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The Association Between C - reactive protein and Metabolic Syndrome Components

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Background: Insulin resistance is associated with metabolic syndrome and is a risk factor for cardiovascular disease. C-reactive protein (CRP) is an inflammatory marker which is demonstrated as a strong predictor of future cardiovascular events.
Material Method: In this study, sixty-three patients who were diagnosed with metabolic syndrome and twenty healthy controls were recruited. Fasting blood glucose, insulin and CRP levels were measured. Homeostasis Model Assessment (HOMA-IR) formula is used to evaluate insulin resistance. We investigated the relationship between insulin resistance and CRP levels and whether CRP is a metabolic syndrome criterion or not.
Results: There were statistically significant differences between patients with metabolic syndrome and controls in terms of waist circumference, fasting glucose, insulin and CRP levels. In patients, we found a poor but significant relationship between fasting glucose levels and CRP (P=0.0001, r=0.3) and between HOMA-IR values and CRP (P=0.007, r=0.29).
Conclusion: We concluded that CRP may have an important role in the diagnosis and follow-up of metabolic syndrome.

Key Words: Diabetes, Metabolic syndrome, CRP, HOMA, Insulin resistance, Waist circumference

CRP ile Metabolik Sendrom Arasındaki İlişki

Giriş: İnsülin direnci metabolik sendrom ile ilişkilidir ve kardiyovasküler hastalıklar için risk faktörüdür. C-Reaktif protein (CRP) gelecekteki kardiyovasküler hastalıkların habercisi olan bir proinflamatuar belirteçdir. Biz bu çalışmada insülin direnci ile CRP düzeylerinin ilişkisini ve CRP'nin metabolik sendromda kriter olup olmayacağını araştırdık.
Gereç ve Yöntem: Bu çalışmaya metabolik sendrom tanısı almış 63 hasta ile 20 sağlıklı kontrol grubu dahil edildi. Açlık kan glukoz seviyeleri, insülin ve CRP düzeyleri ölçüldü. İnsülin dirençleri (Homeostasis Model Assessment=HOMA-IR) formülü kullanılarak değerlendirildi.
Bulgular: Metabolik sendromlu hasta grubu ile kontrol grubu arasında bel çevresi, açlık glukozu, insülin ve CRP değerleri arasında istatistiksel anlamlı farklılıklar vardı.Hasta grubunda açlık glukoz düzeyleri ve CRP arasında (P=0,0001, r=0,3) ve HOMA-IR ile CRP arasında (P=0,007, r=0,29) zayıf fakat anlamlı bir ilişki vardı.
Sonuç: CRP'nin metabolik sendromun tanı ve takibinde önemli bir parametre olduğu sonucuna vardık.

Anahtar Kelimeler: Diabet, Metabolik sendrom, CRP, HOMA, İnsülin direnci, Bel çevresi

Insulin resistance is defined in 1997 as an increased insulin necessity for a normal biological response. Abnormal insulin molecules, cortisol, growth hormone and rarely anti-insulin antibodies are responsible for this resistance. Target tissue defect is the main reason.[1,2] Obesity, especially abdominal obesity, inactivity, carbohydrate predominant diet, hormonal and genetic factors and aging cause insulin resistance. This resistance increases insulin secretion and result in hyperglicemia, hypertension, and dyslipidemia associated with hypertriglyceridemia, low HDL and high LDL cholesterol levels. This clinical picture is called as a Metabolic Syndrome, formerly called Syndrome X, insulin resistance syndrome, dismethabolic syndrome, Reaven syndrome, plurimethabolic syndrome.[3] According to Third Report of the National Cholesterol Education Programme (NCEP) Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III (ATP III) 2002 the metabolic syndrome is identified by the presence of three or more of the components.[4-6]

The etiology of metabolic syndrome can be divided in three categories. These are obesity and fat tissue disorders, insulin resistance and independent factors (vascular, hepatic and immunologic). Many people carrying metabolic syndrome criteria have insulin related disorders of glucose metabolism, but all obese people do not have insulin resistance or people who have insulin resistance can give different phenotype of metabolic syndrome presentation. This lead an importance of genetic transmission.[7,8] Many methods are developed to demonstrate insulin resistance. Hyperinsulinemic-euglisemic insulin clamp technique which is described by Defronzo et al. in 1979 is accepted as a gold standard.[9] Because of difficulty and expensive of this clamp technique, new methods like "homeostasis model assessment" (HOMA), "continuous infusion of glucose with model assessment" (CIGMA) and "minimal model" were developed.[9,10] HOMA test which was developed by Matthews et al. assess both insulin resistance and beta-cell function.[11] In this test, the steady-state basal plasma glucose and insulin concentrations are used to predict the homeostatic concentrations which arise from varying degrees beta-cell deficiency and insulin resistance (IR). The estimate of insulin resistance obtained by homeostasis model assessment correlated with estimates obtained by use of the euglycaemic clamp.[11] The equation for HOMA-IR test is given below.

Insulin resistance (HOMA-IR) = (fasting insulin concentration (μIU/ml) x fasting blood glucose (mg/dl) /22.5

There is no reference value for insulin resistance however; value of 4.5 is significant.[11,14]

Insulin resistance is a risk factor for cardiovascular disease and associated with metabolic syndrome. Other risk factors include: hypertriglyceridemia, low HDL-cholesterol, hyperinsulinemia, hyperglycemia, and hypertension. Almost all individuals with type 2 diabetes mellitus and many with hypertension, cardiovascular disease, and obesity are insulin resistant.[15,17]

C-reactive protein (CRP) is a marker of inflammation that has been shown in multiple prospective epidemiological studies to predict incident myocardial infarction, stroke, peripheral arterial disease, and sudden cardiac death. It is strong predictor of future cardiovascular events as well.[18]

The aim of this study is to asses relationship between insulin resistance and CRP levels and to evaluate CRP as a metabolic syndrome criteria.

MATERIALS METHODS

Sixty-three patients (fifty female and thirteen male) with metabolic syndrome and twenty healthy controls (thirteen female and seven male) were admitted to study. Haseki Education and Resarch Hospital board of ethics approved the trial, and informed concent concerning all issues was obtained. Age distribution for patients and controls were 47.4 ± 8.4 and 42.9 ± 6.8 years, respectively. Waist circumferences were measured. All patients and controls 12 hours fasting blood samples were drawn and centrifugated at 1500xg for 5 minutes. Fasting blood glucose levels were measured immediately (Olympus AU 2700 autoanalyser, Clare, Ireland). Insulin levels were obtained using immunoassay method on Immulite 2000 (DPC, Los Angeles, Ca. USA). Serum samples were stored at -20 ^{O}C and CRP was measured using a high-sensitivity enzyme-linked immunosorbent assay (ELISA) (Axis-Shield AS, Oslo) HOMA-IR was calculated with using formula.

Data are presented as means ± standart deviations.Statistical significance was set at a probability value less than or equal to 0,001. The Mann-Whitney-U test was used for statistical analysis of the difference between binary groups.Pearson Correlation Analysis is applied to all parameters.

RESULTS

In this study all patients and controls waist circumference, fasting blood glucose and fasting blood insulin and blood CRP levels were measured. Results are given in Table 1. Insulin resistance was calculated using HOMA-IR formula.

Table1. All patients and controls waist circumference, fasting blood glucose and fasting blood insulin and blood CRP results (All data are given as a mean±SD).

	Metabolic Syndrome	Control	P
Waist circumference (cm)	110±11.8	78.3±12.4	0.0001
Glucose (mmol/L)	7.6±3.3	4.7±0.7	0.0001
Insulin (uU/ml)	12.5±7.1	9.9±8.2	0.006
HOMA-IR	4.2±2.9	2.0±1.8	0.0001
CRP (mg/L)	8.2±6.8	3.1±2.8	0.0001

A poor but significant relation is detected between fasting blood glucose and CRP levels in metabolic

syndrome group with respect to the control group (P=0.0001, r=0.3). A similar relationship is detected between HOMA and CRP as well (P=0.007, r=0.29).

DISCUSSION

Epidemiologic studies supported that people who have components of the metabolic syndrome, have insulin mediated glucose metabolism disorders. However, all obese people do not have insulin resistance and metabolic syndrome may present different fenotype. Heredity is important factor in patients with insulin resistance.[6] Raven et al. demonstrated that patients with metabolic syndrome have insulin resistance and high plasma insulin levels.[17] In our study, we determined waist circumference, fasting blood glucose, insulin levels and HOMA-IR values and plasma CRP levels in metabolic syndrome and control groups. All these parameters were high and statistically significant in metabolic syndrome group when compared with controls. In addition, we found high levels of CRP in patients with metabolic syndrome and it was statistically significant when compared to control group ($p<0.0001$). The most prominent reason of insulin resistance is abdominal obesity. The real factor is the increase of visseral fatty tissue rather than subcutoneous. Triglyceride formed by the combination of 3 fatty acids with a molecule of glycerole, accumulates in the fatty tissue, and in need of energy, it resolves back in to fatty acids to provide energy. In obese people, more fatty acids are secreted and more accumulation is obtained in the fatty tissue. As a result, excessive amouth of fatty tissue, espacially when located in visser increases the insulin resistance.[17] Recently, Ersanlı et al. demonstrated that strong relation between insulin resistance and waist circumference.[15] We couldn't establish a significant relation between waist circumference and insulin resistance in patients group.

It was demonstrated that CRP levels are increased with the number of manifestations of metabolic syndrome. The more components of metabolic syndrome, the higher CRP levels obtained.[19] In our study, we found close relationship between fasting glucose levels and CRP levels.

Ford et al. observed close correlation with CRP levels and obesity and insulin resistance.[16] In our study, we found close relationship between HOMA-IR and CRP levels (P=0.007). In addition, we demonstrated a poor but significant relation between fasting glucose levels being considered as a metabolic syndrome component and CRP levels (P=0.0001, r=0.3).

Inflammatuary mechanisms are important in the pathogenesis of atherosclerosis and cardiovasculary complications.[18,19] CRP promotes atherosclerotic processess by direct proinflammatory effects on vascular cells.[20,21] According to Ridker, CRP levels of <1, 1 to 3, and >3 mg/L differentiate low, moderate, and high risk, respectively.[18] Ford et al. shown that, metabolic syndrome patients with high CRP levels value of more than 1 mg/L have high risk for cardiovasculary morbidity and morbidity.[15] In our study, we demonstrated that our metabolic syndrome patients have higher CRP levels than controls and only 2 of them (3.17 %) have low risk, CRP value of less than 1 mg/L, 13 of them (20.6 %) have moderate and remaining 48 patients (76.19 %) have high levels of CRP value of more than 3 mg/L.

Chronic inflammation is a risk factor for the development of atherosclerosis. It may also risk factor for insulin resistance and vice versa. As an inflammatuary marker, CRP level is important in metabolic syndrome and it is helpful for risk classification and follow-up these patients.

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