The Relationship Between Inflammation and Metabolic Syndrome (MetS) - A Matter of Gender?

ADELA VIVIANA SITAR TAUT[1,2,#], OLGA ORASAN[1,2,#], ADRIANA FODOR[1,3#], ANCA DANIELA FARCAS[1,4*], SIMINA TARMURE SARLEA[1,2], GABRIELA DOGARU[1,5], DUMITRU TUDOR ZDRENGHEA[1,6], DANA POP[1,6], ANGELA COZMA [1,2,#]

[1] Iuliu Hatieganu University of Medicine and Pharmacy, 8 Victor Babes Str., 400012, Cluj Napoca, Romania

[2] Department of Internal Medicine 4th Medical Clinic, 18 Republicii Str., 400015, Cluj Napoca, Romania,

[3] Clinical Center of Diabetes, Nutrition, Metabolic Diseases, 2-4 Clinicilor Str., 400006, Cluj Napoca, Romania

[4] Emergency Clinical County Hospital, Cardiology Department, 3-5 Clinicilor Str, 400006, Cluj Napoca, Romania

[5] Clinical Rehabilitation Hospital, Department of Medical Rehabilitation, 46-50 Viilor Str., 400437, Cluj Napoca, Romania

[6] Clinical Rehabilitation Hospital, Department of Cardiology, 46-50 Viilor Str, 400437, Cluj Napoca Romania

Were investigated the relationship between gender, cardiovascular risk factors and inflammation in metabolic syndrome (MetS) patients. 100 consecutive patients (75 women), 73 with MetS, mean age 57.52±9.77 years, were examined. Adhesion molecules (sICAM1, sVCAM1) were measured in the stored serum samples collected using the ELISA method. The classification of MetS was based on IDF guidelines. The study was carried out at the Department of Cardiology, Clinical Rehabilitation Hospital, Cluj-Napoca, Romania. MetS patients presented lower sICAM1 values (225.01±86.75 ng/mL vs 234.22±82.23 ng/mL, p=NS), but higher sVCAM1 values (605.34±298.69 ng/mL vs 552.29±233.77 ng/mL, p=NS). Differences between patients with vs without metabolic syndrome were found only in men for sICAM1 (194.73±37.92 ng/mL vs 282±27.15 ng/mL, p<0.001). Considering the HOMA index, a significant difference for sICAM1 was found in men (patients within the upper quartile vs the lower quartile, p=0.002), but also between women and men within the upper quartile of HOMA (for sICAM1 p=0.038). No significant differences were found for sVCAM1. In the case of males, sICAM1 was an independent predictor of metabolic syndrome, with a very good capacity to identify metabolic syndrome (AUROC=0.987, p=0.0001, Se=89.47%, Sp=100%). In conclusion, just in men, sICAM1 seems to have an excellent capacity to differentiate between MetS+ and MetS- patients, to predict MetS development.

Keywords: adhesion molecule, gender, IDF, inflammation, metabolic syndrome

Metabolic syndrome (MetS) represents a constellation of interrelated vascular risk factors, multiple metabolic abnormalities with a role in the development of cardiovascular diseases [1], in increasing mortality [2]. Enhanced atherosclerosis may be an important link between MetS and the higher frequency of cardiovascular events [3,4]. Atherosclerosis is currently recognized as an inflammatory disorder [5,6] low-grade inflammation being involved in all stages of atherosclerosis . In recent years, inflammation markers have been recognized as risk factors for cardiovascular disease (CVD) [7-9]

There are still many unknown facts regarding inflammation in MetS.

We aimed to investigate the relationship between cardiovascular risk factors and inflammation in MetS patients, stratifying the analysis according to the patients' gender.

Experimental part

Subjects

The study was carried out at the Department of Cardiology, Clinical Rehabilitation Hospital, Cluj-Napoca, Romania, between June and September 2014. Consecutive participants completed a questionnaire regarding their personal and family medical history. All were subjected to a complete physical exam. The patients with known cardiovascular diseases (CVD), inflammatory or systemic diseases were excluded.

For each patient, weight, height and abdominal circumference (midway between the inferior margin of the last rib and the iliac crest in horizontal plane while in upright position) were measured. The body mass index (BMI) was calculated (weight (kg)/[height (m)]2); subjects with a BMI ≥30 kg/m^2 were considered obese.

Blood samples were obtained from the antecubital vein, with the patients in seated position, in the morning, after a 12 h overnight fast. Plasma lipid values, plasma glucose and insulin were determined. The HOMA index was calculated as HOMA-IR = glucose * insulin /405 (units mg/dL) [10]. Insulin resistance was defined as a HOMA-IR index in the upper quartile.

A qualified person measured blood pressure (after a 15-min rest), using a standard sphygmomanometer with a cuff size adapted to the subject's arm circumference. A person was considered hypertensive if, according to ESC guidelines8, his/her blood pressure was e ≥140/90 mm Hg or he/she previously took medication for reducing blood pressure.

According to ESC guidelines [11], a patient was considered dyslipidemic if he/she had a total serum cholesterol value ≥200 mg/dL or a serum triglyceride value ≥150 mg%; a patient was considered diabetic if glycemia ≥126 mg/dL or he/she had previous treatment for diabetes.

Adhesion molecules (sICAM1 and sVCAM1 - in ng/mL) were analyzed using commercially available ELISA kits (R&D Systems Inc., Minneapolis, MN, USA).

** email: ancafarcas@yahoo.com; Phone: +40 744780873*

 # Authors with equal contribution.

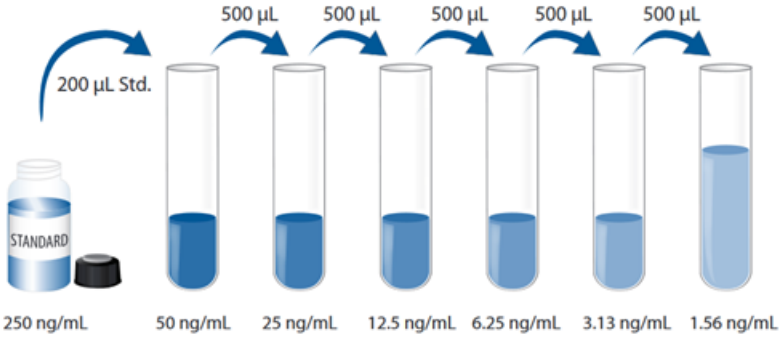

Fig. 1.

Principle of the assay for sICAM1

This assay employs the quantitative sandwich enzyme immunoassay technique. A monoclonal antibody specific for wild type human ICAM1 has been pre-coated onto a microplate. Standards, samples, controls, and conjugate are pipetted into the wells and any ICAM1 present is sandwiched by the immobilized antibody and the enzyme-linked monoclonal antibody specific for human wild type ICAM1. Following a wash to remove any unbound substances and/or antibody-enzyme reagent, a substrate solution is added to the wells and color develops in proportion to the amount of ICAM1 bound. The color development is stopped and the intensity of the color is measured.

Sample preparation

Serum and plasma samples require a 20-fold dilution. A suggested 20-fold dilution is 20 µL of sample + 380µL of Calibrator Diluent RD5-7. Reconstitute the Human ICAM1 Standard with deionized or distilled water. This reconstitution produces a stock solution of 250 ng/mL. Mix the standard to ensure complete reconstitution and allow the standard to sit for a minimum of 15 min with gentle agitation prior to making dilutions. Pipette 800 µL of Calibrator Diluent RD5-7 into the 50 ng/mL tube. Pipette 500 µL into the remaining tubes. Use the stock solution to produce a dilution series (below). Mix each tube thoroughly before the next transfer. The 50 ng/mL standard serves as the high standard. Calibrator Diluent RD5-7 serves as the zero standard (0 ng/mL) (fig. 1.).

Principle of the assay for sVCAM1

This assay employs the quantitative sandwich enzyme immunoassay technique. A monoclonal antibody specific for human VCAM1 has been pre-coated onto a microplate. Standards, samples, controls, and conjugate are pipetted into the wells and any VCAM-1 present is sandwiched by the immobilized antibody and the enzyme-linked monoclonal antibody specific for human VCAM1. Following a wash to remove any unbound substances, a substrate solution is added to the wells and color develops in proportion to the amount of VCAM1 bound. The color development is stopped and the intensity of the color is measured. Linearity: To assess the linearity of the assay, samples spiked with high concentrations of human VCAM1 were serially diluted with calibrator diluent to produce samples with values within the dynamic range of the assay.

The classification of MetS was based on *IDF guidelines:* abdominal obesity (>94 cm in men, >80 cm in women) plus 2 other criteria of the following: fasting plasma glucose >100 mg/dL or previously diagnosed type 2 diabetes, high blood pressure ≥130/85 mmHg or treatment for hypertension, low HDL-cholesterol (< 40 mg/dL in males, <50 mg/dL in females) and high triglycerides ≥150 mg/dL.

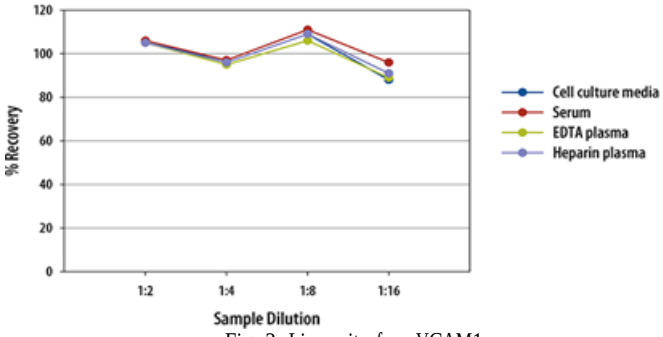

Fig. 2. Linearity for VCAM1

The local institutional Ethics Committee approved the study and all participants gave their written informed consent.

Statistical analysis

The data were analyzed using SPSS 16.0 and MedCalc (v 10.3.0.0, MedCalc Software, Ostend, Belgium) software programs. Normal distribution was assessed using the Kolmogorov test. Descriptive analysis was used to evaluate the patients' demographic and clinical characteristics. Mean and standard deviation for normally distributed quantitative variables and median values for the rest were calculated. The differences between quantitative variables were examined using the Student/Mann Whitney/ANOVA test. For qualitative variables, the χ^2 test was employed. Pearson's/Spearman's correlation coefficients were determined. Multiple regression (the stepwise method) was used to evaluate the relationship between MetS and adhesion molecules. Receiver Operating Characteristic (ROC) and AUROC (Area under Receiver Operating Characteristic) curve analysis was utilized. A p value of less than 0.05 was considered statistically significant.

Results and discussions

One hundred patients (75 women, 25 men) with and without metabolic syndrome (73 MetS+, 27 MetS-), with a mean age of 57.52±9.77 years, were examined. A proportion of 72% of women and 76% of men presented MetS, p=NS. Of all patients, 18% were smokers, 41% were obese, 66% were hypertensive, 17% were diabetic and 76% were dyslipidemic. Significant differences were found between MetS-positive patients and MetS-negative patients regarding almost all cardiovascular risk factors (hypertension 74% vs 44.4%, p=0.006, diabetes 21.9% vs 3.7%, p=0.024, obesity 49.3% vs 18.5%, p=0.004), excepting dyslipidemia (79.5% vs 66.7%, p=NS) and smoking (13.7% vs 29.6%, p=0.06). No significant difference regarding the lipid lowering treatment was found between patients with vs without MetS.

The differences between MetS+ and MetS- patients (global, women, men) are presented in table 1. In patients with MetS, women differed significantly from men regarding weight (p<0.001), waist circumference (p<0.001), systolic blood pressure (p=0.036), diastolic

Table 1
PATIENTS' CHARACTERISTICS MetS+ *vs* MetS-

	Global (100 patients)			*Women (75 patients)*			Men		
	MetS+ (73 patients)	MetS- (27 patients)	p	MetS+ (54 patients)	MetS- (21 patients)	p	MetS+ (19 patients)	MetS- (6 patients)	p
Age (years)	58.42±9.47	55.07±10.32	NS	57.92±9.32	54.19±9.3	NS	59.84±10.01	58.16±13.89	NS
Weight (kg)	83.72±13.58	76.25±13.78	0.017	79.7±11.96	74.09±9.68	0.059	95.15±11.42	83.83±22.88	NS
Waist (cm)	100.12±10.4	88.25±20.48	<0.001	97.55±10.26	86.61±22.13	0.005	107.42±6.84	94±13.14	0.003
BMI (kg/m^2)	29.8±3.92	27.77±3.66	0.022	29.63±4.12	27.83±3.28	0.07	30.27±3.34	27.56±5.14	NS
SBP (mmHg)	137.94±26.08	131.66±15.44	NS	134.16±26.66	130.71±16.67	NS	148.68±21.52	135±10.48	NS
DBP (mmHg)	85.95±15.35	82.03±7.87	NS	83.51±15.97	81.42±8.53	NS	92.89±11.09	84.16±4.91	0.07
Glycemia (mg/dl)	101.47±19.95	83.44±18.39	<0.001	101.22±21.22	86.09±8.17	0.002	102.21±16.26	74.16±36.88	0.014
TC (mg/dl)	220.76±46.38	210.55±52.46	NS	222.7±46.17	218.8±29.63	NS	215.26±47.78	181.66±97.5	NS
LDL-C (mg/dl)	140.32±36.88	141.03±38.5	NS	142.25±36.94	147.23±26.17	NS	134.84±37.13	119.33±65.1	NS
HDL-C (mg/dl)	44.28±6.11	50.37±13.63	0.03	44.59±5.65	51.14±6.45	<0.001	43.42±7.36	47.66±28.07	NS
TG (mg/dl)	180.68±87.51	95.81±35.87	<0.001	179.31±90.17	102.42±29.87	<0.001	184.57±81.66	72.66±47.89	0.004
Insulin*	6 (5-7.5)	4.5 (3.8-5.9)	0.007	5.5 (4.8-6.73)	5 (3.8-6.8)	NS	7.5 (5-10.82)	3.7	0.001
HOMA	2.02±1.74	1.3±0.95	0.05	1.87±1.67	1.43±1.02	NS	2.41±1.9	0.82±0.14	0.08
sICAM1 (ng/ml)	225.01±86.75	234.22±82.23	NS	235.66±96.38	220.57±87.90	NS	194.73±37.92	282±27.15	<0.001
sVCAM1(ng/m)	605.34±298.69	552.29±233.77	NS	626.55±327.72	525.71±232.05	NS	545.05±188.23	645.33±235.44	NS

SBP = systolic blood pressure, DBP = diastolic blood pressure, TC = total cholesterol, LDL-C = LDL-cholesterol, HDL-C = HDL-cholesterol, TG = triglycerides, BMI = body mass index; * median value, 95% confidence interval, Mann-Whitney test; for the other variables, data are presented as mean ± standard deviation, NS p>0.05

blood pressure (p=0.021). In patients without MetS, no significant differences between sexes were found regarding cardiovascular risk factors.

The global mean value of sICAM1 was 227±85.24 ng/mL and that of sVCAM1 was 591.02±282.48 ng/mL. By globally comparing MetS-positive vs MetS-negative patients, we registered in MetS patients lower sICAM1 values (225.01±86.75 ng/mL vs 234.22±82.23 ng/mL, p=NS), but higher sVCAM1 values (605.34±298.69 ng/mL vs 552.29±233.77 ng/mL, p=NS) (table 1).

Stratifying the analysis according to the patients' sex evidenced significant differences between patients with vs without MetS only for men regarding sICAM1 values (194.73±37.92 ng/mL vs 282±27.15 ng/mL, p<0.001) – table 1. When taking into consideration just MetS-positive patients, no significant differences were found between men and women (table 1).

In women with MetS, a significant inverse correlation was found between sICAM1 and HDL-cholesterol (correlation coefficient =-0.289), between sVCAM1 and HDL-cholesterol (correlation coefficient =-0.301) and a power correlation was observed between sICAM1 and sVCAM1 (correlation coefficient =0.747, p<0.001).

In men with MetS, sICAM1 was correlated with systolic and diastolic blood pressure (both correlation coefficients =0.511). A correlation between sICAM1 and sVCAM1 was also present (correlation coefficient =0.565, p<0.05).

Neither in men, nor in women with MetS, significant correlations were found between adhesion molecules and age, weight, waist, BMI, glycemia, total cholesterol, LDL-cholesterol. No correlations were found with the insulin level and the HOMA index.

We studied the difference between adhesion molecules in different groups of insulin resistance (table 2). By comparing patients within the upper quartile vs the lower quartile, a significant difference was found only in men for sICAM1 (193.71±33.71 *vs* 262.4±18.99, p=0.002). Further analysis in the upper quartile of HOMA evidenced higher sICAM1 values in women (249.64±89.95 vs 193.71±33.71, p=0.038). No significant differences were found for sVCAM1.

Multiple regression (the stepwise method – including as variables age, weight, body mass index, waist, systolic blood pressure, diastolic blood pressure, glycemia, total cholesterol, LDL-cholesterol, HDL-cholesterol, triglycerides, sICAM1, sVCAM1), globally and by sex, was used in order to identify the independent factors predicting MetS. Only for male patients, sICAM1 was an independent predictor of MetS (table 3).

Going further with the analysis, we used ROC in order to test the capacity of adhesion molecules to discriminate between the presence and absence of MetS. Globally, the predictive values were approximately equal for sICAM (AUROC=0.589, Se=69.9%, Sp=55.6%) and sVCAM1 (AUROC=0.540, Se=78.1%, Sp=37%). A significant difference was found between men and women for the prediction capacity of sICAM1 (AUROC=0.987, Se=89.47%, Sp=100% for men vs AUROC=0.536, Se=90.7%, Sp=23.1% for women), but not for that of sVCAM1. Stratifying the analysis according to the patients' age, the differences between men and women regarding

Table 2
RELATIONSHIP BETWEEN ADHESION MOLECULES AND HOMA INDEX

		Global	Women	Men	
	HOMA quartiles	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**	**P^T**
sICAM1	Upper quartile	233.33±81.23	249.64±89.95	193.71±33.71	0.038
	Lower quartile	246.09±87.55	241.29±99.31	262.4±18.99	NS
	p*	NS	NS	0.002	
sVCAM1	Upper quartile	553.83±256.69	545.52±284.7	574.0±189.08	NS
	Lower quartile	66454±284.23	638.94± 306.84	751.6±187.84	NS
	p*	NS	NS	NS	

p - between upper vs lower quartile, p^T - between women vs men according to quartile*

Table 3

MULTIPLE REGRESSION – INDEPENDENT FACTORS FOR PREDICTING METABOLIC SYNDROME

Independent variables	Women				Men			
	Coeff.	SE	t	p	Coeff.	SE	t	p
	$R^2 = 0.46$				$R^2 = 0.76$			
Age	0.015	0.004	3.569	0.0007	-	-	-	-
Waist	-	-	-	-	-	-	-	-
Glycemia	-	-	-	-	-	-	-	-
TG	0.002	0.0004	4.52	<0.0001	0.001	0.0005	2.379	0.02
HDL-C	-0.02	-0.0006	-4	0.0002	-	-	-	-
Weight	0.01	0.003	2.769	0.007	-	-	-	-
DBP	-	-	-		0.337	0.004	3.464	0.002
sICAM1	-	-	-	NS	-0.005	0.0009	-5.625	**<0.0001**
sVCAM1	-	-	-	NS	-	-	-	**NS**

SE = standard error, DBP = diastolic blood pressure, HDL-C = HDL-cholesterol, TG = triglycerides

the prediction capacity of sICAM1 remained statistically significant in younger patients (≤55 years of age) - AUROC=1 for men vs AUROC=0.501 for women, p< 0.0001, but also in older patients - AUROC=0.982 for men vs AUROC=0.572 for women, p=0.0024.

Atherosclerosis represents a disease of the arterial wall responsible for many of the most common causes of cardiovascular morbidity and mortality. New opportunities for modifying, and at the same time for treating different aspects of the progression of atherosclerosis have been offered by the latest developments in understanding the pathophysiology of cellular and molecular mechanisms .

The vascular endothelium is defined as a structure playing an essential role in a multitude of fundamental physiological pathways (regulation of vasomotor tone, homeostasis, thrombosis and inflammation) [1,11,12].

In conditions such as dyslipidemia, hypertension and obesity, endothelial dysfunction appears [12] in the early stage of atherosclerotic vascular damage [1,13]. These cardiovascular risk factors activate inflammatory pathways, increasing the transcription of (NF)-kappa B, initiating the adhesion cell expression [12], promoting endothelial adhesion (especially of leukocytes and thrombocytes), alteration of permeability and anticoagulant properties, release of vasoactive molecules and cytokines [14-16].

The assessment of endothelial dysfunction can be useful in the evaluation of atherosclerotic cardiovascular risk [1,17]. Currently, no direct measurement of endothelial function is available [12], but this can be measured by determining the levels of adhesion molecules [12, 18,19]. While sICAM1 is expressed in endothelial cells (in normal endothelium in lower levels [6]), leukocytes, epithelial cells, smooth muscle cells, sVCAM1 is exclusively found in endothelial cells (as a plaque activity indicator, not in normal endothelium) [12, 20]. Soluble forms of sICAM1 and sVCAM1 are detectable in plasma [12,21].

The literature data on the relationship between MetS and subclinical markers of cardiovascular disease and atherosclerosis are limited.

Some previous data show that MetS represents an inflammatory state [22-24], associated with endothelial dysfunction [22], but the results are controversial: some authors found higher sICAM1 values in MetS patients [2, 23, 25], while others reported that only sVCAM1 levels increased in MetS-positive patients [22, 26, 27] or found that both sVCAM1 and sICAM1 increased in MetS patients [8, 28,29]. Finally, Aizawa [1] described no differences in sICAM1 or sVCAM1 between the two groups.

The differences between the reported results can be due to important issues that are not fully understood regarding the association between cardiovascular risk factors, metabolic syndrome and adhesion molecules, as well as to the different MetS definitions used.

Previous studies found that gender influenced adhesion molecule levels. Our study showed that MetS patients, globally, had higher sVCAM1 values, but lower sICAM1 values. When we performed a sex-stratified analysis, important differences were found between sexes (for women both sICAM1 and sVCAM1 values were higher in MetS+, but for men both sICAM1 (p<0.05) and sVCAM1 values were lower in MetS+). Our data are in agreement with those of other authors - higher values for sICAM1 in women with MetS [30] but no differences between genders regarding sVCAM1 [27].

Only in men and for sICAM1, we found significant differences between metabolic syndrome patients vs non-metabolic syndrome patients, 194.73±37.92 ng/mL vs 282±27.15 ng/mL, p <0.001.

The importance of insulin resistance in MetS is already known. The interaction between inflammation, insulin resistance and atherogenesis represents a pathway for cardiovascular disease development [14,22]. The relationship between insulin resistance and inflammatory status seems to be bidirectional, inflammation leading to insulin resistance and insulin resistance further enhancing the pro-inflammatory state [24, 26, 31,32]. We found significant differences in the values of adhesion molecules in relation to HOMA quartiles (similarly to Hsu [31]) (for sICAM1 - difference between men and women p=0.038, but just for the upper quartile of HOMA; for sICAM1 – difference for men between values registered in the upper vs the lower quartile of HOMA p=0.002).

We found a positive correlation between sVCAM1 and sICAM1, in accordance with studies performed by other authors [6, 8, 22, 27, 28]. Like in others studies [6, 8], adhesion molecules negatively correlated with HDL-cholesterol. A possible explanation is related to the fact that HDL-cholesterol inhibits the cytokine-induced expression of endothelial cell adhesion molecules (through inhibition of endothelial cell sphingosine kinase and decrease of NF-kB activation) [6].

When we performed multiple regression, sICAM1 predicted the presence of metabolic syndrome only in men (p<0.0001), like in Thompson's study [33].

To the best of our knowledge, this is one of the first studies that evaluate the capacity of cell adhesion molecules to identify patients with MetS. Recently, a few important studies have been published, but these were conducted on obese adolescents in the absence of metabolic syndrome criteria [34] or on young patients (18-28 years of age) [35].

Furthermore, no such studies have been carried out in our geographical area. We found important differences between the two molecules, the differences being enhanced by sex and age (the best predictive capacity was found for sICAM1 in men younger than 55 years of age).

Limitations of the study – the small number of patients. It should also be mentioned that only the two adhesion molecules were included in the study, without the possibility of studying the role of other inflammatory markers. However, as we mentioned before, this is just the first study, which will be extended in order to characterize as adequately as possible the capacity of adhesion molecules and inflammatory markers to identify patients with MetS and to highlight the differences between sexes.

Conclusions

These findings can suggest the involvement of different mechanisms for sICAM1 and sVCAM1, different capacities to differentiate between MetS+ and MetS- patients, to predict MetS development.

At the same time, more studies are necessary to evaluate the important differences between sexes, encouraging a close examination of these relationships.

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