Introduction

Twenty percent of patients who undergo coronary angiography because of chest pain and abnormal electrocardiographic changes have normal findings on the coronary angiogram. Some of these patients are considered to have Syndrome X (1,2). Impaired myocardial perfusion reserve and resulting angina pectoris are the hallmarks of this syndrome. The terms Syndrome X and microvascular angina are frequently used interchangeably.

The diagnosis of Syndrome X should be established only after exclusion of left ventricular hypertrophy, diabetic heart disease, cardiomyopathy, valvular heart disease, coronary vasospasm and noncardiac chest pain (3). Pathogenesis of Syndrome X is not well understood. Several hypotheses are stated to clarify the underlying mechanism such as endothelial dysfunction, morphological abnormalities at microvascular level, increased sympathetic activity, and metabolic disorders (1,4-6,30).

Syndrome X is more commonly seen in females therefore, it has been suggested that estrogen deficiency might have some role in the pathogenesis (7).

In recent years, insulin resistance and hyperinsulinemia have been reported in patients with Syndrome X (8). The stimulatory effect of insulin on vascular smooth muscle proliferation is thought to play a role in the...
overnight fasting, patients were given 75 g. glucose solution orally. Basal, 60, 120 and 180 minute venous blood samples were collected. Glucose, insulin and C-peptide levels were assessed. Glucose levels were measured by autoanalyzer using the glucose oxydase/peroxydase method. C-peptide levels were measured in order to provide additional information regarding insulin resistance. Insulin biosynthesis takes place in pancreatic beta cells. The initial hormone is preproinsulin. This substance is converted to proinsulin and then to insulin and C-peptide. Subsequently they are released into the circulation, therefore their levels fluctuate together. Plasma insulin and C-peptide levels were measured with immunoassay techniques.

Statistical analysis

Variables were shown as mean±standard deviation. Analysis of variance was performed for numerical variables between groups. Bonferroni correction was applied in order to identify the different group. Statistical significance level was accepted as p<0.05.

Results

Patient characteristics

There was no difference between the 3 groups with regard to age, gender, height, weight, body mass index, waist/hip ratio and blood pressure (p>0.05) (Table 1). In the Syndrome X group none of the patients had myocardial infarction. In the CAD Group, 9 of the 14 patients had previous myocardial infarction, 8 of them had coronary bypass surgery and one patient had coronary angioplasty. None of the subjects in the control group had a history of heart disease. In Group I. all patients had a positive exercise stress test. In Group III. all subjects had a negative exercise stress test.

Glucose tolerance test

Fasting blood glucose levels were normal in the 3 groups. Glucose levels were lowest in the Syndrome X group and highest in the coronary artery disease group at each step. The glucose values in Group II were significantly higher at 120 and 180 minutes than in the Syndrome X group and normal subject.
artery disease group compared with the Syndrome X and control groups. This trend parallels the insulin levels.

### Serum lipids

Total cholesterol, LDL cholesterol and triglyceride levels were not statistically significantly different between the 3 groups.

### Discussion

In this study, patients who were diagnosed with Syndrome X had a normal fasting glucose and normal insulin response to glucose loading. Hyperinsulinemia was detected in patients with coronary artery disease. Although there is still some disagreement about the diagnosis of Syndrome X, descriptive clinical features are angina pectoris, positive exercise ECG test and normal coronary angiogram (3,8). A reduced coronary flow reserve has been demonstrated in some of these patients (12). Several mechanisms have been proposed to explain the pathogenesis of Syndrome X. Impairment of vasodilatory response due to increased sympathetic drive or endothelial dysfunction was thought to cause microvascular ischemia (4-6,13,14).

Inhibition of adenosine receptors by aminophylline can relieve the chest pain and ischemic ECG changes induced by inappropriate adenosine release (15). Mechanisms other than ischemia may also play a role in chest pain such as abnormal pain perception and minor intramyocardial conduction abnormalities causing pain as a consequence of incoordinate myocardial contraction (12,16,17). Generalized vascular and nonvascular smooth muscle cell dysfunction such as esophageal dismotility, methacoline induced bronchoconstriction is observed in patients with Syndrome X (18-20).

Metabolic abnormalities such as hyperinsulinemia and insulin resistance have also been observed in these patients. A metabolic abnormality consisting of glucose intolerance, hypertension, central type obesity with or without hypertriglyceridemia and low HDL cholesterol levels was called metabolic Syndrome X (21,22,29). The question has been raised whether cardiac Syndrome X is a part of metabolic Syndrome X.

In our study, we evaluated patients with cardiac Syndrome X who had no overt metabolic abnormalities (p<0.05) (Table 2). Glucose levels at 120 and 180 minutes were similar in the Syndrome X and control groups.

### Insulin levels

Basal insulin levels were highest in the coronary artery disease group and remained significantly higher than in the Syndrome X group and control group at each step (p<0.05) (Table 2). Insulin levels were similar in the Syndrome X and control groups.

### C-peptide levels

Although basal and 60 minute levels of C-peptide were similar in the 3 groups, 120 minute and 180 minute levels were significantly higher in the coronary artery disease group compared with the Syndrome X and control groups. This trend parallels the insulin levels.
such as diabetes mellitus. In patients with Syndrome X the results of the glucose tolerance test were normal. Contrary to most other studies, basal insulin levels and insulin response to glucose loading were also normal. However, fasting blood glucose levels tended to be higher in the coronary artery disease group compared with the Syndrome X and control group. Similarly, 120 and 180 minute glucose levels after loading were highest in the Syndrome X group. Insulin levels during glucose loading in the coronary artery disease group were higher than in both the control and Syndrome X group. These findings are in accordance with previous studies (9-11,23,24).

Contrary to some previous reports, lipid values of patients with Syndrome X were similar to those in the control group. Some investigators found lower HDL cholesterol and higher triglyceride levels in patients with Syndrome X (8,22,25). However, others reported findings similar to our results (27). Hyperinsulinemia was thought to be the cause of the lipid abnormalities in patients with Syndrome X (28). The absence of abnormal lipid values in Syndrome X patients in our study may be related to the absence of hyperinsulinemia. On the other hand, given the fact that only a proportion of patients with Syndrome X have abnormal coronary flow reserve and a relationship between insulin resistance and microvascular dysfunction, our study group without hyperinsulinemia may not have fallen into this category. The term Syndrome X does not define a homogeneous population. Widely accepted 2 characteristics of Syndrome X are chest pain and normal coronary angiogram. In patients who were diagnosed with Syndrome X, abnormalities of exercise ECG, myocardial lactate metabolism and left ventricular wall motion following exercise or pacing may be observed. Our findings demonstrate that insulin response to glucose loading can not be considered as an integral feature of Syndrome X. But our study can not rule out the role of abnormal glucose metabolism in all patients of Syndrome X.

Limitations of the study

The number of patients in the 3 groups is relatively small. This is an important drawback for establishing a clear conclusion. Another limitation of our study is that coronary vasodilatory reserve was not assessed. We used oral glucose tolerance test to evaluate insulin sensitivity, because it was practical and could be used routinely. The euglycaemic clamp technique may be used as the method for assessment of insulin resistance, but it is more difficult and takes more time than OGTT.

In conclusion; Syndrome X has a heterogeneous clinical presentation. Hyperinsulinemia and insulin resistance is not present in all patients with Syndrome X. On the other hand, coronary artery disease was associated with hyperinsulinemia. It appears that, there is not a single unifying mechanism underlying Syndrome X. Although the metabolic and cardiac Syndrome Xs are considered as the identical entities, we believe that these are different clinical syndromes. Further studies are needed to identify and characterize the underlying mechanisms.

References


