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Review

Therapeutic Potential of FGF21 in Atrial Fibrillation through Regulating Atrial Metabolic Remodeling.

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Abstract

Atrial fibrillation (AF) is the most common sustained arrhythmia encountered in clinical practice. Over decades of research, a vast amount of knowledge has been gathered about the causes and consequences of AF that, it occurs and maintains itself in the context of a morphologically and functionally altered atrial substrate that can be induced by stressors such as underlying diseases (cardiac or non-cardiac) or aging. Accumulating evidence indicates that inflammation, oxidative stress, obesity and insulin resistance may play a central role in the pathogenesis of AF. There are several traditional methods to slow it through affecting these aforementioned factors. However, a more effective way of treatment and prevention of the progression of AF still under research. Fibroblast growth factor 21 (FGF21) is an endocrine hormone that is expressed in numerous tissues, including liver, heart, brown adipose tissue, white adipose tissue (WAT) and pancreas. It increases insulin sensitivity and regulates lipid metabolism and energy homeostasis. Evidence has supported this statement that FGF21 acts as a metabolic regulator and exerts cardio-protective effects. Here, we hypothesize that FGF21 may be a protective factor in AF by attenuating inflammation, oxidative stress, obesity, and insulin resistance. This review aimed to investigate new ways to understand the pathogenesis of AF and help to find a new way to prevent the genesis and progress of AF.

Keywords

Atrial Fibrillation (AF), Fibroblast Growth Factor 21 (FGF21), Inflammation, Obesity, Oxidative Stress, Insulin Resistance.

1. Introduction

Atrial fibrillation (AF) is a disorder of the heart's electrical conduction system that leads to a fast and irregular heart rhythm. The condition is a growing epidemic and a major public health problem, in addition to being the most common cardiac rhythm disorder. The prevalence of AF in the general population ranges from 2.3–3.4% and is expected to double by 2050 (1).

Table 1 Genes which are associated with atrial fibrillation Familial studies.

Gene	Chromosomal location	Function	Reference
ABCC9	12p12.1	ATP binding cassette leads to loss of function of I_{KATP}	(2-4)
GJA5	1q21.2	Mutations in this gene may be associated with atrial fibrillation	(5-7)
KCNA5	12p13.32	Modulation of ultra-rapid depolarizing current IKur	(8-10)
KCNE2	21q22.11	Gain of function mutation of the potassium channel responsible for the IKs current	(11, 12)
KCNH2	7q36.1	Encodes for the channel responsible for the rapidly depolarizing current Ikr	(13-15)
KCNJ2	17q24.3	Encodes for the inward rectifier potassium channel Kir 2.1	(13, 16, 17)
KCNQ1	11p15.5-p15.4	Gain of function of potassium channel contributing to Iks	(14, 18, 19)
LMNA	1q22	Laminin A/C in inner nuclear membrane	(20-22)
MYL4	17q21.32	This gene encodes a myosin alkali light chain that is found in embryonic muscle and adult atria.	(23, 24)
NKX2-5	5q35.1	This gene encodes a homeobox-containing transcription factor, functions in heart formation and development.	(25, 26)
NPPA	1p36.22	Frameshift mutation causes ANP to be resistant to breakdown increasing its half life	(27)
NUP155	5p13.2	Nucleoporin 155, a component of the nucleopore formation reducing nuclear envelope permeability	(28)
PRKAG2	7q36.1	ϒ2 subunit of AMP-activated protein kinase which regulates ATP generation and use.	(29)
RYR2	1q43	Alteration of ryanodine receptor 2 leading to imbalance of calcium homeostasis	(30-32)
SCN1B	19q13.11	Voltage-gated sodium channels are heteromeric proteins that function in the generation and propagation of action potentials in muscle and neuronal cells.	(33, 34)
SCN2B	11q23.3	The protein encoded by this gene is the beta 2 subunit of the type II voltage-gated sodium channel.	(35, 36)
SCN3B	11q24.1	Voltage-gated sodium channels are responsible for the generation and propagation of action potentials in neurons and muscle	(37, 38)
SCN4B	11q23.3	β subunit of the voltage gated sodium channel	(39)
SCN5A	3p22.2	These channels play a major role in signaling the start of each heartbeat, coordinating the contractions of the upper and lower chambers of the heart, and maintaining a normal heart rhythm.	(40)

However epidemiological studies of worldwide shows, the etiology of AF are broadly cardiovascular and non-cardiovascular (41, 42), and the risk factors for AF were primarily age (43), followed by hypertension, peripheral vascular disease diabetes mellitus and body mass index (44-46). Other risk factors include chronic kidney disease, smoking, alcohol, and thyroid dysfunction (47). Moreover, evidence from genetic study release that it is a heritable component, family history is a big risk factor for AF. And a study of more than 2,200 people found an increased risk factor for AF of 1.85 for those that had at least one parent with AF. Various genetic mutations may be responsible (30, 48-51) (Table 1). Where AF contributes to increased mortality and morbidity, especially from stroke (47, 52-58), myocardial infection and other heart-related complications (59). In the initial stage of atrial fibrillation there are no signs and symptoms but with the complication of the disease there are signs and symptoms such as palpitations, angina, dizziness, Dyspnea, fatigue or weakness (57, 60) but the most common is rapid heart rate (41, 55, 56, 61-63).

Cardiac arrhythmias have been treated traditionally with antiarrhythmic drugs that control the rhythm by altering cardiac electrical properties, and anti-inflammatory drugs (53). Catheter ablation is also considered as the antiarrhythmic drugs for maintaining the sinus rhythm (64-66). But it was also seen that after using these medications and therapies problems still be there because the medications and therapies also have some complications (66, 67).

Fibroblast growth factor-21 (FGF-21) has been discovered as a strong hormone (68-70), plays an important role in lipid metabolism, glucose metabolism (71-73) and also involved in cardio-protective function by performing the anti-pathogenic activity (74).

In this review, we will investigate new ways to understand the pathogenic mechanisms involved in this disorder. As well as an outlook for the therapeutic potential of FGF21 in atrial fibrillation through regulating atrial metabolic remodeling.

2. Pathogenesis of Atrial fibrillation

2.1. Inflammation

Inflammation is considering one of the most important pathogenic factors of AF which might play a significant role in the initiation, maintenance, and perpetuation of AF (75-79). The main pathophysiology mechanism involves in developing and progress of AF is electrical and structural remodeling of atria (76, 80). Moreover, atrial fibrillation itself induces inflammation during atrial remodeling which perpetuates the arrhythmia and this is called ‘AF begets AF’ phenomenon (64).
Multiple contributing factors are associated with the initiation of local and systemic infection which might have an underlying mechanism and temporal changes. Different systemic diseases such as coronary artery disease, hypertension, obesity, myocarditis and pericarditis (58, 77, 81). Corresponding to the infection body produces an inflammatory response, the systemic response includes cytokines which are produces by the activated immune cells such as lymphocytes, monocytes, and macrophage (53, 82, 83). These cells produce the pro-inflammatory cytokines such as TNF-α, IL-2, IL-6, IL-8 IL-13,

IL18, C-reactive protein (80, 84-87). High level of cytokines can reach to atria by the circulation or in another way, cause the inflammation of the myocardium and also lead to severe atrial and ventricular arrhythmias by disturbed the resting membrane potential by activation of potassium channel (81, 88-90). Moreover, they induce L-type calcium channel those are also involved in causing

arrhythmias (46, 53, 91). Also due to myocardial injury may be to release of cytokine mediators and/or cellular components of the immune response (53). According to some medical research in mice, cardiac-specific expression of TNF or TGF-β1 can increase the vulnerability to AF and atrial remodeling (92, 93), including fibrosis and heterogeneous conduction (94, 95). The higher level of TNF-α, IL-6, IL-13, IL-18, and a cytotoxic factor which increases vascular permeability and shock (96-100). However, these all condition might lead to myocardial cell apoptosis, fibrosis, and myocardial remodeling. Furthermore, in low-grade chronic inflammatory such as C- reactive protein cause the atherosclerosis complication and inflammation (101-105). And recent studies suggest that atherosclerosis is a systemic inflammatory process affecting the media and intima layer of arteries (82, 98, 106-109). While inflammation is a strong predictor of AF by various population-based studies(110). Atrial fibrillation/flutter (AF/FL) is a common complication of acute myocardial infarction (AMI) (110-112). As evidenced by previous studies it was clear that AF plays a more important role occurring specifically in an inflammatory environment (93, 113). And it is expected to induce myocardial damage and atrial inflammation during the healing process, and might consequently induce AF (87, 98, 99, 114, 115). In addition ischemia cause ventricular arrhythmia that can lead to elevated left ventricular (LV) end-diastolic pressure (116), increased atrial pressures, acute deterioration of the LV function, left atrial (LA) enlargement (79, 115, 117). This anatomical LA enlargement increases the possible number of multiple wavelets and may precipitate better initiation and maintenance of AF under the hostile environment of AMI such as left ventricular systolic function problem, exaggerated inflammatory reaction (117, 118) (Figure 1).

2.2. Oxidative stress

Oxidative stress has been suggested to play a role in the pathogenesis of atrial fibrillation (AF). Indeed, the prevalence of AF increases with age as does oxidative stress. Further study showed that oxidative stress markedly elevated in preclinical and clinical AF patients (119-122). However, investigation about the possible mechanism in oxidative stress may involve the destruction of the cell membrane and cytoskeleton alteration. Growing evidence indicates that many oxidative markers are increased in the AF patient, including protein oxidation, lipid peroxidation and nucleic acid oxidation (123, 124). Reactive oxygen species (ROS), which are cytotoxic byproducts of oxygen metabolism, are driven from the multiple sources such as mitochondria, xanthine oxidase, ischemia-reperfusion (I/R), uncoupling nitric oxide synthase, and NADPH oxidases (125, 126). In AF, an increasing the rate of oxidative stress will finally cause the necrosis, cell dysfunction, apoptosis, and disturbance in cellular signaling mechanism. In addition, vivo study shows that ischemia-reperfusion I/R increase a process autophagic flux in cardiac myocytes through oxidative stress (127, 128). Because of these, structural and electrical remodeling of the cardiac atria will be developed, structural and electrical remodeling of the cardiac atria will develop. A scientific study shows that there is linked to inherited mutations in the intracellular Ca^{2+} release channel/ryanodine receptor (RyR2) that cause intracellular Ca^{2+} leak. Altered intracellular Ca^{2+} homeostasis has been associated with the pathogenesis of AF. The ryanodine receptors (RyRs: RyR1, RyR2, RyR3) and inositol 1, 4,5-trisphosphate receptors (IP3Rs: IP3R1, IP3R2, IP3R3) are the major calcium Ca2+ release channels (CRCs) on the endo/sarcoplasmic reticulum (ER/SR)(129). Oxidation of RyR2 will lead to intracellular oxidative stress in the atrial

myocytes, then calcium starts to leak from the sarcoplasmic reticulum resulting promote the increase in cellular electric activity. And atrial myocytes from both patients and animals with AF display increased diastolic SR Ca^{2+}leak via RyR2. Moreover phosphorylation of protein kinase A (PKA) or catecholaminergic polymorphic ventricular tachycardia (CPVT) mutations (130, 131), trigger a vicious cycle in which leakage of calcium from sarcoplasmic reticulum of atrial myocytes impair the function of mitochondria, that cause the increased production of reactive oxygen species and ROS will promote the RyR2 oxidation that will lead to further leak of calcium Ca2+ and again severity of AF will increase (132) (Figure 2).

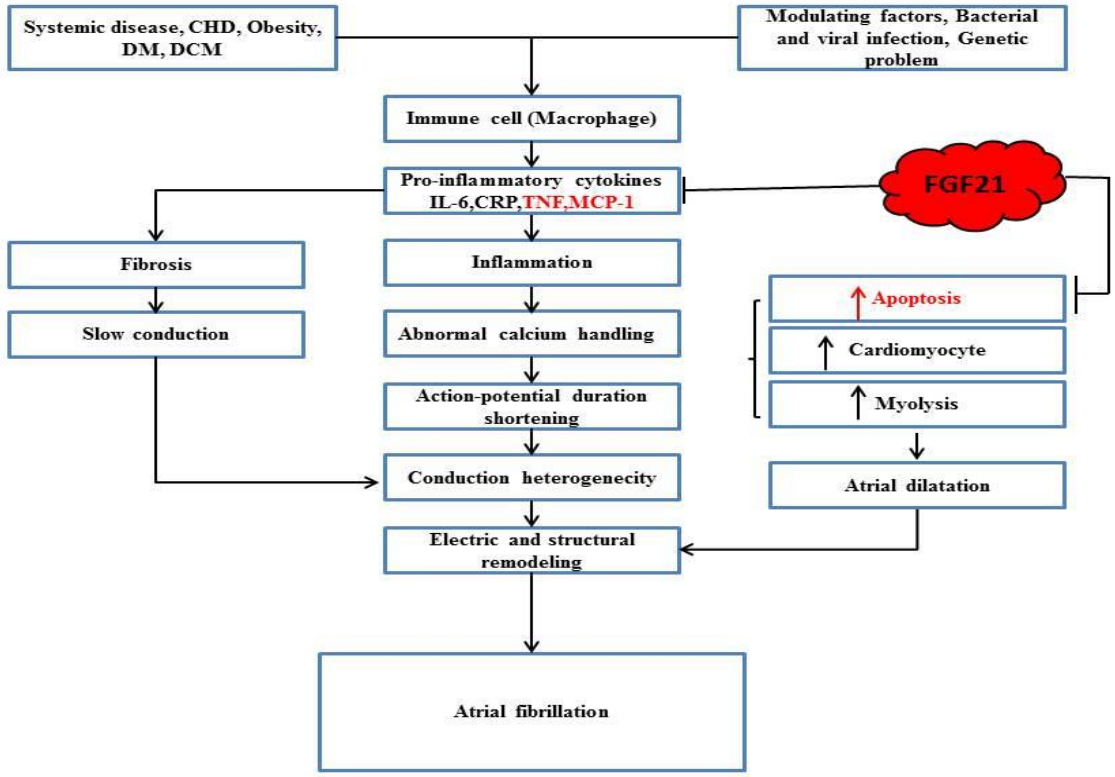

Figure 1. The potential mechanisms of inflammation in AF and the potential targets of FGF21.

1) Inflammation drives from the systemic and non-systemic sources, which is detected by the Immune cell (Macrophage). This Immune cell (Macrophage) secrete the Pro-inflammatory cytokines. 1) The increased level of cytokines causes the inflammation, it is the most important pathogenic process for causing AF, by abnormal calcium distribution in myocardial cells that can disturb the action potential of the myocardiocyte cell membrane. Which leads to the Conduction heterogeneity, here this is a point where electrical and structural remodeling happened. And cardiac cell remodeling continuous process towards AF. 2) The increased cytokines level also have the direct ability to cause the myocardiocyte fibrosis. After fibrosis, the speed of heart electrical conduction system slow, that can lead to the Conduction heterogeneity, cardiac cell remodeling and then cause the AF. 3) some pathologic conductions such as increase apoptosis, myolysis and increase level of Cardiomyocyte which make atria dilate and then after remodeling AF occur. 4) FGF21 can decrease the severity of inflammation and cardiac remodeling decreasing the cytokines level and decease the cardiac cell apoptosis.

2.3.Obesity

Obesity is associated with a new one set of atrial fibrillation (112, 133), is the most common postoperative arrhythmia (134) in the general population or following the cardiac surgery (135-137).

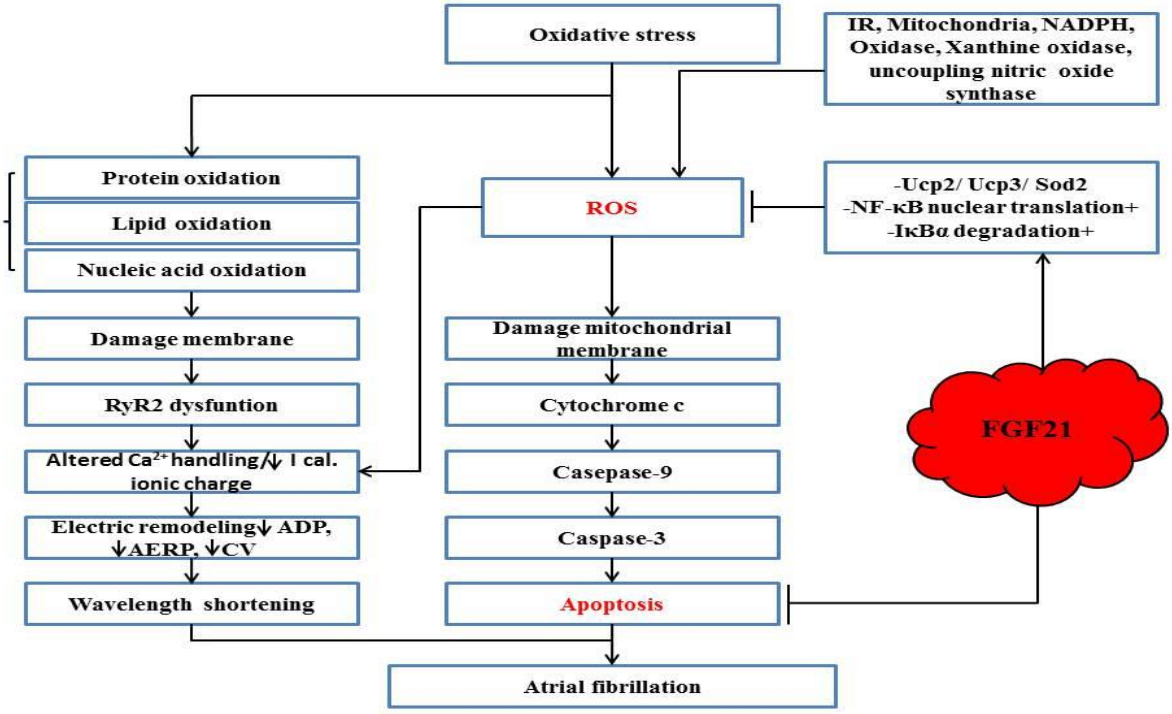

Figure 2. The potential mechanisms of oxidative stress in AF and the potential targets of FGF21.
1) Oxidative stress is another pathogenic for AF, it produces multiple pathways.1) From oxidative stress, ROS are produced that can damage the mitochondrial membrane, Due to mitochondrial membrane damage cytochrome C release. That is a protein which activates Casepase-9 and Casepase-9 activate the Casepase-3. Finally, after activation of this apoptosis occur that can cause the AF. 2) The oxidative stress also causes that oxidation of proteins, lipids and nucleic acid of a cell. Oxidation of them leads to damage of cell membrane that can cause RyR2 dysfunction. Because of this alter the calcium handling, then electrical remodeling occurs. In the end, the wavelength becomes short and develop the AF. 3) Moreover, ROS are directly involved in calcium alteration which leads to AF.4) FGF21 can upregulate the expression of genes encoding proteins involved in antioxidative pathways, including mitochondrial uncoupling proteins (Ucp2 and Ucp3), superoxide dismutase-2 (Sod2), reduced ROS production.FGF21 can decrease cardiac cell apoptosis.

However, according to WHO obesity is defined as a person with a body mass index (BMI) of 30 or more. For a person with a BMI equal to or more than 25 the main source of energy for heart muscles is adipose tissue (138), that is accumulated mainly around the atrioventricular and interventricular grooves and along the coronary arteries; the smaller amount is also seen on atrial appendages.

The cardiac adipose tissue is composed of the paracardial fat outside the visceral pericardium and the epicardial adipose tissue (EAT) adjacent to the epicardium (134, 139, 140). In addition, it was suggested that EAT produces the number of

bioactive substance (adipokines) with both pro-inflammatory and anti-inflammatory properties, that can freely diffuse into the neighboring myocardium (141-143).

Previous studies have highlighted obesity as an independent risk factor for the new onset of AF (143). While a recent study shows that obesity doubled the risk of the occurrence of AF among healthy young women, In addition, duration of elevated BMI had also an impact on the risk of a new incident of AF (144). In the obese patient, overweight. Besides, The Framingham Heart Study showed that increased atrial fat volume was associated with a high risk of AF (138). Although

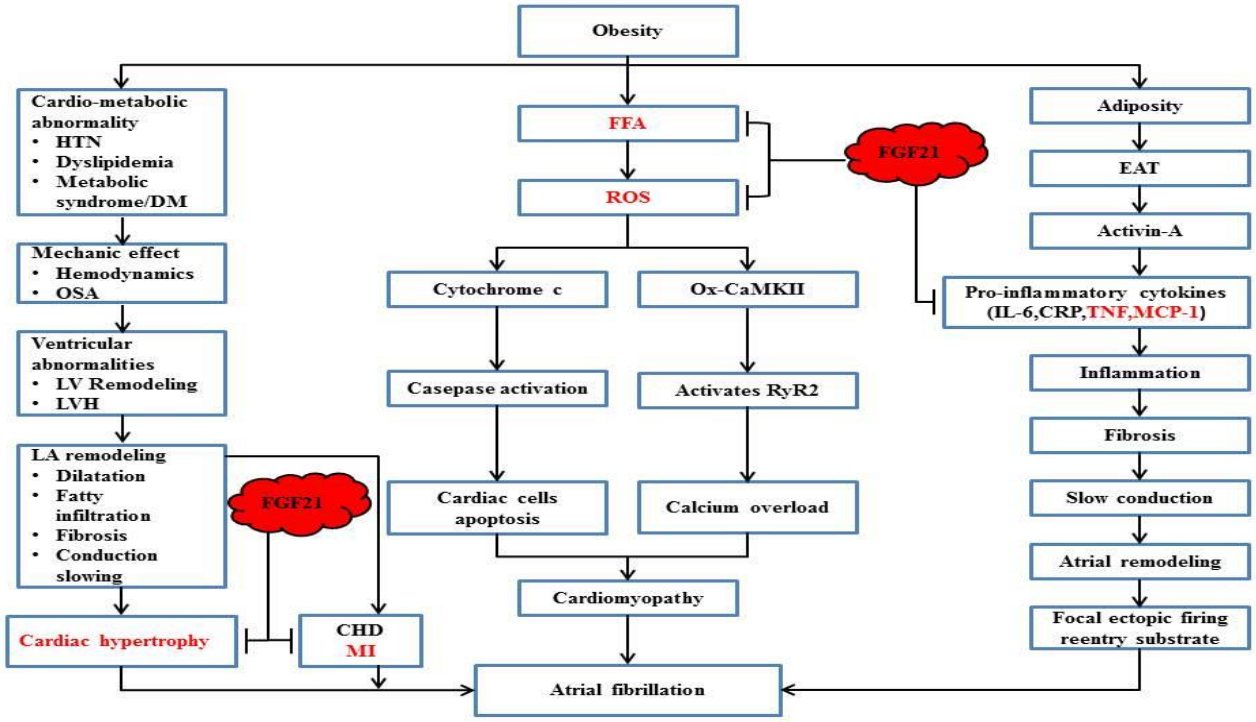

Figure 3. The potential mechanisms of Obesity in AF and the potential targets of FGF21.

Over bodyweight is a metabolic disease and becoming a worldwide health problem, and it is a most important pathogenic factor for AF. 1) In this condition FFA are increased in circulation that can produce the ROS,

a) The increased level of ROS caused the cardiac cell apoptosis as we discussed in figer-1

b) Increased ROS production includes oxidized CaMKII (Ox-CaMKII) and activated nuclear factor-kB (NF-kB). ox-CaMKII activates ryanodine receptor 2 (RyR2) hyperphosphorylation, which in turn causes secondary electrical remodeling and calcium overload-induced cardiac injury.

Both calcium overload and cardiac cell apoptosis leads to AF. 2) The epicardial adipose tissue (EAT) produces activin A that release the cytokines that proceed with the process of inflammation as we explain in figer-1

3) Cardio-metabolic abnormality developed in obese patients due to Mechanic effects such as Hemodynamics and OSA, Ventricular abnormalities happened which cause the atrial remodeling and cardiac hypertrophy, after all, AF occurs in patients. 4) FGF21 can decrease the severity of inflammation, oxidative stress and cardiac remodeling decreasing the cytokines level and decease the FFA level in circulation, Moreover, it also has an anti-myocardial infection and anti- Cardiac hypertrophy activity.

during the cardiac tissue insult immune cell infiltration into the adipose tissue (Pericardial adipose tissue (PAT) and Epicardial adipose tissue (EAT)), particularly by M1 macrophages (a pro--inflammatory phenotype), that cause the secretion of pro-inflammatory cytokines (145). The high level of cytokines can reach to atria from adipose tissues by the circulation or paracrine factors and cause inflammation that leads to the development of AF (64). Establish an inflammatory cycle that leads to increased severity of the arrhythmia. Moreover, a study reveals that AF is associated with the fibrosis of the adipose tissue, which is present in the subepicardial of the atrial myocardium in human and sheep. Immune response could be involved in this remodeling process (143). Several mechanisms show the relationship between EAT and AF. Some previous study assessed inflammation of EAT gradually lead to AF in patients undergoing cardiac surgery (146, 147), because EAT is important local source of the inflammatory mediators tumor necrosis factor-α, CRP and interleukin-6, which might have direct arrhythmogenic effects on atrial tissue and be associated with AF pathogenesis (146, 148). Moreover, a study documented that EAT produces activin A (member of the TGF-beta-superfamily) more plentiful in the adipose tissue of obese (135, 149), compared to lean persons, it increases inflammatory cytokines in macrophages, these cytokines causes fibrosis in surrounding atrial myocardium that might lead to AF (146, 149).

Furthermore, L-type calcium channel is present in myocardiocytes, and the main current generating the plateau phase of the atrial action potential, influenced by cytoskeleton structural changes mediated by gelsolin, where the increasing concentration of gelsolin inactivates the channels (150). While Gelsolin deficiency could lead to an increased opening probability of these Ca2 channels leading to increased excitability of myocardiocytes that promoting AF (150, 151).

These above mechanisms might play an important role in the formation of the AF substrate during the pathogenesis of AF. Therefore, these qualitative changes in EAT may be related to higher EAT density (Figure 3).

2.4. Insulin resistance

Insulin resistance (IR) is considered as a condition in which cells (i.e. muscle, adipose tissue, and liver) fail to respond normally to circulating insulin (152, 153). To prevent hyperglycemia and noticeable organ damage over time, the body produces insulin when glucose starts to be released into the bloodstream (154).

While in this pathologic condition (insulin resistance), the cells are resistant to the insulin and are unable to use it as effectively, But Beta cells in the pancreas subsequently increase their production of insulin, further contributing to a high blood insulin level leading to hyperinsulinemia. A long time of insulin resistance often remains undetected and can contribute to the development of type 2 diabetes, obesity or latent autoimmune diabetes of adults (155).

Discussing type 2 diabetes, it is typically a chronic disease associated the number of metabolic defects including insulin resistance, impaired glucose tolerance, pro-inflammatory mediators, abnormalities of haemostasis, fibrinolysis, angiogenesis and extracellular matrix turnover (133, 156, 157). All of these metabolic changes lead to endothelial dysfunction, abnormal activation of the renin-angiotensin-aldosterone system (RAAS) and acceleration of atherogenesis, have been implicated in AF pathogenesis (158-160). Diabetes could also cause structural, electrical, electromechanical and autonomic remodeling. Moreover, animal-based studies have demonstrated that structural remodeling of the left atrium, primarily atrial

dilatation and interstitial fibrosis is the major trigger of AF in patients with diabetes (161, 162). In addition inflammation oxidative stress, increased expression of transforming growth factor and changing in gap junction proteins play important roles in causing structural atrial remodeling, electrical atrial remodeling and atrial fibrosis (163). And it has been cleared with multiple proofs that these atrial remodeling and atrial fibrosis are leading case of AF (163, 164).

In addition to this, there are numbers of researchers demonstrate the prevalence of obesity is rising worldwide with a high rate, and severe obesity is associated with elevated risks of adverse health consequences (165). And Obesity is the primary cause of ectopic lipid deposition in the heart (166). However, in the case of cardiac lipotoxicity, the cardiac myocytes undergo apoptosis and contractile dysfunction (167-169). Moreover, due to obesity, some different lipid intermediates begin to accumulate, including diacylglycerols and ceramides. Diacylglycerols responsible for the development of myocardial disease including cardiac hypertrophy and diabetic cardiomyopathy working as lipid second messengers that can activate several isoforms of PKC, whereas ceramides function as key components of lipotoxic signaling pathways linking lipid-induced inflammation and inhibition of insulin signaling (170-172). These pathological conditions are the leading cause of AF.

Insulin resistance is the leading step of cardiovascular complications including ischemic heart disease and stroke (173). Moreover, It

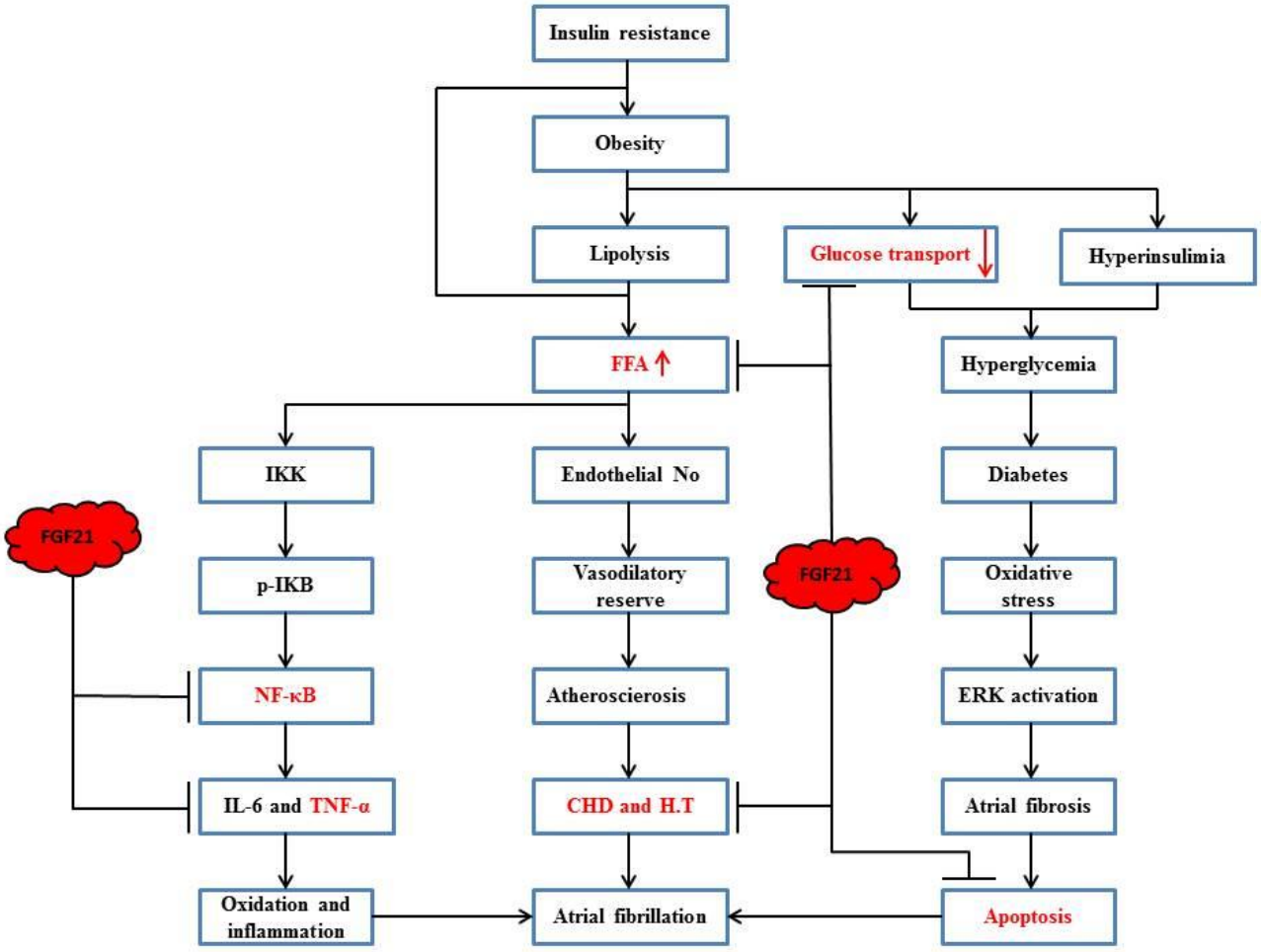

Figure 4. The potential mechanisms of insulin resistance in AF and the potential targets of FGF21.
1)The insulin resistance causes the lipolysis which causes the increase in the level of FFA. And endothelial No develops the Atherosclerosis due to Vasodilatory reserve action continue to this CHD and H.T start later AF also develop. 2) in insulin resistance obesity leads to the hyperglycemia which causes to the DM that leads to the oxidative and inflammation which develop the AF as we illustrate in figure-2. 3) Free fatty acids (FFAs) lead to activation of IKK, the inhibitor of IkB kinase. KK phosphorylates the inhibitor of kB(IkB), causing it to become detached from nuclear factor kB (NF-kB). NF-kB enters the nucleus and induces transcription of pro-inflammatory cytokines such as IL-6 and TNF-a. These cytokines lead to the deterioration of insulin resistance. 4) FGF21 can decrease the severity of inflammation, oxidative stress and cardiac remodeling decreasing the cytokines level and decease the FFA level in circulation, Moreover, it increases the glucose uptake by the cell.

represents a cluster of atherogenic risk factors including hypertension, atherosclerosis, hyperglycemia, obesity, and dyslipidemia (174). Considering that all of these risk factors could influence the development of atrial fibrillation (173). And also an association between atrial fibrillation and the insulin resistance has been suggested (174). Additionally, under insulin resistance oxidative stress and inflammation have been playing a major role in the pathogenesis of atrial fibrillation (175). By increasing the level of some cytokines such as interleukin-1 and CRP and reactive oxygen species (ROS) which enhance the pro-inflammatory responses in my myocardial cells which give the result in the form of myocardium remodeling, enlargement of the atrium, and autonomic neuropathy and this thing will promote the occurrence of atrial fibrillation (176, 177). Because of Diabetic autonomic neuropathy (DAN), a significant increase in P-wave duration and dispersion was observed. Metabolic syndrome is a risk factor for insulin resistance also having a significant clinical relationship with atrial fibrillation (125, 178, 179).

However, the Framingham heart study didn't find any relationship between the atrial fibrillation and the expression of insulin resistance during an analysis of 3,023 middle-aged to elderly participants (hazard ratio 1.18, 95% CI 0.84-165,p=0.34)(180). Insulin resistance itself does not directly lead to the development of AF. But its complication may lead to AF such as diabetic cardiomyopathy, directly or indirectly (Figure 4).

3. Fibroblast growth factor 21(FGF21) in Atrial fibrillation.

FGF21 is a signaling protein which is the 21st most important member of the FGF family (181-183). It is composed of approximately 150 to 300 amino acid (183, 184). The main site for the production and release of FGF21 is considered to the liver (185) or isolated hepatocytes, but other numerous tissues such as brown adipose tissue, white adipose tissue, Brain, and pancreas, are also associated with the production and section of FGF21(68).In addition skeleton muscle also express the FGF21.while the circulating level of FGF21 is mainly driven from the liver. But the expression of the FGF21 is under control of the peroxisome proliferator-activated receptor-alpha (PPAR alpha) and levels rise substantially with both fasting and consumption of ketogenic diet (68, 186, 187). Its play an important role in regulating adaptation to various metabolic abnormalities (188). Acting as endocrine FGF21 promote the glucose uptake of glucose by white adipocytes through induction of the glucose transporter, GLUT1 (189).

It can act as either endocrine or exocrine. For the Endocrine and paracrine signaling

transformation, mostly every member of the FGF family have the FGF receptors (FGFRs). FGFRs Include 1b,1c,2b,2c,3b,3c and 4 with different ligand-binding specificities(190). FGFs are activated when FGF21 bind to the fibroblast growth factor receptors(FGFRs) and its co-receptor β-klotho (KLB) a single-pass transmembrane protein that functions as an obligate cofactor for FGF21 signaling (70, 189-192).

3.1 FGF21 and inflammation

Increasing evidence demonstrated that inflammatory process plays a critical role in AF progression (56, 99). However, FGF21 has demonstrated an anti-inflammatory role in the inflammatory processes of the cardiac cell (193). Moreover, recent studies have demonstrated that FGF21 plays an important role in cardiac remodeling (194-196). FGF21 have an anti-inflammatory role in the cardiac cell, it acted as a positive acute phase response (APR) polypeptides and protect the cardiac cell from stress (68, 193). In addition, the inflammatory cytokines such as interleukin- 6 (IL-6), and monocyte chemoattractant protein-1 (MCP-1) were significantly higher in FGF21 knockout mice (193). While in db/db mice models, FGF21 treatment significantly reduced the mRNA expression level of TNFα (197). Furthermore, FGF21 treatment prevents cardiac hypertrophy development (at least, in neonatal mouse models), enhances fatty acid oxidation, and prevents the induction of pro-inflammatory pathways in the heart, thereby confirming (195). Research shows a significant amount of both FGF21 receptor, FGFR1, and the co-factor, β-Klotho, are present at the protein level in cardiac cells (189). It was found for treatment of cardiomyocytes in culture with FGF21 to activate the extracellular signal-regulated kinase (ERK) signaling pathway, which is considered the main intracellular pathway responsible for FGF21 intracellular actions (195). Other studies have reported that FGF21 also exerts protection after myocardial infarction by inhibiting cardiomyocyte apoptosis (198-200) (Figure 1).

The relationship between FGF21 and coronary heart disease is interest reported that serum FGF21 level was positively associated with coronary artery disease in clinics (201, 202). FGF21 plays an important role in the regulation of lipid metabolism and anti-inflammatory activity (203). Clinical studies showed that increased circulating FGF21 levels were discovered in atherosclerotic patients or individuals with a high risk of developing atherosclerosis (202). Also, an *in vivo* study demonstrated that increased serum FGF21 was observed in aortas of apoE−/− mice (C57BL/6J background) (204). While another study indicated that FGF21-induced prevention of atherosclerosis was associated with suppression of endoplasmic reticulum stress-mediated apoptosis in apoE−/− mice (C57BL/6J background) (204, 205). Moreover, it is clear that exogenous of administration FGF21 significantly improved lipid metabolic disorders and reduced atherosclerotic plaque areas in these animals (206).

FGF-21-induced anti-oxidative function by increased levels of superoxide dismutase reduced glutathione and reduced malondialdehyde in Wistar rat (207). It has been reported that through an AMP-activated protein kinase- (AMPK-) dependent pathway in endothelial cells FGF21 prevent high glucose-induced cell damage and endothelial nitric oxide synthase dysfunction (208, 209).

Myocardial infarction (MI) is an established risk factor for atrial fibrillation (AF) (209).In response to myocardial Ischemia, adipocytes derived FGF21 was up-regulated and secreted into the circulation in the C57BL/6J mouse (210). After interacting with FGFR1 in cardiomyocytes in the presence of β-klotho, FGF21 activates its downstream kinases and proteins including phosphatidylinositol 3-kinase

(PI3K), protein kinase B (PKB/AKT), and Bcl2 antagonist of cell death (BAD), thereby reducing myocardial ischemia-induced apoptosis characterized by a reduction of caspase-3 activity (211). The moreover myocardial ischemic size was significantly smaller in FGF21 transgenic mice than that in wild-type mice (210) (Figure 2).

3.2.Oxidative stress and FGF21

Accumulating evidence suggests that oxidative stress plays a pivotal role in the development and perpetuation of AF (212, 213). In response to cardiac insults such as oxidation, cardiomyocytes induce the expression of FGF21 by the Sirt1–PPARα pathway (212, 214, 215). Recent researches have been shown that FGF21 involves in regulating oxidative stress (216). It demonstrated the expression of genes encoding proteins involved in antioxidative pathways, including mitochondrial uncoupling proteins (Ucp2 and Ucp3), superoxide dismutase-2 (Sod2), reduced ROS production in cardiomyocytes, and ameliorated cardiac tissue injury (189). Moreover, FGF21 gene expression is induced by pro-oxidative stimuli, establishing a feedback loop whereby the pro-oxidative stimuli themselves enhance the production of Fgf21, which confers local protection against ROS formation (196, 217, 218). Therefore, FGF21 stimulates an endogenous antioxidant response in cardiac tissue by acting in an autocrine manner. Other studies have reported that FGF21 also exerts protection after myocardial infarction by inhibiting cardiomyocyte apoptosis (189). The transcription factor, ATF4, might also be involved in the transcriptional control of cardiac *FGF21* expression in response to mitochondrial dysfunction or ER stress situations (219, 220). Most studies have proposed that binding of ATF4 to the *FGF21* gene promoter controls *FGF21* gene transcription in the heart and skeletal muscle in response to signals elicited by mitochondrial dysfunction and ER stress (219). However, an ATF4-mediated pathway of *FGF21* induction by mitochondrial dysfunction involving increased ROS production has been found in skeletal muscle (190, 221). From these pathways, FGF21 may involve cardiac protection from oxidative stress by producing SOD and activation of other anti-oxidative genes.

3.3.FGF21 and obesity

Increasing evidence demonstrated that obesity plays a critical role in AF progression (160, 210). AF is an obesity-associated disease, and the risk of AF increases progressively with rising BMI, metabolic disturbance, progressive insulin resistance, activation of the systemic and cardiac oxidative stress processes, activation of the pro-inflammatory cytokines, increased BP, cardiac mitochondrial redox dis-homeostasis and structural changes (160, 222). While several studies show that these all risk factors are highly associated with a disturbance of cardiac arrhythmia (145, 223). However, FGF21 is recognized as a powerful metabolic regulator (203, 224). In addition, long-term FGF21 administration can reverse the adverse effects of obesity by decreasing metabolic disturbance, systemic and cardiac oxidative stress and cardiac mitochondrial redox dis-homeostasis and structural changes (217, 223, 225-227). It also leads to decreased pro-inflammatory cytokines, reduced BP, thus attenuating FGF21 resistance in the heart, and finally leading to the restoration of arrhythmia(228). The high levels of plasma FGF21 observed in the HFF group were due to the exogenous FGF21administration (195). Moreover, the exogenous FGF21 administration has been shown to cause an up-regulation of the FGF21 synthesis, which might even lead to a further increase in the FGF21 level in the bloodstream, finally increase the level of FGF21 is involved in

lipid metabolism in modulating cardiac lipid metabolism and homeostasis (193). Furthermore, in WAT the FGF21 expression is regulated by PPARγ in response to fatty acids (228). In the heart, FGF21 is expressed and produced in response to insults promoting cardiac hypertrophy and oxidative stress, as part of a cardioprotective response (212). During fasting conditions, peroxisome-proliferator-activated receptor-α (PPARα) induced hepatic FGF21 production which in turn is activated by derivatives of non-esterified fatty acids released into the circulation by lipolysis in WAT (212, 228, 229). From the above evidence, it might give the relationship that FGF21have a therapeutic potential effect against obesity and its complications. The epicardial adipose tissue has been previously identified as a source of inflammatory mediators under basal condition and cardiac surgery increased mRNA expression of pro-inflammatory cytokines in both epicardial and subcutaneous adipose tissue (141, 230). A study demonstrated that circulating FGF-21 levels and its mRNA expression in epicardial adipose tissue are markedly increased by cardiac surgery (230). These findings suggest that FGF21 may reduce body mass index and inflammation.

3.4.Insulin resistance and FGF21

Increasing evidence from update research demonstrate that insulin resistance is closely related to the pathologic process of AF(174). FGF21 acts as one of the metabolic regulators. It has been demonstrated as a potent regulator of glycemia, lipid metabolism and energy homeostasis (231-233). Several findings provide physiological and molecular evidence that FGF-21 functions as a pleiotropic hormone-like protein, improve whole-body insulin sensitivity and reduce plasma levels of glucose and triglycerides in the diabetic monkey (203, 234). Moreover, in mouse 3T3-L1 adipocytes FGF21 stimulate glucose uptake and in primary cultures of human adipocytes (235). While administration of recombinant FGF21 to obese, insulin-resistant ob/ob or db/db mice or Zucker diabetic fatty rats caused similar effects, which include reductions in plasma glucose and insulin concentrations (236). From the above discussion, it might show that FGF21 can potentially protect the heart through improving insulin resistance and prevent the development of AF.

4.Conclusions

The worldwide prevalence of atrial fibrillation is increasing rapidly, culminating in a significant financial and resource burden on the various health care systems and health professionals. Although in recent years there has been a moderate increase in the number of available treatments, including the antiarrhythmic drugs, anti-inflammatory drugs, and Catheter ablation. But all these medications and therapies have multiple complications.

In this article, we have discussed the pathogenic factors mainly included inflammation, oxidative stress, obesity, and insulin resistance. All the pathogenic factors using several mechanical and cellular pathways to cause the AF. However here we have hypothesized that the FGF21 acts as an FGFR-dependent manner with b-Klotho as a cofactor hormone, that may be working as a protective factor in AF by attenuating inflammation, oxidative stress, Obesity, and insulin resistance. It may be a potential therapeutic for AF.

Declarations

1) ***Consent to publication***

We declare that all authors agreed to publish the manuscript at this journal based on the signed Copyright Transfer Agreement and followed publication ethics.

2) ***Ethical approval and consent to participants***
Not applicable.

3) ***Disclosure of conflict of interests***
We declare that no conflict of interest exists.

4) ***Funding***
None

5) ***Availability of data and material***
We declare that the data supporting the results reported in the article are available in the published article.

6) ***Authors' Contributions***
Authors contributed to this paper with the design (SMASN), literature search (SMASN), drafting (SMASN), revision (SMASN, AF, YH), editing (SMASN AF, YH) and final approval (SMASN and YH).

7) ***Acknowledgement***
None

8) ***Authors' biography***
None

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