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**RESEARCH ARTICLE**

# THE ROLE OF HIGH SENSITIVE-CRP AND PENTRAXIN III IN PROGRESSION OF CORONARY ARTERY CALCIFICATION IN PATIENTS WITH CORONARY ARTERY DISEASE

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**ABSTRACT**

**Background:** Inflammation be may plays a central role in atherosclerosis. Coronary artery calcification (CAC) is a specific feature for coronary atherosclerosis. In multiple epidemiologic studies, inflammatory biomarkers such as high sensitive C-reactive protein (hs-CRP), has been associated with increased risk of coronary artery disease (CAD), while Pentraxin III might reflect local inflammation status in tissue and it is used as a new biomarker of inflammation.
The aim of this study was designed to evaluate the association between the serum levels of hs-CRP, Pentaxin III and HbA1C% with coronary artery calcium score values in patients with suspected CAD and to show the role of these parameters in progression and development of CAC.
**Subjects and Methods:** This study was conducted at the Department of Biochemistry, College of Medicine, University of Baghdad and at the Cardiologic Clinics of Ibn-Al-Bitar Hospital, Baghdad, Iraq, during the period from February 2013 to November 2013. Sixty-five patients with suspected CAD and who were not on statin derivatives treatment were included in this study and classified according to their coronary artery Ca score, using Multi-Slice Computed Tomography Scanner (MSCT), into three groups: Group I (GI, n=20) with coronary artery Ca score =0.0 Agatston Score (AS), Group II (GII, n=25) with coronary artery Ca score > 1-399 (AS), and Group III (GIII, n=20) with coronary artery Ca score of more than 400 (AS).
**Results:** The present study showed the changes in serum concentrations of pentraxin III and hs-CRP were increased with increase in the severity of Ca score, but without significant level; GI had (0.83±0.35 ng/dl, 3.13±3.50 mg/l, respectively), GII (0.96±0.30 ng/dl, 3.07±3.79 mg/l, respectively), and GIII (0.99±0.50 ng/dl, 3.71±3.70 mg/l, respectively). Significant increased in the mean value of HbA1c in GIII compared with GI (P=0.03). Also the mean values of non-HDL-cholesterol (for both, P=0.0289) and atherogenic index (P=0.008 and P=0.0011) were significantly higher in GIII than in GII and GI.
**Conclusion:** This study suggested the controversial role of proinflammatory adipokines, the hs-CRP and pentraxin III, in progression of coronary artery calcium calcification. The link among inflammation (hs-CRP, PTX3), hyperglycemia (HbA1C%) and dyslipidemia (non–HDL and atherogenic Index) may play important role in the severity progression of CAC.



## INTRODUCTION

Coronary artery disease (CAD) is one of the leading causes of mortality and morbidity (Gokdeniz *et al*., 2013). Although invasive coronary angiography has been the gold standard for evaluating coronary artery disease, it should not be routinely performed as an initial test to assess the subjects with suspected CAD by the recent guidelines, due to cost, invasiveness, and measurable risk. Coronary computed tomography angiography (CCTA) is a rapidly growing, noninvasive imaging modality that developed quickly over the last decade, and its role for evaluation of CAD becomes of great promise with high diagnostic accuracy (Alani *et al*., 2014). It is also a noninvasive tool for the detection and quantification of coronary artery calcium (CAC), a marker for atherosclerosis (Budoff *et al*., 2009). The presence and extent of CAC correlates with the overall magnitude of coronary atherosclerotic plaque burden and with the development of subsequent coronary events, CAC occurs only in the setting of atherosclerosis, and is a better index of global atherosclerotic burden than stenosis severity and it can be consider as an emerging tool to identify the presence and extent of coronary artery calcium, as well as to stratify risk of future cardiovascular events (Budoff *et al*., 2009). Coronary calcium scans use a special X-ray test called computed tomography (CT) to check for the buildup of calcium in plaque on the walls of the arteries of the heart (coronary arteries). This test is used

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to check for heart disease in an early stage and to determine how severe it is (Maury and Brichard, 2010). The presence of calcium in coronary arteries is known to be a strong indicator for coronary artery disease. It has been shown that quantification of coronary calcium enables the assessment of cardiac event risk stratification (Dijkstra *et al*., 2010). Although artifact issues have created some challenges for CCTA, recent advances including the introduction of more detectors, leading to broader coverage, and faster and higher-definition scanners allow improved precision and fewer uninterruptable studies (Alani *et al*., 2014). Therefore, routinely used CCTA protocols generally incorporate a 'filter scan' for the assessment of Coronary Calcium Scoring (CCS), in order to identify patients with severe coronary calcification, where the usefulness of CCTA for CAD detection is considered uncertain by current guidelines (Gitsioudis *et al*., 2014). C-reactive protein (CRP) is an acute-phase protein (Thompson *et al*., 1999), it is synthesized by the liver in response to factors released by macrophages and fat cells (adipocytes).

It is a member of the Pentraxin family of proteins. It is not related to C-peptide or protein C. C-reactive protein was the first pattern recognition receptor (PRR) to be identified (Mantovani *et al*., 2008). High-sensitivity C-reactive protein (hs-CRP), the first acute phase protein detected by highly sensitive methods, is a sensitive marker of inflammation. The modest changes in serum hs-CRP levels can be extremely useful in predicting cardiovascular. This protein, hs-CRP, has been a novel risk factor for ischemic stroke, coronary ischemic disease, and overall mortality (Wu *et al*., 2013). Inflammation plays a central role in atherosclerosis. Previous studies range from null to weak associations between hs-CRP and coronary artery calcification (CAC) in symptomatic individuals (Jenny *et al*., 2010). The Pentraxin family, named for its electron micrographic appearance, from the Greek penta (five) and ragos (berries), comprises CRP and serum amyloid P component (SAP) in man, and is highly conserved differences between CRPs of different species, including glycosylation, capacity to activate autologous complement, and regulation of basal and acute phase synthesis.

These differences necessitate extreme caution in extrapolating from animal models to man (Hirschfield and Pepys, 2003). Based on the primary structure of the protomer, the Pentraxins branch off into two groups: the short constituents and their long counterparts (Hirschfield and Pepys, 2003). Short Pentraxins are about 25-kDa proteins sharing a common structural organization of five or ten subunits that are assembled in pentameric radial symmetry. The classical short Pentraxins, C-reactive protein (CRP) and serum amyloid P component (SAP) are acute-phase proteins in humans and in mice, respectively (Bottazzi *et al*., 2010). The long pentraxin 3 (PTX3) is a soluble pattern recognition molecule mediating innate immune recognition (Jenny *et al*., 2010). During inflammation PTX3 is rapidly up-regulated and released into the surrounding tissue and into the bloodstream. PTX3 interacts with C1q and participates in activation of the classical complement pathway (Bottazzi *et al*., 1997; Nauta *et al*., 2003). Some studies suggest the role of Pentraxin-3 still controversial in CAD. Recent studies suggested that the role of Pentraxin-3 (PTX3) has emerged as a novel marker thought to be more specific to vascular inflammation than other proteins in the Pentraxin family such as CRP. Higher PTX3 levels are associated with worse cardiovascular outcomes after acute coronary syndromes, independently of CRP. PTX3 is also associated with increased risk of cardiovascular death among elderly persons without established cardiovascular Disease (Dubin *et al*., 2012).

The aim of this study was designed to investigate the association between the serum levels of hs-CRP, Pentaxin III and HbA1C% with coronary artery calcium score values in patients with CAD and to show the role of these parameters in progression and development of CAC.

## MATERIALS AND METHODS

This study was conducted at the Department of Biochemistry, College of Medicine, University of Baghdad and at the Cardiologic Clinics of Ibn-Al-Bitar Hospital, Baghdad, Iraq, during the period from February 2013 to November 2013. A total of 65 subjects with suspected CAD who were not on statin derivatives treatment were included in this study. These patients were investigated firstly for coronary artery calcium score and the percent of coronary artery stenosis (atherosclerotic lesion; less and more than 50 % as well as 70 % lesion) using Multi-Slice Computed Tomography Scanner (MSCT, Brilliance 64, Philips Medical Systems, The Netherlands). The included 65 patients with suspected CAD were classified according to their obtained values of coronary artery Ca score into three groups: Group I (GI) included 20 subjects who had coronary artery Ca score=0.0 AS, aged range (31-65 year), these subjects were considered as control group, Group II (GII) involved 25 patients with coronary artery Ca score 1-399 AS, aged range (47-74 year), and Group III (GIII) included 20 patients who had coronary artery Ca score of more than 400 AS, aged range (49-75 year). CT scan for measurement of Ca Score involved Computed Tomography Scan for measurement of coronary artery Ca Score was performed using a multi detector 64, CT scanner (Brilliance 64, Philips Medical Systems, The Netherlands).

*Coronary Artery Calcification Scoring (CACS): It has as its primary goal of the early detection of Coronary Artery Disease (CAD). CAD is the most common cause of death. Calcification within the coronary artery wall can be an indicator of the presence of coronary artery disease. CACS can detect calcium in many people with CAD at an early stage, before the symptoms of heart disease – such as angina, heart attack or sudden death occur. The first symptom of CAD in up to 25% of people is sudden death. A high calcium score increases the probability that a person may have a clinically significant coronary narrowing in a least one vessel. In some people, additional investigations such as stress testing may be warranted. CT Imaging to be performed needed for the following conditions:*

- ECG: is monitored before and through the scan
- Contrast: Uniform distribution of contrast media throughout study.

- Beta-Blockers: Sometimes required to lower heart rate (< 60 beat per minute).

The protocol for coronary (CTA) includes 0.067 mm slice thickness cuts obtained at 0.64 – millimeter mm interval with a tracing marker placed upon the ascending thoracic aorta. Usually, 100 ml of nonionic contrast media is injected at 6 ml/s through a large–bore, intravenous access in the antecubital fossa. Reconstruction of the raw data was performed using the Philips work stations. Serial axial images, as well as the reconstructed multi planar and maximum intensity projections, were used primarily for diagnostic purposes. Three-dimensional volume rendering was also used to help diagnose patients. The calculator of radiation dose (3-12) Millisiver (MSV) (Shaw and Raggi, 2003). Three-five millilitre (ml) of blood was aspirated from peripheral vein of each subject of the three studied groups I, II and III after an overnight fasting state (10 -12 hour). The blood was divided into two parts, 2.5 ml was transferred into EDTA anti-coagulant tube with immediate mixing for HbA1c measurement, the second part was left to clot for 30 minute, then the serum was obtained by centrifugation at 2500 xg for 15 minutes and stored at -20º C till the time of estimation of the hs-CRP and pentraxin III. Fasting serum glucose and lipid profile parameters were also measured in the same day of blood collection. High sensitive (hs-CRP) C- reactive protein CRPHS (Latex) High Sensitive Assay was measured using the kits Cat. No. 04628918 190; Roch/Hitachi Cobas System. (Roach diagnostic GmbH, D-68298Mannheium for USA distribution, indianpolis, IN, English) according to method reported by (Roberts *et al*., 2001).

Pentraxin 3 (PTX3), also known as Tumor necrosis factor-Stimulated Gene 14 (TSG-14) was estimated according to method of (Jaillon *et al.*, 2007) by using the kit provided from Quantikine® ELISA, Human Pentraxin 3/TSG-14 Immunoassay, Catalog Number DPTX30; UK & Europe | R&D Systems Europe.This assay employs the quantitative sandwich enzyme immunoassay technique. A streptavidin coated plate is incubated with a biotinylated monoclonal antibody specific for human PTX3. Plates are washed, and pretreated standards and samples are added to the wells. Any PTX3 present is bound by the immobilized biotinylated antibody. After washing away any unbound substances, an enzyme-linked conjugate specific for human PTX3 is added to the wells. Following a wash to remove any unbound conjugate, a substrate solution is added to the wells and color develops in proportion to the amount of PTX3 bound. The color development is stopped and the intensity of the color is measured.

Glycated haemoglobin was measured by spectrophotometric method (Burits *et al*., 2008) by using the kit provided from (Human Gesellschaft fùr Biochemical and Diagnostica mbH Max-Planck-Ring 21.62505Wiesbaden.Germany). Fasting serum glucose, total cholesterol, TG, HDL-cholesterol, LDL-cholesterol, non-HDL-cholesterol and atherogenic index were also measured and calculated according to methods reported by (Burits *et al*., 2008). The body mass index (BMI), a measure of relative weight based on an individual's mass and height was calculated using the following equation:

$$\text{BMI} = \frac{\text{Mass (kg)}}{(\text{Height (M)})^2}$$

Statistical analysis analysis of data was carried out using the available statistical package of SPSS-22 (Statistical Packages for Social Sciences- version 22). Data were presented in simple measures of mean and standard deviation values. The significance of difference of different means (quantitative data) were tested using Students-t-test for difference between two independent means, or ANOVA test for difference among more than two independent means. Pearson correlation was calculated for the correlation between two quantitative variables with its t-test for testing the significance of correlation. Statistical significance was considered whenever the P value was less than 0.05.

## RESULTS

The mean value of Ca score in patients of GIII (1510.42 AS) was 15 times higher than that of GII (100.3 AS). The mean age of patients in G I was (45.80±9.70 year) with range (31-65 year) compared to (57.70±5.70 year) with range (49-75 year) in GII and (62.40±7.40 year) with range (47-74 year) in GIII, respectively. Table 1 show that the mean (±SD) values of serum pentraxin III and hs-CRP concentrations were in GI (0.83±0.35 ng/dl, 3.13±3.50 mg/l, respectively), GII (0.96±0.30 ng/dl, 3.07±3.79 mg/l, respectively), and GIII (0.99±0.50 ng/dl, 3.71±3.70 mg/l, respectively). The mean of these two inflammatory parameters were increased with increase in the severity of coronary artery calcium calcification with highest level in group III and II than in group I, but did not reach the significant level. The mean (±SD) values of fasting serum glucose, HbA1c and the lipid profile parameters are presented in table 2. The mean values of serum levels of glycemic index; fasting glucose and HbA1c % of patients enrolled in this study were found to be (5.86±1.97 mmol/l, 5.95±1.21 %) for GI, (6.77±2.25 mmol/l, 6.64±1.84 %) for GII, and (6.49±3.14 mmol/l, 7.07±1.86 %) for GIII, respectively, with only significant increased in GIII than in GI (P=0.03).

The mean value of serum HDL-C concentrations was significantly decreased in GIII when compared with that of GI (1.03±0.25mmol/l, 1.22±0.32mmol/l, respectively, P=0.044). Also, the mean value of non-HDL-cholesterol was increased in GIII (4.03 ±1.19 mmol/l) compared to GII (3.59±0.48 mmol/l) and GI (3.53 ±0.66 mmol/l, for both P=0.0289). Moreover, the mean value of atherogenic index of GIII (0.373±0.178) was significantly higher than that of GII (0.212±0.187, P=0.005) and GI (0.228±0.164, P=0.0011). In addition, the mean values of serum TG and VLDL-C were significantly increased in GIII than in GII (for both, P=0.008). The results of the present study also found that serum hs-CRP concentration was significantly positively correlated with HbA1c values (r=0.509, P=0.022) in GI. Also, significant positive correlation was observed between serum level of pentraxin III and hs-CRP in GI (r= 0.482, P=0.031). However, there was no any significant correlation between the obtained values of coronary artery Ca score and the measured biochemical parameters.

**Table 1. Mean (±SD) Values of Serum Concentrations of hs-CRP and Pentraxin III in Patients of GI, GII and GIII**

| Studied parameters | GI (CAS=0) (n=20) | GII (CAS=1-399) (n=25) | GIII (CAS=>400) (n=20) | P-Value |
|---|---|---|---|---|
| hs-CRP (mg/l) | 3.13±3.50 | 3.07±3.79 | 3.71±3.70 | 0.826 $^{NS}$ |
| PentraxinIII (ng/dl) | 0.83±0.357 | 0.96±0.30 | 0.99±0.50 | 0.397 $^{NS}$ |

**Table 2. Mean (±SD) Values of HbA1c, Fasting Glucose and the Lipid Profile Parameters in Patients of GI, GII, and GIII**

| Studied parameters | GI (CAS=0) (n=20) | GII (CAS=1-399) (n=25) | GIII (CAS=20) (n=20) |
|---|---|---|---|
| HbA1c% | 5.95±1.21 | 6.64±1.84 | 7.07±1.86▲ |
| Fasting Serum Glucose (mmol/l) | 5.86±1.97 | 6.77±2.25 | 6.49±3.14$^{NS}$ |
| Total cholesterol (mmol/l) | 4.75±0.98 | 4.63±0.80 | 5.06±1.44$^{NS}$ |
| TG (mmol/l) | 1.96±0.94 | 1.70±1.02 | 2.58±1.10▲▲ |
| HDL-C (mmol/l) | 1.22±0.32 | 1.04±0.32 | 1.03±0.25• |
| LDL-C (mmol/l) | 3.11±0.95 | 3.11±0.94 | 3.50±1.26$^{NS}$ |
| VLDL-C (mmol/l) | 0.39±0.19 | 0.34±0.20 | 0.51±0.22▲▲ |
| Non-HDL (mmol/l) | 3.53±0.66 | 3.59±0.48 | 4.03 ±1.19•• |
| Atherogenic Index | 0.23±0.16 | 0.21±0.19 | 0.37±0.18•• |

ANOVA and t-test; showed significant differences in TG and VLDL-C between GIII and GII (P=0.008), between GIII and each of GI and GII in non-HDL-C (for both, P=0.0289), between GIII and each of GI (P=0.0011) and GII (P=0.005) in atherogenic index, ▲significant difference between GI and GIII in HbA1c% (P=0.03). ● Significant difference between GIII and GI in HDL-C (P=0.044). NS no significant difference among GI, GII, and GIII.

## DISCUSSION

In general, the higher level of hs-CRP has higher the risk of atherosclerosis development. Levels of hs-CRP below 1 mg/l are considered low, levels of 1 - 3 mg/l are considered moderately elevated and levels greater than 3 mg/l are considered high. Levels greater than 10 mg/l are usually only seen with active, obvious inflammatory processes, such as chronic inflammatory diseases (Yeh, 2005). The present study found insignificant increased in serum concentrations of hs-CRP in patients with suspected CAD according to their Ca score severity with increased in GIII, then GII and GI (table 1). The role of hs-CRP in CAD may be still controversial, therefore the relationship between hs-CRP and coronary artery calcification in symptomatic population did not reveal consistent results. These findings suggested that higher level of hs-CRP consider to make patients under higher risk for progression of atherosclerosis.

Previous study done by (Hecht *et al*., 2003) suggested that hs-CRP levels also have been shown to add prognostic information at all levels of coronary calcium, this information should be used primarily to motivate at-risk individuals to adopt more heart-healthy lifestyles, not to seek aggressive interventional cardiac procedures. They reported that coronary calcium and hs-CRP contribute independently to predicting cardiovascular events (Hecht *et al*., 2003). The associations of biomarkers with coronary artery calcium as a surrogate marker of subclinical CAD are not clear. Previous studies range from null to weak associations between hs-CRP and CAC in asymptomatic individuals (Jenny *et al*., 2010). Other study, explain there was an accumulating body of literature demonstrating a role for CRP as a putative mediator of atherosclerosis, independently and in synergy with other traditional risk factors, such as LDL cholesterol. The results of the hs-CRP blood test are thought to reflect inflammatory process that has been well known to potentiate atherosclerosis. Moreover, hs-CRP is chemotactic for human monocytes and facilitates oxidized LDL uptake by macrophages, resulting in greater foam cell formation and exacerbation of the detrimental endothelial effects of oxidized LDL via increased levels of the lectin-like oxidized LDL receptor-1 protein, Aside from its potential role in the earlier stages of atherogenesis, there is also some evidence that h- CRP may also contribute to later phases of atherosclerosis (Oh *et al*., 2011). The present study also revered that pentraxin III was increased in order of coronary artery calcium severity (GIII, then GII and GI), but insignificantly (Table 1). These findings may explain that the high serum level of pentraxin III may play an important role as proinflamatory adipokines which increase risk for development atherosclerosis via CAC. A study suggested that two of the major cellular components of atherosclerotic lesions, namely macrophages and endothelial cells, are potent producers of PTX3 (but not of CRP) in response to inflammatory stimuli. Given the inflammatory nature of the atherosclerosis disease process and the previously identified involvement of the prototypic pentraxin, CRP in atherosclerosis, this suggests that PTX3 may be involved in the pathogenesis of atherosclerosis (Michael S. Rolph *et al*., 2002). Because macrophages and endothelial cells are major cellular constituents of atherosclerosis, they hypothesized that PTX3 would be expressed in atherosclerotic lesions.

These authors found strong PTX3 staining in macrophages and endothelial cells in advanced atherosclerotic lesions. More recently, a large body of evidence has supported the idea that inflammatory mechanisms play a pivotal role throughout all phases of atherogenesis, from endothelial dysfunction and the formation of fatty streaks to plaque destabilization and the acute coronary events due to vulnerable plaque rupture. Indeed, although triggers and pathways of inflammation are probably multiple and vary in different clinical entities of atherosclerotic disorders, an imbalance between anti-inflammatory mechanisms and pro-inflammatory factors will result in an atherosclerotic progression, therefore coronary artery calcification might be useful in identifying novel risk factors for coronary atherosclerosis in symptomatic subjects (Li, 2011). These results support the hypothesis that PTX3 reflects different aspects of inflammation than CRP, and may provide additional insights into the development and progression of atherosclerosis (Jenny *et al*., 2014). The results of the current study also found that the mean of serum glucose levels did not differ significantly among the studied groups, while the mean value of HbA1c was found to be significantly increased in GIII compared with GI (table 2).

These finding may indicated the role of the coexistence and established D M in precipitation of calcium in coronary arteries. It has been found that the HbA1c levels were correlated with the severity of coronary atherosclerosis in both

diabetic and non-diabetic patients. It has also been evaluated CAD patients and suggested that HbA1c has a high sensitivity and specificity for predicting severe CAD (Graham *et al*., 2007). In the present study the mean of non-HDL value was significantly higher in GIII than in G II and GI. Currently available clinical data in (Orakzai and Nasir, 2009) demonstrated the effect of serum lipids on the process of coronary arteries calcification (CAC), regarded as an early marker of subclinical atherosclerosis can be explain through the relationship between the concentration of non □HDL□C and methods of imaging of atherosclerosis (Orakzai and Nasir, 2009). The present study also suggested the role of atherogenic index (TG/HDL) as high-risk factor for progression of CAD through link to CAC measured by using multi-slice computed tomography scanner. Atherogenic index AI reflects not only the balance between risk and protective lipoproteins, but also correlates with lipoprotein particle size and cholesterol esterification rate (Dobiasova, 2006). In the present study there was significant positive correlation between serum level of hs-CRP and HbA1c% in group I, these finding confirmed the important role of inflammation link to hyperglycemia in progression of atherosclerosis in future. There are accumulating data indicate that insights gained from the link between inflammation and hyperglycemia can yield predictive and prognostic information of considerable clinical utility further risk, list as the following:- some study found that inflammation is one of the primary mechanisms of atherogenesis, and elevation of hs-CRP heralds atherothrombotic events.

Their data show that risk estimates for the progression of atherosclerosis associated with both HbA1c and hs-CRP in the upper quartiles were at least as high as those associated with traditional risk factors and clearly indicate an increased risk for new major vascular events even in symptomatic subjects (Sander *et al*., 2006). Therefore the Inflammation, indicated by hs-CRP and hyperglycemia, indicated by HbA1c, jointly contributes to the cardiovascular risk of patients with advanced atherosclerosis. The finding of this study show positive correlation between serum level of pentraxin III and hs-CRP in group I which may explain that the hs-CRP at level >3.17 mg/dl may indicate that the patients in GI may have higher risk for development of CAD in the future and may be an early predictor of progression of atherosclerosis more than PTX3 which may play an important role in advance stage of atherosclerosis (GIII), further study need to verify the results. hs-CRP is a short pentraxin produced in the liver in response to interleukin-6, whereas PTX-3 is a long pentraxin produced by inflammatory and immune cells in to the presence of interleukin-1. In addition, PTX-3 is also distinct from CRP in legend recognition and innate immunity function (Rocco Barazzoni *et al*., 2013).

**Conclusion**

This study suggested the controversial role of both proinflammatory adipokines (hs-CRP & pentraxin III) combine with high value of HbA1c as early predictor for development of CAD in association with coronary artery calcification. The link between inflammation (hs-CRP), hyperglycemia (HbA1C%) and dyslipidemia (non–HDL and atherogenic index) may play important role in the progression of CAC.

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