Relationship of Metabolic Syndrome and Fibrinolytic Dysfunction to Cardiovascular Disease

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Background—The clustering of impaired glucose metabolism, elevated triglycerides, low HDL cholesterol, and abdominal obesity is known as the metabolic syndrome. Individuals with this syndrome suffer an excess of cardiovascular disease (CVD) for reasons that are unclear.

Methods and Results—We randomly sampled 1276 adults of South Asian, Chinese, European, and Native Indian ancestry from 4 communities in Canada. Participants provided fasting blood samples for glucose, lipids, and fibrinolytic measurements; had an oral glucose tolerance test; and underwent a B-mode carotid ultrasound examination. CVD was determined by history and ECG. The prevalence of the metabolic syndrome was 25.8% (95% CI, 23.5 to 28.2) and varied substantially by ethnic group: 41.6% among Native Indians, 25.9% among South Asians, and 22.0% among Europeans, compared with 11.0% among the Chinese (overall, P=0.0001). People with the metabolic syndrome had more atherosclerosis (maximum intimal medial thickness, 0.78±0.18 versus 0.74±0.18 mm; P=0.0005), CVD (17.2% versus 7.0%; P=0.0001), and elevated plasminogen activator inhibitor-1 (24.2 versus 14.6 U/mL; P=0.001) compared with levels among people without the metabolic syndrome. For the same amount of atherosclerosis, people with the metabolic syndrome had a greater prevalence of CVD, even among nondiabetic individuals. This difference in CVD prevalence among the groups was attenuated after adjustment for plasminogen activator inhibitor-1 levels, suggesting that fibrinolytic dysfunction mediates the increased risk of CVD in individuals with the metabolic syndrome.

Conclusion—CVD among people with the metabolic syndrome is explained by their excess of atherosclerosis and impaired fibrinolysis. Interventions to prevent atherosclerosis progression and improve fibrinolytic function require evaluation in this high-risk group. (Circulation. 2003;108:420-425.)

Key Words: diabetes mellitus ■ atherosclerosis ■ fibrinolysis ■ epidemiology

A large body of epidemiological data indicates that people with glucose intolerance, abdominal adiposity, elevated triglycerides, and low HDL cholesterol levels have an increased risk of cardiovascular disease (CVD). The common clustering of these factors in a single individual is referred to as the metabolic syndrome. In the past decade, explanations for the increased CVD suffered by this group include their accelerated development of atherosclerosis and their increased propensity to develop thrombosis.

The need for systematic comparisons of the prevalence of the metabolic syndrome among ethnic groups has been highlighted. Aboriginal people of North America (Native Indians) and people who originate from the Indian subcontinent (South Asians) have an increased susceptibility to develop the metabolic syndrome. Detailed investigations among these “high-risk” populations have the potential to contribute new insights about the etiology and pathogenesis of CVD.

Among people with the metabolic syndrome, atherosclerosis is increased and fibrinolytic function is abnormal. Specifically, plasminogen activator inhibitor-1 (PAI-1) is increased among type 2 diabetic patients and predicts myocardial infarction and stroke. Also, elevated endogenous tissue-type plasminogen activator (tPA) predicts mortality and myocardial infarction, and is elevated in response to endogenous fibrinolytic inhibitors such as PAI-1.

It is likely, therefore, that high plasma concentrations of PAI-1 and tPA reflect a state of fibrinolytic dysfunction. Fibrinolytic dysfunction increases the propensity to develop arterial thrombosis, which in turn may increase CVD in people with the metabolic syndrome. This hypothesis is supported by the recent observations that diabetes and ab-
dominal obesity are risk predictors of both venous thrombosis and occlusive arterial disease. Although prior studies have documented that markers of fibrinolysis are abnormal in people with the metabolic syndrome, it remains unclear whether these abnormalities reflect fibrinolytic dysfunction or are merely a response to vascular injury or plaque turnover. Functional tests of fibrinolysis are available; however, because of the complexity involved in performing them, they have not been performed on a large scale.

The specific objectives of this investigation were to (1) determine the prevalence of the metabolic syndrome among a multiethnic population in Canada, (2) determine whether fibrinolytic dysfunction is present among people who possess the metabolic syndrome, and (3) determine if fibrinolytic dysfunction could explain the increased prevalence of CVD among people with metabolic syndrome.

Methods

Recruitment of Participants

People of South Asian, Chinese, European, and Native Indian ancestry were randomly sampled from 3 cities (Hamilton, Toronto, Edmonton) and the Six Nations Reservation (Ohsweken, Ontario) in Canada. South Asian and Chinese Canadians were identified by using the previously validated method of unique surname classification. A database of unique surnames was created manually and merged with a compact disk (CD) compilation of public telephone directories. These sampling frames were sorted by postal codes, which created implicit stratification by geographic region. After a South Asian or Chinese respondent was confirmed for a clinic visit, his or her postal code was reentered into the CD program, and a list of individuals with the same postal code was generated. Individuals whose names were not South Asian or Chinese were presumed to be people of European origin. They were also selected randomly and approached for participation in the same manner as the other ethnic groups. Ethnicity was confirmed at the first telephone contact, and only those who were confirmed to be South Asian, Chinese, or European were invited to the clinic visit. Residents of the Six Nations Reservation were randomly selected from a comprehensive list of all Six Nations Band members. From these ethnic-specific lists, households were randomly selected and mailed an introductory letter, which was followed by up to 12 telephone calls inviting the individual with the earliest date of birth in the household to participate in the study. To be eligible, individuals must have lived in Canada for at least 5 years and be between the ages of 35 to 75 years. Individuals with chronic debilitating illnesses such as terminal cancer and renal failure were excluded.

Assessment of Risk Factors, Atherosclerosis, and CVD

After providing informed consent, fasting blood samples were collected in the morning from all participants, and all nondiabetic participants drank a 75 g glucose solution, after which blood samples were repeated 2 hours later. Blood samples were collected and processed according to a standard protocol and were shipped to the core laboratory in Hamilton for analysis. All participants completed a general health questionnaire and had a 12-lead ECG and a carotid B-mode ultrasound examination, as previously described.

Fibrinolysis Substudy

A subset of participants recruited from Hamilton and the Six Nations Reservation (n=472) also underwent an in-depth assessment of fibrinolytic function, which included measurement of PAI-1, tPA-antigen (tPA-Ag), and euglobulin clot lysis time (ECLT) at baseline and after venous cuff occlusion. All participants lay supine for 15 minutes before blood collection, and a 20-gauge needle was used to draw the blood samples with limited occlusion of the arm by a tourniquet. Samples were collected into 3.2% buffered sodium citrate Stabilyte tube and a Diatube (PAI) and were immediately placed in an ice-water bath. Blood pressure was recorded in the other arm, and the pressure cuff was inflated to the midway point between the systolic and diastolic blood pressure. After 10 minutes, before the pressure was released, a second blood sample was taken, as described above, and placed immediately in an ice-water bath. Samples were then centrifuged at 1700g for 15 minutes to obtain platelet-poor plasma, which was stored in plastic tubes and frozen at −70°C. All assays for fibrinolytic markers were conducted at the Hemostasis Reference Laboratory, Hamilton Civic Hospitals Research Centre.

Laboratory Assays

tPA-Ag levels and PAI-1 activity were assayed by using commercially available test kits from Diagnostica Stago and Biopool, respectively. ECLT is the time (in minutes) required to dissolve a clot in vitro. It provides a functional measure of fibrinolysis and reflects the global effect of many factors on fibrinolytic function. Assay results were normalized for the degree of hemoconcentration by using the pre- and postvenous occlusion stress test hemocrit.

Atherosclerosis

The standardized quantitative B-mode carotid ultrasound scanning consisted of a transverse scan followed by a full-circumferential longitudinal scan and obtained images from 6 well-defined carotid artery segments for the right and left carotid arteries (12 segments/patient). The maximal intimal medial thickness (IMT) for each segment was identified. The mean of the maximum IMT (mmIMT) readings for the 12 segments was calculated for each participant. The intraclass correlation coefficients for between and within ultrasonographer (0.91, 0.90) and reader (0.88, 0.92) reliability indicates that our method yielded highly reproducible measures.

Cardiovascular Disease

CVD was classified as (1) coronary artery disease, which was defined as angina (Rose questionnaire), a self-reported hospitalization for a myocardial infarction, silent myocardial infarction (major Q waves by Minnesota criteria), percutaneous coronary angioplasty, or coronary artery bypass graft surgery; or (2) cerebrovascular disease, which was defined by self-report of a prior stroke confirmed by a physician.

Metabolic Syndrome

The metabolic syndrome was defined by using the Third Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (ATP III) criteria. Individuals were classified as having the metabolic syndrome if they had ≥3 of the following abnormalities: waist circumference >102 cm in men and >88 cm in women, serum triglycerides level of at least 1.69 mmol/L, HDL cholesterol level of <1.04 mmol/L in men and <1.29 mmol/L in women, blood pressure of at least 130/85 mm Hg, or serum glucose level of at least 6.1 mmol/L.

Statistical Analysis

All analyses were computed by using SAS (version 6.12). Comparisons of continuous variables were performed by using ANCOVA with adjustment for age, sex, and smoking. Post-hoc pairwise comparisons were performed by using Tukey’s approach to adjust for multiple comparisons. For statistical comparisons of discrete variables between groups, logistic regression was performed with age, sex, and smoking as covariates.

Results

Between October 1996 to April 2000, 1276 men and women (342 South Asians, 317 Chinese, 326 Europeans, and 301 Native Indians) completed the clinic visit. On average, South Asian and Chinese participants had lived in Canada for 19...
years compared with 45 years among Europeans and 44 years among Native Indians. The average age of participants was 50.4 (10.3) years, 51.1% were women, and 64.2% were employed. The prevalence of the metabolic syndrome was 25.8% (95% CI, 23.4 to 28.2), and this varied significantly among the ethnic groups. The prevalence of the metabolic syndrome was 41.6% among Native Indians, 25.9% among South Asians, 22.0% among the people of European origin, and 11.0% among the Chinese (overall, \( P = 0.0001 \)) (Figure 1). In addition to having higher glycosylated hemoglobin levels, more abdominal obesity, lower HDL cholesterol, and higher blood pressure, individuals with the metabolic syndrome were older, were more likely to smoke, and had significantly higher body mass index, fibrinogen, fasting, and post glucose load insulin concentrations compared with levels among people without the metabolic syndrome. No differences in the LDL cholesterol or plasma homocysteine concentrations were observed (Table 1).

**Fibrinolytic Parameters**

People with the metabolic syndrome had significantly higher levels of PAI-1 compared with that of people without the metabolic syndrome (24.2 versus 14.6 U/mL; \( P = 0.001 \)).

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**TABLE 1. Key Comparisons**

<table>
<thead>
<tr>
<th>Metabolic Syndrome</th>
<th>Total (n=332)</th>
<th>With Diabetes (n=148)</th>
<th>Without Diabetes (n=184)</th>
<th>No Metabolic Syndrome (n=944)</th>
<th>( P^* )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>53.8 (10.0)</td>
<td>56.6 (10.4)</td>
<td>51.5 (9.0)</td>
<td>49.2 (10.2)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Male, %</td>
<td>50.6</td>
<td>43.9</td>
<td>56.0</td>
<td>48.5</td>
<td>0.51</td>
</tr>
<tr>
<td>Current smokers, %</td>
<td>26.8</td>
<td>24.7</td>
<td>26.9</td>
<td>13.8</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Former smokers, %</td>
<td>25.3</td>
<td>30.4</td>
<td>25.4</td>
<td>21.5</td>
<td>0.15</td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>38.3</td>
<td>NA</td>
<td>NA</td>
<td>5.3</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Impaired glucose tolerance, %</td>
<td>16.7</td>
<td>NA</td>
<td>17.4†</td>
<td>12.4</td>
<td>0.05</td>
</tr>
<tr>
<td>Impaired fasting glucose, %</td>
<td>4.0</td>
<td>NA</td>
<td>4.8†</td>
<td>1.3</td>
<td>0.002</td>
</tr>
<tr>
<td>Glycosylated hemoglobin, %</td>
<td>6.6 (1.0)</td>
<td>7.9 (1.2)</td>
<td>5.7 (1.2)</td>
<td>5.6 (1.0)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Fasting insulin, pmol/L</td>
<td>136.3 (64.5)</td>
<td>166.3 (105.1)</td>
<td>115.4 (95.4)</td>
<td>73.6 (57.0)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>2-Hour post-OGTT insulin, pmol/L</td>
<td>872.4 (701.5)</td>
<td>876.4 (1367.2)</td>
<td>888.7 (867.8)</td>
<td>495.1 (558.7)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Fasting triglycerides, mmol/L</td>
<td>2.8 (1.1)</td>
<td>3.0 (1.7)</td>
<td>2.6 (1.6)</td>
<td>1.5 (1.1)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>HDL cholesterol, mmol/L</td>
<td>0.89 (0.3)</td>
<td>0.90 (0.2)</td>
<td>0.91 (0.2)</td>
<td>1.20 (0.3)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LDL cholesterol, mmol/L</td>
<td>3.2 (0.8)</td>
<td>3.2 (0.9)</td>
<td>3.4 (0.9)</td>
<td>3.2 (0.8)</td>
<td>0.34</td>
</tr>
<tr>
<td>PAI-1, U/mL</td>
<td>24.2 (9.2)</td>
<td>26.1 (9.5)</td>
<td>22.0 (9.8)</td>
<td>14.6 (9.1)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Body mass index</td>
<td>31.7 (4.9)</td>
<td>31.9 (5.4)</td>
<td>31.4 (5.4)</td>
<td>25.8 (4.9)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Body mass index &gt;27, %‡</td>
<td>81.3</td>
<td>79.4</td>
<td>83.1</td>
<td>32.2</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Waist circumference</td>
<td>104.7 (13.4)</td>
<td>105.5 (13.3)</td>
<td>104.7 (13.2)</td>
<td>87.0 (13.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>WHR</td>
<td>0.94 (0.1)</td>
<td>0.95 (0.1)</td>
<td>0.93 (0.1)</td>
<td>0.87 (0.1)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Abdominal obesity WHR ≥0.90, %‡</td>
<td>75.9</td>
<td>84.7</td>
<td>74.0</td>
<td>27.6</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>125.9 (16.2)</td>
<td>129.3 (18.2)</td>
<td>127.6 (18.1)</td>
<td>116.7 (16.1)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Diastolic BP, mm Hg</td>
<td>76.9 (10.8)</td>
<td>77.0 (12.6)</td>
<td>76.7 (12.7)</td>
<td>71.6 (10.7)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Homocysteine, µmol/L</td>
<td>9.9 (4.2)</td>
<td>9.6 (4.8)</td>
<td>10.7 (4.8)</td>
<td>10.1 (4.2)</td>
<td>0.41</td>
</tr>
<tr>
<td>Fibrinogen, g/L</td>
<td>3.4 (0.9)</td>
<td>3.5 (0.7)</td>
<td>3.3 (0.7)</td>
<td>3.0 (0.9)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Atherosclerosis, mmIMT</td>
<td>0.78 (0.2)</td>
<td>0.85 (0.2)</td>
<td>0.80 (0.2)</td>
<td>0.74 (0.2)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>CVD, %‡</td>
<td>17.2</td>
<td>18.0</td>
<td>11.8</td>
<td>7.0</td>
<td>0.0003</td>
</tr>
</tbody>
</table>

Values are age and sex adjusted. Values represent mean (SD) or percentage of patients.
OGTT indicates oral glucose tolerance test; WHR, waist-to-hip ratio; and BP, blood pressure.
*Statistical comparison between metabolic syndrome vs non–metabolic syndrome categories.
†Unadjusted rate.
‡Age and sex adjusted rate.
the subset of participants (n=472) in the fibrinolysis sub-study, PAI-1 and tPA-Ag were significantly elevated at baseline and after cuff occlusion in people with the metabolic syndrome compared with levels for people without the metabolic syndrome (Table 2). Before cuff occlusion, the time it took to lyse a clot in vitro was significantly longer among people with the metabolic syndrome compared with people without the metabolic syndrome (325.5±68.4 versus 268.7±68.2 minutes; P<0.0001). Further, the reduction in clot lysis time after cuff occlusion (which is expected in response to ischemia induced by the cuff) was significantly impaired among the people metabolic syndrome compared with those without the metabolic syndrome (41%±17.9 versus 50%±15.1 reduction; P=0.002), suggesting a functional impairment in fibrinolytic activity (Figure 2).

Atherosclerosis and CVD

People with the metabolic syndrome had significantly more atherosclerosis, as measured by the B-mode carotid ultrasound (mmIMT=0.78±0.18 versus 0.74±0.18 mm; P=0.0001), and CVD (17.2% versus 7.0%; P=0.0001) compared with levels for people without the metabolic syndrome. The amount of atherosclerosis among nondiabetic individuals with the metabolic syndrome was also signifi-

Table 2. Fibrinolytic Measures Before and After Cuff Occlusion *

<table>
<thead>
<tr>
<th></th>
<th>Metabolic Syndrome (n=127)</th>
<th>No Metabolic Syndrome (n=345)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>PAI, U/mL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>24.2 (9.2)</td>
<td>16.6 (9.1)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Postcuff*</td>
<td>17.5 (6.8)</td>
<td>10.1 (6.8)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>TPA-Ag, ng/mL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>10.7 (3.1)</td>
<td>7.2 (3.1)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Postcuff*</td>
<td>18.1 (7.8)</td>
<td>13.1 (7.8)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Values are expressed as age- and sex-adjusted mean (SD).

*Corrected for by the change in hematocrit.

Figure 2. Time to clot lysis, with age and sex adjusted. Pre indicates baseline sample before cuff occlusion; post, drawn after 10 minutes of cuff occlusion and converted for the change in plasma volume. The baseline clot lysis time is significantly longer in metabolic syndrome compared with nonmetabolic syndrome (P<0.0001), and the percentage of reduction (which is expected) after cuff occlusion is significantly lower (P<0.001).

Figure 3. A, Cardiovascular events by atherosclerosis category (n=1276): group 1, ≤50th percentile of mmIMT; group 2, >50th percentile of mmIMT. *Metabolic syndrome (MS) vs no MS after adjustment for age, sex, and smoking, P=0.001. **MS vs no MS after adjustment for age, sex, smoking, and PAI-1 levels, P=0.10. B, Cardiovascular events by atherosclerosis category in patients without diabetes (n=1059): group 1, ≤50th percentile of mmIMT; group 2, >50th percentile of mmIMT. *MS vs no MS after adjustment for age, sex, and smoking, P=0.03. **MS vs no MS after adjustment for age, sex, smoking, and PAI-1 levels, P=0.54.

Figure 3. A, Cardiovascular events by atherosclerosis category (n=1276): group 1, ≤50th percentile of mmIMT; group 2, >50th percentile of mmIMT. *Metabolic syndrome (MS) vs no MS after adjustment for age, sex, and smoking, P=0.001. **MS vs no MS after adjustment for age, sex, smoking, and PAI-1 levels, P=0.10. B, Cardiovascular events by atherosclerosis category in patients without diabetes (n=1059): group 1, ≤50th percentile of mmIMT; group 2, >50th percentile of mmIMT. *MS vs no MS after adjustment for age, sex, and smoking, P=0.03. **MS vs no MS after adjustment for age, sex, smoking, and PAI-1 levels, P=0.54.
increased propensity of people with metabolic syndrome to develop atherothrombosis.

Other investigators have independently reported that people with diabetes have more atherosclerosis and higher concentrations of markers associated with impaired fibrinolysis. Increased PAI-1 levels are also associated with dyslipidemia, hypertension, and hyperinsulinemia and could explain the predisposition of individuals with metabolic syndrome to develop atherothrombosis. To address the issue of whether or not elevated PAI-1 levels reflect a state of fibrinolytic dysfunction, and hence a propensity to develop atherothrombosis, we performed a functional assessment of fibrinolysis designed to elicit an individual’s maximum fibrinolytic potential. We observed that both basal markers of thrombosis, fibrinolytic activity and function, are substantially impaired among people with the metabolic syndrome, and they suffer from disproportionately more CVD for the same amount of atherosclerosis compared with people without the metabolic syndrome. Among individuals with metabolic syndrome, differences in CVD prevalence can be partly attributable to the higher proportion of people who have established type 2 diabetes. Even among nondiabetic people with the metabolic syndrome, however, an excess of CVD was observed. In both groups, differences in CVD prevalence attributable to the metabolic syndrome were attenuated after adjustment for PAI-1 levels. This may partially explain the excess of CVD suffered by people with the metabolic syndrome. Further, people with metabolic syndrome have significantly more atherosclerosis compared with people without metabolic syndrome, and this is true even among nondiabetic individuals with the metabolic syndrome. This suggests that the higher CVD prevalence among people with metabolic syndrome is due to impaired fibrinolysis and more atherosclerosis.

In our cross-sectional study, people with the metabolic syndrome were on average 36 pounds heavier, had higher blood pressure and lower HDL cholesterol, and were significantly more likely to smoke than were people without the metabolic syndrome. The present study and previous investigations suggest a number of opportunities for CVD prevention in this high-risk group. First, control of body weight and abdominal fat accumulation through a combination of reduced energy intake and increased energy expenditure will likely prevent the development of the downstream components of the metabolic syndrome such as glucose impairment, dyslipidemia, and impaired fibrinolysis.

Weight loss through exercise and dietary modification is highly effective in preventing the development of diabetes in people who have many of the features of the metabolic syndrome. Second, control of the conventional determinants of atherosclerosis, such as lipids, blood pressure, and tobacco, should be heavily promoted. Third, interventions that improve fibrinolytic function may reduce cardiovascular events in people with the metabolic syndrome. There is some evidence that fibrinolytic function is improved by weight loss, exercise, a low-glycemic-index diet, and drugs such as metformin, thiazolidinediones, and ACE inhibitors. Although aspirin is not generally advocated for the primary prevention of CVD in all people, it may have a role to play in people with the metabolic syndrome, given their increased risk of CVD.

Conclusions

The prevalence of the metabolic syndrome varies substantially among ethnic groups. The metabolic syndrome is associated with an excess of CV disease, which is caused in part by an excess of atherosclerosis and in part by fibrinolytic dysfunction. This combination of factors helps to explain the increased propensity of people with metabolic syndrome to develop atherothrombosis and clinical CVD.

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References

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