Insulin Resistance Profile Among Siblings of Type 2 Diabetes Mellitus (Preliminary Study)

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ABSTRACT

Aim: to obtain prevalence of insulin resistance among siblings of subjects with type 2 DM and their metabolic abnormality profiles as measured by their BMI, waist circumference (WC), blood pressure, glucose intolerance, concentration of triglyceride, HDL cholesterol, and uric acid.

Methods: a preliminary, cross sectional study conducted among 30 siblings from seven type 2 DM subjects under medical treatment in Dr. Cipto Mangunkusumo Hospital and other places where the subjects lived. Those subjects underwent interviews, physical examination including weight, height, abdominal circumference, blood pressure and laboratory examinations including glucose tolerance test, fasting insulin, triglycerides, HDL cholesterol and uric acid level. Data processed to obtain body mass index (BMI), homeostasis model assessment of insulin resistance (HOMA-IR) and HOMA-IR cut-off, which is determined based on 75 percentile. The criteria of hypertension, dyslipidemia, central obesity and hyperglycemia are based on Asian modification NCEP/ATP III criteria for metabolic syndrome. Hyperuricemia is diagnosed based on uric acid level >7mg/dl in men and >6 mg/dl in women.

Results: the prevalence of insulin resistance among siblings of type 2 DM in this study is 26.67% with the proportion in each family varies between 0-75%. Central obesity is the most metabolic component commonly found.

Key words: insulin resistance, the siblings of subjects with type 2 DM.

INTRODUCTION

Diabetes mellitus (DM) is a chronic disease with an increase in prevalence.1-3 The most feared complications of diabetes are the chronic complications either macrovascular or microvascular complications. In addition, DM itself is an independent risk factor for coronary heart disease.1,3-6 The risk of cardiovascular disease among DM subjects are greater than those without DM. So far, there have been two hypotheses regarding the occurrence of diabetes; beta cell failure and insulin resistance.3,6,8-10 Insulin resistance occurs several decades before the onset of type 2 diabetes and is the best predictor for future occurrence of type 2 diabetes mellitus.3,4,6,8,9,11 Given the strong genetic influence on the incidence of type 2 DM, it is predicted that insulin resistance is also influenced by genetic factors.8,12-15

Studies have reported the prevalence of insulin resistance in the general population. Some studies in white subjects showed that the prevalence of insulin resistance ranged from 12-23%.16-17 Axelsen et al found that healthy men with a family history of type 2 DM have an increase of postprandial lipid level without glucose intolerance which is estimated to most probably due to insulin resistance.4 Haffner et al discovered the hyperinsulinemia condition as a
prediabetic state among individuals with a family history of type 2 DM, while Warram et al found that individuals who have family history of type 2 DM have a greater risk of metabolic abnormalities than those without family history, and as many as 16% of these individuals will progress to having type 2 DM after being followed for 13 years.7

Previous study mentioned that intervention can be started earlier since insulin resistance state in order to delay the onset of type 2 DM. It is undoubtable that lifestyle modification and weight loss are rational ways to improve insulin resistance.3,5,6,10,18

There are no data about insulin resistance profile among type 2 DM families in Indonesia. Since earlier lifestyle modifications and provision of medicines, especially during the insulin resistance state which is still in normoglycemia state, will delay the onset of type 2 DM better than those with glucose intolerance,19,20 it is needed to conduct a research about insulin resistance profile among type 2 DM families, in this case siblings of type 2 DM. This study will collect some metabolic parameters such as anthropometric examination, blood pressure, lipid profile, glycemia status and uric acid level.

RESULTS

Subjects consisted of 15 men (50%) and 15 females (50%). The youngest and oldest subjects are 29 and 70 years old, respectively, while the age group of 41-50 years old was the most. In this study, the cut-off value of HOMA-IR was 2.04.

The prevalence of insulin resistance among siblings of type 2 DM in this study is 26.67% with the proportion in each family varies from 0% to 75%. Insulin resistance is most widely in the age group of 41-50 years old (37.5%), compared to the age group of 31-40 years old (25%), 51-60 years old (25%) and 61-70 years old (12.5%). The most metabolic component found in this study is central obesity (56.7%), followed by hypertension (46.7%), decreased HDL cholesterol level (26.6%), hypertriglyceridemia (26.6%) and hyperglycemia (20%). As many as three-quarters of subjects with insulin resistance have BMI >25 kg/m². Among subjects with insulin resistance, all have central obesity, half of them have hypertension, decreased HDL cholesterol level and hypertriglyceridemia. While hyperglycemia is found in 37.5% subjects.

METHODS

A preliminary, cross sectional study was conducted among 30 siblings from seven type 2 DM subjects under medical treatment in Dr. Cipto Mangunkusumo Hospital in Jakarta and other places where the subjects lived. Those subjects underwent interviews, physical examination including weight, height, abdominal circumference, blood pressure and laboratory examinations including glucose tolerance test, fasting insulin, triglycerides, HDL cholesterol and uric acid level. Blood sampling was conducted in the morning between the hours of 08:00 to 10:00 a.m. local time, after the subjects underwent 12 hours of fasting. Blood laboratory examinations were conducted at the Prodia Laboratory, Kramat Street, Central Jakarta. Data were processed to obtain body mass index (BMI), homeostasis model assessment of insulin resistance (HOMA-IR) and HOMA-IR cut-off. Cut-off value of HOMA-IR is determined based on 75 percentile. The criteria of hypertension, dyslipidemia, central obesity and hyperglycemia were based on Asian modification NCEP/ATP III criteria for metabolic syndrome. Hyperuricemia was diagnosed based on uric acid level >7mg/dl in men and >6 mg/dl in women.

Table 1. Subject characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Mean (SD)</th>
<th>Median</th>
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<tbody>
<tr>
<td>Age (year)</td>
<td>47</td>
<td>46</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>59.55</td>
<td>60.25</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>156.99</td>
<td>156.25</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>24.19</td>
<td>25.28</td>
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<tr>
<td>Abdominal circumference (cm)</td>
<td>83.1</td>
<td>84</td>
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<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>127.5</td>
<td>122.5</td>
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<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>75.5</td>
<td>72.5</td>
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<tr>
<td>Fasting blood glucose (mg/dl)</td>
<td>92.73</td>
<td>83.5</td>
</tr>
<tr>
<td>2-hour PP blood glucose (mg/dl)</td>
<td>131.33</td>
<td>113</td>
</tr>
<tr>
<td>Fasting blood insulin (µIU/ml)</td>
<td>6.98</td>
<td>6.35</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>1.6</td>
<td>1.36</td>
</tr>
<tr>
<td>Triglyceride (mg/dl)</td>
<td>153.5</td>
<td>98</td>
</tr>
<tr>
<td>HDL cholesterol (mg/dl)</td>
<td>48.63</td>
<td>49</td>
</tr>
<tr>
<td>Uric acid (mg/dl)</td>
<td>4.62</td>
<td>4.5</td>
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Table 2. The frequency of metabolic components based on age group

<table>
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<tr>
<th>Components</th>
<th>n</th>
<th>21-30</th>
<th>31-40</th>
<th>41-50</th>
<th>51-60</th>
<th>61-70</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obesity</td>
<td>16</td>
<td>1</td>
<td>3</td>
<td>7</td>
<td>4</td>
<td>1</td>
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<tr>
<td>Central obesity</td>
<td>17</td>
<td>1</td>
<td>3</td>
<td>6</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Hypertension</td>
<td>14</td>
<td>0</td>
<td>1</td>
<td>5</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Hypcholesterol HDL</td>
<td>10</td>
<td>0</td>
<td>3</td>
<td>4</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Hypertriglyceridemia</td>
<td>8</td>
<td>0</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>3</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Hyperuricemia</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
DISCUSSION

In this study, we examined siblings of diabetic patients aged were 45-55 years old. The average age of the siblings was 47 years old, despite finding a 38-years-old diabetic patient who has siblings aged 29-34 years old. Thus, the results achieved in this study are limited to the population or in families with the same age range.

In this study, the cut-off value of HOMA-IR is 2.04. Cut-off values of HOMA-IR ever reported vary widely, but for the high risk population as in this study have not been reported. Differences in cut-off value of HOMA-IR in previous studies reinforce the perception that insulin resistance is different from one population to another population that is likely determined by other inter-gender, the difference of body fat distribution between men and women, ethnic and age.21

In this study, the cut-off value of HOMA-IR is relatively low compared to previous studies (in the general population). It is very likely due to the number of subjects that is relatively small.36-38

Tripathy and Vaag (EGIR study) reported that individuals with a family history of diabetes (first degree relative) have a higher insulin resistance (represented by the average value of HOMA-IR, not a cut-off HOMA-IR) than individuals without a history of DM.23 The average value of HOMA-IR in the group with a family history of DM on a study by Tripathy is 1.21, whereas in this study is 1.60. In this study, the frequency of insulin resistance varies within families between 0-75%. If the effect of genetic factors being equal on all subjects of the study, significant variations can indicate the strong influence of environment on insulin resistance. While in this study, there are several environmental factors which are not analyzed, such as diet and exercise habits. Influence of a history of type 2 DM in the father or mother or both at the incidence of insulin resistance can not be viewed because it is not performed genetic analysis.

In this research note that in type 2 diabetic subjects with decreased HDL cholesterol, tend to have siblings with decreased HDL cholesterol as well. Although the significance is not determined yet, this possibility supports the findings of De Fronzo that the phenotype picture of insulin resistance is influenced by several genes that form the background of gene D (Diabetic gene), genes of L (lipid gene), gene H (hypertension gene), and gene A (atherosclerotic gene).10,24 Individuals who are insulin resistance, with the influence of the dominant gene D will be type 2 DM, with the dominant influence of the L gene would have dyslipidemia (hypertriglyceridemia or decreased of HDL level), as well as for hypertension and that of atherosclerosis.15,19

In addition, although it is not significant, siblings of type 2 DM who relatively have younger onset of type 2 DM (<40 years old) tend to have an average value of HOMA-IR higher than those with older onset of type 2 DM. This was previously reported by Tripathy et al that siblings of type 2 DM whose age is relatively younger (<44 years) will have siblings with an average value of HOMA-IR higher than those with older onset of type 2 DM (p <0.005).23

The frequency of insulin resistance in all subjects as a group is 26.67%. In this study, incidence of insulin resistance increases with age and is highly found in the age group 41-50 years and then decreases with increasing age most probably caused by the prevalence of bias. Among three quarters of subjects with insulin resistance had a BMI >25 kg/m². This finding is in line with Nasution (2005) who reported the relationship between BMI with insulin resistance (p = 0.017). With different approaches, the relationship between IMT, insulin resistance can be seen from the report by Choi et al, which involved 1314 subjects with age >60 years, and Thomas et al involving 225 Chinese subjects aged 65-74 years. Two studies showed increased BMI with HOMA-IR degrees which are grouped into quartiles.25

In this study, central obesity is highest among the other metabolic components. Pranoto et al in Surabaya and Adam et al in Makassar also reported that central obesity component of metabolic syndrome is most commonly found.22,26 However, several other studies showed different results. Nasution reported hypertension is a component of the metabolic syndrome that most often found in the elderly group (>60 years). These differences are likely influenced by the age range studied. In Bali and Pekalongan, a prominent
component of the metabolic syndrome is a decrease in HDL cholesterol level and hypertension.\textsuperscript{27,28}

Central obesity was also found in all subjects with normal glucose tolerance and insulin resistance. This is in line with research conducted by Carr et al who reported that abdominal circumference is very good for identifying insulin resistance in subjects with normal glucose tolerance (p<0.001).\textsuperscript{29} As explained in the literature review, the central role of obesity on metabolic syndrome considering its function as a source of FFA, adipokin, adinopektin, TNF and IL-6 that affect the emergence of insulin resistance.\textsuperscript{19,29,30}

Increased uric acid was not found on the subject of this research, so this parameter is very insensitive to predict the incidence of insulin resistance. Meanwhile, hypertension, increased triglyceride concentrations, decreased HDL cholesterol concentrations and hyperglycemia (fasting blood glucose >110 mg/dl) can be used to predict insulin resistance, although not as good as central obesity.

Limitations in this study were (1) This study is a preliminary study with a sample of only 30 people (seven families) that can not be used to analyze the relationship (2) the results of this study can not be used to represent high-risk groups in Indonesia, due to the strong influence of ethnic factors on the incidence of insulin resistance (3) genetic analysis can not be done so that the genetic role is not clearly visible, and (4) this study did not use a control group (individuals who had no family history of DM) as a comparator so that the difference between high risk groups and low risk is not visible.

**CONCLUSION**

The prevalence of insulin resistance among siblings of type 2 DM in this study was 26.67% with the proportion in each family varied between 0-75%. Central obesity was the most metabolic component commonly found.

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