

# The role of FGF21 in the pathogenesis of cardiovascular disease

Ying Zhang<sup>1,2</sup>, Dan Liu<sup>1,2</sup>, Xiao-Xue Long<sup>1,2</sup>, Qi-Chen Fang<sup>1</sup>, Wei-Ping Jia<sup>1</sup>, Hua-Ting Li<sup>1</sup>

<sup>1</sup>Department of Endocrinology and Metabolism, Shanghai Diabetes Institute, Shanghai Clinical Center for Diabetes, Shanghai Key Laboratory of Diabetes Mellitus, Shanghai Jiao Tong University Affiliated Sixth People's Hospital, 600 Yishan Road, Shanghai 200233, China;

<sup>2</sup>Department of Medicine, Shanghai Jiao Tong University School of Medicine, Shanghai 200233, China

## Abstract

The morbidity and mortality of cardiovascular diseases (CVDs) are increasing worldwide and seriously threaten human life and health. Fibroblast growth factor 21 (FGF21), a metabolic regulator, regulates glucose and lipid metabolism and may exert beneficial effects on the cardiovascular system. In recent years, FGF21 has been found to act directly on the cardiovascular system and may be used as an early biomarker of CVDs. The present review highlights the recent progress in understanding the relationship between FGF21 and CVDs including coronary heart disease, myocardial ischemia, cardiomyopathy, and heart failure and also explores the related mechanism of the cardioprotective effect of FGF21. FGF21 plays an important role in the prediction, treatment, and improvement of prognosis in CVDs. This cardioprotective effect of FGF21 may be achieved by preventing endothelial dysfunction and lipid accumulating, inhibiting cardiomyocyte apoptosis and regulating the associated oxidative stress, inflammation and autophagy. In conclusion, FGF21 is a promising target for the treatment of CVDs, however, its clinical application requires further clarification of the precise role of FGF21 in CVDs.

**Keywords:** Atherosclerosis; Cardiomyopathy; Cardiovascular disease; Fibroblast growth factor 21; Heart failure; Myocardial infarction

## Introduction

Cardiovascular diseases (CVDs) including coronary heart disease (CHD), atherosclerosis, myocardial infarction (MI), cardiomyopathy (CMP), and heart failure (HF) have the highest mortality rates worldwide.<sup>[1]</sup> In 2019, CVD caused an estimated 18.6 million deaths worldwide and another 39.3 million people lived with disabilities.<sup>[2]</sup> With the continuous development of pathology, some cytokines have proven to be significantly related to the occurrence and development of CVDs and are expected to become new targets for the early diagnosis and treatment of CVDs.<sup>[3]</sup>

The fibroblast growth factor (FGF) superfamily consists of 23 polypeptides. Members of the FGF superfamily usually act in an autocrine or paracrine manner. But FGF15/19, FGF21, and FGF23, which lack heparin-binding domains, are released into the bloodstream to act in an endocrine manner.<sup>[4]</sup> FGF21 was first identified as a member of FGFs in 2000<sup>[5]</sup> and has attracted global attention because of its excellent ability to regulate glucose and lipid metabolism. FGF21 is a polypeptide that contains 209

or 210 (human or rodent) amino acid residues comprising approximately 13 N-terminal and 40 C-terminal residues and extended random coil regions flanking a converged non-canonical b-trefoil fold core domain.<sup>[6]</sup> The FGF21 gene is located on chromosome 19. Its expression is primarily regulated by peroxisome proliferator-activated receptor  $\alpha$  (PPAR $\alpha$ ) in the liver and PPAR $\gamma$  in the adipose tissue.<sup>[7]</sup> Other transcription factors are also involved in regulating the expression of FGF21, such as activating transcription factor 4 (ATF4),<sup>[8]</sup> Kruppel-like factor 15,<sup>[9]</sup> retinoic acid receptor-related orphan receptor  $\alpha$ ,<sup>[10]</sup> Jumonji-D3,<sup>[11]</sup> and carbohydrate-responsive element binding protein.<sup>[12]</sup> FGF21 can activate only homologous FGF receptors (FGFRs) in the target tissues in the presence of coreceptor  $\beta$ -klotho.  $\beta$ -Klotho is a cell surface protein that mediates the targeting signal of FGF21, whereas FGFR mediates intracellular signal transmission. The N-terminal and C-terminal of FGF21 bind to FGFR and  $\beta$ -klotho, respectively.<sup>[13]</sup> Klotho protein is not universally expressed and is expressed at high levels in the liver, gall bladder, colon, pancreas, and adipose tissues,<sup>[14]</sup> which may determine the selective metabolic effects of FGF21. Under physiological conditions, FGF21 is primarily

## Access this article online

Quick Response Code:



Website:  
www.cmj.org

DOI:  
10.1097/CM9.0000000000001890

**Correspondence to:** Prof. Hua-Ting Li, Department of Endocrinology and Metabolism, Shanghai Diabetes Institute, Shanghai Clinical Center for Diabetes, Shanghai Key Laboratory of Diabetes Mellitus, Shanghai Jiao Tong University Affiliated Sixth People's Hospital, 600 Yishan Road, Shanghai 200233, China  
E-Mail: huarting99@sjtu.edu.cn

Copyright © 2021 The Chinese Medical Association, produced by Wolters Kluwer, Inc. under the CC-BY-NC-ND license. This is an open access article distributed under the terms of the Creative Commons Attribution-Non Commercial-No Derivatives License 4.0 (CCBY-NC-ND), where it is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal.

Chinese Medical Journal 2021;134(24)

Received: 08-09-2021 Edited by: Yan-Jie Yin and Xiu-Yuan Hao

secreted by the liver but is also expressed and secreted by other tissues (including adipose, muscle, and pancreatic) under stressed or pathological conditions.<sup>[15]</sup> The physiological functions of FGFs have been widely studied. FGFs have therapeutic potential in a wide array of human diseases, including diabetes mellitus (DM),<sup>[16]</sup> cancer,<sup>[17]</sup> alopecia,<sup>[18]</sup> and kidney disease.<sup>[19]</sup> FGF21 improves hyperglycemia, dyslipidemia, and obesity, providing a therapeutic effect on metabolic diseases.<sup>[20]</sup> In obese rodent models, FGF21 increased energy consumption, improved insulin sensitivity, and decreased bodyweight, blood glucose, and lipid levels.<sup>[21,22]</sup> Similar results were observed in experiments involving obese monkeys and patients with DM.<sup>[23,24]</sup> Moreover, FGF21 has a protective effect on non-alcoholic fatty liver disease.<sup>[25]</sup>

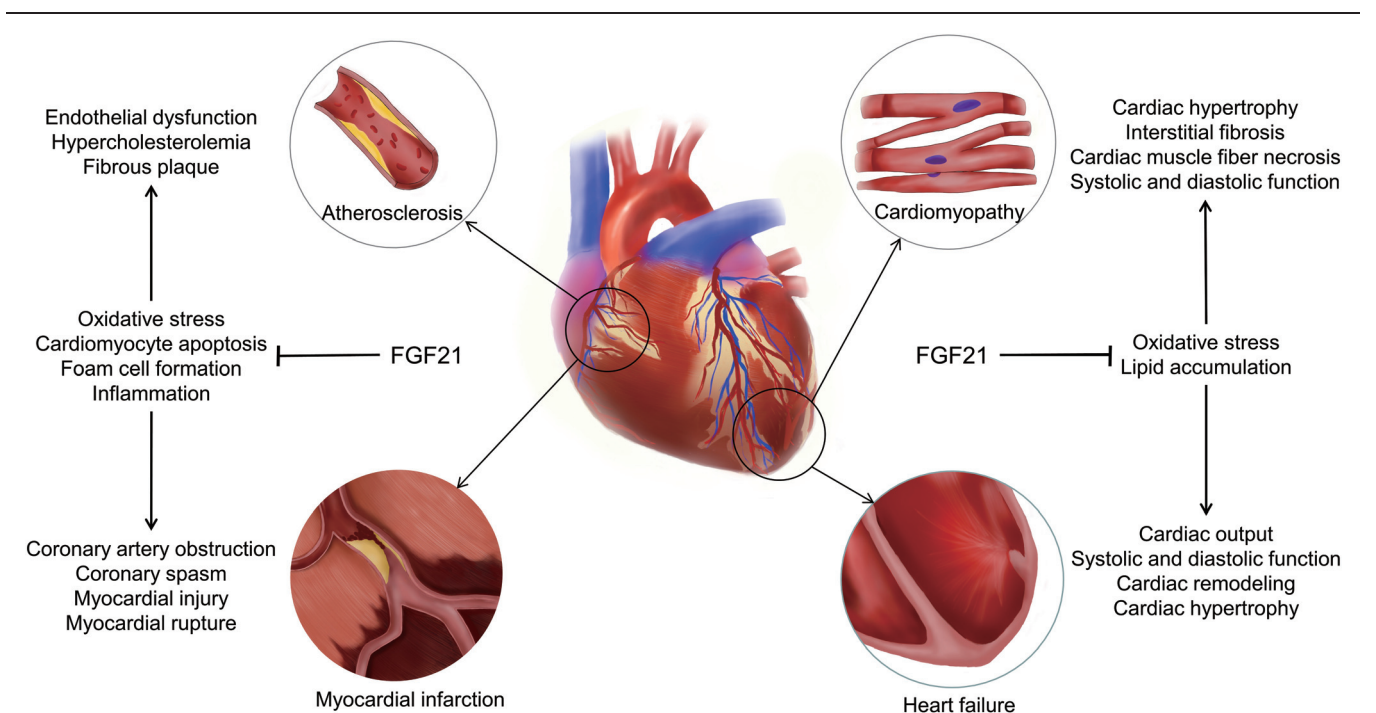
Early studies on FGF21 primarily focused on expression and metabolic regulation in the liver, whereas the relationship between FGF21 and the heart has become the most popular research topic in the past decade. Several studies have reported the relationship between FGF21 and CVDs, such as CHD,<sup>[26]</sup> CMP,<sup>[27]</sup> and HF.<sup>[28]</sup> FGF21 exerts cardioprotective effects partly by regulating oxidative stress,<sup>[29]</sup> lipid metabolism,<sup>[30]</sup> autophagy,<sup>[31]</sup> and apoptosis<sup>[32]</sup> and may be a new target for the prediction and treatment of CVDs. In this study, we attempted to shed light on the recent progress in understanding the relationship between FGF21 and CVDs [Figure 1]. We also explored the cardioprotective mechanisms of FGF21 in CVDs to provide a reference for the prediction, treatment, and prognosis of CVDs. The literature was obtained by searching the PubMed database and covering relevant research articles published up to June 2021 using the keywords “FGF21”, “cardiovascular disease”, “coronary heart disease”, “atherosclerosis”, “myocardial

infarction”, “cardiomyopathy”, “heart failure”, and combinations of these terms. There was no restriction on the type of article.

**Effect of FGF21 on CHD**

*The relationship between FGF21 and CHD*

CHD is characterized by cardiac ischemia, hypoxia, or necrosis caused by coronary artery stenosis or occlusion. The principal pathological change observed in CHD is the formation of atherosclerotic plaque in the coronary arteries.<sup>[33]</sup> Atherosclerosis is the accumulation of lipids and fibrous components in the arterial endothelium to form atherosclerotic plaques that invade the arterial lumen and hinder blood flow.<sup>[34]</sup> Previous studies have found that FGF21 is associated with DM, dyslipidemia, and metabolic syndrome, which are potential precursors of cardiovascular disease, suggesting that the cytokine may be associated with atherosclerosis.<sup>[35]</sup> In support of this notion, subsequent animal and clinical studies provided evidence for the association of FGF21 with atherosclerosis. In atherosclerotic mice, treatment with exogenous FGF21 significantly reduced lipid deposition and plaque area in the aortic root and decreased the severity of the lesion.<sup>[36]</sup> In clinical trials, serum FGF21 levels were lower in patients with subclinical atherosclerosis and peripheral artery disease.<sup>[37,38]</sup> Similarly, serum FGF21 levels were associated with carotid atherosclerosis.<sup>[39]</sup> Therefore, the expression and secretion of FGF21 generally decrease in patients with CHD.<sup>[26]</sup> A recent study reported a positive relationship between FGF21 and subclinical carotid atherosclerosis in women but not in men.<sup>[40]</sup> The Guangdong Coronary Artery Disease Cohort study followed 1668 patients with CHD for an average of 4.9 years and revealed a U-shaped relationship between



**Figure 1:** Pathophysiological changes of cardiovascular diseases and the role of FGF21 in these processes.

serum FGF21 levels and risks for all-cause and cardiovascular mortality. This suggests that low or high serum FGF21 levels increase the risk of mortality.<sup>[41]</sup> Multiple epidemiological investigations show that high levels of FGF21 could predict CHD development.<sup>[42,43]</sup> Similarly, higher plasma FGF21 levels were associated with a higher risk of CHD events in patients using statins.<sup>[44]</sup> Moreover, Cheng *et al*<sup>[45]</sup> found that the concentration of serum FGF21 in patients with unstable angina pectoris (UAP) was significantly higher than that in patients with stable angina pectoris and healthy controls. This indicates that FGF21 is a potential predictor of UAP. The increased FGF21 levels in these pathophysiological situations may be due to the compensatory response caused by FGF21 deficiency or resistance.<sup>[46]</sup> In contrast, some researchers report that FGF21 could not predict cardiovascular events in healthy individuals.<sup>[38,47]</sup> A study recently indicated that FGF21 could be used to predict the incidence or prognosis of CHD in specific patients rather than the general population.<sup>[48]</sup>

The relationship between FGF21 and cardiovascular complications in DM has also attracted much attention. FGF21 can improve endothelial dysfunction in diabetic mice, thus delaying the occurrence of atherosclerosis.<sup>[49]</sup> The administration of the long-acting FGF21 analog (PF-05231023) to obese cynomolgus monkeys and patients with type 2 diabetes (T2DM) significantly reduced body weight, increased adiponectin levels, and reduced circulating atherogenic lipids.<sup>[23]</sup> In patients with multivessel coronary artery disease and DM, the expression of FGF21 in pericardial fat and epicardial fat was significantly decreased.<sup>[50]</sup> The level of serum FGF21 in patients with T2DM positively correlated with markers of early vascular injury and endothelial dysfunction, such as C-reactive protein and high-density lipoprotein cholesterol (HDL-C).<sup>[51]</sup> Furthermore, serum FGF21 levels were also observed to be significantly increased in patients with T2DM and CHD. A cross-sectional study conducted in 504 patients with T2DM reported that serum FGF21 levels in women with lower extremity atherosclerotic disease were significantly higher than those in healthy women.<sup>[52]</sup> Patients with T2DM with newly diagnosed subclinical atherosclerosis had significantly higher serum FGF21 levels than those without subclinical atherosclerosis.<sup>[53]</sup> Moreover, a study that followed Chinese diabetic participants without CVD (at baseline) for 4 years found that baseline serum FGF21 levels in patients with new-onset CHD were significantly higher than those without CHD.<sup>[54]</sup> These results indicated that the serum FGF21 level is an independent predictor of cardiovascular complications in patients with DM. However, because of the instability and short half-life of natural FGF21 molecules, the independent application of FGF21 as a drug in clinical treatment remains to be investigated.<sup>[55]</sup> Recent studies have reported that the combination of FGF21 and glucagon-like peptide-1 is more effective for treating metabolic diseases.<sup>[56]</sup>

### Mechanism of action of FGF21 in atherosclerosis

The protective effect of FGF21 on the cardiovascular system has been demonstrated *in vivo* and *in vitro*. Mechanistic studies have reported that FGF21 enhances the

activity of the antioxidant system and suppresses oxidative stress and endoplasmic reticulum stress (ERS). In addition, FGF21 further reduces endothelial cell injury and apoptosis, thereby inhibiting the development of atherosclerosis.<sup>[29]</sup> FGF21 intervention increased the levels of superoxide dismutase (SOD) and glutathione and decreased malondialdehyde levels in atherosclerotic rats.<sup>[57,58]</sup> The transcription factor E2-related factor 2 (Nrf2) and antioxidant responsive element (ARE) signaling pathways have an anti-atherosclerotic effect by activating cellular antioxidant defense.<sup>[59]</sup> In atherosclerotic rats, the upregulation of FGF21 increased the expression of Nrf2/ARE pathway-related proteins and antioxidant system-related molecules and reduced endothelial dysfunction, whereas downregulation of FGF21 reversed these changes.<sup>[57]</sup> ERS induced the expression and secretion of FGF21 through ATF4 and CCAAT enhancer-binding protein homologous protein (CHOP).<sup>[60]</sup> FGF21 decreased the expression levels of ERS-specific proteins, including glucose-regulated protein-94, caspase-12, and CHOP. FGF21 further alleviated atherosclerosis in apolipoprotein E<sup>-/-</sup> (*ApoE<sup>-/-</sup>*) mice by inhibiting ERS-induced apoptosis.<sup>[61]</sup>

Vascular endothelial cell injury and apoptosis are the basic pathological features of atherosclerosis. Clinical studies have found that increased FGF21 levels are related to a deteriorated endothelial function.<sup>[62]</sup> FGF21 may improve endothelial function in the early stages of atherosclerosis.<sup>[63]</sup> Intravenous injection of adenoviral vectors expressing FGF21 (Ad-FGF21) in mice significantly promoted blood flow recovery and endothelial nitric oxide synthase (eNOS) phosphorylation in ischemic limbs. This suggested that FGF21 promoted endothelial cell function and ischemia-induced vascular remodeling through an eNOS-dependent mechanism.<sup>[64]</sup> FGF21 attenuates the aggravation of aortic endothelial cell injury caused by hyperglycemia. The binding of FGF21 to FGFR activates the calcium/calmodulin-dependent protein kinase kinase 2 and AMP-activated protein kinase (AMPK) signaling pathway, inhibits oxidative stress, and increases levels of eNOS phosphorylation and nitric oxide production in endothelial cells. This subsequently inhibits the decrease in endothelial cell activity and migration induced by high glucose (HG) and alleviates endothelial dysfunction.<sup>[49,65]</sup> This mechanism does not depend on the hypoglycemic or insulin-sensitizing effects of FGF21. In addition, pretreating human umbilical vein endothelial cells (HUVECs) with FGF21 before exposure to HG downregulated the expression of Bim and upregulated the expression of eNOS via the phosphatidylinositol-3-kinase (PI3K)/protein kinase B (Akt)/FoxO3a signaling pathway, thus reducing the production of reactive oxygen species (ROS) and inhibiting apoptosis.<sup>[66,67]</sup> FGF21 inhibited the apoptosis of HUVECs induced by H<sub>2</sub>O<sub>2</sub> or oxidized low-density lipoprotein (Ox-LDL) and decreased the degree of DNA fragmentation and increased the survival rate of HUVECs.<sup>[32,68]</sup> B-cell lymphoma 2 (BCL-2) protein protects cells from apoptosis, whereas BCL2-associated X protein (BAX) protein can induce apoptosis.<sup>[69]</sup> Therefore, the Bax/Bcl-2 ratio is an important regulator of apoptosis pathway activity. Caspase-3 is also an important factor in apoptosis activation. *In vitro*, the cleavage of caspase-3 and the ratio of Bax/Bcl-2 increased in H<sub>2</sub>O<sub>2</sub>-treated

HUVECs but decreased after pretreatment with FGF21.<sup>[70]</sup> Further studies found that FGF21 antagonized apoptosis induced by oxidative stress by blocking the mitogen-activated protein kinase (MAPK) signaling pathway.<sup>[68]</sup> Early studies have found that Ox-LDL promotes Fas-mediated endothelial cell apoptosis and atherosclerosis.<sup>[71]</sup> FGF21 can block this process by inhibiting the expression of the Fas and Fas-associated death domain (FADD) proteins independent of ERK1/2.<sup>[32]</sup> Therefore, the protective effect of FGF21 on atherosclerosis may be partly related to the inhibition of caspase-3 cleavage, BAX protein levels, MAPK pathway signaling, and Fas/FADD-mediated endothelial cell apoptosis.

Endovascular homeostasis imbalance and compensatory angiogenesis disorders are early manifestations of atherosclerosis. FGF21 significantly promotes the formation of neointima and enhances endothelium-dependent relaxation of injured carotid arteries in atherosclerotic rats.<sup>[58]</sup> Previous studies show that FGF21 promotes endothelial angiogenesis through the dynamin-2- and Rab5-dependent pathways.<sup>[72]</sup> A recent study reported that FGF21 promoted angiogenesis and blood perfusion after hind limb ischemia surgery in diabetic mice. FGF21 can directly act on endothelial progenitor cells (EPCs), which are progenitors of the vascular endothelial cells, and increase the level of NAD<sup>+</sup> in an AMPK-dependent manner. The protective effect of NAD<sup>+</sup> on the angiogenesis of EPCs may be regulated by sirtuin 1 (SIRT1).<sup>[73]</sup> Vascular endothelial cell aging is an independent risk factor of age-related CVDs,<sup>[74]</sup> and SIRT1 is considered an anti-aging molecule. Downregulation of SIRT1 expression can lead to oxidative stress, inflammation, foam cell formation, autophagy inhibition, and nitric oxide production, thus promoting vascular aging and atherosclerosis.<sup>[75]</sup> FGF21 reportedly delays the aging of HUVECs in an SIRT1-dependent manner and protects the integrity of endothelial cells, suggesting that FGF21 might prevent age-related vascular diseases, such as atherosclerosis.<sup>[76]</sup>

Dyslipidemia, which includes lipid accumulation and hypercholesterolemia, is an important risk factor for the formation of atherosclerotic plaques.<sup>[34]</sup> A decade ago, researchers discovered the beneficial effect of FGF21 on dyslipidemia in mice.<sup>[77]</sup> In studies using models of atherosclerotic mouse and rat, researchers found that exogenous FGF21 treatment reduced the body weight and improved the blood lipid profile and lipid metabolism which included reduced levels of serum triglyceride (TG), total cholesterol, and low-density lipoprotein cholesterol and increased levels of HDL-C, which were negatively correlated with plaque size.<sup>[68,78]</sup> Therefore, FGF21 can prevent the development of atherosclerosis by reducing hypercholesterolemia. Previous studies have found that FGF21 deficiency leads to further aggravation of hypercholesterolemia in *ApoE*<sup>-/-</sup> mice, accompanied with an increasing expression of cholesterol-producing genes and the transformation from HDL to LDL. Supplementation with FGF21 can inhibit the expression of hepatic sterol regulatory element-binding protein-2, thereby reducing cholesterol production and relieving atherosclerosis.<sup>[79]</sup> Several researchers recently postulated a different point of

view suggesting that FGF21 treatment can increase the expression of genes related to cholesterol synthesis. However, this may only be a compensatory response. In fact, FGF21 reduces hypercholesterolemia by reducing non-HDL cholesterol levels. Specifically, researchers selected *APOE\*3-Leiden CETP* mice, which are sensitive to cholesterol-lowering substances. They found that exogenous recombinant FGF21 promoted the hydrolysis of TG-rich lipoproteins and the absorption of released fatty acids in both white and brown adipose tissue while accelerating cholesterol clearance in the liver. This reduced hypercholesterolemia and effectively prevented the development of atherosclerosis.<sup>[36]</sup> The imbalance of cholesterol homeostasis in macrophages induces the formation of foam cells, which is a sign of early atherosclerosis. Increasing cholesterol outflow from macrophages prevents the progression of atherosclerosis. Researchers observed inhibited foam cell formation after co-culturing THP-1 macrophages with Ox-LDL and FGF21.<sup>[80,81]</sup> Further, studies show that FGF21 increases the expression of liver X receptor (LXR)  $\alpha$ -dependent ATP-binding cassette transporter A1 (ABCA1) and ATP-binding cassette transporter G1 (ABCG1) through the AMPK-ERK1/2-PPAR $\gamma$ -LXR $\alpha$  signaling pathway.<sup>[82]</sup> ABCA1 and ABCG1 promote cholesterol efflux from macrophages and reduce intracellular cholesterol accumulation, thus inhibiting the formation of foam cells.<sup>[81,82]</sup> Moreover, some researchers believed that FGF21 mediates the effects of the above-mentioned pathways on macrophages via an adiponectin-dependent mechanism.<sup>[79,83]</sup> In addition, FGF21 might induce autophagy through activated kinase C receptor 1 to promote the degradation of lipid droplets and to increase cholesterol outflow from foam cells.<sup>[31]</sup> Therefore, FGF21 inhibits the formation of foam cells by regulating lipid metabolism, cholesterol efflux, and autophagy and protecting against atherosclerosis.

Inflammation is also an independent risk factor of coronary artery disease. Macrophages are the principal target cells of FGF21 that exert anti-inflammatory effects. The number of macrophages in the atherosclerotic plaques decreased significantly after FGF21 treatment.<sup>[58]</sup> FGF21 regulates inflammation in macrophages by inhibiting the nuclear factor (NF)- $\kappa$ B signaling pathway.<sup>[81]</sup> FGF21 significantly reduces the expression of circulatory inflammatory factors including interleukin (IL)-1 $\beta$ , IL-6, and tumor necrosis factor (TNF)- $\alpha$  in the liver tissue and aortic arch endothelial cells.<sup>[36,58]</sup> In addition, several studies have found that the Nrf2/ARE signaling pathway may also be involved in the anti-inflammatory and anti-atherosclerotic effects of FGF21.<sup>[57]</sup> The NOD-like receptor protein 3 (NLRP3) inflammasome is composed of NLRP3, ASC, and procaspase-1. NLRP3 activation promotes the transformation of procaspase-1 into active caspase-1 leading to the processing and release of IL-1 $\beta$  and triggering a series of downstream inflammatory reactions.<sup>[84]</sup> The NLRP3 inflammasome is closely related to the occurrence, development, and severity of atherosclerosis.<sup>[85]</sup> Studies have found that FGF21 can inhibit vascular neointima hyperplasia and improve vascular dysfunction. Mechanistic studies have demonstrated that FGF21 significantly inhibits the HG-induced release of activated caspase-1 and IL-1 $\beta$  in mouse VSMCs. This process may be attributed to the inhibition of

FGF21 on HG-induced Syk phosphorylation, which leads to the suppression of NLRP3 inflammasome activation in VSMCs and ultimately reduces the occurrence of vascular remodeling.<sup>[83]</sup> FGF21 reduces the proliferation and migration of VSMCs partly through the above-mentioned pathways.<sup>[83]</sup> Recently, FGF21 was reported to prevent atherosclerosis by inhibiting the pyrolysis of vascular endothelial cells. Pyrolysis (also known as cell inflammatory necrosis) is a type of programmed cell death characterized by cell swelling and membrane rupture followed by the release of cellular contents and the activation of inflammatory responses.<sup>[86]</sup> FGF21 significantly reduced the expression of pyrolysis-related proteins, including NLRP3, caspase1, and IL-1 $\beta$ , in the aorta of *ApoE*<sup>-/-</sup> mice who were fed a high-fat diet.<sup>[78]</sup> Therefore, FGF21 is speculated to mitigate atherosclerosis by inhibiting vascular endothelial cell pyrolysis mediated by the NLRP3 inflammasome.<sup>[78]</sup> Mitochondrial dysfunction and oxidative stress may also play roles in this process. To exert an anti-atherosclerotic effect, FGF21 reduced ROS production by ameliorating mitochondrial dysfunction, oxidative stress, and ERS.<sup>[78]</sup> The deficiency of ubiquinol cytochrome c reductase core protein I (UQCRC1), a member of the respiratory chain complex III, can lead to an increase in ROS production.<sup>[87]</sup> Tet methylcytosine dioxygenase 2 (TET2) participates in the regulation of UQCRC1 expression. Chen *et al*<sup>[88]</sup> confirmed that FGF21 inhibited Ox-LDL-induced pyrolysis of HUVECs through the TET2-UQCRC1-ROS pathway. In summary, FGF21 can inhibit almost all pathogenic events of atherosclerosis, including oxidative stress, endothelial cell injury and apoptosis, lipid accumulation, and inflammation.

## Effect of FGF21 on MI

### The relationship between FGF21 and MI

Further deterioration of coronary atherosclerosis may lead to coronary artery occlusion and myocardial ischemia and eventually result in MI. Coronary artery spasms may also lead to MI.<sup>[89]</sup> In animal models, plasma and cardiac FGF21 levels increased significantly after myocardial ischemia.<sup>[90]</sup> Sunaga *et al*<sup>[91]</sup> found that FGF21 levels in serum and myocardial tissue increased rapidly 1 h after coronary artery ligation and remained elevated after 24 h and 1 week. Moreover, liver-specific FGF21 deficiency in experimental MI-model mice led to further deterioration of cardiac dysfunction.<sup>[92]</sup> After treatment with Ad-FGF21 for 2 weeks, the left ventricular systolic and diastolic functions of these mice improved significantly.<sup>[93]</sup> Li *et al*<sup>[94]</sup> found that the scar size, cardiac ejection fraction, and fractional shortening of mice with MI decreased significantly after 1 and 4 weeks of FGF21 treatment. Increased FGF21 levels after MI may be a spontaneous *in vivo* cardioprotective mechanism.

Consistent with the findings in MI-model mice, circulating FGF21 levels also increased in patients with acute myocardial infarction (AMI), and the expression of FGF21 may be a key response against cardiac ischemic injury.<sup>[91]</sup> Serum FGF21 levels reached a maximum within 24 h after onset, remained at high levels for 7 days, and decreased slightly thereafter. Moreover, the level of FGF21

on day seven was related to the incidence of re-infarction and death within 1 month in patients with AMI.<sup>[95]</sup> These studies suggest that circulating FGF21 levels could be used as a predictor of clinical prognosis in patients with AMI.

### The mechanism of action of FGF21 in MI

Some studies show that myocardial ischemia induces activation of the sympathetic nervous system and resultant lipolysis of adipose tissue,<sup>[96]</sup> which increased levels of catecholamines and saturated fatty acids (SFAs). Subsequently, *in vitro* experiments showed that catecholamines and SFAs induced the activation of AMPK, thereby increasing the production and release of FGF21 in cardiomyocytes and forming a cardiac AMPK-FGF21 feed-forward loop. This is an effective and long-lasting protective signaling pathway against ischemic stress.<sup>[97]</sup> FGF21 can further induce its own expression and activate the expression of AMPK in downstream targets, such as the AMPK/SIRT1/peroxisome proliferator-activated receptor- $\gamma$  coactivator 1  $\alpha$  (PGC-1 $\alpha$ ) signaling pathway,<sup>[97,98]</sup> to regulate the myocardial metabolic dynamic balance and mitochondrial function, thereby protecting against cardiac ischemic injury.<sup>[99]</sup>

The liver contributes to cardioprotective effects in MI by upregulating and releasing protective secretory proteins, such as FGF21.<sup>[100]</sup> Circulating FGF21 interacted with FGFR1 in cardiomyocytes, which then partly inhibited apoptosis by activating the PI3K/Akt1/Bcl-2-associated death promoter (BAD) signal network.<sup>[101]</sup> Moreover, FGF21 inhibited cardiomyocyte apoptosis by reducing caspase-3 activity and modulating galectin-3 in cardiomyocytes.<sup>[92,101]</sup> Furthermore, intramuscular injection of exogenous FGF21 in mice increased the level of plasma adiponectin, a cardioprotective adipokine. Simultaneous inhibition of apoptosis in cardiomyocytes and the improvement of capillary formation in the marginal zone of infarction were also observed. This suggests that muscle-derived FGF21 at least partially improves myocardial pathological remodeling post-MI through an adiponectin-dependent mechanism.<sup>[93]</sup> In addition, the administration of FGF21 could reduce the expression of proinflammatory cytokines such as TNF- $\alpha$  and IL6 during MI, indicating that FGF21 might attenuate pathological myocardial remodeling through anti-inflammatory effects.<sup>[93]</sup>

Patients with AMI are at a high risk of arrhythmias and sudden cardiac death.<sup>[102,103]</sup> Cardiac electrical remodeling, including abnormal cardiac conduction and abnormal action potential duration, is the principal reason for the increase in arrhythmia after MI. Improving cardiac electrical remodeling can increase cardiac performance and reduce MI and cardiac fibrosis.<sup>[104]</sup> In a recent study, Li *et al*<sup>[94]</sup> demonstrated for the first time that FGF21 attenuated ischemia-induced dysfunction of voltage-gated Na<sup>+</sup> channels and K<sup>+</sup> channels in cardiomyocytes by targeting the miR-143/early growth response protein 1 signaling pathway. Therefore, FGF21 effectively improved cardiac electrical conduction and reduced the incidence of ventricular arrhythmias after MI. This discovery provides a new approach for the treatment of ischemic arrhythmia.

### **The mechanism of action of FGF21 in ischemia-reperfusion (I/R) injury**

The restoration of coronary artery perfusion is an essential step in the treatment of AMI. However, the rapid recovery of blood supply to the ischemic tissues or organs can aggravate cell death and tissue injury, leading to I/R injury.<sup>[105]</sup>

Autophagy is involved in protection against myocardial injury during I/R.<sup>[106]</sup> Studies have confirmed that FGF21 plays a cardioprotective role in I/R injury by promoting autophagic flux.<sup>[107]</sup> After co-incubating reoxygenated H9c2 cardiomyocytes with FGF21, the H/R-induced injury of H9c2 cardiomyocytes was alleviated, and the survival rate of myocardial cells increased. These changes may be caused by FGF21-induced upregulation of autophagy flux through the Beclin-1/vacuolar protein sorting 34 pathway.<sup>[107]</sup>

Apoptosis is the primary form of cell death following I/R injury. Some studies have shown that FGF21 can scavenge ROS, eliminate lipid peroxidation, and protect cell membranes from oxidative stress caused by I/R injury through the Akt/glycogen synthase kinase 3  $\beta$ /caspase-3 signaling pathway.<sup>[108]</sup> FGF21 can also alleviate cell injury by improving the energy supply through activating ATP synthase, pyruvate kinase M1, and protein kinase C.<sup>[108]</sup> Furthermore, in the I/R injury model, FGF21 inhibited the expression of angiotensin II (Ang II) and increased the levels of miR-145 and glucose transporter-1. This may improve glucose transport and energy supply, thereby increasing cell migration and decreasing the rate of apoptosis.<sup>[109]</sup> Taken together, FGF21 inhibits cell apoptosis caused by I/R through a variety of pathways to alleviate cardiac dysfunction.

### **Effect of FGF21 on CMP**

#### **The relationship between FGF21 and CMP**

Cardiomyopathy is also a common cardiovascular disease that is divided into primary (genetic, non-genetic, and acquired) and secondary cardiomyopathy (including diabetic, alcoholic, and infectious cardiomyopathy).<sup>[110,111]</sup> Diabetic cardiomyopathy (DCM) is defined as a DM-induced chronic myocardial necrotic disease characterized by abnormal cardiac structure and function in the absence of other cardiac diseases.<sup>[112]</sup> Circulating FGF21 levels were significantly lower in DCM model mice.<sup>[113]</sup> FGF21-knockout (FGF21-KO) mice were more sensitive to DM-induced myocardial injury, cardiac fibrosis, collagen and lipid accumulation, and systolic and diastolic dysfunction. Both exogenous and endogenous supplementation with FGF21 could reverse these changes and prevent the progression of DCM.<sup>[114,115]</sup> These results suggest that FGF21 may have a protective effect against cardiomyopathy. However, most studies on DCM have been conducted on animals. Therefore, clinical trials are needed to confirm the relationship between FGF21 and DCM.

Other types of cardiomyopathies have also been explored by many researchers. A clinical study demonstrated that serum FGF21 levels were associated with the risk, severity,

and prognosis of dilated cardiomyopathy.<sup>[116]</sup> Moreover, cardiac biopsy in patients with hypertension revealed that FGF21 levels in cardiomyocytes were significantly increased, especially in the patients who further developed cardiomyopathy and were positively correlated with the degree of cardiac hypertrophy and fibrosis.<sup>[117]</sup> Animal experiments further confirmed that FGF21 treatment could significantly reduce cardiac hypertrophy and dysfunction induced by Ang II.<sup>[118]</sup> Researchers recently proposed that FGF21 might be a promising diagnostic marker and therapeutic target for alcoholic cardiomyopathy (ACM).<sup>[119]</sup> Studies have found that chronic alcohol consumption induces FGF21 levels in the plasma and cardiomyocytes.<sup>[120]</sup> The deficiency of FGF21 exacerbated cardiac mitochondrial dysfunction and oxidative stress in response to alcohol exposure, suggesting that FGF21 may protect the heart from ACM by activating the antioxidant defense system in the myocardium.<sup>[120,121]</sup> However, more evidence is needed to support this notion.

### **The mechanism of action of FGF21 in DCM**

DCM and other cardiovascular complications related to increasingly prevalent DM are attracting augmented attention. Researchers have found a close relationship between FGF21 and DCM and conducted further research on its internal mechanism.

Efficient suppression of oxidative stress and cardiomyocyte apoptosis is important for preventing DCM. Previous studies have demonstrated that FGF21 inhibits oxidative stress through various pathways. FGF21 treatment prevented oxidative stress in cardiomyocytes by reducing ROS production and inducing the expression of antioxidant genes, including mitochondrial uncoupling protein 2, mitochondrial uncoupling protein 3 (UCP3), and SOD2.<sup>[29]</sup> Moreover, FGF21 increased the phosphorylation of AMPK through ERK1/2 and LKB1, leading to the activation of SIRT1 and the deacetylation of its downstream target genes, including PGC-1 $\alpha$  and histone 3.<sup>[97,122]</sup> Furthermore, both exogenous and endogenous FGF21 could protect the heart from oxidative stress via the AMPK/Akt2/Nrf2-mediated antioxidative pathway.<sup>[123,124]</sup> In addition, paraoxonase 1 (PON1) is considered a potential target against CVDs.<sup>[125]</sup> The protective effect of FGF21 against DM-induced cardiac damage is at least partly mediated by activation of the AMPK/PON1 signaling pathway. This inhibits oxidative stress and reduces local inflammation, fibrosis, and cardiomyocyte apoptosis, thereby preventing the occurrence of DCM.<sup>[115]</sup>

The cardioprotective effect of FGF21 on DCM is primarily attributed to lipotoxicity rather than glucose toxicity. Researchers have shown that inhibition of fatty acid  $\beta$  oxidation partially blocks the protective effect of FGF21 on cardiomyocytes<sup>[123]</sup> and that the AMPK/acetyl-CoA carboxylase (ACC)/carnitine palmitoyltransferase I-mediated lipid metabolic pathway is involved in this process.<sup>[124]</sup> Moreover, PGC-1 $\alpha$  serves as a key transcriptional energy balance regulator and plays an important role in regulating fatty acid oxidation.<sup>[126]</sup> The expression of cardiac PGC-1 $\alpha$  was downregulated in FGF21-KO diabetic mice,<sup>[123]</sup> and inhibition of FGF21 resulted in

excess lipid uptake and increased lipid accumulation. This promoted cardiac remodeling—including cardiac hypertrophy, fibrosis, and dysfunction—and further accelerated DCM development.<sup>[113]</sup> Notably, FGF21 can inhibit cardiac lipid absorption. CD36 and fatty acid transport protein (FATP) are regulators of lipid absorption. Nrf2 mediates the upregulation of CD36 expression and has been reported to play a key role in lipid metabolism in macrophages and within the aorta.<sup>[127,128]</sup> FGF21 deficiency upregulated Nrf2, CD36, and FATP expression in cardiomyocytes, whereas FGF21 supplementation strongly suppressed their expression levels.<sup>[113,123,124]</sup> Additionally, cardiac dysfunction in patients with DM is partly attributed to the accumulation of lipid droplets in cardiomyocytes. Autophagy involves the decomposition of intracellular lipid droplets.<sup>[129]</sup> The upregulation of cardiac FGF21 expression increases SIRT1-mediated autophagy, thus reducing cardiomyocyte injury caused by lipotoxicity.<sup>[130]</sup> Further studies are needed to explore the mechanism of the effects of FGF21 on DCM and other types of cardiomyopathies.

## Effect of FGF21 on HF

### *The relationship between FGF21 and HF*

HF is a clinical syndrome characterized by abnormal cardiac structure, function, rhythm, or conduction and is primarily attributed to cardiac diastolic and systolic dysfunction caused by MI, hypertension, and CMP. According to the level of ejection fraction, HF can be divided into HF with preserved ejection fraction (HFpEF) and HF with reduced ejection fraction (HFrEF).<sup>[131]</sup> Current epidemiological studies show that more than half of patients with HF have a preserved ejection fraction.<sup>[132]</sup> Presently, only a few studies focus on the relationship between FGF21 and HF. Chou *et al*<sup>[28]</sup> found that circulating FGF21 levels increased significantly in patients with HFpEF compared with those in the control group; additionally, plasma FGF21 had good predictive values for adverse cardiac events within 1 year in HFpEF patients. In another study on cardiac cachexia, the researchers reported that serum FGF21 levels were significantly higher in patients with HFrEF and cardiac cachexia than in those without cachexia.<sup>[133]</sup> In addition, a study of 1132 patients with both DM and coronary artery calcification confirmed that lower baseline serum FGF21 levels indicated a lower incidence of major adverse cardiovascular events, including acute coronary syndrome, HF, malignant arrhythmia, and sudden cardiac death.<sup>[48]</sup> These results suggest that FGF21 may be a potential target for the prediction and treatment of HF.

### *FGF21 mechanism in HF*

Few studies have investigated the underlying mechanism of FGF21 in HF focusing on the effects of antioxidation and autophagy promotion. Some studies have shown that the expressions of FGF21 and antioxidant genes (e.g., UCP3 and SOD2) were upregulated in failing human hearts.<sup>[29]</sup> HF triggers the excess intracellular energy signal, weakens the anabolic system, and enhances the catabolic system. The regulation of energy metabolism may be mediated by

the SIRT1 signaling pathway and its downstream molecules, PGC-1 $\alpha$  and FGF21.<sup>[98,134]</sup> Researchers found that sodium-glucose cotransporter 2 (SGLT2) inhibitors activated the SIRT1/PGC-1 $\alpha$ /FGF21 signaling pathway, reduced oxidative stress, and promoted autophagy in cardiomyocytes, thereby reducing the risk of severe HF failure events.<sup>[98]</sup> Additionally, PGC-1 $\alpha$  reportedly interacts with NF- $\kappa$ B in cardiomyocytes of both humans and mice, indicating that the regulation of inflammation may also play a role in HF prevention.<sup>[135]</sup> Therefore, the activation of FGF21 and enhancement of the cardiac antioxidant system may play a cardioprotective role in HF. Hypertension is also an important risk factor for HF. FGF21 may play a role in regulating blood pressure.<sup>[136]</sup> Studies have shown that the levels of circulating FGF21 and FGF21 expression in the myocardium increased in mice and humans.<sup>[117]</sup> Moreover, Pan *et al*<sup>[137]</sup> found that FGF21 deficiency led to a significant deterioration of hypertension and increased vascular damage in Ang II-treated mice, whereas FGF21 supplementation significantly reversed these negative effects. Its underlying mechanism may be the activation of angiotensin-converting enzyme 2/angiotensin-(1–7) axis. Furthermore, adenosine A2 receptor, a Gs protein-coupled receptor in brown adipose tissue, can mediate the release of brown adipose tissue-derived FGF21, which has a protective effect on cardiac remodeling induced by hypertension in an endocrine manner.<sup>[138,139]</sup>

## Conclusion and future perspective

This review summarizes the role of FGF21 in cardiovascular pathology. FGF21 is an important regulator of glucose and lipid metabolism and has clear regulatory effects on a variety of metabolic pathways. However, the molecular mechanisms underlying these effects have not been fully elucidated. Herein, we summarize recent studies on the relationship between FGF21 and CVDs (including CHD, MI, CMP, and HF) and provide evidence that FGF21 plays an important role in the prediction, treatment, and improvement of prognosis in CVDs [Table 1]. We also summarize the related mechanism of the cardioprotective effect of FGF21 [Figure 2]. However, many controversies remain among different studies regarding the exact relationship, and the internal mechanisms between FGF21 and CVDs remain unclear. Further studies with stricter designs and larger sample sizes are needed to clarify this inconsistency.

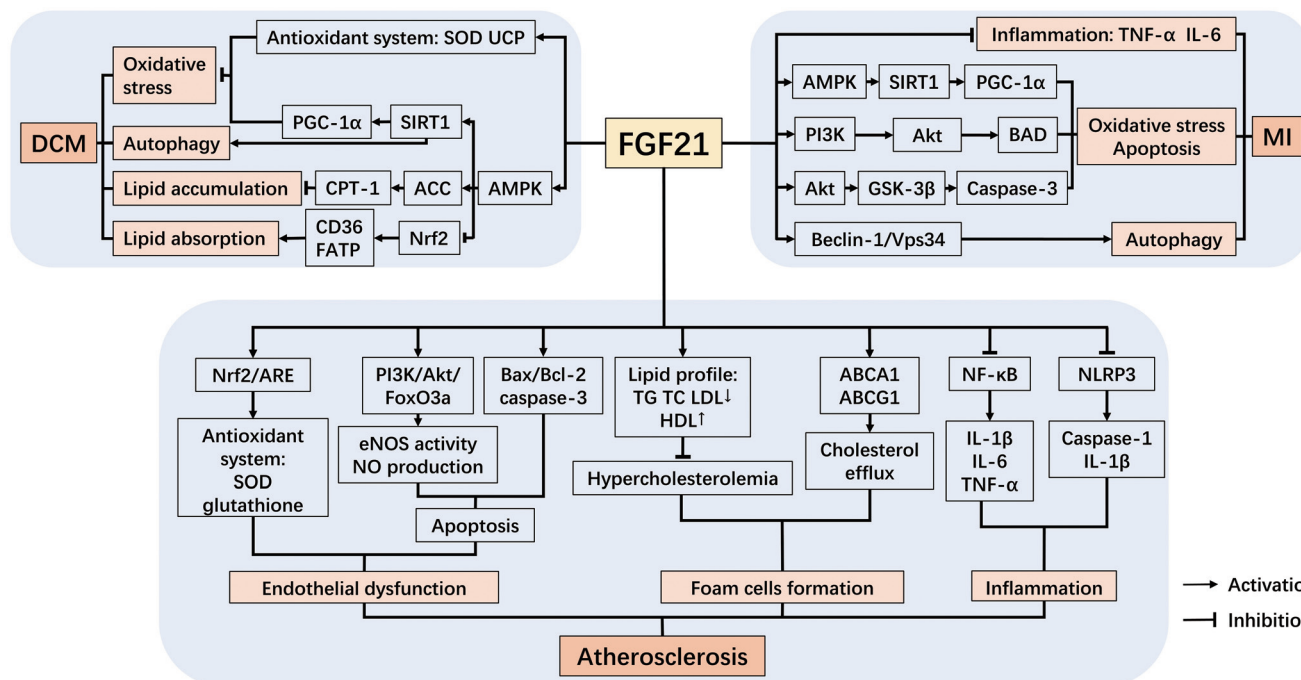
Although many preclinical studies have confirmed that FGF21 has multiple protective effects on metabolic disorders and cardiovascular diseases, the clinical application of FGF21 remains a challenge. First, some studies suggest that FGF21 may have negative effects on bone homeostasis, including bone loss and excessive osteoclasts in rodents,<sup>[140,141]</sup> whereas such effects were not observed in others.<sup>[24,142]</sup> Second, the results obtained in animal experiments cannot be directly applied to humans because of interspecific differences in the pharmacological effects of FGF21.<sup>[143]</sup> Moreover, the pharmacokinetics of natural FGF21 is poor and not suitable for clinical application. In recent years, FGF21 analogs and simulants have been continuously developed,<sup>[20]</sup> and some have been used in

**Table 1: Clinical evidence on the relationship between FGF21 and cardiovascular diseases.**

Diseases	Populations	Samples	Results	Interpretations	References
CHD	CHD ( <i>n</i> = 33)	Serum	DM patients: EF volume↑ RAGE (EF)↑ ADM (EF and PF)↑ FGF21 (EF and PF)↓	The expression of FGF21 in epicardial and cardiac fat decreased in patients with CHD and diabetes.	[50]
	CHD with DM ( <i>n</i> = 33)				
	Subclinical atherosclerosis ( <i>n</i> = 75)				Serum
	Healthy control ( <i>n</i> = 65)				
	CHD ( <i>n</i> = 224; PAD, <i>n</i> = 38)	Plasma	CHD patients and healthy control: FGF21 (no significant difference)	Circulating FGF21 was lower in patients with PAD than in those without PAD.	[38]
	Healthy control ( <i>n</i> = 193)				
	SAP ( <i>n</i> = 66)	Serum	PAD patients: FGF21↓ UAP: FGF21↑	Serum FGF21 was significantly higher in UAP patients than in SAP patients and healthy controls.	[45]
UAP ( <i>n</i> = 76)					
Healthy control ( <i>n</i> = 55)		Positive correlation: FGF21 with cTnI and CK-MB			
CHD ( <i>n</i> = 1668)	Serum	U-shaped correlation: FGF21 with mortality	Serum FGF21 levels and mortality in CHD patients showed a U-shaped correlation.	[41]	
T2DM ( <i>n</i> = 504)	Serum	LEAD: FGF21↑ Positive correlation: FGF21 with systolic blood pressure and femoral intima-media thickness	Serum FGF21 was significantly higher in LEAD women than in healthy women.	[52]	
LEAD ( <i>n</i> = 294)					
non-LEAD ( <i>n</i> = 210)					
AMI	AMI ( <i>n</i> = 50)	Serum	AMI patients: FGF21↑ Positive correlation: FGF21 with peak FABP4 and saturated fatty acids.	Serum FGF21 was higher in AMI patients than in SAP patients.	[91]
	SAP ( <i>n</i> = 43)				
	AMI ( <i>n</i> = 55)	Serum	AMI patients: FGF21↑ Maximum: 24 h after AMI Remained: 7 days	Serum FGF21 was significantly higher in AMI patients than controls.	[95]
CMP	Dilated cardiomyopathy ( <i>n</i> = 241)	Serum	Dilated cardiomyopathy patients: FGF21↑ Negative correlation: FGF21 and NT-proBNP with a survival rate	Serum FGF21 was associated with the risk factors, severity, and prognosis of dilated cardiomyopathy.	[116]
	Healthy control ( <i>n</i> = 80)				
	Hearts from alcoholic donors ( <i>n</i> = 30)	Hearts	Alcoholic patients: Circulating and cardiac FGF21↑ β-Klotho↑ Oxidative stress↑	Circulating and cardiac FGF21 was increased in subjects with chronic alcohol consumption.	[120]
	Healthy control ( <i>n</i> = 11)				
HF	Diastolic dysfunction ( <i>n</i> = 95)	Plasma	Positive correlation: FGF21 with diastolic dysfunction; FGF21 and NT-proBNP with the rate of CVD	Circulating FGF21 showed good predictive power to the 1-year adverse cardiac events.	[28]
	Healthy control ( <i>n</i> = 143)				
	DM and CAC ( <i>n</i> = 1132)	Serum	Correlation: FGF21 with better 1-year prognosis	Lower baseline serum FGF21 was a prediction for a better long-term prognosis.	[48]
	HFrEF with cardiac cachexia ( <i>n</i> = 19)	Plasma	HFrEF with cardiac cachexia patients: FGF21↑ Correlation: FGF21 with lower muscle mass Non-correlation: FGF21 with NT-proBNP	Serum FGF21 was significantly higher in patients with HFrEF and cardiac cachexia than in those without cachexia.	[133]
HFrEF without cachexia ( <i>n</i> = 19)					
Ischaemic heart disease and preserved ejection fraction ( <i>n</i> = 19)					

AMI: Acute myocardial infarction; CAC: Coronary artery calcification; CHD: Coronary heart disease; CK-MB: Creatine kinase-MB; CMP: Cardiomyopathy; cTnI: Cardiac troponin I; CVD: Cardiovascular disease; T2DM: Type 2 diabetes mellitus; EF: Epicardial fat; FABP4: Fatty acid binding protein 4; FGF21: Fibroblast growth factor 21; HF: Heart failure; HFrEF: Heart failure with reduced ejection fraction; LEAD: Lower extremity atherosclerotic disease; MCP-1: Monocyte chemoattractant protein-1; NT-proBNP: N-terminal pro-B-type natriuretic peptide; PAD: Peripheral artery disease; PF: Paracardial fat; SAP: Stable angina pectoris; UAP: Unstable angina pectoris.





**Figure 2:** FGF21 induces protective effect on cardiovascular diseases through multiple signaling pathways. ABCA1: ATP-binding cassette transporter A1; ABCG1: ATP-binding cassette transporter G1; ACC: Acetyl-CoA carboxylase; Akt: Protein kinase B; AMPK: AMP-activated protein kinase; ARE: Antioxidant responsive element; BAD: B-cell lymphoma 2-associated death promoter; Bax: B-cell lymphoma 2-associated X protein; Bcl: B-cell lymphoma; CPT: Carnitine palmitoyltransferase; DCM: Diabetic cardiomyopathy; eNOS: Endothelial nitric oxide synthase; FATP: Fatty acid transport protein; GSK: Glycogen synthase kinase; HDL-C: High-density lipoprotein cholesterol; IL: Interleukin; LDL-C: Low-density lipoprotein cholesterol; MI: Myocardial infarction; NF: Nuclear factor; NLRP3: NOD-like receptor protein 3; NO: Nitric oxide; Nrf2: Transcription factor-E2-related factor 2; PGC: Peroxisome proliferator-activated receptor-γ coactivator; PI3K: Phosphatidylinositol-3-kinase; SIRT1: Sirtuin 1; SOD: Superoxide dismutase; TC: Total cholesterol; TG: Triglyceride; TNF: Tumor necrosis factor; UCP: Uncoupling protein; Vps34: Vacuolar protein sorting 34.

early clinical trials in patients with obesity,<sup>[144]</sup> T2DM,<sup>[145]</sup> and non-alcoholic steatohepatitis.<sup>[146]</sup> However, clinical application in the field of CVDs has not been reported. In conclusion, FGF21 is a promising target for the treatment of CVDs; nevertheless, its clinical application requires further clarification of the precise role of FGF21 in CVDs.

**Funding**

This work was supported by the General Program of National Natural Science Foundation of China (NSFC) (81870598), Excellent Young Scholars of NSFC (82022012), and Two Hundred Program from Shanghai Jiao Tong University School of Medicine (20191830) to HL.

**Conflicts of interest**

None.

**References**

1. Vos T, Lim SS, Abbafati C, Abbas KM, Abbasi M, Abbasifard M, et al. Global burden of 369 diseases and injuries in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet* 2020;396:1204–1222. doi: 10.1016/s0140-6736(20)30925-9.
2. Global Burden of Disease Collaborative Network. Global Burden of Disease Study 2019 (GBD 2019) results. Seattle: Institute for Health Metrics and Evaluation; 2020. Available from: <http://ghdx.healthdata.org/gbd-results-tool> [Accessed May 27, 2021]
3. Williams JW, Huang LH, Randolph GJ. Cytokine circuits in cardiovascular disease. *Immunity* 2019;50:941–954. doi: 10.1016/j.immuni.2019.03.007.

4. Beenken A, Mohammadi M. The FGF family: biology, pathophysiology and therapy. *Nat Rev Drug Discov* 2009;8:235–253. doi: 10.1038/nrd2792.
5. Nishimura T, Nakatake Y, Konishi M, Itoh N. Identification of a novel FGF, FGF-21, preferentially expressed in the liver. *Biochim Biophys Acta* 2000;1492:203–206. doi: 10.1016/s0167-4781(00)00067-1.
6. Zhu L, Zhao H, Liu J, Cai H, Wu B, Liu Z, et al. Dynamic folding modulation generates FGF21 variant against diabetes. *EMBO Rep* 2021;22:e51352. doi: 10.15252/embr.202051352.
7. Kroon T, Harms M, Maurer S, Bonnet L, Alexandersson I, Lindblom A, et al. PPARγ and PPARα synergize to induce robust browning of white fat in vivo. *Mol Metab* 2020;36:100964. doi: 10.1016/j.molmet.2020.02.007.
8. Pereira RO, Marti A, Olvera AC, Tadinada SM, Bjorkman SH, Weatherford ET, et al. OPA1 deletion in brown adipose tissue improves thermoregulation and systemic metabolism via FGF21. *Elife* 2021;10. doi: 10.7554/eLife.66519.
9. Kim YD, Hwang SL, Jeon HJ, Jeon YH, Nedumaran B, Kim K, et al. B-cell translocation gene 2 enhances fibroblast growth factor 21 production by inducing Kruppel-like factor 15. *Sci Rep* 2019;9:3730. doi: 10.1038/s41598-019-40359-2.
10. Hirai T, Nomura K, Ikai R, Nakashima KI, Inoue M. Baicalein stimulates fibroblast growth factor 21 expression by up-regulating retinoic acid receptor-related orphan receptor α in C2C12 myotubes. *Biomed Pharmacother* 2019;109:503–510. doi: 10.1016/j.biopha.2018.10.154.
11. Byun S, Seok S, Kim YC, Zhang Y, Yau P, Iwamori N, et al. Fasting-induced FGF21 signaling activates hepatic autophagy and lipid degradation via JMJD3 histone demethylase. *Nat Commun* 2020;11:807. doi: 10.1038/s41467-020-14384-z.
12. Zhang S, Guo F, Yu M, Yang X, Yao Z, Li Q, et al. Reduced Nogo expression inhibits diet-induced metabolic disorders by regulating ChREBP and insulin activity. *J Hepatol* 2020;73:1482–1495. doi: 10.1016/j.jhep.2020.07.034.

13. Lee S, Choi J, Mohanty J, Sousa LP, Tome F, Pardon E, *et al*. Structures of  $\beta$ -klotho reveal a 'zip code'-like mechanism for endocrine FGF signalling. *Nature* 2018;553:501–505. doi: 10.1038/nature25010.
14. Lan T, Morgan DA, Rahmouni K, Sonoda J, Fu X, Burgess SC, *et al*. FGF19, FGF21, and an FGFR1/ $\beta$ -Klotho-activating antibody act on the nervous system to regulate body weight and glycemia. *Cell Metab* 2017;26:709–718. doi: 10.1016/j.cmet.2017.09.005.
15. Markan KR, Naber MC, Ameka MK, Anderegg MD, Mangelsdorf DJ, Kliewer SA, *et al*. Circulating FGF21 is liver derived and enhances glucose uptake during refeeding and overfeeding. *Diabetes* 2014;63:4057–4063. doi: 10.2337/db14-0595.
16. Degirolamo C, Sabba C, Moschetta A. Therapeutic potential of the endocrine fibroblast growth factors FGF19, FGF21 and FGF23. *Nat Rev Drug Discov* 2016;15:51–69. doi: 10.1038/nrd.2015.9.
17. Turner N, Grose R. Fibroblast growth factor signalling: from development to cancer. *Nat Rev Cancer* 2010;10:116–129. doi: 10.1038/nrc2780.
18. Yu CQ, Zhang H, Guo ME, Li XK, Chen HD, Li YH, *et al*. Combination therapy with topical minoxidil and nano-microneedle-assisted fibroblast growth factor for male androgenetic alopecia: a randomized controlled trial in Chinese patients. *Chin Med J (Engl)* 2020;134:851–853. doi: 10.1097/CM9.0000000000001195.
19. Wang SY, Yang F, Ma S, Cui LJ, Zhang R. Role of fibroblast growth factor 23 in patients with chronic kidney disease. *Chin Med J (Engl)* 2020;134:404–406. doi: 10.1097/CM9.0000000000001148.
20. Geng L, Lam KSL, Xu A. The therapeutic potential of FGF21 in metabolic diseases: from bench to clinic. *Nat Rev Endocrinol* 2020;16:654–667. doi: 10.1038/s41574-020-0386-0.
21. BonDurant LD, Ameka M, Naber MC, Markan KR, Idiga SO, Acevedo MR, *et al*. FGF21 regulates metabolism through adipose-dependent and -independent mechanisms. *Cell Metab* 2017;25:935–944. doi: 10.1016/j.cmet.2017.03.005.
22. Kim KH, Jeong YT, Oh H, Kim SH, Cho JM, Kim YN, *et al*. Autophagy deficiency leads to protection from obesity and insulin resistance by inducing Fgf21 as a mitokine. *Nat Med* 2012;19:83–92. doi: 10.1038/nm.3014.
23. Talukdar S, Zhou Y, Li D, Rossulek M, Dong J, Somayaji V, *et al*. A long-acting FGF21 molecule, PF-05231023, decreases body weight and improves lipid profile in non-human primates and type 2 diabetic subjects. *Cell Metab* 2016;23:427–440. doi: 10.1016/j.cmet.2016.02.001.
24. Andersen B, Straarup EM, Heppner KM, Takahashi DL, Raffaele V, Dissen GA, *et al*. FGF21 decreases body weight without reducing food intake or bone mineral density in high-fat fed obese rhesus macaque monkeys. *Int J Obes (Lond)* 2018;42:1151–1160. doi: 10.1038/s41366-018-0080-7.
25. Tucker B, Li H, Long X, Rye KA, Ong KL. Fibroblast growth factor 21 in non-alcoholic fatty liver disease. *Metabolism* 2019;101:153994. doi: 10.1016/j.metabol.2019.153994.
26. Shen Y, Ma X, Zhou J, Pan X, Hao Y, Zhou M, *et al*. Additive relationship between serum fibroblast growth factor 21 level and coronary artery disease. *Cardiovasc Diabetol* 2013;12:124. doi: 10.1186/1475-2840-12-124.
27. Zhang X, Yang L, Xu X, Tang F, Yi P, Qiu B, *et al*. A review of fibroblast growth factor 21 in diabetic cardiomyopathy. *Heart Fail Rev* 2019;24:1005–1017. doi: 10.1007/s10741-019-09809-x.
28. Chou RH, Huang PH, Hsu CY, Chang CC, Leu HB, Huang CC, *et al*. Circulating fibroblast growth factor 21 is associated with diastolic dysfunction in heart failure patients with preserved ejection fraction. *Sci Rep* 2016;6:33953. doi: 10.1038/srep33953.
29. Planavila A, Redondo-Angulo I, Ribas F, Garrabou G, Casademont J, Giral M, *et al*. Fibroblast growth factor 21 protects the heart from oxidative stress. *Cardiovasc Res* 2015;106:19–31. doi: 10.1093/cvr/cvu263.
30. Maeng HJ, Lee GY, Bae JH, Lim S. Effect of fibroblast growth factor 21 on the development of atherosclerotic plaque and lipid metabolic profiles in an atherosclerosis-prone mouse model. *Int J Mol Sci* 2020;21:6836. doi: 10.3390/ijms21186836.
31. Xiaolong L, Dongmin G, Liu M, Zuo W, Huijun H, Qiufen T, *et al*. FGF21 induces autophagy-mediated cholesterol efflux to inhibit atherogenesis via RACK1 up-regulation. *J Cell Mol Med* 2020;24:4992–5006. doi: 10.1111/jcmm.15118.
32. Yan X, Gou Z, Li Y, Wang Y, Zhu J, Xu G, *et al*. Fibroblast growth factor 21 inhibits atherosclerosis in apoE<sup>-/-</sup> mice by ameliorating Fas-mediated apoptosis. *Lipids Health Dis* 2018;17:203. doi: 10.1186/s12944-018-0846-x.
33. Libby P, Theroux P. Pathophysiology of coronary artery disease. *Circulation* 2005;111:3481–3488. doi: 10.1161/CIRCULATIONAHA.105.537878.
34. Libby P, Buring JE, Badimon L, Hansson GK, Deanfield J, Bittencourt MS, *et al*. Atherosclerosis. *Nat Rev Dis Primers* 2019;5:56. doi: 10.1038/s41572-019-0106-z.
35. Zhang X, Yeung DC, Karpisek M, Stejskal D, Zhou ZG, Liu F, *et al*. Serum FGF21 levels are increased in obesity and are independently associated with the metabolic syndrome in humans. *Diabetes* 2008;57:1246–1253. doi: 10.2337/db07-1476.
36. Liu C, Schonke M, Zhou E, Li Z, Kooijman S, Boon MR, *et al*. Pharmacological treatment with FGF21 strongly improves plasma cholesterol metabolism to reduce atherosclerosis. *Cardiovasc Res* 2021;cvab076. doi: 10.1093/cvr/cvab076.
37. Basurto L, Gregory MA, Hernandez SB, Sanchez-Huerta L, Martinez AD, Manuel-Apolinar L, *et al*. Monocyte chemoattractant protein-1 (MCP-1) and fibroblast growth factor-21 (FGF-21) as biomarkers of subclinical atherosclerosis in women. *Exp Gerontol* 2019;124:110624. doi: 10.1016/j.exger.2019.05.013.
38. Miyazaki Y, Saita E, Kishimoto Y, Ibe S, Seki T, Miura K, *et al*. Low plasma levels of fibroblast growth factor-21 in patients with peripheral artery disease. *J Atheroscler Thromb* 2018;25:821–828. doi: 10.5551/jat.41731.
39. Chow WS, Xu A, Woo YC, Tso AW, Cheung SC, Fong CH, *et al*. Serum fibroblast growth factor-21 levels are associated with carotid atherosclerosis independent of established cardiovascular risk factors. *Arterioscler Thromb Vasc Biol* 2013;33:2454–2459. doi: 10.1161/ATVBAHA.113.301599.
40. Chee Y, Toh GL, Lim CJ, Goh LL, Dalan R. Sex modifies the association of fibroblast growth factor 21 with subclinical carotid atherosclerosis. *Front Cardiovasc Med* 2021;8:627691. doi: 10.3389/fcvm.2021.627691.
41. Li Q, Zhang Y, Ding D, Yang Y, Chen Q, Su D, *et al*. Association between serum fibroblast growth factor 21 and mortality among patients with coronary artery disease. *J Clin Endocrinol Metab* 2016;101:4886–4894. doi: 10.1210/je.2016-2308.
42. Wu L, Qian L, Zhang L, Zhang J, Zhou J, Li Y, *et al*. Fibroblast growth factor 21 is related to atherosclerosis independent of nonalcoholic fatty liver disease and predicts atherosclerotic cardiovascular events. *J Am Heart Assoc* 2020;9:e015226. doi: 10.1161/JAHA.119.015226.
43. Lakhani I, Gong M, Wong WT, Bazoukis G, Lampropoulos K, Wong SH, *et al*. Fibroblast growth factor 21 in cardio-metabolic disorders: a systematic review and meta-analysis. *Metabolism* 2018;83:11–17. doi: 10.1016/j.metabol.2018.01.017.
44. Ong KL, Hui N, Januszewski AS, Kaakoush NO, Xu A, Fayyad R, *et al*. High plasma FGF21 levels predicts major cardiovascular events in patients treated with atorvastatin (from the Treating to New Targets [TNT] Study). *Metabolism* 2019;93:93–99. doi: 10.1016/j.metabol.2018.11.006.
45. Cheng J, Su X, Qiao L, Zhai C, Chen W. Circulating level of fibroblast growth factor 21 is independently associated with the risks of unstable angina pectoris. *Biosci Rep* 2018;38:BSR20181099. doi: 10.1042/BSR20181099.
46. Wang JS, Sheu WH, Lee WJ, Lee IT, Lin SY, Lee WL, *et al*. Associations of fibroblast growth factor 21 with cardiovascular risk and  $\beta$ -cell function in patients who had no history of diabetes. *Clin Chim Acta* 2017;472:80–85. doi: 10.1016/j.cca.2017.07.017.
47. Ong KL, Campbell S, Wu BJ, McClelland RL, Kokkinos J, Szklo M, *et al*. Relationship of fibroblast growth factor 21 with subclinical atherosclerosis and cardiovascular events: multi-ethnic study of atherosclerosis. *Atherosclerosis* 2019;287:46–53. doi: 10.1016/j.atherosclerosis.2019.06.898.
48. Gan F, Huang J, Dai T, Li M, Liu J. Serum level of fibroblast growth factor 21 predicts long-term prognosis in patients with both diabetes mellitus and coronary artery calcification. *Ann Palliat Med* 2020;9:368–374. doi: 10.21037/apm.2020.03.28.
49. Ying L, Li N, He Z, Zeng X, Nan Y, Chen J, *et al*. Fibroblast growth factor 21 ameliorates diabetes-induced endothelial dysfunction in mouse aorta via activation of the CaMKK2/AMPK $\alpha$  signaling pathway. *Cell Death Dis* 2019;10:665. doi: 10.1038/s41419-019-1893-6.
50. Haberka M, Machnik G, Kowalowska A, Biedron M, Skudrzyk E, Regulska-Ilow B, *et al*. Epicardial, paracardial, and perivascular

- fat quantity, gene expressions, and serum cytokines in patients with coronary artery disease and diabetes. *Pol Arch Intern Med* 2019;129:738–746. doi: 10.20452/pamw.14961.
51. Spurna J, Karasek D, Kubickova V, Goldmannova D, Krystynik O, Schovaneck J, *et al.* Relationship of selected adipokines with markers of vascular damage in patients with type 2 diabetes. *Metab Syndr Relat Disord* 2018;16:246–253. doi: 10.1089/met.2017.0179.
  52. Zhang X, Hu Y, Zeng H, Li L, Zhao J, Zhao J, *et al.* Serum fibroblast growth factor 21 levels is associated with lower extremity atherosclerotic disease in Chinese female diabetic patients. *Cardiovasc Diabetol* 2015;14:32. doi: 10.1186/s12933-015-0190-7.
  53. Xiao Y, Liu L, Xu A, Zhou P, Long Z, Tu Y, *et al.* Serum fibroblast growth factor 21 levels are related to subclinical atherosclerosis in patients with type 2 diabetes. *Cardiovasc Diabetol* 2015;14:72. doi: 10.1186/s12933-015-0229-9.
  54. Lee CH, Woo YC, Chow WS, Cheung CYY, Fong CHY, Yuen MMA, *et al.* Role of circulating fibroblast growth factor 21 measurement in primary prevention of coronary heart disease among Chinese patients with type 2 diabetes mellitus. *J Am Heart Assoc* 2017;6:e005344. doi: 10.1161/JAHA.116.005344.
  55. So WY, Leung PS. Fibroblast growth factor 21 as an emerging therapeutic target for type 2 diabetes mellitus. *Med Res Rev* 2016;36:672–704. doi: 10.1002/med.21390.
  56. Pan Q, Lin S, Li Y, Liu L, Li X, Gao X, *et al.* A novel GLP-1 and FGF21 dual agonist has therapeutic potential for diabetes and non-alcoholic steatohepatitis. *EBioMedicine* 2021;63:103202. doi: 10.1016/j.ebiom.2020.103202.
  57. Yu Y, He J, Li S, Song L, Guo X, Yao W, *et al.* Fibroblast growth factor 21 (FGF21) inhibits macrophage-mediated inflammation by activating Nrf2 and suppressing the NF- $\kappa$ B signaling pathway. *Int Immunopharmacol* 2016;38:144–152. doi: 10.1016/j.intimp.2016.05.026.
  58. Zhang Y, Liu Z, Zhou M, Liu C. Therapeutic effects of fibroblast growth factor21 against atherosclerosis via the NF- $\kappa$ B pathway. *Mol Med Rep* 2018;17:1453–1460. doi: 10.3892/mmr.2017.8100.
  59. Ruotsalainen AK, Inkala M, Partanen ME, Lappalainen JP, Kansanen E, Mäkinen PI, *et al.* The absence of macrophage Nrf2 promotes early atherogenesis. *Cardiovasc Res* 2013;98:107–115. doi: 10.1093/cvr/cvt008.
  60. Wan XS, Lu XH, Xiao YC, Lin Y, Zhu H, Ding T, *et al.* ATF4- and CHOP-dependent induction of FGF21 through endoplasmic reticulum stress. *Biomed Res Int* 2014;2014:807874. doi: 10.1155/2014/807874.
  61. Wu X, Qi YF, Chang JR, Lu WW, Zhang JS, Wang SP, *et al.* Possible role of fibroblast growth factor 21 on atherosclerosis via amelioration of endoplasmic reticulum stress-mediated apoptosis in apoE(-/-) mice. *Heart Vessels* 2015;30:657–668. doi: 10.1007/s00380-014-0557-9.
  62. Domouzoglou EM, Vlahos AP, Cholevas VK, Papafaklis MI, Chaliasos N, Siomou E, *et al.* Association of fibroblast growth factor 21 with metabolic syndrome and endothelial function in children: a prospective cross-sectional study on novel biomarkers. *Ann Pediatr Endocrinol Metab* 2021. doi: 10.6065/apem.2040258.129.
  63. Lu Y, Liu JH, Zhang LK, Du J, Zeng XJ, Hao G, *et al.* Fibroblast growth factor 21 as a possible endogenous factor inhibits apoptosis in cardiac endothelial cells. *Chin Med J (Engl)* 2010;123:3417–3421. doi: 10.3760/cma.j.issn.0366-6999.2010.23.008.
  64. Kawanishi H, Ohashi K, Ogawa H, Otaka N, Takikawa T, Fang L, *et al.* A novel selective PPAR $\alpha$  modulator, pemafibrate promotes ischemia-induced revascularization through the eNOS-dependent mechanisms. *PLoS One* 2020;15:e0235362. doi: 10.1371/journal.pone.0235362.
  65. Wang XM, Song SS, Xiao H, Gao P, Li XJ, Si LY. Fibroblast growth factor 21 protects against high glucose induced cellular damage and dysfunction of endothelial nitric-oxide synthase in endothelial cells. *Cell Physiol Biochem* 2014;34:658–671. doi: 10.1159/000363031.
  66. Liu W, Liu B, Liu S, Zhang J, Lin S. Sphingosine-1-phosphate receptor 2 mediates endothelial cells dysfunction by PI3K-Akt pathway under high glucose condition. *Eur J Pharmacol* 2016;776:19–25. doi: 10.1016/j.ejphar.2016.02.056.
  67. Guo D, Xiao L, Hu H, Liu M, Yang L, Lin X. FGF21 protects human umbilical vein endothelial cells against high glucose-induced apoptosis via PI3K/Akt/Fox3a signaling pathway. *J Diabetes Complications* 2018;32:729–736. doi: 10.1016/j.jdiacomp.2018.05.012.
  68. Zhu W, Wang C, Liu L, Li Y, Li X, Cai J, *et al.* Effects of fibroblast growth factor 21 on cell damage in vitro and atherosclerosis in vivo. *Can J Physiol Pharmacol* 2014;92:927–935. doi: 10.1139/cjpp-2014-0227.
  69. Ahagh MH, Dehghan G, Mehdipour M, Teimuri-Mofrad R, Payami E, Sheibani N, *et al.* Synthesis, characterization, anti-proliferative properties and DNA binding of benzochromene derivatives: increased Bax/Bcl-2 ratio and caspase-dependent apoptosis in colorectal cancer cell line. *Bioorg Chem* 2019;93:103329. doi: 10.1016/j.bioorg.2019.103329.
  70. Hu L, Sun Y, Hu J. Catalpol inhibits apoptosis in hydrogen peroxide-induced endothelium by activating the PI3K/Akt signaling pathway and modulating expression of Bcl-2 and Bax. *Eur J Pharmacol* 2010;628:155–163. doi: 10.1016/j.ejphar.2009.11.046.
  71. Sata M, Walsh K. Oxidized LDL activates FAS-mediated endothelial cell apoptosis. *J Clin Invest* 1998;102:1682–1689. doi: 10.1172/JCI3531.
  72. Yaqoob U, Jagavelu K, Shergill U, de Assuncao T, Cao S, Shah VH. FGF21 promotes endothelial cell angiogenesis through a dynamin-2 and Rab5 dependent pathway. *PLoS One* 2014;9:e98130. doi: 10.1371/journal.pone.0098130.
  73. Dai Q, Fan X, Meng X, Sun S, Su Y, Ling X, *et al.* FGF21 promotes ischaemic angiogenesis and endothelial progenitor cells function under diabetic conditions in an AMPK/NAD<sup>+</sup>-dependent manner. *J Cell Mol Med* 2021;25:3091–3102. doi: 10.1111/jcmm.16369.
  74. Tian XL, Li Y. Endothelial cell senescence and age-related vascular diseases. *J Genet Genomics* 2014;41:485–495. doi: 10.1016/j.jgg.2014.08.001.
  75. Kitada M, Ogura Y, Koya D. The protective role of Sirt1 in vascular tissue: its relationship to vascular aging and atherosclerosis. *Aging (Albany NY)* 2016;8:2290–2307. doi: 10.18632/aging.101068.
  76. Jia G, Aroor AR, Jia C, Sowers JR. Endothelial cell senescence in aging-related vascular dysfunction. *Biochim Biophys Acta Mol Basis Dis* 2019;1865:1802–1809. doi: 10.1016/j.bbadis.2018.08.008.
  77. Inagaki T, Dutchak P, Zhao G, Ding X, Gautron L, Parameswara V, *et al.* Endocrine regulation of the fasting response by PPARalpha-mediated induction of fibroblast growth factor 21. *Cell Metab* 2007;5:415–425. doi: 10.1016/j.cmet.2007.05.003.
  78. Zeng Z, Zheng Q, Chen J, Tan X, Li Q, Ding L, *et al.* FGF21 mitigates atherosclerosis via inhibition of NLRP3 inflammasome-mediated vascular endothelial cells pyroptosis. *Exp Cell Res* 2020;393:112108. doi: 10.1016/j.yexcr.2020.112108.
  79. Lin Z, Pan X, Wu F, Ye D, Zhang Y, Wang Y, *et al.* Fibroblast growth factor 21 prevents atherosclerosis by suppression of hepatic sterol regulatory element-binding protein-2 and induction of adiponectin in mice. *Circulation* 2015;131:1861–1871. doi: 10.1161/CIRCULATIONAHA.115.015308.
  80. Li E, Wang T, Wang F, Wang T, Sun LQ, Li L, *et al.* FGF21 protects against ox-LDL induced apoptosis through suppressing CHOP expression in THP1 macrophage derived foam cells. *BMC Cardiovasc Disord* 2015;15:80. doi: 10.1186/s12872-015-0077-2.
  81. Wang N, Li JY, Li S, Guo XC, Wu T, Wang WF, *et al.* Fibroblast growth factor 21 regulates foam cells formation and inflammatory response in Ox-LDL-induced THP-1 macrophages. *Biomed Pharmacother* 2018;108:1825–1834. doi: 10.1016/j.biopha.2018.09.143.
  82. Lin XL, He XL, Zeng JF, Zhang H, Zhao Y, Tan JK, *et al.* FGF21 increases cholesterol efflux by upregulating ABCA1 through the ERK1/2-PPAR $\gamma$ -LXR $\alpha$  pathway in THP1 macrophage-derived foam cells. *DNA Cell Biol* 2014;33:514–521. doi: 10.1089/dna.2013.2290.
  83. Wei W, Li XX, Xu M. Inhibition of vascular neointima hyperplasia by FGF21 associated with FGFR1/Syk/NLRP3 inflammasome pathway in diabetic mice. *Atherosclerosis* 2019;289:132–142. doi: 10.1016/j.atherosclerosis.2019.08.017.
  84. Mangan MSJ, Olhava EJ, Roush WR, Seidel HM, Glick GD, Latz E. Targeting the NLRP3 inflammasome in inflammatory diseases. *Nat Rev Drug Discov* 2018;17:588–606. doi: 10.1038/nrd.2018.97.

85. Hoseini Z, Sepahvand F, Rashidi B, Sahebkar A, Masoudifar A, Mirzaei H. NLRP3 inflammasome: its regulation and involvement in atherosclerosis. *J Cell Physiol* 2018;233:2116–2132. doi: 10.1002/jcp.25930.
86. Shi J, Gao W, Shao F. Pyroptosis: gasdermin-mediated programmed necrotic cell death. *Trends Biochem Sci* 2017;42:245–254. doi: 10.1016/j.tibs.2016.10.004.
87. Shan W, Li J, Xu W, Li H, Zuo Z. Critical role of UQCRC1 in embryo survival, brain ischemic tolerance and normal cognition in mice. *Cell Mol Life Sci* 2019;76:1381–1396. doi: 10.1007/s00018-019-03007-6.
88. Chen JJ, Tao J, Zhang XL, Xia LZ, Zeng JF, Zhang H, *et al.* Inhibition of the ox-LDL-Induced pyroptosis by FGF21 of human umbilical vein endothelial cells through the TET2-UQCRC1-ROS pathway. *DNA Cell Biol* 2020;39:661–670. doi: 10.1089/dna.2019.5151.
89. Pagliaro BR, Cannata F, Stefanini GG, Bolognese L. Myocardial ischemia and coronary disease in heart failure. *Heart Fail Rev* 2020;25:53–65. doi: 10.1007/s10741-019-09831-z.
90. Hirsch E, Patel V, Adya R, Chen J, Ramanjaneya M, Bari MF, *et al.* Novel insights into the cardio-protective effects of FGF21 in lean and obese rat hearts. *PLoS One* 2014;9:e87102. doi: 10.1371/journal.pone.0087102.
91. Sunaga H, Koitabashi N, Iso T, Matsui H, Obokata M, Kawakami R, *et al.* Activation of cardiac AMPK-FGF21 feed-forward loop in acute myocardial infarction: role of adrenergic overdrive and lipolysis byproducts. *Sci Rep* 2019;9:11841. doi: 10.1038/s41598-019-48356-1.
92. Tang TT, Li YY, Li JJ, Wang K, Han Y, Dong WY, *et al.* Liver-heart crosstalk controls IL-22 activity in cardiac protection after myocardial infarction. *Theranostics* 2018;8:4552–4562. doi: 10.7150/thno.24723.
93. Joki Y, Ohashi K, Yuasa D, Shibata R, Ito M, Matsuo K, *et al.* FGF21 attenuates pathological myocardial remodeling following myocardial infarction through the adiponectin-dependent mechanism. *Biochem Biophys Res Commun* 2015;459:124–130. doi: 10.1016/j.bbrc.2015.02.081.
94. Li J, Xu C, Liu Y, Li Y, Du S, Zhang R, *et al.* Fibroblast growth factor 21 inhibited ischemic arrhythmias via targeting miR-143/EGFR1 axis. *Basic Res Cardiol* 2020;115:9. doi: 10.1007/s00395-019-0768-4.
95. Zhang W, Chu S, Ding W, Wang F. Serum level of fibroblast growth factor 21 is independently associated with acute myocardial infarction. *PLoS One* 2015;10:e0129791. doi: 10.1371/journal.pone.0129791.
96. Hu X, Yang X, Jiang H. Role of sympathetic nervous system in myocardial ischemia injury: beneficial or deleterious? *Int J Cardiol* 2012;157:269. doi: 10.1016/j.ijcard.2012.03.016.
97. Chau MD, Gao J, Yang Q, Wu Z, Gromada J. Fibroblast growth factor 21 regulates energy metabolism by activating the AMPK-SIRT1-PGC-1 $\alpha$  pathway. *Proc Natl Acad Sci USA* 2010;107:12553–12558. doi: 10.1073/pnas.1006962107.
98. Packer M. Cardioprotective effects of sirtuin-1 and its downstream effectors: potential role in mediating the heart failure benefits of SGLT2 (sodium-glucose cotransporter 2) inhibitors. *Circ Heart Fail* 2020;13:417–424. doi: 10.1161/CIRCHEARTFAILURE.120.007197.
99. Gerhart-Hines Z, Rodgers JT, Bare O, Lerin C, Kim SH, Mostoslavsky R, *et al.* Metabolic control of muscle mitochondrial function and fatty acid oxidation through SIRT1/PGC-1 $\alpha$ . *EMBO J* 2007;26:1913–1923. doi: 10.1038/sj.emboj.7601633.
100. Liu SQ, Tefft BJ, Roberts DT, Zhang LQ, Ren Y, Li YC, *et al.* Cardioprotective proteins upregulated in the liver in response to experimental myocardial ischemia. *Am J Physiol Heart Circ Physiol* 2012;303:H1446–H1458. doi: 10.1152/ajpheart.00362.2012.
101. Liu SQ, Roberts D, Kharitonov A, Zhang B, Hanson SM, Li YC, *et al.* Endocrine protection of ischemic myocardium by FGF21 from the liver and adipose tissue. *Sci Rep* 2013;3:2767. doi: 10.1038/srep02767.
102. Solomon SD, Zelenkofske S, McMurray JJ, Finn PV, Velazquez E, Ertl G, *et al.* Sudden death in patients with myocardial infarction and left ventricular dysfunction, heart failure, or both. *N Engl J Med* 2005;352:2581–2588. doi: 10.1056/NEJMoa043938.
103. Docherty KF, Ferreira JP, Sharma A, Giredd N, Gregson J, Duarte K, *et al.* Predictors of sudden cardiac death in high-risk patients following a myocardial infarction. *Eur J Heart Fail* 2020;22:848–855. doi: 10.1002/ejhf.1694.
104. Tao B, Liu Z, Wei F, Fan S, Cui S, Xia H, *et al.* Over-expression of Kv4.3 gene reverses cardiac remodeling and transient-outward K (+) current (Ito) reduction via CaMKII inhibition in myocardial infarction. *Biomed Pharmacother* 2020;132:110896. doi: 10.1016/j.biopha.2020.110896.
105. Caccioppo A, Franchin L, Grosso A, Angelini F, D'Ascenzo F, Brizzi MF. Ischemia reperfusion injury: mechanisms of damage/protection and novel strategies for cardiac recovery/regeneration. *Int J Mol Sci* 2019;20:5024. doi: 10.3390/ijms20205024.
106. Wu Y, Mao Q, Liang X. Targeting the microRNA-490-3p-ATG4B-autophagy axis relieves myocardial injury in ischemia reperfusion. *J Cardiovasc Transl Res* 2021;14:173–183. doi: 10.1007/s12265-020-09972-9.
107. Ren Z, Xiao W, Zeng Y, Liu MH, Li GH, Tang ZH, *et al.* Fibroblast growth factor-21 alleviates hypoxia/reoxygenation injury in H9c2 cardiomyocytes by promoting autophagic flux. *Int J Mol Med* 2019;43:1321–1330. doi: 10.3892/ijmm.2019.4071.
108. Cong WT, Ling J, Tian HS, Ling R, Wang Y, Huang BB, *et al.* Proteomic study on the protective mechanism of fibroblast growth factor 21 to ischemia-reperfusion injury. *Can J Physiol Pharmacol* 2013;91:973–984. doi: 10.1139/cjpp-2012-0441.
109. Hu S, Cao S, Liu J. Role of angiopoietin-2 in the cardioprotective effect of fibroblast growth factor 21 on ischemia/reperfusion-induced injury in H9c2 cardiomyocytes. *Exp Ther Med* 2017;14:771–779. doi: 10.3892/etm.2017.4564.
110. Maron BJ, Towbin JA, Thiene G, Antzelevitch C, Corrado D, Arnett D, *et al.* Contemporary definitions and classification of the cardiomyopathies: an American Heart Association Scientific Statement from the Council on Clinical Cardiology, Heart Failure and Transplantation Committee; Quality of Care and Outcomes Research and Functional Genomics and Translational Biology Interdisciplinary Working Groups; and Council on Epidemiology and Prevention. *Circulation* 2006;113:1807–1816. doi: 10.1161/CIRCULATIONAHA.106.174287.
111. McKenna WJ, Maron BJ, Thiene G. Classification, epidemiology, and global burden of cardiomyopathies. *Circ Res* 2017;121:722–730. doi: 10.1161/CIRCRESAHA.117.309711.
112. Dillmann WH. Diabetic cardiomyopathy. *Circ Res* 2019;124:1160–1162. doi: 10.1161/CIRCRESAHA.118.314665.
113. Chen C, Meng Z, Zheng Y, Hu B, Shen E. Fibroblast growth factor 21 inhibition aggravates cardiac dysfunction in diabetic cardiomyopathy by improving lipid accumulation. *Exp Ther Med* 2018;15:75–84. doi: 10.3892/etm.2017.5375.
114. Zhang C, Huang Z, Gu J, Yan X, Lu X, Zhou S, *et al.* Fibroblast growth factor 21 protects the heart from apoptosis in a diabetic mouse model via extracellular signal-regulated kinase 1/2-dependent signalling pathway. *Diabetologia* 2015;58:1937–1948. doi: 10.1007/s00125-015-3630-8.
115. Wu F, Wang B, Zhang S, Shi L, Wang Y, Xiong R, *et al.* FGF21 ameliorates diabetic cardiomyopathy by activating the AMPK-paraoxonase 1 signaling axis in mice. *Clin Sci (Lond)* 2017;131:1877–1893. doi: 10.1042/CS20170271.
116. Gu L, Jiang W, Zheng R, Yao Y, Ma G. Fibroblast growth factor 21 correlates with the prognosis of dilated cardiomyopathy. *Cardiology* 2021;146:27–33. doi: 10.1159/000509239.
117. Ferrer-Curriu G, Redondo-Angulo I, Guitart-Mampel M, Ruperez C, Mas-Stachurska A, Sitges M, *et al.* Fibroblast growth factor-21 protects against fibrosis in hypertensive heart disease. *J Pathol* 2019;248:30–40. doi: 10.1002/path.5226.
118. Li S, Zhu Z, Xue M, Yi X, Liang J, Niu C, *et al.* Fibroblast growth factor 21 protects the heart from angiotensin II-induced cardiac hypertrophy and dysfunction via SIRT1. *Biochim Biophys Acta Mol Basis Dis* 2019;1865:1241–1252. doi: 10.1016/j.bbdis.2019.01.019.
119. Romanello V. FGF21: a promising therapeutic agent for alcoholic cardiomyopathy? *J Pathol* 2021;254:213–215. doi: 10.1002/path.5654.
120. Ferrer-Curriu G, Guitart-Mampel M, Ruperez C, Zamora M, Crispí F, Villarroya F, *et al.* The protective effect of fibroblast growth factor-21 in alcoholic cardiomyopathy: a role in protecting cardiac mitochondrial function. *J Pathol* 2021;253:198–208. doi: 10.1002/path.5573.

121. Fernandez-Sola J, Planavila Porta A. New treatment strategies for alcohol-induced heart damage. *Int J Mol Sci* 2016;17:1651. doi: 10.3390/ijms17101651.
122. Xu Z, Sun J, Tong Q, Lin Q, Qian L, Park Y, *et al.* The role of ERK1/2 in the development of diabetic cardiomyopathy. *Int J Mol Sci* 2016;17:2001. doi: 10.3390/ijms17122001.
123. Yan X, Chen J, Zhang C, Zhou S, Zhang Z, Chen J, *et al.* FGF21 deletion exacerbates diabetic cardiomyopathy by aggravating cardiac lipid accumulation. *J Cell Mol Med* 2015;19:1557–1568. doi: 10.1111/jcmm.12530.
124. Yang H, Feng A, Lin S, Yu L, Lin X, Yan X, *et al.* Fibroblast growth factor-21 prevents diabetic cardiomyopathy via AMPK-mediated antioxidation and lipid-lowering effects in the heart. *Cell Death Dis* 2018;9:227. doi: 10.1038/s41419-018-0307-5.
125. Kotur-Stevuljevic J, Vekic J, Stefanovic A, Zeljkovic A, Ninic A, Ivanisevic J, *et al.* Paraoxonase 1 and atherosclerosis-related diseases. *Biofactors* 2020;46:193–205. doi: 10.1002/biof.1549.
126. Potthoff MJ, Inagaki T, Satapati S, Ding X, He T, Goetz R, *et al.* FGF21 induces PGC-1 $\alpha$  and regulates carbohydrate and fatty acid metabolism during the adaptive starvation response. *Proc Natl Acad Sci USA* 2009;106:10853–10858. doi: 10.1073/pnas.0904187106.
127. Yang XJ, Liu F, Feng N, Ding XS, Chen Y, Zhu SX, *et al.* Berberine attenuates cholesterol accumulation in macrophage foam cells by suppressing AP-1 activity and activation of the Nrf2/HO-1 pathway. *J Cardiovasc Pharmacol* 2020;75:45–53. doi: 10.1097/FJC.0000000000000769.
128. Ishii T, Itoh K, Ruiz E, Leake DS, Unoki H, Yamamoto M, *et al.* Role of Nrf2 in the regulation of CD36 and stress protein expression in murine macrophages: activation by oxidatively modified LDL and 4-hydroxynonenal. *Circ Res* 2004;94:609–616. doi: 10.1161/01.RES.0000119171.44657.45.
129. Ruperez C, Lerin C, Ferrer-Curriu G, Cairo M, Mas-Stachurska A, Sitges M, *et al.* Autophagic control of cardiac steatosis through FGF21 in obesity-associated cardiomyopathy. *Int J Cardiol* 2018;260:163–170. doi: 10.1016/j.ijcard.2018.02.109.
130. Zhang J, Cheng Y, Gu J, Wang S, Zhou S, Wang Y, *et al.* Fenofibrate increases cardiac autophagy via FGF21/SIRT1 and prevents fibrosis and inflammation in the hearts of Type 1 diabetic mice. *Clin Sci (Lond)* 2016;130:625–641. doi: 10.1042/CS20150623.
131. Borlaug BA. Evaluation and management of heart failure with preserved ejection fraction. *Nat Rev Cardiol* 2020;17:559–573. doi: 10.1038/s41569-020-0363-2.
132. Dunlay SM, Roger VL, Redfield MM. Epidemiology of heart failure with preserved ejection fraction. *Nat Rev Cardiol* 2017;14:591–602. doi: 10.1038/nrcardio.2017.65.
133. Refsgaard Holm M, Christensen H, Rasmussen J, Johansen ML, Schou M, Faber J, *et al.* Fibroblast growth factor 21 in patients with cardiac cachexia: a possible role of chronic inflammation. *ESC Heart Fail* 2019;6:983–991. doi: 10.1002/ehf2.12502.
134. Furukawa N, Koitabashi N, Matsui H, Sunaga H, Umbarawan Y, Syamsunarno M, *et al.* DPP-4 inhibitor induces FGF21 expression via sirtuin 1 signaling and improves myocardial energy metabolism. *Heart Vessels* 2021;36:136–146. doi: 10.1007/s00380-020-01711-z.
135. Alvarez-Guardia D, Palomer X, Coll T, Davidson MM, Chan TO, Feldman AM, *et al.* The p65 subunit of NF- $\kappa$ B binds to PGC-1 $\alpha$ , linking inflammation and metabolic disturbances in cardiac cells. *Cardiovasc Res* 2010;87:449–458. doi: 10.1093/cvr/cvq080.
136. Semba RD, Crasto C, Strait J, Sun K, Schaumberg DA, Ferrucci L. Elevated serum fibroblast growth factor 21 is associated with hypertension in community-dwelling adults. *J Hum Hypertens* 2013;27:397–399. doi: 10.1038/jhh.2012.52.
137. Pan X, Shao Y, Wu F, Wang Y, Xiong R, Zheng J, *et al.* FGF21 prevents angiotensin ii-induced hypertension and vascular dysfunction by activation of ACE2/angiotensin-(1-7) axis in mice. *Cell Metab* 2018;27:1323–1337. doi: 10.1016/j.cmet.2018.04.002.
138. Ruan CC, Kong LR, Chen XH, Ma Y, Pan XX, Zhang ZB, *et al.* A2A receptor activation attenuates hypertensive cardiac remodeling via promoting brown adipose tissue-derived FGF21. *Cell Metab* 2018;28:476–489. doi: 10.1016/j.cmet.2018.06.013.
139. Villarroya F, Cereijo R, Gavalda-Navarro A, Peyrou M, Giralt M, Villarroya F. New insights into the secretory functions of brown adipose tissue. *J Endocrinol* 2019;243:R19–R27. doi: 10.1530/JOE-19-0295.
140. Wang X, Wei W, Krzeszinski JY, Wang Y, Wan Y. A liver-bone endocrine relay by IGFBP1 promotes osteoclastogenesis and mediates FGF21-induced bone resorption. *Cell Metab* 2015;22:811–824. doi: 10.1016/j.cmet.2015.09.010.
141. Li H, Sun H, Qian B, Feng W, Carney D, Miller J, *et al.* Increased expression of FGF-21 negatively affects bone homeostasis in dystrophin/utrophin double knockout mice. *J Bone Miner Res* 2020;35:738–752. doi: 10.1002/jbmr.3932.
142. Li X, Stanislaus S, Asuncion F, Niu QT, Chinookoswong N, Villasenor K, *et al.* FGF21 is not a major mediator for bone homeostasis or metabolic actions of PPAR $\alpha$  and PPAR $\gamma$  agonists. *J Bone Miner Res* 2017;32:834–845. doi: 10.1002/jbmr.2936.
143. Kiewer SA, Mangelsdorf DJ. A dozen years of discovery: insights into the physiology and pharmacology of FGF21. *Cell Metab* 2019;29:246–253. doi: 10.1016/j.cmet.2019.01.004.
144. Kim AM, Somayaji VR, Dong JQ, Rolph TP, Weng Y, Chabot JR, *et al.* Once-weekly administration of a long-acting fibroblast growth factor 21 analogue modulates lipids, bone turnover markers, blood pressure and body weight differently in obese people with hypertriglyceridaemia and in non-human primates. *Diabetes Obes Metab* 2017;19:1762–1772. doi: 10.1111/dom.13023.
145. Charles ED, Neuschwander-Tetri BA, Pablo Frias J, Kundu S, Luo Y, Tirucherai GS, *et al.* Pegbelfermin (BMS-986036), PEGylated FGF21, in patients with obesity and type 2 diabetes: results from a randomized phase 2 study. *Obesity (Silver Spring)* 2019;27:41–49. doi: 10.1002/oby.22344.
146. Ritchie M, Hanouneh IA, Nouredin M, Rolph T, Alkhouri N. Fibroblast growth factor (FGF)-21 based therapies: a magic bullet for nonalcoholic fatty liver disease (NAFLD)? *Expert Opin Investig Drugs* 2020;29:197–204. doi: 10.1080/13543784.2020.1718104.

**How to cite this article:** Zhang Y, Liu D, Long XX, Fang QC, Jia WP, Li HT. The role of FGF21 in the pathogenesis of cardiovascular disease. *Chin Med J* 2021;134:2931–2943. doi: 10.1097/CM9.0000000000001890