Turkish Journal of Endocrinology and Metabolism, (2002) 3 : 105-109 **ORIGINAL ARTICLE**

Relationship Between Hyperinsulinemia, Coronary Artery Disease and Syndrome X

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Abnormal coronary flow reserve has been reported in patients with Syndrome X. Recent studies have also reported insulin resistance and subsequent hyperinsulinemia in these patients. It has been suggested that hyperinsulinemia plays a role in microvascular dysfunction. In this study, insulin and C peptide response to oral glucose loading was compared in patients with microvascular angina and coronary artery disease with normal controls. Sixteen patients with Syndrome X, 14 normotensive, nondiabetic patients with coronary artery disease and 9 normal individuals comprised the three study groups. After having basal blood glucose, insulin and C-peptide levels, 75 g. oral glucose solution was given to patients. Blood samples were taken 60, 120 and 180 minutes later. Blood total cholesterol, LDL cholesterol, HDL cholesterol and triglycerides levels were also measured. Basal glucose and insulin levels were not different between groups. Insulin response to oral glucose in patients with microvascular angina was not different from the control group. However, increased insulin levels were observed in patients with coronary artery disease. Conclusions; 1) Patients with coronary artery disease may have hyperinsulinemia and insulin resistance, 2) There is not insulin resistance in all patients with Syndrome X, 3) Cardiologic and metabolic Syndrome X are probably different entities.

Key words: Coronary artery disease, hyperinsulinemia, syndrome X

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.

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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

pathogenesis of this syndrome. However others have reported contradictory findings (9-11).

Accordingly, we sought to assess the role of insulin resistance in patients with a diagnosis of Syndrome X. In this study, normotensive, nondiabetic patients with microvascular angina, and patients with coronary artery disease are compared with a normal control group with regard to insulin response to oral glucose loading. It was aimed to investigate if metabolic and cardiac Syndrome X have joint features.

Methods

The study population was divided into 3 groups. Group I. consisted of 16 patients (7 males, 9 females) with angina pectoris, positive exercise ECG test and normal coronary angiography (Syndrome X group). Group II. consisted of 14 patients (9 males, 5 females) with a luminal diameter stenosis >50% in at least one major coronary artery (Coronary artery disease-CAD-group). Nine healthy individuals (4 males, 5 females) comprised Group III. (control group). Patients in the first two groups were on regular treatment consisting of nitrates and calcium antagonist. None of the control group was on any medication. Patients with hypertension (>140/90 mmHg), diabetes mellitus, family history of diabetes, left ventricular hypertrophy, valvular disease and cardiomyopathy were excluded.

All patients in Group I and Group II had undergone coronary angiography. There were no ST-T changes during angina pectoris, therefore we did not performe an ergonovin test routinely. Exercise ECG test using Bruce protocol was performed in all patients. At least 1.0 mm horizontal or downsloping ST segment depression was required for a positive test result. Demographic characteristics of patients, and clinical history of prior Q wave MI, CABG and PTCA, and family history for diabetes mellitus and coronary artery disease were obtained from chart reviews.

In all patients, glucose, insulin and C-peptide levels were measured during a glucose tolerance test. Prior to the glucose tolerance test, all study subjects were on a normal diet (200 g. carbohydrate/day, for 3 days before the test), and on a similar physical activity, and they did not smoke for at least 24 hours before the test in order to eliminate confounding factors that could affect insulin sensitivity. Following 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.

Fasting total cholesterol, HDL cholesterol, and trygliceride levels were also determined with standard enzymatic methods. LDL cholesterol level was calculated with Friedwald formula.

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 subjects

Table 1. Clinical variables of patient and control groups

	Syndrome X (n=16)	CAD (n=14)	Control (n=9)	P value
Age	51±6	53±6	48±6	>0.05
Height (cm)	163±10	168±7	170±12	>0.05
Weight (kg)	67±10	69±9	71±10	>0.05
BMI (kg/m^2)	25±2	24±3	24±2	>0.05
Waist/hip ratio	0.87±0.08	0.90±0.05	0.85±0.08	>0.05
Blood pressure(mmHg)				
systolic:	111±11	116±16	120±12	>0.05
diastolic:	72±7	71±11	76±7	>0.05
T.Cholesterol (mg/dl)	228±48	237±57	201±36	>0.05
LDL cholesterol (mg/dl)	151±39	161±54	120±38	>0.05
HDL cholesterol (mg/dl)	52±16	42±6*	51±10	*<0.05
Triglycerides (mg/dl)	142±108	169±45	144±63	>0.05

Table 2. Glucose tolerance test results in groups (*= p<0.05)

	Syndrome X (n=16)	CAD (n=14)	Control (n=9)
Glucose (mg/dl)			
Fasting	80±8	93±11	86±8
60 min.	145±37	188±47	172±46
120 min.	110±29	157±53*	130±27
180 min.	89±21	110±48*	101±56
Insulin (μu/ml)			
Fasting	16±8	22±6*	18±3
60 min.	129±77	202±46*	127±74
120 min.	84±46	220±95*	120±60
180 min.	43±35	139±113*	48±29
C-peptide (ng/ml)			
Fasting	3.8±2.5	3.6±1.3	3.2±0.4
60 min.	8.6±3.4	11.1±2.3	9.0±4.1
120 min.	7.2±2.9	13.8±3.7*	8.5±2.8
180 min.	4.5±2.2	8.4±1.8*	5.8±2.7

(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.

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

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.

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