Insulin and cardiovascular risk factors in newly diagnosed diabetes mellitus patients

Wilfried Herdin Sibuea, Suzanna Ndraha

Abstrak

Tujuan penelitian ini ialah untuk meneliti adanya hiperinsulinemia dan faktor risiko kardiovaskuler pada kelompok DMTTI yang baru terdiagnosis dibandingkan dengan kelompok kontrol. Sebanyak 60 subyek yang terdiri dari 30 orang penderita DMTTI yang baru terdiagnosis dan 30 orang sehat ikut dalam penelitian ini. Kelompok penderita DMTTI yang baru terdiagnosis dan kelompok kontrol mempunyai umur, jenis kelamin dan indeks massa tubuh yang sebanding. Pada kedua kelompok diukur tekanan darah sistolik, diastolik dan rasio pinggang-bokong. Dilakukan tes toleransi glukosa oral (TTGO) untuk menilai respons insulin terhadap glukosa . Darah vena diambil saat puasa untuk menilai kadar insulin, glukosa, trigliserida, kolesterol total, kolesterol HDL dan kolesterol LDL. Terdapat beberapa perbedaan yang bermakna antara penderita DMTTI baru dan kelompok kontrol. Tekanan sistolik, kadar glukosa plasma, HbA1c, trigliserida, kolesterol total dan kolesterol LDL lebih tinggi, namun pada waktu TTGO kadar insulin maupun rasio insulin dengan glukosa pada menit ke-30 dan menit ke-120 lebih rendah pada kelompok DMTTI.

Disimpulkan bahwa pada DMTTI yang baru terdiagnosis didapatkan defisiensi insulin dan ditemukan juga faktor risiko kardiovaskuler yaitu hipertensi sistolik, trigliserida, kolesterol total dan kolesterol LDL, tetapi tidak ditemukan korelasi antara insulin dengan faktor risiko kardiovaskuler tersebut.

Abstract

The purpose of this study is to assess the insulin resistance and cardiovascular risk factors in newly diagnosed NIDDM compared with normal control subjects. 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. Oral glucose tolerance test was performed to measure the insulin response to oral glucose. In both groups, waist to hip ratio, systolic and diastolic blood pressure were measured. Venous blood samples were taken at fasting for insulin, glucose, HbA1c, triglyceride, total cholesterol, LDL cholesterol and HDL cholesterol determinations. Several characteristics of metabolic abnormalities distinguished the newly diagnosed NIDDM from control subjects. The type-2 diabetes subjects had significantly higher systolic blood pressure, plasma glucose, glycosilated hemoglobin, triglyceride, total cholesterol and LDL cholesterol levels compared with controls, but during OGTT, the insulin levels and insulin to glucose ratio at 30-min and 120-min were lower in newly diabetes subjects. In this study we found the presence of insulin deficiency and cardiovascular risk factors such as higher systolic blood pressure, hypertriglyceridemia, hypercholesterolemia in newly diagnosed NIDDM but there was no correlation between insulin with those risk factors.

***Keywords**: Insulin, newly diagnosed NIDDM, cardiovascular risk factors*

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.

Department of Internal Medicine, Faculty of Medicine, University of Indonesia, Dr. Cipto Mangunkusumo Hospital Jakarta, Indonesia

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.[6]

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".[8]

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 (m^2). 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.[9]

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.[10] 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.[11,12]

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[13] 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 analysis 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

Table 1. Clinical details and baseline biochemical data of the Study Subjects

Characteristic	Newly diagnosed NIDDM	Control subjects	p
No. subjects	30	30	1
Gender	22M, 8F	F22M, 8F	1
Age (years)	50.6 ± .4	49.6 ± 8.3	0.6
BMI	26.9 ± 3.6	25.5 ± 5.9	0.27
W/H ratio	0.9 ± 0.06	0.89 ± 0.09	0.5
Systolic BP (mmHg)	131 ± 20.7	123.2 ± 13.4	0.04
Diastolic BP(mmHg)	84 ± 10.7	82.3 ± 7.3	0.38
HbA1c (%)	10.5 ± 4.9	5.5 ± 0.9	0.0001
Total cholesterol (mg/dl)	231.8 ± 55.8	203.8 ± 34.6	0.02
Triglyceride(mg/dl)	203.5[108-940]	156.5[48-559]	0.03
HDL cholesterol (mg/dl)	49.9 ± 12.3	49.4 ± 11.6	0.87
LDL cholesterol (mg/dl)	173.1 ± 44.6	148.1 ± 47.5	0.04

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 (Fasting I/G 0.08 vs 0.12; 30-min I/G 0.15 vs 0.5; 120-min I/G 0.16 vs 0.6; total I/G 0.2 vs 0.45) in newly diagnosed NIDDM than in normal control subjects. It meant that in diabetic subjects, there was no insulin resistance.

Table 3 shows the correlation of insulin and cardiovascular risk factors. The insulin levels do not correlate with W/H ratio, systolic blood pressure, triglyceride, total cholesterol as well as LDL cholesterol.

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 exceed 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 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

Table 2 : The glucose and insulin concentrations during the OGTT

Characteristic	Newly diagnosed NIDDM	Control subjects	p
Fasting plasma glucose (mg/dl)	199.4 ± 72	91 ± 12.1	0.0001
30 min plasma glucose(mg/dl)	278.3 ± 87	151.9 ± 28.5	0.0001
120 min plasma glucose(mg/dl)	317.4 ± 94	128.4 ± 33.8	0.0001
Fasting plasma insulin(mU/L)	15.3 ± 8.1	11.8 ± 6.8	0.07
30 min plasma insulin(mU/L)	42.2 ± 51	80.8 ± 49.6	0.04
120 min plasma insulin(mU/L)	52.6 ± 39.3	84.4 ± 53.3	0.01

Table 3. Correlation between insulin and cardiovascular risk factors

	r	p
Insulin and W/H ratio	0.08	0.5
Insulin and systolic blood pressure	0.18	0.2
Insulin and triglyceride	0.04	0.7
Insulin and total cholesterol	10.17	0.2
Insulin and LDL cholesterol	10.23	0.07

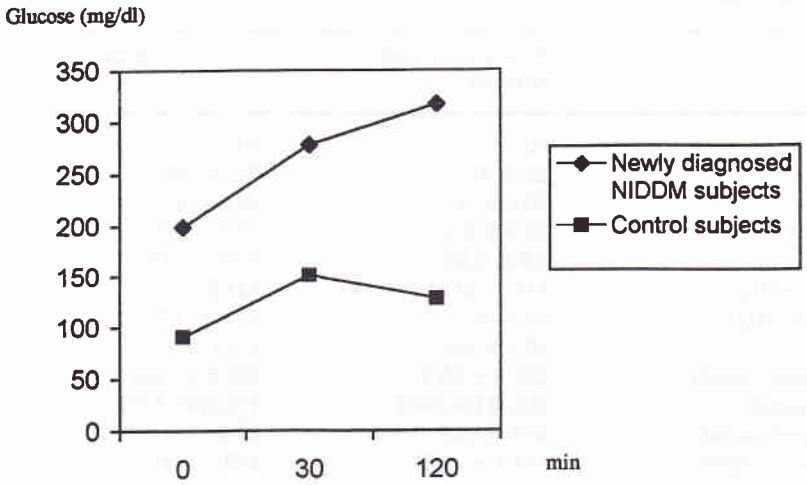

Figure 1a. Glucose levels during the OGTT

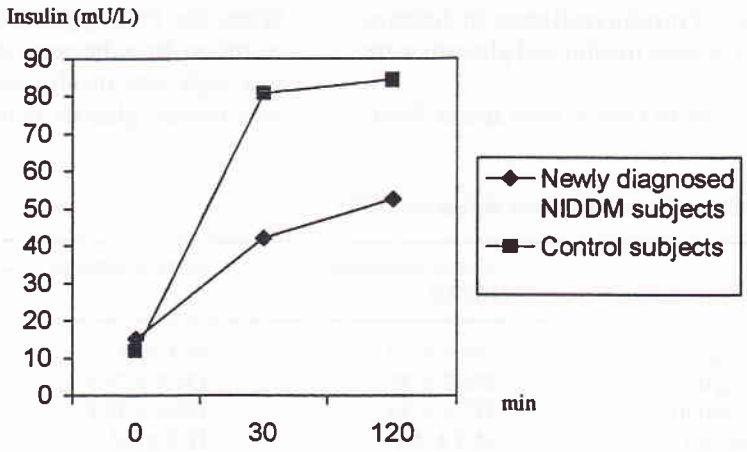

Figure 1b. Insulin levels during the OGTT

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.

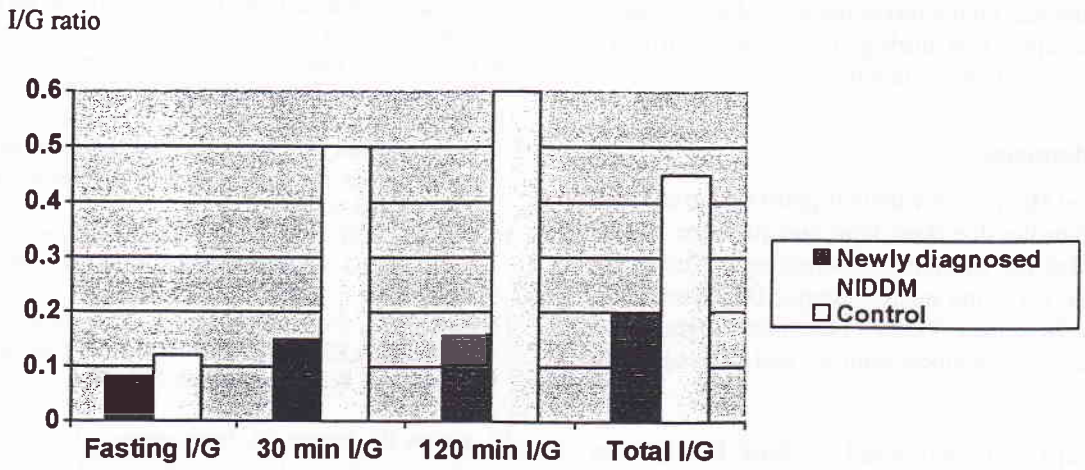

Figure 2. Insulin resistance (I/G ratio) between newly diagnosed NIDDM and control

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.[12,14] In diabetic subjects the early phase of insulin secretion during both IVGTT and OGTT is reduced due to the lost of acute insulin release.[11,12,16] 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.[6] In the Paris Prospective study, high triglyceride levels predicted the development of coronary heart disease[17]; and in the East West Study in Finland, both high triglyceride and low HDL cholesterol predicted the development of coronary heart disease.[7] 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[19]. By this method, Ndraha found higher insulin resistance in the overweight Indonesian NIDDM subjects and there was a significant correlation between BMI and fasting insulin level.[20] In this study we didn't perform euglycemic clamp technique because of the expense, but determined the insulin resistance by using I/G ratio.[11,12]

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.[18] Reaven suggested that insulin resistance may underlie hypertension, high triglyceride, low HDL cholesterol, impaired glucose tolerance and coronary heart disease.[8] 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[21], it is still possible that during these years coronary heart disease risk factors developed.

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