

The Levels of Serum High Sensitivity C-reactive Protein in Subjects with Impaired Fasting Glucose

Erkan Çoban*

Ramazan Sarı**

*Akdeniz University Faculty of Medicine, Antalya, Turkey** *Department of Internal Medicine*** *Division of Endocrinology and Metabolism*

High-sensitivity C-reactive protein is a well-known risk factor for cardiovascular heart diseases. In this study we aimed to determine the levels of serum high-sensitivity C-reactive protein in patients with newly diagnosed type diabetes mellitus and impaired fasting glucose, and to obtain clinical results by comparing impaired fasting glucose group with type 2 diabetes mellitus and normal groups. Age, sex and body mass index matched 30 normal subjects, 30 patients with impaired fasting glucose, and 30 patients with diabetes were included in the study. We measured levels of serum high-sensitivity C-reactive protein in all groups. Subjects with impaired fasting glucose had significantly lower hs-CRP levels than patients with type 2 diabetes mellitus [0.2 (0.04-1.6), 0.48 (0.07-3.12) mg/dl, respectively, $p<0.05$]. Normal subjects had significantly lower hs-CRP levels than subjects with impaired fasting glucose ($p<0.05$). The levels of serum high-sensitivity C-reactive protein were correlated to fasting glucose in type 2 diabetes mellitus and impaired fasting glucose groups ($p<0.05$). Our data suggest that subjects with impaired fasting glucose pose a cardiovascular risk, although this was low patients with diabetes.

Key words: Impaired fasting glucose, high-sensitivity C-reactive protein, cardiovascular risk

Introduction

In 1997, the American Diabetes Association (ADA) proposed new criteria for defining diabetes based on fasting plasma glucose. A new diagnostic entity, impaired fasting glucose (IFG). In subjects with IFG, fasting plasma glucose concentrations range between 110 and 126 mg/dl. IFG is probably a frequent glycemic disorder in the general population and is considered as a prediabetic state (1). Cardiovascular risk associated with IFG has been examined various studies with conflicting results (2-9).

Coronary heart disease is the major cause of death in the developed world. Atherosclerosis, the underlying cause of most coronary heart disease (10).

Correspondence address:

Erkan Çoban
Akdeniz University Faculty of Medicine
Department of Internal
Antalya, Turkey
Tel : 0242 227 43 43
Fax : 0242 227 44 90
E-mail : ecoban@akdeniz.edu.tr

Inflammatory processes are now recognized to play a central role in the pathogenesis of atherosclerosis and its complications (11). C-reactive protein is one of the most sensitive markers of systemic inflammation. It is synthesized by the liver in response to cytokines (12). Numerous studies have found that baseline levels of C-reactive protein are associated with risk of future myocardial infarction, stroke, peripheral vascular disease and cardiovascular death amongst apparently healthy populations (11). The relative risk associated with C-reactive protein is independent of other cardiovascular disease risk factors. High-sensitivity assays are needed for the measurement of C-reactive protein concentration for the purpose of predicting the risk of future coronary events (13). Levels of high sensitive C-reactive protein (hs-CRP) have been shown to correlate with cardiovascular disease risk (14). Multiple prospective studies now demonstrate that hs-CRP is a potent predictor of future first or recurrent cardiovascular events (15-18). Two studies have demonstrated extension of this prognostic capacity from indivi-

duals with active ischemic heart disease to include those with risk factors but free of clinical atherosclerosis (19,20).

In this study, we aimed to determine the levels of serum hs-CRP in patients with type 2 diabetes mellitus and IFG, and to obtain clinical results by comparing IFG group with type 2 diabetes mellitus and normal groups.

Patients and Methods

Patients

We selected 30 normal subjects, 30 patients with IFG (fasting glucose 110 to 126 mg/dl), and 30 patients with newly diagnosed type 2 diabetes mellitus (fasting glucose \geq 126 mg/dl) matched for age, gender, and body mass index. Exclusion criteria for entry into the study were smoking habit, sustained hypertension, dyslipidemia, obesity [body mass index (BMI) \geq 30 kg / m²], renal failure (serum creatinine > 1.5 mg/dl, blood urea nitrogen > 30 mg/dl), heart failure, peripheral vascular disease, acute or chronic infection, cancer, and hepatic disease. We also excluded type 2 diabetic patients with acute illness and recent (<6 months) myocardial infarction, unstable angina, or stroke. Smokers and non-smokers were grouped as their current smoking status. The BMI was calculated as the weight (kg)/height squared (m)². All patients gave their informed consent to participate in the study.

Biochemical measurements

Blood samples were drawn after a fasting period of 12 h. Glucose, creatinine, alanine aminotransferase, total cholesterol, and triglycerides were determined

by standard methods. Hs-CRP was determined in serum by immunonephelometric principle using BN II Systems, Dade Behring, USA.

Statistical analysis

Statistical analysis was done by SPSS statistical software. The values were given as median (minimum and maximum). Statistical analysis was performed using Kruskal-Wallis, Mann-Whitney U, and Spearman's correlation tests. P<0.05 was accepted as statistically significant.

Results

The main characteristics of study population are reported in Table 1. Age, gender distribution and BMI did not differ among the groups by selection. Metabolic parameters were not different among the study groups as a result of the selection process (Table 1).

The serum levels of hs-CRP in patients with type 2 diabetes, IFG, and normal subjects were 0.48 (0.07-3.12), 0.29 (0.04-1.6), and 0.16 (0.01-0.84) mg/dl, respectively. Patients with IFG had significantly lower hs-CRP levels than type 2 diabetic patients (p<0.05). There were significantly higher hs-CRP levels in patients with IFG than in normal subjects (p<0.05). The levels of serum hs-CRP were related to fasting glucose in type 2 diabetes mellitus and IFG groups (p<0.05) (Table 1).

Discussion

IFG has been widely studied in the last years but its cardiovascular risk profile is not yet completely clear. Tominaga et al concluded that impaired

Table 1. Clinical and laboratory parameters in study groups.

Parameters	Type 2 diabetes mellitus	Impaired fasting glucose	Normal group
No	30	30	30
Sex (males/females)	16/14	15/15	15/15
Age (years)	47 (39-56)	48 (38-55)	47 (40-56)
BMI (kg/m ²)	23 (21.5-24)	23.5 (22-24.5)	23 (21.5-24)
Fasting glucose (mg/dl)¶	144 (132-168)** †	119 (112-124)*	88 (78-96)
Creatinine (mg/dl)	0.8 (0.6-1.0)	0.9 (0.5-1.0)	0.8 (0.6-0.9)
ALT (U/l)	29.1 (22-34)	30.0 (23-35)	28.6 (18-32)
Total-cholesterol (mg/dl)	187 (176-196)	186 (174-197)	188 (170-195)
Triglyceride (mg/dl)	152 (144-169)	154 (148-167)	150 (145-165)
hs-CRP (mg/dl)¶	0.48 (0.07-3.12) **†	0.29 (0.04-1.6)*	0.16 (0.01-0.84)

ALT: alanine aminotransferase; hs-CRP: high sensitivity C-reactive protein.

* p<0.05, ** p<0.01 vs normal group; † p<0.05 vs impaired fasting glucose;

¶ p<0.05, correlation between fasting glucose and hs-CRP, in type 2 diabetes mellitus and impaired fasting glucose groups.

glucose tolerance was a risk factor for cardiovascular disease but not IFG (8). Crook et al reported that serum total sialic acid, a strong cardiovascular risk factor with increased concentrations being associated with increased mortality, is not elevated in subjects with IFG. In contrast, the role of fasting glucose on cardiovascular mortality has been reported (7). Bjørnholt et al. described the excess risk of cardiovascular deaths in nondiabetic men in the upper normal range of fasting blood glucose (4). Balkau et al. found a linear relationship between death from cardiovascular disease and fasting blood glucose levels (2). Furthermore, in the Rancho Bernardo Study, an increase of fasting plasma glucose from 5 to 7 mmol/l was associated with a doubling of cardiovascular disease mortality in men and a tripling in women (3). Our data show that subjects with IFG have lower serum hs-CRP levels than type 2 diabetic patients suggesting that they are at lower cardiovascular risk. These results could contribute to explain the lower reported cardiovascular morbidity and mortality in subjects with IFG in comparison with patients with type 2 diabetes mellitus.

In our study, patients with clinically overt cardiovascular disease (such as coronary artery disease, cerebrovascular disease and renal failure) were excluded to clarify the specific levels of glucose-related abnormalities. Although the association of the metabolic syndrome with elevated hs-CRP is now well established, the relation of CRP to fasting glucose is controversial despite its theoretical importance. Aranson et al, and Mendall et al. found an association between CRP levels and fasting glucose, but in several other studies CRP levels were not associated with fasting glucose concentrations (21-25). In the Insulin Resistance Atherosclerosis Study, the correlation of CRP with fasting glucose was weak and not significant in multivariate analysis (26). In our study, the levels of serum hs-CRP were related to fasting glucose in type 2 diabetes mellitus and IFG groups.

Insulin resistance and hyperglycemia may be an expression of diffuse arterial dysfunction contributing to atherosclerosis, may lead directly to arterial damage through toxic effects of hyperinsulinemia, or may act indirectly through atherogenic effects of the constellation of risk factors. One potential factor in this process may be variation in

serum levels of hs-CRP. Furthermore, there may be relationship between insulin resistance and chronic inflammation. It is possible that chronic inflammation may represent a triggering factor in the origin of insulin resistance syndrome, type 2 diabetes, and impaired fasting glucose (27). On the other hand, decreased insulin sensitivity may lead to enhanced CRP expression by counteracting the physiological effect of insulin on hepatic acute phase protein synthesis (28). Resistance to this effect would then lead to increased synthesis of acute phase proteins, such as CRP.

Finally, our data show that patients with IFG, without other cardiovascular risk factors have lower serum hs-CRP levels than type 2 diabetic patients suggesting that they are at lower cardiovascular risk. This findings suggest potential benefits of anti-inflammatory or insulin-sensitizing treatment strategies in these subjects. Prospective studies are clearly needed to address these issues.

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