

The association between adipokines dysregulation and the occurrence of atrial fibrillation and obese patients, is it relevant?

La asociación entre la desregulación de adipocinas y el desarrollo de la fibrilación auricular en pacientes obesos, ¿es realmente relevante?

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Abstract

Atrial fibrillation (AF) is the most common arrhythmia, affecting approximately 33.5 millions of people worldwide. Unfortunately, the prevalence of this arrhythmia will increase within the following two decades, resulting in a higher mortality rate and a higher economic burden for public health services. Obesity, specifically central obesity, plays an essential role in developing AF by increasing pericardial fat and epicardial adipose tissue thickness, generating a chronic inflammation state where dysregulation of the serum concentration of several proinflammatory proteins occurs and indirectly promotes AF. Therefore, recent research has focused on analyzing the circulating concentration of different molecules, including pro and anti-inflammatory adipokines, and their association with AF. Herein, we review several studies addressing the association of adipokines with the onset or recurrence of AF to establish such association as a potential biomarker for the prevention or adequate treatment of this arrhythmia. We concluded that the insight into this topic is very controversial and needs further research.

Keywords: Atrial fibrillation. Obesity. Adipokines. Inflammation. Biomarkers.

Resumen

La fibrilación auricular (FA) es la arritmia más común, la cual afecta aproximadamente al 33.5 millones de la población mundial. Desafortunadamente esta prevalencia aumentará en las próximas dos décadas, lo que resultará en una mayor tasa de mortalidad y una mayor carga económica para los sistemas de salud pública. La obesidad, específicamente la obesidad central, juega un papel esencial en el desarrollo de la fibrilación auricular, al aumentar tanto el volumen de grasa pericárdica como el grosor de la grasa epicárdica, lo que contribuye a generar un estado de inflamación crónica donde se produce una desregulación de la concentración sérica de varias proteínas proinflamatorias que indirectamente promueven la FA. Por ello, investigaciones recientes se han centrado en analizar la concentración circulante de diferentes moléculas, incluidas las adipocinas pro y anti-inflamatorias, y su asociación con la fibrilación auricular. En este trabajo se revisan varios estudios que abordan la asociación de las adipocinas con la aparición o recurrencia de la fibrilación auricular para establecer dicha asociación como un potencial biomarcador para la prevención o el tratamiento adecuado de esta arritmia. Llegamos a la conclusión de que la información sobre este tema es controversial y requiere ahondar en su investigación.

Palabras clave: Fibrilación auricular. Obesidad. Adipocinas. Inflamación. Biomarcadores.

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Introduction

Atrial fibrillation (AF) is a supraventricular arrhythmia characterized by a disorganized electrical atrial activity resulting from a dysregulation of the atria's excitation process and the irregular activation of the cardiac ventricles¹. It is the most common cardiac arrhythmia, affecting 33.5 millions of individuals worldwide. Unfortunately, this prevalence is increasing so much that it will be duplicated by 2040²⁻⁴. In general, AF is a degenerative, progressive, and multifactorial disease, often associated with other cardiovascular alterations such as hypertension, ischemia, or structural modifications of the heart, increasing the risk of stroke and death. This arrhythmia is an electrophysiological pathology that presents a dynamic progression from paroxysmal to permanent AF, mainly because of molecular, ionic, and structural remodeling⁵.

AF and obesity

Due to its high prevalence, obesity is a severe global health problem (41.9%)². Because this pathology is closely associated with the development of AF, this arrhythmia is also on the rise within the obese population⁶. Specifically, pericardial fat volume increases the risk for this condition because it correlates with left atrial enlargement and electrical abnormalities⁷. Pericardial fat comprises paracardial adipose tissue and epicardial adipose tissue (EAT); the latter is near the myocardium, which enables paracrine signaling between EAT and the myocardium. Because EAT secretes different adipokines, a high-fat percentage in the epicardium could dysregulate this adipokine synthesis and promote macrophage infiltration within the cardiac tissue, which in turn could predispose to the development of AF⁸⁻¹¹. Several studies pointed out a direct and independent association between EAT abundance and the occurrence of this arrhythmia^{10,11}.

Moreover, EAT can promote fibrosis within the atrial myocardium by synthesizing and secreting profibrotic factors, such as IL-6, 8, 1 β , and TNF- α , as well as several members of the transforming growth factor- β superfamily, as activin A which pertain fibrotic effects on the myocardium¹²⁻¹⁴. Likewise, the activation of non-canonical WNT signaling pathways promotes myofibroblast and metalloproteinase activation or the expression of genes involved in this inflammatory process, leading to AF¹⁵.

Association of adipokines circulating concentrations with the onset or re-emergence of AF

Adipokines are essential in different physiological mechanisms, including cardiovascular function¹⁶. Thus, adipokine dysregulation could contribute to the development of AF. Although the precise mechanisms by which adipokines participate in the development of this arrhythmia have not been completely elucidated, several studies have addressed this issue by describing the association between anti-inflammatory and proinflammatory adipokines and the surge of AF¹⁷.

Several studies associate adipokines, like adiponectin and apelin, with cardioprotective effects against AF. On the contrary, other associate adipokines, like resistin and lipocalin-2 or neutrophil gelatinase-associated lipocalin (NGAL), with the development of cardiac pathologies¹⁷.

Because several studies have reported contradictory associations between these adipokines and the presence of AF, we decided to gather information regarding such association under impaired metabolic conditions (Table 1). To write this review, we selected scientific articles related to this topic published in the PubMed database of the National Library of Medicine from the National Center for Biotechnology Information. As search strategy, we employed MeSh (Medical subject headings) using the words adipokines and AF, plus the word review. No filters were applied to retrieve the articles.

Adiponectin

Adiponectin is an anti-inflammatory, anti-atherogenic, insulin-sensitizing adipokine vital in several metabolic pathways, including triggering through the adipoR1 receptor, a specific type of T-channels (Cav3.2) within the trigeminal ganglion neurons responsible for the nociceptive behavior in mice¹⁸. This 30 kDa multimeric protein is mainly synthesized within white adipose tissue but is also present in others, including cardiac tissue¹⁹. To establish the association of serum concentrations of four adipokines with AF or the risk of developing it, Peller et al. (2020)²⁰ quantified baseline serum levels of adiponectin, leptin, resistin, and tumor necrosis factor- α in diabetic patients with or without AF. Patients with known AF presented higher baseline levels of adiponectin and resistin than those without it, whereas the two groups did not differ in leptin and tumor necrosis-alpha. Moreover, no significant association was determined between adiponectin

Table 1. Studies reporting an association between adipokines' serum concentration and atrial fibrillation

Adipokine	Studies reporting a positive association with atrial fibrillation	Studies reporting a negative association with atrial fibrillation	Studies reporting a non-statistically significant association with atrial fibrillation
Adiponectin	Peller, et al., 2020 Ermakov, et al., 2016 Macheret, et al., 2015 Shimano, et al., 2008		Peller, et al., 2020
Apelin		Ellinor, et al., 2006 Gurger, et al., 2014 Salska, et al., 2018 Bohm, et al., 2021	Kim, et al., 2020
Resistin	Peller, et al., 2020 Samanidis, et al., 2020 Chang, et al., 2020 Rachwalk, et al., 2023		Muse, et al., 2015
NGAL	Mlodawska, et al., 2017		Sonmez, et al., 2014

concentration and the development of AF after a 5.4-year patient follow-up. In contrast, a study on female patients with controlled diabetes described the strong association between high adiponectin levels and the risk of developing AF²¹. Likewise, another study also described a strong association between high circulating adiponectin levels and an increased risk of AF onset in elderly patients without a previous diagnosis of cardiovascular diseases²². Moreover, following these two previous studies, Shimano et al. (2008)²³ compared adiponectin serum levels among patients with persistent or paroxysmal AF with the corresponding serum levels of healthy patients, stating that patients with persistent AF had the highest serum levels of adiponectin, followed by those corresponding to patients with paroxysmal AF and finally those of healthy patients. The latter constitutes a paradox since adiponectin is considered an anti-inflammatory, insulin-sensitizing, anti-atherogenic adipokine; therefore, its high circulating levels are usually associated with advantageous health conditions. Many researchers have addressed this inconsistency, reaching the following conclusions: high serum levels of adiponectin in heart patients are caused by other inflammatory processes to counteract the damaging effects of such inflammation²⁴. Alternatively, an increase in adiponectin concentration under adverse health conditions could result from a deficient regulation of adiponectin signaling mechanism often observed in elderly patients²⁵. However, the exact cause of adiponectin's increase in patients with some pathologies under which the adiponectin concentration is generally low has yet to be determined.

Apelin

Apelin is considered an adipokine due to its expression within the adipose tissue; nevertheless, this peptide hormone is present in various organs, including the heart²⁶. Apelin binds to a G-coupled membrane receptor (APJ) to trigger physiological processes such as homeostasis and energy metabolism²⁷. The apelin receptor was isolated in 1993; later, in 1998, Tatemoto et al. identified an endogenous ligand for this receptor within the bovine stomach, naming it apelin²⁸. The apelin gene translates into a prepropeptide with a secretory signal that, after cleavage, produces several active peptide forms that act on different organs on binding to the APJ receptor. The apelin isoforms 36 and 13 significantly participate in the cardiovascular system, making apelin-13 the most potent peptide²⁹. This isoform participates in several functions within the cardiovascular system, such as myocardial contraction, vascular relaxation, blood pressure regulation, and insulin sensitivity³⁰. On the other hand, the apelin receptor regulates ventricular excitability, conduction, contractility, and refractoriness³¹.

Interestingly, studies conducted on APJ knockout mice showed that these mice did not develop a heart at all, resulting in prenatal mortality³². On the contrary, the apelin knockout mice presented a full-term development³³. The latter suggests that the APJ receptor could bind to different ligands to trigger the corresponding mechanisms of action. In fact, in 2013, a second ligand for this receptor was discovered in zebrafish during its embryonic development. This ligand, named Elabela

for “epiboly late because endoderm late,” was found by two research groups^{34,35}, and apelin is also involved in cardiovascular function³⁶.

Because apelin participates in the action potential length through different ionic channels, both clinical and experimental studies have focused on the association between apelin concentration and the presence of AF; in the clinical studies, results appeared to be controversial since some described a decrease in apelin serum levels of patients with paroxysmal or persistent AF in comparison with the levels observed in patients with normal sinus rhythm³⁷⁻³⁹. In contrast, other studies reported reduced content within the right atrial appendages but no difference in serum apelin concentration between patients with and without AF⁴⁰. Based on the fact that apelin negatively regulates oxidative stress due to elevated NADPH oxidase activity, experimental studies conducted on apelin knockout mice revealed that NADPH oxidase activity increased in apelin knockout mice in comparison with the activity observed in WT controls⁴¹; it is necessary to consider that while studies on animal models demonstrate that apelin is directly involved in preventing *in situ* oxidative stress and possibly in preventing AF, a change in apelin serum levels does not necessarily imply the development or recurrence of this arrhythmia.

Resistin

Resistin is an adipokine widely associated with insulin resistance and a chronic inflammatory state generated by metabolic dysregulation⁴². This protein comprises 106 amino acids with a 12.5 kDa weight, whose serum levels increase due to different cardiac diseases, including EAT augmentation, which is related to ventricular dysfunction and myocardial fibrosis that promotes AF^{43,44}. Nevertheless, as it occurs with the two adipokines mentioned above, clinical studies correlating the concentration of this adipokine with the risk of developing AF are contradictory. For instance, Muse et al. (2015)⁴⁵ cataloged resistin as an independent risk factor for several cardiac pathologies but not for AF. On the contrary, Samanidis et al. (2020)⁴⁶ reported that patients with permanent AF presented statistically higher resistin levels than those observed in the control subjects. Similarly, Chang et al. (2020)⁴⁷ also observed a higher resistin plasma concentration in patients with AF compared to the concentration of this adipokine in healthy subjects. Moreover, these authors indicated an independent and statistically significant correlation of resistin with the recurrence of AF following catheter

ablation. Furthermore, this study stated that plasma resistin was associated with other adipokines whose levels also increased with inflammation derived from fat accumulation (epicardial fat specifically) and metabolic dysregulation. In the same manner, to assess the relevance of measuring resistin levels to predict the onset of AF after cardiac surgery, Rachwalik et al. (2023)⁴⁸ conducted a study in which they quantitated resistin concentration from perivascular adipose tissue (PVAT) and plasma obtained from patients who underwent coronary artery bypass grafting; the results indicated a statistically significant correlation between high levels of resistin from both PVAT and plasma and the occurrence of AF after the surgical procedure, thus establishing this parameter as a possible marker for post-operative complications.

Lipocalin-2

Lipocalin-2, known as NGAL, is an adipokine expressed in various tissues. This 25 kDa protein, comprised of 198 amino acids, participates in many physiological mechanisms by binding to different ligands, including steroids, fatty acids, and pheromones, through its calix-like structure⁴⁹. To date, three different isoforms or variants of the lipocalin-2 protein have been characterized; moreover, the concentration within serum and plasma of these three isoforms (hLcn2, C87A, and R81E) is associated with the risk of developing cardiometabolic alterations, while an increment in the urine levels of all variants relates to renal dysfunction⁵⁰. Therefore, this adipokine is a biomarker for diagnosing and predicting outcomes in metabolic and kidney diseases. Its covalent binding identified it to the matrix metalloproteinase-9 (MMP-9) in human neutrophils⁵¹. Numerous scientific reports referred to NGAL as an anti-inflammatory adipokine whose circulating levels tend to increase during a pathological process^{52,53}. In this regard, different studies have reported the correlation of serum, plasma, and urine levels of lipocalin-2 with metabolic, immune, and cardiac disorders⁴⁹. Within the latter, several researchers reported the association between the rise of circulating NGAL levels and the occurrence of AF but as a comorbidity to chronic heart failure or renal dysfunction^{54,55}. Unfortunately, there are few studies describing its direct association with the occurrence of AF; in 2014, Sonmez et al., to associate new markers with the presence of AF, measured circulating levels of NGAL, Galectin-3, matrix metalloproteinase-9, N-terminal propeptide of Type III procollagen, Hs-Crp, and neutrophil-to-lymphocyte ratio and found that NGAL

concentration was the only one neither elevated nor statistically correlated with the presence of non-valvular AF⁵⁶. In contrast, Mlodawska et al. (2017)⁵⁷ reported the increment of the MMP-9/NGAL complex as a promising biomarker to predict the recurrence of AF in obese patients who underwent successful cardioversions. The main difference between these two studies was the BMI within the population study.

Conclusions

AF is the most common arrhythmia affecting millions of people worldwide. One of the main factors involved in the pathogenesis of AF is the presence of pericardial fat, which produces the dysregulation of pro and anti-inflammatory adipokines, whose alteration contributes to the structural remodeling and promotion of fibrosis within the myocardial atrium. Because fibrosis promotes AF, it is considered a prognostic factor for the emergence of AF or its progression and recurrence after pulmonary vein isolation. However, sometimes, the degree of fibrosis does not coincide with the state of AF; for example, there are patients with paroxysmal AF with a high degree of atrial fibrosis, and on the contrary, there are patients with persistent AF with a low degree of atrial fibrosis. Therefore, looking for early markers and associating them with the disease can help in the best selection of patients and the ideal time for catheter ablation since early ablation is also associated with interruption in the progression of fibrosis and AF. Unfortunately, to this day, the insight into this topic is very controversial and needs further research.

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Conflicts of interest

The authors declare no conflicts of interest.

Ethical considerations

Protection of humans and animals. The authors declare that no experiments involving humans or animals were conducted for this research.

Confidentiality, informed consent, and ethical approval. The study does not involve patient personal

data nor requires ethical approval. The SAGER guidelines do not apply.

Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in the writing of this manuscript.

References

1. Westerman S, Wenger N. Gender differences in atrial fibrillation: a review of epidemiology, management, and outcomes. *Curr Cardiol Rev.* 2019;15:136-44.
2. Middeldorp ME, Kamsani SH, Sanders P. Obesity and atrial fibrillation: prevalence, pathogenesis, and prognosis. *Prog Cardiovasc Dis.* 2023;78:34-42.
3. Go AS, Hylek EM, Phillips KA, Chang Y, Henault LE, Selby JV, et al. Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: the AnTicoagulation and Risk Factors in Atrial Fibrillation (ATRIA) study. *JAMA.* 2001;285:2370-5.
4. Lloyd-Jones D, Adams RJ, Brown TM, Carnethon M, Dai S, De Simone G, et al. Executive summary: heart disease and stroke statistics--2010 update: a report from the American Heart Association. *Circulation.* 2010;121:948-54.
5. Sagris M, Vardas EP, Theofilis P, Antonopoulos AS, Oikonomou E, Tousoulis D. Atrial fibrillation: pathogenesis, predisposing factors, and genetics. *Int J Mol Sci.* 2021;23:6.
6. Benjamin EJ, Levy D, Vaziri SM, D'Agostino RB, Belanger AJ, Wolf PA. Independent risk factors for atrial fibrillation in a population-based cohort. The Framingham Heart Study. *JAMA.* 1994;271:840-4.
7. Apovian CM. Obesity: definition, comorbidities, causes, and burden. *Am J Manag Care.* 2016;22:S176-85.
8. Al Chekatie MO, Welles CC, Metoyer R, Ibrahim A, Shapira AR, Cytron J, et al. Pericardial fat is independently associated with human atrial fibrillation. *J Am Coll Cardiol.* 2010;56:784-88.
9. Hotamisligil GS. Inflammation and metabolic disorders. *Nature.* 2006;444:860-67.
10. Xu H, Barnes GT, Yang Q, Tan G, Yang D, Chou CJ, et al. Chronic inflammation in fat plays a crucial role in the development of obesity-related insulin resistance. *J Clin Invest.* 2003;112:1821-30.
11. Thanassoulis G, Massaro JM, O'Donnell CJ, Hoffmann U, Levy D, Ellinor PT, et al. Pericardial fat is associated with prevalent atrial fibrillation: the Framingham Heart Study. *Circ Arrhythm Electrophysiol.* 2010;3:345-50.
12. Wong CX, Abed HS, Molaee P, Nelson AJ, Brooks AG, Sharma G, et al. Pericardial fat is associated with atrial fibrillation severity and ablation outcome. *J Am Coll Cardiol.* 2011;57:1745-51.
13. Hatem SN, Redheuil A, Gandjbakhch E. Cardiac adipose tissue and atrial fibrillation: the perils of adiposity. *Cardiovasc Res.* 2016;109:502-9.
14. Greulich S, Maxhara B, Vandenplas G, de Wiza DH, Smiris K, Mueller H, et al. Secretory products from epicardial adipose tissue of patients with type 2 diabetes mellitus induce cardiomyocyte dysfunction. *Circulation.* 2012;126:2324-34.
15. Akoumianakis I, Polkinghorne M, Antoniadou C. Non-canonical WNT signalling in cardiovascular disease: mechanisms and therapeutic implications. *Nat Rev Cardiol.* 2022;19:783-97.
16. Kapton-Cieślicka A, Postula M, Rosiak M, Peller M, Kondracka A, Serafin A, et al. Association of adipokines and inflammatory markers with lipid control in type 2 diabetes. *Pol Arch Med Wewn.* 2015;125:414-23.
17. Agbaedeng TA, Zacharia AL, Iroga PE, Rathnasekara VM, Munawar DA, Bursill C, et al. Associations between adipokines and atrial fibrillation: a systematic review and meta-analysis. *Nutr Metab Cardiovasc Dis.* 2022;32:853-62.
18. Zhang Y, Wei Y, Zheng T, Tao Y, Sun Y, Jiang D, et al. Adiponectin receptor 1-mediated stimulation of Cav3.2 channels in trigeminal ganglion neurons induces nociceptive behaviors in mice. *J Headache Pain.* 2023;24:117-34.
19. Achari AE, Jain SK. Adiponectin, a therapeutic target for obesity, diabetes, and endothelial dysfunction. *Int J Mol Sci.* 2017;18:1321.
20. Peller M, Kapton-Cieślicka A, Rosiak M, Tymniska A, Ozieranski K, Eyi-leten C, et al. Are adipokines associated with atrial fibrillation in type 2 diabetes? *Endokrynol Pol.* 2020;71:34-41.
21. Ermakov S, Azarbal F, Stefanick ML, LaMonte MJ, Li W, Sharp KM, et al. The associations of leptin, adiponectin and resistin with incident atrial fibrillation in women. *Heart.* 2016;102:1354-62.
22. Macheret F, Bartz TM, Djousse L, Ix JH, Mukamal KJ, Ziemann SJ, et al. Higher circulating adiponectin levels are associated with increased risk of atrial fibrillation in older adults. *Heart.* 2015;101:1368-74.
23. Shimano M, Shibata R, Tsuji Y, Kamiya H, Uchikawa T, Harata S, et al. Circulating adiponectin levels in patients with atrial fibrillation. *Circ J.* 2008;72:1120-4.

24. Ouchi N, Walsh K. A novel role for adiponectin in the regulation of inflammation. *Arterioscler Thromb Vasc Biol.* 2008;28:1219-21.
25. Kizer JR, Arnold AM, Strotmeyer ES, Ives DG, Cushman M, Ding J, et al. Change in circulating adiponectin in advanced old age: determinants and impact on physical function and mortality. the cardiovascular health study all stars study. *J Gerontol A Biol Sci Med Sci* 2010;65:1208-14.
26. Liu J, Liu M, Chen L. Novel pathogenesis: regulation of apoptosis by Apelin/APJ system. *Acta Biochim Biophys Sin (Shanghai).* 2017;49:471-8.
27. Hu G, Wang Z, Zhang R, Sun W, Chen X. The role of apelin/apelin receptor in energy metabolism and water homeostasis: a comprehensive narrative review. *Front Physiol.* 2021;12:632886.
28. Tatemoto K, Hosoya M, Habata Y, Fujii R, Kakegawa T, Zou MX, et al. Isolation and characterization of a novel endogenous peptide ligand for the human APJ receptor. *Biochem Biophys Res Commun.* 1998;251:471-6.
29. Folino A, Montarolo PG, Samaja M, Rastaldo R. Effects of apelin on the cardiovascular system. *Heart Fail Rev.* 2015;20:505-18.
30. Li C, Cheng H, Adhikari BK, Wang S, Yang N, Liu W, et al. The role of apelin-APJ system in diabetes and obesity. *Front Endocrinol (Lausanne).* 2022;13:820002.
31. Farkasfalvi K, Stagg MA, Coppen SR, Siedlecka U, Lee J, Soppa GK, et al. Direct effects of apelin on cardiomyocyte contractility and electrophysiology. *Biochem Biophys Res Commun.* 2007;357:889-95.
32. Kang Y, Kim J, Anderson JP, Wu J, Gleim SR, Kundu RK, et al. Apelin-APJ signaling is a critical regulator of endothelial MEF2 activation in cardiovascular development. *Circ Res.* 2013;113:22-31.
33. Charo DN, Ho M, Fajardo G, Kawana M, Kundu RK, Sheikh AY, et al. Endogenous regulation of cardiovascular function by apelin-APJ. *Am J Physiol Heart Circ Physiol.* 2009;297:H1904-13.
34. Chng SC, Ho L, Tian J, Reversade B. ELABELA: a hormone essential for heart development signals via the apelin receptor. *Dev Cell.* 2013;27:672-80.
35. Pauli A, Norris ML, Valen E, Chew GL, Gagnon JA, Zimmerman S, et al. Toddler: an embryonic signal that promotes cell movement via Apelin receptors. *Science.* 2014;343:1248636.
36. Ellinor PT, Low AF, Macrae CA. Reduced apelin levels in lone atrial fibrillation. *Eur Heart J.* 2006;27:222-6.
37. Gurger M, Celik A, Balin M, Gul E, Kobat MA, Bursali KB, et al. The association between apelin-12 levels and paroxysmal supraventricular tachycardia. *J Cardiovasc Med (Hagerstown).* 2014;15:642-6.
38. Salska A, Dziuba M, Salski W, Chizynski K, Zielinska M. Apelin and atrial fibrillation: the role in the arrhythmia recurrence prognosis. *Dis Markers.* 2018;2018:5285392.
39. Kim YM, Lakin R, Zhang H, Liu J, Sachedina A, Singh M, et al. Apelin increases atrial conduction velocity, refractoriness, and prevents inducibility of atrial fibrillation. *JCI Insight.* 2020;5:e126525.
40. Bohm A, Snopek P, Tothova L, Bezak B, Jajcay N, Vachalcova M, et al. Association between apelin and atrial fibrillation in patients with high risk of ischemic stroke. *Front Cardiovasc Med.* 2021;8:742601.
41. Foussal C, Lairez O, Calise D, Pathak A, Guilbeau-Frugier C, Valet P, et al. Activation of catalase by apelin prevents oxidative stress-linked cardiac hypertrophy. *FEBS Lett.* 2010;584:2363-70.
42. Silswal N, Singh AK, Aruna B, Mukhopadhyay S, Ghosh S, Ehtesham NZ. Human resistin stimulates the pro-inflammatory cytokines TNF-alpha and IL-12 in macrophages by NF-kappaB-dependent pathway. *Biochem Biophys Res Commun.* 2005;334:1092-101.
43. Venteclef N, Guglielmi V, Balse E, Gaborit B, Cotillard A, Atassi F, et al. Human epicardial adipose tissue induces fibrosis of the atrial myocardium through the secretion of adipo-fibrokinases. *Eur Heart J.* 2015;36:795-805a.
44. Langheim S, Dreas L, Veschini L, Maisano F, Foglieni C, Ferrarello S, et al. Increased expression and secretion of resistin in epicardial adipose tissue of patients with acute coronary syndrome. *Am J Physiol Heart Circ Physiol.* 2010;298:H746-53.
45. Muse ED, Feldman DI, Blaha MJ, Dardari ZA, Blumenthal RS, Budoff MJ, et al. The association of resistin with cardiovascular disease in the multi-ethnic study of atherosclerosis. *Atherosclerosis.* 2015;239:101-8.
46. Samanidis G, Gkogkos A, Bousounis S, Alexopoulos L, Perrea DN, Perreas K. Blood plasma resistin and atrial fibrillation in patients with cardiovascular disease. *Cardiol Res.* 2020;11:286-93.
47. Chang TY, Hsiao YW, Guo SM, Chang SL, Lin YJ, Lo LW, et al. Resistin as a biomarker for the prediction of left atrial substrate and recurrence in patients with drug-refractory atrial fibrillation undergoing catheter ablation. *Int Heart J.* 2020;61:517-23.
48. Rachwaik M, Matusiewicz M, Jasinski M, Hurkackz M. Evaluation of the usefulness of determining the level of selected inflammatory biomarkers and resistin concentration in perivascular adipose tissue and plasma for predicting postoperative atrial fibrillation in patients who underwent myocardial revascularisation. *Lipids Health Dis.* 2023;22:2.
49. Jaber SA, Cohen A, D'Souza C, Abdulrazzaq YM, Ojha S, Bastaki S, et al. Lipocalin-2: structure, function, distribution and role in metabolic disorders. *Biomed Pharmacother.* 2021;142:112002.
50. Li D, Li H, Bauer C, Hu Y, Lewis JR, Xu A, et al. Lipocalin-2 variants and their relationship with cardio-renal risk factors. *Front Endocrinol (Lausanne).* 2021;12:781763.
51. Buonafina M, Martinez-Martinez E, Jaisser F. More than a simple biomarker: the role of NGAL in cardiovascular and renal diseases. *Clin Sci (Lond).* 2018;132:909-23.
52. Kjeldsen L, Johnsen AH, Sengelov H, Borregaard N. Isolation and primary structure of NGAL, a novel protein associated with human neutrophil gelatinase. *J Biol Chem.* 1993;268:10425-32.
53. Kjeldsen L, Bainton DF, Sengelov H, Borregaard N. Identification of neutrophil gelatinase-associated lipocalin as a novel matrix protein of specific granules in human neutrophils. *Blood.* 1994;83:799-807.
54. Palazzuoli A, Ruocco G, Pellegrini M, De Gori C, Del Castillo G, Franci B, et al. Comparison of neutrophil gelatinase-associated lipocalin versus B-type natriuretic peptide and cystatin C to predict early acute kidney injury and outcome in patients with acute heart failure. *Am J Cardiol.* 2015;116:104-11.
55. Ventoulis I, Mantziari L, Mouratoglou SA, Kamperidis V, Giannakoulas G, Ziakas A, et al. NGAL and ST2 levels in ambulatory patients with chronic heart failure. Clinical and echocardiographic correlates. *Scand Cardiovasc J.* 2015;49:213-9.
56. Sonmez O, Ertem FU, Vatankulu MA, Erdogan E, Tasal A, Kucukbuzcu S, et al. Novel fibro-inflammation markers in assessing left atrial remodeling in non-valvular atrial fibrillation. *Med Sci Monit.* 2014;20:463-70.
57. Mlodawska E, Tomaszuk-Kazberuk A, Lopatowska P, Waszkiewicz E, Bachorzewska-Gajewska H, Malyszko J, et al. Matrix metalloproteinase neutrophil gelatinase-associated lipocalin complex predicts atrial fibrillation recurrence after electrical cardioversion in obese patients. *Cardiovascular Med.* 2016;7:11-20.