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RESEARCH ARTICLE

Role of Cystatin C in coronary heart disease patients with metabolic syndrome

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Abstract

Introduction: Cystatin C is a non-glycosylated protein. It is used mainly as a biomarker of renal functions. All of the components of metabolic syndrome (MetS) have been regarded as risk factors for coronary artery disease (CAD). Cystatin C, which has been proposed as a novel marker of renal dysfunction, is correlated with mortality in CAD.

Aim of work: This present study was designed to investigate the association of cystatin C with the presence and severity of CAD in patients with MetS with normal kidney function and to explore the relationship between cystatin C and other risk factors for atherosclerosis.

Materials and Methods: The study included 35 MetS patients with CAD (group I) and 35 MetS patients without CAD (group II). All patients were submitted to full clinical assessment including: history taking, clinical examination, body mass index (BMI) , waist circumference (WC), fasting blood sugar, 2-hours postprandial blood sugar, liver and kidney function tests, uric acid, microalbuminuria, lipid profiles and HbA1c . In addition to measurement of serum fibrinogen, serum cystatin C, coronary angiography, electrocardiograph study and radiological investigations.

Results: Cystatin C levels were significantly higher in MetS patients with CAD than MetS patients without CAD. Serum cystatin C was positively correlated with WC, low density lipoprotein -cholesterol (LDL-C), uric acid (UA), serum creatinine (SCr) and fibrinogen and negatively correlated with glomerular filtration rate (GFR) and high density lipoprotein -cholesterol (HDL-C). After further adjustment for age, sex and GFR, correlations remained significant between cystatin C and UA, fibrinogen, WC, LDL-C and HDL-C, also new positive correlations were observed between cystatin C and TG and BMI. Cystatin C was the most significant predictor of CAD followed by fibrinogen and FPG. Patients with higher cystatin C values had higher degrees of coronary artery injuries compared with patients with lower levels. At a cut off value of≤0.82 mg/L; Cystatin C had a sensitivity of (76.5%) and specificity of (75.4%) for prediction of CAD.

Conclusion: Serum cystatin C was significantly associated with the presence and severity of CAD in MetS patients with normal kidney function, suggesting that cystatin C could be a new marker for prediction of the presence and severity of CAD in patients with metabolic syndrome.

Introduction

Metabolic syndrome (MetS), a common cluster of interrelated cardio-metabolic factors including obesity, insulin resistance, dyslipidemia, and elevated blood pressure, is also predictive of atherosclerotic diseases and related mortality [(1)].The pathophysiology of MetS is not well defined [(2)].

Each of the components have been recognized as risk factors for coronary artery disease (CAD) [3], and a series of previous studies have demonstrated that the presence of MetS is associated with an increased risk of developing CAD [4].

According to National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III), underlying risk factors for CAD are obesity (especially abdominal obesity), physical inactivity and atherogenic diet other than the major risk factors, which are cigarette smoking, hypertension, elevated low density lipoproteins-cholesterol(LDL-C), low high density lipoproteins-cholesterol (HDL-C) and family history of premature CAD. Other risk factors include elevated triglycerides, chylomicrons, insulin resistance, glucose intolerance, pro-inflammatory state and pro-thrombotic state. Majority of these factors can be identified and modified [5]. CAD is the leading cause of morbidity and mortality in both developing and developed countries [6].

Cystatin C belongs to the cystatin superfamily of cystatin protease inhibitors. It is unique among all known cystatins that is produced at a constant rate by nucleated cells [7]. It is involved in the catabolism of protein. It is produced in all nucleated cells as a chain of (120) aminoacids (non glycosylated 13 KD protein) [8]. Cystatin-C or 3 formerly a gamma trace encoded by CYT3 gene [9] is freely filtered by glomeruli without secretion or subsequent reabsorption to the blood [10].

Compared with serum creatinine, cystatin C is less influenced by age, sex, and race, and a combined creatinine-cystatin C equation performed better than equations that used creatinine alone for classification of the estimating glomerular filtration rate (eGFR) [11].

Therefore, serum cystatin C is superior to serum creatinine as a marker of renal function [12]. In addition it has emerged as a novel sensitive marker for detecting renal dysfunction [13].

Several other publications have demonstrated that cystatin C was closely associated with incident congestive heart failure [14], carotid atherosclerosis [15] and peripheral vascular disease [10], superior to serum creatinine or creatinine-based eGFR.

Atherosclerosis is an inflammatory disease of the cardiovascular system, which is characterized by extensive remodeling of the extracellular matrix of arterial walls. It has been implicated that an imbalance between the expression of cathepsines and their endogenous inhibitor cystatin C is one of the most important mechanisms in atherogenesis [16].

Connections between cystatin C and features of MetS have also been illustrated by a few published studies [17]. **Servais et al.,** found that a progressive increase in serum cystatin C occurred in parallel with an increase in the number of MetS components [18].

This present study was designed to investigate the association of cystatin C with the presence and severity of CAD in MetS patients with normal kidney function and to explore the relationship between cystatin C and other biochemical risk factors for atherosclerosis.

Subjects and methods:

This study was carried out on 70 patients, in the department of Internal medicine, Cardiology and Clinical pathology, Faculty of Medicine, Zagazig University. Our study was observational, cross sectional and analytic.

Subjects: The included subjects in this study were divided into 2 groups:

(1) MetS with CAD (Group I): It included 35 known patients with MetS with CAD (19 men, 16 women), with a mean age of 48.7± 9.3years.

The diagnosis of CAD was made on the basis of abnormal ECG findings include the ST segment and T wave abnormalities, and other abnormalities indicate myocardium ischemia and referred to a coronary artery angiography for suspected CAD.

(2) MetS without CAD (Group II): It included 35 known patients with MetS without CAD (18 men, 17 women), with a mean age of 45.7± 10.5years.

Exclusion criteria: Patients with renal dysfunction ((GFR using Cockcroft–Gault equation; CG-GFR = [(140-age in years) X (actual weight in kg) X 0.85 (if female)]/[(72 X serum creatinine in mg/dl)]))[19], hepatic dysfunction, malignancy, inflammatory disease, valvular heart disease, use of drugs such as glucocorticoids, oral anti-diabetic medications or insulin and thyroid dysfunction were excluded from the study, because these factors may affect the plasma lipid and cystatin C levels.

Ethical Clearance: Informed written consents from the patients to participate in the study were taken.

Methods:

All patients were submitted to:

1-Full clinical assessment: including history taking, full clinical examination including: body mass index (BMI) , waist circumference (WC), waist to hip (W/H) ratio, systolic blood pressure (SBP) and diastolic blood pressure (DBP).

2-Routine laboratory investigations including:

- Complete blood count.
- Fasting and 2 hours postprandial blood glucose.
- Liver function tests.
- Kidney function tests.
- Uric acid.
- Microalbuminuria measured by ELISA.
- Lipid profile: total cholesterol (total-C), triglyceride (TG), LDL-C and HDL-C were measured on integra 400 by Roche diagnostics.
- HbA1c estimation by hemoglobin A1C chromatographic-spectrophotometric ion exchange.

3-Imaging:

- Electrocardiograph study.
- Plain x-ray (chest and heart) and abdominal ultrasonography.

4-Specific investigations:

- **Cystatin C:** was determined using ELISA technique. The kit was provided by Biovendor ®, Germany.
- **Fibrinogen**: was measured using Von Clauss methods on an electromechanical coagulometers (STA-R, Diagnostica Stago, Asnieres, France).
- **Coronary angiography** was performed with the modified Judkins techniques. Coronary artery disease was defined as stenosis of a coronary artery of 75% or greater. **Multivessel disease** was defined as the involvement of any three or more of the following four arteries: the left main artery, the left descending artery, the left circumflex artery and the right coronary artery. **Multilesion disease** was defined as three or more lesions in a single vessel. **Extensive lesion** was defined as a stenosis of more than 10 mm in length. **Smaller vessel disease** was defined as a lesion with a diameter of less than 2.5 mm in the distant part of the left descending artery, the left circumflex artery, the right coronary artery or their septal branches, or in the obtuse marginal or posterior descending arteries.
- **Metabolic syndrome** was diagnosed according to the ATP-III criteria [(20)] to classify patients as being with or without the metabolic syndrome on the basis of the presence or absence of ≥3 of the following factors:
  - **Waist circumference** > 88 cm in women or > 102 cm in men.
  - **Triglycerides** ≥150 mg/dL.
  - **HDL cholesterol** <50 mg/dL in women or <40 mg/dL in men.
  - **Blood pressure** ≥130/85 mmHg.
  - **Fasting glucose** ≥110 mg/dL.

Statistical analysis:

Statistical analysis was performed using statistical package for social science (SPSS) version 13. Quantitative data are presented as means ± SD. Qualitative data are presented as number and percentage. The unpaired t-test was used for comparison of means of the continuous variables to evaluate differences between the two groups. A multiple stepwise logistic regression analysis was performed to assess the association between the presence of CAD and cystatin C levels. Best cut off, sensitivity, specificity, positive and negative predictive values and diagnostic accuracy were calculated in accordance with standard methods. Comparison of qualitative variables was done using Chi-square test. Pearson´s correlation was used for detection of relation between 2 variables. r was considered weak if <0.25 ,mild if ≥ 0.25 - < 0.5 , moderate if ≥ 0.5 - < 0.75 and strong if ≥ 0.75. p- Value is considered significant if ≤ 0.05.

Results:

Table (I): Comparison of mean ± SD of different biochemical parameters between Groups I, II: MetS patients with CAD, in comparison to MetS patients without CAD showed higher age, BMI, WHR, current smokers, systolic and diastolic BP, TC, TG, LDL-C, SCr and UA, and lower HDL-C and GFR but without significant difference. WC, FPG, fibrinogen and serum Cystatin C levels were significantly higher in MetS patients with CAD (Group I) than MetS patients without CAD (Group II).

Table (II): Correlation coefficient between serum cystatin C (mg/L) and different parameters: Serum cystatin C was positively correlated with WC, LDL-C, UA, SCr and fibrinogen and negatively correlated with GFR and HDL-C. After further adjustment for age, sex and GFR, correlations remained significant between cystatin C and UA, fibrinogen, WC, LDL-C and HDL-C. New positive correlations were also observed between cystatin C and TG and BMI after further adjustment.

Table (III): Multiple stepwise logistic regression analysis of the risk factors predicting CAD: Cystatin C was the most significant predictor of CAD followed by fibrinogen and FPG.

Table (IV): Association between cystatin C and angiography results in MetS patients with CAD according to cystatin C quartiles: Angiography results shows significant difference as regarding: multivessel, and multilesion vessel diseases in the 4th quartile only when compared to the 1st quartile but, there was a significant difference in both the 3rd and 4th quartiles when compared to the 1st quartile regarding extensive and smaller vessel diseases.

Table (V): Sensitivity, specificity of cystatin C in diagnosis of CAD: At a cut off value of≤ 0.82 mg/L, cystatin C had a sensitivity of (76.5%) and specificity of (75.4%) for prediction of CAD.

Table (I): Comparison of mean ± SD of different biochemical parameters between Groups I, II .

Parameters	MetS with CAD (Group I) (N = 35) Mean±SD	MetS without CAD (Group II) (N = 35) Mean±SD	p
Age(years)	48.7± 9.3	45.7±10.5	NS
BMI(kg/m2)	27.25 ± 2.37	27.23±2.30	NS
WHR	1.03±0.035	1.02±0.014	NS
WC (cm)	97.65±19.35	87.91±13.36	**< 0.05***
Current smokers (n) %	27(77.1)	20(57.1)	NS
Systolic BP(mmHg)	138.8±18.2	135.1±16.3	NS
Diastolic BP(mmHg)	83.2±13.3	81.08±12.3	NS
FPG(mg/dL)	95.4±26	85.2±14	**< 0.05***
TC(mg/dL)	192.10±42.06	185.7±41.29	NS
TG(mg/dL)	183.1±63.4	168.04±18.7	NS
LDL-C(mg/dL)	109.5±35.96	107.03±30.85	NS
HDL-C(mg/dL)	33.5±6.3	36.6±7.4	NS
SCr(mg/dL)	0.80±0.19	0.79±0.15	NS
GFR(ml/min/1.73 m2)	109.94 ± 22.1	117.84 ± 21.60	NS
UA(mg/dL)	5.57±1.6	5.36 ±1.4	NS
Fibrinogen(mg/dL)	368±68	329±58	**< 0.05***
Cystatin C(mg/L)	0.97±0.2	0.85±0.14	**< 0.05***

***= P is significant**

BMI= body mass index, **WC=** waist circumference, **WHR=** waist hip ratio**, BP=** blood pressure**, FPG=** fasting plasma glucose**, TG=** Triglyceride, **TC=**total cholesterol**, HDL-C=** high-density lipoprotein cholesterol**, LDL-C=** low-density lipoprotein cholesterol**, SCr=** serum creatinine, **UA=** uric acid, **GFR=** glomerular filtration rate.

Table (II): Correlation coefficient between serum cystatin C (mg/ L) and different parameters.

Variables	Cystatin C		Cystatin C (adjust for age sex and GFR)	
	r	P	r	P
Age(years)	0.077	NS	-	-
BMI(kg/m2)	0.053	NS	0.336	**<0.001***
WHR	0.034	NS	0.045	NS
WC (cm)	0.40	**<0.05***	0.39	**<0.05***
Systolic BP(mmHg)	0.013	NS	0.025	NS
Diastolic BP(mmHg)	0.038	NS	0.057	NS
FPG(mg/dL)	0.105	NS	0.120	NS
TC(mg/dL)	0.132	NS	0.155	NS
TG(mg/dL)	0.037	NS	0.254	**<0.05***
LDL-C(mg/dL)	0.39	**<0.05***	0.38	**<0.05***
HDL-C(mg/dL)	-0.37	**<0.05***	-0.35	**<0.05***
SCr(mg/dL)	0.574	**<0.001***	-	-
GFR(ml/min/1.73 m2)	-0.585	**<0.001***	-	-
UA(mg/dL)	0.397	**<0.001***	0.386	**<0.001***
Fibrinogen(mg/dL)	0.263	**<0.05***	0.254	**<0.05***

***= P is significant**

Table (III): Multiple stepwise logistic regression analysis of the risk factors predicting CAD.

Parameters	(B)	S.E.	Sig.	Exp(B)	95.0% C.I for exp (B)	
					Lower	Upper
Cystatin C	1.695	0.720	0.000	3.406	1.965	15.098
Fibrinogen	1.511	0.489	0.047	2.105	1.218	9.772
FPG	1.239	0.445	0.001	2.164	1.136	8.259

Table (IV): Association between cystatin C and angiography results in MetS patients with CAD according to cystatin C quartiles.

Cystatin C quartiles (mg/ L) / Angiography results		I <0.83 mg/L N=9	II 0.83-0.99 mg/L N=9	III 0.99-1.09 mg/L N=9	IV >1.09 mg/L N=8	p
Multivessel disease	**n (%)**	1 (11.1)	4 (44.4)	4 (44.4)	5 (62.5)	**p^2 >0.05 p^3 >0.05 p^4<0.05***
Multilesion disease	**n (%)**	3 (33.3)	5 (55.6)	6 (66.7)	7 (87.5)	**p^2 >0.05 p^3 >0.05 p^4<0.05***
Extensive disease	**n (%)**	1 (11.1)	2 (22.2)	6 (66.7)	5 (62.5)	**p^2 >0.05 p^3 <0.05* p^4<0.05***
Smaller vessel disease	**n (%)**	3 **(33.3)**	1 **(11.1)**	8 (88.9)	7 (87.5)	**p^2 >0.05 p^3<0.05* p^4<0.05***

***= P is significant**
p^2: 2nd quartile indices compared to the 1st quartile.
p^3: 3rd quartile indices compared to the 1st quartile.
p^4: 4th quartile indices compared to the 1st quartile.

Table (V): Sensitivity, specificity of cystatin C in diagnosis of CAD.

Parameter	Sensitivity	Specificity	PP value	NP value	Accuracy
Cystatin C (mg/L) Cut level ≥0.82	76.5%	75.4%	75%	87%	81%

Discussion:

It is well recognized that, patients with impaired renal function are at significantly higher risk for cardiovascular disease, congestive heart failure, all-cause mortality and adverse long-term outcomes in contrast to patients without renal disease [(21)].

Cystatin C participates in intracellular and extracellular proteolytic modulation, and prevents cellular hydrolysis from endogenous and exogenous proteases. Cystatin C has diverse bioactivity not only in tumor invasion, metastasis, degradation of ossein, and anti-infection neutrophil migration, but also in cardiovascular diseases [(22)]. The clearance of circulatory cystatin C uniquely depends on the kidney. Because of its low molecular weight (13.3 kDa) and positive charge at physiologic pH levels, cystatin C is freely filtered by the kidney and cannot be reabsorbed or re-secreted from the kidney tubules [(23)]. Cystatin C is relatively stable and its serum concentration is independent of age, sex, race, and nutrition [(24)]. Therefore, cystatin C is an ideal endogenous marker that is more sensitive and accurate than creatinine in reflecting renal function [(25)].

Cystatin C is not only a more sensitive indicator of renal function than creatinine or creatinine clearance but is also an independent and strong predictor of cardiovascular events, diabetes and all-cause mortality. **Taglieri et al.,** has shown that, cystatin C is closely associated with the inflammatory process and other inflammation factors [(26)].

As, each component of MetS may lead to renal function impairment [(18)]. When renal function is impaired, ultrafiltration rate and loss of charge selectivity may contribute to the increased serum cystatin C concentrations in MetS patients [(27)].

So, in this study, we assessed the association between cystatin C and CAD in MetS patients with normal kidney function in order to avoid the well-known effect of overt renal insufficiency on coronary atherosclerosis, and

evaluate whether cystatin C has an ability to identify individuals at a higher risk for CAD among patients belonging to a low-risk category according to GFR.

In our study, we found that, the MetS components including WC, TG, systolic and diastolic BP and FPG were higher while, HDL-C was lower in MetS patients with CAD than MetS patients without CAD but without significant difference.

Our study results are in accordance with those obtained by **Qing et al., and Liu et al., [28, 29].**

Also, cystatin C and fibrinogen were significantly higher in MetS patients with CAD than MetS patients without CAD in our study.

As MetS is the most important etiological factor of cardiovascular disease, so MetS is probably intimately associated with cystatin C **[30].**

In our study, serum cystatin C was positively correlated with WC, LDL-C, UA, SCr and fibrinogen and negatively correlated with GFR and HDL-C. These correlations remained significant between cystatin C and UA, fibrinogen, WC, LDL-C and HDL-C even after further adjustment for age, sex and GFR. In addition, a positive correlation was also observed between cystatin C and TG and BMI after further adjustment.

In the Heart and Soul Study, data from patients with CAD indicated significant associations between cystatin C and pro-inflammatory parameters like C-reactive protein (CRP) or fibrinogen [31] .

Hosokawa et al., and Vigil et al., also found that, cystatin C was significantly positively correlated with uric acid in patients with type 2 diabetes [32] and in a hypertensive population **[33].**

Uric acid has been shown to be related with increased production of oxygen free radicals, to promote the oxygenation of LDL-C and to facilitate lipid peroxidation [34]. Studies have shown increased uric acid levels are associated with atherosclerosis [35].

Central obesity is a key factor in the occurrence and development of MetS [36]. Although BMI is widely applied in the assessment of overweight and obesity, it does not distinguish fat from muscle or different fat distribution. The main limitation of the waist–hip ratio is that both waist and hip circumference can change with weight variation and as a consequence alterations in the ratio are frequently small [37]. WC is a sensitive indicator of central obesity; it not only reflects visceral fat content but is also the principal parameter for predicting obesity health-related risk. WC is also strongly related to central obesity. Nevertheless, it does not take into account differences in individual stature [29].

It has been shown that cystatin C is closely linked to adipose tissue. Preadipocytes differentiated in vitro can express and release cystatin C; subcutaneous and omental fatty tissue overexpress cystatin C in vivo. Cystatin C produced by adipose tissue may be a fat-derived secretory adipocytokine. It not only has the potential to affect adipose tissue and vascular homeostasis through local and/or systemic inhibition of cathepsins but also affects the functions of adipose tissue and induces obesity-linked complications **[38].**

In this study, cystatin C was positively correlated with TG and LDL-C, and negatively correlated with HDL-C.

Clinical data have demonstrated that serum cystatin C levels are closely connected to LDL-C and TG in patients with CAD **[39].**

The hallmark of atherogenic dyslipidemia (AD) consists of decreased HDL-C together with raised TG. AD is associated with insulin resistance (IR), and confers a marked increase in residual vascular risk, even when LDL-C is low **[40].**

Cystatin C and mean LDL particle size are significantly and independently associated with the presence of CAD events in patients ≤45 years with normal kidney function **[41].**

High TG and low HDL-C have been associated with metabolic syndrome, and hyperinsulinemia may contribute to dyslipidemia by increasing the synthesis of VLDL by the liver [42], resulting in increased concentrations of triglycerides. Low concentrations of HDL may indicate an increased rate of apoAI catabolism seen in subjects with high levels of insulin [43].

In the current study, multiple logistic regression analysis was performed using the presence of the CAD as a dependent variable As a result; serum cystatin C followed by fibrinogen and FPG were independent predictors of the presence of the CAD, but not SCr and GFR

Qing et al., also proved that serum levels of cystatin C, but not SCr and eGFR , were independently associated with the development of asymptomatic CAD, even after a variety of potential confounders were controlled [28].

In accordance with our study, **Wang et al.,** demonstrated elevated cystatin C was associated with the presence of CAD in subjects with mild renal impairment, while creatinine and eGFR were not able to predict CAD occurrence **[44].**

The close relationship between cystatin C and all-cause cardiovascular mortality has been illustrated in subjects with normal eGFR which further confirmed that cystatin C may not simply be regarded as an indicator of

the association between renal dysfunction and an increased risk of CAD, the information contained by cystatin C represents more than just a marker of renal function [(45)].

Cystatin C's association with MetS remains unclear. Cystatin C levels correlate significantly with insulin resistance [(46)] , participates in the process of cell apoptosis and has direct toxic effects on cells [(47)]. Also, Cystatin C is intimately linked to inflammatory and procoagulant factors [(39)], including homocysteine, CRP, interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), intercellular adhesion molecule-1, fibrinogen, and others. Moreover, cystatin C is independently related to CRP [(26)]. In addition, cystatin C and its fragments may affect the phagotrophic and chemotactic functions of granulocytes, and participate in the inflammatory process [(48)]. Cystatin C is relevant to hypermetabolism [(49)]. Cystatin C may induce MetS by an oxidative stress mechanism [(50)].

In current study, Angiography results showed significant difference as regarding: multivessel, and multilesion vessel diseases in the 4th quartile only when compared to the 1st quartile but, there was a significant difference in both the 3rd and 4th quartiles when compared to the 1st quartile regarding extensive and smaller vessel diseases.

Qing et al., found positive relationship between serum levels of cystatin C and the number of diseased vessels [(28)].

Cystatin C is expressed in all of the nucleated cells, regulates the activity of cysteine protease, and plays a role in the dynamic balance of production and degradation of extracellular matrix (ECM). Cystatin C and its fragments may also affect the phagocytic and chemotactic ability of neutrophil, participates in the inflammatory process and regulates inflammatory responses. Inflammation plays an important role in the development of atherosclerosis [(51)].

Moreover, ECM degradation and positive arterial remodeling relate closely to plaque destabilization, suggesting that cystatin C may reflect an increased inflammatory state that contributes to atherosclerotic plaque vulnerability and a higher risk of plaque rupture and thrombotic complications [(52)].

The obtained results showed that the best cut off value of cystatin C to distinguish MetS patients with CAD from those without CAD, was ≤0.82 mg/L, as the diagnostic sensitivity was 76.5% and specificity of 75.4%, positive predictive value was 75 %, negative predictive value was 87% and diagnostic accuracy was 81 %.

Koc et al., also found that, at 0.82 mg/L cut-off value of cystatin C predicted CAD with a sensitivity and specificity of 75.5% and 75.0%, respectively [(53)].

In conclusion, cystatin C is not only closely related to MetS but is also intimately linked to the components of MetS. In addition, it was significantly associated with the presence and severity of CAD in MetS patients with normal kidney function, suggesting that cystatin C could be a new marker for prediction of the presence and severity of CAD in patients with metabolic syndrome.

Recommendations:

Further research is warranted to clarify the pathophysiologic mechanisms responsible for the association between serum cystatin C, MetS components and prediction the presence or severity of atherosclerosis in CAD patients.

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