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Beta-Trace Protein as a Marker of Chronic Kidney Disease - A Case Control Study

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Abstract
Introduction: Chronic Kidney Disease (CKD) encompasses a spectrum of different pathophysiologic processes associated with abnormal kidney function and a progressive decline in Glomerular Filtration Rate (GFR). Because of limitations of creatinine as a biomarker of GFR, new alternative biomarkers are being investigated, such as low molecular weight proteins. **Aim:** To estimate the levels of Serum Beta-Trace Protein in patients with CKD and to compare them with normal subjects. **Methodology**: It is a case control study conducted for a period of one year. A total of 100 subjects were selected. (50 cases with CKD and 50 age and gender matched healthy individuals). Student's t-test was employed for statistical analysis. **Results:** Beta-Trace Protein concentrations were found to be significantly increased in patients with CKD (mean 52.24 ± 29.6) when compared to control (mean 33.86 ± 12.1). Serum BTP increases as renal function declines and inversely correlated with Creatinine clearance (r = - 0.765). Serum creatinine and blood urea were progressively increased in cases than controls and shows positive correlation with BTP (r = 0.630 and r = 0.721) respectively. **Conclusions:** Serum BTP levels are significantly increased in patients with CKD. Serum BTP is more precise and accurate marker than serum creatinine in detecting renal dysfunction.

Keywords: Beta-Trace Protein, Glomerular filtration rate, Chronic kidney disease

Introduction

Chronic Kidney Disease (CKD) encompasses a spectrum of different pathophysiologic processes associated with abnormal kidney function and a progressive decline in Glomerular Filtration Rate (GFR).CKD is defined as either kidney damage or a glomerular filtration rate (GFR) of less than 60mL/min/1.73 m^2 for 3 or more monthsirrespective of the cause[1].CKD is a growing public health problem with increasing incidence and prevalence rates, poor outcomes, and high healthcare costs. Usually, CKD is a progressive disease leading to end-stage renal disease (ESRD), complications of decreased renal function, cardiovascular disease, and premature death.

CKD is an international public health problem affecting about 5- 10% of the population and the expected incidence every year is approximately 5-8%[2]. Incidence of CKD is increased two-fold in the last 15 years globally. The reported global annual growth of number of ESRD patients is 7%. It is an underestimate of the disease because most of the CKD patients die of CVD than to reach ESRD. CKD is the 12th cause of death and 17th cause of disability worldwide[3]. Approximate prevalence of CKD in Delhi is 7852 per million population and the incidence of ESRD is 785 per million (10% of total CKD.) DM has emerged as the most frequent cause (30-40%) followed by Hypertension (14-22%)[4].

Risk factors and predictors for CKD progression include ethnicity, type of renal disease, and modifiable risk factors, such as blood pressure, proteinuria, smoking, dyslipidaemia, obesity, and anaemia, as well as exposure to nephrotoxins and baseline kidney function[5].

One of the prominent criteria for the diagnosis of CKD is decreased GFR value (< 60 mL/min/1.73m2). GFR is widely accepted as the best index of kidney function. The normal value in young adult men and woman is approximately 125 mL/min/1.73m2. Values below 15 mL/min/1.73m2 indicate kidney failure and the person can be identified as a candidate for dialysis or renal replacement therapy/kidney transplantation[6].To define CKD, the GFR should be below 60ml/min/1.73m2 because it represents over a 50% reduction in kidney function as compared to the level for young healthy adults.

Because of limitations of creatinine as a biomarker of GFR, new alternative biomarkers are being investigated, such as low molecular weight proteins. Different low-molecular-weight proteins (LMWP), with a molecular weight in the range 10–25 kDa, have renal handling compatible with that of an "ideal" marker of GFR. In fact, they are cleared by the plasma through free glomerular filtration, subsequent complete tubular resorption, and degradation inside tubular cells. As a consequence, their serum concentrations increase progressively with the reduction of GFR. Furthermore, age, gender, and body composition have a low influence on serum concentrations of LMWP[7].

Due to this behaviour, the measurement of serum concentrations of various LMWP has been proposed as a useful tool for evaluating an impairment of GFR, possibly more sensitive than serum creatinine[7].Beta-trace protein (BTP) is a glycosylated LMWP, primarily isolated as lipocalin-type prostaglandin D2 synthase from cerebrospinal fluid. It is freely filtered through the glomerular basement membrane and almost completely excreted via kidneys. Serum BTP concentration is not associated with C-reactive protein and inflammation.[8]This marker is not changed by body composition changes and it reflects GFR status in the third trimester of pregnancy.

Its serum concentration is unaffected by thyroid function and corticosteroid administration and it is a better GFR marker in new-borns than creatinine and cystatin C.[9] Because of its low molecular mass, its constant production rate and its stability, BTP has been proposed as a new endogenous marker of glomerular filtration rate[10].

Hence in the present study, the serum levels of beta-trace protein are estimated in patients with different stages of CKD and aims to assess its utility as an early biomarker of CKD.

Aim & Objectives

The objectives of the study were

1. To estimate the serum level of Beta-Trace Protein in patients with chronic kidney disease
2. To correlate the serum Beta-Trace Protein level with serum creatinine and Creatinine clearance
3. To evaluate the correlation between serum Beta-Trace Protein level and other several known risk factors such as Blood pressure, Random blood sugar and blood urea.

Materials & Methods

It is a case control study conducted at a tertiary care hospital for a period of one year from April 2017 to April 2018 after getting approval from the ethical committee (No.360 dated 01.03.2017). A total of 100 subjects were selected for the study which includes 50 cases with CKD from the outpatients and wards of the Nephrology Department and 50 age and gender matched healthy individuals were selected as control. Student's t-test was employed for statistical analysis. **Inclusion criteria**: Patients with established diagnosis of CKD and age greater than 18 years were included in the study.**Exclusion criteria**: Patients with primary tubular diseases, recent or concurrent administration of potentially nephrotoxic drugs, acute kidney injury, terminal kidney failure requiring dialysis, patients with known neurological disease were all excluded from the study. After obtaining informed consent, under aseptic precautions, 5ml of venous blood sample was collected after an overnight fasting of 12 hours from all subjects. After retraction of the clot, samples were centrifuged at 2000rpm for 15 minutes for separation of serum.Serum was taken for the estimation of Beta-Trace Protein by Enzyme immunoassay method. Serum Creatinine was estimated by Modified and normal level of creatinine is 0.7 to 1.4 mg/dL.Blood Urea was estimated by Urease –Glutamate Dehydrogenase (GLDH) method and normal level of urea is 13 to 45 mg/dL. Glucose was estimated by glucose-oxidase/ peroxidase method. The normal random blood glucose level is 65-100 mg/dL and normal post prandial blood glucose is 90-140 mg/dL.

Statistical Analysis

Student t-test was employed for the statistical analysis of data. The data were expressed in terms of mean and standard deviation. 'p value < 0.05 was taken as the significant value. Correlation between the measured parameters was assessed using Pearson's correlation coefficient.

Results

A total of 100 subjects were selected as the study group for the study. This includes 50 cases with Chronic Kidney Disease and 50 age matched healthy controls.Serum Beta-Trace Protein concentrations were found to be significantly increased in patients with Chronic Kidney Disease (mean 52.24 ± 29.6) when compared to the control group (mean 33.86 ± 12.1) as shown in [Table/Fig-1].Serum creatinine and blood urea were progressively increased in cases than controls and shows positive correlation with Beta-Trace Protein (r = 0.630 and r = 0.721) respectively which is depicted in [Table/Fig-2].Serum Beta-Trace Protein increases as renal function declines and inversely correlated with Creatinine clearance (r = - 0.765) as shown in [Table/Fig-3,5].

Random Blood Sugar is significantly higher in cases (116 ± 39.8) than in controls (93.94 ± 6.97) and it shows strong positive correlation (r =0.700) with Beta-Trace Protein, indicates Chronic Kidney Disease is prevalent in diabetes mellitus [Table/Fig-6,7]. Blood pressure were significantly higher in cases than controls which indicates Chronic Kidney Disease is more prevalent in hypertension [Table/Fig-6,7].

Table 1. Comparison of S. BTP among cases and controls

T-TEST			
S. BTP(ng/ml)	**MEAN**	**SD**	**Statistical Inference**
Control (n=50)	33.86	12.1	p value < 0.001
Cases (n=50)	52.24	29.6	Significant

Table 2. Comparison of S. Creatinine among cases and controls

T-TEST			
S.Creatinine(mg/l)	**MEAN**	**SD**	**Statistical Inference**
Control (n=50)	0.89	0.13	p value < 0.001
Cases (n=50)	4.7	2.5	Significant

Table 3. Comparison of Creatinine clearance among cases and controls

T-TEST			
Ccr(ml/min)	**MEAN**	**SD**	**Statistical Inference**
Control (n=50)	115.13	8.6	p value< 0.001
Cases (n=50)	43.32	12.8	Significant

Table 4. Comparison of Blood urea among cases and controls

T-TEST			
Urea(mg/dl)	**MEAN**	**SD**	**Statistical Inference**
Control (n=50)	37.5	4.82	p value< 0.001 Significant
Cases (n=50)	60.7	40.15	

Table 5. Comparison of serum btp in the study group in relation to creatinine clearance

Creatinine Clearance (ml/min)	**BTP (ng/ml)**	
	Mean	**S.D.**
60-90 (n=5)	26.6	5.2
30-59 (n=37)	53.51	20.1
15-29 (n=6)	72.1	8.1
<15 (n=2)	147	2.8

Table 6. Comparison of RBS, SBP, DBP among cases and controls

T-TEST				
		Mean	**SD**	**Statistical Inference**
RBS (mg/dl)	Control (n=50)	93.94	6.97	p value < 0.001
	Cases (n=50)	116.96	39.8	Significant
SBP (mm/Hg)	Control (n=50)	118	8	p value<0.001
	Cases (n=50)	130	26.03	Significant
DBP	Control (n=50)	78	4.46	p value<0.001

(mm/Hg)	Cases (n=50)	84	11.14	Significant

Table 7. Karl Pearson Coefficient correlation between serum BTP and other parameters in cases

Parameters	**Correlation Coefficient (R)**	**Correlation**
Creatinine	0.630	Correlated
Ccr	-0.765	Correlated
Urea	0.721	Correlated
Random Blood Sugar	0.700	Correlated
Systolic blood pressure	0.009	Not Correlated
Diastolic blood pressure	0.046	Not Correlated

Discussion

Chronic kidney disease is a clinical syndrome that occurs when there is a gradual decline in renal function over time[11]. Early detection and treatment are needed to prevent progression to kidney failure and complications such as coronary vascular disease[12]. The definition of CKD is "Kidney damage for ≥ 3 months, as defined by structural or functional abnormalities of the kidney with or without decreased GFR manifested by either Pathological abnormalitiesor markers of kidney damage including the abnormalities in the composition of the blood or urine or abnormalities in imaging tests"[13,14]. It is also defined as Glomerular filtration rate < 60ml/min/1.73 m^2 for ≥3 months with (or) without kidney damage[15].

End Stage Renal Disease is defined as either GFR<15ml/min/1.73m^2 (or) a need to start Renal Replacement Therapy either in the form of dialysis (or) renal transplantation[16]. Most of the CKD patients will progress to ESRD and they require dialysis or kidney transplantation. Till date standard test to detect Chronic Kidney Disease is serum creatinine[17,18.] However measurement of creatinine is a crude marker, detecting changes in renal function only when there is 50% reduction in GFR.

In the present study serum Beta-Trace Protein concentrations were found to be significantly increased in patients with Chronic Kidney Disease (mean 52.24 ± 29.6) when compared to the control group (mean 33.86 ± 12.1). When patients in different stages of Chronic Kidney Disease were compared, serum Beta-Trace Protein levels were found to be progressively increased from stage 3 to stage 5. This observation shows that serum Beta-Trace Protein increases as renal function declines and inversely correlated with Creatinine clearance (r = - 0.765).

Serum creatinine and blood urea were progressively increased in cases than controls and shows positive correlation with Beta-Trace Protein (r = 0.630 and r = 0.721) respectively. Random Blood Sugar is significantly higher in cases (116 ± 39.8) than in controls (93.94 ± 6.97) and it shows strong positive correlation (r =0.700) with Beta-Trace Protein, indicates Chronic Kidney Disease is prevalent in DM. Blood pressure were significantly higher in cases than controls which indicates Chronic Kidney Disease is more prevalent in hypertension[19]. Unlike serum creatinine, Beta-Trace Protein are unaffected by muscle mass composition. Earlier studies have shown that Beta-Trace Protein is a more suitable marker of GFR because of less extra renal interferences[19,20].

Thus Serum Beta-Trace Protein is more precise and accurate marker than serum creatinine in detecting renal dysfunction.When patients in different stages of Chronic Kidney Disease were compared, serum Beta-Trace Protein levels were found to be progressively increased from stage 3 to stage 5. This observation shows that serum Beta-Trace Protein increases as renal function declines and inversely correlated with Creatinine clearance (r = - 0.765). Earlier studies have shown that Beta-Trace Protein is a more suitable marker of GFR because of less extra renal interferences.[21,22]

BTP is emerging as an alternate marker in cases of mild renal impairment and in cardiovascular risk cases. Role of BTP in stabilization of atherosclerotic plaque and the protective role of BTP under hypoxia and ischemia have been studied.[23] Thus, Serum Beta-Trace Protein is more precise and accurate marker than serum creatinine in detecting renal dysfunction.

Conclusions

The present study demonstrated that serum Beta-Trace Protein levels are significantly increased in patients with Chronic Kidney Disease. This increase in serum Beta-Trace Protein level is progressive from stage 3 to 5, as renal function declines. It is more precise and accurate marker than serum creatinine in detecting renal dysfunction. Thus Beta-Trace Protein can be used as a novel biomarker in the diagnosis of Chronic Kidney Disease.

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