Effect of Insulin Resistance on the Endothelial Vasomotor Function of the Coronary Artery of Nondiabetic Patients

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Attention has been paid to the relationship between insulin resistance and coronary artery disease. The present study investigated the relationship between insulin resistance and the endothelial vasomotor function of the coronary artery of nondiabetic patients with chest pain and a positive exercise tolerance test. Twenty-five nondiabetic patients with chest pain were included. Patients with a steady state plasma glucose (SSPG) level of greater than or equal to 135 mg/dl were placed in the insulin resistant (IR) group, and those with a SSPG level less than 135 mg/dl were placed in the noninsulin resistant (NIR) group. The effect of acetylcholine, papaverine, and isosorbide dinitrate on the vasomotor response of the coronary endothelium was studied. The percent change in diameter of the coronary artery after injection of acetylcholine (20 μg ml⁻¹ min⁻¹) was 84±17% in the IR group, and 109±18% in the NIR group. The difference in the degree of the vasodilative response is statistically significant (p<0.01). The percent change in coronary flow velocity after injection of acetylcholine (20 μg ml⁻¹ min⁻¹) in the IR group was 120±67%, whereas that in the NIR group was 256±58%; the increase in coronary artery flow velocity of the IR group was significantly smaller than that of the NIR group (p<0.01). Nondiabetic patients with insulin resistance have endothelial vasomotor dysfunction, which raises an important question as to whether nondiabetic patients with insulin resistance should be treated to prevent the development of coronary heart disease. (Jpn Circ J 1999; 63: 589–592)

Key Words: Coronary endothelial function; Insulin resistance; Nondiabetic patients

Insulin resistance is a state in which cells and organs have decreased sensitivity to insulin and individuals with insulin resistance have reduced glucose uptake. ‘Syndrome X’, proposed by Reaven in 1988, is characterized by insulin resistance, abnormal glucose tolerance, hyperinsulinemia, increased VLDL-triglyceride, decreased HDL-cholesterol, and hypertension. He reported that patients with this syndrome have a high risk for ischemic heart disease. Kaplan added the concept of obesity to Syndrome X. The ‘deadly quartet’ is characterized by upper-body obesity, glucose intolerance, hypertriglyceridemia, and hypertension. Thus, insulin resistance is associated not only with metabolic diseases, but also with arteriosclerotic diseases such as ischemic heart disease. We studied the relationship between insulin resistance and the endothelial vasomotor function of the coronary artery of nondiabetic patients, and discuss the significance of insulin resistance in coronary artery disease (CAD).

Methods

Study Subjects

Twenty-five subjects with chest symptoms and a positive exercise tolerance test, who did not have diabetes mellitus by the hemoglobin A1C test and the fasting value of blood glucose (FBS), were included in this study. None of the subjects had significant stenosis of the right coronary artery (RCA); the stenosis in each case was less than 25% by American Heart Association (AHA) classification. Written informed consent was obtained from all 25 patients and their family members after explaining the protocol of the present study. The patients ranged in age between 39 and 68 years (mean±SD: 57.2±9.1), and included 15 females and 10 males.

Coronary Flow Velocity

Absence of significant stenosis of the RCA was confirmed by the Judkins technique. A 0.018F flow wire (Cardiometrics, Mountain View, CA, USA) was inserted into the RCA to measure the coronary flow velocity, which was measured after it became steady. Following initial measurement of the baseline velocity, physiological saline was injected into the RCA at an infusion rate of 1 ml/min through a 5F Judkins catheter for 2 min. The following drugs were then each injected at least 5 min after administration of the previous drug and after the initial flow velocity was restored. First, acetylcholine (Ach; Daiichi Seiyaku, Tokyo, Japan) at a concentration of 2 μg ml⁻¹ min⁻¹ was injected for 2 min. The average peak flow velocity (APV) and coronary angiogram were recorded. When the flow velocity returned to its initial level, 20 μg ml⁻¹ min⁻¹ of Ach was injected for 2 min after which the APV and coronary angiogram were recorded. Next, 10 mg of papaverine hydrochloride (PAP; Nihon Seiyaku, Tokyo, Japan) was injected over 5 s, soon after which the APV and coronary angiogram were recorded. Finally, a bolus dose (2 mg) of isosorbide dinitrate (ISDN; Eisai, Tokyo, Japan) was injected, and again the APV and coronary angiogram were recorded. The coronary artery flow velocity, blood pressure, heart rate, and 12-lead electrocardiogram were...
monitored continuously during the protocol, and recorded if necessary. The patients were asked to stop taking vasodilators at least 48 h before the test; patients were permitted to take sublingual nitroglycerin tablets.

**Determination of the Diameter of the Coronary Artery by Coronary Angiography**

Angiograms were taken on 35 mm films and the diameter of the target site of the coronary artery (3 mm from the tip of the flow wire) was determined by the edge detection method with a MHD93-300 Quantitative Coronary Angiography Analysis System (Baxter, Tokyo, Japan). The diameter of the 5F Judkins catheter was used as the standard to calibrate the diameter of the coronary artery.

**Evaluation of Insulin Resistance**

The steady state plasma glucose (SSPG) level was measured after an overnight fast of 12 h. Somatostatin (10 mg, Sandostatin; Novartis Pharma kk, Tokyo, Japan) and insulin (15 mU/kg, NovolinR 40; Yamanouchi, Tokyo, Japan) were given in a bolus injection. Then, Somatostatin (7.5 mg/h) was injected at the beginning of the procedure to suppress the secretion of endogenous insulin during the next 2 h in which 12% glucose at 6 mg kg−1 min−1 and (7.5 mg/h) was injected at the beginning of the procedure to suppress the secretion of endogenous insulin during the next 2 h in which 12% glucose at 6 mg kg−1 min−1 and insulin at 0.77 mU kg−1 min−1 were continuously infused. The serum concentration of glucose 2 h after the beginning of the test was considered to be the SSPG level! Patients who had a SSPG level equal to or greater than 135 mg/dl were considered to have insulin resistance and were placed in the insulin resistant (IR) group. Patients who had a SSPG level less than 135 mg/dl were placed in the non-insulin resistant (NIR) group.

**Calculation of the Change in the Diameter of the Coronary Artery and Blood Flow Velocity**

In each subject, the diameter of the coronary artery, as measured on the 35 mm films after each administration of Ach, PAP and ISDN, was expressed as a percentage of the baseline diameter of the coronary artery of that subject. The blood flow rate through the coronary artery after each administration of Ach, PAP and ISDN, was expressed as a percentage of the baseline value of that subject.

**Statistical Analysis**

Values are expressed as mean ± SD. The data were analyzed by the unpaired t-test and correlation analysis test. The difference was considered to be statistically significant at p<0.05.

**Results**

The 25 subjects were divided into IR and NIR groups based on the SSPG level. The sex, age, FBS, fasting value of blood insulin (F-insulin), HbA1c, body mass index (BMI), blood pressure, total cholesterol, triglyceride, HDL-cholesterol and remnant lipoprotein P of all the subjects are shown in Table 1. Only the BMI and F-insulin values of non-insulin resistant and insulin resistant groups differed significantly.

The percent change in diameter of the coronary artery of the subjects in the IR group after administration of Ach (20 μg ml−1 min−1) was 84±17%, and that of the NIR group was 109±18%. The vasodilative response of the coronary artery of the IR and NIR groups to Ach differed significantly (Fig 1). The percent change in APV through the coronary artery of the IR group was 120±67%, and that of the NIR group was 256±58%. Upon administration of Ach, the APV of blood through the coronary artery of the IR group increased by a lesser degree than that of the NIR group (Fig 2).

The percent change in diameter of the coronary artery after administration of ISDN in the IR and NIR groups to Ach differed significantly. The percent change in diameter of the coronary artery upon administration of 20 μg ml−1 min−1 Ach was 0.599 (R²=0.359, p=0.0026). The correlation coefficient between the SSPG level and the percent change in diameter of the coronary artery was 0.266 (R²=0.71, p=0.20).

**Discussion**

It has been suggested that insulin resistance is involved not only in diabetes mellitus, but also in other pathological states such as obesity, abnormal lipid metabolism and...
Insulin Resistance and Endothelium

The relationship between insulin resistance and arteriosclerosis has been studied from various aspects. Insulin resistance has been considered to promote arteriosclerosis by directly affecting blood vessels. Insulin resistance plays an important role in promoting ischemic heart disease and the degree of insulin resistance is correlated with the severity of coronary artery disease, although there are different theories as to how insulin resistance affects coronary artery disease. Mansfield et al. reported the involvement of coagulation factors, and Han et al. reported the importance of the NO level in endothelial cells. Seibaek et al., on the other hand, reported that a direct relationship between insulin resistance and the degree of coronary atherosclerosis does not exist.

Assuming that endothelial cells are involved in this mechanism, we studied the relationship between insulin resistance and coronary artery disease by comparing the response of the coronary artery to Ach in nondiabetic patients who have insulin resistance and those who do not. Our results showed that the percent change in diameter of the coronary artery of the IR and NIR groups after administration of Ach, an endothelium-dependent vasodilator, differed significantly (Fig 2), whereas the percent change in the diameter of the coronary artery of the IR and NIR groups after administration of ISDN, an endothelium-independent vasodilator, did not differ significantly. These results suggest that the endothelial cells that line the epicardial artery of individuals with IR are functionally abnormal, which is in accordance with previous findings that enhanced insulin response is related to Ach-induced vasoconstriction in patients with vasospastic angina.

To estimate the function of the endothelial cells that line the coronary artery, we measured the APV through the coronary artery after administration of Ach, and found it was less in the IR patients than in the NIR patients. When a higher concentration of Ach was administered, the APV in the IR group was reduced further. We then determined the coronary flow reserve (ie, the percent change in coronary flow velocity). The coronary flow velocity can be calculated by dividing the maximum APV from the baseline.
APV, where the maximum APV is obtained by dilating the coronary artery to the maximum degree by administering PAP. The coronary flow reserve of the IR and NIR groups did not differ significantly. These findings indicate that in patients with insulin resistance the endothelial cells that line the epicardial artery, as well as the endocardial coronary artery, have a functional abnormality, which may be the initial step in the development of coronary arteriosclerosis and coronary heart disease.

Our study may provide a method for detecting coronary artery disease at an early stage. In this study, we defined insulin resistance by the SSPG 2-h value. We consider that individuals whose SSPG level is lower than 100 mg/dl have normal insulin resistance, whereas those whose SSPG level is higher than 200 mg/dl have abnormally high insulin resistance. The borderline between normal and abnormal SSPG levels has not been established. If such a value is determined, it may be used as a parameter in addition to plasma glucose level and HbA1c, in the assessment of diabetes. We obtained the value of 135 mg/dl as the average SSPG 2-h value of the 25 patients in the present study. Whether this number is appropriate or not must await further studies. The SSPG 2-h value may have been affected by the degree of development of arteriosclerosis in the NIR group. Further studies that investigate the relationship between insulin resistance, and the development and prognosis of arteriosclerosis and other coronary heart diseases, are needed.

The F-insulin was higher in the IR group than in the NIR group, which suggests that the dysfunction of the endothelial cells is caused not only by insulin resistance but also by hyperinsulinemia. An important question is which of these 2 factors is the primary cause. We could not answer that question from our results, because at the time when insulin resistance was noted, hyperinsulinemia had already been detected. Our results also could not conclude which is the primary factor affecting the functional properties of endothelial cells. These results suggest that arteriosclerosis in patients with ischemic heart disease is a multiple risk factor syndrome and cannot be attributed to one specific factor.

Regarding treatment of the endothelial cells that are functionally abnormal, treatment of the underlying disease and the reduction of risk factors, such as smoking, have been proposed. Angiotensin-converting enzyme inhibitors improve endothelium-dependent vasomotor dysfunction in patients with coronary artery disease. The present study demonstrated that insulin resistance is related to the vasomotor dysfunction of the endothelial cells that line the coronary artery. This result leads to an important question as to whether nondiabetic patients with insulin resistance should be treated to prevent the development of coronary heart disease.

References