行政院國家科學委員會專題研究計畫  成果報告

葡萄糖耐性正常、空腹血糖異常／葡萄糖耐性異常及第二型糖尿病者「代謝異常症候群」發生率及相關因素之探討

計畫類別：個別型計畫
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Topic: The incidence and associated risk factors of dysmetabolic syndrome in subjects with normal glucose tolerance, impaired fasting glucose, impaired glucose tolerance and type II diabetes --- six years follow-up community-based study in Southern Taiwan.

Introduction:

The concept of syndrome X for the clustering of cardiovascular risk factors like hypertension, glucose intolerance, obesity, and dyslipidemia was well known to be introduced by Gerald Reaven in 1988. [1] However, this syndrome seems even older, having been already observed in 1923 by Kylin, who described the clustering of hypertension, hyperglycemia, and gout as a syndrome. [2] Subsequently, several other metabolic abnormalities have been reported to associate with this syndrome, including central obesity, microalbuminuria, and abnormalities in fibrinolysis and coagulation [3–5]. The syndrome has also been given several other names, including the metabolic syndrome, the insulin resistance syndrome, the plurimetabolic syndrome, and the deadly quartet [6–8]. The name "insulin resistance syndrome" has been widely used and refers to insulin resistance as a common denominator of the syndrome [9].

The prevalence of the metabolic syndrome has varied markedly between different studies, most likely because of the lack of accepted criteria for the definition of the syndrome [10–11]. In 1998, WHO proposed a unifying definition for the syndrome and chose to call it the metabolic syndrome rather than the insulin resistance syndrome. [12] This name was preferred mainly because it was not well accepted established that insulin resistance was the cause of all the components of the syndrome. As the condition reflects a condition of abnormal metabolism, some researchers have preferred to call it a dysmetabolic syndrome. [13] A unifying definition would allow us to assess whether the clustering of risk factors is associated with an increased risk of cardiovascular disease in addition to the risk associated with the individual components. Importantly, the presence of dysmetabolic syndrome was associated with a threefold increased risk of coronary heart disease, myocardial infarction and stroke (odds ratio of 3), and consequently, increased mortality (odds ratio of 1.8). [14] In subjects with IFG/IGT, the presence of the metabolic syndrome was also associated with reduced survival, particularly because of increased cardiovascular mortality. If we can understand the risk factors of the development of dysmetabolic syndrome and find out the way to control them, then we can prevent the future occurrence of CHD morbidity and mortality. Thus, the aim of the current study was to assess the incidence of and associated risk factors of dysmetabolic syndrome development during the 6 years
follow-up by applying the modified WHO definition in Taiwanese population.

**Research design and method:**

The subjects were participants in a community-based study for chronic disease conducted in Tainan, the oldest city in southern Taiwan with a population of 700000. Detail of the study have been described elsewhere [15]. Briefly, in 1996, 2416 eligible Chinese subjects (48.4% men) were selected by a stratified systemic cluster random sampling method from 7 administrative districts throughout Tainan City. From January to December, 1638 participants above 20 years of age (47.6% of men) had finished the screening health examination with the response rate of 67.8%. There were no significantly different characteristics between responders and non-responders. Written consents were obtained from all the participants and the research committee of National Cheng Kung University Hospital, Taiwan, approved this study.

In this baseline cross-sectional study performed in Tainan city 6 years ago, the crude prevalence of diabetes and IGT were 9.0% and 14.0%, respectively [15]. The prevalence of metabolic syndrome was 51.0% for DM, 33.2% for IGT, 25.0% for IFG, and 5.6% for NGT (unpublished data). After excluding the subjects having developed metabolic syndrome, the number of eligible subjects without dysmetabolic syndrome for NGT, IFG/IGT and DM were 1162, 170(21/149) and 75, respectively. Following up these subjects, we will investigate the incidence of the dysmetabolic syndrome six years later and explore the associated risk factors of its development.

For all the subjects in the base-line study, we have kept a detail personal contact file including the address and telephone number of two other potential accessible persons for each of our subjects. We have maintained a good relationship with our subjects, and the above file was also updated three years ago. According to previous experience in following the subjects of our study community, apart from the subjects of deceased, severely ill, refusal, moving-out, the estimated response rate could hopefully be larger than 70%.

After approval by the research committee of National Cheng Kung University Hospital, we will invite all the eligible subjects to receive a health examination in our hospital. A standardized health questionnaire was completed by specially-trained nurses, covering the subjects’ past medical history, including current and previous medication, information about other diseases (particularly hypertension, coronary heart disease [CHD], myocardial infarction [MI],...
stroke, and diabetes), smoking habits, alcohol consumption, physical activity, and family history of diabetes and cardiovascular diseases.

After getting the written consent, blood samples of all the eligible subjects are drawn after 12-hr fasting for the following analysis: Serum total cholesterol, HDL-cholesterol, triglyceride (TG), creatinine, GPT, and serum insulin concentration. Early morning spot urine is collected for the analysis of urine creatinine and microalbumin level to calculate the albumin-creatinine ratio (ACR). Then 75-gm glucose tolerance test is also applied. BMI was calculated after body weight and height were measured with subjects in light clothing without shoes. Waist circumference (WC) was measured with a soft tape on standing subjects midway between the lowest rib and the iliac crest. Hip circumference (HC) was measured over the widest part of the gluteal region, and the waist-to-hip ratio (WHR) was calculated as a measure of central obesity. Two readings of systolic and diastolic blood pressure were measured from the right arm of patients in a sitting position with the DINAMP vital sign monitor (Model 1846SX, Critikon Inc., Irvine, CA) [16] after 30 min of rest at 5-min intervals, and their mean value was calculated.

**Assay:**

Plasma glucose was analyzed by the standard glucose-oxidase method (Synchron CS3, Beckman). The coefficients of variation (CV) for intra-assay and inter-assay were 1.2% and 1.5%, respectively. Fasting serum total cholesterol, triglyceride and HDL-cholesterol were measured enzymatically using automated methods. The intra-assay and inter-assay were 1.8% & 1.2% for total cholesterol and 3.5% & 2.5% for triglyceride. Serum insulin concentrations were measured with radioimmunoassay with an intra- and inter-assay coefficient of variation (CV) under 5%. Urine albumin concentrations were measured by an immunoturbidimetric method, with an inter-assay CV of 5%.

**Definition of NGT, IFG, IGT, and DM**

by using diagnostic values for fasting and 2 hours post-loading plasma glucose level:

(单位: mg/dL) [17]

NGT: AC<110 and 2-h PC<140  
IFG: AC ≥ 110 & <126 and 2-h PC<140  
IGT: AC<126 and 2-h PC ≥ 140 & <200  
DM: AC ≥ 126 or 2-h PC ≥ 200

Ps: NGT: normal glucose tolerance; IFG: impaired fasting glucose; IGT: impaired glucose tolerance;

**Definition of metabolic syndrome**

The first unifying definition for metabolic syndrome was proposed by WHO in 1998. In accordance to the WHO proposal, a
A person with type 2 diabetes or impaired glucose tolerance (IGT) has the dysmetabolic syndrome if not less than two of the criteria listed below are fulfilled. A person with normal glucose tolerance (NGT) had the dysmetabolic syndrome if he fulfills two of the criteria in addition to being insulin resistance. Insulin resistance is defined as highest quartile of fasting insulin or homeostasis model assessment (HOMA) insulin resistance index in the population studied.

In 2001, the National Cholesterol Education Program (NCEP) Adult Treatment Panel III report provided an alternative and more convenient definition of the syndrome in national guideline.

According to NCEP ATP III report, the metabolic syndrome is defined as three or more of the following characteristics:

1) Hypertension: defined as SBP/DBP ≥ 130/85 mmHg and/or under antihypertensive medication.

2) Hypertriglyceridemia: defined as TG ≥ 150 mg/dL (≥ 1.69mmol/L)

3) Low HDL cholesterol: <40 mg/dL (<1.04 mmol/L) in men, <50 mg/dL (<1.29 mmol/L) in women,

4) Abdominal obesity: WC > 102 cm in men; > 88 cm in women. (We modified this by Asia-Pacific definition for central obesity, i.e., WC > 90 cm in men; > 80 cm in women)

5) High fasting glucose: ≥ 110 mg/dL (≥ 6.1 mmol/L) and/or under antidiabetic medication.

Ps: SBP: systolic blood pressure; DBP: diastolic blood pressure; TG: triglyceride; HDL: high density lipoprotein; WC: Waist circumference

◆ Statistical methods

Due to the variable follow-up time, both the incidence density, the number of cases divided by the observed time at risk, and the cumulative incidence for dysmetabolic syndrome will be calculated. The 95% confidence intervals (95% CI) are also reported. The baseline characteristics of non-developers and developers to dysmetabolic syndrome will be reported in subgroups of NGT, IFG/IGT and DM, respectively. For the normally distributed variables means and standard deviation are reported. The group frequencies are compared by chi-square (χ²) or Fisher’s exact tests. Spearman rank correlations were used to demonstrate relationships between variables. A multiple logistic regression analysis was carried out with the newly developed metabolic syndrome as dependent variable and age, sex, SBP, DBP, AC, WC, TG, HDL, BMI, Total amount of physical activity, as independent variables. In the multiple regression analysis assessing risk factors for cardiovascular morbidity and mortality. The statistical analyses were performed...
with an SPSS program for Windows version 10.0. A $P$ value <0.05 was considered statistically significant.

**Result and Discussion:**

We followed up these 1367 subjects free from metabolic syndrome in the cross-sectional study in 1996, after excluding the subjects of deceased, severely ill, refusal, moving-out, and totally 957 subjects received follow-up examination in 2001-2 with the response rate 71%, close to our previous estimation. The incidence rate of metabolic syndrome of subjects with NGT, IGT, DM in this cohort were 8.3%, 26.3% and 32.1%, respectively, as shown in table 1. Baseline demographic, anthropometric, and metabolic characteristics of participants without metabolic syndrome in baseline were shown in table 2. Approximately one in 9 subjects without metabolic syndrome developed the metabolic syndrome over 6 years.

We put age, sex, socio-economic status, physical activity, BMI, WC, SBP, DBP, Cholesterol, HDL-cholesterol, TG, IGT, and DM as independent variables and applied the stepwise variable selection procedure to predict the incident of metabolic syndrome. The best predictors for this model were WC, TG, SBP, HDL, sex and IGT according to their predicting powers. Finally we force in the age and DM into our final model as shown in Table 3. We chose the probability 0.12 to be cutoff point, where the sensitivity was 0.77 and the specificity was 0.78.

From a clinical perspective, the waist circumference was best predictor in the development of metabolic syndrome, and much better than the more common measurement of BMI. Furthermore, IGT was a better predictor of metabolic syndrome than DM while SBP was a better predictor than DBP.

<table>
<thead>
<tr>
<th>Metabolic syndrome</th>
<th>Normal</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>NGT</td>
<td>68(8.3)</td>
<td>747(91.7)</td>
</tr>
<tr>
<td>IGT</td>
<td>30(26.3)</td>
<td>84(73.7)</td>
</tr>
<tr>
<td>DM</td>
<td>9(32.1)</td>
<td>19(67.9)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>107(11.2)</strong></td>
<td><strong>850(88.8)</strong></td>
</tr>
</tbody>
</table>
Table 2. Baseline demographic, anthropometric, and metabolic characteristics of participants without metabolic syndrome in baseline.

<table>
<thead>
<tr>
<th>Baseline variable</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>957</td>
</tr>
<tr>
<td>AGE</td>
<td>46.4±13.5</td>
</tr>
<tr>
<td>Sex</td>
<td>496/461</td>
</tr>
<tr>
<td>Total amount of physical activity</td>
<td>61.3±57.4</td>
</tr>
<tr>
<td>Body mass index</td>
<td>23.1±3.2</td>
</tr>
<tr>
<td>Waist circumference</td>
<td>77.8±10.1</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>190.4±38.8</td>
</tr>
<tr>
<td>High Density Lipoprotein cholesterol</td>
<td>51.2±13.4</td>
</tr>
<tr>
<td>Triglyceride</td>
<td>109.8±83.7</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>113.9±16.2</td>
</tr>
<tr>
<td>Diastolic blood pressure</td>
<td>69.1±9.2</td>
</tr>
<tr>
<td>Fasting blood sugar</td>
<td>91.5±10.8</td>
</tr>
<tr>
<td>Post-load blood sugar</td>
<td>109.5±35.6</td>
</tr>
<tr>
<td>Proportion with IGT</td>
<td>11.9%</td>
</tr>
<tr>
<td>Proportion with DM</td>
<td>2.9%</td>
</tr>
<tr>
<td>Proportion that develops incident metabolic syndrome</td>
<td>11.2%</td>
</tr>
</tbody>
</table>

Data are means ± SD unless noted otherwise

Table 3. Predictors for incident metabolic syndrome

<table>
<thead>
<tr>
<th>Predictor</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic blood pressure (per 20 mmHg)</td>
<td>1.56</td>
<td>(1.17-2.10)</td>
</tr>
<tr>
<td>Triglyceride (per 50 mg/dL)</td>
<td>1.37</td>
<td>(1.18-1.61)</td>
</tr>
<tr>
<td>IGT vs NGT</td>
<td>2.11</td>
<td>(1.17-3.80)</td>
</tr>
<tr>
<td>DM vs NGT</td>
<td>2.46</td>
<td>(0.90-6.72)</td>
</tr>
<tr>
<td>Waist circumference (per 1cm)</td>
<td>1.10</td>
<td>(1.07-1.13)</td>
</tr>
<tr>
<td>HDL cholesterol (per 10 mg/dL)</td>
<td>0.63</td>
<td>(0.49-0.80)</td>
</tr>
</tbody>
</table>

Age sex adjusted

Table 4.

<table>
<thead>
<tr>
<th>Predicted</th>
<th>Actual</th>
<th>+</th>
<th>−</th>
<th>+</th>
<th>−</th>
<th>+</th>
<th>−</th>
<th>+</th>
<th>−</th>
<th>+</th>
<th>−</th>
</tr>
</thead>
<tbody>
<tr>
<td>Predicted</td>
<td></td>
<td>79</td>
<td>23</td>
<td>183</td>
<td>650</td>
<td>262</td>
<td>673</td>
<td>935</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Sensitivity=79/102=0.7745
Specificity=650/833=0.7803
Corrected Classification rate= (79+650)/935=0.7796

Reference:

4. Mykkanen L, Zaccaro DJ, Wagenknecht LE, Robbins DJ, Gabriel M, Haffner SM:


