Evaluation of Insulin Resistance in Normoglycemic Patients with Coronary Artery Disease

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ABSTRACT

Background: Insulin resistance is clearly associated with coronary artery disease (CAD) in diabetics. Insulin resistance may also be present in normoglycemic individuals, and some of these patients can be diagnosed as having metabolic syndrome (MS) according to various definitions. However, the relationship between hyperinsulinemia and CAD is obscure in normoglycemic individuals, especially in patients who do not meet the criteria for MS.

Hypothesis: This study evaluated insulin resistance in normoglycemic patients with CAD, and investigated the association of insulin resistance with inflammation and lipid levels.

Methods: Fifty-six CAD patients, and 57 age- and sex-matched controls with normal coronary arteries confirmed by conventional coronary arteries angiography were included in the study. Participants were considered for the diagnosis of MS according to criteria of the National Cholesterol Education Program (NCEPATP III) and the International Diabetes Federation (IDF). Fasting plasma glucose, insulin, lipids, and c-reactive protein (CRP) levels were studied. The homeostasis model assessment insulin resistance index (HOMA IR) was calculated.

Results: The ratio of subjects with MS was similar in the 2 groups. Insulin, CRP, low-density lipoprotein (LDL) cholesterol, and HOMA IR were higher in the study group than in the controls. The HOMA IR, LDL cholesterol, and serum CRP levels were determined as predictors of CAD.

Conclusion: Our data revealed that insulin resistance and subclinical inflammation are present in normoglycemic patients with CAD. As the proportion of patients with MS was similar in the 2 groups, we suggest that HOMA IR values may provide more sensitive information than MS definitions about the association between insulin resistance and CAD in normoglycemic patients.

Key words: hyperinsulinemia, homeostasis model assessment insulin resistance index, cardiovascular, inflammation

Introduction

Type-2 diabetes is a well known cause of accelerated coronary artery disease (CAD). Insulin resistance is the main item in the pathogenesis of the development of type-2 diabetes. Elevated insulin levels and insulin resistance may be present several years prior to the diagnosis of type-2 diabetes.[1] Insulin resistance has been shown to be associated with CAD.[2] However, the results from several studies are conflicting. Despite the clear relationship between type-2 diabetes and CAD, the association of insulin resistance and CAD is more obscure in people without diabetes.[3,4] Some studies did not find any increase in the risk for CAD related to hyperinsulinemia.[5,6]

Insulin resistance can be estimated using several techniques. The euglycemic hyperinsulinemic clamp technique is the gold standard method for evaluation.[7] However, performing this technique in daily practice is difficult, and the method is expensive. The homeostasis model assessment insulin resistance index (HOMA IR) evaluates insulin resistance via calculation from fasting insulin and glucose concentrations. The HOMA IR is widely used in clinical trials. The HOMA IR model has been shown to be correlated with the results obtained from the euglycemic clamp technique.[8]

Atherosclerosis is an inflammatory disorder initiated by endothelial dysfunction. Several serum markers of inflammation have been found to be associated with atherosclerotic disease. C-reactive protein (CRP) is a major player in the atherosclerotic process at all stages.[9] Elevated serum CRP has been shown to be a strong predictor of cardiovascular outcomes.[10] It has been shown that there is a direct correlation between CRP and endothelial dysfunction, which is driven by the effects of adiposity.[11]

The aims of this study were to investigate the presence of insulin resistance in normoglycemic patients with CAD, and to evaluate the association of insulin resistance with inflammation and lipid levels.

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Methods

Fifty-six consecutive CAD patients who underwent elective coronary angiography because of clinically suspected CAD at the Ataturk Education and Research Hospital (Izmir, Turkey) were included in the study. In addition to obstructive CAD, patients with nonobstructive CAD were also recruited for the study. The control group was composed of 57 age-, sex-, and body mass index (BMI)-matched healthy people who had normal coronary arteries confirmed by conventional coronary angiography. The study was approved by the local ethics committee, and written informed consent was obtained from all participants.

Subjects were screened for type-2 diabetes with a plasma fasting glucose assay.[12] Individuals with a plasma glucose level >100 mg/dL (5.6 mmol/L) were excluded. Blood pressure was measured using a sphygmomanometer in the sitting position after a 5-min rest. Subjects having a blood pressure level >130 mm Hg for systolic and >85 mm Hg for diastolic at the examination, or patients using antihypertensive drugs were defined as hypertensive. Antihypertensive medications were recorded. Subjects were evaluated for the diagnosis of metabolic syndrome (MS) according to the criteria of the National Cholesterol Education Program (NCEPATP III) and the International Diabetes Federation (IDF). The individuals were classified either as nonsmokers, or as past or present smokers. Family histories for CAD and diabetes were recorded.

Patients with severe cardiac failure (classes 3–4) renal, hepatic, and other systemic diseases, morbid obesity, history of malignancy, and alcohol consumption were not enrolled in the study. Patients being administered lipid-lowering drugs, including statins, were also excluded.

Height (m), weight (kg), and waist circumflex (cm) were measured under fasting conditions with subjects in light clothing and without shoes. Waist circumference (WC) was measured at the high point of the iliac crest at minimal respiration. All measurements were done with the subject standing upright. The BMI was calculated as the weight in kilograms divided by the height in meters squared.

Coronary angiography was performed by standard angiographic techniques. Fasting blood samples were obtained after a resting period of 30 min between 8:00 AM and 9:00 AM from the cannulated antecubital vein. Serum and plasma were obtained by centrifugation at 3,000 rpm for 15 min at 4 °C. The samples were stored at −80 °C until use.

Fasting glucose levels were measured by the hexokinase method on a modular system (Roche Diagnostics Ltd., Basel, Switzerland). Insulin concentrations were measured by the electrochemiluminescence immunoassay (ECLIA) on an Elecsys E-170 analyzer (Roche Diagnostics Ltd., Basel, Switzerland). The HOMA IR was calculated using the following formula: HOMA IR = fastinginsulin (mU/L) × fasting glucose (mmol/L)/22.5. Triglycerides, total cholesterol, and high-density lipoprotein (HDL) cholesterol were measured by a Roche/Hitachi D/P Modular System Autoanalyzer (Roche Diagnostics Ltd., Basel, Switzerland). The LDL cholesterol was calculated by the Friedewald equation method. Uric acid (mg/dL) was measured using enzymatic–colorimetric methods. Serum high-sensitive CRP was measured by a Cobas Integra 400 autoanalyzer using a particle-enhanced turubidimetric assay (Roche Diagnostics Ltd., Indianapolis, Ind., USA). The sensitivity of CRP was 0.11 mg/L. The intra-assay and interassay coefficients of variation were 1.34 and 5.70, respectively.

Statistical Analysis

Data were analyzed by SPSS 11.0 for Windows (SPSS, Inc., Chicago, Ill., USA). Normality of continuous variables was checked by the Kolmogorov–Smirnov test. According to distribution of the data, differences between the groups were assessed using the independent *t* test or Mann–Whitney *U* test. Categorical data were compared by the chi-square test. Correlation analyses were conducted using Pearson's test. Logistic regression analysis was used to determine the relationship between CAD and studied parameters. A p value <0.05 (2-tailed) was considered statistically significant. Data are expressed as mean±standard deviation (SD).

Results

Baseline characteristics of the study groups are shown in Table 1. There was no statistically significant difference between groups in age, sex, smoking habits, hypertension, antihypertensive medication, family history of CAD or diabetes, BMI and WC. The proportion of subjects who met diagnostic criteria for MS was similar.

Total cholesterol, LDL cholesterol, and triglyceride levels were higher in the study group than in the controls. The HDL cholesterol was found to be lower in patients with CAD. Insulin levels were elevated in the study group, although fasting glucose values were similar. The HOMA IR was calculated to be higher in the study group compared with the control group. Serum CRP levels were increased in patients with CAD when compared with control subjects (Table 2). Seven patients in the study group and 3 patients in the control group had a HOMA IR value >2.71, whereas they did not meet the diagnostic criteria for MS according to IDF or NCEPATP III.

There were significant correlations between HOMA IR and BMI ($r = 0.345$, $p<0.001$), WC ($r = 0.357$, $p<0.001$), and triglyceride level ($r = 0.352$, $p<0.001$). Logistic regression analysis showed that HOMA IR, LDL cholesterol, and serum CRP levels were predictors of CAD in the present study (Table 3).

Discussion

The MS is a constellation of risk factors for vascular disease and diabetes, in which insulin resistance plays the central

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TABLE 1: Demographic and clinical characteristics of the study (CAD+; n = 56) and control (CAD−; n = 57) groups

	CAD+	CAD−	p-value
Age (y)	59.52±12.28	59.54±11.3	0.82
Male	41 (73.2%)	40 (70.2%)	0.835
Weight (kg)	71.07±12.55	70.58±14.11	0.373
BMI (kg/m²)	27±4.27	26.31±4.58	0.115
Waist (cm)	91.45±10.28	89.67±11.83	0.158
MS according to IDF	21 (37.5%)	16 (28.1%)	0.321
MS according to NCEPATP III	16 (28.6%)	13 (22.8%)	0.524
Current or past smoker	33 (58.9%)	35 (61.4%)	0.849
Family history of CHD	10 (17.9%)	9 (15.8%)	0.806
Family history of DM	14 (25%)	8 (14%)	0.161
Hypertension	23 (41.1%)	23 (40.4%)	0.938
Antihypertensive medications			
Beta-blockers	14 (25%)	10 (17.5%)	0.366
ACE inhibitors	14 (25%)	14 (24.6%)	0.957
ARB	3 (5.4%)	4 (7%)	0.714
Ca channel blockers	3 (5.4%)	9 (15.8%)	0.124
Diuretics	8 (14.3%)	12 (21.1%)	0.461

Data are expressed as means±SD or as frequencies (%). P-values were calculated using the independent *t* test (means of continuous variables) or the chi-square test (frequency data). *Abbreviations*: ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; BMI = body mass index; Ca = calcium; CAD = coronary artery disease; DM = diabetes mellitus; IDF = International Diabetes Federation; MS = metabolic syndrome; NCEPATP III = National Cholesterol Education Program Adult Treatment Panel III.

role. Insulin resistance is also the major player in the development of type-2 diabetes. Insulin resistance may be present before the diagnosis of type-2 diabetes. People with MS are candidates for developing type-2 diabetes. Both MS and type-2 diabetes are well-established disorders associated with CAD.[1,3] However, the relationship between hyperinsulinemia and CAD is more obscure.[4,6] Our results revealed that patients with CAD had elevated insulin levels and were more insulin resistant, even in the absence of diabetes. The critical point of our study was that there was no significant difference between groups in the proportion of subjects with the diagnosis of MS; however, the differences in insulin levels and HOMA IR were statistically significant. Seven patients in the study group (12.5%) did not meet the diagnostic criteria for MS according to NCEPATP III or IDF, but they had a HOMA IR value >2.71, which was consistent with decreased insulin sensitivity.[14] Therefore, calculation of HOMA IR seems to be a sensitive test in the determination of insulin resistance in normoglycemic CAD patients who do not meet diagnostic criteria for MS.

Two very similar definitions for MS provided by IDF[15] and NCEP III[16] are commonly used in daily practice. Both include high blood pressure, increased fasting glucose, elevated WC, increased triglyceride levels, and a decrease in HDL cholesterol.[15,16] Although increased WC is compulsory for MS diagnosis according to IDF,[15] it is not so according to NCEPATP III criteria.[16] Another difference is that NCEPATP III criteria[16] has only 1 cut-off for WC, regardless of geography. The problem is that these criteria do not address insulin resistance, which can be assayed. However, some of the patients with CAD in our study had insulin resistance, which can be shown by HOMA IR, although they had no MS according to definitions of IDF or NCEPATP III. There is a phase in which there is no clinical sign of insulin resistance; however, patients may be hyperinsulinemic.[13] Although confirmation of insulin resistance by biochemical assays cannot be counted as diagnostic criteria according to IDF or NCEPATP III,[15,16] the World Health Organization (WHO)[17] has established that insulin resistance, which is defined as "under hyperinsulinemic,

TABLE 2: Biochemical characteristics, lipid levels, CRP levels, and HOMA IR values of the study (CAD+; n = 56) and control (CAD−; n = 57) groups

	CAD+	CAD−	p-value
Glucose (mg/dL)	85.59±8.09	83.18±7.92	0.112
Uric acid (mg/dL)	6.38±1.64	6.23±1.8	0.655
Total cholesterol (mg/dL)	206.7±39.6	188.12±41.22	0.016*
Triglyceride (mg/dL)	171.55±87.86	128±67.99	0.001*
HDL cholesterol (mg/dL)	39.82±7.43	44.51±11.42	0.013*
LDL cholesterol (mg/dL)	132.86±31.88	117.97±32.82	0.016*
Insulin (mU/L)	7.99±5.15	5.72±4.2	0.011*
HOMA IR	1.69±1.1	1.19±0.91	0.009*
CRP (mg/L)	1.19±1.64	0.67±1.01	0.008*

Data are expressed as means±SDs. P-values were calculated using independent-sample *t* test or Mann–Whitney *U* test. *p<0.05. *Abbreviations*: CAD = coronary artery disease; CRP = C-reactive protein; HDL = high-density lipoprotein; HOMA IR = homeostasis model assessment insulin resistance index; LDL = low-density lipoprotein. Conversion factor (CF) for lipid levels (CF × C = SI): 0.02586. Conversion factor for plasma glucose (CF × C = SI): 0.0555.

TABLE 3: Logistic regression analysis showing factors associated with the presence of CAD

	OR	95% CI	p-value
Age	1.003	0.965–1.042	0.881
Sex	0.8	0.299–2.138	0.656
HOMA IR	1.641	1.079–2.495	0.021*
LDL Cholesterol	1.015	1.002–1.028	0.022*
CRP	1.432	1.007–2.036	0.045*

*p<0.05. *Abbreviations*: CAD = coronary artery disease; CI = confidence interval; CRP = c-reactive protein; HOMA IR = homeostasis model assessment insulin resistance index; LDL = low-density lipoprotein; OR = odds ratio.

euglycemic conditions, glucose uptake below lowest quartile for background population under investigation," can be used as a criterion in the diagnosis of MS. However, this method seems not to be useful in daily practice because composing a hyperinsulinemic euglycemic condition is very expensive and complex.[7] The HOMA IR is an inexpensive and practical method. The HOMA IR requires only a single sample assayed for insulin and glucose, and is comparable with other methods.[7,18]

On the other hand, there are also some pitfalls of the HOMA IR. First, use of immunoreactive insulin assays may alter the specificity of the method. The coefficient of variation (CV) for HOMA is 31% when immunoreactive insulin assays are used.[18] However, recent studies have shown CVs between 7.8%[19] and 11.7%[20] when specific insulin assays are used in many more subjects. Second, although routinely not applied, obtaining a mean from 3 assays taken at 5-min intervals is better than a single sample, as insulin secretion is pulsatile.[18] In addition, the normal range should be determined for different populations.[8]

In accordance with our results, insulin resistance has been defined as the indicator of metabolic risk in nondiabetic persons.[21] In addition to insulin resistance, CRP and LDL cholesterol levels were predictors of CAD in our study. Recent studies have suggested the role of subclinical inflammation in the pathogenesis of CAD.[9] A widely used marker of inflammation, CPR has been shown to be associated with cardiovascular outcomes.[10,22,23] In accordance with these studies, our data suggest that elevated CRP levels are associated with CAD.

Conclusions

Our results suggest that insulin resistance is present in normoglycemic patients with CAD. As there were no significant differences between the groups in the proportion of subjects with MS, the use of the HOMA IR may be a more sensitive method than the definitions of MS for the evaluation of the relationship between insulin resistance and CAD in normoglycemic patients.

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