Role of Fibroblast Growth Factor 21 in Diagnosis of Diabetic Nephropathy

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Abstract

Background: Diabetic nephropathy (DN) is the main cause of chronic kidney disease and represents the most common and serious complication of diabetes. An early diagnosis and intervention may slow down disease progression. The diagnosis of diabetic kidney disease (DKD) is based on clinical findings. It is defined by a decrease in GFR, the presence of albuminuria, or the existence of both dysfunctions in a patient with diabetes. A persistent reduction of estimated GFR below 60 mL/min/1.73 m2 and/or the existence of albuminuria (albumin-to/creatinine urine ratio ≥30 mg/g) in two measurements with at least a 3-month difference is sufficient to make a diagnosis of DKD in a patient with diabetes. FGF21, a hormone mainly produced in liver, is induced directly by peroxisome proliferator-activated receptor-α (PPARα). The level of FGF21 in the plasma of diabetic patients significantly increased and was identified as an independent predictor of type 2 diabetes predicting the development of diabetes. Moreover, in type 2 diabetes patients, the level of serum FGF21 is significantly linked to the occurrence of nephropathy, proteinuria, and the progression of end-stage renal disease (ESRD)

Keywords: Fibroblast Growth Factor 21, Diabetic Nephropathy

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Diabetes mellitus is a multifactorial system disorder that affects most tissues of the body, but still defined only by elevation of blood glucose level above a certain threshold. The most frequent type is type 2 diabetes mellitus (T2DM) that is explained by impairment of insulin sensitivity and of pancreatic β-cell function**.** However, degrees of insulin sensitivity, pancreatic islet function and T2DM-related complications vary among people at the time of diagnosis **(1).**

In the Middle East and North Africa region, about 40 million have diabetes (18-99 years) which is expected to be 84 million in 2045. Egypt is among the world top 10 countries with diabetes prevalence (15.6%). Furthermore, reports indicate that further 4.5 million patients are undiagnosed **(2).**

According to "100 million health" survey, which was conducted in Egypt in 2019 and screened 49.7 million adult Egyptians ,39.8% of adult Egyptians suffered from obesity (BMI ≥ 30 kg/m^2). Obesity was more prevalent in adult females than adult males (49.5% vs 29.5% respectively)**.** Patients With Diseases Attributable to Obesity,T2DM had the highest prevalence attributable to obesity in adult Egyptians. Eighty five percent of females and 62% of males with diabetes mellitus type 2 can be attributed to obesity **(3).**

Diabetes-related complications are responsible for the majority of morbidity and mortality in patients with diabetes**.** American Diabetic Association (ADA) 2022 reported that The prevalence of acute and chronic complications in 2019 was 13.3% and 73.1%, respectively. The most common acute complications were

infections (54.4%), followed by abnormal blood glucose or related metabolic abnormalities (22.3%) and myocardial infarction or transient coronary artery ischemia (7.6%). The most common chronic complications were endocrine or metabolic complications (20.9%), followed by cardiovascular disease (19.7%), neurological symptoms (16.5%), and renal (14.0%) and ophthalmic (5.2%) complications **(4).**

Chronic complications:

Microangiopathy:

The damage to small blood vessels leads to a microangiopathy, which can cause one or more of the following:

Diabetic nephropathy:DN affects 30-40%of people with diabetes.It is main cause of end stage renal disease **(5).**

Diabetic neuropathy, abnormal and decreased sensation, usually in a 'glove and stocking' distribution starting with the feet but potentially in other nerves, later often fingers and hands. Neuropathy can lead to diabetic foot. Other forms of diabetic neuropathy may present as mononeuritis or autonomic neuropathy. Diabetic amyotrophy is muscle weakness due to neuropathy **(6).**

Diabetic retinopathy, growth of friable and poor-quality new blood vessels in the retina as well as macular edema which can lead to severe vision loss or blindness. Retinopathy is the most common cause of blindness among non-elderly adults in the developed world **(7).**

Diabetic encephalopathy, Cognitive dysfunction is increasingly recognized as an important comorbidity of diabetes mellitus. Different stages of diabetes-associated cognitive dysfunction can be discerned, with different cognitive features, affected age groups, prognosis. Relatively subtle, slowly progressive cognitive decrements occur in all age groups. More severe stages, particularly mild cognitive impairment and dementia, with progressive deficits, occur primarily in older individuals. Various mechanisms are proposed, like alterations to the vascular supply of the brain and the interaction of insulin with the brain itself **(7).**

Diabetic cardiomyopathy, damage to the heart muscle, leading to diastolic dysfunction and eventually heart failure; this condition can occur independent of damage done to the blood vessels over time from high levels of blood glucose **(8).**

Erectile Dysfunction: Estimates of the prevalence of erectile dysfunction in men with diabetes range from 20 to 85%. Among men with erectile dysfunction, those with diabetes are likely to have experienced the problem as much as 10 to 15 years earlier than men without diabetes **(9).**

Periodontal disease is associated with diabetes which may make diabetes more difficult to treat. A number of trials have found improved glycemic control in T2DM who have undergone periodontal treatment **(9).**

Macrovascular disease:

Macrovascular disease leads to cardiovascular disease, to which accelerated atherosclerosis is a contributor:

Coronary artery disease, leading to angina or myocardial infarction **(8).**

Diabetic myonecrosis. Peripheral vascular disease, defined as partial or complete occlusion of the peripheral vessels of the upper and lower limbs. Diabetic patients having more than two-fold increased prevalence of Peripheral vascular disease compared with the general population that may leads to diabetic foot ulcers, limb amputation and physical disability **(8).**

Stroke (mainly the ischemic type) **(10).**

Carotid artery stenosis does not occur more often in diabetes, and there appears to be a lower prevalence of abdominal aortic aneurysm. However, diabetes does cause higher morbidity, mortality, and operative risks with these conditions **(8).**

Diabetic foot, often due to a combination of sensory neuropathy and vascular damage, increases rates of skin ulcers (diabetic foot ulcers) and infection and, in serious cases, necrosis and gangrene. It is why it takes longer for diabetics to heal from leg and foot wounds and why diabetics are prone to leg and foot infections. In the developed world it is the most common cause of non-traumatic adult amputation, usually of toes and or feet **(11).**

Diabetic Nephropathy (DN)

25–35% of patients with type 1 or type 2 diabetes mellitus develop diabetic nephropathy. The disease progresses from hyperfiltration to microalbuminuria to macroalbuminuria to nephrotic protienuria to progressive chronic kidney disease, which at last will develop end-stage renal disease. Various renal structures are affected, the glomerulus, the tubules, the vasculature, and the interstitium. With elevated blood glucose level, many metabolites and end-products like advanced glycation end-products and reactive oxygen species, are increased. These metabolites together with angiotensin II will lead to diabetic renal pathology **(12).**

While patients with type 2 diabetes mellitus may present with albuminuria at the time the diabetes is detected, diabetic nephropathy develops in type 1 diabetes 15 to 20 years later. This difference is mainly because the precise onset of type 2 diabetes is unclear. Structural and functional changes occur in the kidney on account of diabetes and result in proteinuria, hypertension, and progressive reduction of kidney function, which is the hallmark of diabetic nephropathy **(13).**

Certain racial groups like African Americans, Native Americans, and Mexican Americans are at high risk of developing diabetic nephropathy. Studies have noted familial clustering, hinting that genetics plays a part in the risk of developing nephropathy **(13).**

Diabetic nephropathy is characterized by structural and functional changes. In glomeruli, there is mesangial expansion, thickening of the basement membrane, nodular glomerulosclerosis (Kimmelstiel–Wilson nodules). In early DN, tubular hypertrophy is present but eventually interstitial fibrosis with tubular atrophy develops, along with arteriolar hyalinosis. In advanced cases, there is an infiltrate of macrophages and T-lymphocytes **(5).**

Oxidative stress and generation of reactive oxygen species damage DNA and protein, or function as signalling amplifiers to activate cellular stress pathways such as protein kinase C (PKC), mitogen-activated protein kinase (MAPK) and nuclear factor-κB(NF-κB). Activation of the polyol pathway, with aldose reductase converting excess glucose to sorbitol, and subsequent conversion to fructose by sorbitol dehydrogenase contributes to oxidative stress by increasing the NADH/NAD+ ratio **(5).**

A recently described novel mechanism of injury also involves endogenous fructose production with activation of fructokinase in the proximal tubule. The formation of advanced glycation end-products by nonenzymatic binding of glucose to proteins, lipids, and nucleic acids can lead to alteration of protein structure and function, oxidative stress, and expression of proinflammatory cytokines and growth factors **(14).**

Activation of Transforming growth factor-β (TGF-β) and its downstream cytokine, connective tissue growth factor (CTGF), induce extracellular matrix formation and fibrosis. In kidney biopsies, glomerular expression of TGF-β1 and CTGF were higher in diabetics compared to controls and correlated with albuminuria. Platelet-derived growth factor (PDGF)expression is also increased in DN, which can modulate chemotaxis, vascular tone, and platelet aggregation. Vascular endothelial growth factor (VEGF) is crucial in angiogenesis but also mediates vasodilatation and leukocyte trafficking in DN **(15)**

Cell signalling and transcription factors:

Increased renal gene transcription of PKC-β showed a strong relationship with glycemic control. PKC activation has wide ranging effects, including enhancing angiotensin II actions, nitric oxide dysregulation, endothelial dysfunction, and activation of MAPK and NF-κB. MAPKs are intracellular kinases which integrate cell signalling into cellular responses **(16).**

MAPKs activate a number of nuclear transcription factors, including NF-κB, which then regulates the gene expression of various cytokines, chemokines, and adhesion molecules. The activation of p38α isoform of the p38 MAPK pathway is most strongly associated with renal inflammation and DN. There may also be a role for toll-like receptors (TLR2, TLR4) and B7-1 costimulatory signalling in modulating inflammation and injury in DN **(17).**

Finally, transcription factors bind to the promoter regions of genes and modulate transcription of messenger RNA. NF-κB has been the best studied in DN. Activation of NF-κB in both human peripheral

blood mononuclear cells and kidney biopsies correlate with severity of proteinuria and glycemic control **(13).**

Screening of DN:

Most guidelines recommend screening by measuring albuminuria with spot urine albumin/creatinine ratio (ACR; normal >30 mg/g creatinine), from either first morning (preferred) or random specimens. An abnormal result is repeated once or twice over a few months for consistency**.** This is coupled with an assessment of renal function using Chronic Kidney Disease Epidemiology Collaboration formulas for estimated GFR (eGFR) in order to stage chronic kidney disease (CKD). American diabetic association recommends that screening begins at diagnosis of type 2 diabetes because ~7% of them already have microalbuminuria at that time and usually 5 years after onset of type 1 diabetes. Screening test should be repeated annually if the diabetic patient is normoalbuminuric. if the patient has increased albuminuria the test should be repeated within 3 to 6 months to confirm it **(16).**

Diagnosis:

The diagnosis of diabetic kidney disease (DKD) is based on clinical findings. It is defined by a decrease in GFR, the presence of albuminuria, or the existence of both dysfunctions in a patient with diabetes. A persistent reduction of estimated GFR below 60 mL/min/1.73 m^2 and/or the existence of albuminuria (albumin-to/creatinine urine ratio ≥30 mg/g) in two measurements with at least a 3-month difference is sufficient to make a diagnosis of DKD in a patient with diabetes **(18).**

Early in the course of the disease, patients are often asymptomatic and are diagnosed during screening with levels of 30 to 300 mg/g creatinine. Once nephropathy sets in, patients present with fatigue, foamy urine (urine protein greater than 3.5 g per day), and pedal edema due to hypoalbuminemia and nephrotic syndrome. They may also have associated peripheral vascular disease, hypertension, coronary artery disease, and diabetic retinopathy **(16).**

The criteria for diagnosis include:Elevated blood pressure, Progressive decline in glomerular filtration rate (GFR), Persistent albuminuria (greater than 300 mg/d) **(5).**

Investigations:

1. **Proteinuria**: It is the hallmark of diabetic nephropathy. The absence of retinopathy makes diabetic nephropathy less likely in T1DM. The scenario is more difficult in T2DM than with T1DM. The exact time of the onset of T2DM is unclear in most patients. However, history and clinical exam play a crucial role in diagnosing diabetic nephropathy in T2DM **(15)**

The 2012 Kidney Disease Improving Global Outcomes (KDIGO) guidelines for CKD suggested the use of three categories to describe severity of albuminuria **(19).**

Table (1):KDIGO definitions of albuminuria category:

Measure	**Urinary albumin category**		
	Normal or mild increased(A1)	**Moderate increased(A2)**	**Severely increased(A3)**
Albumin excretion rate (mg per 24 h)	<30	30-300	>300
Albumin-to-creatinine ratio (mg/g)	<30	30-300	>300
Albumin-to-creatinine ratio (mg/mmol)	<3	3-30	>30

(A1) correlates with normoalbuminria, **(A2)** correlates with microalbuminuria**, (A3)**correlates with macroalbuminuria **(19).**

Albuminuria should be present in at least 2 out of 3 samples over a period of 3 to 6 months, to avoid confounding by transient increases in conditions such as exercise, fever, haematuria, urinary tract infection and congestive heart failure **(20).**

Twenty-four-hour timed collection remains the method of reference for albumin quantification, but numerous international guidelines recommend measuring ACR on a spot sample because creatinine excretion is fairly constant through the day**.** Indeed, 24-hour timed collection is cumbersome and prone to

errors (spills, errors in timing, incomplete bladder emptying) and may lead to misestimation of albuminuria. There is a good concordance between ACR on a random urine sample and 24 hour collection sample **(21).**

Urine analysis: It is used to quantify urea, creatinine, and protein. Microscopy is done to rule out a nephritic cause. Serum and urine electrophoresis is done to rule out multiple myeloma, and renal ultrasound is done to assess the kidney size **(13).**

Biomarkers: It was formerly considered that albuminuria preceded kidney function decline in DKD, but recent epidemiological studies revealed that a distinct group of patients presented kidney dysfunction without developing albuminuria**.** Additional biomarkers of glomerular and/or tubular injury have been proposed to uncover early renal dysfunction and structural lesions, even before microalbuminuria (MA) occurs **(22).**

Renal biopsy: It is the only way to confirm a diagnosis of kidney disease in a patient with diabetes and CKD, as well as the possibility of a non-diabetic renal disease diagnosis. However, it is not always possible to perform a kidney biopsy in patients with diabetes, and thus, in these cases patients' clinical history and clinical findings must be relied upon to guide the diagnosis of DKD **(23).**

Fibroblast growth factor 21 (FGF21)

In the past few decades, some new biomarkers have been discovered, which contributes to recognizing renal function impairment earlier. Fibroblast growth factor 21 (FGF21), one of the emerging biomarkers, has been associated with CKD. Studies have verified that serum FGF21 levels in patients with CKD increase progressively and reach 20 times over the normal range **(24).**

Molecular Structure of FGF21:

As a member of the superfamily of fibroblast growth factors, FGF21 is composed of similar structure containing 150–300 amino acids. FGF21, initially discovered in 2000, was most similar to FGF19 with approximately 35% similarity in the members of human FGFs. FGF21 precursor is composed of 209 amino acids encoded by 4 exons. Next, undergoing cleavage of a signal peptide, FGF21 precursor is converted into mature FGF21 containing 181 amino acids with molecular weight of approximately 20 kDa **(25).**

Receptors of FGF21:

Studies have found that FGFs exert biological functions by binding to FGF receptors (FGFRs) belonging to tyrosine kinase receptors. However, the endocrine FGFs (FGF19, FGF21, and FGF23) have a low affinity with FGFRs, and require the participation of specific transmembrane glycoproteins (α or β-klotho) in the target organs **(26).**

Klotho protein is an important part of the endocrine FGF receptor complex and is indispensable to the high-affinity binding between FGF and FGFR. In recent years, a growing body of research have revealed that the FGF-Klotho complex also participates in the pathophysiology of some diseases, involving CKD, diabetes, arteriosclerosis and cancer. Consequently, through the thorough research on the FGF-Klotho-FGFR complex, the development of drugs targeting the FGF-Klotho endocrine axis may bring clinical benefits in multiple systems **(27).**

The specific binding between FGF21 and corresponding FGFR relies on β-Klotho protein. β-Klotho protein preferentially combines with FGFR for inhibiting paracrine FGFs signalling, which helps endocrine FGFs to specifically bind to FGFRs in target cells avoiding the interference of paracrine FGFs. FGF signalling pathway with abundant structural information extensively modulates distinct biological process in development, tissue homeostasis and metabolism **(28).**

At present, FGF21, deemed as a metabolism-related hormone, is an emerging therapeutic target for metabolic diseases. Furthermore, FGF21 can improve tissue damage caused by the harmful effects of metabolic abnormalities, including oxidative, inflammatory, and immune stress stat. Consequently, some targeting FGF21 analogues have been developed for the treatment of metabolic disorders **(26).**

The latest research evidence confirms that FGF21 can improve metabolic status with anti-fibrotic effects and has the potential treatment for non-alcoholic steatohepatitis A new type of long-acting FGF21 (LAPS-FGF21) has been developed for potential therapeutic effects on obesity. LAPS-FGF21 is chemically

coupled with human IgG4 Fc fragment for a longer half-life in the serum, which can effectively reduce body weight and improve glucose tolerance in a dose-dependent manner at the same time **(29).**

FGF21 is highly expressed in the exocrine glands of the pancreas, the mechanism of which requires the FGFR-Klotho signalling transduction. Under physiological conditions, acute exercise can upregulate the expression level of FGF21 in skeletal muscle. At the same time, FGF21 has a higher level in patients with mitochondrial diseases affecting skeletal muscle, which can be used as a biomarker for mitochondrial respiratory chain defects in muscles **(27).**

FGF21 is released by cardiomyocytes for avoiding hypertrophy, and also participates in regulating the expression of antioxidant pathway genes for reducing reactive oxygen species (ROS) mediated oxidative stress in cardiomyocytes and acting as an antioxidant factor in the heart to control inflammation and cardiac hypertrophy **(30).**

Moreover, FGF21 can prevent atherosclerosis by regulating the interconnection among adipose tissue, liver and blood vessels, and activating the angiotensin converting enzyme 2-angiotensin axis for preventing angiotensin II-induced hypertension and vascular damage. In addition, FGF21 can also play a therapeutic effect on atherosclerosis through the NF-κB pathway **(28).**

During cardiac remodelling in uremic cardiomyopathy, the effect of increased FGF21 expression on cardioprotective is needed to be further clarified. FGF21 partially ameliorates hyperglycemia by reducing renal glucose reabsorption based on the sodium glucose cotransporter 2 (SGLT2) pathway **(29).**

Since FGF21 is mainly excreted by the kidney, it can be predicted by the relative change of creatinine. The estimated glomerular filtration rate (eGFR) is a strong independent negative predictor of FGF21. Synergistic therapy of glucagon-like peptide-1 (GLP-1) and glucagon receptors can upregulate the expression of FGF21 and abate renal insufficiency induced by diabetes **(31).**

Furthermore, FGF21 has a protective effect on kidney against low protein diet-induced renal damage and inflammation. It has been reported that the level of circulating FGF21 is independently correlated with the occurrence of contrast-induced nephropathy and corresponding kidney injury in patients receiving coronary angiography **(25).**

FGF21 and Chronic Kidney Disease:

In clinical practice, it has been found that the level of serum FGF21 is correlated with renal function of the patients with CKD. Furthermore, the elevated plasma FGF21 level significantly correlated with the state of CKD progression and is independently linked to renal function and poor blood lipid levels **(29).**

The determination of FGF21 may help evaluate CKD and its complications, which is expected to become a relevant biomarker of CKD. Serum FGF21 levels in CKD patients are positively associated with oxidative stress, and negatively associated with eGFR **(24).**

The increase in FGF21 concentration in CKD patients may be related to the metabolism of lipids and carbohydrates, and FGF21 levels in CKD patients can be reduced through hemodialysis and transplantation. In peritoneal dialysis patients, FGF21 can be used as a hormone signal exerting a protective role in maintaining blood glucose homeostasis and preventing potential insulin resistance **(30).**

There exert potential roles of FGF21 in CKD patients with other pathological situations. Growing evidence points to the potential interplay between non-alcoholic fatty liver disease (NAFLD) and CKD, the patients with NAFLD can result in renal injury by means of the alterations of FGF21 secretion **(26).**

Similar findings have uncovered that FGF21 can serve as a biomarker for CKD progression and is associated with an increased risk of vascular calcification in CKD patients. FGF21 can be deemed as a sensitive predictor associated with osteoporosis in hemodialysis patients with worse renal function. Serum FGF21 has been confirmed as a biomarker for predicting rapid progression of CKD patients with type 2 diabetes through eGFR decline **(31).**

Some studies have shown that acute kidney injury may accelerate the progression of CKD. Therefore, prevention of acute kidney injury is an important part of the treatment for CKD. In a mouse model of acute kidney injury induced by cisplatin, the application of recombinant FGF21 can remarkably downregulate the relevant protein levels of kidney injury **(27).**

Additionally, another study demonstrates that the protective role of FGF21 in kidney injury can be induced by vascular calcification. Higher circulating FGF21 levels in patients with ESRD, but not with cardiovascular events, are associated with high mortality, which indicates that circulating FGF21 level can be used as a predictor for the prognosis of patients with CKD. Although the metabolic disorder in CKD is usually thought to be the cause of the elevated FGF21, its precise mechanism has not been illustrated so far **(25).**

❖ **FGF21 as a Potential Therapeutic Target:**

FGF21 has been clarified to have the effect on lowering blood glucose and lipids, so it is expected to be a potential candidate for development of CKD therapeutic. However, short half-life and poor stability of FGF21are the bottleneck of clinical application of natural FGF21 protein **(29).** This drawback is overcomed by constructing long-acting FGF21 with controlled site-specific modification. It was done by mutating lysine residues in human FGF21 to other amino acids, which limited PEGylation to the N-terminus of FGF21. Then a long acting mutant FGF21 (mFGF21) was obtained with significantly increased expression level, stability, and biological activity **(32).**

FGF21 can enter the body to play a continuous inhibitory effect on blood glucose, which is expected to become a new biological therapy for metabolic disorders including diabetes. In addition, the FGF21 analogue, LY2405319 (LY), with improved half-life exerts an inhibitory effect on blood sugar and lipids, which indicates that the FGF21 pathway may be an ideal candidate for the treatment of metabolic diseases **(28).**

The new long-acting FGF21 analogue PF-05231023 is a promising potential drug for the treatment of type 2 diabetes, obesity and obesity-related diseases. The current research on targeting FGF21 therapy in CKD has certain limitations with a lack of corresponding clinical trials. At the same time, the current research results of some animal models may not be applicable to humans **(24).**

Fenofibrate is a common lipid-lowering drug that prevents renal dysfunction and pathological changes caused by diabetes, renal fibrosis, oxidative stress, inflammation, and apoptosis by activating PPAR α. Fenofibrate protects kidney damage by up-regulating the expression of FGF21, which activates the PI3K/Akt2/GSK-3β/Fyn-mediated Nrf2 and AMPK pathway **(33).**

❖ **FGF21 and Diabetic Nephropathy:**

FGF21 is closely related to metabolic disorders including diabetes. In order to clarify the relationship between FGF21 and blood glucose, the results of many studies demonstrated that the level of FGF21 in the plasma of diabetic patients significantly increased and was identified as an independent predictor of type 2 diabetes predicting the development of diabetes **(30).**

Moreover, in type 2 diabetes patients, the level of serum FGF21 is significantly linked to the occurrence of nephropathy, proteinuria, and the progression of end-stage renal disease (ESRD) **(24).**

The high serum FGF21 level is correlated with low urinary glucose excretion (UGE) in type 2 diabetes patients. Moreover, FGF21 levels in the plasma of type 2 diabetes patients significantly increase compared with healthy subjects, which is affected by the variables of body mass index (BMI), total cholesterol and triglycerides **(26).**

There is evidence existing to support that genetic variation in the FGF21 gene region is related to the renal function of type 2 diabetes patients and affects the eGFR of diabetic patients **(34).** Studies have found that FGF21 levels can be used as a biomarker related to the prognosis of patients with diabetic nephropathy **(31).**

Serum FGF21 levels are closely associated with early diabetic nephropathy in high-risk groups of type 2 diabetes patients. So that effectively targeting FGF21 therapy may contribute to early detection and prevention of diabetic microvessels complication **(25).**

Elevated serum FGF21 level may be a useful biomarker for predicting the progression of kidney disease, especially in the early stage of diabetic nephropathy. Additionally, a recombinant human FGF21, PEGylated rhFGF21 (PEG-rhFGF21), has been developed for the treatment effect on diabetic nephropathy in diet induced obesity animal model **(29).**

Insulin resistance is a pivotal process in the occurrence and development of diabetic nephropathy. Studies have found that alprostadil (prostaglandin E1) can reduce the insulin resistance via the autophagy-dependent FGF21 pathway for preventing the progression of diabetic nephropathy. FGF21 can negatively regulate TGF-β-p53-Smad2/3-mediated epithelial-to-mesenchymal transition by activating AKT, a serine/threonine kinase previously known as protein kinase B used for reducing diabetes-induced renal fibrosis **(24).**

Based on the db/db which is animal model of type 2 diabetes charachterized by severe obesity,polyrphagia,polydipsia and polyuria, targeting FGF21 treatment could function as a potential therapeutic strategy in type 2 diabetic nephropathy for significantly down-regulating FGF21 receptor components, activating ERK phosphorylation, reducing the excretion of urinary albumin and mesangial expansion, inhibiting the synthesis of pro-fibrotic molecules, and improving renal lipid metabolism and oxidative stress damage **(27).**

FGF21 protects kidney from damage by alleviating renal lipid accumulation and inhibiting inflammation, and fibrosis effects in diabetic nephropathy. Through upregulating the expression of FGF21 and activating Akt2/GSK-3β/Fyn/Nrf2 antioxidants and the AMPK pathway, fenofibrate can exert a role in preventing diabetic nephropathy in the patients with type 1 diabetes. In addition, activation of FGF21 pathway may correlate with the effect of SGLT2 inhibitors on protecting the renal function in type 2 diabetes and delaying progression of CKD **(25).**

FGF21 is closely related to metabolic disorders including diabetes. In order to clarify the relationship between FGF21 and blood glucose, the results of many studies demonstrated that the level of FGF21 in the plasma of diabetic patients significantly increased and was identified as an independent predictor of type 2 diabetes predicting the development of diabetes. Moreover, in type 2 diabetes patients, the level of serum FGF21 is significantly linked to the occurrence of nephropathy, proteinuria, and the progression of end-stage renal disease (ESRD)

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