Insulin and cardiovascular risk factors in newly diagnosed diabetes mellitus patients

Wilfried Herdin Sibuea, Suzanna Ndrah

INTRODUCTION

Subjects with type II diabetes have a two or fourfold increase risk of developing cardiovascular disease.1,2 In type II diabetes, degree of hyperglycemia and duration of clinical diabetes have been strong and consistent risk factors for microvascular complication of diabetes,3,4 while cardiovascular disease has often not been associated with these factors.

In the World Health Organization study the combination of total cholesterol, triglyceride and blood pressure levels was associated with myocardial infarction in diabetes,3 and both high triglyceride and low HDL cholesterol levels predicted coronary heart disease,5 while central obesity expressed by the W/H ratio is itself an independent risk factor for coronary artery disease.5

Hyperinsulinemia predictive of the development of type II diabetes, in some studies have been shown to be predictive of coronary heart disease development.7 Reaven has proposed that insulin resistance may underlie a number of disorders including hypertension,
dyslipidemia, impaired glucose tolerance and coronary heart disease, which he called "Syndrome X".  

The purpose of this study was to study the insulin concentrations during the Oral Glucose Tolerance Test (OGTT) in newly diagnosed type II diabetes and then to assess the correlation between known cardiovascular risk factors with insulin.

**METHOD**

Thirty subjects with newly diagnosed NIDDM and 30 healthy control subjects with no family history of NIDDM, matched for age, gender and body mass index participated in this study. At the time of recruitment, no subjects received medications known to affect glucose metabolism. Body weight was measured to the nearest 0.1 kg and height to the nearest 0.1 cm with the head parallel to the floor. Body mass index was calculated as the ratio of weight (kg) to the square of height (m²). Waist circumference was measured as the smallest circumference between the costal margin and the iliac crest. Hip measurements were made at the level of the most lateral point on the great trochanter. Minimum waist and maximum hip measurements were taken to calculate the waist to hip (W/H) ratio.

Systolic and diastolic blood pressure using sphygmomanometer were measured by a single observer on 2 occasions after 30 min of resting. The mean of these values is given (mmHg).

**Blood sampling**

A 75 gram oral glucose tolerance test (OGTT) was performed to assess glucose tolerance and to measure the insulin response to oral glucose. After a 12 hour overnight fast, all subjects were given a 75-g oral glucose load. Venous blood samples were taken at fasting, 30 min and 120 minutes after the glucose administration for determination of plasma glucose and serum insulin concentrations. Glucose tolerance was interpreted according to WHO criteria. Yallow and Berson defined insulin resistance as a state of a body in which greater-than-normal amounts of insulin are required to elicit a quantitatively normal response. Insulin resistance was determined by the method of Yallow and Berson with modification. The ratio of plasma insulin to plasma glucose (fasting I/G, 30-min I/G and 120-min I/G) was calculated in each group and was interpreted as the higher the ratio the greater the insulin resistance.

Glycosilated hemoglobin (HbA1c), total cholesterol, HDL cholesterol, LDL cholesterol, and triglyceride were measured on fasting samples.

**Laboratory determinations**

Plasma glucose was assayed with a glucose oxidase method (GOD PAP). HbA1c was measured with an enzymatic ion-captured method (normal range 3%-6.4%). Total cholesterol, HDL cholesterol, and triglyceride were measured with a calorimetric enzymatic method (CHOD/PAP). LDL cholesterol was calculated with Friedwald formula. Plasma insulin concentration was measured using DPC reagents Coat-A-Count according to standard Radioimmunoassay procedure performed by Research Center for Medical Science and Technology, School of Medicine, University of Indonesia, WHO Laboratory no. 104 for Matched Reagent Programme and no. 21 Zone B for External Quality Control.

**Statistical Analysis**

Mean SD is given for normally distributed variables and matched groups are compared by pair-t test. For skewed data, the median [range] is given; Wilcoxon rank test for matched groups and Mann Whitney U test for unmatched groups were used to compare the groups. Linear regression was used to assess the correlation of two variable. All statistical analyses were performed by using SPSS for windows.

**RESULTS**

A total of 60 persons were studied: 30 subjects with newly diagnosed NIDDM and 30 healthy control subjects with no family history of NIDDM.

Table 1 shows the clinical details and baseline biochemical data in the 2 groups of subjects. Although the groups were well matched in terms of age, sex and BMI, but surprisingly the subjects with type-2 diabetes had a similar W/H ratio with the normal control subjects. The type-2 diabetes group had significantly higher systolic blood pressure, triglyceride, total cholesterol and LDL cholesterol levels than controls.

Table 2 and Figure 1 show the glucose and insulin concentrations during the OGTT. There was a significant increase of fasting, 30-min and 120-min glucose concentrations from control to diabetes subjects. Fasting insulin levels were similar (15.3 mU/L 8.1 mU/L vs 11.8 mU/L 6.8 mU/L, p=0.07). But there was a progressive reduction in 30-min insulin and
120-min insulin concentrations from control to diabetes subjects.

To clarify the presence of insulin resistance in diabetes subjects, the ratios of plasma insulin and glucose were calculated. As shown in Figure 2, the I/G ratios were lower (Fast-

Table 2: The glucose and insulin concentrations during the OGTT

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Newly diagnosed NIDDM</th>
<th>Control subjects</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting plasma glucose (mg/dl)</td>
<td>199.4 ± 72</td>
<td>91 ± 12.1</td>
<td>0.0001</td>
</tr>
<tr>
<td>30 min plasma glucose (mg/dl)</td>
<td>278.3 ± 87</td>
<td>151.9 ± 28.5</td>
<td>0.0001</td>
</tr>
<tr>
<td>120 min plasma glucose (mg/dl)</td>
<td>317.4 ± 94</td>
<td>128.4 ± 33.8</td>
<td>0.0001</td>
</tr>
<tr>
<td>Fasting plasma insulin (mU/L)</td>
<td>15.3 ± 8.1</td>
<td>11.8 ± 6.8</td>
<td>0.07</td>
</tr>
<tr>
<td>30 min plasma insulin (mU/L)</td>
<td>42.2 ± 5.1</td>
<td>80.8 ± 49.6</td>
<td>0.04</td>
</tr>
<tr>
<td>120 min plasma insulin (mU/L)</td>
<td>52.6 ± 39.3</td>
<td>84.4 ± 53.3</td>
<td>0.01</td>
</tr>
</tbody>
</table>

insulin level declines to values observed in control subjects.14 The current study confirms that subjects with type-2 diabetes well matched for age, sex and lifestyle factors have fasting glucose levels below 140 mg/dl and a fasting insulin level below 200 mU/L.

Table 3. Correlation between insulin and cardiovascular risk factors

<table>
<thead>
<tr>
<th></th>
<th>r</th>
<th>p</th>
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</thead>
<tbody>
<tr>
<td>Insulin and W/H ratio</td>
<td>0.08</td>
<td>0.5</td>
</tr>
<tr>
<td>Insulin and systolic blood pressure</td>
<td>0.18</td>
<td>0.2</td>
</tr>
<tr>
<td>Insulin and triglyceride</td>
<td>0.04</td>
<td>0.7</td>
</tr>
<tr>
<td>Insulin and total cholesterol</td>
<td>10.17</td>
<td>0.2</td>
</tr>
<tr>
<td>Insulin and LDL cholesterol</td>
<td>10.23</td>
<td>0.07</td>
</tr>
</tbody>
</table>

**DISCUSSION**

According to De Fronzo, the relationship between fasting glucose and insulin levels resembled an inverted U. As the fasting glucose increases from 80 mg/dl to 140 mg/dl there is a progressive rise in fasting insulin, representing a compensatory response by the pancreas. When the fasting glucose exceeds 140 mg/dl, insulin secretion drops because the pancreas is unable to maintain high rate insulin secretion. In diabetic subjects with fasting glucose concentrations > 200 mg/dl, the
BMI, have similar fasting insulin concentrations with normal control subjects. However, as diabetic subjects had significantly higher fasting glucose concentration, their 'normal' fasting insulin levels could be regarded as inability of pancreas to compensate the deterioration in glucose metabolism.

After a glucose load, the insulin concentrations decreased remarkably in the diabetic subjects who had fasting hyperglycemia (199.4 mg/dl). In addition as shown in figure 2, there was no insulin resistance in diabetic subjects because the insulin-glucose ratios were lower compared to normal controls. By these results we presumed that the type-2 diabetes subjects was insulinopenic. These findings are consistent with the earlier study and explained by the Starling's curve of the pancreas as proposed by de Fronzo. In diabetic subjects the relation of plasma insulin response to ingestion of glucose is like inverted U-shaped curve where plasma insulin increases progressively until the fasting plasma glucose reaches 120 mg/dl. Thereafter, further increases in the fasting plasma glucose level concentrations to > 160 mg/dl, the plasma insulin response becomes insulinopenic.15

The 30-min insulin concentration was lower in diabetic subjects than in normal controls. Normally, pancreatic beta cells respond rapidly to secrete insulin 3-5 min after glucose injection during an intravenous glucose tolerance test (IVGTT) and lasts about 10 minutes.
This is called acute insulin release (AIR). Some authors said that the 30-min insulin concentration during OGTT is similar with the AIR during IVGTT. This suggests that in the absence of IVGTT, this measurement may give the best estimate of changes in the first phase of insulin secretion. In diabetic subjects the early phase of insulin secretion during both IVGTT and OGTT is reduced due to the lost of acute insulin release. We found the same result in this current study.

From these results (inability of pancreas to compensate the deterioration in glucose metabolism, insulinopenia and reduced early phase of insulin secretion), it would be presumed that beta cells dysfunction and insulin deficiency are major features of type-2 diabetes in this study.

Increased mortality from cardiovascular disease is seen in subjects with type-2 diabetes due to the macrovascular complications. In the World Health Organization (WHO) study, the combination of high cholesterol, high triglyceride and blood pressure levels was associated with higher prevalence of myocardial infarction in diabetics. In the Paris Prospective study, high triglyceride levels predicted the development of coronary heart disease; and in the East West Study in Finland, both high triglyceride and low HDL cholesterol predicted the development of coronary heart disease. In the current study we found a significant higher systolic blood pressure, triglyceride, total cholesterol and LDL cholesterol levels. These findings showed that in newly diabetes subjects cardiovascular risk factors were already present.

The insulin resistance was determined indirectly in this study. The gold standard for insulin resistance determination is euglycemic clamp technique in which insulin is infused systemically and plasma glucose is maintain constant by exogenous glucose infusion. Glucose is clamped at euglycemia level. Glucose infusion rate equals some of decrease in hepatic glucose release and increase in glucose uptake. By this method, Ndaha found higher insulin resistance in the overweight Indonesian NIDDM subjects and there was a significant correlation between BMI and fasting insulin level. In this study we didn’t perform euglycemic clamp technique because of the expense, but determined the insulin resistance by using I/G ratio.

According to the San Antonio Heart Study, increase of fasting insulin level significantly predicted the development of type-2 diabetes, low HDL cholesterol, high triglyceride levels and hypertension over an 8 years follow-up. Reaven suggested that insulin resistance may underlie hypertension, high triglyceride, low HDL cholesterol, impaired glucose tolerance and coronary heart disease. In this study, we could not find the correlation between insulin and various conventional coronary heart disease risk factors such as W/H ratio, systolic blood pressure, high triglyceride, total cholesterol and LDL cholesterol levels due to the absence of fasting hyperinsulinemia and insulin resistance.

The lack of hyperinsulinemia in this study does not exclude the presence of hyperinsulinemia prior to the development of type-2 diabetes. As many years of
hyperinsulinemia characterize the prediabetic stage, it is still possible that during these years coronary heart disease risk factors developed.

Acknowledgments

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