Predicting New Onset Diabetes Mellitus in Older Taiwanese: Metabolic Syndrome or Impaired Fasting Glucose?

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Aim: Metabolic syndrome (MS) has been shown to predict diabetes mellitus (DM) in previous studies, but little is known about older adults. The main purpose of this study is to evaluate whether MS predicts new onset diabetes (NOD) in older community-living Taiwanese.

Methods: Community-living people aged over 40 who participated in annual health examinations held by community health clinics were invited to enrol in the study in 2000 and the status of DM was determined in 2005.

Results: In total, 480 subjects (mean age: 63.7 ± 10.8 years in year 2000, 43.8% males) were enrolled in this study. The prevalence of MS in 2000 was 25.4%. Overall, the 5-year cumulative incidence of NOD was 10.8%, and it was significantly higher in the MS group than non-MS group (17.2% vs. 8.7%, p = 0.011). Adjusted for age and gender, MS significantly predicts NOD (OR: 2.20, 95% CI: 1.21–4.00, p = 0.010). Moreover, both impaired fasting glucose (IFG) (OR: 4.48, 95% CI: 2.41–8.33, p<0.001) and hypertriglyceridemia (OR: 2.03, 95% CI: 1.04–3.94, p = 0.037) significantly predicted NOD among all 5 diagnostic components. In terms of predicting NOD, IFG showed a higher positive predictive value than MS (42.9% vs. 17.2%).

Conclusion: Both MS and IFG can effectively predict NOD among community-living older Taiwanese in 5-year follow-up; however, IFG alone may be a more efficient predictor of NOD because of a higher positive predictive value and lower laboratory cost.


Key words: Central obesity, Diabetes mellitus, Elderly, Insulin resistance, Metabolic syndrome

Introduction

The phenomenon of multiple cardiovascular risk factor clustering has been noted for decades1), but received little attention until Reaven described “syndrome X” in 19882). Increasingly, “syndrome X” became interchangeable with “insulin resistance syndrome” or “metabolic syndrome” (MS), the most commonly used term to date. Syndrome X is characterized by insulin resistance and its compensatory hyperinsulinemia, and studies have documented a linkage between insulin resistance and cardiovascular diseases (CVD)3-5). The World Health Organization first defined MS in 19996), which was followed by the Third Report of National Cholesterol Education Program’s Adult Treatment Panel III (ATP III) in 20017). Despite extensive research efforts on MS, the American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD) mutually stated that all individual CVD risk factors should be carefully treated irrespective of MS until more critical information on MS is available8). Nevertheless, the statements of American Heart Association and the National Heart Lung Blood Institute disagreed with the ADA/EASD statement...
and strengthened the importance of MS\(^9\).

In spite of the abovementioned controversies, the ultimate purpose of defining MS is to identify people who are at a higher risk of developing type 2 diabetes mellitus (DM) and CVD\(^9\). In terms of predicting DM, MS has been proved to be a good predictor of type 2 DM\(^{11-16}\), but some contradictory reports have challenged the effectiveness of MS to fulfill this role\(^{17, 18}\). A recent report indicated that MS did not predict NOD in a middle-aged Chinese population\(^{18}\); however, the effectiveness of MS to predict NOD in older adults remains uncertain. The clinical significance of DM onset at later age has been challenged\(^{19}\); therefore, using a diagnosis of MS to predict NOD in the elderly population may be logically problematic. In spite of the aforementioned challenges, MS is reported to be closely associated with coronary artery disease and cerebrovascular events in elderly Turks, which supported the benefits of diagnosing MS in older adults\(^{20}\). Therefore, the main purpose of this study was to evaluate the effectiveness of MS in DM prediction among community-living older Taiwanese.

**Methods**

**Subjects**

In 2000, a community study focusing on individuals aged over 40 in 3 townships (Tou-Cheng, Tonshan, Shanshing) of I-Lan County in Taiwan was conducted to explore the metabolic characteristics of insulin resistance\(^{21-23}\). Residents participating in the annual health examinations held by the Bureau of National Health Insurance were recruited after they were fully consented. Subjects with DM and those who were receiving anti-hypertensive treatment were excluded from further analysis. The study was approved by the ethics committee of Taipei Veterans General Hospital. In 2005, subjects recruited from Tou-Cheng Township were invited for a follow-up study.

**Demographic and Physical Examinations**

Experienced research staff recorded each subject’s age, sex, and we measured each subject’s height and weight to calculate the body mass index (BMI). Obesity and central obesity were defined by the Recommendations of the International Obesity Task Force\(^{24}\). In 2000, the Taiwanese official definition of obesity required no measurements of waist circumference. Personal medical history was also recorded in detail but the family history of DM was not obtained because of the inability of participants to recall their parents’ DM status. Blood pressure was measured according to the sixth report of the Joint National Committee on the prevention, detection, evaluation, and treatment of high blood pressure\(^{25}\).

**Laboratory Examinations**

All subjects underwent blood testing after a 10-h overnight fast to measure serum levels of glucose, total cholesterol (TC), triglyceride (TG), and high-density lipoprotein cholesterol (HDL-C) using an automatic analyzer (Model 736; Hitachi, Tokyo, Japan), and fasting insulin (FI) was measured by radioimmunoassay (Diagnostic Product Corporation, CA, USA).

**Diagnosis of Diabetes and Metabolic Syndrome**

The diagnosis of DM was made using the ADA criteria in 2001\(^{26}\), and the diagnosis of MS by the ATP III definition\(^7\), which was modified in this study, including lower fasting plasma glucose of 100 mg/dL by ADA recommendations, and waist circumference was replaced by BMI \(\geq\) 27 kg/m\(^2\), as previously reported in Taiwanese\(^{27, 28}\). NOD was defined as those who were DM-free in 2000 and became DM in 2005 (including plasma glucose re-testing and current anti-hyperglycemic agent usage).

**Insulin Resistance**

Insulin resistance was expressed by the Homeostasis Model Assessment (HOMA), in which HOMA-IR was calculated by multiplying FPG (in mmole/L) by FI (in mU/L), and dividing the result by 22.5\(^{29}\). The cutoff for HOMA-IR to determine insulin resistance for all subjects was defined as the highest quartile of HOMA-IR among lean subjects (BMI < 25 kg/m\(^2\)), and subjects with a higher HOMA-IR were considered insulin resistant\(^{30}\).

**Effectiveness of NOD Prediction**

The effectiveness of NOD prediction is evaluated by the positive predictive value of IFG and MS in predicting NOD. The positive predictive value is usually defined as (number of true positives) / (number of true positives + number of false positives); therefore, the positive predictive value of MS is defined as the number of NOD in MS (+) subjects in 2005 divided by all MS subjects in 2000. The positive predictive value of IFG is defined as the number of NOD in IFG (+) subjects in 2005 divided by all IFG subjects in 2000.

**Data Analysis**

Data in the text and tables are expressed as the mean ± standard deviation (mean ± SD). Groups with subjects with and without MS were composed with the Chi square test, Fisher’s Exact test, or Student’s
Comparisons of community-living older Taiwanese with and without metabolic syndrome

Table 1. Comparisons of community-living older Täiwanese with and without metabolic syndrome

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>MS (+)</th>
<th>MS (-)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case Number</td>
<td>480</td>
<td>122</td>
<td>358</td>
<td></td>
</tr>
<tr>
<td>Age (year)</td>
<td>63.7 ± 10.8</td>
<td>64.1 ± 10.1</td>
<td>63.5 ± 11.1</td>
<td>0.60</td>
</tr>
<tr>
<td>Sex (Female %)</td>
<td>56.3</td>
<td>55.0</td>
<td>59.8</td>
<td>0.20</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>24.3 ± 3.6</td>
<td>27.0 ± 4.0</td>
<td>23.4 ± 3.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Obesity (%)</td>
<td>37.8</td>
<td>65.6</td>
<td>28.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>35.0</td>
<td>55.7</td>
<td>27.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>129.6 ± 20.3</td>
<td>139.8 ± 17.0</td>
<td>126.1 ± 20.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>78.9 ± 12.7</td>
<td>83.9 ± 11.6</td>
<td>77.2 ± 12.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pulse pressure (mmHg)</td>
<td>50.7 ± 15.7</td>
<td>55.9 ± 16.7</td>
<td>49.0 ± 15.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fasting plasma glucose (mg/dL)</td>
<td>95.7 ± 10.4</td>
<td>100.4 ± 11.5</td>
<td>94.0 ± 9.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Serum total cholesterol (mg/dL)</td>
<td>208.6 ± 38.4</td>
<td>216.1 ± 38.8</td>
<td>206.0 ± 37.9</td>
<td>0.012</td>
</tr>
<tr>
<td>Serum triglyceride (mg/dL)</td>
<td>127.4 ± 91.7</td>
<td>197.7 ± 132.8</td>
<td>103.4 ± 55.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Serum HDL-C (mg/dL)</td>
<td>47.8 ± 18.1</td>
<td>35.9 ± 12.8</td>
<td>51.9 ± 17.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>1.1 ± 1.2</td>
<td>1.7 ± 1.5</td>
<td>0.9 ± 1.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Insulin resistance (%)</td>
<td>26.6</td>
<td>45.2</td>
<td>19.9</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Obesity was defined as body mass index (BMI) ≥ 25 kg/m², hypertension was defined according to the JNC 6 report, and insulin resistance was defined when HOMA-IR > 1.23. HDL-C: high density lipoprotein-cholesterol.

Results

Demography

Overall, 721 subjects who participated in the community survey in 2000 were successfully followed in 2005. Among them, 96 were diabetic in 2000 (with or without treatment), 88 were currently taking anti-hypertensive agents, and 57 had died of various etiologies. Due to the lack of precise death statistics, subjects who died within the study period were excluded from further analysis. After exclusion of aforementioned subjects, 480 non-diabetic and anti-hypertensive agent-free subjects were the primary cohort for study (mean age: 63.7 ± 10.8 years in 2000, 43.8% males).

Metabolic Syndrome

The overall prevalence of MS was 25.4%. The mean age and gender distributions in MS and non-MS subjects were similar (64.1 ± 10.1 vs. 63.5 ± 11.1 years, p=0.598; 59.8% females vs. 55.0% females, p=0.398). Compared with non-MS subjects, MS subjects had significantly higher BMI, mean systolic blood pressure, and pulse pressure. Moreover, MS subjects were more prone to be obese, hypertensive and insulin resistant (defined by HOMA-IR higher than 1.23). In laboratory reports, MS subjects had higher fasting plasma glucose, serum levels of TC, TG and lower HDL-C (Table 1).

New-Onset DM

The 5-year cumulative incidence of NOD in this study was 10.8%, which was significantly higher in the MS group than the non-MS group (17.2% vs. 8.7%, p=0.011). Adjusted for age and gender, MS significantly predicts NOD in this study (Odds ratio: 2.20, 95% Confidence interval: 1.21–4.00, p=0.010). Moreover, both impaired fasting glucose (IFG) and hypertriglyceridemia were significant risk factors for NOD among all 5 diagnostic components of MS (Table 2). The positive predictive value of IFG for NOD was better than MS (42.9% for IFG and 17.2% for MS).

Discussion

Impaired carbohydrate homeostasis in older adults is a well-known age-related phenomenon. Along with advancing age, fasting and postload plasma glucose levels were slightly but significantly increased. Despite these age-related phenomena in glucose metabolism, there are no age-adjusted criteria for DM diagnosis in older people. Based on current diagnostic criteria, the epidemiology of DM in the elderly popu-
lation remains unclear\textsuperscript{35}, and it is suggested that approximately 20\% of people aged 75 and over were diabetic\textsuperscript{36}. Although many previous reports supported the ability of MS to predict DM, little is known in the elderly Chinese population. In this study, we confirmed that MS may significantly predict NOD in older Taiwanese in a 5-year period. To our knowledge, this is the first study confirmed the effectiveness of MS to predict DM in older Taiwanese.

Defining DM in older adults is a complex issue, especially when DM onset in later life showed no association with mortality in men\textsuperscript{18}; therefore, the necessity of defining MS in the elderly population deserves further investigation. Whether the central etiological factor of MS is insulin resistance or central obesity is under debate, although the International Diabetes Federation favors the role of central obesity. It is well known that aging is featured by progressive loss of lean body mass and increased waist circumference; therefore, adverse effects derived from these age-related anthropometric changes may also increase the probability of central obesity and insulin resistance. Overall, older adults are naturally more prone to be diabetic with or without MS. The report of ADA/EASD has indicated that pre-diabetes is a more powerful predictive factor for NOD than MS, which was also confirmed in this study and its effectiveness successfully extended into older age.

Nevertheless, there are several limitations of this study. First, subjects were enrolled from participants in community health examinations instead of a systematic sampling; however, from the perspective of community health, staff of all community-based health clinics had invited all eligible residents in their townships to participate in the health examinations; therefore, we believe that the study cohort is representative enough for the whole community. Second, this study adopted ADA criteria for DM diagnosis, which needs no glucose loading test. The vast majority of study participants were farmers in rural communities, and they mostly refused oral glucose tolerance tests because they need to go to their farms in the early morning. The primary purpose of the ADA criteria is to enhance community-based screening programs and diagnosis; therefore, we believe that the study results still provide certain important information for community healthcare professionals. Third, this study modified the ATP-III criteria for MS, in which waist circumference was replaced by BMI. In 2000, the official diagnostic criteria for obesity included BMI, and similar modifications have been made in other reports\textsuperscript{26, 27}; therefore, we also believe this modified ATP-III criterion still defined MS well. In conclusion, both MS and IFG can effectively predict NOD among community-living older Taiwanese in 5-year follow-up. Adjusted for age and gender, IFG and hypertriglyceridemia were both independent risk factors for NOD among the 5 diagnostic components of MS. In terms of predicting NOD for older people, IFG may be a more efficient predictor than MS due to the higher positive predictive value and lower laboratory cost.

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