The Effectiveness and Importance of Insulin Resistance in the Etiopathogenesis and Progression of Coronary Artery Disease

İNSULİNE DİRENCİN KORONER ARTER HASTALIĞININ ETYOPATOGENEZ VE PROGRESYONUNDAKİ ETKİSİ VE ÖNEMİ

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Summary

Background and **Aim:** Risk factors for coronary artery disease (CAD) including family histoiy, cigarette smoking, lipid and lipoprotein abnormalities may be metabolically interlinked with insulin resistance and hyperinsulinemia. This study evaluates the relation between insulin resistance and some other metabolic and anthropometric parameters with the presence and severity of CAD.

Methods: The study subjects comprised 90 (72 male, 18 female; mean age 55.03 ± 0.89 years) patients with angiographically demonstrated coronary artery disease and 43 (32 male, 11 female; mean age 51.62 ± 1.66 years) angiographically normal control subjects. Glucose and insulin metabolism, C-peptide, lipids and lipoproteins and some anthropometric parameters were evaluated and compared in both groups. The patient group was divided into 2 subgroups according to whether if they had hyperinsulinemia and insulin resistantce. The role of hyperinsulinemia in etiopathogenesis and severity of CAD was assessed.

Results: On univariate analyses, significant correlations were found between CAD and positive family history of CAD ($p<0.01$), cigarette smoking ($p<0.01$), insulin resistance, ($p<0.05$), C-peptide ($p<0.001$), total Cholesterol ($p<0.0001$), LDL-Cholesterol ($p<0.0001$), HDL-Cholesterol ($p<0.05$), triglyceride ($p<0.01$), Apo Al ($p<0.05$), Apo B ($p<0.001$) and Lp(a) ($p<0.005$) levels. Age, body weight, body mass index, subcutaneous adipose tissue thickness, waist-hip ratio, glucose intolerance, and alcohol consumption showed no statistical differences in the patient and control groups. Fasting 120th

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Özet

Amaç: Koroncr arter hastalığı (KAH)'nın risk faktörlerinden aile anamnezi, sigara, lipid ve lipoprotein anormallikleri insulin direnci ve hiperinsulinemi ile metabolik bir etkileşim gösterebilir. Bu çalışma insulin direnci ile bazı metabolik ve antropometrik parametrelerin KAH'nın varlığı ve ağırlığı ile ilişkisini değerlendirmek amacıyla planlanmıştır.

Metodlar: Çalışma grubunu KAH anjiyografik olarak gösterilen 90 (72 erkek, 18 kadın, ortalama yaş 55.03±0.89) hasta, kontrol grubunu da anjiyografik olarak KAH olmadığı gösterilen 43 (32 erkek, 11 kadın, ortalama yaş 51.62±1.66) olgu oluşturdu. İki grup arasında glukoz ve insulin değerleri, C-peptid, lipid ve lipoproteinler ve bazı antropometrik parametreler değerlendirildi ve karşılaştırıldı. Hasta grubu, hiperinsulinemisi olanlar ve olmayanlar olarak 2 alt gruba ayrılarak, hiperinsulincminin KAH'nın etiyopatogenezi ve ağırlığındaki rolü değerlendirildi.

Bulgular: Univariate analizlerde KAH ile aile anamnezi (pO.01), sigara içimi ($p<0.01$), insuline direnç ($p<0.05$), C-peptid (pO.001), total kolesterol (pO.0001), LDL-kolesterol ($p<0.0001$), HDL-kolesterol ($p<0.05$), trigliserid ($p<0.01$), Apo Al ($p<0.05$), Apo B ($p<0.001$), ve Lp(a) ($p<0.005$) düzeyleri arasında anlamlı korelasyonlar saptandı. Yaş, vücut ağırlığı, vücut kitle indeksi, cilt altı yağ dokusu kalınlıkları, göbek-kalça oranı, glukoz intoleransı ve alkol tüketimi bakımından kontrol grubu ile hasta grubu arasında anlamlı bir farklılık bulunmadı. İnsuline direnç saptanan ve koroner lezyon ağırlıkları Gensini skoru ile değerlendirilen hastalarda oral glukoz tolerans testi sırasında elde edilen 120. dakika açlık kan şekeri ve toplam insulin değerleri, KAH'nın ağırlığı ile anlamlı düzeyde korelasyon gösteriyordu. Multivariate ve lojistik regresyon analizlerinde koroner arter lezyon skoru kolesterol düzeyleriyle pozitif ($p<0.05$), HDL-kolesterol düzeyleriyle negatif bir korelasyon gösterirken, diğer

minute and sum of insulin levels during Oral Glucose Tolerance Test (OGTT) were significantly correlated with severity of C A D, as evaluated by Gensini coronary artery lesion score, in C A D patients with insulin resistance (p<0.05, p<0.01 and pO.001 respectively). On multivariate and logistic regression analyses, coronary artery lesion score also was correlated positively with total cholesterol (p<0.05) and negatively with HDL-cholesterol (p<0.01), but was not correlated with the other lipid fractions, smoking and C-peptide levels.

Conclusions: These findings may suggest the role of insulin resistance and hyperinsulinemia in the atherogenesis of C A D. Furthermore, these data may suggest that in patients with C A D, insulin resistance may be not only an important risk factor, but also may be a significant correlated factor for severity of C A D.

Key **Words:** Coronary risk factors, Insulin resistance, Coronary lesion score

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lipid fraksiyonları, sigara ve C-peptid düzeyleriyle anlamlı bir ilişki saptanmadı.

Sonuç: Bu sonuçlar KAH'nm patogenezinde hiperinsulineminin bir rolü olabileceğini gösterebilir. Dahası, bu veri-ler insulin direncinin koroner arter hastalarında sadece önemli bir risk faktörü değil, KAH'nm ağırlığı ile de yakından ilişkili olabileceğini gösterebilir.

Anahtar Kelimeler: Koroner risk faktörleri, İnsuline direnç, Koroner lezyon skoru

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The risk factors related to etiopathogenesis of C A D, a growing public health problem all over the world, has been investigated. In order to discuss etiopathogenesis of C A D, several risk factors have been determined and suspected (1,2). The precise level and pathogenesis of some of these factors have been elucidated while several others are currently being investigated (3,4).

Besides the classical risk factors for atherosclerosis namely; hypertension, hyperlipidemia, smoking, and diabetes, it is now being recognized that insulin resistance may be a fundamental underlying metabolic defect, which is causing atherosclerosis (5, 6). Recently, some clinical and epidemiological data have also implicated that insulin resistance may be an independent risk factor for C A D (7-11).

The hypothesis that insulin in excessive amounts is atherogenic was first promulgated by Stout and Owen (12). A few experimental and clinical studies were carried out to determine the mechanisms of the atherogenic action of insulin (13,14). Spallorassa et al. (15) found positive association between plasma insulin levels and angiographically documented significant C A D strengthening the epidemiological view that hyperinsulinemia may be associated with an increased risk for C A D mortality and nonfatal myocardial infarction. Some other studies showed that there was positive correlation between serum insulin levels and coronary lesion score (16-18).

insulin promotes the atherogenesis by direct and indirect mechanisms. In physiological concentrations, insulin stimulates proliferation and migration of arterial smooth muscle cells, an action mediated by growth factors. In addition, insulin increases cholesterol synthesis and binding of L D L-cholesterol to arterial smooth muscle cells. The indirect modes of action include the effects on the other risk factors for C A D such as stimulation of the sympathetic nervous system and its hypertensive property (19).

Insulin resistance has been implicated in the etiopathogenesis of hypertension for a long time (13, 20-22). More recently, it is hypothesized that insulin takes a role directly in the etiopathogenesis and progression of C A D (23). In the light of this information, it was planned to investigate the correlation between C A D and insulin resistance in-patients without hypertension and diabetes mellitus.

Material and Methods

This prospective study was performed between June 1996 and July 1998 on the patients who were hospitalized for coronary angiography at Uludağ University, School of Medicine, Cardiology Department, Bursa, Turkey.

Patients and Control Subjects: A11 subjects in this study were referred to the cardiology clinic for coronary angiographic assessment. The study included 440 men and 164 women totaly 604 consecutive cases ranging in age from 37 -70 years.

Inclusion Criteria

1. Normal fasting serum blood glucose levels.

2. Normal systemic arterial pressures (Arterial pressure < 140/90 mm/Hg).

Exclusion Criteria

1. Diabetes mellitus (94 cases).

2. History of diabetes mellitus in the family (56 cases).

3. Hypertension (161 cases).

4. Previous CABG or PTCA (36 cases).

5. Metabolic diseases such as familial dyslipidemia, uremia, hypertiroidism, or hypotiroidism (16 cases).

6. Congenital or acquired valve disease (37 cases).

7. Patients using beta blocker or diuretics (36 cases)

8. Patients refusal to participate (43 cases).

Eligible patients, who met exclusion criteria, were given informed consent. Cardiovascular medications including calcium antagonists, nitrates, aspirin, and ACE inhibitors were not discontinued before the study. The selected subjects consisted of 90 patients (72 male, 18 female 55.03±0.89 [mean±SEM] years) with angiographically documented CAD and 43 control cases (32 male, 11 female 51.61Ü.66 [mean±SEM] years) with negative exercise test and normal angiography.

Left ventriculography and selective coronary angiography were performed by standard Judkins or Sones techniques. Coronary angiograms were examined digitally by two observers unaware of the study. Overall severity of CAD was assessed according to the 15 segment coding system of the AHA and modified Gensini scoring system (24, Table 1).

Table 1. Gensini scoring system

Lumen obstruction	Score	Multiplication factor
< 25%	1	
26-50%	2	
51-75%	4	
76-90%	8	
91-99%	16	
100%	32	
Left Coronary Artery		
Left Main		5
Left Anterior Descending		
Proximal segment		2.5
Mid segment		1.5
Apical segment		1
First diagonal		1
Second diagonal		0.5
Left Circumflex		
Proximal segment		2.5 (3.5)*
Mid segment		1(2)
Distal segment		1(2)
Obtuse marginal branch		1
Posterolateral branch		0.5
Right Coronary Artery		
Proximal segment		1
Mid segment		1
Distal segment		1
Posterior descending		1

**// was used in the parenthesis multiplication factors if circumflex is dominant*

OGTT (Oral Glucose Tolerance Test): The cases were instructed to consume a carbohydrate-rich diet (>200 g carbohydrate/day) and not to smoke for 3 days before the tests. Following coronary angiography, after overnight fasting, basal samples were taken at 6.00 o'clock in the morning for the biochemical parameters and baseline glucose and insulin levels. The subjects were then given a 75 g oral glucose load and blood was drawn 30, 60, 90, 120 and 180 minutes later for repeated measurements of plasma glucose and insulin concentrations. Plasma glucose was measured using a glucose analyzer. Plasma insulin and C-peptide was measured by RIA technique. OGTT and hyperinsulinemia (Basal insulin levels >40 ng/ml, peak insulin levels >160 ng/ml and 120th minute insulin levels >40 ng/ml) was assessed according to criteria of WHO (25).

The lipid subfractions, which were measured, are total cholesterol, HDL-cholesterol, triglyceride, apo A l , apo B and Lp(a). Serum total cholesterol

Table 2. Comparing of demographic characteristics of the patient and control groups

DEMOGRAPHIC CHARACTERISTICS	PATIENTS	CONTROLS	p VALUES
AGE	55.03±0.89	51.62 ± 1.66	p >0.05
MALE/FEMALE	72/18	32/11	p >0.05
HEIGHT	167.65 ±2.34	168.54 ±2.12	p >0.05
WEIGHT	79.87 ± 9.42	78.34 ±8.98	p >0.05
W/H	1.01 ±0.01	0.98 ±0.01	p >0.05
BMI	26.94 ± 0.38	26.38 ± 0.44	p >0.05
SCINFOLDS	104.53 ±2.36	102.23 ±4.14	p >0.05

Table 3. Comparing of risk factor rates of the patient and control groups

RISK FACTORS	PATIENTS (%)	CONTROLS (%)	OR	% 95 CI	p VALUES
SEX (MAN)	80	74	1.84	0.78-4.32	p >0.05
SMOKING	67	40	3.00	1.25-7.28	p<0.01
HYPERINSULINEM1A	56	34	2.40	1.09-5.86	p<0.05
GLUCOSE INTOLERANCE	40	29	1.78	0.69-4.69	p>0.05
FAMILY HISTORY	58	34	2.75	1.13-6.73	pO.01
ALCOHOL	16	14	1.45	0.40-5.68	p>0.05

OR: Odd Ratio, CI: Confidence Interval

and triglyceride was estimated by enzymatic method. HDL-cholesterol was estimated by the method based on manganese phosphotungstate precipitation procedure. LDL-cholesterol values were calculated by Friedwald formula. Apo A l , apo B were estimated by immunoturbidimetric methods and Lp(a) levels were estimated by a special kit. Age, weight and height were recorded; body mass index (BMI= weight/height^2) was calculated and assessed to Bray classification (26). Waist to hip ratio (W/H) was calculated as a measure of abdominal obesity. Skinfold thicknesses were measured with Holtain calipers to the nearest millimeter at four standard sites: biceps, triceps, subscapular and suprailiac. It was expressed as skinfolds the sum of different sites values.

Statistical Analyses: Data for male-female ratio, hyperinsulinemia, glucose intolerance, smoking, alcohol consumption, and family history for C A D were assessed chi-square and Fischer's exact chi-square tests. The results are expressed as mean ± S E M and were analyzed by SPSS standard package programs. Pharmacological, biochemical and demographic differences between the groups compared with Student's t test. In the patient group the relations between coronary lesion score and insulin levels, family history, smoking, C-peptide and lipid subfractions were assessed by Pearson correlation coefficients and logistic regression analyses. Statistical significance was defined as a p value < 0.05.

Results

The patient and control groups were compared for C A D risk factors, demographic, anthropometric and biochemical parameters. No differences between control and patient groups were observed in age, sex and anthropometric parameters (Table 2).

The correlations between risk factors and C A D including cigarette smoking, family history, hyperinsulinemia, glucose intolerance and alcohol consumption were evaluated (Table 3). C A D was significantly correlated with smoking and family history ($p< 0.01$, $p< 0.01$) respectively, but not correlated with alcohol consumption.

Anthropometric correlations between two groups were also evaluated. There were no differ-

Table 4. Comparing of serum lipid concentrations of the patient and control groups

LIPID SUBGROUPS	PATIENTS	CONTROLS	p VALUES
TOTAL CHOLESTEROL	246.94± 4.63	209.60 ±5.86	pO.0001
LDL CHOLESTEROL	164.56 ±4.18	133.09 ±5.54	pO.0001
HDL CHOLESTEROL	35.89 ± 0.73	39.23 ± 0.98	p<0.05
TRIGLYCERIDE	226.10 ± 8.86	186.40 ±11.07	p<0.01
Apo-A,	121.52 ± 2.89	131.86 ±4.85	p<0.05
Apo-B	166.03 ±4.02	136.60 ±6.12	p<0.001
Lp(a)	33.31 ±2.09	19.34 ±2.59	p<0.005

Table 5. Comparing of risk factors of the insulin resistant and non-insulin resistant groups

RISK FACTORS	INSULIN RESISTANT	NON-INSULIN RESISTANT	p VALUES
SUM OF CORONARY LESION SEVERITY	87	36	p<0.001
FASTING INSULIN LEVELS	56	29	p<0.05
120th MINUTE INSULIN LEVELS	97	31	p<0.01
SUM OF INSULIN LEVELS	845	324	pO.001
TOTAL CHOLESTEROL	256.54 ± 5.14	219.60 ±6.45	p<0.05
HDL CHOLESTEROL	29.84 ±0.45	35.23 ± 0.76	p<0.01

ences in the body mass index, the waist-to-hip ratio and skinfolds (Table 2) between two groups. Plasma total cholesterol, triglyceride, LDL-cholesterol, apo A 1 , apo B, and Lp(a) levels were significantly higher and HDL-cholesterol was significantly lower in the patient group (Table 4). There was a statistically significant difference between two groups in terms of hyperinsulinemia (p< 0.05) but no difference in glucose intolerance.

In other biochemical parameters including hemoglobin, hematocrit, leucocyte, platelet, urea, creatinine, uric acid, Na, K, CI levels, no significant differences were found between two groups.

The patient group was separated into 2 subgroups as insulin resistant and non-insulin resistant according to WHO criteria. Coronary lesion severity was assessed by using Gensini scoring system. The correlations between coronary lesion severity and risk factors (family history, smoking and hyperinsulinemia), anthropometric (body mass index, waist-hip ratio and skinfolds) and biochemical parameters (C-peptide and serum lipid concentrations) were investigated with univariate and multivariate analysis. In the insulin resistant group there was a positive correlation between coronary lesion severity with fasting, 120th minute and also sum of insulin levels during OGTT (p<0.05, pO.O1 and pO.001, respectively). A positive correlation was also found between coronary lesion severity and total cholesterol (p<0.05) and negative correlation with serum HDL-cholesterol levels (p<0.01, Table 5). There were no correlations between coronary lesion score and anthropometric parameters, LDL-cholesterol, triglyceride, apo A 1 , apo B and Lp(a) levels.

Discussion

There are several factors that may affect insulin resistance (27-30). In this study, these factors were considered and evaluated as part of patient se-

lection. Patients with diabetes mellitus, family history of diabetes mellitus, and hypertension were excluded from the study. The strength and confidence of the study lies in the similarity of age between the patient and control groups, the fact that there was no case over age of 70 and lower than 37 in either group, and the lack of statistically significant difference between the two groups in terms of age and glucose intolerance.

In this study, the importance of family history, smoking, hypercholesterolemia and hypertriglyceridemia, which are known as risk factors of coronary artery disease were shown, once more. Since hyperinsulinemia was statistically different between the patient and the control groups, it may have an important role in the etiopathogenesis of the coronary artery disease.

In our study, the patient and control groups were compared for anthropometric parameters and there were no statistical differences in body-mass index, waist-hip ratio and subcutaneous tissue thickness. This finding might implicate that insulin resistance is effective as an independent factor.

It was also shown that there were positive correlations between presence of C A D and total cholesterol, L D L cholesterol, and a negative correlation with H D L cholesterol with prospective studies (31-33). In the present study, total cholesterol, LDL-cholesterol, triglycerides, apo B and Lp(a) levels were found significantly higher and H D L-cholesterol and apo Al levels significantly lower in the patient group. Recent studies have shown that there is a correlation between the severity of C A D and apolipoproteins and Lp(a) (34). In some papers, it is stated that apo B levels are more reliable than LDL-cholesterol and HDL-cholesterol to evaluate the severity of coronary artery lesions (16, 35). Krishnaswami et al. (36) showed a weak positive correlation between severity of C A D and total cholesterol and LDL-cholesterol by using Gensini scoring system. In the present study, we found a positive correlation between coronary artery lesion score and the level of total cholesterol and a negative correlation with the level of HDL-cholesterol. No correlation was found among LDL-cholesterol, triglyceride, apo A l , apo B and Lp(a) levels with coronaiy artery lesion severity.

We also investigated whether there was a correlation between severity of C A D and insulin levels. When the patients were separated according to insulin levels, coronary lesion scores were higher in the insulin resistant group. This relationship appeared to be significant for fasting, 120th minute and the sum of insulin levels obtained during O G T T in those subgroup patients. Zamboni et al. (16) showed a positive correlation between the severity of coronary artery lesion scores and visceral fat tissue, triglyceride, apo B and sum of the insulin levels during OGTT. The same correlation was also shown by Negri et al. (17). It was also shown that there was a positive correlation between the severity of coronary artery lesion scores, and fasting and the sum of insulin levels during OGTT in the subgroup patients. Spallarossa et al. (15) indicated a positive correlation between the severity of C A D and fasting and the second hour insulin levels during OGTT. These results support our findings. Fujiwara et al. (18) showed that basal insulin levels were not significantly different between the patient and the control group, but the sum of insulin levels during O G T T were significantly higher in the patient group. In that study, the number of cases was pretty low when only those with normal O G T T were evaluated. The superiority of our study is exclusion of the hypertensives and diabetics, and the absence of significant difference between the patient and the control groups in terms of glucose intolerance. In a recent study (37) was implicated that the patients with documented C A D are insulin resistant independently of obesity. This result was also affirmed using by hyperinsulinemic euglycemic clamp technique in the patients with C A D (38). In the present study also shown that insulin resistance is a risk factor for severity of C A D independently of anthropometric parameters.

It is proposed that one of the mechanisms to accelerate the atherogenesis in hyperinsulinemia is a direct effect of insulin on the cells that synthesize plasminogen activator inhibitor-1 (39). It is also argued that insulin can stimulate the synthesis and release of endothelin, which is a great vasoconstrictor and mitogen for vascular smooth muscle cells (5,40,41). It was also demonstrated that hyperinsulinemia significantly potentiates the mitogenic properties of platelet-derived growth factor (42). These points need to be investigated in the future with prospective studies.

In conclusion, insulin resistance may be an important risk factor both at the onset and the progression of atherosclerosis in patients with CAD. The role of hyperinsulinemia and insulin resistance on the etiopathogenesis and acceleration of CAD needs to be further investigated.

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