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Research Article

Role of Beta Trace Protein and Cystatin C as a Potential Biomarker for Early Detection of Type 2 Diabetic Nephropathy

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ABSTRACT

Background: One of the most well-known diabetic microvascular consequences is diabetic nephropathy, which affects 40 percent of people with diabetes mellitus type 2. It develops into end stage renal disease, and diabetes biomarkers can be used as a predictor.
Objectives: This study aimed to determine the concentration levels of serum Beta Trace Protein and serum Cystatin C in all stages of diabetic nephropathy disease.
Subjects And Methods: A Case- control study included 120 Persons (30-persons appeared healthy as control and 90 patients proved with T2DM of both gender (64 males and 56 females), split into four groups by using urinary micro-albumin and albumin to creatinine ratio (UACR) as following: group-I: includes 30persons as a healthy control (UACR < 30 mg/g creatinine). Group-II: includes 30patients with type2 DM normoalbuminuria (UACR < 30 mg/g creatinine) as a positive control. Group-III: includes 30 patients with type 2 DM microalbuminuria (UACR 30 – 300 mg/g creatinine). Group-IV: includes 30 patients with type 2 DM macroalbuminuria (UACR> 300 mg/g creatinine), all groups with ages ranges between (40-69) years. in all groups, Beta Trace Protein and Cystatin C quantitative enzyme immunoassay (double-antibody sandwich), calculated in serum and both biomarkers using the same methods.
Results: Patients with diabetes have statistically substantially increased blood levels of Beta trace protein and Cystatin C. with macro-albuminuria groups in comparison to micro-albuminuria, normo-albuminuria and healthy control in addition, the mean for the micro-albuminuria group was greater than for the healthy control and normo-albuminuria groups.
Conclusion: A rise in blood Beta trace protein and Cystatin C levels in the early nephropathy group microalbuminuria, which may be used as a predictor for early diagnosis of diabetic nephropathy.

Introduction

Diabetes mellitus (DM) is an endocrine and metabolic disease that has a serious impact on people's health (1). One of the most prevalent microvascular issues of diabetes is diabetic nephropathy (DN), which affects 40 percent of individuals with type 2 diabetes. Diabetes biomarkers can be utilized to detect it before it progresses into end-stage renal disease (ESRD) (2).

Beta trace protein is a monomeric glycoprotein containing 168 amino acids that is also known as lipocalin type prostaglandin D2 synthase(L-PGDS), and it has a low molecular weight (23–29 KD) (3). From cerebral fluid, Beta trace protein was largely extracted as prostaglandin D2 synthase (4). Beta trace protein be regarded as a protein with two roles: First, BTP functions as an enzyme in the formation of PGD2, which is crucial for maintaining vascular Function, BTP transforms prostaglandinH2 (PGH2) into prostaglandin D2(PGD2) (5), and second, because of its lipophilic character, BTP also functions as an extracellular transporter after being secreted. Beta trace protein levels have since been determined in a variety of tissues, comprising stomach tissue, proximal tubules, a loop of Henle, skin melanocytes, arachnoid cells, vascular endothelial cells, and the glomerulus (6). Beta trace protein has a half-life of around 1.2h and is nearly eliminated by the kidneys. Because of its stability, regular production rate, and low molecular mass (7).

Cystatin C (Cyst C) is a 13 KDa low-molecular weight protein that acts as an endogenous inhibitor of lysosomal cysteine proteinases and has been linked to both pathological and normal processes. Cystatin C is continuously produced by all nucleated cells, unaffected by variables like food and muscle mass (8).

The aim of this study is to evaluate the levels of serum BTP and serum Cystatin C in all stages of diabetics nephropathy disease.

Subjects and Methods

A Case-control study included of 120 Persons (30-person apparently healthy control and 90 patients proved with T2DM of both gender genders (64 males and 56 females), there are 90 samples of patients Type2 Diabetes Mellitus (T2DM) at duration 5-19 years of the diagnosis of diabetes was split into four groups ׀by using proteinuria and UACR as following: group-I: includes 30 persons as a healthy control (U׀ACR < 30 mg/g creatinine). group-II: includes 30 patients with type 2 DM normoalbuminuria (׀UACR < 30 mg/g creatinine) as a control. group-III: includes 30 patients with type 2 DM microalbuminuria (UACR 30 – 300 mg/g creatinine) and group-IV: includes 3\0 patients׀ with type 2 DM macroalbuminuria׀(UACR > 300 mg/g creatinine). Collected during the period from January to September 2022. ׀Patient's eligible for inclusion: Patients with T2DM who have had the disease for more than five years of the occurrence of diabetes. patient exclusion standards: patients with cardiovascular disease (CVD) were excluded, less than five years' duration of type 2 diabetes, pregnancy, and acute infections.

Ethical approval All subjects gave their informed consent for inclusion before they participated in the study. The study was approved by the ethics committee of Chemistry Department, College of Sciences, University of Çankiri Karatekin, Turky.

Estimation of Glomerular filtration rate GFR formulary developed by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI), as in table 1.

Blood samples ranging from 5 to 7 ml were obtained from both healthy individuals and T2DM patients. dividing each blood sample into two parts:

A) The initial portion of whole blood is kept in EDTA tubes for measurement HbA1c by Cobas C311.

B) The second part samples of blood were kept at room temperature for 30 minutes, allowing samples to clot in plain tubes. serum was separated by centrifugation at 3000 rpm for 10 minutes following coagulation. In Eppendorf tubes, serum was aspirated and split into two aliquots for: Aliquot1: measurements of serum Creatinine, serum Urea, serum Cholesterol, serum Triglycerides and High-density lipoprotein. The experiment was conducted utilizing Cobas C311. Aliquot2׀: The rest were stored׀ at (< -35C°) until assayed for Serum Beta Trace׀ Protein (BTP). Was measured׀ using enzyme-linked׀ immunosorbent׀ assay (ELISA) by device HumaReader HS.

Five to ten milliliters (ml) of freshly collected morning urine samples were placed in a clean, dry container. Utilizing the Dimension EXL 200 integrated chemistry system evaluated basic urine testing that covers Urine Albumin/Creatinine Ratio, Microalbumin.

Statistical analysis: To evaluate patient data, SPSS version 26.0 was used. The results cleared as (mean ± SD), the mean, standard deviation, and standard error were tabulated as descriptive statistics. The (ANOVA) test was used to assess how the mean levels of the numerical data varied, and the Chi-square test was employed to examine the relationship between the qualitative variables. regression using Pearson correlation When evaluating the correlation between numerical data (r) was employed; values below 0.2 indicate weak correlation, between 0.2 and 0.8 show moderate connection, and over 0.8 indicate significant correlation. To display the correlation between the variables, scattered dot diagrams were utilized. P value 0.05 was regarded as significant.

Table 1: CKD׀-EPI equations for eGFR Cr

equations
CKD-EPI equations for eGFRCr. (9).
eGFRCr = 141 × min (S.Cr/ κ, 1) α × max (S.Cr/ κ, 1)-1.209 × 0.993age (× 1.018 if female) (× 1.159 if black)"
Abbreviations / Units
"Scr = standardized׀ serum creatinine in mg/dL; divide׀ by 88.4, for creatinine in μmol/L, κ = 0.7 (females) or 0.9 (males), α = -0.241 (female׀) or -0.302 (male), min(Scr/κ, 1) is the minimum׀ of Scr/κ or 1.0, max(Scr/κ, 1) is the maximum of Scr/κ or 1.0, age (years)".

Results

Patients and healthy control: included 120 subjects from both sexes (female and male), which is the into four groups according׀ to their (UACR׀). the clinical׀ characteristics of the four study groups statistically significant difference was shown in the table (2). Participant were divided׀ into four groups according׀ to Albumin Creatinine Ratio (ACR) and HbA1c, the mean ± SD difference of S. Cys C and S. BTP between the 4 groups was assessed using ANOVA test. That is a statistically significant difference in mean ± SD level of S. Cyst. C between the groups (p< 0.001), macroalbuminuria have a significantly greater than microalbuminuria and normoalbuminuria all in compare to healthy control, that is a statistically significant

difference in mean ± SD level of S. B-TP between the groups ($p< 0.001$), macroalbuminuria have statistically significantly greater S. BTP in compare to microalbuminuria and normoalbuminuria all in compare to healthy control , as presented in table (2).

Table 2: Clinical characteristic of parameters in all studied groups

Clinical Variables		Group I (n=30) Non diabetics (Control)	Diabetics (N=90) Group II (n=30) (Normo)	Group III (n=30) (Micro)	Group IV (n=30) (Macro)	P-value*
Age (years)	M±SD	51.133 ± 8.215	52.166 ± 8.034	54.766 ± 8.736	55.333 ± 5.797	0.001
	SE	1.499	1.466	1.595	1.058	
BMI (Kg/m^2)	M±SD	25.154 ± 2.344	27.010 ± 2.775	28.300 ± 2.641	28.027 ± 4.024	0.001
	SE	0.427	0.506	0.482	0.734	
Duratio Diabetic	M±SD	-	5.700 ± 0.836	8.266 ± 1.048	12.733 ± 2.958	0.001
years	SE	-	0.152	0.191	0.540	
SBP (mmHg)	M±SD	130.300 ± 4.332	140.70 ± 4.878	145.00 ± 6.581	150.566 ± 4.074	0.001
	SE	0.790	0.890	1.201	0.743	
DBP (mmHg)	M±SD	81.033 ± 4.230	84.333 ± 4.887	88.100 ± 4.171	91.233 ± 3.530	0.001
	SE	0.772	0.892	0.761	0.644	
S. Chol. (mg/dl)	M±SD	184.300±10.181	189.933±7.995	192.70±10.389	196.166 ± 9.577	0.001
	SE	1.858	1.459	1.896	1.748	
S. Tg. (mg/dl)	M±SD	92.866 ± 4.826	152.500±5.940	182.333±6.864	206.866 ± 8.528	0.001
	SE	0.881	1.084	1.253	1.557	
HDL (mg/dl)	M±SD	61.533 ± 4.621	57.100 ± 4.513	55.400 ± 4.047	52.633 ± 4.278	0.001
	SE	0.843	0.823	0.739	0.781	
HbA1c%	M±SD	5.366 ± 0.332	6.896 ± 0.547	8.143 ± 0.636	9.846 ± 1.362	0.001
	SE	0.060	0.099	0.116	0.248	
S. Cre. (mg/dl)	M±SD	0.761 ± 0.061	0.800 ± 0.082	0.870 ± 0.081	1.257 ± 0.160	0.001
	SE	0.011	0.015	0.014	0.029	
S. Urea (mg/dl)	M±SD	33.633 ± 3.547	35.166 ± 3.733	38.166 ± 2.320	47.633 ± 6.950	0.001
	SE	0.647	0.681	0.423	1.268	
ACR (mg/g)	M±SD	16.893 ± 2.670	18.206 ± 3.299	123.406±23.19	339.016±19.773	0.001
	SE	0.487	0.602	4.234	3.610	
eGFR Cr. (ml/min)	M±SD	99.966 ± 6.954	96.813 ± 4.707	86.440 ± 5.050	56.776 ± 5.971	0.001
	SE	1.269	0.859	0.922	1.090	
BTP (pg/ml)	M±SD	617.066±68.182	692.56±33.713	797.63±44.446	991.866±82.985	0.001
	SE	12.448	6.155	8.114	15.151	
Cys. C (ng/ml)	M±SD	133.068±19.146	142.84±20.608	180.35±17.198	272.065±40.510	0.001
	SE	3.495	3.762	3.140	7.396	

Table 3: The correlation between Beta Trace Protein and Cystatin-C in three diabetics groups

Correlations				
Group	**Variable**	**R** / Pvalue	**BTP**	**Cys. C**
Normoal	BTP pg/ml	R	1	-0.193
		Pvalue		0.308
	Cys. C ng/ml	R	-0.193	1
		Pvalue	0.308	
Micro	BTP pg/ml	R	1	0.322
		Pvalue		0.082
	Cys. C ng/ml	R	0.322	1
		Pvalue	0.082	
Macro	BTP pg/ml	R	1	0.095
		Pvalue		0.616
	Cys. C ng/ml	R	0.095	1
		Pvalue	0.616	

Table 4: ROC test for all groups

All Groups					
Variable	**AUC**	**Cut off value**	**p-value**	**Sensitivity**	**Specificity**
BTP	0.963	698.00	0.001	84.4 %	100 %
Cys. C	0.875	165.80	0.001	68.9 %	100 %

Using the Pearson correlation coefficient, the relationship between S. BTP and S. Cys C. in the three diabetics groups was evaluated. there was no statistically significant association between the markers in normoalbuminuria, microalbuminuria and macroalbuminuria groups, according in table (3). To evaluate B-TP and Cys-C in detection of all gruops, (ROC) test was used, figure (1). All markers had excellent (AUC), BTP (0.963), Cys. C (0.875), Cut of value of BTP (698), Cys. C (165.80), higher sensitivity of BTP (84.4 %), Cys. S (68.9 %) and higher specificity of BTP (100 %), Cys. S (100 %), as presented in Table (4).

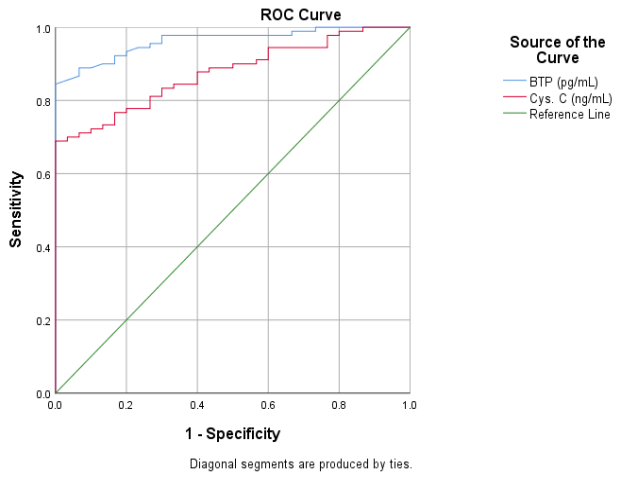

Figure 1: ROC diagram of Beta trace protein and Cystatin C to detect all groups.

Discussion

Diabetes can be linked to a variety of illnesses. If left untreated, it might eventually result in major health problems like heart disease, vascular disease, kidney disease, and even blindness (10). Because the development of chronic kidney disease requires significant time and resources, is expensive, and negatively affects a person's quality of life, researchers have focused their attention on early type 2 diabetes nephropathy detection.

The majority of diabetic people will eventually acquire renal dysfunction (11). Diabetic kidney Disease DKD, a microvascular complication that is currently the world's leading cause of CKD and ESRD, develops in almost half of those with T2DM and one-third of those with T1DM (12).

The duration of diabetes has an impact on diabetic nephropathy in the long term, which leads to renal failure. As some researchers have shown, this may lead to serious health problems including heart disease, vascular disease, renal disease, and even blindness if not treated. most of the patients with the diabetic disease will develop renal disease, approximately half of the individuals with T2DM development to DKD, a microvascular complication that is now the leading cause of CKD and ESRD of the world (12). Type 2 diabetes is one of the main causes that lead to the end stage of renal failure, as it leads to cirrhosis and loss of nephron functions (13, 14).

High blood pressure is the second leading cause of renal failure. There are several mechanisms common to DM and HT, such as abnormal activations of the angiotensin aldosterone system, excessive production of reactive oxygen species, activation of the sympathetic nervous system and abnormal handling of renal sodium, over time, uncontrolled high blood pressure can cause the arteries around the kidneys to narrow, weaken, or harden. These damaged arteries are unable to deliver enough blood to the kidney tissues (15).

The table 2 show statically significantly level of serum cholesterol and serum triglyceride (Mean ± SD) in normalbumin, microalbumin and microalbumin groups compared to the healthy control group respectively. On the other hand, the serum level of HDL-C was significantly lower in the normalbumin (Mean ± SD), microalbumin and macroalbumin group than in the healthy control group. This result is consistent with other studies on dyslipidemia in diabetic patients (16), There is no statically significant difference in serum concentration of cholesterol, triglycerides and HDL-C levels between the groups including diabetic patients in the three groups, a result that is not consistent with what has been demonstrated in previous studies (17), High levels of bad cholesterol and low levels of good cholesterol in the body may lead to its accumulation in vessels that carry blood in and out of the kidneys, affecting the kidneys' ability to do their job efficiently, and making more likely to develop high blood pressure and diabetes.

The HbA1c levels in diabetic patients, studies showed a significant difference in microalbuminuria in patients with microalbuminuria compared with normal albuminuria reason for this is cumulative evidence, however, diabetic nephropathy is closely associated with poor glycemic control (17).

Glomerular Filtration Rate is an important clinical investigation utilized to monitor renal function decline. Routine annual surveillance is recommended for all diabetic patients to monitor the progression and rate of decline of renal function. GFR are proposed as the best indicators of kidney function, with low GFR being associated with a high risk of kidney failure (18).

A study involving diabetic and healthy control groups found that the eGFR rate in the control group was higher (due to the absence of renal dysfunction) than the diabetic group patient which is identical to the present study which found a statistical difference in the rate of eGFR between the healthy control and diabetic groups (19).

The role of both Serum Beta Trace Protein and Cystatin C as early diagnostic markers for Diabetic Nephropathy was studied. In this study, laboratory chemical measurements were made, all of which are shown in table (2).

The results indicated that there were significant differences between all studied parameters in patients' groups compared to control. the serum level of cystatin C was high in group of macro albuminuria comparable to microalbumiuria group as well as to normoalbuminuria group and healthy control P value (0.001).

There is a study that showed that the levels of Cystatin C may be a sign of damage or early kidney failure among patients with type 2 diabetes (20). suggesting that cyst-C may play major role in development of nephropathy in prediabetes and the study demonstrated also that the blood cyst- C level in the patient groups was statistically significantly higher than the usual level (normoalbuminuria, microalbuminuria and macroalbuminuria) (21).

In line with previous research, individuals with T2DM had statistically significantly higher serum cystatin C concentrations. Cystatin C concentration rises when nephropathy worsens in people with type 2 diabetes (22).

Another study found that the levels of the protein cystatin C in the serum were higher in the diabetic group in comparison to the control group, and this distinction was statistically significant for a sizeable portion of the diabetic individuals. Consequently, it can be utilized to detect diabetic kidney damage early (23). Serum cystatin C was shown to be a measure of renal function in a different investigation. the prevalence of diabetic nephropathy was greater in patients with high serum cystatin C levels than those with non-diabetic nephropathy (24). All of these studies suggest to cystatin C as a viable biomarker for type 2 diabetics' early DN (25).

The serum Beta Trace Protein (BTP) level as shown in the table (2), where high in the macroalbumin group, compared with the other groups, microalbumin, normalbumin and healthy control, P value (0.001).

All this confirms that the biomarker Beta trace protein is good in early diagnosis of DN[1], as confirmed in a previous study and there are other study according to a research done by Motawi, showed that type 2 diabetes (T2D) CKD patients with microalbuminuria had greater serum BTP levels than those with normoalbuminuria, pointing to the possibility that BTP may be used an early predictor of diabetic nephropathy. (26). Also, there are studies, that found higher S.BTP levels in diabetic than control groups related to renal dysfunction in a T2DM patient in which S.BTP clearance is restricted by the kidneys. A statistically significant rise is seen in the early stages of the condition because the elevated levels of S.BTP in the blood and urine correspond closely with the decrease in glomerular filtration in CKD patients (5, 19). According to a recent study, S. BTP levels in diabetic patients with nephropathy were statistically significant higher, and the rise was more severe in the microalbuminuria, group than the normoalbuminuria group (2).

Serum Beta-trace protein was shown to have greater sensitivity and specificity than Cys. C in the normoalbuminuria, microalbuminuria and macroalbuminuria groups, as well as in all groups, according to table (4). Considering these findings, S. BTP is now more efficient than S. Cys. C in detecting early diabetic nephropathy.

As nephron damage increases, these biomarkers' concentrations change, correlating with the progression of renal insufficiency. Due to their low molecular weight (both the diagnostic markers beta-trace protein and cystatin-c), most of these resulting biomarkers are filtered through the glomerulus and reabsorbed into the proximale tubule. if the renal tubules are damaged, the reabsorption of biomarkeres decreases while their production by epithelial cells increases, which subsequently leads to an increase in their levels in the blood and urine.

Conclusion

A rise in the blood levels of BTP and Cyst-C in the early nephropathy group microalbuminuria may be regarded as a predictor for the early identification of diabetic nephropathy (DN). Also, BTP is more sensitive than Cys-C, as a marker for the prediction of nephropathy in patients with (type2 DM). This is true in the microalbuminuria group. Therefore, these biomarkers are promising biomarkers for the detection of diabetic nephropathy in the early stages.

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Conflict of Interest

Authors declare no conflict of interest.

Data availability

Data are available upon reasonable request.

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