

Serum concentration of visfatin is decreased in patients with chronic heart failure

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Background. There is an increasing interest in the role of adipocytokines in cardiovascular pathophysiology. **Aim.** The aim of the study was to compare visfatin levels, a novel adipokine, in patients with heart failure (HF) due to the left ventricular systolic dysfunction with those in age- and body mass index (BMI) — matched healthy controls in relation to the parameters of glucose metabolism and high sensitivity C-reactive protein (hsCRP) levels. **Material/Subjects and Methods.** The study population consisted of 28 males with systolic HF referred for cardiopulmonary exercise testing, divided into two subgroups based on their NYHA class (HF patients NYHA_{I+II}, n=17, and HF patients NYHA_{III+IV}, n=11), and 23 controls. The following indices were measured in a serum samples: visfatin, hsCRP, glucose and lipid metabolism parameters, and the insulin resistance index HOMA_{IR} (homeostasis model assessment insulin resistance) was calculated. **Results.** Concentrations of visfatin and high-density lipoprotein cholesterol (HDL-cholesterol) in the HF subjects were significantly lower ($p \leq 0.01$) than in controls. The Kruskal-Wallis test showed significant differences between three groups (controls and both subgroups of heart failure patients) in mean levels of visfatin, hsCRP, glucose, HOMA_{IR} and HDL-cholesterol. **Conclusion.** Serum visfatin concentrations in patients with systolic HF, particularly with more advanced NYHA classes, are significantly lower in comparison to healthy controls and are independent of age or anthropometric and metabolic parameters.

Key words: visfatin, insulin resistance, C-reactive protein, lipoproteins, heart failure

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INTRODUCTION

Heart failure (HF) becomes a serious problem in contemporary medicine because of an increasing number of patients developing this pathology and its relation with high morbidity and mortality. According to the “muscle hypothesis”, the main symptom, i.e., exercise intolerance, results from complex peripheral abnormalities, in which low-grade systemic inflammation and metabolic abnormalities play an important role (Clark *et al.*, 1996).

Visfatin is a novel adipocytokine predominantly secreted by visceral adipocytes and is presumed to have proinflammatory properties (Moschen *et al.*, 2007). There is an increasing interest in the role of adipocytokines in cardiovascular pathophysiology (Dahl *et al.*, 2007; Liu *et al.*, 2009; Kadoglou *et al.*, 2011). There are some reports

on the relationship between levels of leptin (Wolk & Somers, 2006) and apelin — another new adipokine — (Chong *et al.*, 2006; Ho *et al.*, 2009) and heart failure severity. Their role in pathophysiology of heart failure is suggested. We have found only one report on visfatin in the HF (Ho *et al.*, 2009).

Our aim was to compare the serum visfatin concentrations in patients with heart failure due to the left ventricular systolic dysfunction with those in age- and BMI-matched healthy controls in relation to the parameters of glucose metabolism and C-reactive protein levels.

MATERIALS AND METHODS

The study population consisted of 28 males with systolic heart failure referred for cardiopulmonary exercise testing and 23 healthy subjects. Heart failure was diagnosed according to the European Society of Cardiology guidelines. All patients had left ventricular ejection fraction (LVEF) <45% as measured by echocardiography. Coronary artery disease (CAD) was diagnosed in 12 patients (43%) and non-ischemic dilated cardiomyopathy (DCM) in 16 (57%). The patients with heart failure were divided into two subgroups based on their NYHA class: heart failure patients NYHA_{I+II} (n=17) and heart failure patients NYHA_{III+IV} (n=11).

At the time of examination, all subjects were stable and on optimal medical therapy. Twenty-four patients (86%) were treated with angiotensin-converting enzyme inhibitor (ACEI) or angiotensin II receptor blocker (ARB), 26 (93%) with beta-blocker, 24 ones (86%) received furosemide, 14 (50%) were on aldosterone antagonist, 8 (30%) — on digoxin, 17 (60%) — on aspirin and 18 (64% in NYHA_{I+II} group and 65% in NYHA_{III+IV} group) — on statins. The exclusion criteria were as follows: acute or chronic inflammatory condition, recent myocardial infarction or revascularization (≤ 3 months), exertional angina or arrhythmias, atrial fibrillation, diabetes mellitus, severe lung disease, severe renal insufficiency or other organ disorders significantly compromising subjects' physical capacity.

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Abbreviations: BMI, body mass index; CAD, coronary artery disease; CRP, C-reactive protein; DBP, diastolic blood pressure; DCM, dilated cardiomyopathy; HF, heart failure; HDL, high-density lipoprotein; HOMA_{IR}, homeostasis model assessment insulin resistance; LDL, low-density lipoprotein; LVEF, left ventricular ejection fraction; MCP-1, monocyte chemoattractant protein; peak VO₂, peak oxygen consumption; SBP, resting systolic blood pressure; TG, triglyceride

All enrolled subjects underwent maximal cardiopulmonary exercise treadmill test performed according to the modified Bruce protocol (adding stage 0: 3 min, 1.7 km/h, 5% grading). The peak oxygen consumption (peak VO_2), carbon dioxide production, and minute ventilation were measured using a breath-by-breath technique (Sensor Medics, model $\dot{V}_{\text{max}}29$). The equipment was calibrated before each test. There was continuous ECG monitoring and blood pressure measurement at each stage of exercise. Peak VO_2 was defined as the highest 20-second average during the last 60 seconds of exercise.

The control group consisted of male volunteers declaring good health status. The inclusion criteria were age, body mass and BMI as similar as possible to the patients' characteristics.

All subjects gave their informed consent to participate in the study. The study was conducted in compliance with the Helsinki Declaration and was approved by the local Ethics Committee.

Blood samples were collected between 8.00 and 9.00 a.m., fasting, from the antecubital vein. The samples were centrifuged at 5000 rpm and 4°C. Serum was separated and stored at -70°C. The following serum parameters were measured: glucose, total cholesterol, high-density lipoprotein (HDL) cholesterol, triglyceride (TG) concentrations with commercially available assays (Cormay, Poland), insulin level with a radioimmunoassay (BioSource Europe S.A., Belgium), visfatin concentration with enzyme-linked immunoassays (ALPCO Diagnostics, USA, assay sensitivity=30 pg/ml, within-assay precision 4.32% and between-assay precision 7.58%). Serum C-reactive protein (hsCRP) was determined with a high-sensitive nephelometric method (Dade Behring, Germany).

Low-density lipoprotein (LDL) cholesterol concentrations were calculated using the formula of Friedewald *et al.* (1972). The insulin sensitivity index HOMA_{IR} was calculated using the formula of Matthews *et al.* (1985):

$$\text{HOMA}_{\text{IR}} = \text{fasting insulin } (\mu\text{U/ml}) \times \text{fasting glucose } (\text{mmol/L}) / 22.5.$$

The values are given as mean, standard deviation (SD), median (Me), standard error (SE) and interquartile ranges. The normal distribution of the data was verified with the Shapiro-Wilk test. Comparisons between

the heart failure patients and controls for age, anthropometric measurements, and biochemical parameters were made using the Student *t*-test or Mann-Whitney test. Comparisons for maximal oxygen uptake ($\text{VO}_{2\text{max}}$) between the heart failure subgroups (by NYHA class) and for visfatin levels between the patients with ischemic heart disease and dilated cardiomyopathy or between patients treated and not treated with statins were made using the Mann-Whitney test. Comparisons between three groups of subjects (heart failure subgroups divided according to NYHA class and the controls) for biochemical parameters were made using the Kruskal-Wallis one-way analysis of variance by ranks with post-hoc test. The Spearman's rank analysis was used to calculate correlation coefficients. A $p < 0.05$ was taken to be statistically significant. Statistical analyses were performed with the Statistica 8.0 software package.

RESULTS

Basic characteristics of the examined groups of subjects are presented in Table 1.

The heart failure group and controls did not differ significantly regarding age, body weight, BMI and waist circumference. The heart failure subjects had significantly lower resting systolic blood pressure ($p \leq 0.01$) and diastolic blood pressure ($p < 0.05$), and a higher heart rate ($p \leq 0.01$) than the controls.

Results of the laboratory assessments are shown in Table 2. Concentrations of visfatin and HDL-cholesterol in the HF subjects were significantly lower ($p \leq 0.01$) than in the controls. There were significantly higher levels of triglycerides ($p < 0.05$), glucose ($p \leq 0.01$) and HOMA_{IR} ($p < 0.05$) in the HF patients in comparison to the control group. In 53% and 26% of subjects from the heart failure and control groups, respectively, the values of HOMA_{IR} represent insulin resistance ($\text{HOMA} \geq 2.5$).

In the HF group there were no significant differences in visfatin concentrations between the patients with ischemic heart disease ($n=12$) and dilated cardiomyopathy ($n=16$), (Me \pm SE respectively: 0.74 ± 0.81 ng/ml *vs* 0.51 ± 0.54 ng/ml; $p=0.5155$) and between the patients treated ($n=18$) and not treated with statins ($n=10$),

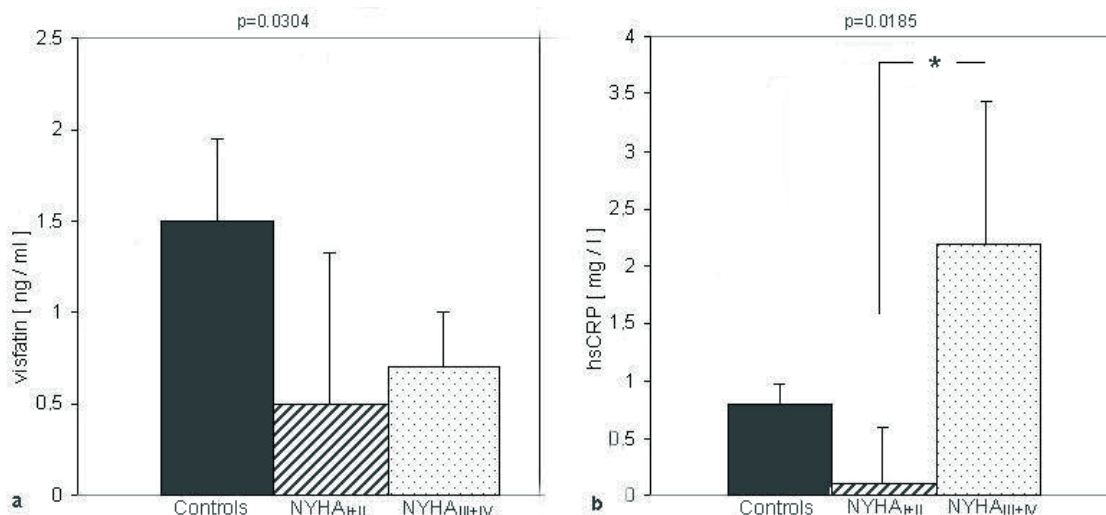


Figure 1. Serum visfatin and C-reactive protein (hsCRP) concentrations in controls and heart failure patients divided into NYHA_{I+II} and NYHA_{III+IV} class.

* $p < 0.05$, significantly different between two subgroups of heart failure patients, results are expressed as median \pm SE; (a) serum visfatin concentrations in controls and in both subgroups of HF patients; (b) C-reactive protein (hsCRP) concentrations in controls and in both subgroups of HF patients.

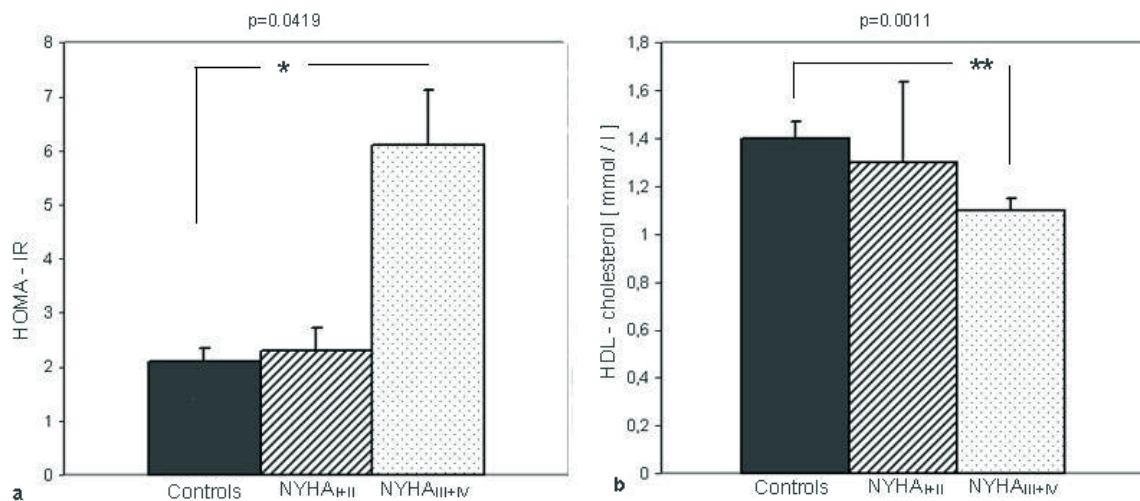


Figure 2. Homeostasis Model Assessment Insulin Resistance index (HOMA_{IR}) values and high density lipoprotein (HDL) cholesterol concentrations in controls and heart failure patients divided into NYHA_{I+II} and NYHA_{III+IV} class.

** $p < 0.01$, * $p < 0.05$, significantly different between subgroup of heart failure patients with NYHA_{III+IV} and controls, results are expressed as median \pm S.E. (a) homeostasis model assessment insulin resistance index (HOMA_{IR}) in controls and in both subgroups of HF patients (b) high density lipoprotein (HDL) cholesterol concentrations in controls and in both subgroups of HF patients.

($Me \pm SE$ respectively: 0.60 ± 0.36 ng/ml *vs* 0.82 ± 1.28 ; $p = 0.2862$).

The Kruskal-Wallis test showed significant differences between three groups (the controls and both subgroups of HF patients divided according to NYHA I+II *vs* III+IV class) in levels of visfatin, hsCRP (figure 1, a and b, respectively), HOMA_{IR}, HDL-cholesterol (Fig. 2, a and b, respectively) and glucose ($p = 0.0038$). The NYHA_{III+IV} subjects had significantly lower HDL-cholesterol concentrations ($p \leq 0.01$) and only the tendency to decreased visfatin concentrations ($p = 0.061$). Moreover, they had higher hsCRP, HOMA_{IR} and glucose levels ($p < 0.05$) than the controls. In the NYHA_{I+II} subjects, the levels of all these biochemical parameters did not differ from the controls. There was a significant difference between the two heart failure subgroups with respect to hsCRP concentrations ($p = 0.0255$). No significant differences were found between three investigated groups with respect to age, body mass, BMI and waist circumference.

The NYHA_{I+II} subjects had significantly higher mean peak VO_2 (21.7 ± 3.66 ml/kg/min) than the NYHA_{III+IV} ones (14.4 ± 4.79 ml/kg/min; $p = 0.0018$).

In all heart failure patients, HDL-cholesterol levels correlated positively with visfatin ($r = 0.39$, $p = 0.0444$) and negatively with hsCRP concentrations ($r = -0.52$, $p = 0.0053$), and the NYHA class correlated with hsCRP concentrations ($r = 0.53$; $p = 0.0030$). A trend was found

between hsCRP and peak VO_2 ($r = -0.32$; $p = 0.0990$). In the control group, a relationship between visfatin concentrations and BMI was revealed ($r = 0.43$, $p = 0.0422$). Positive correlations were also found between BMI and insulin levels ($r = 0.53$, $p = 0.0088$), BMI and HOMA_{IR} ($r = 0.48$, $p = 0.0204$), waist circumference and insulin levels ($r = 0.71$, $p = 0.0002$), waist circumference and HOMA_{IR} ($r = 0.64$, $p = 0.0014$).

DISCUSSION

The presented data show that serum visfatin concentrations are significantly lower in male subjects with heart failure due to systolic dysfunction in comparison to healthy controls. Furthermore, visfatin concentrations are lower in patients with more severe HF (NYHA_{III+IV}) in comparison to mild HF (NYHA_{I+II}). Concentrations of visfatin were independent of age, BMI, levels of glucose, insulin, cholesterol, and triglycerides, HOMA_{IR}, heart rate, and peak VO_2 .

An adipocytokine exerting insulin-mimicking effects, visfatin, attracts particular interest of investigators dealing with diabetes and obesity (Fukuhara *et al.*, 2005). Despite many studies published recently, visfatin's role is unclear and results of the studies are inconsistent. It is shown that serum visfatin concentrations are increased in patients with type 2 diabetes independently of obesity (measured as BMI or waist circumference), and insulin resistance (Alghasham & Bakarar, 2008; Esteghamati *et al.*, 2011). But it is no more so clear in gestational diabetes, where some investigators have found increased levels of visfatin while others decreased in comparison to controls with normal glucose metabolism (Chan *et al.*, 2006; Lewandowski *et al.*, 2007). It has also been shown that visfatin concentrations are increased in obesity in some studies (Zahorska-Markiewicz *et al.*, 2007), while others could not demonstrate any difference in visfatin levels between obese and non-obese groups

Table 1. Baseline characteristics of heart failure subjects and control group

Characteristic	Heart failure group	Control group	
Age (years)	51.0 \pm 7.88	53.0 \pm 11.47	0.3203
Body weight (kg)	82.6 \pm 11.94	86.3 \pm 12.61	0.3487
Height (cm)	174.0 \pm 4.98	178.6 \pm 6.28	0.0100*
BMI (kg/m ²)	27.3 \pm 3.84	26.9 \pm 3.90	0.7404
Waist circumference (cm)	98.9 \pm 9.53	95.8 \pm 9.99	0.2256
HR (beats/min)	86.8 \pm 16.14	74.2 \pm 10.08	0.0035**
SBP (mm Hg)	118.2 \pm 19.49	133.9 \pm 18.26	0.0013**
DBP (mm Hg)	79.3 \pm 10.2	87.0 \pm 11.45	0.0206*

** $p < 0.01$; * $p < 0.05$. Results are expressed as mean \pm S.D. BMI, body mass index; HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure.

Table 2. Biochemical parameters of heart failure subjects and control group

Parameter	Heart failure group	Control group	<i>p</i> -value
Visfatin (ng/ml)	0.6 (0.4-1.1)	1.5 (1.0-2.5)	0.0095**
Insulin (μU/ml)	11.2 (8.0-22.5)	9.5 (7.0-13.9)	0.1851
Glucose (mmol/l)	5.7 (5.3-6.2)	4.8 (4.1-5.6)	0.0009**
HOMA _{IR}	2.9 (2.0-5.6)	2.1 (1.5-2.9)	0.0231*
Total cholesterol (mmol/l)	5.0 (4.3-6.0)	4.8 (4.0-5.6)	0.3114
HDL-cholesterol (mmol/l)	1.1 (0.9-1.3)	1.4 (1.2-1.9)	0.0032**
LDL-cholesterol (mmol/l)	3.2 (2.4-3.9)	2.4 (2.1-3.3)	0.1578
TG (mmol/l)	1.8 (0.9-2.2)	0.9 (0.6-1.2)	0.0102*
hsCRP (mg/l)	1.1 (0.0-2.8)	0.8 (0.6-1.5)	0.8424

***p*≤0.01; **p*<0.05. Results are expressed as median (interquartile range). HOMA_{IR}, Homeostasis Model Assessment Insulin Resistance; HDL-cholesterol, high density lipoprotein cholesterol; LDL-cholesterol, low density lipoprotein cholesterol; TG, triglycerides; hsCRP, C-reactive protein.

and subjects with or without visceral fat accumulation (Ersoy *et al.*, 2010). A study conducted in women with rheumatoid arthritis showed lower plasma visfatin concentrations in patients with abdominal obesity in comparison to those without abdominal obesity (Straburzyńska-Lupa *et al.*, 2010). The results regarding relations between anthropometric parameters and visfatin levels are also inconsistent. Some investigators found correlations between visfatin and BMI, others show no correlations (Zahorska-Markiewicz *et al.*, 2007; Alghasham & Bakarar, 2008; Jin *et al.*, 2008; Caixàs *et al.*, 2009) or even negative correlations (Chen *et al.*, 2006). In our study there were no differences in the BMI or waist circumference between the patients and controls. We demonstrated that there was no significant correlations between visfatin levels and BMI in the HF group, while there was significant positive correlation in the control group.

Similarly controversial are results regarding relationships between visfatin and both, glucose and insulin resistance. In obesity and type 2 diabetes there is a well established association between visceral adipose tissue, lipid metabolism and insulin resistance, which in turn are associated with increased cardiovascular risk (Wajchenberg, 2000). Correlations of visfatin and insulin resistance were shown in some studies (Chen *et al.*, 2006; Lewandowski *et al.*, 2007) and no correlations were found in others (Pagano *et al.*, 2006; Alghasham & Bakarar, 2008; de Luis *et al.*, 2008). Heart failure is regarded as an insulin resistance state in which glucose metabolism abnormalities are related to the disease severity and prognosis (Doehner *et al.*, 2005; Straburzyńska-Migaj *et al.*, 2007). We have demonstrated significantly higher glucose and insulin levels, and HOMA_{IR} in our patients compared to the healthy controls, which were further higher in NYHA_{III+IV} vs. NYHA_{I+II}; however, we failed to demonstrate any correlations between visfatin and serum levels of glucose, insulin or HOMA_{IR}.

Some investigations imply that visfatin may play a role in lipid metabolism (Jin *et al.*, 2008; Esteghamati *et al.*, 2011), while others (Zahorska-Markiewicz *et al.*, 2007; de Luis *et al.*, 2008; Ersoy *et al.*, 2010) have shown no correlations between visfatin and lipid parameters in various study populations. We have demonstrated significant correlation between visfatin and HDL-cholesterol in heart failure male patients, which confirms the results of a few other studies (Smith *et al.*, 2006; Jin *et al.*, 2008). No correlations were found between visfatin and lipids in the healthy controls. Wang *et al.* (2007), in studies on Caucasian subjects, have proposed that the association of visfatin with HDL-cholesterol may be the effect of en-

zymatic function of visfatin in NAD metabolism. Recent studies have documented that statin therapy may suppress visfatin serum levels (Kadoglou *et al.*, 2011). However, in our study the comparative analysis of visfatin levels between heart failure individuals treated and not treated with statins did not show any significant difference, but the small sample size and the large variation in visfatin concentrations could blunt the results.

Recently, a role of visfatin in inflammatory processes such as atherosclerosis or subclinical inflammation with concomitant type 2 diabetes is suggested (Alghasham & Bakarar, 2008; Liu *et al.*, 2009). Liu *et al.* (2009) have documented that plasma visfatin concentrations are significantly higher in patients with

chronic coronary artery disease and acute coronary syndromes compared with control groups. In their study serum visfatin concentrations correlated with inflammatory factors (monocyte chemoattractant protein — MCP-1 and interleukin-6), but not with hsCRP or fasting glucose levels, age, waist circumference, BMI, HOMA_{IR}, or levels of cholesterol and triglycerides. Heart failure is also considered a low grade inflammatory process in which inflammatory parameters are related to disease severity and prognosis (Rauchhaus *et al.*, 2000; Straburzyńska-Migaj *et al.*, 2004). In the presented study we have shown that hsCRP levels are significantly higher in NYHA_{III+IV} patients compared to NYHA_{I+II} ones, but we documented no correlations between hsCRP and visfatin. Furthermore, we found no significant differences in visfatin levels between the patients with ischemic and non-ischemic heart failure. However, the limitation of our study is the small number of participants and the results must be approached with caution.

We have found one paper evaluating the role of visfatin and four other adipocytokines as potential prognostic factors in patients with severe heart failure and high levels of B-type natriuretic peptide (Ho *et al.*, 2009). Visfatin was found to have no clinical importance in those patients.

Visfatin has been reported to exert several different effects with respect to cardiovascular disease (Hausenloy, 2009). On the one hand, these include endothelial dysfunction, angiogenesis, atherosclerotic plaque instability, and on the other — cardioprotection. Interesting and potentially important is a finding that visfatin may directly protect myocardium against the effects of acute ischemia-reperfusion injury at the cardiomyocyte level (Hausenloy, 2009). We are clearly at the beginning of a difficult way to explaining the role of visfatin in cardiovascular disease, including heart failure.

Concluding, we can state that serum visfatin concentration in patients with heart failure due to systolic dysfunction is significantly lower in comparison to healthy subjects. Furthermore, patients with higher NYHA classes have even lower visfatin level. Concentration of visfatin in patients with HF is independent of age, anthropometric and metabolic parameters.

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