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Comparison between Serum Beta -Trace Protein and Soluble α-Klotho as Early Predictors of Diabetic Nephropathy in Patients with Type 2 Diabetes Mellitus

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ABSTRACT

Background: Diabetes mellitus (DM) is a systemic disease with serious micro- and macro-vascular complications. Beta-trace protein (BTP), a novel low-molecular weight glycoprotein and α-Klotho (α-KL) that are promising biomarkers of diabetic nephropathy (DN). Further, the upregulation of α-KL (internal or external) seems to protect the kidneys from renal insults. The aim of this study was to compare between serum BTP and soluble α- KL as early predictors and prognostic biomarkers of diabetic nephropathy in patients with type-2 diabetes.

Patients and methods: This was a prospective study, which was carried out at the department of internal medicine, DFM, Al-Azhar University between January 2020 to January 2022. It included 60 patients with type-2 diabetes mellitus, who were divided into three equal groups, and a comparison group (control group) of 20 apparently healthy individuals.

Results: There was highly statistically significant difference between the four groups regarding Albumin/creatinine ratio ($p<0.05$), BTP ($p<0.001$) and soluble α-klotho ($p<0.001$). Soluble α klotho was negatively correlated with BTP, both of these markers was significantly correlated with Albumin/creatinine ratio.

Conclusion: Both BTP and soluble α-klotho can be used as early predictors and biomarkers for diabetic nephropathy in type 2 diabetes mellitus.

Keywords: Beta-Trace Protein; Soluble α-Klotho; Diabetic Nephropathy; Type 2 diabetes.

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INTRODUCTION

Diabetes mellitus (DM) as a chronic systemic disease, is associated with serious micro- and macro-vascular complications (e.g. diabetic nephropathy (DN), retino-pathy, neuropathy, cerebrovascular, cardiac and peripheral vascular diseases [1]. DN recognized by persistent albuminuria, a progressive decrease in glomerular filtration rate (GFR), hypertension, end stage renal disease (ESRD) and finally, higher cardiovascular morbidity and mortality [2]. Microalbuminuria is considered as the best non-invasive biomarker for the diagnosis of DN [3]. However, it had its limitations, as patients may show a reduction or even loss of glomerular filtration even without the development of albuminuria [4].

Beta-Trace Protein (BTP) and Klotho (KL, originally defined as anti-aging protein) are new elements, showed a promising results as markers of GFR, especially in newborns marker [5,6].

The alpha-KL expressed in high concentrations in the distal convoluted tubule (DCT) with extreme pleiotropic functions [7]. An emerging evidence suggests that the serum soluble α- KL could serve as an early biomarker for chronic kidney disease (CKD) [8].

It has been reported that soluble α-KL were significantly reduced in the early stage of CKD and there was a significant negative correlation between soluble α-KL and reduction of the kidney function [9].

Other studies reported that the upregulation of α-KL had protective effects for the kidneys from different renal insults, preserving the kidney function, and suppressing renal fibrosis [10]. Further study reported that humans with CKD exhibit a marked decrease of α-klotho in their serum [11]. Insulin can increase soluble α-KL concentration through the cleavage and release of the extracellular part of α-klotho [12].

The role of BTP and α-KL as biomarkers of renal injury did not sufficiently addressed. Thus, this study aimed to address the role and compare between serum BTP and soluble α-KL as early predictors and prognostic biomarkers of DN in patients with type-2 diabetes

PATIENTS AND METHODS

This study included 60 patients with confirmed diagnosis of type-2 DM attending the Internal Medicine Outpatient Clinic, Department of Internal Medicine, Al-Azhar University, Damietta, Egypt. In addition, twenty (20) apparently healthy volunteers were recruited as a comparison group.

The diabetic patients were divided into three equal groups according to albuminuria. The A-Group comprised 20 patients who had Type-2 DM (T2DM) with normoalbuminuria (ACR <30mg/g). The B-Group included 20 patients with T2DM with microalbuminuria (ACR between 30 and 300 mg/g). The C-group included 20 patients with T2DM with macroalbuminuria (ACR >300mg/g). The D-Group is the comparison group and included 20 apparently healthy subjects.

Exclusion criteria:

Patients with type-1 DM, infections, systemic disorder, on anti-inflammatory drugs, systemic or topical steroids, alcoholics, diseases affecting urinary protein excretion, and patients had low GFR without microalbuminuria were excluded from the study.

Methods

All the studied persons were subjected to the full history taking, inquiring about the personal data, duration of T2DM, drug therapy, special habits (e.g., smoking, alcohol intake) and other chronic illness. The detailed clinical examination included the measurement of vital signs, general. examination, chest, heart, neurological and abdominal examination, carried out in a systematic manner

The laboratory investigations include complete blood count, fasting and postprandial blood glucose levels, glycated hemoglobin (HbA1c) , C peptide, fasting lipid profile (cholesterol, triglycerides (TGs), low density lipoprotein (LDL), high density lipoprotein (HDL)), renal function assessment (serum creatinine and uric acid), complete urine analysis, urinary albumin to creatinine ratio (ACR), estimated glomerular filtration rate (eGFR) using modification of diet in renal disease (MDRD) formula. The urinary albumin (mg/dl) was measured by ELISA using a morning urine sample. Then, specific measurement of BTP (Human Beta-Trace Protein (BTP) ELISA Kit Cat. No: MBS9908358, MyBioSource Company, San Diego, CA 92195-3308, USA) and α-KL (Catalog Number: MBS702872) from the same company, were measured by ELISA. Finally, abdomino-pelvic ultrasound especially for both kidneys, was performed.

Data analysis:

The collected data was firstly anonymized, coded and fed to personal computer, running by Microsoft Windows 10. All data were of numerical type and thus, were presented by their mean and standard deviation, and sometimes their minimum and maximum. Groups were compared by one-way analysis of variance, with post-hoc least significant differences (LSD) for comparison between each two groups. P value < 0.05 was considered significant.

RESULTS

Table (1) shows comparison between the three studied groups regarding duration of DM. Duration of DM in group B and group C was significantly higher compared to group A (p<0.001). There was no significant difference between the group B and group C regarding duration of DM (p= 0.131). Table (2) compares between the four studied groups regarding kidney function tests. There was a statistically significant difference between the four groups regarding Albumin/ creatinine ratio (p<0.001). There was no significant difference between the four groups regarding serum albumin (p= 0.224), serum creatinine (P =0.253), serum uric acid (p= 0.468) and eGFR (P= 0.102).

Table (3) compares between the four studied groups regarding fasting blood sugar (FBS), two-hours post-prandial blood sugar (2hPPBS), glycated hemoglobin (HbA1c), and C-peptide. There was a statistically significant differences between the four groups regarding fasting blood glucose (p<0.001), two-hours post prandial blood glucose (p<0.001), HbA1c (p<0.001). However, there was no statistically significant difference between the four groups regarding C-Peptide (p= 0.910) and hemoglobin (p= 0.133). Table (4) compares between the four groups regarding lipid profile and electrolytes. There was a statistically significant differences between the four groups regarding triglycerides (p=0.038), HDL (p=0.003), LDL (p=0.038). However, there was no significant differences between the four groups regarding cholesterol (p= 0.06), total calcium (p= 0.858), ionized calcium (p= 0.480) and PO4 (p= 0.379).

Table (5) compares between the four studied groups regarding BTP and soluble α-klotho. There was a statistically significant differences between the four groups regarding BTP (p<0.001), and soluble α-klotho (p<0.001).

Table (1): Comparison between the three studied groups regarding duration of DM

Group		Group A (N= 20)	Group B (N= 20)	Group C (N= 20)	F	P-value
Duration of DM	Mean± SD	4.50± 1.70	6.80± 1.94	7.70± 1.92	15.8	<0.001
	Range	1.0 -7.0	4.0 – 10.0	4.0 – 11.0		
Two-groups comparisons	A-B<0.001		A-C <0.001		B-C=0.131	

Table (2): Comparison between the four studied groups regarding kidney function tests

	A-Group	B-Group		C-Group		D-Group		P-value
Albumin	3.91±0.36	3.82±0.35		3.76±0.44		3.93±0.30		0.224
Creatinine	1.05±0.31	0.96±0.28		0.89±0.36		0.92±0.23		0.253
Uric acid	5.50±1.86	5.42±1.67		4.8±1.5		5.44±1.05		0.468
eGFR	101.3±3.4	100.8±4.4		101.6±4.5		104.8±5.5		0.102
Albumin/creatinine ratio	18.0±4.97	122.05	47.84	381.30	43.61	7.80	1.51	<0.001
Two groups comparison	AD=0.007		B-D <0.001		C-D <0.001		A-B = 0.006	
	A-C < 0.001				B-C = 0.006			

Table (3): Comparison between the four studied groups regarding FBS, PPBS, C peptide and HbA1c

	Group A (N= 20)	*Group B (N= 20)*	*Group C (N= 20)*	*Group D (N= 20)*	*p*	*Two-group Comparison*
FBS	*129.7± 28.9*	*148.4± 41.4*	*171.3± 52.0*	*93.6± 23.6*	*<0.001*	*A-D=0.003; B-D=0.000 C-D=0.001; A-B=0.267 A-C=0.025; B-C=0.259*
2h PP BS	*196.7± 38.4*	*248.7± 55.0*	*266.1± 74.1*	*135.5± 11.13*	*<0.001*	*A-D=0.001; B-D=0.001 C-D=0.001; A-B=0.027 A-C=0.010; B-C=0.718*
HbA1C	*7.24± 0.54*	*8.75± 1.07*	*8.97± 1.53*	*4.83± 0.42*	*<0.001*	*A-D=0.001; PB-D=0.001 C-D=0.001; A-B=0.000 A-C=0.001; B-C=0.496*
C peptide	*2.54± 1.13*	*2.37± 1.00*	*2.31± 1.04*	*2.38± 1.02*	*F= 0.180*	*0.910*
Hemoglobin	*12.22± 1.14*	*12.13± 1.08*	*12.45± 1.03*	*12.83a 1.17*	*F=5.7*	*0.133*

Table (4): Comparison between the four studied groups regarding lipid profile and electrolytes.

	Group A (N= 20)		Group B (N= 20)		Group C (N= 20)		Group D (N= 20)		Test	Two-groups comparison
	Mean	SD	Mean	SD	Mean	SD	Mean	SD		
Cholesterol	166.30± 50.53		175.10± 62.33		197.75± 61.42		151.05± 65.18		F=7.40 P = 0.06	0.06
Triglycerides	168.20± 63.68		176.80± 75.64		194.15± 63.56		134.90± 54.10		F= 2.96 P = 0.038	A-D=0.108; PB-D=0.044 C-D=0.005, A-B=0.675 A-C=0.209, B-C=0.399
HDL	41.12± 10.29		37.32± 8.10		36.40± 8.54		46.35± 9.28		F= 4.95; P = 0.003	A-D=0.073, B-D=0.002 C-D=0.001, A-B=0.190 A-C=0.104, B-C=0.749
LDL	115.85± 40.14		114.20± 52.24		130.20± 52.20		91.20± 54.48		F=8.42; P = 0.038	A-D=0.028; B-D=0.099 C-D=0.006; A-B=0.584 A-C=0.588; B-C=0.276
Total Ca.	9.54	.86	9.41	.81	9.31	.86	9.47	0.75	F=0.766	0.858
Ca-ionized	4.77	.50	4.55	.52	4.59	.58	4.56	0.37	F=2.48	0.480
PO4	4.52	.24	4.56	.28	4.64	.28	4.48	0.20	F=3.08	0.379

Table (5): Comparison between the study groups regarding BTP and soluble α-klotho

		Group A (N= 20)	Group B (N= 20)	Group C (N= 20)	Group D (Control group) (N= 20)	Test	P-value
BTP (pg/ml)	Mean± SD	133.05± 16.37	195.75± 26.49	332.95± 15.63	72.5± 24.45	F=47.0, P < 0.001	A-D=0.006; B-D=0.001 C-D=0.001; A-B=0.007 A-C=0.001; B-C=0.006
	Min.-Max.	115.0 – 165.0	162.0 – 261.0	305.0 – 378.0	35.0 – 109.0		
Soluble α klotho (ng/ml)	Mean± SD	7.33± 0.53	2.14± 0.93	0.15± 0.05	10.21± 0.78	F= 74.1; p <0.001	A-D=0.006; B-D=0.000 C-D=0.006; A-B=0.006 A-C=0.001; B-C=0.006
	Min.-Max.	6.50 – 8.20	0.50 – 3.60	0.08 – 0.24	9.0 – 11.6		

DISCUSSION

DN is a critical etiology of the CKD and frequently leads to ESRD [13]. α-KL, an anti-aging substance as described for the first time. However, subsequently it is found to have an important pleotroic actions on the kidneys [14]. Patients with CKD had significant reduction the α-klotho in the early stages of the CKD, with progressive decrease with advancement of the disease stages [15].

BTP known is a novel low-molecular weight glycol-protein [16] being investigated as a biomarker of GFR. It is advantageous over serum creatinine as Cystatin-C, being independent of subject demographics and shows an increased sensitivity, chiefly in the creatinine blind range [17]. It is upregulated in cases of increased glomerular permeability due to lesions affecting the capillaries of glomeruli capillary lesion. Urinary excretion of BTP can be used as a biomarker of kidney damage as it may detect renal injury earlier than albuminuria [18].

This study aimed to compare between serum BTP and soluble α- KL as early predictors and prognostic markers of DN in patients with T2DM. The comparison between the three studied groups regarding duration of DM showed that duration of DM in group B and group C was significantly higher compared to group A. There was no statistically significant difference between the group B and group C regarding gender. In harmony with our results the study by **Lee EY *et al.*** [19] reported that there was statistically significant difference between the three sub-groups regarding duration of DM.

In addition, the study by **Kadoos *et al.*** [20] reported that there was statistically significant difference between the

studied groups regarding duration of DM.

In contrast to our results, **Lamacchia *et al.*** [21] reported that the duration of DM was comparable in both microalbuminuria and normoalbuminuria groups. This disagreement due to the variation in sample size and main characteristics.

The current results of blood pressure are supported by **Lamacchia *et al.*** [21] who compared patients with albuminuria 676 (48.5%), with the remaining 719 (51.5%) patients having normoalbuminuria renal impairment. And reported that both SBP and DBP were significantly higher in microalbuminuria group in comparison to normo-albuminuria group. However, the study by **Lee EY *et al.*** [19] reported that there was statistically significant difference between the three sub-groups regarding SBP while DBP had non-significant difference.

Also, the study by **Fountoulakis *et al.*** [22] reported that the SBP was non-significantly higher in residual albuminuria group in comparison to Normoalbuminuria.

Regarding the severity of albuminuria was determined according to the ACR ratio so it was predictable that ACR was significantly differed between the studied groups. However, the study by **Kadoos *et al.*** [20] reported that macroalbuminuric patients were significantly associated with the highest serum creatinine and the lowest GFR.

Results regarding lipid profile are comparable to the study by **Mohammed *et al.*** [23] intended to compare the usefulness of serum values of BTP for the discovery of renal dysfunction in chronic kidney disease. They compared these values with the values of the other renal markers (creatinine and cystatin C). They enrolled 150 patients, who were divided into three groups with a wide range of renal dysfunction that included chronic kidney disease stages from (I-IV). The studied groups showed statistically significant differences as regard age and sex. Also, the study by **Yang *et al.*** [24] showed significant differences between normoalbuminuria, microalbuminuria and macroalbuminuria regarding serum creatinine and eGFR. This disagreement could be explained by the variation in sample size and sample characteristics.

In line with our results, the study by **Lee EY *et al.*** [19] reported that there was significant difference between the three sub-groups regarding Hemoglobin and HbA1c.

In agreement with our results **Lamacchia *et al.*** [21] reported that s HbA1c was significantly differed in micro-albuminuria group in comparison to normo-albuminuria group.

Also, **Kadoos *et al.*** [20] aimed to assess whether sKlotho predicts estimated glomerular filtration rate (eGFR) decline in patients with type 2 diabetes mellitus (T2DM) with relatively preserved renal function is unknown.

Our results regarding BTP were supported by **Wang *et al.*** [25] who concluded that a significant proportional correlation had been found between soluble α-Klotho and eGFR in patients with chronic kidney disease. However, there was a significant inverse correlation between α-Klotho and FGF23 levels. These finding raises the hope to use α-Klotho and FGF23 as biomarkers of chronic kidney diseases with high sensitivity and specificity. It is dramatically decline with different stages of chronic kidney disease and disturbance of CKD mineral metabolism.

Also, our results were in line with **Ohiri *et al.*** [18] who reported that BTP showed a significant increase at the start of the study among 80.0% of diabetic patients with median values of 410 ng/ml when compared with healthy subjects, with median of 200 ng/ml. BTP at a cutoff of 260 ng/ml is a good test for the diagnosis of DN, as the area under curve (AUC) was 0.848 and 95% confidence interval (CI) of 0.726–0.969. the sensitivity was 80.0%, Specificity 80%and the positive predictive value was 91.4%, while negative predictive value was 50%. After 3 months, BTP significantly increased in DM group to 440 ng/ml, and increased in controls to 275 ng/ml. Values of BTP at 3 months, were positively correlated with blood urea in diabetics (r=0.321, P=0.043).

We can summarize that soluble α klotho was negatively correlated with BTP in all groups and both of them was significantly correlated with Albumin/creatinine ratio. This suggesting the capacity of these markers to be used as early predictors of DN in patients with type 2 DM.

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