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Assessment of correlation between serum βTP and cystatin C as biomarkers for the detection of early nephropathy in Iraqi patients with type 2 diabetes

Aya Yassin Taher
Department of Clinical Biochemistry, College of Medicine, University of Baghdad, Iraq
Email: aya.yassin1209f@comed.uobaghdad.edu.iq

Mohammed Hannon Alsodani
Ass. Professor, Consultant Nephrologists, Department of Medicine, College of Medicine, University of Baghdad, Iraq

Hedef D. El-Yassin
Department of Clinical Biochemistry, College of Medicine, University of Baghdad, Iraq

***Abstract*---**Background: Diabetic nephropathy (DN) is one of the most well-known diabetic microvascular complications, affecting around 40% of individuals with type 2 diabetes mellitus (T2DM). It progresses to end-stage renal disease (ESRD), and its primary detection can be done via diabetes biomarkers. The power of early biomarker identification of DN in T2DM serum is evaluated in this study. Aim: This study aimed to assess the possibility of using BTP and Cys. C as earlier markers for the detection of nephropathy in patients with type 2 DM. Materials and Methods: This is a cross-sectional study. It included one hundred twenty patients with T2DM, composed of 66 males and 45 females, and aged 40–69 years, who were divided into 3 groups by using the urinary albumin/creatinine ratio (ACR): Group I: (N = 40 Normoalbuminuria UACR < 30 mg/g as control), Group II: (N = 40 Microalbuminuria UACR 30–300 mg/g), Group III: (N = 40 Macroalbuminuria UACR > 300 mg/g). In all groups, βTP and Cys. C were estimated in the serum of patients, and both biomarkers had the same methodology by quantitative enzyme immunoassay (double-antibody sandwich). Results: There was a statistically significant difference in the mean level of BTP and cystatin C between the groups. The macro-albuminuria groups showed a statistically higher BTP (34.94 ± 3.14 µg/ml) in comparison to micro-albuminuria (22.48 ±

6.02 µg/ml) and normo-albuminuria (9.33 ± 3.06 µg/ml), p 0.00, and the micro-albuminuria groups had a higher mean of BTP in comparison to normo-albuminuria, p 0.00. The macro-albuminuria groups showed a statistically higher Cys. C (291.96 ± 66.12 ng/ml) in comparison to micro-albuminuria (193.64 ± 30.75 ng/ml) and normo-albuminuria (138.23 ± 17.86 ng/ml), p 0.00. The micro-albuminuria groups had a higher mean of Cys. C in compared to normo-albuminuria, p 0.00. Conclusion: Serum βTP in diabetic patients with type 2, can be considered a valuable biomarker for early detection of DN.

***Keywords*---**βTP, Cystatin C, Diabetic Nephropathy, Type 2-diabetes mellitus.

Introduction

Diabetes mellitus (DM) is the most prevalent metabolic condition, with an annual rise that is quickly increasing throughout the world **(1)**. Diabetic Nephropathy is one of the most major diabetic MICRO complications, affecting up to 40% of patients with type 2 diabetes and potentially leading to End-Stage Renal Disease (ESRD), increasing the morbidity and mortality of T2DM patients **(2)**.

Beta trace protein (βTP) also, called lipocalin-type prostaglandin D2 synthase (L-PGDS), It is a monomeric glycoprotein with 168 amino acids and low-molecular-weight glycoprotein (23-29 KD) depending on the degree of glycosylation **(3)**. βTP is a novel endogenous marker of glomerular filtration rate (GFR). First described in 1961, it was noted to be increased in the serum of patients with renal disease in 1997 **(4)**. Beta-trace protein (BTP) was primarily isolated as prostaglandin D2 synthase from cerebrospinal fluid **(5)**. can be considered a protein with a double function: **first**, βTP acts as an enzyme in the production of PGD2 by βTP which converts Prostaglandin H2 (PGH2) into Prostaglandin D2 (PGD2) and plays an essential role in the maintenance of vascular function **(6)**. and **second**, after being secreted, βTP acts as an extracellular transporter due to its lipophilic nature. Since then, βTP levels were measured in other tissues like arachnoid cells, vascular endothelial cells, skin melanocytes and gastric tissue, proximal tubules, a loop of Henle and glomerulus as well **(7)**. Serum and urine BTP levels may be elevated in patients with renal impairment **(8)**. It has also been detected in serum, urine, amniotic fluid, and seminal plasma **(9)**. The half-life of BTP is approximately 1.2 hours and it is almost completely excreted via the kidneys. 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)**. studies suggest age, muscle mass, gender, ethnicity, serum albumin levels, urine protein excretion and body weight may have an effect on BTP serum concentrations **(11)**.

The βTP is an emerging marker of GFR, several studies have documented βTP strong association with GFR, ESRD, CVD and death in a variety of different patient populations. On the other hand, the studies investigating Serum βTP as a reliable biomarker of renal dysfunction in T2DM are still very scarce **(12)**. Also,

there is a lack of data on the value of serum βTP in different stages of nephropathy in T2DM patients **(13)**. Cystatin C is a is a low-molecular weight protein with a molecular mass of 13 KDa, is produced by all nucleated cells at a constant rate, unaffected by such factors as muscle mass and diet **(14)**. Cystatin C (Cyst C) is an endogenous inhibitor of lysosomal cysteine proteinases, which has been shown to play a role in several normal and pathological processes **(15)**. it is directly and freely filtered through the glomerulus with complete tubular reabsorption and catabolization, no reabsorption into the bloodstream, and no renal tubular secretion. As such, CysC is regarded as a good filtration marker **(10)**. Numerous studies have validated serum Cystatin C may be considered as an early marker than microalbuminuria and serum creatinine, the commonly used marker for nephropathy, for declining renal function, in diabetic subjects **(16)**. This study aimed to assess the possibility of using BTP and Cys. C as earlier markers for the detection of nephropathy in patients with type 2 DM.

Materials and Methods

This cross-sectional study included 120 patients with T2DM, 66 males and 54 females, with an age range of 40–69 years. During the period between November 2021 and February 2022, the study has approval from the ethical committee at the Faculty of Medicine, Baghdad University. Informed consent was taken from each participant. Also, permission to do the research was obtained for outpatients by the consultation unit of the diabetes consultant in Baghdad Teaching Hospital/Medical City.

Patient's criteria for inclusion: Iraqi patients with T2DM at duration more than 5 years of the occurrence of diabetes.

Patient criteria for exclusion: Excluded patients with CVD, Duration of type 2 DM less than 5 years, pregnancy, acute infections, tumors.

Quantitative parameters

Anthropometric measurement included age, gender, weight, height, and body mass index (BMI), eGFR (by using the formulary of chronic kidney diseased epidemiological collaboration (CKD-EPI).

eGFRcr = 141 × **Min** (**S. Cr/ k**, 1) $^{\alpha}$ × **Max** (**SCr/ k**, 1)$^{1.209}$ × 0.993^{Age} [× 1.018 **if female**] or [× 1.159 if **black**]

where S. Cr is serum creatinine in (mg/ dL), k is 0.7 for females and 0.9 for males, α is -0.3 for females and -0.411 for males, Min is the minimum of S. Cr/ k or 1 and Max is the maximum of S. Cr/k or 1

About 6 ml of blood samples were taken from patients for measuring HbA1c, S. Cr, S. Urea, serum BTP and Serum Cystatin C. The biomarkers (βTP and Cystatin C) were measured using ELISA technique. About (5-10 ml) of freshly morning urine samples were collected in clean and dry container, by using Urinalysis Hybrid FUS-3000Plus tested general urine examination which includes Protein, Microalbumin, urine Alb/Cr. Ratio. All patient (N=120) was divided into three groups by using proteinuria, microalbuminuria test and urinary Albumin to Creatinine Ratio (UACR): Group I: UACR < 30 mg/g creatinine, (N = 40 T2DM with Normoalbuminuria as control); Group II: UACR 30–300 mg/g creatinine, (N = 40

T2DM with Microalbuminuria), Group III: UACR > 300 mg/g creatinine, (N = 40 T2DM with Macroalbuminuria).

Statistical analysis

Data of patients were analyzed using SPSS version 25.0 software. Descriptive statistics were tabulated as mean, range, stander deviation, frequency and percentage. ANOVA test was used to evaluate the difference in mean level of numeric data, Chi-square test used to test association between qualitative variables. Pearson correlation regression r was used to evaluate correlation between Numeric data, when r < 0.2 indicate week correlation, 0.2-0.8 indicate moderate correlation, > 0.8 indicate strong correlation. Scattered dot diagrams were used to show correlation between the variables. p value was <0.05 considered significance.

Results

One hundred twenty patients were enrolled in this study. The mean age was 52.25 ±7.254, 50% of them were 41-50 years old, 35.8% were 51-60 years old, and 45% were female, 55% were male. Of the patients, 82.5% had the disease between 5 and 10 yrs., with a mean of 8.52 ± 3.295. The mean HbA1c of participants was 8.525± 1.787 and 61.7% had good glycemic control. The mean BMI was 28.684 ± 4.548 kg/cm^2 and 40.8% were overweight and 36.7% were obese. The mean of urea, s. creatinine, and eGFR were 39.503 ± 17.515 mg/dl, 0.927 ± 0.380 mg/dl, 88.046 ± 21.083 mL/min/1.73 m^2, respectively. Details are shown in Table 1.

A Statistically significant difference in mean of eGFR between the groups (p 0.00), macro-albuminuria groups show a statistically lower eGFR (68.030 ± 20.72) in compare to micro-albuminuria (94.480 ± 14.22) and normo-albuminuria (101.62 ± 9.05), p 0.009, also micro-albuminuria group had lower mean of eGFR in compare to normo-albuminuria, p 0.00, as presented in table 2, statistically significant difference in mean level of BTP between the groups (p 0.00), macro-albuminuria groups show a statistically higher BTP (34.94 ± 3.14 µg/ml) in compare to micro-albuminuria (22.48 ± 6.02 µg/ml) and normo-albuminuria (9.33 ± 3.06 µg/ml), p 0.00, also micro-albuminuria group had higher mean of BTP in compare to normo-albuminuria, p 0.00, And a statistically significant difference in mean level of cystatin C between the groups (p 0.00), macro-albuminuria groups show a statistically higher Cys. C (291.96 ± 66.12 ng/ml) in compare to micro-albuminuria (193.64 ± 30.75 ng/ml) and normo-albuminuria (138.23 ± 17.86 ng/ml), p 0.00, also micro-albuminuria group had higher mean of Cys. C in compare to normo-albuminuria, p 0.00, as presented in table 2. The correlation between BTP, Cys C and eGFR in the three group was assessed using Pearson correlation coefficient.

No statistically significant correlation between the markers in normo-albuminuria groups. Regarding microalbuminuria group, BTP had a statistically significant positive moderate correlation with Cystatin C (r 0.53, p 0.00). Regarding macro-albuminuria group, BTP had a statistically significant positive moderate correlation with and Cystatin C (r 0.47, p 0.00), as presented in table 3.

Table 1: The clinical characteristic of included participant

Variables		N (%)	Mean ± SD (SE)
Age	≤40 yrs.	1 (0.8%)	52.25 ±7.254
	41-50 yrs.	60 (50.0%)	(0.662)
	51-60 yrs.	43 (35.8%)	
	>60 yrs.	16 (13.3%)	
Gender	Female	54 (45.0%)	/
	Male	66 (55.0%)	
Duration of disease	5-10 yrs.	99 (82.5%)	8.52 ± 3.295 (0.301)
	more than 10 yrs.	21 (17.5%)	
HbA1c	excellent glycemic control	22 (18.3%)	8.525± 1.787 (0.163)
	good glycemic control	74 (61.7%)	
	poor glycemic control	24 (20.0%)	
BMI	normal BMI	27 (22.5%)	28.684 ± 4.548 (0.415)
	Overweight	49 (40.8%)	
	Obese	44 (36.7%)	
Urea			39.503 ± 17.515 (1.598)
s. creatinine			0.927 ± 0.380 (0.034)
eGFR			88.046 ± 21.083 (1.92)

Table 2: The mean difference of BTP and Cys C between the 3 groups

		Mean ± SD	SE	Range	p †	p ††	p †††	p ††††
eGFR	Normo	101.62 ± 9.05	1.4321	80.9-118.1	0.009*	0.00*	0.00*	0.00*
	Micro	94.480 ± 14.22	2.2485	57.6-116.4				
	Macro	68.030 ± 20.72	3.2769	15.0-94.9				
	Total	88.046 ± 21.08	1.9246	15.0-118.1				
BTP	Normo	9.33 ± 3.06	0.48	5.16-39.12	0.00*	0.00*	0.00*	0.00*
	Micro	22.48 ± 6.02	0.952	10.612-40.03				
	Macro	34.94 ± 3.14	0.497	30.911-42.99				
	Total	22.25 ± 6.06	0.958	5.167-42.998				
Cys C	Normo	138.23 ± 17.86	2.824	102.10-190.53	0.00*	0.00*	0.00*	0.00*
	Micro	193.64 ± 30.75	4.86	156.34-				

			280.40
Macro	291.96 ± 66.12	10.45	195.57-473.68
Total	207.94 ± 76.95	7.025	102.10-473.68

*p-value ≤ 0.05, p-value † between Normo-albuminuria and micro-albuminuria, p-value †† between Normo-albuminuria and Macro-albuminuria, p-value ††† between micro-albuminuria and Macro-albuminuria, p-value †††† between all the groups

Table 3: The correlation between BTP, Cys C and eGFR in the three groups

Correlations					
Type			BTP	Cys C	eGFR
Normo-albuminuria	BTP	Pearson Correlation	/	-0.192	-0.255
		p-value		0.235	0.112
	Cys C	Pearson Correlation	-0.192	/	-0.124
		p-value	0.235		0.446
	eGFR	Pearson Correlation	-0.255	-0.124	/
		p-value	0.112	0.446	
micro-albuminuria	BTP	Pearson Correlation	/	0.537**	0.134
		p-value		0.000	0.411
	Cys C	Pearson Correlation	0.537**	/	-0.071
		p-value	0.000		0.663
	eGFR	Pearson Correlation	0.134	-0.071	/
		p-value	0.411	0.663	
Macro-albuminuria	BTP	Pearson Correlation	/	0.475**	-0.179
		p-value		0.002	0.270
	Cys C	Pearson Correlation	0.475**	/	0.070
		p-value	0.002		0.668
	eGFR	Pearson Correlation	-0.179	0.070	/
		p-value	0.270	0.668	

**. Correlation is significant at the 0.01 level (2-tailed).

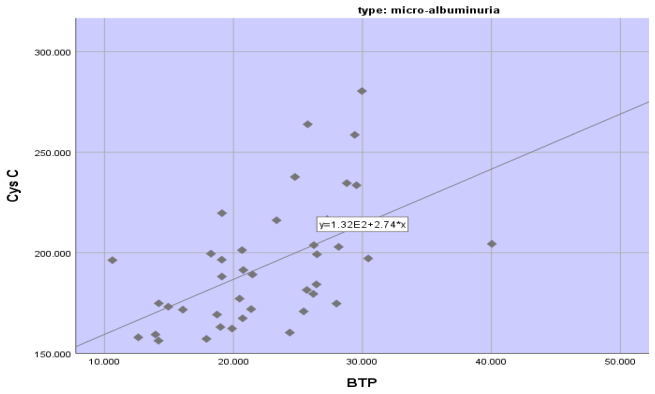

Figure 1: Scattered dot diagram of correlation between BTP and Cys. C in micro-albuminuria group

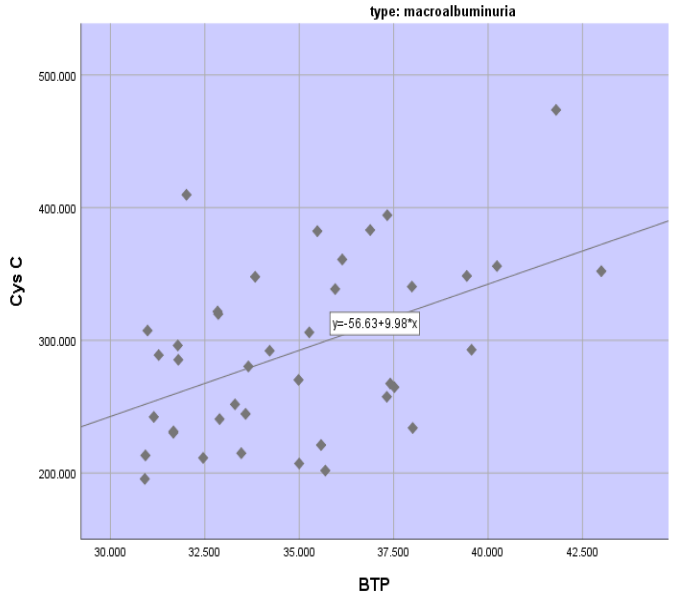

Figure 2: Scattered dot diagram of correlation between BTP and Cys. C in macroalbuminuria group

To evaluate Cys-C and BTP in detection of microalbuminuria, ROC test was used. Both markers had small AUC 0.51, 0.498, higher sensitivity 80.0%, 97.5% and low specificity 47.5%, 48.7%, respectively, as presented in table 4

Table 4: ROC test in detection microalbuminuria

Variables	Area	Cut off value	p-value	Sensitivity	Specificity
Cys-C	0.51	>168.4	0.73	80%	47.5%
BTP	0.498	>12.25	.978	97.5%	48.7%

Regarding detection macro-albuminuria, both markers Cys-c and BTP had an excellent AUC 0.966, 0.977, with cut off > 201.5, 30.68 with very high Sensitivity 97.5%, 100% and Specificity 99.85, 97.5% respectively, as presented in table 5.

Table 5: ROC test in detection macroalbuminuria

Variables	Area	Cut off value	p-value	Sensitivity	Specificity
Cys-C	0.966	>201.5	0.00	97.5%	99.85%
BTP	0.977	>30.68	0.00	100%	97.5%

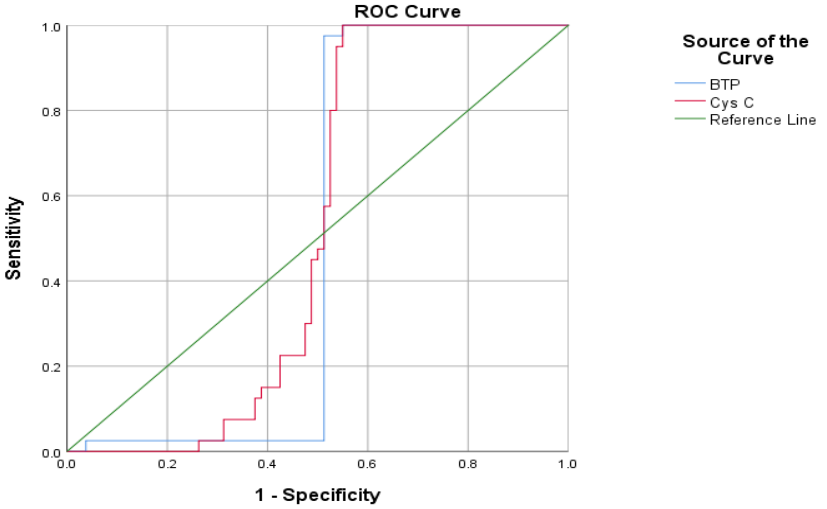

Figure 3: ROC diagram of CYS- C and BTP to detect microalbuminuria.

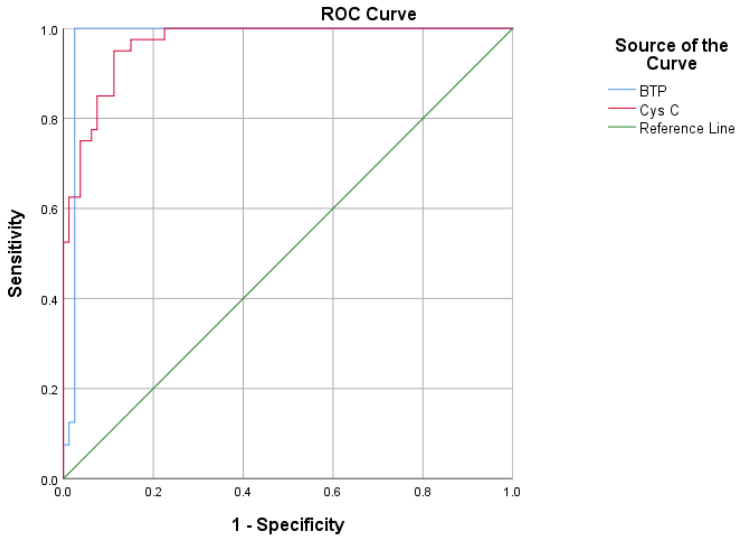

Figure 4: ROC diagram of CYS- C and BTP to detect macroalbuminuria.

Discussion

Renal disease is caused by an initial loss of nephrons; then, as a consequence of the kidney functional adaptations to the damage, disease progresses sequentially through different pathophysiological processes, leading to an irreversible state of fibrosis **(17)**. Diabetic people are more likely to suffer renal disease **(18)**. The search for new biomarkers should focus on better indicators of renal dysfunction than GFR, and on markers of specific types of kidney injury, assessed in serum and/or urine. The study of specific biomarkers would allow the identification of kidney damage, and they should reflect the underlying pathophysiological processes of kidney damage **(6)**. In this study, the role of S. βTP and S. Cystatin C levels in Type 2 Diabetic Mellitus patients was determined to predict DN even if the kidney function was normal.

The result of Table 2 revealed a statistically significant difference in Serum βTP level between the groups (p 0.00), macro-albuminuria groups show a statistically higher BTP (34.94 ± 3.14 µg/ml) in compare to microalbuminuria (22.48 ± 6.02 µg/ml) and normo-albuminuria (9.33 ± 3.06 µg/ml) (p 0.00), also micro-albuminuria group had higher mean of BTP in compare to normo-albuminuria (p 0.00).

The present study is in an agreement with **(12)** study that revealed the serum βTP was significantly elevated in Type 2 DM patients with microalbuminuria compared with Type 2 DM patients with normoalbuminuria. In another study that reported S.βTP level was significantly higher in diabetic patients with nephropathy compared with Health Control and the elevation was more pronounced in microalbuminuria than normoalbuminuria group (550 ± 100 ng/ml) **(19)**.

In the current study, table 2 show a statistically significant difference in mean level of serum cystatin C between the groups (p 0.00), macroalbuminuria groups show a statistically higher Cys. C (291.96 ± 66.12 ng/ml) in compare to microalbuminuria (193.64 ± 30.75 ng/ml) and normoalbuminuria (138.23 ± 17.86 ng/ml) p 0.00, also microalbuminuria group had higher mean of Cys. C in compare to normoalbuminuria (p 0.00).

The current study is in an agreement with Elsayed MS **(16)** that showed the level of serum cystatin C was significantly higher than the normal level in patient's groups when compared with control group, in Normoalbuminuria 0.74 ± 0.22, Microalbuminuria 1.07± 0.31 and Macroalbuminuria 3.25 ±1.09. In another similar study to current study, Serum cystatin C concentration was significantly higher in T2DM patients than in healthy control. Concentration of cystatin C increases with the progression of nephropathy in T2DM patients. A significant difference in serum cystatin C ($p < 0.001$), patients with macroalbuminuria had higher cystatin C as compared to patients with microalbuminuria and normoalbuminuria **(20)**.

In another study Serum cystatin C is a marker of kidney function. The mean serum cystatin C level was higher in diabetic nephropathy patients than non-diabetics nephropathy, and the difference was significant with *p*-value <0.001 **(21)**. Another study showed that Serum cystatin C was raised in diabetic group as

compared to control group, Serum cystatin C levels were raised significantly in a considerable number of diabetic participants as compared to controls ($p<0.05$). Therefore, it can be used in early diagnosis of diabetic kidney disease **(22)**. In table 4 and 5, the ROC curves were carried out to assess the diagnostic performance of S. Cys-C and S. BTP and whether they can be used as diagnostic tools. The present study found that S. BTP has **more sensitivity** and **specificity** than Cys. C in microalbuminuria and macroalbuminuria groups, so these results made S.βTP more useful than S. Cys. C in detecting early DN.

Conclusion

In this study, we reach the following conclusion:

1. In early diabetic nephropathy group (microalbuminuria), there was an increase the level of serum βTP and Cystatin C which may be considered as a predictive marker for early detection of DN.
2. In microalbuminuria group, βTP had higher sensitivity 97.5%, with specificity 48.7% more than Cys. C (sensitivity 80% with specificity 47.5%),so βTP is good and earlier markers for the detection of nephropathy in patients with type 2 DM than Cystatin C.

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