Clinical Research

Profile and prevalence of aspirin resistance in patients with metabolic syndrome

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Objective  Aspirin has been used extensively in primary and secondary prevention of cardiovascular disease, particularly for subjects at high risk such as metabolic syndrome. However, the responsiveness to aspirin treatment may vary among individuals. The present study was conducted to investigate the profile and prevalence of aspirin resistance in patients with metabolic syndrome.

Methods  In 221 consecutive patients, platelet aggregation induced by arachidonic acid (0.5mg/ml) was assessed after 10 days of aspirin treatment (200mg/d). Aspirin resistance was defined as mean optical platelet aggregation ≥20%. Results  Aspirin resistance occurred in 39 patients (17.6%). Serum fibrinogen level was higher in patients with than in those without aspirin resistance (2.6±0.4g/l vs 2.4±0.4g/L, P=0.017). The 2 groups, aspirin resistance group and no aspirin resistance group, did not differ significantly, with regard to gender, age, body mass index, waist-hip ratio, blood pressure level, serum cholesterol level and history of myocardial or cerebral infarction. Multivariate logistic regression analysis revealed that only serum fibrinogen level entered the model (odds ratio 2.973, p=0.023). Subgroup analysis further showed that aspirin resistance occurred more in male patients with myocardial infarction (50% vs14.5%, P=0.02) and in female patients with diastolic blood pressure=85mmHg (34% vs 15.5%, P=0.043). But after multifactor logistic regression, in women blood pressure=85mmHg was not a predictor any more.

Conclusions  In patients with metabolic syndrome, aspirin resistance is not uncommon, especially for men with history of myocardial infarction. Patients with aspirin resistance have an increased serum fibrinogen level. (J Geriatr Cardiol 2008; 5:7-10)

Key Words  metabolic syndrome; aspirin resistance; fibrinogen

Introduction

Aspirin (acetylsalicylic acid) inhibits platelet activation and aggregation with irreversibly acetylating 530-serine residual of cyclooxygenase-1. Furthermore, some studies showed that aspirin might suppress the atherosclerosis by inhibiting COX-2 expression to reduce the inflammation that had been proven play a key role in atherosclerosis plaque formation and rupture. A large body of evidence has shown that the use of aspirin effectively reduces cardiovascular events including death, myocardial infarction and stroke in primary and secondary prevention population. However, benefits from regular treatment with recommended daily dose of aspirin may vary among patients, due partly to different responsiveness states to the agent. The degree of inhibition of platelet aggregation can be assessed by a variety of tests, such as optical platelet aggregation, PFA-100, expression of platelet surface receptor. Therefore, optical platelet aggregation is the most popular way to determine aspirin resistance status.

Metabolic syndrome is a cluster of multiple cardiovascular risk factors, including disturbance of glucose and lipid metabolism, high blood pressure and abnormal fat distribution. Deficiency of fibrinolytic function and hyperactivity of platelet aggregation are also features of metabolic syndrome. Previous studies have indicated that the efficacy of aspirin in primary prevention of cardiovascular events for type 2 diabetic patients was reduced, and metabolic syndrome patients were prone to develop cardiovascular disease because of platelet hyperactivity and conferred a higher risk of long term MACCE (Major Adverse Cardiac and Cerebral Events) in patients with CAD. In this study, we sought to investigate the profile and prevalence of aspirin resistance in patients with metabolic syndrome.

Materials and methods

Patients

The study population consisted of 221 consecutive patients recruited from Shougang community between May and July, 2005 after obtaining a written informed consent. All patients reached the NCEP ATP criteria modified by racial variety and met at least 3 of the following criteria: 1. Abdominal obesity (waist circumference ≥90cm in men and ≥80cm in women). 2. Elevated blood pressure (systolic blood pressure ≥130mmHg or diastolic pressure ≥85mmHg). 3. Elevated fasting plasma total cholesterol (≥5.7mmol/L). 4. Elevated fasting plasma glucose (≥6.1mmol/L) or history of treated diabetes mellitus. 5. Low HDL cholesterol (≤0.9mmol/L in men and ≤0.59mmol/L in women).
abdominal obesity (waist circumference>85cm in men and>80cm in women), high serum triglycerides (>1.7mol/L), low HDL cholesterol (<1.0mmol/L in men, <1.3mmol/L in women), high blood pressure (=130/85mmHg), fasting glucose=6.1mmol/L. Patients with liver or renal dysfunction or malignant tumor, allergy or intolerance to aspirin, administration of warfarin or other non-steroidal anti-inflammatory agents (e.g., ibuprofen), or platelet count<100×10^9/L or >500×10^9/L were excluded.

**Study protocol**

All patients received aspirin (200mg daily) for 10 days. Fasting blood samples were collected with 3.8% sodium citrate between 1-3 hours after last dosing. Conventional hematological measurement, optical platelet aggregation, and biochemical assessments were performed.

For assessing optical platelet aggregation, the specimens were kept at room temperature and processed within 2 hours of blood sample collection. The blood sample was centrifuged at 1000r/min for 7 minutes to obtain platelet rich plasma (PRP). The remaining sample was centrifuged at 3000r/min for 10 minutes to obtain platelet poor plasma (PPP). Platelet count in PRP was determined with automatic hematology analyzer, and adjusted to 200×10^9/L or >200×10^9/L or <100×10^9/L with PPP. The baseline optical density was set with PPP. Platelet aggregation was measured with LBY-NJ4 platelet aggregometer (Beijing PRECIL Instrument Co.) using 0.5mg/ml arachidonic acid. Aspirin resistance was defined as a mean aggregation=20%. Other hematologic measurements were performed with an automatic analyzer.

**Statistical analysis**

Data analysis was made using SPSS 11.0. Continuous variables are expressed as mean ± SD, and categorical variables are presented as frequencies and percentages. Student t test was used to compare the means of continuous variables, and chi-square test was applied to compare the frequencies of categorical variables between the two groups. Multifactor logistic regression was performed to adjust confounding factors. A p value ≤0.05 was considered statistically significant.

**Results**

Aspirin resistance was documented in 39 out of total 221 patients (17.6%) with metabolic syndrome. The mean values of platelet aggregation were 32.5±15.7% for patients with aspirin resistance and 8.8±7.3% for those without aspirin resistance, respectively.

Clinical features for patients with and without aspirin resistance are shown in Table 1. Both groups did not differ significantly with respect to age, blood pressure, fasting plasma glucose, serum cholesterol, body mass index, waist circumference, gender, smoking, and history of myocardial infarction or cerebral infarction. Serum fibrinogen level was significantly higher in patients with than in those without aspirin resistance (2.6±0.4g/L vs 2.4±0.4g/L, p=0.017). After converting continuous variables of blood pressure, serum cholesterol, waist circumference and fasting plasma glucose to categorical variables according to the enrolling criteria, there was no significant association between these variables and aspirin resistance. Multivariate logistic regression analysis showed that only serum fibrinogen level entered the model (odds ratio 2.973, p=0.023).

After stratification with gender, history of myocardial infarction (50% vs 14.5%, p=0.02) and blood pressure=85mmHg (34.8% vs 15.5%, p=0.043) were associated with aspirin resistance in male and female patients, respectively (Table 2). Multifactor logistic regression analysis showed that in men serum fibrinogen level and history of myocardial infarction kept to be predictors of aspirin resistance (odds ratio 5.873, p=0.037 for fibrinogen and odds ratio 16.13, p=0.018 for history of myocardial infarction), however in women blood pressure>85mmHg was not a predictor any more (odds ratio 3.36, p=0.055).

**Discussion**

Several previous studies have reported unfavorable results of aspirin for the primary prevention of cardiovascular events in type 2 diabetic patients, and aspirin resistance was thought to be a clinically important issue. Metabolic syndrome was thought to be a more complicated clinic...
syndrome than diabetes mellitus, but the aspirin efficacy was not fully understood in this setting.18 Our study indicates that around one-fifth of patients with metabolic syndrome developed aspirin resistance, suggesting that this population may be at high risk of developing cardiovascular events, and require aggressive therapeutic intervention.

In this study, plasma fibrinogen level was significantly higher in patients with than in those without aspirin resistance. Serum fibrinogen level acted as a predictor of aspirin resistance, even after justifying certain confounding factors such as sex, age and history of cerebral and myocardial infarction, highlighting the presence of underlying mechanisms. Fibrinogen molecules in blood were main factors that induced platelet aggregation and adhesion through binding to the receptors on the platelet membrane surface (i.e. activated GP \( \epsilon \delta b/ \epsilon \delta a \) receptor).19 It has been shown that serum fibrinogen level was increased in patients with metabolic syndrome, and aspirin could block fibrinogen binding to its receptor.20 Therefore, at the same dose of aspirin, an increased serum fibrinogen level could reduce its anti-platelet efficacy, likely causing aspirin resistance.

In this study, further analysis after stratification with gender indicated that history of myocardial infarction in men (50% vs 14.5%, \( P = 0.02 \)) and diastolic blood pressure > 85mmHg in women (34% vs 15.5%, \( p = 0.043 \)) were predictors of aspirin resistance. Our results are consistent with previous studies that patients with ischemic heart disease were prone to develop aspirin resistance,21 especially for men. However, because the number of each group was relatively small after stratification, and the mechanism how gender affected responsiveness to aspirin remained unclear, the results after stratification with gender should be explained more carefully. And the results of this study should be validated with studies with larger sample size.

The other predictors of aspirin resistance found in previous studies included disturbance of lipid metabolism, diabetes mellitus, hypertension and heart failure.16,22 All patients with metabolic syndrome enrolled in this study were under medical therapy, and the total serum cholesterol level was not greatly increased. This may explain why no association between cholesterol level and aspirin resistance status was present in this study. Smoking was reported to be an additional predictor of aspirin resistance, but this was not established in our study due probably to small number of cigarette smokers (15.4%) in the population. Different methods to identify the sensitivity of platelet to aspirin focused in different aspects of the platelet activation or COX-1 metabolism, for example, optical platelet aggregation which was used in this study focused in platelet aggregation after the activation to determine the reactivity to aspirin while flow cytometry looked the expression of surface receptors, such as P-selectin, as markers of platelet activation. Thus the aspirin resistance status judged by different methods will show different results, which may partly responsible for the inconsistency between different studies.

In summary, our study demonstrates a relatively high incidence of aspirin resistance in patients with metabolic syndrome, particularly for those with an increased serum fibrinogen level. Although the mechanism of aspirin resistance is still unclear, the prediction of aspirin resistance may be important for the patients who take aspirin regularly for the prevention of atherothrombosis. Further studies are needed to establish standard methodology of assessing the individualized effect of anti-platelet therapy and to explore its safety.

**References**


**Table 2 Distribution of history of MI and DBP > 85mmHg**

<table>
<thead>
<tr>
<th>History of MI</th>
<th>AR (%)</th>
<th></th>
<th>Value</th>
<th>Female</th>
<th>AR (%)</th>
<th></th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>AR</td>
<td>No-AR</td>
<td></td>
<td></td>
<td>AR</td>
<td>No-AR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>History of MI</td>
<td>Yes</td>
<td>4</td>
<td>4</td>
<td>50.0%</td>
<td>6</td>
<td>1</td>
<td>11</td>
</tr>
<tr>
<td>of MI</td>
<td>No</td>
<td>11</td>
<td>76</td>
<td>14.5%</td>
<td>23</td>
<td>91</td>
<td>20.2%</td>
</tr>
<tr>
<td>DBP &gt; 85mmHg</td>
<td>5</td>
<td>33</td>
<td>13.2%</td>
<td>0.775#</td>
<td>8</td>
<td>15</td>
<td>34.8%</td>
</tr>
<tr>
<td>&lt; 85mmHg</td>
<td>10</td>
<td>47</td>
<td>17.5%</td>
<td>16</td>
<td>87</td>
<td>15.5%</td>
<td></td>
</tr>
</tbody>
</table>

AR, aspirin resistance; MI, myocardial infarction; DBP, diastolic blood pressure.
* Patients with vs without history of MI;
# Patients with DBP > 85mmHg vs those with DBP < 85mmHg


