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ASSOCIATION BETWEEN PROİNSULİN AND CARDIOVASCULAR EVENTS

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Aim: Coronary artery disease (CAD) still remains an important cause of death in spite of all advances in treatment. There are many risk factors for CAD. The aim of the present study was to evaluate the effect of of-of proinsulin on cardiovascular morbidity and mortality in non-diabetic coronary artery disease.

Material & Method: Nondiabetic 38 (8 female, 30 male) patients diagnosed with the acute coronary syndrome (ACS) admitted to coronary ICU of Haseki Training and Investigation Hospital and 21 control cases (9 female, 12 male) without diabetes and any cardiovascular disease were included in the present study. Proinsulin and other biochemical parameters of the patients were recorded. Five years later, among patients with the acute coronary syndrome (ACS), those who have recurring ACS and those who do not have were compared in terms of proinsulin and other biochemical parameters.

Results: There was no significant difference between acute coronary syndrome patients and controls with regard to proinsülin, Proinsulin /İnsulin ratio, and HOMA-IR values. However, a significant difference was found in age and glucose/insulin ratio. Respectively p=0.017, p=<0.001. After five years of follow up, significant difference was found between ACS patients who experienced cardiac event again and those who did not do so in terms of systolic blood pressure and proinsulin levels. Respectively p=0.013, p=0.031. No statistically significant difference was found in other parameters.

Conclusion: No significant difference was found between patients with ACS and control groups with respect to proinsulin levels. p=0.072. However, after five years of follow up, proinsulin levels were found to be high (p=0.031)in the group who reexperienced cardiac events, suggesting that proinsulin may be a marker or risk factor of cardiovascular risk in the long term.

INTRODUCTION AND AIM:

Coronary artery disease (CAD) is a chronic progressive disease. There are many risk factors for CAD: Type II diabetes mellitus (DM), is an independent risk factor for ACS and is even considered equivalent to CAD in this respect at present. However, recently it has been recognized that clinical pictures of DM and metabolic syndrome, which is considered its precursor, insülin resistance (IR) and impaired fasting glucose are more serious risk factors than previously thought. (1-2): Proinsulin and similar molecules have a weaker hypoglycemic effect than insulin and when their level in blood increases, they bind insulin receptors, decreasing the effect of insulin and increasing insulin resistance. In parallel to insulin resistance, the risk of coronary heart disease increases as well. IR plays an important role in the pathogenesis of Type 2 DM. Prior to the development of Frank DM, there is a prediabetic period characterized by an increase in IR. It has been reported that cardiovascular mortality and morbidity increases also in the prediabetic period accompanied frequently by cardiovascular risk factors such as obesity, dyslipidemia, and hypertension (HT). The contribution of IR and hyperinsulinemia developing in response to it too high cardiovascular risk independent of accompanying risk factors is controversial. In patients with Type 2 DM, the levels of proinsulin and other associated peptides in circulation increase 2-4 fold., which is one of the reasons why peripheric insülin effect cannot be obtained in spite of hyperinsulinemia. In the study of Kahn et al, it has been reported that disproportional hyperproinsulinemia is one of the main and earliest beta cell disorders occurring in NIDDM. (3). In another study, it was demonstrated that the basic functional defect is beta cells is the deficiency in the response of insülin to glucose, leading to a relative increase in proinsulin(4). In the prediabetic stage, there is a rise in insülin resistance, and hyperproinsulinemia develops and as age and BMI increases so do proinsulin levels.

In cases with NIDDM, whether obese or not, baseline proinsulin levels and those of associated products such as Des 32,33 split proinsulin AND Des 65,66 split proinsulin increase markedly (5).

MATERIALS AND METHOD:

38 consecutive nondiabetic patients (8 female, 30 male) admitted to coronary ICU of Haseki Hospital with a diagnosis of the acute coronary syndrome (unstable angına, MI without ST elevation, MI with ST elevation) were included in the present study. 21 (p female, 12 male) healthy cases without diabetes who referred consecutively to the internal medicine outpatient clinic and did not have any cardiovascular disease were included as the control group. The patient group was reevaluated five years later for cardiovascular morbidity and mortality. Inpatient and control groups, those diagnosed with Diabetes Mell, thus according to criteria of ADA and WHO, those with hepatic and renal dysfunction, pregnant ones and those who have malignity or other diseases were not included in the study.

Fasting plasma glucose, fasting plasma C-peptide concentration for the evaluation of pancreatic beta cell function, as well as proinsulin, serum lipid levels (total cholesterol, HDL-LDL–VLDL-cholesterol, triglyceride) and fibrinogen levels, were measured and the same procedures were carried out in the control group as well. In addition, for all study groups, demographic information (age, sex, family history), whether it is accompanied by hypertension (if so, its duration) were recorded. Blood samples were drawn from patients and control groups after overnight fasting. Plasma glucose and insülin levels were quantified. In proinsulin measurements, radioimmunoassay

method was used. For this method, Trasylol was added to whole blood and kept in ice and plasma was separated in cold centrifuge. C-peptide measurements were made with the competitive chemoluminescent immuno-metric method using Immunity device belonging to BioDPC. Serum creatinine was measured with the calorimetric method and, serum total cholesterol, trigliceride, and HDL-cholesterol levels were measured in autoanalyzer using the enzymatic calorimetric method. In fibrinogen measurement, Clauss method was employed. Although euglycemic hyperinsulinemic clap method is the gold standard in the measurement of insülin resistance, as it is method difficult to use in clinical and epidemiological studies, HOMA and QUICKI measurements were used (6). Quantitative insülin sensitivity control index(QUICKI), was calculated based upon the formula reported by Katz et al using fasting plasma glucose (FPG) and fasting immune reactive insülin measurements (FIRI) QUICKI =1/ log FIRI (mU/l) +log FPG (mg/dl). HOMA-IR is calculated as below based upon the formula reported by, Matthews et al.: HOMA-IR=AİRİ (mU/l) x APG (mg/dl)/405. $p<0.05$ was considered significant in all tests.

RESULTS:

No significant difference was present between patients diagnosed with ACS and those in the control groups in terms of sex. p=0.077. Mean age was found to be higher in patients diagnosed with ACS than those in control group. p=0.017. BUN values were higher in ACS patients than in control groups. p=0.033. In addition, uric acid levels were also higher in patients with ACSp=0.003, Significant difference was found also in triglyceride (p=0.002), HDL cholesterol (p=<0.001) and VLDL cholesterol (p=<0.001) levels Leukocyte level was found to be higher in patients with ACS. (p=0.001), Glucose level was found to be significantly higher in patients with ACS, 100.10±11.36 mg/dl (p=<0.001) while there was no significant difference in insulin levels. (p=0.863), There was no significant difference in proinsulin levels between control groups and ACS patients (respectively 9.83±5.21 and 7.52±2.58 (p=0072) Glucose/Insulin ratio was 10.16±3.86 in control group, while it was 27.82±20.87 (p=<0.001) in patients with ACS. There was no significant difference in Proinsulin/İnsulin ratio between ACS and control groups. p=0.068, HOMA-IR was 2.46±3.87 p=0.783 in ACS patients while QUICKI value was 0.38±0.06 p=0.079 in the same group, with no difference between groups. Table 1

After five years of follow up in ACS patients, a significant difference was found between patients with cardiovascular disease and those without it with respect to systolic blood pressure and proinsulin levels respectively p=0.013, p=0.031. No significant difference was found in other parameters. Of 38 patients with ACS, 4 patients (3 male, 1 female) could not be reached and evaluated. table 2

DISCUSSION:

Proinsulin and similar mıolecules exert weaker hypoglycemic effect than insulin and when they increase in the blood, they bind insulin receptors, reducing the effect of insulin and increasing insulin resistance. Whether they are obese or not, in subjects with NIDDM, baseline proinsulin levels and levels of its products i.e. Des 32,33 split proinsulin and Des 65,66 split proinsülin is considerably high(5) and it is accepted that hyperproinsulinemia develops in association with conversion impairment in the beta cell (7). In the study of Kahn et al, it has been reported that disproportionate hyperproinsulinemia is one of the most basic and earliest beta cell impairments occurring in NIDDM(8) .The real functional defects in the beta cell is the deficiency in the response of

insulin to glucose, which causes a relative increase of proinsulin (4). In the study of Pfutzner et al, it was demonstrated that proinsulin has a strong relation with insulin resistance (9). In parallel to insulin resistance, the risk of coronary heart disease increases. In a study conducted by Fujiwara et al, it was shown that IR increases the risk of CAD: (10). In another study by Masanobu Yanase et al, it was reported that in patients with normal glucose tolerance, fasting hyperinsulinemia and high IR increased the rate of new cardiovascular events in patients with complex CAD:(11). In the study of Takahashi et al, it was stated that hyperinsulinemia may be an independent marker of atherosclerotic lesions(12). The mechanisms whereby hyperinsulinemia and increased IR influence the physiopathology of ACS are not clear. However, many theories have been put forward on this issue. i.e. decrease in NO production, increase in inflammation, oxidative stress, increase in the proliferation of vascular smooth muscles, increase in the synthesis of endothelin, rise in the level of PAI-1 and activation of the renin-angiotensin system (2).It is thought that these all ultimately lead to endothelium dysfunction, contributing to the atherosclerotic process. Many vasodilator and vasoconstrictor substances are synthesized in endothelium cell for the maintenance of vascular tonus some recent studies, increasing evidence has been found that in the presence of IR(in the absence of diabetes and MS), endothelial dysfunction develops. In small studies, it has also been found that tyzaolidinedion class drugs, which enhance insulin sensitivity, improve endothelial functions (13). In another study, it was demonstrated insülin sensitizing treatments may play a potential role in relieving angina.(14)In the study of Alssema et al, the relation between proinsulin and mortality risk was found to be stronger than that between insülin and mortality.(15), This was observed in another prospective study (16) and in cross-sectional studies (17,18). In various studies, it has been established that PAI-1 levels rise in people with insulin resistance, impaired glucose tolerance and metabolic syndrome (19). Therefore, high triglyceride level, impaired glucose tolerance, hypertension, a metabolic syndrome defined by abdominal obesity and /or low HDL are confounding risk factors in the relation between proinsulin and CAD risk (20).Increased circulating intact proinsulin concentration, is associated with increased MetS severity and risk of cardiovascular (CV) mortality (21). A recent study that followed 9396 non-type 2 diabetic individuals for 6 years showed fasting intact proinsulin concentration to be a predictor of both the worsening of hyperglycemia and incidence of type 2 diabetes, with no difference in predictive capacity compared with intact proinsulin concentration level derived from a dynamic state (22). Moreover, several studies have also found increased fasting intact proinsulin concentration to be an independent predictor of all-cause and cardiovascular (CV) mortality(23,24).In the present study, no significant difference was found between patient with ACS and control subjects in terms of proinsulin levels. p=0,072, The reason why no difference was found may be that proinsulin levels were measured in ACS patients, who may have many other confounding risk factors. The facts that after five years follow up of patients with ACS, proinsulin levels were found to be significantly high in the groups who experienced acute cardiac events again suggests that proinsulin may be a cardiovascular risk factor in the long term.

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TABLES

Table 1: The comparison of the control group and ACS patients

Parameters	control (N:21)	ACS study group (N:38)	P
Sex (F/M)	9/12	8/30	0,077
Age	46,57±14,67	56,14±12,34	**0,017**
Systolic BP	122,62±20,10	126,30±21,86	0,565
Diastolic BP	79,29±10,76	78,70±8,69	0,842
BUN	11,71±2,47	21,90 ± 20,22	**0,033**
Creatinine	0,78±0,12	1,44±1,69	0,098
Ürik asit	4,17±1,52	5,78 ±1,59	**0,003**
GGT	16,67±9,42	76,63 ± 89,98	**0,018**
Albumin	4,57±0,28	4,41±0,31	0,103
Total cholesterol	180,38±33,73	196,76 ± 39,48	0,176
Trigliceride	81,81 ± 42,20	193,53± 122,08	**0,002**

HDL cholesterol	56,33±11,38	42,12±9,51	**<0,001**
LDL cholesterol	107,57±30,87	117,19±40,99	0,421
VLDL cholesterol	16,48±8,44	33,94±14,84	**<0,001**
Hematocrite	39,43±4,81	39,776±6,07	0,840
Hemoglobin	13,67±1,76	13,638±2,26	0,964
Leukocyte	7257±1759	10224,76±3093,18	0,001
Thrombocyte	237571±56996	258190,48±73778,47	0,317
Fibrinogen	321,37±75,20	439,00±204,59	0,078
Glucose	82,52±14,43	100,10±11,36	**<0,001**
İnsulin	10,29±7,08	9,67±15,23	0,863
Proinsulin	9,83±5,21	7,52±2,58	0,072
Glucose / Insulin	10,16±3,86	27,82±20,87	**<0,001**
Proinsulin/İnsulin	1,34±1,18	2,06±1,52	0,068
HOMA-IR	2,21±1,69	2,46±3,87	0,783
QUICKI	0,35±0,04	0,38±0,06	0,079

Table 2: Comparison of cases with acute cardiac events after five years follow up with those without acute cardiac events in ACS group

Parameters	**Without acute cardiac event (N:19)**	**With Acute cardiac event (N:15)**	**P**
Sex (F/M)	4/15	3/12	0,940
Age	54,47±14,09	60,25±11,89	0,335
Systolic BP	118,33±17,49	141,25±22,32	**0,013**
Diastolic BP	76,67±7,24	82,50±10,35	0,128
BUN	16,71±7,40	32,29±32,50	0,255
Creatinine	0,95±0,19	2,343±2,74	0,229
Total Cholesterol	192,00±23,79	208,20±66,69	0,622
Trigliceride	171,75±81,06	245,80±191,59	0,268
HDLCholesterol	42,50±10,79	41,20±6,30	0,807
LDLCholesterol	115,17±29,69	123,25±71,42	0,839
VLDL Cholesterol	34,33±16,10	32,75±12,15	0,861
Fibrinogen	425,90±205,63	504,50±263,75	0,643
Glucose	98,88±13,34	101,62±8,62	0,528
İnsulin	11,77±19,38	7,08±7,64	0,419
Proinsulin	8,39±3,17	6,45±0,83	**0,031**
Glucose / Insulin	24,97±21,31	31,33±20,59	0,425
Proinsulin/Insulin	2,09±1,70	2,02±1,34	0,907
HOMA-IR	2,92±4,85	1,89±2,19	0,482
QUICKI	0,37±0,05	0,39±0,06	0,433