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REVIEW

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Sex-related differences of fatty acid-binding protein 4 and leptin levels in atrial fibrillation: an updated review

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Abstract

Atrial fibrillation (AF) is a prevalent cardiac arrhythmia affecting millions of individuals worldwide and posing significant challenges to healthcare systems. The growing body of research has uncovered sex-related differences in AF pathophysiology, including the role of fatty acid-binding protein 4 (FABP4) and leptin as potential biomarkers. FABP4 and leptin, key adipokines involved in cardiovascular health, have been linked to inflammation, oxidative stress, and endothelial dysfunction, all of which may contribute to AF development. These adipokines exhibit sex-specific differences in their concentrations, with females generally showing higher FABP4 levels and males displaying distinct leptin profiles. Furthermore, hormonal influences, particularly estrogen, and testosterone, play significant roles in shaping AF risk and atrial remodeling. Estrogen is associated with cardioprotective effects, while testosterone may exert proarrhythmic effects. Understanding these sex-specific mechanisms could lead to more tailored and effective clinical management of AF. The future of AF research holds promise for precision medicine, novel therapeutic targets, artificial intelligence integration, and personalized care approaches. Emphasizing patient-centered care, telemedicine, and multidisciplinary collaboration can further enhance AF management and improve patient outcomes. In conclusion, recognizing and addressing sex-related factors in AF pathophysiology offer opportunities for gender-responsive interventions and advancements in AF management. Implementing these insights may pave the way for targeted therapies and improved quality of life for individuals affected by AF.

Keywords Adipocytes, Arrhythmia, Metabolism, Metabolic syndrome

Introduction

Atrial fibrillation (AF), a prevalent cardiac arrhythmia, has become a significant global health concern due to its rising incidence and associated morbidity and mortality rates [1]. This complex disorder affects millions of individuals worldwide and is characterized by irregular electrical impulses within the heart's atria, leading to abnormal and often rapid heart rhythms [2]. Numerous studies have shed light on various risk factors contributing to the development and progression of AF, including age, hypertension, obesity, and diabetes [3]. However, an emerging area of research focuses on the role of sex-related factors in influencing AF pathogenesis and

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progression [4]. Sex differences have been increasingly recognized as important determinants in cardiovascular diseases, and atrial fibrillation is no exception. While both sexes can be affected by AF, disparities in disease prevalence, presentation, and outcomes between men and women have been observed [5]. Although numerous studies have investigated the influence of sex hormones and other physiological factors in AF, recent attention has turned toward the role of specific biomarkers that may differ between males and females. Fatty acid-binding protein 4 (FABP4) and leptin, two key adipokines, have emerged as potential markers that could play crucial roles in AF pathophysiology [6, 7]. FABP4 is predominantly expressed in adipose tissue and is involved in fatty acid transport and lipid metabolism regulation [8]. It has been implicated in various metabolic disorders and cardiovascular diseases. Leptin, another adipokine, is known for its role in appetite regulation and energy homeostasis, but it also exerts effects on cardiac structure and function [9]. Notably, recent research has suggested that both FABP4 and leptin may exhibit sex-specific variations in their levels and effects on cardiovascular health [10, 11]. These differences could potentially contribute to the observed disparities in AF prevalence and outcomes between males and females. As such, understanding the sex-related differences in FABP4 and leptin levels and their association with AF could open new avenues for targeted therapies and personalized management approaches in this debilitating arrhythmia. In this review, we aim to explore the existing body of literature on the sex-related difference between FABP4 and leptin levels in atrial fibrillation. By analyzing the available data and identifying potential gaps in knowledge, we hope to contribute to a deeper comprehension of the interplay between sex-specific factors and the pathophysiology of AF. Ultimately, such insights may pave the way for novel therapeutic strategies and improved clinical outcomes for both male and female patients affected by atrial fibrillation.

Methods

A comprehensive literature search was conducted to identify relevant studies exploring the sex-related differences between fatty acid-binding protein 4 (FABP4) and leptin levels in atrial fibrillation. The search encompassed electronic databases such as PubMed, Embase, Scopus, Web of Science, and Google Scholar, with a focus on studies published up to the time of this review (September 2021). The search strategy involved the utilization of specific keywords and medical subject headings (MeSH) terms related to atrial fibrillation, sex differences, FABP4, leptin, and adipokines. The combinations of these terms were tailored to extract relevant information while ensuring a comprehensive search approach. Additionally, reference lists of relevant articles and reviews were manually examined to identify potential additional studies that may have been missed in the electronic search. Inclusion criteria were set to encompass studies that investigated the association between FABP4 and leptin levels and atrial fibrillation while highlighting sex-specific differences. Various types of studies, including clinical trials, observational studies, cross-sectional studies, and case–control studies, were considered for inclusion in this review. The studies had to be published in the English language to ensure a cohesive and accessible analysis. Conversely, exclusion criteria were applied to remove studies that were not directly related to the topic or did not meet the specified criteria. Duplicate publications, conference abstracts, and articles published in languages other than English were excluded from the review. After the initial search and application of inclusion and exclusion criteria, relevant studies were carefully assessed for their methodological quality and the relevance of their findings to the research question. Data from selected studies were extracted, and key findings were summarized to provide a clear and concise overview of the observed sex-related differences in FABP4 and leptin levels in the context of atrial fibrillation. The methodology employed in this review aimed to bring together the existing evidence on the sex-related differences of FABP4 and leptin levels in atrial fibrillation. By consolidating findings from various studies, this review sought to contribute valuable insights into potential sex-specific mechanisms underlying the pathophysiology of atrial fibrillation and identify potential avenues for future research and therapeutic interventions.

Main text

Sex-specific differences in FABP4 and leptin levels

Role of FABP4 in cardiovascular physiology

FABP4, also known as adipocyte fatty acid-binding protein (A-FABP), is primarily expressed in adipose tissue and plays a crucial role in lipid metabolism and transport [8]. FABP4 functions as an intracellular lipid chaperone, facilitating the uptake and trafficking of fatty acids within cells [12]. It is involved in the regulation of lipid storage, lipid droplet formation, and the release of fatty acids for energy production or lipid synthesis [13]. Apart from its role in adipocytes, FABP4 is also found in macrophages and endothelial cells, implicating its involvement in various aspects of cardiovascular physiology [8]. Studies have linked FABP4 to several metabolic disorders, including obesity, insulin resistance, and type 2 diabetes [8, 12, 13]. Additionally, emerging evidence suggests that FABP4 may play a significant role in cardiovascular diseases, including atherosclerosis, myocardial infarction, and heart failure [13]. Increased levels of FABP4 have

been associated with inflammation, oxidative stress, and endothelial dysfunction, all of which contribute to the development and progression of cardiovascular pathologies [14].

Gender-specific variations in FABP4 levels

Sex-related differences in FABP4 levels have been a subject of growing interest in recent research. Several studies have reported variations in FABP4 concentrations between males and females [15]. For instance, some investigations have found higher circulating FABP4 levels in women compared to men, particularly in the context of obesity and metabolic syndrome [16]. This observation may be linked to the higher percentage of body fat in women and the greater production of FABP4 by adipose tissue. Moreover, hormonal influences, particularly estrogen, have been proposed as potential mediators of the observed sex-specific differences in FABP4 levels [17]. Estrogen has been shown to modulate adipose tissue metabolism FABP4 expression, possibly explaining the discrepancies in FABP4 concentrations between males and females [18]. However, further research is required to fully elucidate the complex interplay between sex hormones and FABP4 regulation.

Leptin's impact on cardiac structure and function

Leptin, an adipokine predominantly produced by adipose tissue, is well known for its role in appetite regulation and energy homeostasis [19]. However, it is now evident that leptin also exerts significant effects on the cardiovascular system [20]. Leptin receptors are expressed in various cardiac tissues, including cardiomyocytes and endothelial cells, indicating that leptin can directly influence cardiac structure and function [21]. Leptin has been linked to the regulation of cardiac contractility, cardiac remodeling, and the modulation of sympathetic nervous system activity [22]. Additionally, it plays a role in the regulation of blood pressure and vascular tone [23]. Animal studies have demonstrated that leptin deficiency or resistance can lead to adverse cardiovascular outcomes, while excess leptin levels may contribute to cardiac hypertrophy and fibrosis [24].

Sex-related differences in leptin concentrations

Gender-specific differences in leptin levels have been consistently observed, with women generally exhibiting higher circulating leptin concentrations than men [25]. This variation is primarily attributed to the influence of sex hormones, particularly estrogen, on leptin production and secretion. Estrogen has been shown to upregulate leptin gene expression, leading to increased leptin synthesis and release from adipose tissue. Interestingly, the gender-specific differences in leptin levels are more prominent in premenopausal women compared to postmenopausal women, suggesting a diminishing influence of estrogen on leptin regulation after menopause [26]. This finding underscores the importance of hormonal fluctuations across the lifespan in shaping leptin concentrations and its potential implications for cardiovascular health.

Association of atrial fibrillation and fatty acid-binding protein 4 and leptin levels

The association between AF and FABP4 and leptin levels has been the subject of growing interest in cardiovascular research. While the exact mechanisms underlying this relationship are not fully elucidated, several potential pathways have been proposed based on experimental evidence and observational studies.

FABP4 and AF

FABP4, a key adipokine involved in lipid metabolism, has been linked to various metabolic and cardiovascular disorders. In the context of atrial fibrillation, the following mechanisms have been suggested: (a) Inflammation and Oxidative Stress: Elevated FABP4 levels have been associated with increased systemic inflammation and oxidative stress. Chronic inflammation and oxidative stress can promote atrial remodeling, leading to structural changes in the atrial tissue, which predisposes the heart to AF. (b) Endothelial Dysfunction: FABP4 has been implicated in endothelial dysfunction, impairing the endothelium's ability to regulate vascular tone and maintain vascular integrity. Endothelial dysfunction can contribute to increase the risk of AF development. (c) Insulin Resistance and Diabetes: FABP4 is closely linked to insulin resistance and type 2 diabetes. Insulin resistance can impact the myocardium and contribute to atrial fibrosis, electrical remodeling, and increased susceptibility to AF. (d) Cardiac Adiposity: FABP4 is predominantly expressed in adipose tissue, including pericardial adipose tissue surrounding the heart. The release of FABP4 from pericardial adipose tissue may directly affect adjacent cardiac tissue, contributing to atrial electrical and structural changes. (e) Autonomic Nervous System Dysfunction: FABP4 has been implicated in autonomic nervous system dysfunction, leading to an imbalance between sympathetic and parasympathetic tone [27–31].

Leptin and AF

Leptin, another adipokine, plays a critical role in appetite regulation and energy homeostasis. In the context of AF, several mechanisms linking leptin the arrhythmia have been proposed: (a) Cardiac Remodeling: Leptin receptors are expressed in cardiac tissue, and leptin has been shown to promote cardiac hypertrophy and fibrosis.

These changes can lead to alterations in the atrial substrate, increasing the risk of AF. (b) Sympathetic Nervous System Activation: Leptin can stimulate the sympathetic nervous system, leading to increased heart rate and contractility. Chronic sympathetic activation can contribute to electrical remodeling and AF initiation. (c) Inflammation and Fibrosis: Leptin has pro-inflammatory properties and can activate immune cells, leading to atrial inflammation and fibrosis, which are hallmarks of AF development. (d) Oxidative Stress: Leptin can induce oxidative stress in the myocardium, promoting atrial remodeling and electrical instability. (e) Autonomic Dysfunction: Leptin is involved in autonomic nervous system regulation, and disruptions in autonomic balance have been implicated in AF pathogenesis [32–36].

Sex-related factors and atrial fibrillation

Sex hormones, particularly estrogen, and testosterone, play a significant role in modulating various physiological processes, including cardiovascular function. It has been observed that there are sex-related differences in the prevalence, presentation, and outcomes of AF, suggesting a potential influence of sex hormones on AF pathogenesis. Here, we review the role of sex hormones in AF and their impact on cardiac electrophysiology. Figure 1 demonstrates the mechanism behind sex hormones and AF.

Estrogen and AF

Estrogen is a primary female sex hormone produced predominantly by the ovaries [37]. Premenopausal women generally have higher estrogen levels compared to men. Several lines of evidence suggest that estrogen may have protective effects against AF: (a) Anti-inflammatory and Antioxidant Properties: Estrogen has anti-inflammatory and antioxidant properties that may help reduce atrial inflammation and oxidative stress, contributing to a lower risk of AF development. (b) Enhancing Nitric Oxide Production: Estrogen has been shown to enhance nitric oxide production, promoting vasodilation and improving endothelial function. This can have a favorable impact on atrial conduction and reduce the risk of AF. (c) Modulation of Ion Channels: Estrogen has been reported to influence ion channels involved in cardiac electrophysiology, potentially affecting atrial repolarization and refractoriness [38–40]. However, the protective effects

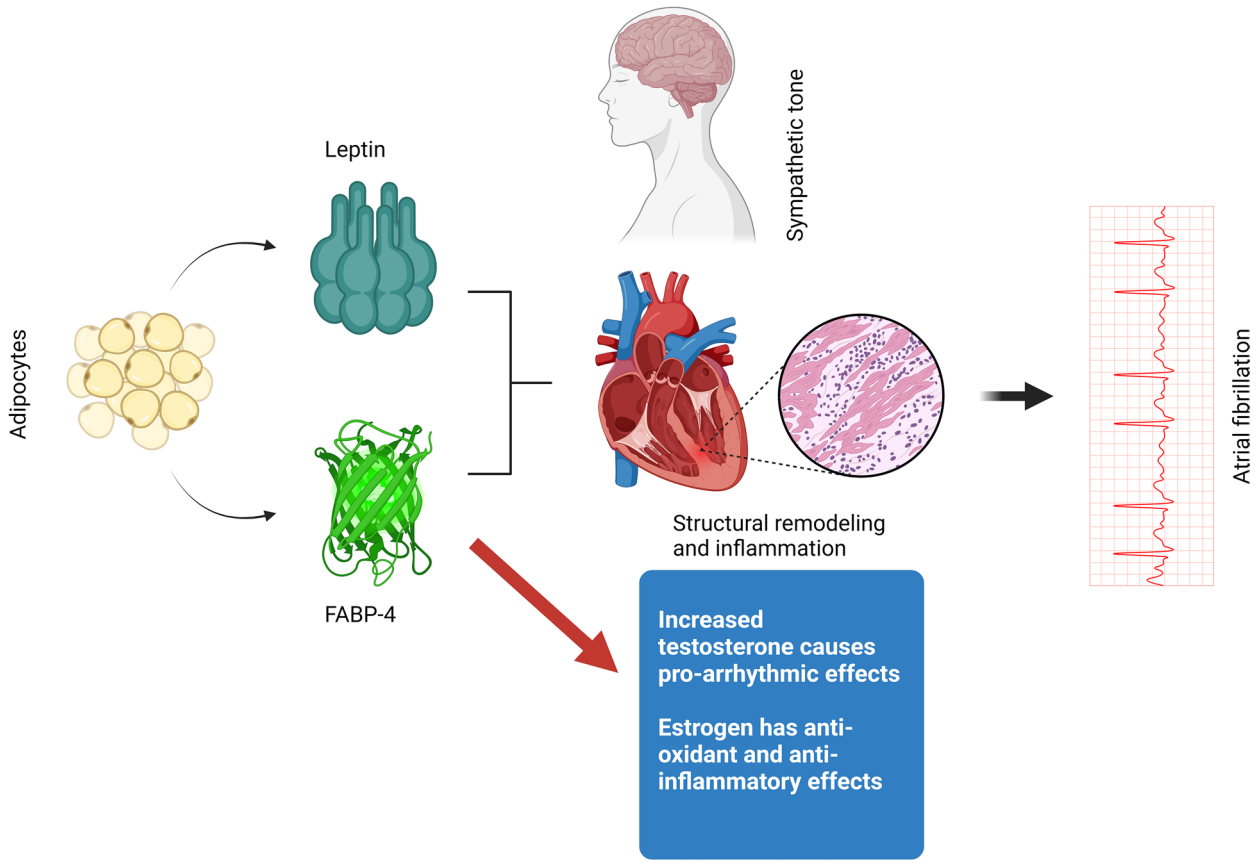

Fig. 1 Mechanism of sex hormones in causing AF

of estrogen on AF are complex and may be influenced by factors such as age, hormonal fluctuations during the menstrual cycle, and the presence of other risk factors.

Testosterone and AF

Testosterone is the primary male sex hormone synthesized mainly in the testes [41]. While estrogen's role in AF has received more attention, emerging evidence suggests that testosterone may also influence AF risk: (a) Proarrhythmic Effects: Testosterone has been associated with increased sympathetic activity, which may promote arrhythmogenic triggers and facilitate AF initiation. (b) Androgen Receptor Expression: The expression of androgen receptors in the heart may contribute to the direct effects of testosterone on atrial electrical properties. (c) Interaction with Other Risk Factors: Testosterone levels may interact with other risk factors, such as obesity and metabolic disorders, to influence AF risk [42, 43].

Mechanistic insights into sex-specific differences in AF pathophysiology

Sex-specific differences in AF pathophysiology have been increasingly recognized, with males and females exhibiting variations in AF prevalence, risk factors, and response to treatment. Understanding the underlying mechanisms contributing to these sex-related disparities is essential for developing more tailored and effective therapeutic strategies.

Potential interactions between FABP4, leptin, and AF

FABP4 and leptin, two adipokines implicated in cardiovascular health, may play roles in the pathophysiology of AF, and their effects could differ between males and females. (a) FABP4 and Leptin Cross talk: FABP4 has been shown to induce the expression of leptin in adipocytes, establishing a possible interplay between these adipokines. Leptin, in turn, can modulate FABP4 production, indicating a complex regulatory relationship between the two molecules [15]. (b) Inflammation and Atrial Remodeling: Both FABP4 and leptin have been associated with inflammation and oxidative stress, which are key contributors to atrial remodeling and the development of AF. The interactions between these adipokines and their combined effects on inflammation may contribute to sex-specific differences in AF susceptibility. (c) Hormonal Modulation: The expression and secretion of FABP4 and leptin can be influenced by sex hormones, suggesting that hormonal fluctuations across the lifespan may contribute to sex-specific variations in their levels and impact AF pathogenesis [16]. The epicardial fat-secreted adipokines that cause myocardial lipidosis, inflammation, and fibroblast proliferation are factors in the atrium's gradual fibrotic remodeling. The atrial myocardium is thought to be the substrate for the emergence and maintenance of electrophysiological abnormalities due to its disorder and loss of homogeneity.15 The clinical manifestation of these degenerative alterations is atrial fibrillation. To categorize these atrial pathologies/stages into distinct cohorts, the EHRAS classification (EHRAS Class I–IV) is a first attempt. Obesity-related cardiomyopathy was specifically categorized as EHRAS Class IVf and EHRAS III due to the presence of collagen depositions as well as adipocyte infiltration into the heart and atrial fibrosis [15]. The biomarkers analyzed here could aid in the sex-specific characterization of the atrial substrate, which is highly important. Important because the predictive ability for each type of AF appears to change over time and depend on the underlying substrate, with extrapulmonary vein triggers frequently present in persistent AF and a heavier emphasis placed on a modified and complex substrate in paroxysmal AF.

One study showed that: (i) fatty acid-binding protein 4 (FABP4) and leptin levels were higher in women than in men in both cohorts ($P<0.01$). In women, FABP4 levels were higher on AF cohort (20 ± 14 control, 29 ± 18 paroxysmal AF and 31 ± 17 ng/mL persistent AF; $P<0.01$). In men, leptin levels were lower on AF cohort (22 ± 15 control, 13 ± 16 paroxysmal AF and 13 ± 11 ng/mL persistent AF; $P<0.01$). (ii) In female with paroxysmal AF, there was a lower acetylcholinesterase and higher carbonic anhydrase levels with respect to men ($P<0.05$). (iii) Adipokines have an important role on discriminate AF recurrence after ablation. In persistent AF, FABP4 was the best predictor of recurrence after ablation (1.067, 95% confidence interval 1–1.14; $P=0.046$) [15].

Hormonal influences on atrial remodeling

Sex hormones, particularly estrogen, and testosterone, play pivotal roles in shaping atrial tissue properties and remodeling processes. (a) Estrogen and Atrial Structure: Estrogen exerts protective effects on the heart, promoting ng maintenance of healthy atrial structure and function. It has been associated with improved atrial contractility, reduced fibrosis, and enhanced endothelial function, all of which can attenuate AF risk. (b) Testosterone and Atrial Remodeling: On the other hand, testosterone has been implicated in cardiac remodeling, potentially promoting atrial fibrosis and electrical instability, leading to an increased susceptibility to AF. (c) Menopause and Hormonal Changes: Menopause represents a critical phase when hormonal changes can impact atrial tissue properties, leading to an increased risk of AF in post-menopausal women [17–19].

The impact of sex on cardiac electrophysiology

Sex-specific differences in cardiac electrophysiology can influence the initiation and maintenance of AF. (a) Electrical Properties of Atrial Myocytes: Males and females may exhibit variations in atrial myocyte electrophysiological properties, including action potential duration and refractoriness, which can impact arrhythmia susceptibility. (b). Autonomic Nervous System: Sex differences in autonomic nervous system function can lead to variations in heart rate variability and autonomic modulation of atrial electrophysiology, potentially influencing AF development. (c) Ion Channels: Expression and function of ion channels involved in cardiac repolarization can differ between sexes, impacting atrial conduction and the occurrence of reentrant circuits in AF. (d) Sex-Specific Gene Expression: Sex hormones can influence gene expression in the heart, leading to the differential regulation of ion channels and other proteins involved in atrial electrophysiology.

Clinical implications

The emerging understanding of sex-specific differences in fatty acid-binding protein 4 (FABP4) and leptin levels in atrial fibrillation (AF) could have significant implications for clinical management. Incorporating sex-specific biomarkers, such as FABP4 and leptin, into AF risk assessment may improve risk stratification and prognosis. For instance, higher FABP4 levels in females and specific Leptin concentrations in males could be considered indicators of increased AF risk in each respective sex. With this information, clinicians may develop personalized treatment plans for AF patients, tailoring therapeutic interventions based on individual sex-related factors. For example, females with elevated FABP4 levels might benefit from targeted interventions to mitigate inflammation and oxidative stress, while males with higher leptin concentrations may require approaches to reduce sympathetic activation. Such tailored treatment strategies could lead to better outcomes and enhanced patient care.

Sex-related factors extend beyond biomarkers, encompassing the entire spectrum of AF risk factors and pathophysiology. As part of gender-responsive approaches to AF prevention, healthcare providers should be aware of sex-specific risk profiles and take them into account during patient evaluation. For women, understanding the impact of hormonal fluctuations, especially during menopause, can guide discussions on the risks and benefits of hormone replacement therapy and other interventions. For men, recognizing the potential influence of testosterone on atrial remodeling may prompt lifestyle modifications or targeted therapies to reduce AF risk. Furthermore, addressing sex-specific risk factors such as obesity and diabetes in a gender-tailored manner may enhance preventive efforts.

The mechanistic insights into the role of FABP4, leptin, and sex hormones in AF pathophysiology may highlight novel therapeutic targets. Developing pharmaceutical agents or interventions that target the pathways influenced by these biomarkers could offer innovative approaches to AF treatment. For example, therapies that mitigate the inflammatory response associated with elevated FABP4 levels or modulate leptin-mediated cardiac remodeling might hold promise in AF management. Additionally, sex hormone-based therapies or interventions that consider hormonal fluctuations during the menopausal transition could be explored for their impact on AF prevention and outcomes. However, it is crucial to note that translating these mechanistic insights into clinical applications requires rigorous research, including randomized controlled trials and long-term outcome studies. Identifying safe and effective therapeutic targets is a complex process, and any interventions must undergo rigorous evaluation to ensure patient safety and efficacy.

Future directions

Advancements in genomic research and biomarker discovery may pave the way for precision medicine in AF. Identifying genetic variants associated with AF susceptibility and treatment response could enable tailored therapies based on an individual's genetic profile. Additionally, the integration of sex-specific biomarkers, such as fatty acid-binding protein 4 (FABP4) and leptin, could further enhance precision medicine approaches, enabling more targeted interventions and optimized treatment strategies for each patient. Continued research into the underlying mechanisms of AF pathophysiology may uncover novel therapeutic targets. Identifying specific pathways, ion channels, or molecular mechanisms that contribute to AF initiation and maintenance could lead to the development of innovative pharmacological agents or gene therapies that address the root causes of AF. Targeting these novel pathways could offer more effective treatments with fewer side effects. The integration of artificial intelligence and machine learning algorithms in AF research holds immense potential. Predictive modeling and data-driven approaches can aid in identifying high-risk AF populations, predicting disease progression, and optimizing treatment plans. Machine learning algorithms can analyze vast amounts of patient data to identify patterns and risk factors, assisting clinicians in making more informed decisions. A greater emphasis on sex-specific AF research is crucial, considering the observed disparities in AF prevalence, presentation, and outcomes between males and females. Future

studies should include larger, well-designed cohorts that account for sex-related factors and investigate the interactions between sex hormones, adipokines, and AF pathophysiology. Understanding these sex-specific mechanisms may lead to more targeted and sex-responsive therapeutic approaches. Emphasizing patient-centered care and shared decision-making is vital for optimizing AF management. Tailoring treatment plans to individual patient preferences, values, and lifestyle factors can improve treatment adherence and overall patient satisfaction. Empowering patients with information and engaging them in the decision-making process can lead to better long-term outcomes and improved quality of life. Telemedicine and digital health solutions have gained prominence, especially in light of global health challenges. Utilizing telemedicine for remote patient monitoring, teleconsultations, and virtual follow-ups can enhance access to specialized AF care, particularly in underserved areas. Digital health solutions, including mobile applications and wearable devices, may facilitate patient self-management and improve AF detection and monitoring. AF management requires a multidisciplinary approach, involving cardiologists, electrophysiologists, nurses, pharmacists, and other healthcare professionals. Collaborative efforts and interdisciplinary research can foster a comprehensive understanding of AF pathophysiology and lead to holistic and innovative management strategies.

Conclusion

The investigation FABP4 and leptin as potential biomarkers in AF has provided valuable insights into the complex pathophysiology of this arrhythmia. Both FABP4 and leptin exhibit sex-related differences in their levels and effects on cardiovascular health. Elevated FABP4 levels have been associated with inflammation, oxidative stress, and endothelial dysfunction, all of which may contribute to AF pathogenesis. Leptin, on the other hand, influences cardiac structure, autonomic function, and inflammation, which can impact AF development. These sex-specific differences in FABP4 and leptin concentrations highlight the importance of considering gender-specific factors in AF research and clinical management. Moreover, hormonal influences, such as estrogen and testosterone, play critical roles in AF pathophysiology. Estrogen has been associated with cardioprotective effects, whereas testosterone may exert proarrhythmic effects. These sex hormones influence atrial remodeling, electrical properties, and autonomic modulation, contributing to sex-related differences in AF risk. The future of AF research and clinical practice offers exciting prospects for improved patient care. Precision medicine, utilizing genomic research and sex-specific biomarkers, holds promise for personalized treatment approaches. Identifying novel therapeutic targets and integrating artificial intelligence into AF research can lead to innovative pharmacological interventions and predictive modeling for better risk assessment. Emphasizing patient-centered care, telemedicine, and multidisciplinary collaboration can enhance patient outcomes and access to specialized AF management.

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JM contributed to concept; SS and BAA were involved in methodology; MSW contributed to validation; MHHK, UK, and JM were involved in literature search; SS, BAA, MSW, MHHK, and UK contributed to first draft; and JM and SS were involved in final draft.

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