Comparison of the Effect of the Metabolic Syndrome and Multiple Traditional Cardiovascular Risk Factors on Vascular Function

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Abstract

Objective: To assess the effect of the metabolic syndrome (MetS) on endothelial function and compare these findings to those in individuals with a similar burden of traditional cardiovascular (CV) risk factors (≥ 3) without MetS.

Patients and Methods: Both MetS and multiple CV risk factors were identified from 1103 individuals who underwent the evaluation of endothelial function at the Mayo Clinic, in Rochester, Minnesota, from July 1, 2000, through July 31, 2011. Endothelial function was measured using digital arterial tonometry by assessing reactive hyperemia–induced vasodilation in one arm and adjusting for changes in the contralateral arm (reactive hyperemia index [RHI]).

Results: A total of 316 individuals with MetS and 210 with multiple risk factors were assessed. Endothelial dysfunction was more pronounced in the MetS group compared with the multiple risk factor group (mean $\pm$ SD natural logarithmic RHI, 0.61 ± 0.25 and 0.68 ± 0.28 , respectively; $P = .006$). Leukocyte count ($7.00 \pm 1.89 \times 10^9/L$ vs $6.41 \pm 1.76 \times 10^9/L$, respectively; $P = .001$) and high-sensitivity C-reactive protein level (1.78 ± 1.53 mg/L vs 1.48 ± 1.42 mg/L, respectively; $P = .01$) were higher in the MetS group compared with the multiple risk factor group. After adjustment for covariates and 6 traditional CV risk factors in a multivariate regression model, MetS had a significant and independent influence on natural logarithmic RHI ($\beta = -.11$; $P = .01$).

Conclusion: The current study found that individuals with MetS have a higher degree of endothelial dysfunction and inflammation compared with individuals with multiple CV risk factors and may therefore have an increased CV risk beyond the contributions of multiple traditional risk factors.

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The metabolic syndrome (MetS) is a constellation of metabolic disorders, including central obesity, abnormal blood pressure, hyperglycemia, hypertriglyceridemia, and low high-density lipoprotein cholesterol level. It is a common condition associated with atherosclerosis and a high risk of cardiovascular (CV) events.¹ During the past 2 decades there has been a striking increase in the worldwide prevalence of MetS,² and the National Cholesterol Education Program (Adult Treatment Panel III) is emphasizing MetS as an important CV risk factor.³

Epidemiologic studies have identified the importance of certain risk profiles for the prediction and prevention of coronary artery disease, leading to the development of specific risk scores (Framingham Heart Study, Prospective Cardiovascular Münster Heart Study, or Systematic Coronary Risk Evaluation).⁴⁻⁶ Although controversy exists about

whether MetS is a true syndrome or a mixture of unrelated phenotypes,⁷⁻¹² MetS is a unique collection of risk factors with an emphasis on metabolic changes, such as body weight and central obesity, factors commonly not taken into account in most CV risk models.

Endothelial dysfunction, a pathologic condition characterized by an imbalance between endogenous vasodilating and vasoconstricting substances, is the earliest detectable functional disturbance in the natural history of atherosclerosis and a powerful predictor of future CV events.^{13,14} Most, if not all, CV risk factors have been associated with endothelial dysfunction, and their modification leads to improved vascular function.¹⁵ Thus, endothelial function serves as an important surrogate for vascular health. In light of the discussion regarding whether MetS provides additional valuable information on vascular health beyond the mere addition of risk

factors, we aimed to evaluate endothelial function in patients with MetS compared with patients with multiple traditional CV risk factors (≥ 3).

PATIENTS AND METHODS

Study Population

In this retrospective study, patient information came from a registry for the screening of endothelial dysfunction using EndoPAT (Itamar Medical Inc, Caesarea, Israel), a noninvasive testing device used at Mayo Clinic in Rochester, Minnesota, from July 1, 2000, through July 31, 2011. Of the 1103 patients identified, 433 (39.2%) were outpatients of the preventive cardiology clinic, 425 (38.5%) were inpatients of the cardiology clinic, 153 (13.9%) were volunteers, and 92 (8.3%) were outpatients of the internal medicine clinic. The medical records of the 1103 patients were screened for multiple risk factors and MetS. A total of 142 patients were excluded because of incomplete information on risk factors or MetS components. Those who met the inclusion criteria were included in this study. Exclusion criteria were acute coronary syndromes, uncontrolled hypertension, heart failure, pregnancy, inflammatory disorders, or other severe chronic diseases. This study was approved by the Mayo Clinic Institutional Review Board, and all individuals gave informed consent.

Demographic, Clinical, and Laboratory Characteristics

Demographic characteristics (age and sex) and CV risk factors were recorded in all patients. Measurements related to CV risk included resting arterial blood pressure, heart rate, body mass index, waist circumference, lipid profile (total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and triglyceride levels), fasting blood glucose level, and serum creatinine level. Serum high-sensitivity C-reactive protein (hsCRP) concentrations were measured using a latex particle-enhanced immunoturbidimetric assay. Blood samples were obtained with patients in the fasting state. Information about obstructive sleep apnea was retrieved from the medical records according to standard diagnostic criteria.¹⁶ Calculation of the estimated glomerular filtration rate was performed with use of the Mayo quadratic formula.¹⁷

Individuals with multiple risk factors were defined as having 3 or more of the following: (1) hypertension (resting blood pressure of 140/90 mm Hg or treatment with antihypertensive medications), (2) diabetes mellitus (fasting blood glucose level ≥ 126 mg/dL [to convert to mmol/L, multiply by 0.0555] and/or treatment with insulin or oral hypoglycemic agents), (3) family his-

tory of coronary artery disease in first-degree relatives younger than 55 (male) years of age or younger than 65 (female) years of age, (4) hypercholesterolemia (serum low-density lipoprotein cholesterol level ≥ 160 mg/dL [to convert to mmol/L, multiply by 0.0259] or treatment with lipid-lowering drugs), (5) smoking history (current cigarette smoking), and (6) overweight or obesity (body mass index ≥ 25 [calculated as the weight in kilograms divided by the height in meters squared]).

Individuals with MetS were defined according to the recent international guidelines¹² as those with 3 or more of the following 5 components: (1) waist circumference of 102 cm or greater in males and 88 cm or greater in females, (2) elevated triglyceride level of 150 mg/dL or higher (to convert to mmol/L, multiply by 0.0113) or specific treatment for this lipid abnormality, (3) reduced high-density lipoprotein cholesterol level of less than 40 mg/dL in males and less than 50 mg/dL in females (to convert to mmol/L, multiply by 0.0259) or specific treatment for this lipid abnormality, (4) elevated systolic blood pressure of 130 mm Hg or greater or diastolic blood pressure of 85 mm Hg or greater or treatment of previously diagnosed hypertension, and/or (5) elevated fasting glucose level of 100 mg/dL or greater or drug treatment of this glucose disorder or previously diagnosed type 2 diabetes.

Peripheral Endothelial Function Measurement

Patients were instructed to start fasting at least 12 hours before measurement and to refrain from smoking and strenuous exercise during that period. The use of all vasoactive medications was discontinued at least 24 hours before testing. Peripheral artery tonometry signals were obtained using the EndoPAT 2000 device.

A peripheral artery tonometry finger probe was placed on each index finger. Pulsatile volume changes of the distal digit induced pressure alterations in the finger cuff, which were sensed by pressure transducers and transmitted to and recorded by the EndoPAT 2000 device. Endothelial function was measured via a reactive hyperemia index (RHI) as previously described.^{15,18} The ratio of the peripheral artery tonometry signal after cuff release compared with baseline was calculated through a computer algorithm automatically normalizing for baseline signal and indexed to the contralateral arm. The calculated ratio (RHI) is a validated measure of endothelial function, with a higher RHI value correlating with better endothelial function¹⁹ (RHI > 1.67 is considered normal).

Statistical Analyses

The normality of each variable was assessed with the Kolmogorov-Smirnov test. Because RHI, the measure of endothelial function, was skewed, a natural log transformation was used. Continuous variables were presented as mean $\pm$ SD, and categorical variables were presented as number (percentage). Continuous variables were compared using the 2-sample *t* test or a Wilcoxon rank sum test. Categorical variables were compared using the Pearson χ^2 test.

Three multivariate regression models were constructed. The following procedure was used to assess the difference in how much variation is explained by the covariates among each of the 3 models. First, model A was constructed. The dependent variable was the natural logarithmic RHI. In model A, all covariates with a significant influence on endothelial function in the univariate model or those with a known influence on endothelial function were included (age, sex, the presence of obstructive sleep apnea, the history of coronary artery disease, leukocyte count, and the intake of renin-angiotensin-aldosterone system inhibitors, statins, or nitrates). R^2 was calculated with multivariate regression. Next, model B was constructed. The dependent variable was the natural logarithmic RHI. Model B included these covariates and the 6 classic CV risk factors: hypertension, diabetes, hypercholesterolemia, smoking, overweight or obesity, and family history of premature coronary artery disease. R^2 was calculated with multivariate regression. Finally, model C was constructed. The dependent variable was the natural logarithmic RHI. In model C, the covariates, the 6 CV risk factors, and MetS were added. R^2 was calculated with multivariate regression. The R^2 value from model B was compared with the R^2 value from model A (R^2 model B minus R^2 model A). The difference in the R^2 value between model B and model A represents the additional amount of variation in the natural logarithmic RHI that is explained by the additional covariates used in model B. The R^2 value from model C was compared with the R^2 value from model B (R^2 model C minus R^2 model B). The difference in the R^2 value between model C and model B represents the additional amount of variation in the natural logarithmic RHI that is explained by the additional covariates used in model C. Stepwise regression was used in each model to identify independent predictors of endothelial function. In the regression model, leukocyte count was not available in 21 patients, and the information was replaced by the mean value.

All tests were 2-tailed, and $P < .05$ was considered statistically significant. Statistical analyses were

performed using SPSS statistical software (version 11.5; SPSS Inc, Chicago, IL).

RESULTS

Demographic and Clinical Characteristics

A total of 316 patients fulfilled the criteria for MetS, and 210 were identified as having multiple risk factors (≥ 3 risk factors) without the simultaneous presence of MetS. The remaining patients were not otherwise eligible for inclusion in the study. The demographic and clinical characteristics of the 2 groups are listed in Table 1. Higher prevalence of diabetes, hypertension, overweight or obesity, and obstructive sleep apnea and lower prevalence of smoking, hypercholesterolemia, and family history of premature coronary artery disease were found in the MetS group.

Laboratory Characteristics

The laboratory characteristics of the 2 groups are listed in Table 2. The hsCRP plasma levels (1.78 ± 1.53 mg/L vs 1.48 ± 1.42 mg/L, respectively; $P = .01$) and leukocyte counts ($7.00 \pm 1.89 \times 10^9/L$ vs $6.41 \pm 1.76 \times 10^9/L$, respectively; $P = .001$) were significantly higher in the MetS group compared with the multiple risk factor group. In addition, fasting blood glucose and triglyceride levels were significantly higher and the high-density lipoprotein cholesterol level was significantly lower in the MetS group.

Multivariate Analysis

The R^2 values resulting from models A, B, and C were 0.08, 0.09, and 0.10, respectively (Table 3). R^2 model B minus R^2 model A (0.09-0.08) equals 0.01 ($P = .38$), indicating that model B (including 6 risk factors) does not add new information from that of model A. The difference between models C and B equals 0.01 (0.10-0.09), suggesting that the change in the natural logarithmic RHI is explained by the addition of MetS as a covariate used in model C; thus, the presence of MetS has additional independent information on endothelial function. Stepwise regression revealed that apart from MetS, leukocyte count, use of nitrates, obstructive sleep apnea, and history of coronary artery disease were independently associated with endothelial function.

DISCUSSION

In the present study, we found a significant incremental effect of the MetS constellation beyond the 6 traditional CV risk factors to impair endothelial function. This observation was paralleled by significantly higher plasma levels of the inflammatory

TABLE 1. Demographic and Clinical Characteristics in the MetS and Multiple Risk Factor Study Groups

Characteristic	MetS (n=316)	Multiple risk factors (n=210)	P value
Age (y), mean $\pm$ SD	56.26 $\pm$ 12.38	57.06 $\pm$ 12.42	.47
Male sex, No. (%)	159 (50.3)	93 (44.3)	.17
Known CAD, No. (%)	76 (24.1)	42 (20.0)	.27
SBP (mm Hg), mean $\pm$ SD	128.50 $\pm$ 18.04	126.02 $\pm$ 17.43	.11
DBP (mm Hg), mean $\pm$ SD	76.15 $\pm$ 11.67	74.98 $\pm$ 10.57	.24
Heart rate (/min), mean $\pm$ SD	70.35 $\pm$ 11.45	68.63 $\pm$ 11.28	.09
Waist circumference (cm), mean $\pm$ SD	105.08 $\pm$ 13.37	92.06 $\pm$ 12.21	<.001
BMI, mean $\pm$ SD	33.55 $\pm$ 5.47	28.68 $\pm$ 3.94	<.001
Hypertension, No. (%)	236 (74.7)	126 (60.0)	<.001
Diabetes mellitus, No. (%)	83 (26.3)	5 (2.4)	<.001
Cigarette smoking, No. (%)	38 (12.0)	32 (15.2)	.04
Hypercholesterolemia, No. (%)	258 (81.6)	188 (89.5)	.01
Overweight or obesity, No. (%)	305 (96.5)	189 (89.5)	.002
Family history of premature CAD, No. (%)	132 (41.8)	128 (61.0)	<.001
Obstructive sleep apnea, No. (%)	102 (32.4)	28 (13.3)	<.001
Postmenopausal women, No. (%)	114 (36.1)	84 (40.0)	.36
Medications, No. (%)			
Aspirin	207 (65.5)	128 (61.0)	.28
β -Blocker	126 (39.9)	77 (36.7)	.45
CCB	72 (22.8)	57 (27.1)	.22
Insulin	18 (5.7)	1 (0.5)	.002
Nitrates	70 (22.2)	46 (21.9)	.07
Oral hypoglycemics	44 (13.9)	2 (1.0)	<.001
RAAS inhibitor	126 (39.9)	67 (31.9)	.10
Statins	181 (57.3)	114 (54.3)	.72
Natural logarithmic RHI, mean $\pm$ SD	0.61 $\pm$ 0.25	0.68 $\pm$ 0.28	.006

BMI = body mass index; CAD = coronary artery disease; CCB = calcium channel blocker; DBP = diastolic blood pressure; MetS = metabolic syndrome; RAAS = renin-angiotensin-aldosterone system; RHI = reactive hyperemia index; SBP = systolic blood pressure.

markers hsCRP and leukocyte count in the MetS group. Patients with coexisting endothelial dysfunction and inflammation have a particularly high risk of future adverse events¹³; thus, this finding in individuals with MetS emphasized the potential effect of elevated CV risk compared with individuals with multiple CV risk factors alone.

The relationship between the 6 CV risk factors and endothelial function and between the MetS and endothelial function has been clearly reported.^{15,20} Each of the 6 risk factors may impair endothelial function,²¹⁻²³ and the extent of endothelial dysfunction has been correlated with the number of those CV risk factors.^{23,24} To our knowledge, this is the first report that MetS has a greater effect on endothelial function compared with multiple traditional CV risk factors. We found that coronary artery disease, obstructive sleep apnea, nitrate use, and leukocyte count were associated with endothelial function in this population. This finding is consistent

with those from previous studies.²⁵⁻²⁸ Although the 6 risk factors had no further influence on endothelial function after adjusting for covariates, MetS remains a significant and independent determinant of endothelial function.

The components of the MetS and multiple risk factor groups partly overlap, which may have masked some of the differences between the 2 groups. However, our results revealed that MetS was a unique combination of metabolic changes that appear to have a particularly damaging effect on vascular health beyond mere addition of CV risk factors. Although the pathogenesis behind this remains unclear, recent interest has focused on the possible involvement of insulin resistance as a linking factor between MetS and endothelial dysfunction. For example, insulin resistance is closely associated with abnormalities in nitric oxide bioavailability and reduced *PI3K/Akt* signaling in the vascular wall. Insulin resistance itself also

TABLE 2. Laboratory Characteristics in the MetS and Multiple Risk Factor Study Groups^{a-c}

Characteristic	MetS (n=316)	Multiple risk factors (n=210)	P value
Hemoglobin (g/dL)	1.40±0.13	1.39±0.13	.86
Leukocytes (×10 ⁹ /L)	7.00±1.89	6.41±1.76	.001
Platelets (×10 ⁹ /L)	242.84±57.52	248.49±73.34	.35
Glucose (mg/dL)	114.32±29.62	96.72±13.26	<.001
TCH (mg/dL)	192.36±47.13	188.54±45.56	.38
Triglycerides (mg/dL)	203.53±126.52	107.17±47.03	<.001
HDL-C (mg/dL)	43.23±11.66	56.99±14.36	<.001
LDL-C (mg/dL)	110.83±42.96	107.69±38.68	.44
Creatinine (mg/dL)	1.01±0.27	0.99±0.21	.25
eGFR (mL/min)	91.48±19.42	91.74±15.24	.87
hsCRP (mg/L)	1.78±1.53	1.48±1.42	.01

^ae-GFR = estimated glomerular filtration rate; HDL-C = serum high-density lipoprotein cholesterol; hsCRP = high-sensitivity C-reactive protein; LDL-C = low-density lipoprotein cholesterol; MetS = metabolic syndrome; TCH = total cholesterol.

^bSI conversion factors: to convert hemoglobin values to g/L, multiply by 10; to convert fasting plasma glucose levels to mmol/L, multiply by 0.0555; to convert total cholesterol, LDL-C, and HDL-C values to mmol/L, multiply by 0.0259; to convert triglyceride values to mmol/L, multiply by 0.0113; to convert creatinine from mg/dL to μ mol/L, multiply by 88.4; and to convert hsCRP to nmol/L, multiply by 9.524.

^cData are presented as mean $\pm$ SD.

results in structural or functional damage to the endothelium and apoptosis.²⁹

Similar to the findings of previous studies,^{30,31} our study found that patients with MetS had significantly higher levels of hsCRP, a nonspecific inflammatory marker. Whether the increase in inflammatory markers contributes directly to the pathogenesis of MetS or is a secondary response to inflammation in this disease state is unclear,³² but a high hsCRP level has been found to be a powerful independent predictor of increased CV risk.³³⁻³⁵ Atherosclerosis is considered an inflammatory disease, and indeed in experimental models of inflammation, endothelial function is impaired.³⁶ Recent reports provide provocative evidence that hsCRP may impair insulin signaling, which may be a fundamental mechanism of MetS.³⁷ Furthermore, elevated hsCRP levels are associated with reduced basal and stimulated nitric oxide release from arterial endothelial cells through various mechanisms,³⁸ which may have contributed to our findings. In addition, leukocyte count, a marker of inflammation and an independent predictor of CV risk,³⁹ was also significantly higher in the MetS group. High leukocyte counts may result in secretion of inflammatory cytokines and cytotoxic products, affecting endothelial cells,^{40,41} and catalyze reactions that consume vascular nitric oxide via polymorphonuclear neutrophil-derived prooxidative enzymes, such as NADPH oxidase and myeloperoxidase, resulting in impaired endothelial function.⁴²

Besides insulin resistance and inflammation, central obesity may be another possible mechanism to have an effect on endothelial function. Evidence

indicates that MetS begins with excess central adiposity.⁴³ In a previous study from our group, the early phase of obesity in an experimental model was characterized by coronary endothelial dysfunction before the occurrence of insulin resistance.⁴⁴ Visceral fat tissue leads to production of proatherogenic adipokines that are important contributors to oxidative stress and chronic inflammation,⁴⁵ both factors with an important harmful effect on endothelial function. Reduced nitric oxide bioavailability due to excess reactive oxygen species generation might become the major cause of endothelial dysfunction in obesity.⁴⁶

Although a clear cause-and-effect relationship may not be established by our study, insulin resistance, inflammation, and central obesity are likely the most important determinants of endothelial dysfunction in MetS. In addition to traditional CV risk factors, these factors may become specific targets for improvement of endothelial function and reduction in CV risk.⁴⁷ In the Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin, statin therapy was associated with a significant reduction of hsCRP (37%), 44% fewer CV events, and a 20% reduction in all-cause mortality compared with placebo.⁴⁸ Some studies also have reported that nonpharmacologic and pharmacologic strategies targeting central obesity improved endothelial function and ameliorated low-grade inflammation.⁴⁹⁻⁵² Thus, the reversal of some of the parameters of MetS may be associated with a reduction in CV events and may be mediated by improvement in endothelial function. Moreover,

TABLE 3. Sequential Multivariate Regression for the Relationship of MetS and Endothelial Function^a

Variable	Model A (covariates ^b)		Model B (covariates and 6 risk factors ^c)		Model C (covariates, 6 CV risk factors, and MetS)	
	β	P value	β	P value	β	P value
Age	0.08	.06	0.08	.06	0.08	.06
Sex	0.07	.10	0.07	.09	0.09	.05
Nitrates	−0.13	.004	−0.13	.004	−0.14	.002
RAAS inhibitor	0.04	.93	0.04	.35	0.05	.30
Statins	0.05	.30	0.05	.30	0.04	.32
Leukocytes	−0.14	.001	−0.14	.001	−0.13	.003
OSA	−0.11	.009	−0.11	.009	−0.09	.04
CAD	−0.09	.04	−0.09	.03	−0.09	.004
Hypertension			0.08	.05	0.08	.07
Hypercholesterolemia			0.06	.20	0.06	.16
Overweight or obesity			−0.03	.43	−0.006	.90
Diabetes mellitus			−0.03	.49	−0.02	.71
Smoking			−0.02	.71	−0.03	.47
FH			0.04	.40	0.009	.84
MetS					−0.11	.01
R ²	0.08		0.09		0.10	
F change			1.10		4.93	
P value	<.001		.38 ^d		.03 ^e	

^aCAD = coronary artery disease; CV = cardiovascular; FH = family history of premature CAD; MetS = metabolic syndrome; OSA = obstructive sleep apnea; RAAS = renin-angiotensin-aldosterone system.

^bAge, sex, nitrates, RAAS inhibitor, statins, leukocyte count, OSA, and history of CAD.

^cHypertension, hypercholesterolemia, overweight or obesity, diabetes, smoking, and FH.

^dTest for an incremental change in R² between model A and model B.

^eTest for an incremental change in R² between model B and model C.

the detection of endothelial dysfunction may serve to identify individuals at risk.^{53,54}

This is a single-center, retrospective, and non-randomized study; therefore, a certain selection bias is inevitable. However, the larger number of individuals compared with prior studies will mitigate this risk. In this study we defined MetS according to the most recent interdisciplinary joint statement.¹² However, because MetS is an agglomeration of risk factors characterized arbitrarily by categorical variables, our conclusion may not be extrapolated to other definitions. Notably, we previously performed the same analysis with the definition of the International Diabetes Federation guidelines.⁵⁵ Although some patients were reclassified, the overall results did not differ. Because the hemoglobin A_{1c} level, insulin level, and insulin sensitivity were not available for this study, we could not reveal a causal relation between endothelial function and insulin resistance in patients with MetS. Some individuals included in the study were using medications known to affect endothelial function, such as renin-angiotensin-aldosterone system inhibitors or st-

atins. In the multivariate model we attempted to account for potential confounders. Furthermore, all individuals discontinued use of vasoactive medications at least 24 hours before EndoPAT testing.

Although most of the studies using noninvasive measures of endothelial function have assessed flow-mediated vasodilatation of the brachial artery, we used EndoPAT as a measure of endothelial function at the fingertip. This is a Food and Drug Administration–approved measure of endothelial function used in clinical practice. Although EndoPAT has a weak correlation with flow-mediated dilation, it is known to correlate strongly with coronary microvascular function and gives important prognostic information. In addition, a major advantage of the method is its standardized protocol with very low interobserver variability.

CONCLUSION

In this study, we found that MetS led to a greater degree of endothelial dysfunction than multiple traditional CV risk factors. Factors associated with sys-

temic inflammation and central obesity may cause endothelial dysfunction in MetS. Thus, in patients with MetS, intense risk factor modifications should be considered. Additional studies are needed to better understand the relationship between the metabolic components of MetS and endothelial dysfunction. Furthermore, future studies should focus on improving endothelial function and evaluation of whether this translates to better CV outcomes.

Abbreviations and Acronyms: CV = cardiovascular; hsCRP = high-sensitivity C-reactive protein; MetS = metabolic syndrome; RHI = reactive hyperemia index

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