Correlation of Beta Trace Protein Levels with Serum Creatinine-Based Estimated Glomerular Filtration Rate Equations in Chronic Kidney Disease

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ABSTRACT

Background. Estimated GFR (eGFR) is calculated using serum creatinine (SCr) based equations which have their own limitations. Novel biomarkers like beta trace protein (BTP) are studied for eGFR estimation. The aim of this study is to determine the serum levels of BTP in healthy controls and chronic kidney disease (CKD) cases and to find out the correlation of BTP levels with that of SCr and SCr-based eGFR formulas.

Methods. The control group comprised of 20 healthy adults. The cases comprised of 20 patients each in CKD stages 3, 4, and 5, categorized based on eGFR calculated using MDRD formula. Baseline characteristics of the study population were recorded. BTP was measured by ELISA (Enzyme Linked Immunosorbent Assay) method and SCr by modified Jaffe's method. The statistical analyses were performed with the SPSS for Windows, version 16.0.

Results. The median value of blood urea nitrogen (BUN) in the cases was 26.50 mg/dL (IQR 19.25-37) and for control it was 9.5 mg/dL (IQR 8-12). The median value of SCr in the cases was 2.75 mg/dL (IQR 1.725-4.45) and in the controls, it was 0.7mg/dL (IQR 0.6 -0.8). The median value of BTP in cases was 6389.25 ng/ml (IQR 5610.875-10713.75) and in controls, it was 1089.5 ng/ml (IQR 900.5-1309.75).

Conclusion. Serum BTP levels correlated with SCr levels and renal function. We could establish the relationship between the two biomarkers, SCr and BTP, and derive a regression equation.

KEYWORDS: Beta trace protein, estimated GFR, CKD, correlation

Introduction

Any structural or functional abnormalities of the kidneys that persist beyond 3 months irrespective of the etiology is defined as chronic kidney disease (CKD) [1]. In clinical practice, renal function is assessed indirectly using serum creatinine (SCr) values and SCr-based glomerular filtration rate (GFR) equations. The 'gold standard' for GFR estimation, the inulin clearance cannot be used routinely, because of the difficult and cumbersome nature of the procedure. Serum cystatin C based equations have also been recently developed [2, 3]. Notable equations are Cockroft-Gault formula, Chronic Kidney Disease Epidemiology (CKD-EPI) equation and Modification of Diet in Renal Disease Study (MDRD) equation [4, 6]. However, each equation has its own inherent limitations such as a lack of accuracy, precision, and variations with ethnicity [7, 8].

Factors such as protein intake and muscle mass determine SCr levels. Due to lower muscle mass, SCr levels are lower in women and in older individuals. SCr level has a curvilinear relationship with GFR because of its tubular secretion in mild-to-moderate degrees of renal failure. A SCr value of 1.5 mg/dl could represent a GFR of anywhere between 30-90 ml/min. Such wide range of eGFR is not acceptable and hence, SCr-based assays are not considered ideal. The need for better biomarkers need not be overemphasized.

Beta Trace Protein (BTP) is a monomeric low-molecular-weight glycoprotein with 168 amino acids. The molecular mass of BTP is estimated to be between 23000 and 29000 daltons. It depends on N-glycosylation at three positions in its structure. BTP mRNA is expressed in the choroid plexus, pachymeninges, and oligodendrocytes. BTP synthesis occurs in testes, epididymis, and heart in small quantities. The elimination of BTP is by glomerular filtration. It is reabsorbed by the proximal tubular cells and actively degraded within the lysosomes. The t- 1/2 of BTP is about 1.2 hours [9, 12].

Hence, BTP-based GFR equations could mitigate the limitations of SCr-based equations for GFR estimation. No studies on correlation of serum BTP levels with SCr-based eGFR are available yet from South Asian population.

Methods

This study was done as a cross-sectional study at Sri Ramachandra Institute of Higher Education and Research (SRIHER), after obtaining Institutional ethics committee clearance (Ethics Reg No: CSPMED/19/NOV/57/170). Informed consent in written form was obtained from all study participants prior to this study.

The control group was comprised of 20 healthy male and female adults. The 'cases' group comprised of 20 patients each in CKD stages 3, 4, and 5. The CKD stages were categorized based on eGFR calculated using MDRD formula. Baseline characteristics of the cases and controls such as age, gender, body mass index (BMI), and blood pressure were recorded. Based on the SCr levels, eGFR was estimated for both the cases and controls using existing formulae, MDRD and CKD-EPI. Blood pressure was measured using aneroid sphygmomanometer.

Renal failure patients of > 18 years of age in CKD stages 3, 4 and 5, who visited nephrology outpatient department were recruited for this study. Controls were healthy males and females who had attended master health check-up facility in the hospital. The study excluded paediatric and adolescent population, pregnant women and transplant recipients. A venous blood sampling was carried out by trained phlebotomist.

The quantitative estimation of urea was determined by Kinetic UV / Urease – GLDH method. The quantitative estimation of SCr was determined by modified Jaffe's method. Both the assays were done in Beckman Coulter AU 5800 and AU 680 Automated Clinical Chemistry Analyzers. BTP was

assayed by immunometric (sandwich) ELISA from Cayman chemicals – Prostaglandin D synthase lipocalin type human ELISA kit, Item no: 10007684.

Statistical analyses

The statistical analyses were performed with the Statistical Package for the Social Sciences (SPSS) statistical software package for Windows, version 16.0. Shapiro-Wilks test was used as test for normality. Mean and standard deviation were calculated for the age and BMI. Independent sample-t test was performed and a two-tailed 'p' value of < 0.05 was considered statistically significant. For parameters such as BUN, SCr, MDRD equation based eGFR, CKD-EPI equation based eGFR, serum BTP levels, systolic and diastolic BP that followed non-normal distribution, median and interquartile range (IQR) were calculated. Mann-Whitney U test and Kruskal-Wallis test were used for parameters of non-normal distribution and 'p' value of < 0.05 was considered statistically significant. One way ANOVA was performed for parameters of normal distribution and 'p' value of < 0.05 was considered statistically significant. Correlation analysis between BTP and BUN, Creatinine, MDRD eGFR, CKD-EPI eGFR, SBP and DBP was done by Spearman correlation in the study cohort and 'p' value of < 0.001 was considered statistically significant.

Results

This study cohort (n=80) included 48 males (60%) and 32 females (40%). The mean age of controls was 40.3±10.702 years and that of CKD cases was 55.53±15.285 years (p <0.05). The mean BMI of controls was 25.150±3.618 kg/m^2 and that of cases was 26.88±5.297 kg/m^2 (p 0.407). The median and IQR for systolic blood pressure (SBP) in the cases was 140 mm Hg (IQR 130 -140) and in the controls was 110 mm Hg (IQR 100-110). The median diastolic blood pressure (DBP) in the cases was 80 mm Hg (IQR 80-90), and in the controls it was 70 mm Hg (IQR 70-80). The blood pressure was significantly higher in all stages of CKD when compared to the control group (p <0.001).
The median value and IQR of BUN in the cases was 26.50 mg/dL (19.25-37) and in the controls was 9.5 mg/dL (8-12). The median value of SCr in the cases was 2.75 mg/dL with IQR (1.725-4.45), and in the controls it was 0.7 mg/ dL (IQR 0.6 – 0.8). The median value of eGFR using MDRD equation for cases was 23.950 ml/ min/1.73m^2 (IQR 12.825-37.5), and for controls it was 105.6 ml/ min/1.73 m^2 (IQR 100.8-115.875). Median value of GFR estimated using CKD-EPI for cases was 23.5 ml/min/1.73m^2 (IQR 12-38.5) and for controls, it was 112.5 ml/min/1.73m^2 (106.25-116.5) (Table I). BUN and SCr were significantly increased in the cases than in controls, as expected (p < 0.001). MDRD eGFR and CKD-EPI eGFR were significantly decreased in the cases than in controls (p <0.001).

Parameter	CKD (n=60)	Control (n=20)	*p-value*
BUN (mg/dL)	26.50 (19.25-37)	9.5 (8-12)	<0.001**
Creatinine (mg/dL)	2.75 (1.725-4.45)	0.7 (0.6-0.8)	<0.001**
MDRD eGFR (ml/min/1.73m^2)	23.950 (12.825-37.5)	105.6 (100.8-115.875)	<0.001**
CKD-EPI eGFR (ml/min/1.73m^2)	23.5 (12-38.5)	112.5 (106.25-116.5)	<0.001**

Table I. Comparison of BUN, Creatinine, MDRD eGFR, and CKDEPI eGFR between chronic kidney disease patients (CKD group) and control group (normal healthy individuals).
Data represented as median with interquartile range. Comparison done via Mann-Whitney U test. *Statistically significant (p<0.05) * *Statistically significant (p<0.001)

The median value and IQR of BTP in 'cases' were 6389.25 ng/ml (5610.875-10713.75), and in controls it was 1089.5 ng/ml (900.5-1309.75). Serum BTP levels were significantly increased in all CKD stages when compared with the control group (p <0.001) (Table II).

Parameter	CKD (n=60)	Control (n=20)	*p*-value
BTP (ng/ml)	6389.25 (5610.875-10713.75)	1089.5 (900.5-1309.75)	<0.001**

Table II. Comparison of Beta trace protein (BTP) between chronic kidney disease patients (CKD group) and control group (normal healthy individuals).
Data represented as Median with interquartile range. Comparison done via Mann Whitney U test. *Statistically significant (p<0.05) * *Statistically significant (p<0.001)

The parameters were compared among groups CKD 3, CKD 4, CKD 5, and control group. Normal distribution was seen for parameters BMI, BTP, MDRD eGFR and CKD-EPI eGFR. Non-normal distribution was seen for parameters age, BUN, SCr, SBP and DBP. The median and IQR of BUN in CKD Stage 3 group was 19.5 mg/dl (15.25-22.5), in CKD Stage 4 group was 26 mg/dL (19.5-32), in CKD Stage 5 group was 38.5 mg/dL (34.25 -45) and in control was 9.5 mg/dL (8-12). The values are statistically significant, ($p < 0.001$) as calculated by Kruskal-Wallis test. BUN levels were significantly higher in all stages of CKD when compared with the control group. There was significant difference between stage 3 and stage 5 CKD cohorts, but significance was not demonstrated between stage 3 and stage 4, and stage 4 and stage 5 groups. The median and IQR of SCr in CKD stage 3 group was 1.6 mg/dL (1.4-1.775), in CKD stage 4 group was 2.75 mg/dL (2.43-3.15), in CKD stage 5 group was 5.2 mg/dL (4.35 – 5.775), and in control group it was 0.7 mg/dL (0.6-0.8). The values are statistically significant, ($p < 0.001$) as calculated by Kruskal-Wallis test. SCr levels were significantly higher in all stages of CKD when compared with the control group. There was significant difference in SCr levels between CKD stage 3 and 5 and also between CKD stage 4 and 5. There was no significance seen between stage 3 and stage 4 CKD cohorts.
The mean BMI of CKD stage 3 group was 27.24 ± 5.13 kg/m^2, CKD stage 4 group was 27.63 ± 6.32 kg/m^2, CKD stage 5 group was 25.77 ± 4.33 kg/m^2, and in control group it was 25.82 ± 3.62 kg/m^2. There was no statistical significance among the groups for BMI. The mean MDRD eGFR of CKD stage 3 group was 42.86 ± 7.42 ml/ min/1.73m^2, CKD stage 4 group was 22.84 ± 4.37 ml/ min/ 1.73m^2, CKD stage 5 group was 10.41 ± 2.63 ml/ min/1.73m^2, and in control group it was 107.25 ± 8.88 ml/min/1.73m^2. The mean CKD-EPI eGFR of CKD stage 3 group was 45.8 ± 9.73 ml/min/1.73m^2, CKD stage 4 group was 23.75 ± 4.62 ml/ min/1.73m^2, CKD stage 5 group was 10.3 ± 2.56 ml/min/1.73m^2, and in control group it was 112.35 ± 8.29 ml/min/1.73m^2. There was statistical significance among the groups for eGFR by MDRD and CKD-EPI equations. The mean BTP levels of CKD stage 3 was 5222.33 ± 900.15 ng/ml, CKD stage 4 was 6234.23 ±575.31 ng/ml, CKD stage 5 was 11628.3 ± 1695.39 ng/ml, and in control group was 1130.35 ± 314.42 ng/ml. BTP levels were significantly higher in the CKD groups when compared to the control group. BTP levels were significantly higher in CKD stage 5 when compared to CKD stage 3 and CKD stage 4. BTP levels were significantly higher in CKD stage 4 when compared to CKD stage 3 (Table III).

Parameter	CKD3 (n=20)	CKD4 (n=20)	CKD 5 (n=20)	Control (n=20)	*p-value*
BMI (Kg/m^2)	27.24 ± 5.13	27.63 ± 6.32	25.77 ± 4.33	25.82 ± 3.62	0.522
MDRD eGFR (ml/min/1.73m^2)	42.86 ± 7.42	22.84 ± 4.37	10.41 ± 2.63	107.25 ± 8.88	<0.001**
CKD-EPI eGFR (ml/min/1.73m^2)	45.8 ± 9.73	23.75 ± 4.62	10.3 ± 2.56	112.35 ± 8.29	<0.001**
BTP (ng/ml)	5222.33 ± 900.15	6234.23 ± 575.31	11628.3 ± 1695.39	1130.35 ± 314.42	<0.001**

Table III. Comparison of BMI, MDRD eGFR, CKD-EPI eGFR and BTP among the groups CKD stage 3, CKD stage 4, CKD stage 5 and control group. ***Data represented as Mean ± standard deviation (SD). Comparison done by One way ANOVA test. *Statistically significant (p<0.05) * *Statistically significant (p<0.001).***

The correlation analysis between BTP and BUN, SCr, MDRD eGFR and CKD-EPI eGFR was done by Spearman correlation in the study cohort (n=80) (Table IV). In the correlation analysis between BTP and BUN, the correlation coefficient (R-value) was 0.835, implying a positive correlation between the two parameters. The correlation was statistically significant (p <0.001). The correlation coefficient (R-value) for correlation analysis between BTP and SCr was 0.917 with p<0.001, implying a statistically significant positive correlation between these two parameters. In the correlation analysis between BTP and eGFR based on MDRD equation, the correlation coefficient (R-value) was –0.913 (p<0.001) and R-value for BTP and eGFR based on CKD-EPI equation was –0.909 (p<0.001). This showed a statistically significant negative correlation between eGFR based on MDRD equation and eGFR based on CKD-EPI equation with BTP.

Regression Equation

Using SCr values and BTP levels, we could establish the relationship between the two biomarkers and derive a regression equation.

$$\text{Serum creatinine} = 0.014 + 0.422 \times \text{BTP} / 1000$$

BTP scores over serum creatinine values in CKD stages 3, 4, and 5. BTP detects CKD (stage 3 and above) above the cut-off of 2818.5 ng/ml when compared to SCr (Figure 1).

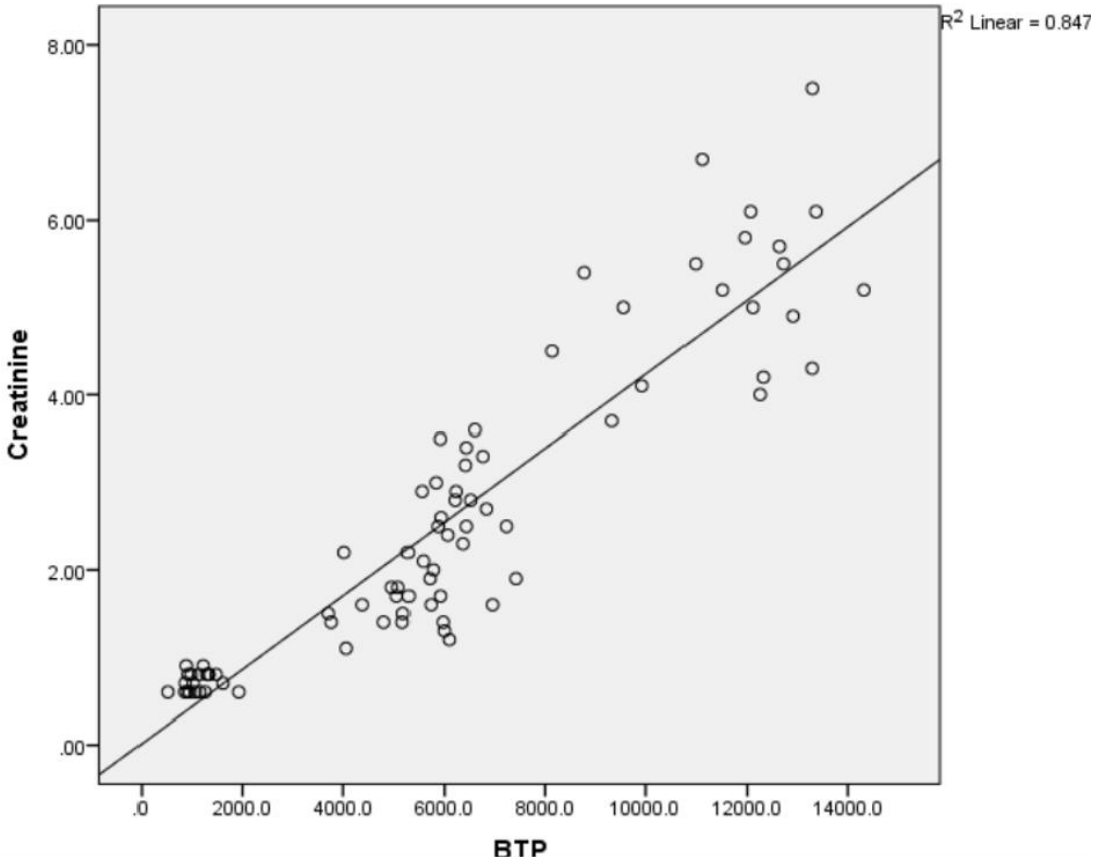

Figure 1. Linear regression analysis between serum creatinine and BTP.

Discussion

Low-molecular-weight-proteins such as BTP and beta-2 microglobulin (B2M) are recently studied as new endogenous markers for GFR estimation [9, 12]. BTP has been investigated for assessment of GFR in adult and paediatric population.

Pöge et al. developed eGFR equations from 85 adult kidney transplant recipients with mean age of 50 years and mean GFR 39 ml/min/1.73 m^2. They developed two equations, which required SCr and blood urea levels in addition to BTP levels [13].

$$GFR1 = 89.85 \times BTP^{-0.5541} \times urea^{-0.3018}$$

$$GFR2 = 974.31\times BTP^{-0.2594} \times \text{serum creatinine}^{-0.647}$$

In another similar study, White et al. developed two GFR estimation equations from 163 adult kidney transplant recipients with mean age of 53±12 years and mean GFR of 59±23 ml/min/1.73 m^2. Male population constituted 67% and whites 90% in this study cohort. They included a correction factor for females in their equation [14].

$$GFR1 = 112.1 \times BTP^{-0.662}\times urea^{-0.280} \times (0.880 \text{ if female})$$

$$GFR2 = 167.8 \times BTP^{-0.758} \times \text{serum creatinine}^{-0.204} \times (0.871 \text{ if female})$$

Bhavsar et al. studied the role of BTP for predicting hypertensive CKD progression to ESRD in African Americans. They compared BTP levels and cystatin C with measured GFR using iothalamate clearance. 246 individuals reached ESRD and at the end of follow-up period of 102 months, it was demonstrated that BTP levels fared better in predicting ESRD when compared to other markers [15]. In a similar study by Katharina-Susanne Spanaus et al. in primary nondiabetic CKD, the investigators demonstrated that the diagnostic performance of all three biomarkers – SCr, serum cystatin C, and serum BTP levels – for detecting even minor degrees of deterioration of renal function was good. The study was done in 177 patients with 7 years follow-up. All 3 markers provided similar risk prediction for progression to CKD [16]. Foster et al. demonstrated that the use of multiple biomarkers improves risk prediction in individuals with moderate CKD. Serum levels of BTP and B2M might contribute in predicting additional risk information beyond conventional eGFR equations. The study was prospective cohort study, which included 3,613 adults from the Chronic Renal Insufficiency Cohort (CRIC) study. The mean age of the study cohort was 57.9 years. Females constituted 45%, diabetics 51.9% and non-Hispanic Blacks 41% of the study cohort [17].

Clinical investigations did not establish the superiority of BTP over conventional markers consistently. Natalie Ebert et al. in their study in 566 elderly (more than 70 years of age) participants concluded that BTP did not outperform serum creatinine and cystatin C levels in estimating GFR [18]. Karin Werner et al. demonstrated the superiority of GFR estimation using combined SCr and serum cystatin C levels over GFR estimation done using BTP and B2M levels. They concluded this from their validation study in 126 elderly participants aged between 72 years and 98 years with a mean measured GFR (mGFR) of 54 ml/min/1.73 m^2. The mGFR was done using iohexol clearance [19].

Studies similar to those carried out in adults using BTP for GFR estimation were conducted in children by Abbinkwt al., Benlarmi et al., and Witzel et al. [20, 22]. It is to be noted that none of these BTP based equations have been validated in a large sample size for GFR estimation. Hence, clinicians still rely on SCr and SCr-based eGFR equations.

Measurement of BTP is done by nephelometric method or by ELISA [23]. Published studies on BTP have used mostly nephelometry-based assays. Bhavsar et al. in their study on the role of BTP for predicting hypertensive CKD progression used nephelometric assay for BTP estimation. [15] Nephelometric BTP estimation was also used by Katharina Susanne Spanaus et al. in primary nondiabetic CKD, where the investigators demonstrated that the diagnostic performance of all three biomarkers – SCr, serum cystatin C, or serum BTP – for detecting even minor degrees of deterioration of renal function was good [16]. The same nephelometric BTP assay was used by Lesley A. Inker and his colleagues when estimating GFR using BTP and B2M in CKD and dialysis population [24]. Natalie Ebert et al. and Karin Werner et al. used the same techniques for BTP estimation in their studies [18]. In our study, BTP levels were estimated using ELISA.

There was a significant positive correlation between BUN and SCr with BTP levels. Hebaha et al. have also reported a positive correlation among these parameters in their prospective cohort study comprising 40 Type II Diabetes mellitus patients and 10 controls [22]. Significant negative correlation between MDRD eGFR and CKD-EPI eGFR with BTP was seen in our study (Table IV).

Parameter	Correlation coefficient (R-value) with BTP	*p-value*
BUN	0.835	<0.001**
Creatinine	0.917	<0.001**
MDRD eGFR	-0.913	<0.001**
CKD-EPI eGFR	-0.909	<0.001**

Table IV. Correlation analysis between Beta trace protein (BTP) and BUN, Creatinine, MDRD eGFR and CKD-EPI eGFR. Spearman correlation; Correlation coefficient expressed as R-value. *Statistically significant (p<0.05) * *Statistically significant (p<0.001)

Although several studies on GFR estimation using serum BTP levels had been done in the West, no studies are available from South Asia. Even studies demonstrating the correlation between SCr and SCr-based eGFR with serum BTP levels are not yet available. This might be due to the fact that 'normal' values of BTP are not yet arrived and the values obtained from the studies have not been validated in a larger population to be accepted universally.

Our study has several advantages. To our knowledge, this is the first study of BTP level estimation using ELISA method in an Indian population. In our study, BTP levels correlated well with SCr levels and SCr-based eGFR formulas in CKD. We could derive a regression equation using SCr and BTP levels. Hence, serum BTP levels may be a useful and reliable biomarker for identifying the magnitude of renal dysfunction in CKD patients.

The main limitation of our study is that it is a single centre study and study population were only from Indian ethnicity. BTP levels were assayed by ELISA method only. BTP estimation using nephelometry in addition to ELISA technique would have added more value to the study.

Having demonstrated the correlation of BTP with SCr and SCr-based eGFR formulas, we recommend validating this study findings in a larger cohort. Development of an eGFR formula using BTP levels with or without SCr, cystatin C and B2M could be attempted. BTP can also be studied as a biomarker for adverse clinical outcomes including cardiovascular diseases in early stages of CKD [25]. Urinary BTP levels and its correlation with early GFR impairment in cases of acute kidney injury (AKI) and CKD could be explored in the future [26].

Conclusion

Serum BTP levels, estimated by ELISA correlates with SCr levels and renal function. As the renal function deteriorates in advanced stages of CKD, there is corresponding increase in serum BTP levels. A relationship between the two biomarkers, SCr and BTP was established and a regression equation was derived. BTP detects CKD (stage 3 and above) above the cut-off of 2818.5 ng/ml when compared to SCr. Serum BTP levels could be superior to SCr levels in diagnosing CKD in stages 3 to 5. Serum BTP is a potential biomarker for GFR estimation and could overcome the limitations of SCr-based eGFR equations.

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