectional transference of adipose fat and blood glucose from the liver[83,84]. Similarly, one of the five main categories of lipoproteins is HDL. Lipoproteins are multiprotein complex particles that move all lipids (fat molecules) through the body's extracellular fluid (water). A total of 80-100 proteins on average make up each particle, which is structured by one, two, or three apolipoproteins (ApoA). While moving through the circulation, HDL particles grow, accumulating additional fat molecules and carrying up to hundreds of fat molecules per particle[85].

The most frequent comorbidity in patients with cardiovascular disease is dyslipidemia. Studies[86-89] examining the connection between AF and blood lipid profiles have been divergent. Li et al[86] explained that patients with AF had lower blood lipid levels than healthy controls, particularly lower LDL-C and HDL-C levels. Hypolipoproteinemia may make a patient more susceptible to AF development[86]. Boudi et al[87] pointed to a potential protective function for HDL-C in the management of ACS-related arrhythmias.

When additional cardiometabolic risk variables were taken into consideration in two community-based cohorts, HDL-C and TG, but not total cholesterol (TC) or low-density lipoprotein cholesterol (LDL-C) were linked to an increased risk of AF[88]. In the same way, high TC and LDL-C in midlife were associated with a lower risk of AF, but this association was present only within 5 years from lipid measurement and not thereafter[89]. On the contrary, low ApoA-I and HDL-C, as well as high TG/HDL-C ratio were related to a higher risk of AF over a follow-up of nearly 35 years. ApoB/ApoA-I ratio was not associated with AF risk[89].

Also, the risk of new AF is highly correlated with lower HDL-C levels while receiving therapy[89]. These results imply that in hypertensive patients with left ventricular hypertrophy, serial HDL-C testing can estimate AF risk more accurately than baseline HDL-C. Future research may examine if treatments that increase HDL-C can reduce the probability of having AF[90-92].

Conclusions

Leptin, adiponectin, HbA1c, ceramide, ferritin, fibrinogen, hematological indices (WBC, neutrophils, monocytes, NLR, RDW), IL-18, TSP-1, acyl-carnitine, PAI-1, TG, and HDL-C as biomarkers of diabetes play a significant role in the pathogenesis of AF as explained in Figure 2 and 3. However, no data was found, including fructosamine, glycated albumin, 1,5 anhydroglucitol, fetuin-A, α-hydroxybutyrate, mannose-binding lectin serine peptidase, transferrin, IL-1 receptor antagonist in AF. Understanding the interplay between diabetes and AF through the measurement of relevant biomarkers can contribute to better risk assessment, early detection, and the development of targeted therapeutic strategies for individuals at risk or already affected by these conditions. However, it is important to note that research in this field is ongoing, and new biomarkers and insights may emerge over time.

Conflict of Interest

The authors declare that they have no conflict of interests.

Ethics Approval and Informed Consent

Not applicable.

ORCID ID

S. Rafaqat: 0000-0001-7177-5602
A. Klisic: 0000-0001-7870-0996

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Availability of Data and Materials

Not applicable.

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