Fibroblast Growth Factor 21 Association with Renal Function Decline in Type II Diabetes Mellitus

Zainab A. Hussein [1], Sura A.Abdulsattar [2], Essam N.Salman [3]

[1]M.Sc. Student, Department of Chemistry and Biochemistry, College of Medicine, Mustansiriyah University, Iraq. [2]Prof. Dr. Department of Chemistry and Biochemistry, College of Medicine, Mustansiriyah University, Iraq. [3]Assist. Prof. Dr. National Diabetes Center for Research and Treatment /Mustansiriyah University, Iraq

Abstract

Serum FGF21 level is strongly associated with the onset of nephropathy in T2D patients and is an independent predictor of loss of renal function in these patient.The study aimed to evaluate the role of FGF21 in early detection of diabetic nephropathy in type 2 diabetes patents. The study included Eighty-eight(88) samples divided in to four groups, three of which included type 2 diabetes patients, according to mircal test (urine albumin / creatinine ratio), they were classified as :22normalbuminuria , 22 microalbuminuria, and 22 macroalbuminuria. The fourth group included 22 apparently healthy subjects with (matched gender and age).

The mean ±SD of serum fibroblast growth factor 21 of normoalbuminuria group was (225.00±38.62), microalbuminuria group was (267.78±51.08) and macroalbuminuria group was (230.84±50.33) .The comparison results indicated significant increase ($p<0.05$) of FGF21 in microalbuminuria group in comparison to that level in normoalbuminurea and macroalbuminuria groups. Also highly significant increase of FGF21 was observed in microalbuminuria group in comparison to that level in control group. We conclude that FGF21 may be a useful marker for early detection of nephropathy.

Keyword: *Fibroblast growth factor 21; diabetic nephropathy; microalbuminuria; glomerular filtration rate; Insulin resistant ; Type II diabetes Mellitus.*

Introduction

The most common and serious complication of DM is diabetic nephropathy (DN), DN has become the leading cause of chronic kidney failure, starting with normoalbuminuria, microalbuminuria, macroalbuminuria and ultimately leading to end stage renal disease (ESRD),longer duration of diabetes is more prone to developing nephropathy Elevated blood pressure is another important independent risk factor for nephropathy [1] Dyslipidemia , Obesity [2] and Both oxidative stress [3] and subclinical inflammation appear to contribute to the pathogenesis of diabetic nephropathy [4] Fibroblast growth factor 21 (FGF21) which is a peptide hormone that belong to Fibroblast growth factor (FGF family) with 210 amino acids (about 21-kD).. It is produced preferentially in the liver. [5] and synthesized by several organs . There are many sites of FGF21 synthesis ,white adipose tissue, brown adipose tissue, pancreas, skeletal muscle, and cardiac endothelial cells, but the liver is the most important one(Davis D, et al 2017) .FGF21 has been identified as an endocrine and metabolic hormone because of its potent effect on lipid and glucose metabolism and on insulin sensitivity and energy balance [6]. It was found in type 2diabetes and obese patients, The abnormal rise in circulating FGF21 levels in T2D patients is considered to be a protective, compensatory response [7] . Also it was positively associated with obesity, fasting insulin, and triglycerides, and negatively with high density lipoprotein (HDL) [8] .The mechanism of FGF21 resistance in patients with metabolic disorders including type 2 diabetes may be multifactorial.FGF21 may play an important role in the DN development and progression. As a small polypeptide, FGF21 is likely filtered and excreted in the urine, as an important route of FGF21 clearance ,as the glomerular filtration rate (GFR) declines, the circulating FGF21 level increases progressively from

the early to end stages of chronic kidney disease (CKD) and is associated with the renal function [9]. Its levels are also independently associated with urinary albumin excretion in Chinese patients with type 2 diabetes with macroalbuminuria or microalbuminuria(10)In diabetic nephropathy, serum FGF21 levels correlate with the severity of albuminuria and faster loss of glomerular filtrate rate and can potentially be a biomarker of poor prognostic. [11] administration of therapy rFGF21Are markedly decreased albuminuria, meningeal cell expansion, profibrotic cytokines, and improved kidney lipid metabolism and oxidative stress injury [12].

This study aimed to evaluate the role of FGF21 in early detection of diabetic nephropathy in type 2 diabetes patients.

Methods

This case-control study was conducted at national diabetes center for treatment and research (Mustansiriyah University) .Eighty-eight(88) samples included in this study and divided into four groups, three of which included type 2 diabetes patients, and they were divided, according to mircal test (urine albumin / creatinine ratio), into three groups classified as : 22normalbuminuria , 22 microalbuminuria, and 22 macroalbuminuria. The fourth group included 22 apparently healthy subjects with (matched gender and age) healthy group in term of non-diabetic, Patients with type 1diabets, Gestational diabetes, Cardiovascular and other complication, Patients with chronic disease , Patients on insulin therapy and Multiple myeloma, lymphoma, and leukemia.

Serum Fibroblast growth factor 21 was determined by an enzyme immunoassay for quantitative measurement in vitro using kit manufactured by Mybiosource (ELIZAKit),insulin by Demeditec (ELIZA KIT) renal profile and blood sugar and HbA1c were done by Roche/ hitachi cobas c311 device.

Results

The mean ±SD of serum fibroblast growth factor 21 of normoalbuminuria group was (225.00±38.62), microalbuminuria group was (267.78±51.08) and macroalbuminuria group (230.84±50.33) .The comparison results indicated significant increase ($p<0.05$) of FGF21 in microalbuminuria group in comparison to that level in normoalbuminurea and macroalbuminuria groups. Also highly significant increase of FGF21 was observed in microalbuminuria group in comparison to that level in control group. The profile of blood sugar for studied groups indicated highly significant differences ($p<0.01$) of FBG, Insulin, HbA1C, HOMA-IR, and HOMA-- β were observed between all studied groups as shown in table (1). Meanwhile the renal function tests for studied groups revealed Highly significant differences ($p<0.01$) of serum urea, creatinine, GFR, and Albumine/ Creatinine ration in urine between all studied groups as shown in table 1. Also The results of lipid profile showed non-significant ($p>0.05$) differences of cholesterol, triglyceride, LDL and VLDL between studied groups. While a significant deference of HDL was observed .

Table 1. Mean value of FBG, INS, HbA1C, HOMA-IR, HOMA—β, renal function tests and lipid profile in the four studied groups.

Parameter	Control group (n=22)	Type 2 Diabetes with normoalbuminuria group (n=22)	Type 2 Diabetes with Microalbuminuria group (n=22)	Type 2 Diabetes with Macroalbuminuria group (n=22)	P
FBG (mg/dl)	89.72±9.49	166.00±73.05	192.80±78.10	213.59±80.7	0.00
INS (U/mL)	13.27±2.83	9.70±3.47	12.55±3.31	16.28±5.98	0.02
HbA1c (%)	5.57±0.36	8.68±1.76	8.79±1.47	9.34±2.00	0.00

Cont... **Table 1. Mean value of FBG, INS, HbA1C, HOMA-IR, HOMA—β, renal function tests and lipid profile in the four studied groups.**

HOMA-IR	53.31±18.87	74.27±27.48	118.57±29.09	187.99±82.1	0.00
HOMA-β (%)	2.69±0.92	1.46±0.34	1.57±0.49	1.62±0.66	0.00
B. urea (mg/dl)	25.11±5.66	26.69±6.91	29.82±9.82	43.10±5.31	0.00
S. creatinine (mg/dl)	0.60±0.11	0.72±0.21	0.87±0.25	1.60±0.39	0.00
GFR(mL/min/1.73 m2)	123.57±27.1	113.06±33.01	89.17±27.81	47.54±14.14	0.00
A/C Ratio (mg/ mmol)	1.46±0.44	2.05±1.14	10.82±5.49	34.00±9.34	0.00
TC (mg/dl)	188.81±35.9	164.13±47.49	153.90±43.19	168.63±36.8	0.06
TG (mg/dl)	164.19±53.3	174.56±57.61	164.76±55. 9	175.54±48.1	0.83
HDL-C (mg/dl)	48.87±21.43	34.50±9.53	35.11±10.68	43.31±22.89	0.02
VLDL-C (mg/dl)	32.81±10.04	34.85±12.54	32.99±11.27	35.10±11.43	0.90
LDL-C (mg/dl)	99.42±44.62	93.39±34.01	82.78±23.52	99.86±36.10	0.38

A/C Ratio= Albumine: Creatinine Ratio

As shown in Table 2 , the person correlation analysis of fibroblast growth factor 21 results showed a positive correlation with HOMA-β and urea ,while it was observed highly significant ($p<0.01$) negative correlation with (A/C Ratio) .

Fibroblast growth factor 21of microalbuminuria group showed a highly significant ($p<0.01$) negative correlation with creatinine while it showed a highly significant ($p<0.01$) positive correlation with (HOMA-IR, urea and GFR).

The results of fibroblast growth factor 21of macroalbuminuria group showed a highly significant ($p<0.01$) positive correlation with (urea and creatinine, Meanwhile indicate a highly significant ($p<0.01$) negative correlation with (GFR).

Table 2: The person correlation analysis of FGF-21 with studied variables in the patients groups.

Variable	**Patients groups**					
	Type 2 Diabetes with normoalbuminuria group		**Type 2 Diabetes with Microalbuminuria group**		**Type 2 Diabetes with Macroalbuminuria group**	
	r	**P**	**r**	**P**	**r**	**P**
Age (years)	-0.13	0.53	-0.34	0.13	-0.13	0.53

Cont... **Table 2: The person correlation analysis of FGF-21 with studied variables in the patients groups.**

BMI (Kg/m2)	0.21	0.33	0.30	0.17	0.32	0.13
FBG (mg/dl)	-0.24	0.26	-0.00	0.97	0.04	0.86
FPI (U/mL)	0.15	0.47	-0.21	0.35	-0.09	0.68
HbA1c (%)	-0.40	0.08	0.12	0.60	0.10	0.65
HOMA-IR	-0.11	0.63	0.71	0.00	0.05	0.82
HOMA-β (%)	0.46	0.03	0.23	0.31	0.10	0.64
B. urea (mg/dl)	0.22	0.00	0.24	0.00	0.35	0.00
S. creatinine (mg/dl)	0.00	0.58	0.44	0.00	0.27	0.00
GFR (mL/min/1.73 m^2)	-0.01	0.43	-0.48	0.00	-0.22	0.00
A/C Ratio (mg/mmol)	0.56	0.00	-0.08	0.72	0.10	0.64
TC (mg/dl)	-0.03	0.87	-0.07	0.75	0.28	0.19
TG (mg/dl)	-0.16	0.44	-0.21	0.35	-0.14	0.51
VLDL-C (mg/dl)	-0.04	0.82	0.25	0.26	-0.27	0.21
HDL-C (mg/dl)	-0.07	0.74	-0.25	0.28	0.08	0.70
LDL-C (mg/dl)	0.27	0.19	-0.12	0.57	0.10	0.63

Discussion

Diabetic nephropathy is a serious kidney-related complication of type 2 diabetes. The classification of nephropathy is based on albuminuria and eGFR level. However new biomarkers in urine or blood that could improve diagnostic and prognostic in early or later stages of diabetic kidney disease has been established during the past decades [13]. One of these marker was serum FGF21 levels which is used to evaluate among different group with T2D patients who were at multiple grade of albuminuria according to urinary albumin/ creatinine ratio. According to the present study results of the diabetes examination, it was found that the cause of diabetes is insulin resistance rather than insulin deficiency. The systemic disorder insulin resistance affects many organs and insulin-regulated pathways. The disorder is characterized by a reduced action of insulin despite increased insulin concentrations (hyperinsulinaemia).in diabetic kidney disease. High-glucose concentrations induce specific cellular effects, which in the kidney affect many types of cell causing abnormalities of the glomerulus and preglomerular vessels and increased amounts of proteins, growth factors, and advanced glycation end products (AGEs) an Albuminuria and proteinuria indicate relevant tissue damage in the diabetic kidney .this was agreement with mandal , & Hiebert, L study which showed that FBG relates significantly to renal function change by measured serum creatinine levels or estimated glomerular filtration rate ,and FBG can be used as an important marker to predict renal function changes in diabetes [14]. Also Sheuly F,et al reported that the level of glycemic control seems to be the strongest factor determining conversion from normoalbuminuria to microalbuminuria in patients with type 2 diabetes mellitus [15]. Meanwile study by Huang,et al and Muhammad Bilal Habib1& Noreen Sher Akbar reported a significant association between HbA1c levels and risks of albuminuria .HbA1c that can be a possible

threat of renal failure in patients with type II diabetes [16,17]. In the current study the result of Homeostatic model assessment for insulin resistance demonstrated a highly significant increase ($p<0.01$) in sera of Microalbuminuria and Macroalbuminuria in comparison to that level of control group which is similar to other study were Min-Tser Liao,et al show IR promotes kidney disease and plays important role in declining renal function [18] ,also Huang,et al indicated incidence of microalbuminuria generally increased with HOMA-IR. Moreover (HOMA-IR) and beta cell function (HOMA-β) has a relation with incidence of type 2 diabetes and diabetic kidney disease [19]. Similar finding of Kim GS,et al and Wang,et al studies were recorded [20,21]. Also study of Zhou,et al was agreement with the current study which indicated that abnormal pancreatic beta-cell function plays an important role in the development of microalbuminuria [22]. Our finding in renal function tests for studied groups revealed highly significant differences ($p<0.01$) of serum urea, creatinine, GFR, and Albumine/ Creatinine ration in urine were observed between all studied groups. which agreement with Yassin MM,et al and Campion,et al whos reported that urea, creatinine ,and albumin creatinine ratio (ACR) ,decline in GFR were increased in diabetic groups compared to non-diabetics, and reaching their maximum increase in macroalbuminuria, and a decline in glomerular filteration rate increase from to microalbuminuria to macroalbuminuria [23,24]. Diabetic nephropathy causes quantitative as well as compositional abnormalities in lipids. The lipid profile show a statistically non-significant ($p>0.05$) differences of cholesterol, triglyceride, LDL and VLDL between studied groups. While a significant deference of HDL was observed. According to the pervious study of Palazhy, S., & Viswanathan, V. which indicate that dyslipidemia was highly prevalent among diabetic nephropathy patients [25]. Meanwhile Aziz KMA. indicate a significant association of triglycerides and TG/ HDL ratio with elevated levels of serum creatinine, and microalbuminuria. [26], Demihova, et al study indicated that the degree of albuminuria was positively correlated with (Tg), (TC), (LDL), (VLDL) and inversely with HDL [27]. Our finding was agreement with previous study that Serum FGF21 levels correlate positively with creatinine, blood-urea-nitrogen (BUN) and cystatin C and inversely with the GFR and residual renal function . Kohara M, et al. who reported that FGF21 levels were higher in 200 CKD patients (146 pre-dialysis and 54 hemodialysis patients) than in 40 controls [28]

Conclusion

In this study there was a positive correlation of FGF21 with urea and creatinine diabetic nephropathy patient, which may be a useful marker for early detection of nephropathy

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Conflict of Interest: None to declare.

Ethical Clearance: All experimental protocols were approved under the Department of Chemistry and Biochemistry and all experiments were carried out in accordance with approved guidelines.

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