Atherosclerosis 257 (2017) 259–265

Contents lists available at ScienceDirect

Atherosclerosis

journal homepage: www.elsevier.com/locate/atherosclerosis

Review article

The role of fibroblast growth factor 21 in atherosclerosis

John Kokkinos, Shudi Tang, Kerry-Anne Rye, Kwok Leung Ong*

School of Medical Sciences, UNSW Australia, Sydney, NSW, Australia

ARTICLE INFO

Article history:
Received 21 September 2016
Received in revised form
7 November 2016
Accepted 30 November 2016
Available online 1 December 2016

Keywords:
Atherosclerosis
Fibroblast growth factor 21
Inflammation
Lipid profile
Oxidative stress

ABSTRACT

The metabolic properties of the endocrine fibroblast growth factor 21 (FGF21) have been extensively studied in the past decade. Previous studies have demonstrated the lipid-lowering, anti-inflammatory and anti-oxidant properties of FGF21. FGF21 is mainly secreted in the liver and adipose tissue in response to a range of physiological and pathological stimuli. In animal and *in vitro* studies, FGF21 has been shown to improve lipid profiles and inhibit key processes in the pathogenesis of atherosclerosis. It exerts its effects on the cardiovascular system via adiponectin dependent and independent mechanisms. However, the signalling pathways by which FGF21 exerts its effects on endothelial cells remains unknown and needs to be further investigated. The elevation of circulating FGF21 levels in cardiovascular disease has also raised questions as to whether FGF21 can be used as a biomarker to predict subclinical atherosclerosis and cardiovascular events. Recent findings from population studies must be validated in independent cohorts before FGF21 can be used as a biomarker in the clinical setting. The anti-atherosclerotic effects of FGF21 have been investigated in two recent clinical trials, where treatment with an FGF21 analog significantly improved the cardiometabolic profile in obese patients with type 2 diabetes. This review will evaluate recent advances that suggest there may be a role for FGF21 in atherosclerosis.

1. Introduction

Cardiovascular disease (CVD) remains a global health issue despite extensive progress in the past few decades [1]. The challenge in the management of atherosclerosis is the early detection of the disease before clinical manifestation is apparent. Atherosclerosis is commonly diagnosed only after a cardiovascular event such as a myocardial infarction or stroke; which can leave vital organs in a critical condition. Hence the search for biomarkers of subclinical atherosclerosis and the pharmacological alleviation of cardiovascular risk factors remains a popular research focus [2].

The role of fibroblast growth factors (FGFs) in metabolism has been comprehensively studied in the past decade [3]. The majority of FGFs act through an autocrine or paracrine mechanism which activate FGF receptors (FGFR) 1–4 by interacting with heparin or heparin sulphate glycosaminoglycans [4]. Endocrine FGFs include FGF19, FGF21 and FGF23 which require the transmembrane glycoproteins αklotho and βklotho in order to bind to FGFRs. The expression pattern of the klotho proteins in different tissues determines the targeting sites of the endocrine FGFs.

FGF21 was first isolated from mouse embryos, and was reported to consist of 210 amino acids [5]. Human FGF21 consists of 209 amino acids and has 75% identity to mouse FGF21 [5]. It is mainly secreted in the liver, but is also found in other metabolic tissues such as pancreas and adipose tissue [3]. The secretion of FGF21 is regulated by a number of receptors in response to a wide range of pathophysiological conditions [6,7].

Initial studies on FGF21 focussed on its metabolic properties, especially its role in type 2 diabetes [8]. Recent evidence, however, has shed light on the anti-atherosclerotic role of FGF21. These studies have suggested the use of FGF21 as a biomarker for subclinical atherosclerosis and its potential role in the treatment of established atherosclerotic CVD. While recent reviews have analysed different aspects of the biology of FGF21 [2–4,6,8–13], this review focuses on recent advances in our understanding of FGF21 and provides an assessment of its clinical potential.

This review firstly describes factors that regulate FGF21 expression and secretion. The understanding of FGF21 regulation is vital, as agonists that induce endogenous secretion might prove to be more effective than recombinant FGF21, which has a relatively short half-life in the circulation [14]. The review will also address

* Corresponding author. School of Medical Science, UNSW Australia, UNSW Sydney, 2052, Australia.
E-mail address: oklws@yahoo.com.hk (K.L. Ong).

http://dx.doi.org/10.1016/j.atherosclerosis.2016.11.033
0021-9150/

recent studies that have reported an anti-atherosclerotic role for FGF21. Finally, the use of FGF21 as a biomarker of subclinical atherosclerosis and its therapeutic potential will be addressed.

2. Regulation of FGF21 expression and secretion

FGF21 is mainly secreted from the liver where it is regulated by the activity of peroxisome proliferator-activated receptor-α (PPARα) – a key regulator of lipid metabolism [6]. The PPARα selective agonist GW7647 increases the expression of FGF21 in mouse liver and human hepatocytes [15]. Tri-iodothyronine (T3) treatment in mice has shown a dose dependent increase in FGF21 expression [16]. T3 has no effect on FGF21 expression in PPARα knockout mice, suggesting that the effects of T3 are mediated by a PPARα-dependent mechanism. PPARα dependent-FGF21 expression has also been recently shown to play a key role in the metabolic response to a ketogenic diet [17]. PPARγ activation in mouse adipocytes also increases the expression and secretion of FGF21 [18].

FGF21 is also regulated by PPAR-independent mechanisms [7,19–21]. Table 1 shows a summary of the effects of activation of different receptors and microRNA-577 (miRNA-577) on FGF21 expression. The FGF21 promoter contains a functional retinoic acid receptor-related orphan receptor response element (RORE) [7]. Retinoic acid receptor-related orphan receptor-α (RORα), a regulator of the circadian rhythm, induces the expression of FGF21 and may have a role in the basal expression of FGF21.

It is well established that starvation induces the hepatic secretion of FGF21, which plays a role in the induction of gluconeogenesis, ketogenesis and fatty acid oxidation [15,22–25]. Glucagon is thought to be involved in the secretion of FGF21 in hepatocytes during starvation [19]. This regulation probably occurs via a post-transcriptional mechanism, as activation of the glucagon receptor has no effect on FGF21 mRNA levels.

Bioinformatic analysis has revealed that miR-577, which is significantly increased in diabetes, directly targets FGF21 [26]. miR-577 transfected INS-1 insulinoma cells show a significant decrease in FGF21 expression, and treatment with an anti-miR-577 upregulates FGF21 expression. These findings suggest that treatment with anti-miR-577 is a potential mechanism for increasing plasma FGF21 levels in diabetic patients.

Several other factors have been implicated in the regulation of FGF21. Carbohydrate response element-binding protein (ChREBP) upregulates FGF21 expression under hyperglycemic conditions [21]. Non-fasting aryl hydrocarbon receptor (AHR)-knockout mice display an increased level of FGF21 expression [20]. AHR was classically believed to be involved in the response to xenobiotics, but recent evidence suggests it also has a role in cellular regeneration in response to stressful environments [27]. Mice that are exposed to the AHR agonist, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD), show a decreased level of FGF21 expression in hepatocytes [20]. In primary human hepatocytes treated with TCDD, FGF21 expression is also downregulated, suggesting that the FGF21 lowering effect of the active AHR is not mouse-specific. This study revealed that AHR attenuates FGF21 expression through the inhibition of ChREBP and PPARα, suggesting that AHR is another potential target for regulating endogenous FGF21 levels.

It is important to understand the underlying mechanisms behind the regulation of FGF21 expression and secretion, in order to inform the development of FGF21 variants with longer half-life that are potential candidates for CVD treatment. As circulating FGF21 has a short half-life, an agonist that can induce the endogenous expression and secretion of FGF21, may be of greater therapeutic potential than recombinant FGF21 [14].

3. Anti-atherosclerotic properties of FGF21

3.1. FGF21 improves lipid profiles and protects against atherosclerosis in vivo

Recent studies suggest a role of FGF21 in protection against atherosclerosis. ApoE/FGF21 double knockout (DKO) mice have exacerbated atherosclerotic plaque formation, severe hypercholesterolemia and hypoadiponectinemia, premature death, increased macrophage recruitment, smooth muscle cell proliferation and increased brachiocephalic artery cholesterol ester content, compared with apoE knockout (KO) control mice [28].

ApoE/FGF21 DKO mice treated with recombinant FGF21 showed a greater reduction in plaque formation compared to mice treated with recombinant adiponectin [28]. It has been suggested that FGF21 stimulates the expression of adiponectin which suppresses proliferation and migration of smooth muscle cells and reduces

Table 1. FGF21 regulation.

Receptor/ MicroRNA	Species	Effect on FGF21		Notes	Ref.
		mRNA	Protein		
PPARα	Mouse liver	↑	↑	PPARα selective agonist GW7647 increases expression and secretion of FGF21 in mouse liver and human hepatocyte primary cultures	[15,55]
	Human hepatocytes	↑	↑		
PPARγ	Mouse adipocytes	↑	↑	Diabetic *db/db* mice treated with a PPARγ agonist show a 2–3-fold increase in FGF21 mRNA levels in adipocytes, and a 5-fold increase in plasma FGF21 levels	[18]
RORα	HepG2 cells	↑	↑	The FGF21 promoter contains a functional RORE. RORα, a regulator of the circadian rhythm, induces the expression of FGF21, suggesting that RORα might have a role in the basal expression of FGF21	[7]
Glucagon receptor	Rat hepatocytes	–	↑	Glucagon has been suggested to play a role in the secretion of FGF21 in hepatocytes during starvation. This occurs via a post-transcriptional mechanism, as activation of the glucagon receptor has no effect on FGF21 mRNA levels	[19]
AHR	Mouse hepatocytes	↓	–	Non-fasting AHR-knockout mice display an increased level of FGF21 expression. Mice that are exposed to the AHR agonist TCDD, show a decreased level of FGF21 expression in hepatocytes, but no effect on circulating FGF21 levels	[20]
	Human hepatocytes	↓	N/A	TCDD downregulates FGF21 expression, suggesting that the FGF21 lowering effect of the active AHR is not mouse-specific	
miR-577	INS-1 cells	↓	↓	miR-577, which is significantly increased in diabetes, directly targets FGF21. miR-577 transfected INS-1 cells show a significant decrease in FGF21 expression, and treatment with an anti-miR-577 upregulates FGF21 expression. These findings suggest that anti-miR-577 should be investigated as a potential therapeutic mechanism to increase FGF21 expression in pancreas of diabetic patients	[26]

↑, increased expression or secretion of FGF21; ↓, decreased expression or secretion of FGF21; -, no effect; AHR, aryl hydrocarbon receptor; FGF21, fibroblast growth factor 21; PPARα, peroxisome proliferator-activated receptor-α; PPARγ, peroxisome proliferator-activated receptor-γ; RORα, retinoic acid receptor-related orphan receptor-α; RORE, retinoic acid receptor-related orphan receptor response element; TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin.

uptake of oxidised LDL by macrophages. The activation of the FGFR1/β-klotho receptor complex by circulating FGF21 activates PPARγ and upregulates both the transcription and secretion of adiponectin from adipose tissue (Fig. 1) [29]. As activation of PPARγ can stimulate FGF21 expression in white adipose tissue [30], this positive feedback loop results in an exponential increase in adiponectin expression [31]. Hence, adiponectin can function as the downstream mediator of the anti-atherosclerotic effect of FGF21. However, further studies are needed to assess the signalling pathway that allows an activated FGFR1/β-klotho receptor complex to activate PPARγ.

FGF21 can also decrease total plasma cholesterol levels in apoE KO mice in an adiponectin-independent manner by suppressing sterol regulatory element-binding protein-2 (SREBP2), a key factor in the hepatic biosynthesis of cholesterol [28]. This inhibition of SREBP2 is mediated by activation of the FGFR2-βklotho receptor complex. Moreover, rats fed a high-fat diet also have significant improvements in their lipid profile (decreased total cholesterol, triglycerides, LDL cholesterol, and increased HDL cholesterol) when treated with FGF21 [32]. Thus, FGF21 can protect against some of the key processes involved in the pathogenesis of atherosclerosis. It also alleviates cardiovascular risk factors via adiponectin dependent and independent mechanisms.

3.2. FGF21 protects against oxidative stress in vitro and in vivo

Recent studies suggest a role for FGF21 in protection against oxidative stress. For example, FGF21 treatment shows a dose-dependent reduction in the cytotoxic and apoptotic effects of hydrogen peroxide in human umbilical vein endothelial cells (HUVECs) [32]. This is mediated by the suppression of caspase 3, inhibition of p38 activation and a decrease in apoptotic activity, as measured by an increase in the ratio of BCL-2 to BAX expression [32]. Also, FGF21 significantly decreases the level of reactive oxygen species production in alcohol treated HepG2 cells [33]. In rats, administration of FGF21 also reverses high-fat-diet-induced oxidative stress, as measured by a reduction in the levels of circulating superoxide dismutase, glutathione, and malondialdehyde [32]. The fact that FGF21 has been reported to have antioxidant activity is interesting since endothelial injury due to oxidative stress has been suggested to play a major role in the pathogenesis of atherosclerosis [34].

3.3. FGF21 inhibits inflammation in vitro and in vivo

Several studies have reported that FGF21 has anti-inflammatory properties [33,35–37]. In cultured mouse macrophages stimulated with lipopolysaccharide (LPS), FGF21 increases the antioxidant activity of nuclear transcription factor E2-related factor (ERF2) and suppresses the LPS-induced activation of nuclear factor (NF)-κB by degrading I-κB and inhibiting p65 nuclear translocation [37]. FGF21 increases the activity of AMPK and Sirt1 expression in mice with alcoholic fatty liver disease and alcohol treated HepG2 cells [33].

Monosodium glutamate (MSG) has been shown to induce obesity, chronic inflammation, type 2 diabetes and nonalcoholic steatohepatitis in rodents [38,39]. Rats treated with MSG display an increase in systemic inflammation, as assessed by increased white blood cell count and C-reactive protein (CRP) level [36]. Treatment with FGF21 reduces these parameters back to control levels. FGF21 treatment also decreases the expression of tissue necrosis factor-α (TNF-α) and interleukin-6 in adipose tissue of MSG-treated rats.

In a recent study, apoE/FGF21 DKO mice had increased expression of inflammatory markers in the aorta, as well as increased circulating levels of intercellular adhesion molecule-1, vascular cell adhesion molecule-1, monocyte chemotactic protein-1 and TNF-α, compared with apoE KO mice [28]. This suggests that FGF21 deficiency can cause both local and systemic inflammation, which may enhance the development of atherosclerosis.

While sufficient evidence suggests that FGF21 can reduce several risk factors of atherosclerosis and inhibit some of the key mechanisms involved in the pathogenesis of atherosclerosis [28,29,32,33,37,40], little is known about the direct effects of FGF21 on endothelial cells, which plays an important role on the development of atherosclerosis [41]. It has been reported that FGF21 acts on endothelial cells to protect against oxidative stress [32,40], but there is no evidence to suggest that FGF21 inhibits endothelial

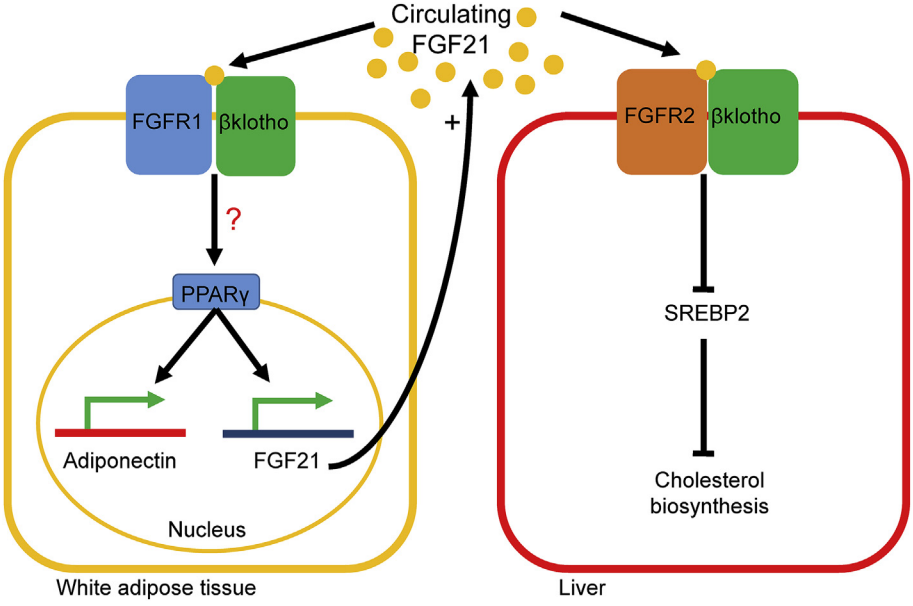

Fig. 1. FGF21 improves atherosclerosis via adiponectin dependent and independent mechanisms. FGF21 activation of the FGFR1/β-klotho receptor complex activates PPARγ by an unknown mechanism, which leads to the increased expression and secretion of adiponectin and FGF21. FGF21 can also inhibit SREPB2 and decrease cholesterol biosynthesis in the liver, independent of adiponectin. FGF21, fibroblast growth factor 21; FGFR, fibroblast growth factor receptor; PPARγ, peroxisome proliferator-activated receptor-γ; SREBP2, sterol regulatory element-binding protein-2.

inflammation. Circulating inflammatory mediators are down-regulated with FGF21 treatment, and upregulated when FGF21 is knocked down [28,33,35,37,40], but the mechanism by which this occurs remains unknown.

4. FGF21 as a biomarker for atherosclerotic CVD

Although FGF21 has anti-atherosclerotic properties in animal and cell culture studies, circulating FGF21 levels are often elevated in humans with cardiometabolic diseases such as obesity, dyslipidaemia, and type 2 diabetes [3,42]. An elevated circulating level of FGF21 has been implicated as a potential biomarker for the early detection of these cardiometabolic disorders [3]. This elevation may be due to a compensatory response to the underlying metabolic stress, or FGF21 resistance [43] as a result of impaired FGF21 signalling. Table 2 summarizes the major findings from studies that have suggested a role of FGF21 as a biomarker for atherosclerotic CVD.

Increasing evidence suggests that FGF21 can be used as a biomarker of subclinical atherosclerosis. In a study of 253 Chinese patients, an elevated serum FGF21 level was reported as an independent risk factor for coronary artery disease (CAD), with an odds ratio of 2.98 per one unit increased in log-transformed FGF21 level [44]. By contrast, in another Korean study which compared 60 CAD subjects with 129 controls matched for body mass index (BMI), the serum FGF21 level was not associated with CAD [45]. This discrepancy could be attributed to the fact that subjects in the former study were not matched for BMI, inflammatory markers and lipid profiles, and they were older and had much higher serum FGF21 levels than the latter study. Moreover, the reported association of serum FGF21 levels with CAD could be confounded by other CVD risk factors.

A much larger study of 670 Chinese subjects reported that serum FGF21 levels are positively correlated with carotid atherosclerosis, independent of risk factors such as a poor lipid profile and elevated CRP levels [46]. Although this study has a larger sample size than the previous two studies, it has the limitation of a large proportion of the subjects having diabetes or dysglycemia. Further studies are needed to assess the relationship of FGF21 levels with different CVD risk factors in the general population.

In a study of 212 newly diagnosed subjects with type 2 diabetes, FGF21 serum levels were higher in patients with subclinical atherosclerosis, and correlated positively with carotid intima-media thickness (IMT) and iliac IMT, especially in women [47]. A similar study, that compared 213 subjects with a normal glucose tolerance and type 2 diabetes, identified a positive correlation between serum FGF21 levels and type 2 diabetes [48]. Patients in this study that also had carotid artery plaques had even higher FGF21 levels. Several other studies have also shown relationships between FGF21 levels and type 2 diabetes, with stronger correlations being reported in subjects with subclinical atherosclerosis [49,50].

The largest study to assess the role of FGF21 as a CVD biomarker is a recent study of 9697 patients with type 2 diabetes from the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) trial [51]. FGF21 plasma levels added to a risk prediction model that includes traditional cardiovascular risk factors and provided a better indication of the risk of a CVD event compared to the traditional model, as assessed by C-statistics, integrated discrimination improvement and net reclassification index analyses.

These studies suggest that FGF21 can be used as a biomarker for subclinical atherosclerosis, particularly among patients with other risk factors such as diabetes which predisposes them to developing CVD. However, these studies are based on large populations, so individual variances make it difficult to predict cardiovascular risk on a case-by-case basis. Further studies need to be conducted to assess these models in the clinical setting.

Table 2. Association of circulating FGF21 levels with cardiovascular disease.

Study	Disease	Study design	Sample size	Results	Ref.
Shen et al., 2013	CAD	Cross sectional	n = 253	• Elevated FGF21 level is an independent risk factor for CAD (odds ratio = 2.98) • FGF21 levels are higher in patients with NAFLD ($p < 0.01$) • Higher FGF21 levels are associated with higher total cholesterol ($p < 0.05$) and triglycerides ($p < 0.01$)	[44]
Lee et al., 2014	Metabolic disease, obesity, CAD	Cross sectional	CAD (−): n = 129 CAD (+): n = 60	• FGF21 levels not associated with CAD ($p = 0.633$) or diabetes ($p = 0.300$) • Higher FGF21 levels associated with atherogenic lipid profiles, insulin resistance, pericardial fat accumulation and metabolic syndrome	[45]
Chow et al., 2013	Carotid atherosclerosis	Cross sectional	n = 670	• FGF21 levels positively correlated with carotid IMT in women (r = 0.32) but not in men (r = 0.06) • Elevated FGF21 level is a risk factor for carotid IMT, independent of established cardiometabolic risk factors ($p = 0.01$)	[46]
Xiao et al., 2015	Subclinical atherosclerosis	Cross sectional	n = 212	• FGF21 levels show positive correlation with carotid IMT in women (r = 0.23) • Positive correlation with iliac IMT in both genders (women: r = 0.27, men: r = 0.22)	[47]
An et al., 2012	T2DM, carotid atherosclerosis	Cross sectional	Lean, NGT: n = 27 Overweight, NGT: n = 31 IGT: n = 14 T2DM: n = 141	• FGF21 levels are higher in T2DM subjects compared with lean, NGT subjects ($p = 0.028$) • Subjects with carotid artery plaques have higher levels of FGF21 compared to subjects without complications ($p = 0.024$)	[48]
Kim et al., 2015	CAD, T2DM	Cross sectional	T2DM(−), CAD (−): n = 30 T2DM(−), CAD (+): n = 30 T2DM(+), CAD (−): n = 30 T2DM(+), CAD (+): n = 30	• FGF21 levels are higher in patients with T2DM ($p = 0.014$) • FGF21 levels are correlated with CAD (Gensini score: r = 0.358, extent score: r = 0.324)	[49]
Lenart-Lipińska et al., 2013	Cardiovascular events, T2DM	Longitudinal	n = 87	• Patients with T2DM with high levels of FGF21 had an increased risk of cardiovascular morbidity and mortality (hazard ratio = 4.7)	[50]
Ong et al., 2015	Cardiovascular events, T2DM	Longitudinal	n = 9697	• High baseline plasma FGF21 levels in T2DM subjects are associated with increased risk of cardiovascular events ($p < 0.01$)	[51]

CAD, coronary artery disease; FGF21, fibroblast growth factor 21; IGT, impaired glucose tolerance; IMT, intima-media thickness; NAFLD, non-alcoholic fatty liver disease; NGT, normal glucose tolerance; T2DM, type 2 diabetes mellitus.

Table 3. FGF21 analogs in two recent clinical trials.

	LY2405319 [52]	PF-05231023 [54]
Number of subjects	38	50
Highest dose of drug (mg)	20	140
Length of treatment (days)	28	42
Study design	Randomised, placebo controlled, double blind	Randomised, placebo controlled, double blind
Subjects	Obese, type 2 diabetic	Obese, type 2 diabetic
Administration of drug	Subcutaneous, daily	Intravenous, twice weekly
Change in metabolic profiles, %		
Body weight	−1.7*	−5.2*
Total cholesterol	−15.4	−16*
Triglycerides	−44.6*	−50*
LDL cholesterol	−20.2*	−26*
HDL cholesterol	19.5*	15*
Adiponectin	81.0*	1800*
Fasting glucose	−5.8	–
Mean daily glucose	–	−17

-, not reported; FGF21, fibroblast growth factor 21; HDL, high-density lipoprotein; LDL, low-density lipoprotein.
*$p < 0.05$.

5. Therapeutic potential of FGF21

Several pharmaceutical companies have recently carried out preclinical studies with specific antibodies that bind to the FGF21 receptor with high affinity thus mimicking FGF21 action. Studies of long-acting derivatives of FGF21 have also been undertaken with a view to conferring benefit in diabetes and obesity-associated disorders. Table 3 summarizes the findings on clinical trial studies of two different FGF21 analogs. The effects of the FGF21 analog, LY2405319 (LY) were assessed in a 28-day proof-of-concept placebo-controlled clinical trial of obese patients with type 2 diabetes [52]. LY treatment resulted in a statistically significant improvement in the lipid profiles in these subjects. Decreased total cholesterol, LDL cholesterol and triglyceride levels, and an increase in HDL cholesterol levels were observed as early as two days after the commencement of treatment, and peaked between 7 and 21 days. There was a trend towards glucose lowering but this did not reach statistical significance. Also, adiponectin levels were increased in subjects that received LY compared to the placebo group.

A long-acting FGF21 mimetic that combines two modified FGF21 molecules onto an antibody scaffold [53] has also been developed (PF-05231023). In obese non-human primates, PF-05231023 administration markedly reduce food intake and body weight [54]. In a placebo-controlled clinical trial in obese/overweight human subjects with type 2 diabetes, PF-05231023

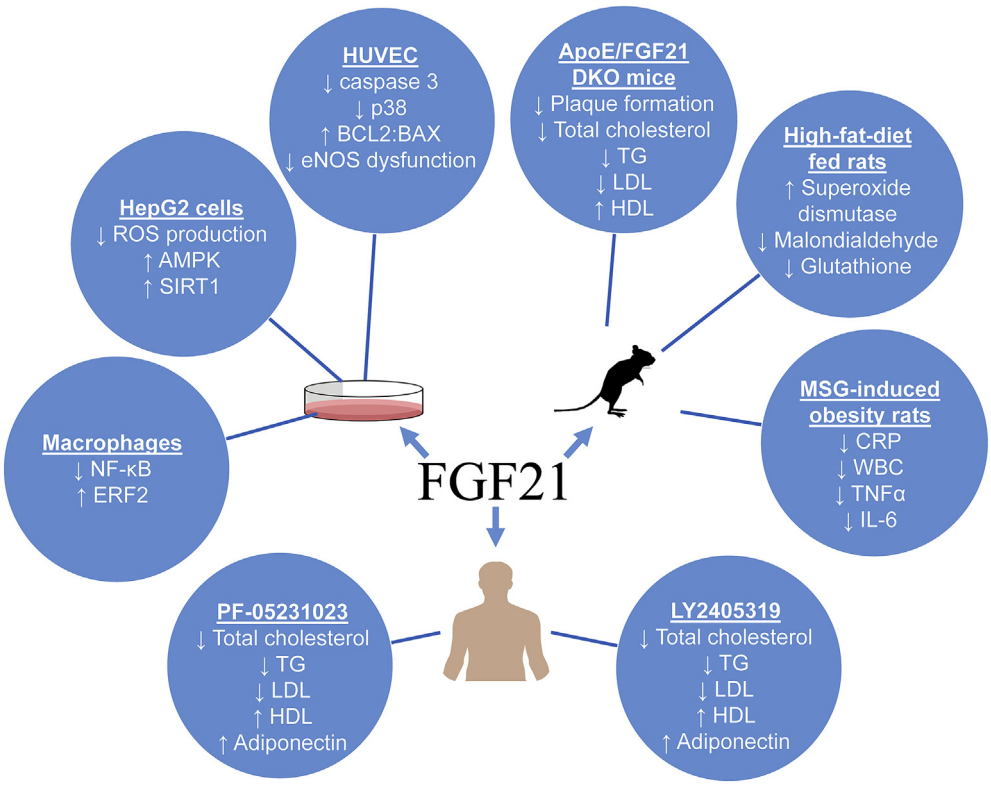

Fig. 2. The anti-atherosclerotic properties of FGF21. AMPK, 5′ AMP-activated protein kinase; CRP, C-reactive protein; eNOS, endothelial nitric oxide synthase; ERF2, nuclear transcription factor E2-related factor; FGF21, fibroblast growth factor 21; HDL, high-density lipoprotein; HUVEC, human umbilical vein endothelial cells; IL-6, interleukin 6; LDL, low-density lipoprotein; MSG, monosodium glutamate; PPARγ, peroxisome proliferator-activated receptor-γ; ROS, reactive oxygen species; SIRT1, silent mating type information regulation 2 homolog 1; SREBP2, sterol regulatory element-binding protein-2; TG, triglycerides; TNFα, tissue necrosis factor α; WBC, white blood cell count.

treatment led to a statistically significant improvement in the lipid profiles within 8 days [54]. Adiponectin levels were also increased from day 15 and remained elevated until day 25 but plasma glucose levels did not change.

These clinical trials are significant as they confirm the ability of FGF21 to improve the lipid profiles and increase adiponectin levels in diabetic and obese subjects who are predisposed to CVD and identify a potential role for FGF21 analogs in the treatment of atherosclerosis. However, the administered doses were up to 300 times the normal plasma level of FGF21. The requirement for supraphysiological doses of FGF21 to halt the pathogenesis of these diseases is consistent with FGF21 resistance in type 2 diabetes and CVD. Further studies are needed to determine whether FGF21 resistance is involved in the pathogenesis of diabetes and atherosclerosis, and if there mechanism to overcome this resistance can be identified.

6. Concluding remarks

FGF21 has been studied extensively in metabolic diseases such as obesity and diabetes over the past decade. Fig. 2 summarizes the anti-atherosclerotic effects of FGF21 as assessed in experimental models and in two recent clinical trials. The lipid-lowering, anti-inflammatory and antioxidant properties of FGF21 suggest it may have a potential role in atherosclerosis and CVD [28,29,31,35,40,55]. FGF21 inhibits key processes in the pathogenesis of atherosclerosis and alleviates cardiovascular risk factors by direct and indirect mechanisms. It acts on endothelial cells to protect locally against atherosclerosis and also improves lipid profiles and reduces systemic inflammation. However, many of these studies were conducted in murine models, so future research is needed to investigate the potential role of FGF21 as a therapeutic target in human disease.

The elevation of circulating FGF21 levels in CVD has prompted research on the potential use of FGF21 as a biomarker for subclinical atherosclerosis [44–50]. This is particularly useful, as atherosclerosis is often diagnosed only after a cardiovascular event. Early diagnosis could provide an opportunity for early treatment and better outcomes. However, before FGF21 levels can be used as a CVD biomarker in the clinical setting, findings from population studies need to be validated in other independent cohorts.

The elevation of FGF21 in CVD and metabolic diseases has also raised questions as to whether FGF21 secretion is a physiological response to such conditions, or if these diseases are a state of FGF21 resistance, in which impaired FGF21 signalling leads to the secretion of higher FGF21 levels to exert its normal physiological function. No studies to date have addressed this question.

Two recent clinical trials have reported promising effects of FGF21 analogs in improving the cardiometabolic profile in obese or overweight patients with type 2 diabetes [52,54]. These studies support the potential use of FGF21 as a therapeutic target for atherosclerosis and CVD treatment.

In summary, our understanding of the biology of FGF21 has grown exponentially over the past decade, but there are several important questions that need to be addressed. Nevertheless, there is emerging evidence that FGF21 will have a future role in the diagnosis and management of CVD.

Conflict of interest

The authors declared they do not have anything to disclose regarding conflict of interest with respect to this manuscript.

Financial support

KL Ong was supported by the Vice-Chancellor's Postdoctoral Fellowship from the University of New South Wales. KL Ong received a Grant-in-Aid (G 12S 6681) and the NSW CVRN Research Development Project Grant (100715) both from the National Heart Foundation of Australia to investigate the role of FGF21 in atherosclerosis and CVD risk factors.

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