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Review

Fibroblast growth factor 21 in chronic kidney disease

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ABSTRACT

The association between fibroblast growth factor 21 (FGF21) and kidney function has been extensively studied in recent years in both animal and human studies. However, the exact functional role of FGF21 in the kidney remains unclear. Previous animal studies have shown that administration of FGF21 ameliorates kidney function, morphological glomerular abnormalities, dyslipidemia, hyperglycemia, insulin resistance, oxidative stress and obesity. In human studies, FGF21 levels negatively correlated with estimated glomerular filtration rate. FGF21 levels were elevated in patients with end-stage renal disease. The elevation of FGF21 levels in presence of kidney disease has also raised questions as to whether FGF21 is a potential biomarker for detecting a decline in renal function. In recent clinical trials, an FGF21 analogue reduced insulin levels and body weight, and ameliorated dyslipidemia in patients with type 2 diabetes mellitus and obesity, all of which are well-known risk factors for kidney disease. Thus, FGF21 may be a potential therapeutic target for the treatment of kidney disease, although adverse side effects should also be considered when administering FGF21 since FGF21 may affect bone development and reproduction. This review will assess current knowledge on the relationship between FGF21 and kidney function.

1. Introduction

Chronic kidney disease (CKD) is a common disease affecting approximately 8–16% of the adult population globally [1]. According to the Kidney Disease: Improving Global Outcomes (KDIGO) guideline, CKD is defined as kidney damage or glomerular filtration rate (GFR) < 60 ml/min/1.73 m^2 for 3 months or more, regardless of cause [2]. Kidney damage is determined by the presence of albuminuria which is defined as albumin-to-creatinine ratio > 30 mg/g in two of three spot urine samples.

The prevalence rate of CKD is continuously rising, along with other risk factors such as the metabolic syndrome, obesity and diabetes. From 1990 to 2013, the global prevalence of CKD increased by 48%, which translates into an increase of about 2.1% per year [3]. Therefore, CKD poses an increasing significant burden on the society, particularly when it progresses to end-stage renal disease (ESRD). ESRD is the last stage of kidney disease in which GFR is < 15 ml/min/1.73 m^2. Patients with ESRD require regular dialysis or kidney transplantation and are at a 2 to 4-fold increased risk of cardiovascular disease [4,5]. CKD progresses over many years and is often asymptomatic during a long latent period, thus, it is important to detect the disease early so that lifestyle and pharmacological interventions can be implemented. Currently, the most widely used methods of measuring renal function are glomerular filtration rate (GFR) and albuminuria. Unfortunately, it is time-consuming and difficult to measure GFR and therefore estimated GFR (eGFR) is often preferred which involves measuring endogenous markers such as creatinine and cystatin C [6]. Several new biomarkers have been discovered in the past decades with the potential to detect renal function decline earlier than existing markers. One promising biomarker is fibroblast growth factor 21 (FGF21).

FGF21 is a member of the fibroblast growth factor (FGF) gene family which includes proteins responsible for cell growth and differentiation, embryogenesis, wound repair and angiogenesis [7,8]. Since the discovery of the first FGF (FGF1 or αFGF) in mouse embryos in 1976, the FGF family has expanded gradually and currently consists of 22 members (FGF1–23) [7,8]. FGF21 is a multifaceted metabolic regulator with beneficial effects on glucose and lipid metabolism. It also ameliorates many diseases [9]. Mouse FGF21 contains 210 amino acids, whereas human FGF21 consists of 209 amino acids (~20 kDa) that have a 75% homology with mouse FGF21 [10].

There is limited evidence in the literature on the relationship of FGF21 with kidney function, although increasing interest in this field has heightened the need for more research. This review discusses FGF21 functions in different tissues and organs, evaluates current knowledge on FGF21 function in animal and human diseases, and lastly assesses the potential role of FGF21 as a therapeutic target, with an emphasis on renal function.

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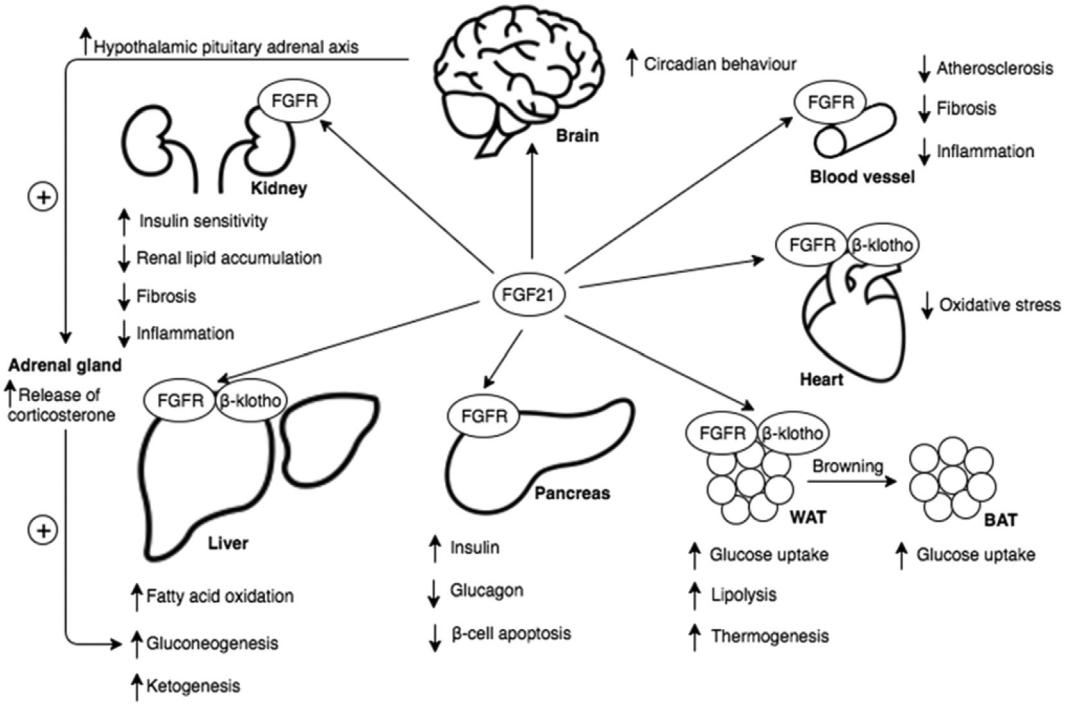

Fig. 1. Effects of FGF21 on different tissues.
Abbreviations: FGF21; fibroblast growth factor 21; FGFR, fibroblast growth factor receptor, WAT; white adipose tissue, BAT; brown adipose tissue.

2. Functions of FGF21 in different tissues

FGF21 is primarily produced in the liver where it is regulated by peroxisome proliferator-activated receptor-α (PPARα), an important regulator of lipid metabolism [10,11]. FGF21 is also expressed to a lesser extent in adipose tissue, skeletal muscle, thymus and pancreas [9,12].

The biology of FGFs has been widely studied in recent years. FGFs act on FGF receptors (FGFRs) via an autocrine or paracrine mechanism which involves the interaction with heparin or heparin sulphate glycosaminoglycans. However, endocrine FGFs such as FGF19, FGF21 and FGF23 bind to FGFRs with low affinity and therefore require transmembrane glycoproteins such as α-Klotho or β-Klotho as co-receptors for binding to FGFRs. Klotho proteins are expressed in different patterns across different tissues which may contribute to the tissue-specific actions of FGFs [13]. Fig. 1 shows the effect of FGF21 on different tissues.

FGF21 requires β-Klotho in order to bind specifically to FGFR. Since the liver and white adipose tissue (WAT) express both FGFR and β-Klotho, they are the primary target sites for FGF21 [14,15]. In the liver, FGF21 stimulates fatty acid oxidation, gluconeogenesis and ketogenesis [16], while in WAT, FGF21 stimulates glucose uptake, lipolysis, thermogenesis and conversion of WAT into brown adipose tissue (BAT) [17]. It has been proposed that FGF21 may act in the central nervous system (CNS) to regulate circadian behaviour and stimulate the hypothalamic pituitary adrenal axis. This increases corticosterone secretion from the adrenal gland and further increases gluconeogenesis in the liver [18,19]. FGF21 protects β-cells in the pancreas from apoptosis possibly due to its glucose and lipid lowering effects, thereby reducing glucolipotoxicity [20]. Both FGFR and β-Klotho are expressed in the heart, and FGF21 may protect the heart from oxidative stress which subsequently reduces the risk of myocardial ischemia, heart failure and cardiac hypertrophy [21–23]. FGF21 has also been shown to ameliorate atherosclerosis [24].

Little is known about the role of FGF21 in the kidney. A study from China found that FGF21 has many beneficial effects including reduced renal lipid accumulation, fibrosis, inflammation and oxidative stress, thereby preventing diabetic renal injury [25]. These investigators further found that deficiency of FGF21 aggravated these conditions. Interestingly, they also discovered that FGF21 directly suppresses triglyceride levels and lipid accumulation in kidney tissues without suppressing plasma triglyceride and lipid levels. This suggests that the renal-protective effect of FGF21 was predominantly via the lipid-lowering effect in the kidney rather than via systematic lipid reduction. In fact, a recent study has also demonstrated that the association of increased plasma FGF21 levels and FGF21 expression in kidney proximal tubular cells (PTCs) with production of ketone bodies in the liver in prolonged starvation [26]. This study suggests FGF21 may play a role in the autophagic degradation of lipid droplets in PTCs during prolonged starvation for energy homeostasis [26]. Moreover, FGF21 has been shown to prevent hyperglycemia-induced fibrogenesis in renal mesangial cells [27]. This suggests FGF21 could protect against renal fibrosis, which is often found in CKD patients.

3. Role of FGF21 in animals

The role of FGF21 in animals has been extensively studied in recent years. A comprehensive study by Kim et al. found that daily administration of a small dose of FGF21 in diabetic *db/db* mice significantly ameliorated renal function and morphological glomerular abnormalities [28]. They further observed that FGF21-related components such as FGFR and β-klotho were up-regulated in the diabetic kidney, and that administration of FGF21 significantly suppressed these components. These findings raised the question as to whether reduced kidney function is due to FGF21 resistance. In contrast, other studies found that FGFR and β-Klotho were down-regulated in liver and WAT of *ob/ob* and mice with diet-induced obesity (DIO mice) [29,30].

FGF21 has many beneficial effects in animal models including anti-inflammatory, anti-diabetic and hypolipidaemic effects [31,32]. For example, administration of FGF21 decreases plasma glucose, insulin, glucagon, triglyceride, and low-density lipoprotein (LDL) cholesterol levels. It also reduces oxidative stress, prevents obesity and increases in high-density lipoprotein (HDL) cholesterol levels in both diabetic mice and monkeys (Fig. 2) [28,30–32]. Interestingly, FGF21 ameliorates hyperglycemia without inducing mitogenicity or causing weight gain in

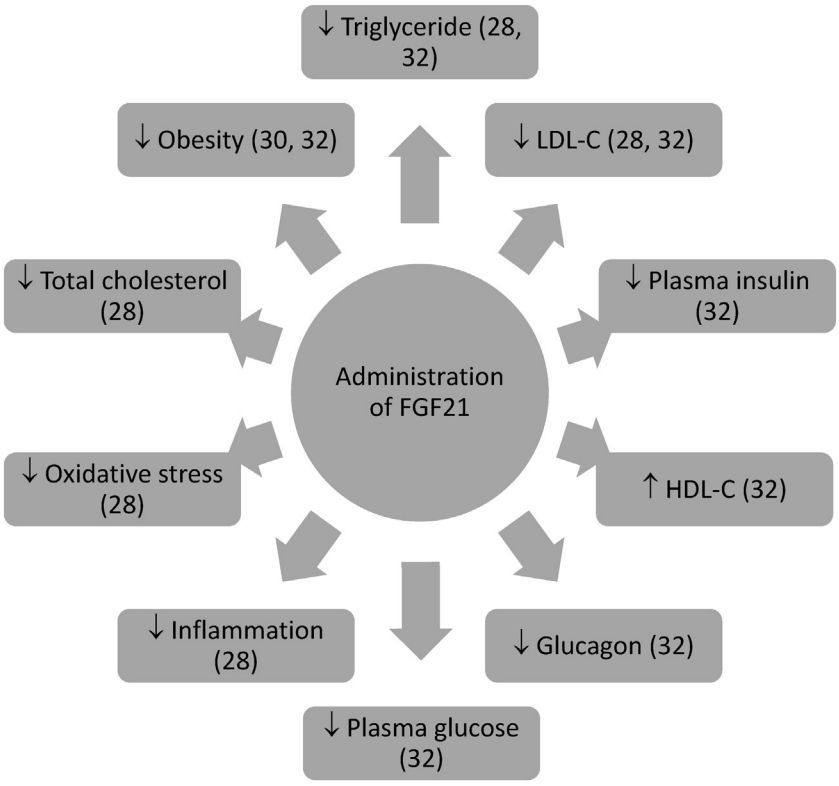

Fig. 2. Effects of FGF21 administration on diabetic mice [28,30] and monkeys [32].
Abbreviations: FGF21; fibroblast growth factor 21; LDL, low-density lipoprotein; HDL, high-density lipoprotein.

vivo, unlike traditional insulin therapy, thus, making FGF21 a potential therapeutic target [31,33]. Furthermore, it has recently been found that fenofibrate treatment prevents renal damage in mice with type 1 diabetes by increasing FGF21 levels and enhancing nuclear factor (erythroid-derived 2)-like 2 (Ndf2) function [34].

Nonetheless, a human study conducted by Jian et al. [35] did not find any association between FGF21 and obesity or plasma glucose concentrations, which is consistent with findings from a study by Galman et al. [36]. The reason for these differences between animal and human studies remains elusive, but suggests that the physiological role of FGF21 in humans may differ from that in animals.

4. Role of FGF21 in human diseases and renal function

Associations between FGF21 levels in the circulation and several human diseases have been reported. Circulating FGF21 levels are elevated in dyslipidemia, insulin resistance, the metabolic syndrome, type 2 diabetes mellitus (T2DM), non-alcoholic fatty liver disease, atherosclerosis, coronary artery disease and CKD [37–43]. These diseases have direct and indirect adverse effects on the kidney [44]. Many cardiovascular risk factors for atherosclerosis such as obesity, oxidative stress, inflammation, dyslipidemia and hypercholesterolemia are associated with CKD [13,45]. For example, an excess of ectopic fat deposition, such as in the renal sinus (RS), is often found in obese subjects, and excess accumulation of perirenal adipose tissue in the RS is associated with poor renal function and CKD [46]. Circulating FGF21 levels correlate positively with the amount of adipose tissue in RS [47]. While the FGF21 level is increased in the presence of these cardiometabolic disorders, it is uncertain whether FGF21 does, in fact, have a direct relationship with the kidney. Therefore, there is a need to investigate the relationship between FGF21 levels and renal function, free of clinically apparent cardiovascular disease at baseline.

A few studies have found an association between serum FGF21 concentrations and eGFR (Table 1). Stein et al. found that serum FGF21 levels were elevated 15-fold in patients receiving long-term hemodialysis [48]. Similarly, a more recent study by Han et al. found that serum FGF21 concentrations were increased 8-fold in patients receiving peritoneal dialysis compared to healthy control subjects [49]. In agreement with these findings, Lin et al. proposed that serum FGF21 concentration gradually increase as CKD progresses from early- to end-stage disease, with data indicating that serum FGF21 levels were elevated 10-fold in patients with ESRD in comparison to healthy participants [50]. In a more recent study by Trakarnvanich et al., the inverse relationship between FGF21 levels and eGFR was also found in patients with renal transplant [51].

A cross-sectional study by Hindricks et al. covering the whole spectrum of CKD stages ranging from stages 1–5 found that serum FGF21 concentrations were increased in patients with CKD and patients with acute renal dysfunction following nephrectomy [42]. Moreover, FGF21 concentrations varied between the five CKD stages. However, in contrast with other studies, they found that LDL cholesterol levels were negatively correlated with FGF21 levels and not associated with FGF21 or insulin resistance. Crasto et al. [52] found that FGF21 concentrations were independently associated with renal function and CKD in community-dwelling adults, even after adjustment for diabetes [52]. In harmony with this, Lee et al. found that elevated FGF21 levels can predict kidney disease progression in subjects with T2DM and normoalbuminuria [53].

A recent large-scale cohort study by Ong et al. found a significant inverse relationship between FGF21 levels and eGFR in T2DM patients. Moreover, it was reported that higher FGF21 levels at baseline were associated with increased albuminuria and a greater risk of microvascular complications including nephropathy over five years of follow-up [43]. This is consistent with two studies, showing the independent association of FGF21 levels with urinary albumin excretion (UAE) or albuminuria in T2DM patients [35,54].

The elevation of FGF21 levels in cardiometabolic disease and renal dysfunction may be a compensatory protective response to metabolic stress. It could also be caused by FGF21 resistance due to impaired FGF21 signalling, which implies the need for supraphysiological doses of FGF21 to achieve a beneficial effect. The concept of FGF21 resistance was first proposed by Fisher et al., who demonstrated that obese mice

Table 1
Human studies investigating the relationship between serum FGF21 concentration and renal function.

Author (year), citation, country of study	Study design	Study sample	eGFR calculation and classification of renal function	Limitations	Key findings
Stein et al. (2009) [48], Germany	Cross-sectional study	- Healthy control subjects (n = 60) - Subjects receiving hemodialysis (n = 60)	- MDRD equation	- Study with only Caucasian subjects - Small sample size	- FGF21 levels were 15 times higher in patients receiving hemodialysis than control subjects. - FGF21 levels positively correlated with serum creatinine - FGF21 levels negatively correlated with eGFR
Han et al. (2010) [49], South Korea	Cross-sectional study	- Healthy control subjects (n = 63) - Nondiabetic subjects receiving peritoneal dialysis (n = 72)	- Urea and creatinine clearance	- Study with only one ethnicity - Cross-sectional study - Small sample size - Study with only nondiabetic PD patients	- FGF21 levels were 8 times higher in patients receiving PD than in healthy control subjects - FGF21 levels negatively correlated with residual renal function but positively correlated with inflammatory markers and HOMA-IR in PD patients - Hyperfibrinogenemia was significantly associated with elevated FGF21 levels
Lin et al. (2011) [50], China	Cross-sectional study	- Healthy control subjects (n = 40) - CKD subjects (n = 200)	- MDRD equation - Renal function classification: Early-stage CKD (eGFR 60–90 ml/min/1.73 m^2) Middle-stage CKD (eGFR 30–60 ml/min/1.73 m^2) ESRD (eGFR < 30 ml/min/1.73 m^2)	- Study with only Chinese ethnicity - Small sample size	- FGF21 levels in patients with ESRD were 10 times higher compared with healthy control subjects - Elevated FGF21 levels were associated with diabetes, hypertension, coronary heart disease, hyperlipidemia and left ventricular hypertrophy
Jian et al. (2012) [35], China	Cross-sectional study	- Healthy control subjects (n = 50) - T2DM subjects with normoalbuminuria (n = 158) - T2DM subjects with microalbuminuria (n = 68) - T2DM subjects with macroalbuminuria (n = 38)	- MDRD equation - UAE	- Study with only Han Chinese ethnicity - Cross-sectional study - Small sample size - Only UAE as a variable for diabetic nephropathy - Diabetic nephropathy not diagnosed by renal biopsy - UAE was only measured once on patients' admission	- FGF21 levels were higher in T2DM patients than in healthy control subjects - FGF21 levels were higher in T2DM patients with higher UAE
Crasto et al. (2012) [52], USA	Cross-sectional study	- CKD patients (n = 144) - Healthy control subjects (n = 600)	- CKD-EPI creatinine equation	- Cross-sectional study	- FGF21 levels were independently associated with renal function and CKD
Hindricks et al. (2014) [42], Germany	Study population 1: - Cross-sectional study Study population 2: - Longitudinal cohort study	Study population 1: - CKD patients (n = 499) Study population 2: - Patients undergoing nephrectomy (n = 32)	Study population 1: - MDRD equation - CKD stages 1–5 classified according to the National Kidney Foundation – Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines Study population 2: - CKD-EPI creatinine equation	- Cross-sectional study - Study population 2 had small sample size	- FGF21 levels were higher in patients with CKD and AKD following nephrectomy - FGF21 levels positively correlated with the metabolic syndrome - FGF21 negatively correlated with LDL cholesterol - FGF21 was not associated with insulin resistance
Ong et al. (2015) [43], Australia	Longitudinal cohort study	- T2DM subjects (n = 9697)	- MDRD equation	- Different outcomes were assessed at the same time which may produce false-positive results - All patients had T2DM at baseline and findings may not be generalisable to healthy population	- FGF21 levels negatively correlated with eGFR - Elevated FGF21 levels at baseline can predict changes in eGFR during 5-year follow-up
Lee et al. (2015) [53], Hong Kong	Longitudinal cohort study	- T2DM subjects (n = 1136)	- MDRD equation - Renal function classification: Stage 1 (eGFR ≥ 90 ml/min/1.73 m^2) Stage 2 (eGFR 60–89 ml/min/1.73 m^2)	- Study with only Chinese ethnicity - Short duration of follow-up - Diabetic nephropathy not diagnosed by renal biopsy	- Elevated FGF21 levels predict kidney disease progression

(*continued on next page*)

Table 1 (*continued*)

Author (year), citation, country of study	Study design	Study sample	eGFR calculation and classification of renal function	Limitations	Key findings
			Stage 3a (eGFR 45–59 ml/min/1.73 m^2) Stage 3b (eGFR 30–44 ml/min/1.73 m^2) Stage 4 (eGFR 15–29 ml/min/1.73 m^2) Stage 5 (eGFR < 15 ml/min/1.73 m^2)		
Esteghamati et al. (2016) [54], Iran	Cross-sectional study	- Healthy control subjects (n = 42) - T2DM subjects with normoalbuminuria (n = 44) - T2DM subjects with microalbuminuria (n = 44)	- CKD-EPI creatinine equation - UAE	- Study with only one ethnicity - Cross-sectional study - Small sample size - Only UAE as a variable for diabetic nephropathy - Diabetic nephropathy not diagnosed by renal biopsy	- FGF21 levels were higher in T2DM patients with microalbuminuria than in healthy control subjects and T2DM patients with normoalbuminuria - FGF21 levels were higher in T2DM patients with higher UAE
Trakarnvanich et al. (2017) [51], Thailand	Cross-sectional study	- Renal transplant patients (n = 90)	- Equation for eGFR not specified	- Study with only one ethnicity - Cross-sectional study - Small sample size - Study with kidney transplant patients only	- FGF21 levels negatively correlated with eGFR and positively correlated with C-reactive protein levels.

Abbreviations: T2DM, type 2 diabetes mellitus; MDRD, modification of diet in renal disease; FGF21, fibroblast growth factor 21; eGFR, estimated glomerular filtration rate; CKD, chronic kidney disease; PD, peritoneal dialysis; HOMA-IR, homeostasis model assessment-estimated insulin resistance; UAE, urinary albumin excretion; ESRD, end-stage renal disease; AKD, acute kidney disease; LDL, low-density lipoprotein; CKD-EPI, chronic kidney disease epidemiology collaboration.

had increased endogenous FGF21 levels, but responded poorly to exogeneous FGF21 administration [30]. However, we could not exclude the possibility that the increased FGF21 levels could also be due to decreased FGF21 excretion via the kidney since eGFR is reduced in patients with CKD. This is particularly important given the small molecular size of FGF21 (32–36 kDa) which allows it to cross the glomerular barrier [7]. Future studies should clarify the route of FGF21 elimination in animal models. Elevated FGF21 levels in CKD patients suggest that FGF21 is a potential biomarker or therapeutic agent for CKD. Nevertheless, previous studies have suggested that FGF21 may delay growth plate development, and may have adverse side effects on reproduction [55,56]. Therefore, it is crucial that possible adverse side effects of FGF21 are emphasised in order to determine risk-benefit ratio of FGF21 administration.

5. Potential role of FGF21 as a therapeutic target

As FGF21 has been shown to reduce glucose and lipid levels, it has been suggested as a potential therapeutic agent for the treatment of diabetes, obesity and dyslipidemia, all of which are risk factors for CKD progression. Nevertheless, problems with using a native FGF21 protein as a therapeutic agent include poor stability and a short half-life of 1 h in vivo [32]. The FGF21 analogue, LY2405319 (Lily Research Laboratories), which has a half-life of 1.5 to 3 h, was developed to circumvent this problem [57]. LY2405319 has comparable efficacy to native FGF21, with similar effects including glucose, insulin and body weight reduction in diabetic mice and monkeys [57,58]. LY2405319 has recently undergone a phase 1 clinical trial in which it was found to reduce insulin levels and body weight, and ameliorate dyslipidemia in patients with T2DM and obesity [59]. These findings are mostly consistent with animal studies, except for the absence of glycemic effects. This may be explained by the short period of study, and the possibility that the relatively short half-life of LY2405319 did not provide sufficient stimulus required to achieve glucose-lowering effects [60]. As a result, current research is focusing on increasing the half-life of FGF21 analogues in order to allow less-frequent dosing and improved patient compliance. These FGF21 analogues include fragment crystallisable-FGF21 and polyethylene glycol-conjugated FGF21 which increase the half-life of FGF21 to 12–30 h [61–63].

6. Limitations of studies

The literature and evidence regarding the relationship of FGF21 and CKD are limited. Previous studies had limitations such as small sample size, low ethnic diversity, different animal models, use of cross-sectional studies, and differences in FGF21 assay method and eGFR formula used.

The current literature fails to take into consideration the ethnic diversity which is an important confounder for CKD. Many studies were conducted in Asian in countries including China and South Korea. However, according to the United States Renal Data System the rate of ESRD in African-Americans is four times higher than in Caucasians [64]. Hence, it is likely that African-Americans may have higher circulating FGF21 levels due to reduced renal function. It is therefore necessary for future research to recruit participants from different ethnic groups in order to determine if FGF21 levels vary between these groups and whether ethnic differences contribute to CKD risk. Furthermore, many studies suffered from small sample sizes with the majority of studies recruiting < 300 participants. This is particularly important in the context of FGF21 since the level varies greatly between individuals and therefore a large sample size is required to identify these differences with sufficient statistical sensitivity.

Limitations in the animal studies include the use of different animal models in different studies. For instance, the method used to induce diabetes in animals may cause disparate results between studies. Zhang et al. used streptozotocin (STZ) to establish a type 1 diabetes model in

their study [25]. However, mice with STZ-induced diabetes do not develop atherosclerosis or hypertension, both of which are prevalent in humans. Thus, the findings from these studies may not be applicable to humans [65]. Other studies utilised genetically modified mice as a T2DM model, which is a risk factor for renal disease. As mentioned previously, Kim et al. used *db/db* mice while Hale et al. used DIO and *ob/ob* mice as animal models of T2DM [28,29]. However, no study to date has investigated FGF21 concentrations in mice with renal dysfunction induced by other more direct methods such as unilateral ureteral obstruction (UUO) or folic acid-induced nephropathy. The advantage of the UUO model is its high reproducibility. It is also simple and fast, and the contralateral kidney can be used as a control [66]. Nevertheless, the kidney is completely obstructed which prevents the assessment of renal function and FGF21 excretion. Therefore, the folic acid nephropathy model is preferable as it allows for the assessment of renal function as a measure of CKD [66]. Animal studies should also include mice with other risk factors for CKD such as spontaneously hypertensive rats [67].

As the studies investigating the relationship of FGF21 with renal function are predominantly cross-sectional, causal relationship cannot be established. Longitudinal study designs would provide a clearer evidence of causality since they will allow for the analysis of the temporal relationship between FGF21 and renal function.

The methods used to measure circulating FGF21 levels may also cause discrepancies in results. ELISAs are the most commonly used method for FGF21 quantification. However, this approach estimates FGF21 concentrations to be in the low hundred picogram range in contrast with radioimmunoassay (RIA) based methods, which estimate FGF21 levels to be 10-fold higher. Hence, one must be wary when comparing results between different studies which use different methods of FGF21 quantification [8].

Many studies calculated eGFR using different formulas, although the Modification of Diet in Renal Disease (MDRD) was the most commonly used. However, there are controversies surrounding the use of the MDRD formula since the cohort used for its development was a CKD cohort in which GFR values differ from those in healthy people [68]. Thus, it tended to underestimate GFR at high values (> 60 ml/min/1.73 m^2) [69]. A formula developed by the CKD Epidemiology Collaboration (CKD-EPI) seems to outperform the MDRD formula [70]. Nevertheless, both the MDRD and CKD-EPI equations require measurement of serum creatinine which may be affected by various factors such as muscle mass, age, medications and the amount of meat in the diet. Cystatin C has therefore been recognised as an alternative or complementary marker to creatinine. It has been found that use of a combined creatinine and cystatin C (CKD-$EPI_{creat\text{-}cys}$) equation resulted in a more accurate estimation of GFR [69,71]. As a result, the KDIGO 2012 Clinical Practice Guidelines for the Evaluation and Management of CKD has recommended use of the CKD-$EPI_{creat\text{-}cys}$ equation [2]. Currently, very few studies use the CKD-EPI or CKD-$EPI_{creat\text{-}cys}$ equations to explore the relationship of FGF21 with renal function, with the exception of two recent studies by Crasto et al. which used CKD-EPI equation and Hindrick et al. where both the MDRD and CKD-EPI equation were used in two study populations [42,52].

7. Conclusion

Despite extensive research on metabolic roles of FGF21, its role in the kidney has not been widely explored. Many studies point to FGF21 levels negatively correlating with renal function. However, these studies had several limitations. In order to overcome these problems, future research should include larger sample sizes, different ethnicities, use of different animal models and longitudinal rather than cross-sectional studies to determine causality. A recommended eGFR formula, CKD-$EPI_{creat\text{-}cys}$, should also be considered in future studies. Lastly, future research should clarify the mechanisms in which FGF21 is eliminated using animal models.

Competing interests

The authors have no other competing interests or conflicts of interest to declare.

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