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Association between Protein Kinase C –B Isoform Level and Insulin Resistance in Pathogenesis of Iraqi Patients with Type 2 Diabetic Nephropathy Complications

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Abstract

Objective The aim of the present study is to evaluate the association between serum PKC-B isoform activity levels and various biomarkers such as insulin resistance in sera of Iraqi patients with diabetic nephropathy complications.

Methods A cross-sectional study was performed on 100 samples obtained from Al-Hussein Teaching Hospital, Al-Hussein Medical City, Kerbala Health Directorates/Kerbala – Iraq during Nov., 2019 to Sep. 2020. Thirty patients have type 2 diabetic nephropathy, 40 patients with type 2 diabetic without nephropathy and 30 samples as apparently healthy control. Biochemical data, comprising serum PKC-B level, lipid profile, blood glucose, insulin, HOMA-IR and renal function tests such as urea, creatinine and GFR were investigated.

Results The study included 63% male and 37% female. The results indicated that there was a significant difference in blood glucose, HbA1c%, Homeostatic Model Assessment for Insulin Resistance (HOMA-IR), urea, creatinine, GFR and PKC-B between diabetic nephropathy and non-diabetic nephropathy groups (*P*-value <0.05). Serum PKC-B activity was significantly correlated with blood glucose, HOMA-IR, creatinine and GFR among diabetic nephropathy group, while, HbA1c% and blood glucose was positively correlated with PKC-B level in non-diabetic nephropathy group.

Conclusion The observed data conclude that PKC-B level is higher in patients with diabetic nephropathy complication as compared with T2DM and healthy control. Also there is a significant correlation between PKC-B level and renal function tests in DN group which indicate an important role of PKC-B level in pathogenesis of diabetic nephropathy complications.

Keywords Diabetic nephropathy, type 2 diabetes mellitus, PKC-B, insulin resistance

Introduction

The most common and chronic metabolic disorder worldwide is diabetes mellitus (DM) identified as type 2 diabetes mellitus (T1DM) which characterized by deficiency of insulin while in type 2 diabetes mellitus (T2DM) it characterized by insulin resistance and insulin action within insulin dependent tissues such as adipose tissues, muscle and liver.[1–3] Diabetic nephropathy is the leading cause of end-stage renal disease worldwide and an independent risk factor for all-cause and cardiovascular mortalities in diabetic patients in which 40% of all individuals with type 2 diabetes develop diabetic nephropathy.[4] New insights into the molecular mechanisms that underlie the development and progression of micro-vascular complications of diabetes including nephropathy are emerging rapidly from experimental and clinical studies. Chronic hyperglycemia has been shown to be the major risk factor responsible for the development and progression of micro-vascular complications of diabetes.[5]

Diabetic nephropathy complications are clinically identified by an increase in the excretion of albumin in urine and a decrease in GFR which result in decline in renal functions. The classification of diabetic nephropathy is based on "estimated glomerular filtration rate (eGFR)" and the level of proteinuria.[6] Both hemodynamic and metabolic pathways contribute to trigger the progression of DKD.[7] The characteristics of DN are severe proteinuria > 300 mg/day and severe decline in GFR "glomerular filtration rate" < 15 ml/min 1.73 m^2. These signs result from structural and cellular abnormalities in the nephron, the functional unit of the kidney, such as vascular permeability, podocytes apoptosis, accumulation of extracellular matrix (ECM) in the mesangium (mesangium expansion) and thickening of glomerular basement membrane. Then, the formation of mesangial nodules which also called Kimmelsteil-Wilson nodules (glomerulosclerosis) and ultimately tubule-interstitial fibrosis.[8]

Protein kinase C "PKC" is a family of serine/threonine kinases involve in numerous signaling processes such as modification of gene expression, cell division, migration, proliferation, differentiation, cell survival and apoptosis.[9] Based on the requirement of co-factors phosphatidyl serine (PS), diacylglycerol (DAG) and calcium ion (Ca^{2+}) which determined the activation characteristic. Protein kinase-C protein family has been separated into three subgroups, classical or conventional PKC (cPKC), novel PKC (nPKC), and atypical PKC (aPKC). The cPKC has four isoforms, α, βI, βII, and γ, which require PS, Ca^{2+} and DAG for optimal activity, whereas the novel PKC (nPKC; δ, θ, ε and η) is unresponsive to Ca^{2+} and activated in the presence of DAG and PS. The third, structurally distant subfamily of PKC known as atypical PKC (aPKC; ζ, λ/ι) is unresponsive to both DAG and Ca^{2+}.[10]

Activation of diacylglycerol (DAG)-protein kinase C (PKC) pathway, enhanced polyl pathway, increased oxidative stress, and overproduction of advanced glycation end products have all been proposed as potential cellular mechanisms by which hyperglycemia induces diabetic vascular complications. The DAG-PKC pathway contributes to vascular function in many ways such as the regulation of endothelial permeability, vasoconstriction, extracellular matrix synthesis/turnover, cell growth, angiogenesis, cytokine activation and

leukocyte adhesion.[11–13] In the kidney, several reports have suggested that hyperglycemia can increase PKC activities leading to activation of several isoforms of nicotinamide adenine dinucleotide phosphate (reduced form; NADPH) oxidases to produce the excessive oxidants. The elevated levels of oxidants in combination with PKC induced activations of mitogen-activated protein kinase will lead to the over expression of fibrotic growth factors, see Figure 1.

Many studies have suggested that transforming growth factor (TGF)-b1 play a key role in the accumulation of extracellular matrix (ECM). It has been reported that PKC activation can increase the production of ECM and TGF-b1 expression, and that PKC inhibitors can prevent hyperglycemia or diabetes-induced increases in ECM accumulation and TGF-b1 production in mesangial cells or renal glomeruli.[14]

Many studies reported that elevated glucose levels in the media from 5.6 to 22 mm result in increased cellular DAG contents and subsequently increased PKC activities. It has been reported that hyperglycemia can increase DAG-PKC activities leading to increase the expression of transforming growth factor-1 (TGF-1) which play a key role in increased production of type IV collagen and fibronectin in mesangial cells and also increase the expression of vascular endothelial growth factor "VEGF" which contribute in increase vascular permeability which could be mimicked and reversed by PKC–B inhibitors.[5,15] The characteristic feature of type 2 diabetes mellitus is "insulin resistance" which is defines as incapability of insulin–sensitive tissues such as muscle, liver and adipose tissues to be interrogated to the highest level of insulin. Obesity is the most common cause of insulin resistance result in un-control secretion of "adipokines" that are group of active factors secreted from adipose tissues involve in maintenance of energy homeostasis as well as resistance to insulin include leptin, adiponectin, resistin, TNF-α (tumor necrosis factor-alpha) and IL-6 (interleukin-6). With obesity, there are changes in adipose secretions that result in insulin resistance.[16–18]

The aim of this study was to find the relationship between the levels of PKC-B with insulin resistance and other parameters in Iraqi patients with type 2 diabetic nephropathy complications.

Materials and Methods

This study was a cross-sectional study. The subjects of the study (100) classified into three groups: 30 patients of type 2 diabetes mellitus with nephropathy complications, 40 patients of type 2 diabetes mellitus without nephropathy and 30 healthy obtained from healthy individuals as apparently control group. These samples were obtained from Al-Hussein Teaching Hospital, Al-Hussein Medical City, Kerbala Health Directorates/ Kerbala – Iraq during Nov., 2019 to Dec. 2020. Subjects with eGFR < 60 ml/min 1.73 m^2 and Urinary Albumin Excretion "UAE" > 300 mg/day were considered as the DN group. While subjects with eGFR >60 ml/min 1.73 m^2 and UAE< 30 mg/day consider as T2DM without nephropathy and control group.

From each subject (5 ml) of blood samples was taken, the serum using to perform various biochemical investigations, such as (lipid profile, HbA1c%, insulin, urea, creatinine, blood glucose and PKC-B levels were determined. The activity of PKC-B isoform was assayed by ELISA/Melison kit, the ARCHITECT PLUS i 1000 SR was used for automatic calculation of insulin while the other biomarkers were assessed, using the Roche COBAS c311.

The statistical analysis was presented as the means ± SD. Pearson's correlation test was performed in order to test any correlation among the values of the above biochemical parameters in type 2 diabetic patients with nephropathy complications. The results were considered statistically significant when *P* value < 0.05.

Results

The current study included 100 subjects (30 patients with DN complications, 40 patients of T2DM without DN complications and 30 subjects as apparently healthy control). The gender distribution in DM group include (63% male and 37% female), whereas in patients with diabetic nephropathy complications group the gender distribution include (53% male and 47% females), as compared with apparently healthy control group (66% male and 34% females) as shown in Figure 2.

In addition, the age distribution of the study subjects were in patients with T2DM were 37% (40–49), 40% (50–59), and 22%(60–69), whereas, in patients of T2DM with DN complications were 10% (40–49), 33% (50–59) and 57% (60–69) as compared with apparently control group which were 66% (40–49), 16% (50–59) and (60–69) 16% as shown in Figure 3. The higher incidence of patients of T2DM with DN complications was observed in (60–69 years) age group. There was non-significant difference in age and gender between T2DM with DN complication and without DN complication groups (*P* value >0.05 for both).

The clinical and biochemical characteristics which presented in Table 1 show a significant difference between the

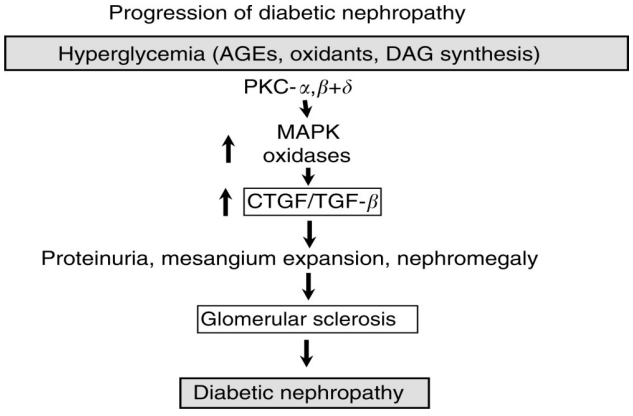

Fig. 1 **Hypothesis of diabetic nephropathy complication.[5]**

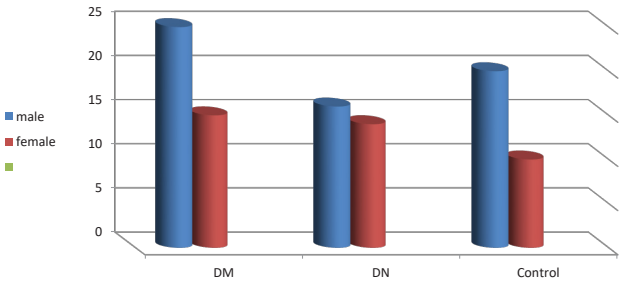

Fig. 2 **Gender distribution of the study individuals.**

three selected groups in some parameters (FBG, HbA1c%, urea, creatinine, eGFR and PKC-B) P value < 0.05. The mean values of the variables (FBS, HbA1c%) are significantly higher in T2DM group as compared to that found in apparently healthy control and type 2 diabetic patients with nephropathy complications groups. The mean of eGFR was very low in T2DM with DN complication group.

In diabetic nephropathy group there is a significant positive correlation between PKC-B level with FBS, HOMA-IR, and creatinine respectively (r = 0.7, P = 0.03, r = 0.9, P = 0.01, r = 0.9, P = 0.02) While the same table show that there is a significant negative correlation between PKC-B level and GFR (r = –0.6, P = 0.05), also there is a positive correlation but not significantly between PKC-B level and each of insulin and HbA1c% (r = 0.5, P = 0.1, r = 0.5, P = 0.08) as shown in Table 2.

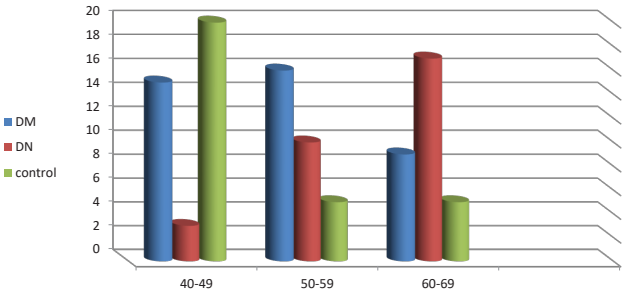

Fig. 3 **Age distribution of the study subjects.**

Discussion

Various studies concerning genetic polymorphisms, biomarkers in obese T2DM and renal diseases including diabetic nephropathy complications have been performed in patients of Iraqi populations.[19–21] The results obtained in this study indicated that the activity of protein kinase C-B is significantly higher in patients with type 2 diabetic nephropathy complications (43.35 ± 18.69) as compared with T2DM and control. These data were in agreement with another results performed previously which found that the expression and activity of PKC-B and other clinical parameters such as "FBG, HbA1c%, GFR and serum creatinine" were significantly higher in type 2 diabetic patients with nephropathy as compared with "diabetic patients without nephropathy"[22,23] and also agree with other study shown that in glomeruli of DN patients the activity of PKC-MAPK pathway and the expression of TGFB-1 is significantly higher than glomeruli of normal subjects.[24]

These results approved that activation of protein kinase C (PKC) is a major signaling pathway for transforming growth factor (TGF)–B stimulate extracellular matrix (ECM) production in diabetic nephropathy (DN) and activation of PKC-MAPK pathway have an critical role in the progression of glomerular damage in DN.

The present study shows significant differences in mean values of fasting insulin level as well as HOMA-IR between the three groups studied. Homeostatic model assessment (HOMA) is a method for estimation "insulin resistance from fasting glucose and insulin". Insulin resistance is found to be significantly higher in patients with type 2 diabetic with nephropathy

Table 1. **Clinical and biochemical characteristics of study subjects**

Parameters	Control Mean ± SD N = 30	T2DM Mean ± SD N = 40	T2DM with DN Mean ± SD N = 30	P value
Age (y)	56.62 ± 6.55	57.72 ± 7.13	59.29 ± 7.55	0.1
BMI (Kg/m^2)	28.3 ± 3.3	29.4 ± 5.4	28.3 ± 3.5	0.5
Duration of T2DM, (year)	–	10.7 ± 3.7	16.36 ± 5.02	0.001*
FBG, (mg/dl)	96.15 ± 10.4	168.4 ± 30.6	173.2 ± 22.02	<0.001*
HbA1c%	5.2 ± 0.9	8.93 ± 2.7	6.8 ± 1.32	<0.001*
Insulin, (µU /ml)	4.54 ± 1.24	30.6 ± 11.49	41.82 ± 14.3	<0.001*
HOMA-IR	1.21 ± 0.49	9.91 ± 3.07	22.6 ± 11.2	<0.001*
Urea, (mg/dl)	27.86 ± 6.83	30.4 ± 13.9	136.25 ± 14.6	<0.001*
Creatinine, (mg/dl)	0.6 ± 0.16	0.8 ± 0.2	7.6 ± 1.8	<0.001*
GFR, (ml/min.1.732 m^2)	114.3 ± 19.2	106.16 ± 24.5	7.5 ± 2.7	<0.001*
TC, (mg/dl)	143.62 ± 28.2	168.4 ± 40.8	163.1 ± 34.5	0.03*
Triglyceride, (mg/dl)	136.18 ± 40.3	188.3 ± 39.2	173.76 ± 21.6	0.01*
HDL-C, (mg/dl)	40.73 ±7.6	36.26 ± 7.77	38.39 ± 10.5	0.14
LDL-C, (mg/dl)	78.02 ± 19.2	118.1± 34.5	97.8 ± 11.3	<0.001*
PKC-B, (IU/min)	27.42 ±10.31	30.35 ± 11.96	43.35 ± 18.69	<0.001*

BMI, body mass index; FBG, fasting blood glucose; eGFR, estimated glomerular filtration rate; TC, total cholesterol; TG, triglycerides; HDL-C, high-density lipoproteins cholesterol; LDL-C, low-density lipoproteins cholesterol; VLDL-C, very low density lipoproteins cholesterol; DN, diabetic nephropathy; T2DM, type 2 diabetes mellitus. Data were expressed as mean ± SD, *P value < 0.05 is significant, by One Way ANOVA test.

Table 2. **Correlation between PKC-B level and some biomarkers inT2DM with DN complications and T2DM**

Biomarkers	PKC-B Activity (IU/min)			
	T2DM with DN (*N* = 30)		T2DM, (*N* = 40)	
	Correlation	*P*-value	Correlation	*P*-value
FBG, (mg/dl)	0.703	0.03*	0.44	0.1
HbA1c %	0.59	0.1	0.704	0.07
Insulin, (µU /ml)	0.51	0.08	0.100	0.3
HOMA-IR	0.90	0.02*	0.64	0.05*
Urea, (mg/dl)	0.406	0.1	0.34	0.17
Creatinine, (mg/dl)	0.94	0.01*	0.92	0.01*
GFR, (ml/min 1.732 m^2)	–0.72	0.05*	–0.604	0.05*
TC, (mg/dl)	0.43	0.1	0.58	0.4
TG, (mg/dl)	0.58	0.3	0.24	0.2
HDL-C, (mg/dl)	–0.60	0.2	–0.05	0.3
LDL-C, (mg/dl)	0.43	0.09	0.28	0.09

*Significant $P < 0.05$, TC, total cholesterol; TG, triglyceride; GFR, glomerular filtration rate; PKC-B, protein kinase c- Bisoform; FBS, fasting blood sugar.

complications as compared to T2DM and controls groups. These data was agreed with another work performed in 2018.[25]

The significant positive correlation between FBG, HOMA-IR and the activity of PKC-B levels in T2DM with nephropathy complications was agreed with another results.[26] Over many decades there is an intense research which involves the activity of several glucose-dependent pathways in the pathogenesis of the long-term complications of diabetes; one of them is the activation of PKC. The major role of PKCs and particularly the β-isoform in the pathogenesis of diabetic complications has been attributed to high glucose level which stimulate synthesis and over production of DAG, resulting in enzyme activation (Langham et al., 2008). While the positive correlation between HOMA-IR which represent the level of insulin resistance and PKC-B activity was explained by[27] which shown that the pathogenesis of type 2 diabetes mellitus "non-insulin-dependent diabetes mellitus (NIDDM)" is resulting from resistance of many tissues to insulin "insulin resistance" inhibition of insulin receptor tyrosine kinase (IRK) activity lead to impaired insulin signaling and cause insulin resistance. Up-regulation and activation of protein kinas C (PKCs) is main cause of inhibition of IRK activity in various cell types. The impact of PKCs on IRK activity might be through phosphorylation of specific serine residues of the insulin receptor b-subunit instead of tyrosine residue. Estimation of GFR considers the most useful general index for the evaluation the severity of kidney damage. Losing of 75 % of renal tissue result a decline in GFR of 50 % (less than 60 ml/min 1.73 m^2). As glomerular function deteriorates, compounds that are normally cleared by the kidneys, such as urea and creatinine, accumulate in plasma so that with a decline in GFR as in T2DM with DN (due to the structural abnormalities in glomerular such as mesangial expansion and thickening of GBM), plasma urea concentration and creatinine tend to rise, these results were agree with another.[28]

The PKC-B has 2 subtypes (PKC-BI and PKC-BII) produced by the same gene PRKCB by "alternative splicing". High glucose level regulate the expression and activity of PKCB-II while PKCB-I not effected.[29,30] In diabetic nephropathy group there is a significant correlation between PKC-B level with creatinine and eGFR respectively ($r = 0.7$, $P = 0.03$, $r = –0.6$, $P = 0.05$). Estimation of GFR considers the most useful general index for the evaluation the severity of kidney damage. Losing of 75% of renal tissue result a decline in GFR of 50% (less than 60 ml/min 1.73 m^2). As glomerular function deteriorates, compounds that are normally cleared by the kidneys, such as urea and creatinine, accumulate in plasma so that with a decline in GFR as in DN (due to the structural abnormalities in glomerular such as mesangial expansion and thickening of GBM), plasma urea concentration and creatinine tend to rise. These data were in agreement with another study performed by Noor et al., in 2020.

All these structural abnormalities in the glomerular of diabetic nephropathy patients can be reverse by using selective PKC-B inhibitor[31] reported that "ruboxistaurin" normalized "glomerular filtration rate, decreased urinary albumin excretion, preserved kidney function, and reduced mesangial expansion, glomerulosclerosis".

Conclusion

According to the data observed in this study we can conclude that:

1. No significant difference in age and gender between patients of T2DM with DN complications and non-diabetic nephropathy group.
2. A significant positive correlation was found between serum PKC-B level, fasting insulin, HOMA-IR and serum creatinine among T2DM with DN group.

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