Serum uric acid level is an independent risk factor for presence of calcium in coronary arteries: an observational case-controlled study

Serum ürik asit düzeyi koroner arter kalsiyum varlığının bağımsız bir belirleyicisidir: Bir gözlemsel vaka kontrollü çalışma

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Abstract

Objective: A link between uric acid levels and cardiovascular diseases has been previously reported. Coronary artery calcium score (CACS) is a marker of atherosclerotic disease and a predictor of cardiovascular events. We sought to determine if serum uric acid level is an independent risk factor for the presence of calcium in coronary arteries.

Methods: Four hundred and forty-two patients who were evaluated in the cardiology outpatient clinic for suspected coronary heart disease with a low-moderate risk for coronary artery disease were included in this observational case-controlled study. Serum uric acid levels were measured with colorimetric methods. CACS were performed using a 64-slice CT scanner. Patients were divided to 3 groups according to their CACS value (Group 1: CACS=0, Group 2: CACS 1-100, Group 3: CACS>100).

Results: The demographical characteristics and laboratory findings of 3 groups were similar, except age, fasting glucose levels and serum uric acid levels. Serum uric acid levels were found to increase significantly with increasing CACS (p=0.001). Patients were grouped according to presence CAC (CACS=0 and CACS≥1) and in the multiple regression analysis, age (OR, 1.11, 95% CI, 1.07-1.16), smoking (OR, 3.83, 95% CI, 2.06-7.09), serum uric acid levels (OR, 1.26, 95% CI, 1.04-1.54) and average 10-year total risk of Framingham risk score (OR, 1.13, 95% CI, 1.04-1.09) appeared as independent factors predictive of presence of CAC (p<0.05).

Conclusion: Serum uric acid level is an independent risk factor for presence of coronary calcium. Moreover, increasing levels of serum uric acid are associated with increasing CACS. *(Anadolu Kardiyol Derg 2013; 13: 139-45)*

Key words: Uric acid, coronary artery calcium score, coronary heart disease, logistic regression analysis

ÖZET

Amaç: Serum ürik asit düzeyinin kardiyovasküler hastalıklarla ilişkisi farklı klinik durumlarda gösterilmiştir. Koroner arter kalsiyum skoru (KAKS) ateroskleroz belirteçlerinden biri olup kardiyovasküler olay gelişiminin bir belirleyicisidir. Biz serum ürik asit düzeyinin koroner arter kalsiyum varlığının bağımsız bir belirleyicisi olup olmadığını değerlendirmeyi amaçladık.

Yöntemler: Kardiyoloji polikliniğinde koroner arter hastalığı şüphesi ile değerlendirilen ve koroner arter hastalığı gelişimi için düşük-orta risk taşıyan 442 hasta bu gözlemsel vaka kontrol çalışmasına alındı. Serum ürik asit düzeyi kolorimetrik yöntemle ölçüldü. KAKS 64 kesit bilgisayarlı tomografi ile hesaplandı. Hastalar KAKS değerlerine göre 3 gruba ayrıldı (Grup 1: KAKS=0, Grup 2: KAKS 1-100, Grup 3: KAKS>100).

Bulgular: Demografik ve laboratuvar özellikleri 3 grup arasında yaş, açlık kan şekeri ve serum ürik asit düzeyi dışında benzerdi. Serum ürik asit düzeyi KAKS seviyesi ile uyumlu ve anlamlı olarak artmış olarak bulundu (p=0.001). Hastalar KAK varlığına göre gruplandığında (KAKS=0 ve KAKS≥1) çoklu değişken analizinde yaş (OR, 1.11, %95 CI, 1.07-1.16), sigara (OR, 3.83, %95 CI, 2.06-7.09), serum ürik asit düzeyi (OR, 1.26, %95 CI, 1.04-1.54) ve 10 yıllık toplam koroner arter hastalığı gelişme riski (OR, 1.13, %95 CI, 1.04-1.09) KAK varlığının bağımsız belirleyicisi olarak bulundu (p<0.05).

Sonuç: Bu çalışmada artmış serum ürik asit düzeyinin artmış KAKS ile birlikte olduğu gösterilmiştir. Serum ürik asit düzeyinin KAK varlığının bağımsız belirleyicisi olduğu bulunmuştur. *(Anadolu Kardiyol Derg 2013; 13: 139-45)*

Anahtar kelimeler: Ürik asit, koroner arter kalsiyum skoru, koroner kalp hastalığı, lojistik regresyon analizi

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Introduction

In today's epidemic of cardiovascular disease, preventive cardiology is the current clinical practice. The patient's cardiovascular risk status determines the intensity of treatment, counting on the principle that the higher-risk patients will benefit more from drug treatments. Traditional tests of cardiovascular risk, such as Framingham risk score, still fail to identify many people who will experience a coronary heart disease (CHD) event in the future (1). Therefore, new tests that will improve the global CHD assessment are being evaluated.

Coronary artery calcium score (CACS) has been shown to provide CHD risk prediction beyond traditional risk factors (2-5). CACS detected by computerized tomography (CT) is an important marker of atherosclerosis and its severity correlates with coronary plaque burden (2, 3). CACS is also an independent marker of CHD risk (4, 5). However it requires high technology tomography equipment is fairly expensive compared to traditional risk assessment tests and the patient receives a considerable amount of radiation.

Uric acid is the final product of purine nucleotides metabolism in humans and hyperuricemia is an important metabolic problem that has become increasingly common worldwide over the past decades. Previous studies demonstrated a strong relation between serum uric acid levels and CHD and some studies suggest that uric acid may be an independent risk factor for cardiovascular disease (6-12). Recently a meta-analysis showed that hyperuricemia may increase the risk of CHD events, independently of traditional CHD risk factors (13).

However, there are contradicting data about the relation between CACS and serum uric acid levels. Previously some studies demonstrated a relation between CACS and serum uric acid levels (14-16) but one large-scale study did not support these findings (17).

We wanted to investigate if serum uric acid levels are independently associated with CACS in patients without known CHD, and thus provide support for the reliability of serum uric acid level as an additional test in cardiovascular risk assessment.

Methods

Study design

Patients were selected from a cohort that underwent CT for evaluation of coronary heart disease. Blood tests for serum uric acid measurement were drawn once without follow- up. Therefore this is an observational case-controlled study.

Study population

A-thousand-one-hundred-and ninety patients who were evaluated in the Fatih University cardiology outpatient clinic for suspected CHD with a low-intermediate risk for coronary artery disease were studied and 442 patients in whom CT was performed that did not have any exclusion criteria were included in this observational case-controlled study. Patients with a history of myocardial infarction, heart failure or cardiomyopathies, stroke, peripheral arterial disease, renal dysfunction, hepatic and hemolytic disorders, concomitant inflammatory diseases, neoplastic diseases, thyroid disease, gout, intake of vitamins or uric acid lowering medications like allopurinol and patients taking diuretic medications were excluded from the study.

The study protocol was approved by the local ethical committee and an informed consent was obtained from each patient.

Study protocol

The clinical demographical data from the patients who were eligible to be included in the study, were recorded. CT scans were performed to determine CACS. Serum uric acid levels were measured concomitantly once, without follow-up. First, patients were stratified according to CACS into 3 groups: normal (Group 1: CACS=0), low (Group 2: CACS=1 to 100), and high (Group 3: CACS>100) as recommended by Rumberger et al. (18). Second, patients were divided two groups according to presence of coroner artery calcium (CAC) and then statistical analysis was performed.

Study variables

Baseline clinical and demographical properties of study population were recorded. The predictor (grouping) variable was coronary calcium score, and the primary outcome variable was serum uric acid.

Laboratory analysis

Standard techniques were used to measure creatinine, blood glucose, total cholesterol, high density lipoprotein (HDL), low-density lipoprotein (LDL), and calcium and C-reactive protein levels, from blood samples drawn after 12 hours fasting. Serum uric acid levels were measured with colorimetric methods at 1-3 days before CAC measurements (Roche/Hitachi Modular Analytics, Roche Diagnostics, GmBH, Mannheim, Germany). Reference values for uric acid were 2.6-6 mg/dL.

Measurement of CACS

All CT scans were performed on a 64-slice scanner (Philips Brilliance 64, Philips Medical Systems, Eindhoven, The Netherlands) with a 0.42-second rotation time with a pitch of 0.2, tube voltage of 120 kV, and tube current of 600-1050 mAs. Patients with heart rates >70 beats/min received, unless they had known any contraindication for beta-blocker usage, intravenous metoprolol 5 to 15 mg or orally metoprolol 100 mg 1 hour before the scan. Thirty to 40 consequent 3-mm-thick transverse images of the heart were obtained during maximal breath holding with electrocardiogram triggering. All data sets were reconstructed using retrospective electrocardiographic-gating at 40%, 75%, and 80% of the RR interval. All scans were scored at a dedicated workstation (EBW, Philips Medical Systems, Eindhoven, The Netherlands). The calcium score for each subject was the sum of calcium scores of the left main, left anterior

descending, left circumflex and right coronary arteries according to the Agatston method as previously described (19).

The Framingham risk score calculation

The Framingham risk score for CHD was calculated according to the version described by Wilson et al. (20) for all patients. Framingham risk score predicts 10- year risk of developing CHD using the following factors: age, gender, LDL and HDL cholesterol, smoking status, blood pressure level and presence of diabetes.

Statistical analysis

The statistical package SPSS (Statistical Package for the Social Sciences, version 17.0, SSPS Inc, Chicago, Ill, USA) was used for statistical analyses. Continuous variables were expressed as mean±standard deviation. Categorical variables were expressed as total number (percentage). All continuous variables were checked with Kolmogorov-Smirnov normality test to show their distributions. Continuous variables with normal distributions were compared using the unpaired Student t test and ANOVA with posthoc Tukey test. Continuous variables with abnormal distributions were compared using the Mann-Whitney U test and ANOVA with posthoc Tukey test. For categorical variables, the Chi-square test was used. Values for p less than 0.05 were considered statistically significant for all tests.

The relationship between CACS and uric acid, age, male sex, diabetes mellitus, hypertension, smoking status, total cholesterol, LDL cholesterol and HDL cholesterol levels and average 10-year total risk of Framingham risk score were examined by Pearson's correlation analyses.

The area beneath the receiver operating characteristics (ROC) curve was used to calculate the discriminative ability of uric acid to determine CAC. Sensitivity, specificity, negative predictive values, and positive predictive values were calculated for these markers on the basis of ROC curves. P<0.05 was regarded as significant.

A multiple logistic regression analysis was performed to examine the probability of CACS ≥1. The alternative test hypothesis was built as two-sided for each statistical analysis. The tests were independent and so the experiment wise. Type I error does not exceed 0.05 alpha levels. Significant univariate variables (Age, sex, hypertension, smoking, fasting blood glucose, uric acid, Framingham risk score) with p<0.05 were included in the multiple logistic regression analysis for odds ratios and 95% confidence intervals.

Results

Patients characteristics

A total of 442 consecutive subjects who were referred to coronary artery calcium scoring after being evaluated for CHD in the cardiology outpatient clinic were included in the study. The subjects were grouped according to their CACS (Group 1: n=240, mean age 49.3±9.7 years, 67 females; Group 2: n=142, mean age 57.2±8.7 years, 24 females; Group 3: n=60, mean age 62.0±9.2 years, 11 females). Baseline demographic and clinical characteristics and laboratory data of participants are demonstrated in Table 1. Age, gender, presence of hypertension, smoking status, fasting glucose levels, serum uric acid levels and average 10-year total risk of Framingham risk score were significantly different between groups (Table 1). Serum uric acid levels were found to increase significantly with increasing CACS (p=0.001) (Table 1).

When the 3 patient groups were analyzed for a high serum uric acid level (serum uric acid level >5.6 mg/dL), percentage of patients with a high uric acid level was highest in group three, p<0.001 (Fig. 1).

Correlation between CACS and parameters

Positive correlations were found between log CACS and uric acid (r=0.198, p<0.001), age (r=0.376, p<0.001), male gender (r=0.290, p<0.001), smoking status (r=0.343, p<0.001), hypertension (r=0.098, p<0.034) and average 10-year total risk of Framingham risk score (r=0.436, p<0.001) (Table 2). Negative correlations were found between log GGT and HDL (r=-0.095, p=0.048) (Table 2). No correlations were found between log CACS and diabetes mellitus, total cholesterol and LDL cholesterol.

Relation between uric acid and CACS

Receiving operating characteristic (ROC) curve was plotted to determine the cut-off level of uric acid for predicting CAC (Fig. 2). The area under the ROC curve (Fig. 2) was 0.59 (SE=0.03, 95% CI value: 0.541-0.647). A uric acid level of 5.6 mg/dL resulted in 61.4% sensitivity and 47.9% specificity for detecting CAC, with a positive predictive value of 49.8% and a negative predictive value of 59.6%.

Predictors of coronary artery calcium presence

Patients were stratified into 2 groups according to presence CAC: CACS=0 and CACS≥1 to show if uric acid is an independent predictor of CACS. In the univariate analysis, age, gender, hypertension, smoking, fasting glucose levels, serum uric acid levels and average 10-year total risk of Framingham risk score were significantly correlated with presence of CAC (Table 3). In the multiple regression analysis, age, smoking, serum uric acid levels and average 10-year total risk of Framingham risk score appeared as independent factors predictive of presence of CAC (Table 4).

Discussion

In this study, we aimed to assess the association between serum uric acid levels and presence and severity of CAC detected by CT. Our results demonstrated that serum uric acid level is positively correlated with CACS, increasing as CACS increased. Moreover, uric acid seems to be an independent risk factor for the presence of CAC. This study also showed that traditional risk factors such as age, smoking, and average 10-year total risk of cardiovascular disease determined by Framingham risk score are independent determinants of CAC presence.

Table 1. Baseline clinical and laboratory features of patients

Variables	Ca++ score 0 (n=240)	Ca++ score 1-100 (n=142)	Ca++ score >100 (n=60)	*F	*p
Age, years	49.3±9.7	57.2±8.7	62.0±9.2	60.296	<0.001[a]
Sex, male, n (%)	173 (72.1)	118 (83.1)	49 (81.7)	-	0.031
Diabetes mellitus, n (%)	51 (21.3)	41 (28.9)	15 (25.0)	-	0.241
Hypertension, n (%)	129 (53.8)	94 (66.2)	43 (71.7)	-	0.008
Smoking, n (%)	30 (12.5)	38 (26.8)	39 (65)	-	<0.001
Mean LVEF, %	63.4±5.6	63.0±6.6	62.7±2.8	0.103	0.903
Creatinine, mg/dL	0.8±0.2	0.9±0.2	0.8±0.2	0.093	0.120
Fasting blood glucose, mg/dL	96±22	106±38	107±26	6.414	0.002[b]
CRP, mg/dL	4.1±5.8	4.2±4.5	3.7±3.5	0.165	0.848
Calcium, mg/dL	9.4±0.8	9.4±0.5	9.6±0.5	1.449	0.237
Uric acid, mg/dL	5.6±1.2	6.0±1.3	6.1±1.5	6.674	0.001[c]
Total cholesterol, mg/dL	200±40	204±35	196±48	0.830	0.437
LDL, mg/dL	124±36	126±34	119±41	0.862	0.423
HDL, mg/dL	46±13	46±13	45±12	0.166	0.847
Framingham risk score. 10-year total risk, %	8.9±5.9	14.5±8.1	18.1±11.2	47.505	<0.001[d]

Data are presented as number (percentage) and mean±SD values

*Chi-square and ANOVA with posthoc Tukey test

Posthoc analysis results

[a]Ca score 0 group - p<0.001 compared with Ca score 0-100 group; p<0.001 compared with Ca score >100 group. Ca score 0-100 group - p=0.002 compared with Ca score >100 group

[b]Ca score 0 group - p=0.005 compared with Ca score 0-100 group; p=0.035 compared with Ca score >100 group. Ca score 0-100 group - p=0.981 compared with Ca score >100 group

[c]Ca score 0 group - p=0.010 compared with Ca score 0-100 group; p=0.011 compared with Ca score >100 group. Ca score 0-100 group - p=0.768 compared with Ca score >100 group

[d]Ca score 0 group - p<0.001 compared with Ca score 0-100 group; p<0.001 compared with Ca score >100 group. Ca score 0-100 group - p=0.007 compared with Ca score >100 group

CRP-C - reactive protein, HDL - high-density lipoprotein, LDL - low-density lipoprotein, LVEF - left ventricular ejection fraction

Table 2. Correlation between of CAC and clinical variables

Variables	All patients	
	*r	*p
Uric acid	0.198	<0.001
Age	0.376	<0.001
Sex, male	0.290	<0.001
Diabetes mellitus	0.019	0.685
Hypertension	0.098	0.039
Smoking	0.343	<0.001
Total cholesterol	0.030	0.534
LDL	0.029	0.541
HDL	-0.095	0.048
Framingham risk score, 10-year total risk	0.436	<0.001

*Pearson correlation analysis

CAC - coronary artery calcification, HDL - high-density lipoprotein, LDL - low-density lipoprotein

There are several studies in literature documenting the relationship between serum uric acid levels and cardiovascular diseases (6-14). Increased serum uric acid was found to be associated with important risk factors for atherosclerosis like hypertension (21-24), abdominal obesity (23), diabetes mellitus (24, 25), the metabolic syndrome (16), hypertriglyceridemia (26), endothelial dysfunction (27) and renal failure (28). Serum uric acid has antioxidant properties by scavenge ring free radicals, in the late stages of atherosclerosis the antioxidant state is reversed (29). The association between serum uric acid and inflammatory markers such as CRP and interleukins was demonstrated in a large study of elderly subjects (30). The exact pathophysiologic mechanism of the role of uric acid in the process of atherosclerosis is yet unknown.

The close correlation between the atherosclerotic plaque burden and the extent of CAC has been confirmed both by histopathology and intravascular ultrasound studies (3).

There seems to be a strong relationship between serum uric acid levels and CACS in this study. Some studies demonstrated a relation between CACS and serum uric acid levels in patients with type 1 diabetes mellitus (31), in asymptomatic patients (32) but other studies did not support these findings (17). Some of these studies showed that high uric acid levels were independently associated with CAC presence (14-16) but in the other studies uric acid was not associated with presence of CAC after adjusting other risk factors for cardiovascular disease (32). ARIC study is one of the largest studies investigating the relation between CHD incidence and serum uric acid levels in a middle

Table 3. Univariate analysis for presence of coronary artery calcium

Variables	Patients with coronary artery calcification (n=240)	Patients without coronary artery calcification (n=202)	*p
Age, years	49.3±9.7	58.6±9.1	<0.001
Sex, male, n (%)	173 (72.1)	167 (82.7)	0.009
Diabetes mellitus, n (%)	51 (21.3)	56 (27.7)	0.120
Hypertension, n (%)	129 (53.8)	137 (67.8)	0.003
Smoking, n (%)	30 (12.5)	77 (38.1)	<0.001
Mean LVEF, %	63.4±5.6.	62.9±6.0	0.667
Creatinine, mg/dL	0.8±0.2	0.8±0.2	0.942
Fasting blood glucose, mg/dL	96.5±21.6	106.3±35.9	<0.001
CRP, mg/dL	4.1±6.0	4.0±4.2	0.957
Calcium, mg/dL	9.4±0.8	9.5±0.5	0.241
Uric acid, mg/dL	5.6±1.2	6.0±1.4	<0.001
Total cholesterol, mg/dL	200±40	202±39	0.716
LDL, mg/dL	124±36	124±36	0.953
HDL, mg/dL	46±13	46±13	0.709
Framingham risk score. 10-year total risk, %	8.9±5.9	15.6±9.2	<0.001

Data are presented as number (percentage) and mean±SD values
*Chi-square, unpaired Student-t test and the Mann-Whitney U test
*CRP- C - reactive protein, HDL - high-density lipoprotein, LDL - low-density lipoprotein, LVEF - left ventricular ejection fraction

Table 4. Predictors of coronary artery calcium presence

Variables	OR	95% CI	*p
Age	1.11	1.07-1.16	<0.001
Smoking	3.83	2.06-7.09	<0.001
Uric acid	1.26	1.04-1.54	0.020
Framingham risk score. 10-year total risk, %	1.13	1.04-1.09	0.002

*Multiple logistic regression analysis

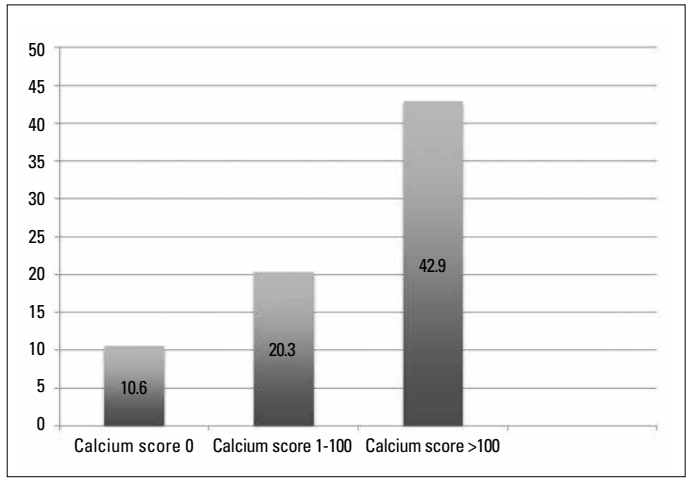

Figure 1. Percentage of patients with a serum uric acid level >5.6 mg/dL in the three patient groups according to calcium scores

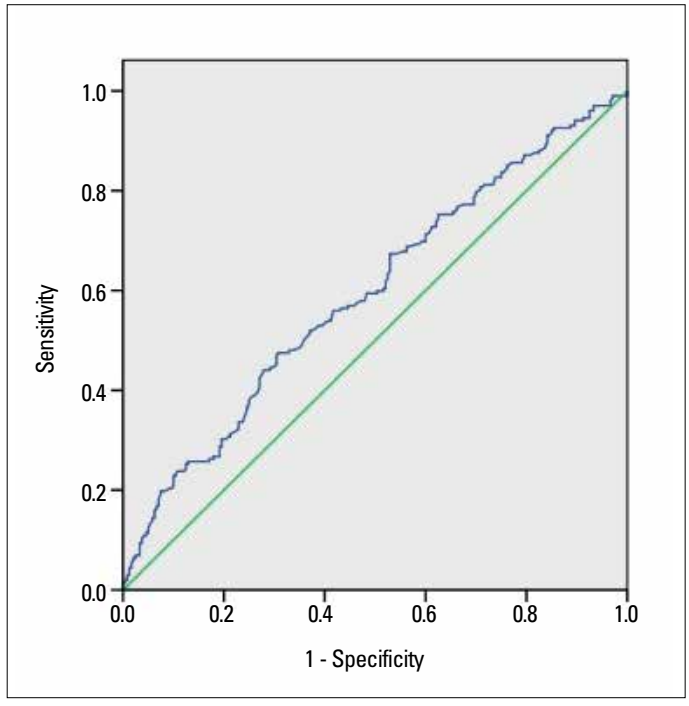

Figure 2. Receiving operating characteristic (ROC) curve plotted to determine the cut-off level of uric acid for predicting coronary artery calcium

aged population of men and women (33). The incident CHD was defined as death due to CHD or probable MI. Serum uric acid was not independently associated with incident CHD in this study. Our results seem to be conflicting with the results of ARIC study. However, CACS was used instead of clinical CHD events as a sign of atherosclerosis in our study. CACS is a more sensitive method of detecting atherosclerosis. This fact may be the reason of conflicting results.

This is the first study in the literature investigating the relationship between CACS and uric acid levels in a population of subjects with a low to intermediate risk for CHD. Santos and friends showed that uric acid was an independent marker for presence of CAC in subjects with metabolic syndrome (32). Our study population is different from their population as it includes 23.1% of females and subjects have a higher risk of CHD. In this study group, serum uric acid level was an independent marker for presence of CAC, regardless of the metabolic syndrome status.

We do not recommend measurement of uric acid levels as a screening test for coronary calcification as it does not have the necessary sensitivity or specificity. However serum uric acid level does have a relationship with coronary calcification and we think that it should be considered as a risk factor.

Study limitations

This study was a cross-sectional study in a group of patients who needed non-invasive assessment for CHD. Therefore, prospective studies are needed to further clarify the role of serum

uric acid in coronary atherosclerotic process. Secondly, because of racial differences between the prevalence and morphology of atherosclerosis, the results cannot be generalized to the whole population. The difference in the number of patients in groups when grouped according to CACS may have influenced the statistical analyses results.

Conclusion

Our study revealed that serum uric acid level, age, smoking and Framingham risk score are independent risk factors for presence of coronary calcium.

Conflict of interest: None declared.

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