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Editorial

Fibroblast growth factor 21: A role in cardiometabolic disorders and cardiovascular risk prediction?

In this issue of *Metabolism*, Ong et al. [1] report that fibroblast growth factor 21 (FGF21) levels could predict major cardiovascular (CV) events (MCVE) in statin-treated patients with stable coronary heart disease (CHD) using data from the Treating to New Targets (TNT) trial (n = 10,001; median follow-up = 4.9 years) [2]; MCVE were defined as a composite of CHD death, cardiac arrest, fatal or non-fatal stroke and non-fatal myocardial infarction (MI). In the Ong et al. study [1], 1996 patients with plasma FGF21 concentrations available at baseline were analyzed; 1835 of them had also FGF21 measurements at the 1-year timepoint. Analyses were adjusted for age, race, gender, body mass index (BMI), smoking, hypertension, diabetes, triglycerides, high-density lipoprotein cholesterol (HDL-C), white blood cell count, blood urea nitrogen and treatment allocation [1]. Higher baseline FGF21 levels were related to a significantly raised incidence of MCVE [adjusted hazard ratio (aHR) per standard deviation (SD) increase: 1.18; $p = 0.019$]. This association was also evident for FGF21 levels at 1 year (aHR per SD increase: 1.24; $p = 0.009$) [1].

Ong et al. [1] also demonstrate that, adding baseline FGF21 concentrations to a model of traditional CV risk factors (see adjustments above), led to a net correction of upward (with events) and downward (without events) reclassification of 16.4 and 4.5%, respectively, thus highlighting the potential clinical utility of FGF21 levels as a CV biomarker in statin-treated CHD patients. The authors highlight the fact that this study is the largest one evaluating the role of FGF21 in CV risk prediction in humans [1].

Patients on atorvastatin 80 mg had significantly lower FGF21 levels compared with those on atorvastatin 10 mg at 1 year (186.9 vs. 207.5 pg/mL; $p = 0.006$). The decrease in FGF21 concentrations was twice as much at the high vs. the low dose group, supporting the hypothesis that atorvastatin can possibly reduce FGF21 levels at a dose-dependent way. This statin effect could be attributed to improved FGF21 resistance or decreased FGF21 liver production/secretion, as discussed by the authors, but the mechanism remains to be fully elucidated [1]. Importantly, changes in FGF21 levels over the first year of follow-up did not predict subsequent MCVE risk [1]. This finding suggests that statin-induced decreases in FGF21 levels may not contribute directly to statin-related CV benefits. Alternatively, FGF21 concentrations may mainly affect MCVE risk at the long- rather than the short-term [1] or they may simply reflect an underlying association with a third confounding factor that was not assessed herein. These possibilities need to be further explored in the future.

FGF21 is a growth factor that has been proposed to modulate glucose, lipid (fatty acid) and energy metabolism [3–5]. Its physiology in humans may not be directly reflected by findings in studies in animals. In humans, under basal conditions, the FGF21 gene is almost exclusively expressed in the liver, and, to a lesser extent, in the brain and the pancreas [6]. During starvation, the FGF21 gene expression is modulated by the peroxisome proliferator-activated receptor-α (PPAR-α), whereas after feeding, it is regulated by PPAR-γ [7]. Certain pathological or physiological stimuli may provoke local production of FGF21 in extrahepatic sites, including the muscles and adipose tissue, apart from the brain and the pancreas [6]. Furthermore, under metabolic or cellular stress, FGF21 is upregulated, acting as a catabolic factor to reduce excessive glucose and lipids, thus re-establishing the energy and metabolic balance [4]. FGF21 has been reported to exert anti-oxidant, anti-immunological and anti-inflammatory properties, as well as to ameliorate tissue damage induced by metabolic abnormalities. It has also been suggested that FGF21 may have anti-atherosclerotic properties via its effects on the adipose tissue (e.g. induction of adiponectin secretion) and the liver [e.g. enhanced expression and stability of the low-density lipoprotein (LDL) receptor, as well as suppression of cholesterol synthesis through inhibition of the transcription factor sterol regulatory element-binding protein-2 (SREBP-2) in hepatocytes] [8,9]. The FGF21-related suppression of SREBP-2 in the hepatocytes may be more beneficial in the presence of statin therapy, since statins stimulate its expression [10]. In this context, FGF21 administration could be protective against both functional and structural changes on the vasculature, heart, liver, pancreas and kidney in the presence of obesity, diabetes and other metabolic disorders [4].

Metabolic syndrome (MetS), non-alcoholic fatty liver disease (NAFLD) and chronic kidney disease (CKD) and increased CV risk have all been linked to each other as metabolic disorders associated with ectopic deposition of excess fat [11–16]. FGF21 administration was reported to improve morphological glomerular abnormalities, renal function, oxidative stress and insulin resistance as well as obesity and dyslipidemia in animal studies [17]. In humans, FGF21 was negatively associated with estimated glomerular filtration rate (eGFR) and positively with inflammatory markers, insulin resistance, comorbidities and mortality in the presence of renal dysfunction [17–19]. In CKD, elevated FGF21 levels can be attributed to both impaired renal and non-renal clearance and increased production [18]. Furthermore, in the presence of diabetic nephropathy, high FGF21 levels correlated with poor prognosis, more severe albuminuria and faster reduction of eGFR [18,20]. Similarly, the FGF21 signaling pathway has been also implicated in NAFLD and non-alcoholic steatohepatitis (NASH) development [21]. FGF21 administration was shown to reduce liver fat accumulation, inflammation and fibrosis, and reverse hepatic steatosis, thus highlighting its potential role in the treatment of NAFLD/NASH [21,22]. Apart from NAFLD, high FGF21 levels have been reported in patients with obesity, MetS, type 2 diabetes mellitus (T2DM), gestational diabetes, hypertension, atherosclerosis or CHD [23–26]. The presence of high FGF21 levels in these cardiometabolic disorders has

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been largely attributed to the existence of FGF21 resistance [27] but experimental studies to fully prove this hypothesis are lacking.

Thus, FGF21 has been studied as a potential therapeutic and/or a biomarker for these disorders. Several studies have evaluated the potential role of the FGF21 pathway as a therapeutic target in MetS, diabetes and obesity related metabolic disorders [21,28,29]. Of note, obstructive sleep apnea (OSA) is also associated with obesity and increased CV risk via several metabolic and hormonal disorders [30] but no data exist on FGF21 levels in patients with OSA. FGF21 administration was reported to reduce body weight, triglycerides and LDL-cholesterol (LDL-C), promote lipolysis and improve insulin sensitivity in peripheral tissues in both human and animal studies [7]. Very recently, a randomized phase 2 trial reported that subcutaneous administration of pegbelfermin (a form of recombinant pegylated human FGF21) for 12 weeks significantly improved HDL-C, triglycerides, adiponectin and liver fibrosis biomarkers in obese T2DM patients (n = 96) compared with placebo (n = 24) [31]. FGF21 has also been positively associated with disease prevalence and progression (HR: 1.35; 95%CI: 1.06–1.72; $p < 0.05$) as well as with kidney dysfunction (HR: 1.06; 95%CI: 1.03–1.09; $p < 0.0001$) [32]. A positive link between diabetic micro- and macro-vascular diabetic complications and FGF21 concentrations has also been described [33].

FGF21 has been reported to be superior in predicting incident diabetes than other adipokines, independently of age, smoking, BMI, dyslipidemia, hypertension, fasting glucose and family history [34]. With regard to CHD, FGF21 is regarded as an important hepatokine linking obesity (and related metabolic disorders) with CV disease via endothelial dysfunction and vascular inflammation [7]. It has been suggested that FGF21 expression may be upregulated in the presence of cardiac endothelial cell injury, representing a marker of cardiac dysfunction [7]. In this context, a previous study showed that FGF21 was an independent predictor of major adverse CV events occurrence in CHD patients (n = 229) followed up for a median of 57 months [35]. FGF21 levels were also positively associated with the risk of unstable angina (odds ratio: 2.781; 95%CI: 1.476–5.239; $p = 0.002$) [36], as well as with the angiographic extent and severity of CHD assessed by the Gensini and Extent score [37]. Similarly, carotid atherosclerosis and increased arterial stiffness have been linked to high FGF21 concentrations in humans [7,38].

A recent meta-analysis (including 28 studies) found that FGF21 predicted the incidence of CHD (HR: 1.29; 95% confidence interval (CI): 1.06–1.55; $p < 0.01$) and MetS (HR: 1.70; 95%CI: 1.35–2.15; $p < 0.0001$), as well as CV death (HR: 2.33; 95%CI: 1.08–4.99; $p < 0.05$) and total mortality (HR: 3.00; 95%CI: 1.23–7.33; $p < 0.05$) [32]. Interestingly, in Chinese T2DM patients (n = 3528) without CV disease, FGF21 levels independently predicted CHD incidence (HR: 1.55; 95%CI: 1.10–2.19; $p = 0.013$) and improved net reclassification of CV risk, after adjustment for several traditional risk factors, preferably using an optimal cut-off of 206.22 pg/mL [39].

Similar findings were observed in the 5-year follow-up Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study (n = 9697 T2DM patients), in which baseline FGF21 concentrations were associated with total CV events, coronary and carotid revascularisation [40]. In the same study [40], the addition of GF21 levels to a prediction model with traditional risk factors (such as age, gender, BMI, smoking, diabetes duration, history of CV disease, glycated A1c, LDL-C, HDL-C, triacylglycerol or eGFR) improved net reclassification for total CV events, stroke and hospitalization for angina pectoris, thus supporting a role for FGF21 as a biomarker for CV risk assessment in T2DM patients. Of note, fenofibrate was found to significantly increase FGF21 concentrations (by 81%) compared with placebo over 1 year [40].

Overall, including FGF21 to predictive models was shown to improve CV risk reclassification in 3 studies: one in statin-treated CHD patients [1], one in fenofibrate-treated T2DM patients [40] and one in Chinese T2DM patients without known CV disease (with on mentioning of lipid-lowering drugs use) [39]. This improvement in CV risk prediction was independent of conventional risk factors (such as age, gender, dyslipidemia, obesity, hypertension, diabetes duration, glycemic control, history of CV disease and smoking). This finding is important since several of these factors may be involved in the increased residual CV risk observed in statin-treated patients.

Further larger studies with different patient populations, including the general population, are needed to elucidate whether FGF21 should be added in CV prediction scores and to quantitate the value added by its inclusion in such prediction scores. Appropriate cost effectiveness analyses and establishing appropriate cut-off points for FGF21 levels in such predictive models are also needed. Moreover, the effect of FGF21 on CV risk prediction in patients treated with hypolipidemic drugs other than statins [e.g. ezetimibe and proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors] should be investigated. In summary, FGF21 is a molecule that holds promise as a diagnostic biomarker but many gaps still exist and future research in these yet to be clarified areas is needed.

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Declaration of Interest

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