Research Article

Cihan Coşkun*, Alper Gümüş, Hümeysra Öztürk Emre, Birol Özkan, Selçuk Pala and Macit Koldas

Concentrations of circulating adiponectin and adipocyte-fatty acid binding protein in patients with three-vessel coronary artery disease: a comparison with coronary lesion complexity as characterized by syntax score

doi:10.3515/tjb-2016-0140
Received September 3, 2016; accepted December 6, 2016; previously published online March 16, 2017

Abstract

Objective: In this study, we investigated the correlation between coronary lesion complexity as characterized by syntax score (SS) with circulating adiponectin and adipocyte-fatty acid binding protein (A-FABP4) concentrations in the presence of stable coronary artery disease affecting three coronary vessels (three-vessel stable CAD).

Methods: The study groups consisted of 41 control subjects (28 males and 13 females, non-CAD group) and 115 affected subjects (79 males and 36 females, three-vessel stable CAD group). We divided into tertiles the three-vessel stable CAD group according to SS and estimated circulating concentrations of adiponectin and A-FABP4.

Results: We did not find any correlation between the coronary lesion complexity with either the adiponectin and/or A-FABP4. We found lower the A-FABP4 of the non-CAD group than those of the groups with three-vessel stable CAD (p<0.001). Adiponectin were lower in DM subjects (p<0.05 for each group); though A-FABP4 were found to be higher (p<0.05 for each group) according to non-DM subjects in intra-group comparisons.

Conclusion: Adiponectin is not a suitable parameter for demonstrating the existence of CAD or predicting coronary lesion complexity. A-FABP4 is more useful for the proof of the presence of CAD but A-FABP4 are not correlated with the severity of CAD.

Keywords: Coronary artery disease; Syntax score; Adiponectin; Adipocyte-fatty acid binding protein; Diabetes mellitus.

*Corresponding author: Cihan Coşkun, Department of Biochemistry Laboratory, Haseki Training and Research Hospital, Istanbul 34096, Turkey, e-mail: kuzeycihan2012@gmail.com

Alper Gümüş: Department of Biochemistry Laboratory, Haseki Training and Research Hospital, Istanbul, Turkey; and Department of Cardiology, Kartal Kosuyolu High Specialty Education and Research Hospital, Istanbul, Turkey

Hümeysra Öztürk Emre and Macit Koldas: Department of Biochemistry Laboratory, Haseki Training and Research Hospital, Istanbul, Turkey

Birol Özkan and Selçuk Pala: Department of Cardiology, Kartal Kosuyolu High Specialty Education and Research Hospital, Istanbul, Turkey

Özet

Amaç: Bu çalışmada, syntax skoru (SS) ile karakterize edilen koroner lezyon kompleksitesi ile sirkülasyondaki adiponectin ve adiposit yağ asidi bağlayıcı protein (A-FABP4) konsantrasyonları arasındaki ilişkiyi üç koroner damar tutulumu stabil koroner arter hastalığı (üç damar stabil KAH) varlığında araştırdık.
**Introduction**

Coronary artery disease (CAD) is a progressive inflammatory disease, with atherosclerosis playing a role in its etiology. Cardiovascular diseases (CVDs), including CAD, are the most prevalent diseases worldwide and the leading causes of mortality in developing countries and in Turkey [1]. The prevalence of CAD is reported to be between 4.4% and 10% in Turkey [2]. Accumulating evidence supports a critical role for inflammation in the pathogenesis of CAD and other manifestations of atherosclerosis [3]. Systemic blood markers of inflammation such as white blood cell count and C-reactive protein have emerged as conventional and powerful predictors of coronary events [4]. The search for more convenient and specific parameters related to CAD continues, and recently, increasing interest has been developing in the role of adipokines in the triggering of this systemic inflammatory response.

Adipose tissue has been traditionally considered a fat-storage organ, but it is now known that adipose tissue is a complex and highly active metabolic and endocrine organ [5]. It expresses and secretes a variety of metabolites, hormones, and cytokines, including adipokines. These adipokines can target distant organs and have major effects on body weight, energy storage, insulin sensitivity, glucose regulation, and the inflammatory response. Evidence also supports the notion that the adipose tissue of different body compartments has different adipokine secretion profiles [6]. Among the fat storage compartments in the body, visceral fat has been found to be an important source of proinflammatory adipokines [7]. In recent years, there has been a growing interest in the potential role of adipokines in contributing to the inflammatory processes involved in the development of CAD [8].

Two recently identified adipocytokines, adiponectin and adipocyte fatty acid binding protein (A-FABP, also known as aP2 or FABP4), appear to be important in regulating metabolic and inflammatory responses [9]. Adiponectin circulates in plasma as three forms: a trimer (low–molecular weight (LMW)), a hexamer (trimer-dimer) of medium–molecular weight (MMW), and a larger multimeric high–molecular weight (HMW) form [10–13]. Although the findings are controversial, in some studies, HMW has been reported to be a biologically active form [10–14].

A-FABP4 is a cytoplasmic protein that binds with saturated and unsaturated fatty acids to control the distribution of fatty acids in various inflammatory response and metabolic pathways [15]. It is one of the most abundant proteins in adipocytes and macrophages [16, 17]. Recent studies showed that A-FABP4 plays an essential regulatory role in energy metabolism and inflammation [18].

Clinical studies indicate that serum and plasma concentrations of adiponectin are lower and those of A-FABP4 are higher in individuals with CAD [19, 20]. The relationships between these parameters and the severity of CAD have been investigated previously. Different scoring systems have been used to measure the degree of severity of CAD [20, 21]. Syntax score (SS) is currently a widely used scoring system. In the literature, we observed that there are insufficient numbers of studies examining the relationship between adiponectin and A-FABP4 concentrations with SS [22]. The purpose of this study was primarily to evaluate the correlation, if any, between the SS, which represents the coronary lesion complexity in three-vessel stable CAD groups, with adiponectin and A-FABP4 concentrations. SS is used to estimate the extent and severity of CAD through an assessment of the number of angiographically detected coronary lesions, their functional effects, locations, and complexity. The following variables are taken into consideration for SS estimates: coronary dominance; location at bifurcation, trifurcation, or ostial lesions; tortuosity; calcifications; the content of the thrombus; presence of diffuse disease; and elongated lesions [22]. Patients with three-vessel stable CAD can be divided into tertiles: a low score, defined as ≤ 22 (low SS group); an intermediate score,
defined as 23–32 (intermediate SS group); and a high score, comprising individuals with scores ≥33 (high SS group).

The association of diabetes mellitus (DM) with CAD is a well-known phenomenon. Moreover, it has been reported that there is a relationship between insulin sensitivity and adipokine concentrations [19]. Consequently, we aimed to evaluate serum adiponectin and A-FABP4 concentrations in CAD patients and its interaction with the presence of DM. Furthermore, we investigated whether there were correlations between adiponectin, and/or A-FABP4 concentrations and SS values, along with gender, age, body mass index (BMI), current smoking, blood pressure, triglyceride (TG), total cholesterol (TC), low density lipoprotein-cholesterol (LDL-C), high density lipoprotein-cholesterol (HDL-C), fasting blood glucose (glucose), creatinine (Cr) and high sensitive C-reactive protein (hsCRP).

Materials and methods

Systematic search strategy

In our cross-sectional study, the 3-sCAD group consisted of 115 subjects (79 males, 36 females) who were evaluated at the Department of Cardiology, Koşuyolu Hospital, as meeting the following definition of symptoms: no episodes of angina at rest but angiographically demonstrated organic stenosis of >50% in three of the main coronary arteries. The non-CAD group consisted of a total of 41 subjects (28 males, 13 females), none of whom had any cardiac disorder or the coronary disease. The study was approved by the Ethics Committee of Haseki Hospital. We carried out all procedures according to institutional ethical standards and obtained written consent of the volunteers.

Excluding criteria

None of the cases of this study had acute coronary disease or acute myocardial infarction (MI). In addition, we excluded patients who had (underwent) percutaneous coronary intervention (PCI)/coronary artery by-pass grafting (CABG) or had evidence of hemodynamically significant valvular heart disease, surgery, or trauma within the previous month, known cardiomyopathy, known cancer, advanced liver and/or kidney diseases, infection and inflammatory diseases.

Syntax score analysis

The SS was calculated using dedicated software (SYNTAX Score Calculator Version 2.11; Cardialysis Clinical Trial Management-Core Laboratories Company, Rotterdam, The Netherlands) that integrates the following characteristics: first, the number of lesions, with their specific weighting factors based on the amount of myocardium distal to the lesion according to the score of Leaman et al. [23], and second, the morphologic features of each single lesion, as previously reported [24]. All angiographic variables pertinent to the SS calculation were computed by two experienced cardiologists who were blinded to the baseline clinical characteristics, procedural data, clinical outcomes, and previously calculated SS. From the diagnostic angiogram, each coronary lesion producing ≥50% diameter stenosis in vessels ≥1.5 mm is scored separately and added together to provide the overall SS. The scores of the three-vessel stable CAD group were then divided into tertiles, as follows: a low score defined as ≤22 (low SS group), an intermediate score as 23–32 (intermediate SS group) and a high score as ≥33 (high SS group) [25].

Patient characteristics and angiographic findings of all groups

Information regarding the genders, ages, smoking habits of the patients, as well as the medicines they use, was collected through standardized face-to-face interviews performed by a single physician. Smoking status was classified as positive if the patient was currently a smoker. Anthropometrical measurements, including height and body weight, were performed according to standardized procedures, and the BMI was calculated as weight divided by height squared (kg/m²). The presence of DM in all groups was determined as defined by the World Health Organization study group. After the blood pressure of all subjects was measured with an automatic sphygmomanometer (using a cuff size fitted to the upper arm perimeter), right arm blood pressure was measured twice, and the average value was calculated for the analysis. Measurements were performed after a minimum of 5-min rest. Medical history was collected through a standardized questionnaire [26]. Selective coronary angiography of patients was performed by two experienced cardiologists using the standard Judkins technique via the right femoral approach, and the angiographically determined coronary artery lesions were identified.
Blood sampling and measurement of analytes

For the patients’ serum adiponectin, A-FABP4 and other routine biochemical measurements, serum and plasma samples were drawn vacutainers containing gel separator and K2EDTA (Becton, Dickinson and Company, NJ, USA), respectively after a period of 12 h of fasting. Within 30 min after being obtained, the samples were centrifuged (1000 × g, 10 min). The eluted sera and plasmas were aliquoted into portions and preserved until the day of analysis under the laboratory conditions at −70°C. All the biochemical examinations except hsCRP were performed spectrophotometrically method in an AU2700 biochemical auto-analyzer (Beckman Coulter, Inc., USA), while hsCRP was analyzed by the immunoturbidimetric method in same auto-analyzer; HbA1c analysis was performed using the ARKRAY ADAM A1c HA-8180V Automatic Glyc hemoglobin Analyzer (ARKRAY Co. Ltd., Inc. Japan), which exploits the principles of ion exchange high performance liquid chromatography for its analyses. Adiponectin and A-FABP4 were analyzed using an ELX-50 micro-plate washer and an ELX-800 ELISA absorbance micro-plate reader (BioTek U.S, Winooski, VT, USA), according to the enzyme linked immune sorbent analysis (ELISA) methodology. The analytic sensitivity, intra-assay CV, and inter-assay CV for adiponectin were 0.026 μg/mL, 4.9%, and 6.5%, respectively. The analytic sensitivity, intra-assay CV, and inter-assay CV for A-FABP4 were 0.05 ng/mL, 2.5%, and 3.9%, respectively.

Statistical analysis

The findings from our study were evaluated using the SPSS (Statistical Package for Social Sciences) 21 package program (IBM, New York, NY, USA). The mean; standard deviation (SD); and median, minimum (min) and maximum (max) values were calculated as descriptive statistics. The quantitative data were independent and conformed to normal distribution characteristics, as verified by the Kolmogorov Test, and the groups were homogenous according to the Levene Test. Thus, one-way ANOVA was applied to investigate the differences between the groups in terms of the measured parameters, with a 95% confidence interval. The probability value cut-off for significance (p) was set at < 0.05. The Tukey HSD and Student-t tests were applied for one-to-one group comparisons with a 95% confidence interval, and the p-value for significance was set at 0.017 for the three groups using the Bonferroni correction. The Pearson correlation analysis was applied to evaluate the relationship between the parameters. The power of this study was calculated using the PASS 12 package program (NCSS, UT, USA).

Results

Descriptive analysis

First, the power of this study, which contains four groups, was calculated to be 1. The type I error was set at 80%, and the type II error (p) was set at 0.05. The information for each group and the descriptive statistics of the measured parameters are given in Table 1. In both groups, sex and age had no significant effect on measured parameters (p = 0.144 and p = 0.985, respectively). Moreover, among all groups, there were no differences that could be attributed to BMI (p = 0.782), current smoking (p = 0.976), hypertension (p = 0.848), DM (p = 0.951) or drug use. When we evaluated all groups as to serum concentrations of adiponectin and A-FABP4, we did not find any significant difference among groups for adiponectin (p > 0.05) (Figure 1A). On the other hand, it was found that the non-CAD group had statistically higher concentrations of A-FABP4 level compared to the CAD groups (p < 0.001) (Figure 1B).

In terms of the presence of DM, while adiponectin concentrations in all groups were lower in DM subjects when compared to N-DM subjects (p < 0.05 for each group) (Figure 2A); A-FABP4 levels were found to be higher (p < 0.05 for each group) (Figure 2B). While there was no significant difference between the adiponectin concentrations of the non-CAD group with DM compared to the three-vessel stable CAD group with DM (p = 0.622), a difference was found between the A-FABP4 concentrations of the non-CAD group with DM and all of the three-vessel stable CAD groups (p < 0.001).

Group comparison

For all groups, within each group, the adiponectin (p < 0.001 for each group) and A-FABP4 (p < 0.001 for each group) concentrations of male patients were observed to be lower compared to the levels of the women. While there were no differences among the all groups regarding serum TC, LDL-C, HDL-C, glucose, HbA1c, and Cr concentrations (p < 0.001 for each of them), the serum TG concentrations of the non-CAD and low SS groups were found to be lower (p = 0.001) according to the other groups. Another
observation was that the hsCRP concentration of the non-CAD group was lower than those levels of the three-vessel stable CAD groups \((p < 0.001)\). The results for adiponectin, A-FABP4 and other biochemical parameters of all of the patient groups and their statistical assessments are given in Table 2.

The intra-group and inter-group adiponectin and A-FABP4 concentrations of all the groups, including comparisons made according to presence or absence of DM, are presented in Table 3.

**Correlation of evaluated parameters**

No correlation could be found either between the SSs and the adiponectin concentrations of the three-vessel stable CAD groups \([\text{low SS} (r = -0.004, p = 0.982), \text{intermediate SS} (r = 0.127, p = 0.449), \text{high SS} (r = -0.211, p = 0.210)]\), nor between the SSs and A-FABP4 concentrations \([\text{low SS} (r = -0.234, p = 0.146), \text{intermediate SS} (r = 0.209, p = 0.208), \text{high SS} (r = 0.184, p = 0.278)]\). In addition, when the correlation between the intra-group adiponectin and A-FABP4 concentrations was evaluated for each group, only a negative correlation between \((r = -0.846; p < 0.001)\) was observed between the adiponectin and A-FABP4 concentrations in the non-CAD group with DM. But no correlation was between the SSs and the other parameters including serum TC, LDL-C, HDL-C, glucose, HbA1c, Cr and BMI. Adiponectin was negatively correlated with TGs \((r = -0.411; p < 0.001)\) and BMI \((r = -0.329; p < 0.001)\). A-FABP4 concentrations were also positively correlated with BMI \((r = 0.214; p = 0.018)\).
Discussion

We investigated the relationship between adiponectin and A-FABP4 concentrations and the severity of CAD. To that end, the three-vessel stable CAD group was divided into tertiles: a low score defined as ≤22 (low SS group), an intermediate score as 23–32 (intermediate SS group) and a high score as ≥33 (high SS group). The SS is an angiographic scoring system based on coronary anatomy and lesion characteristics, such as presence of total occlusion, bifurcation or trifurcation, angle and involvement of branch vessels, calcification, lesion length, ostial location, tortuosity and presence of thrombus. The SS not only quantifies lesion complexity but also predicts early and late outcomes after PCI in patients with multi-vessel disease [22]. In previous studies, the SS generally was used to predict early and late development of major
All values are expressed as the mean ± standard deviation. p < 0.05 is set as the significance level.

Table 2: Comparisons of the biochemical parameters of all groups, with significance assessed by p-value.

| Variables             | Non-CAD     | Low SS      | Intermediate SS | High SS     | p-Value    |
|-----------------------|-------------|-------------|-----------------|-------------|------------|
| Triglyceride (mmol/L) | 1.54 ± 0.59 | 1.45 ± 0.52 | 1.78 ± 0.43     | 1.85 ± 0.39 | 0.001      |
| Total cholesterol (mmol/L) | 4.86 ± 1.17 | 5.01 ± 1.12 | 5.10 ± 0.58     | 5.00 ± 0.72 | 0.741      |
| LDL-C (mmol/L)        | 2.98 ± 1.02 | 3.12 ± 1.16 | 3.23 ± 0.53     | 3.21 ± 0.60 | 0.555      |
| HDL-C (mmol/L)        | 1.07 ± 0.21 | 1.09 ± 0.27 | 1.08 ± 0.22     | 1.10 ± 0.24 | 0.932      |
| Glucose (mmol/L)      | 5.60 ± 1.12 | 5.71 ± 0.87 | 5.63 ± 0.56     | 5.76 ± 0.82 | 0.850      |
| HbA1c (mmol/molHb)    | 45.4 ± 6.6  | 45.5 ± 8.2  | 44.3 ± 5.5      | 45.5 ± 8.3  | 0.745      |
| Creatinine (μmol/L)   | 74.26 ± 18.56 | 78.68 ± 14.14 | 78.68 ± 12.38 | 76.91 ± 10.61 | 0.607     |
| hsCRP (nmol/L)        | 12.67 ± 3.81 | 16.86 ± 3.52 | 16.48 ± 4.38    | 17.24 ± 5.24 | <0.001     |
| Adiponectin (mg/L)    | 8.02 ± 2.27 | 7.87 ± 2.16 | 7.69 ± 2.13     | 7.82 ± 2.58 | 0.941      |
| A-FABP4 (μg/L)        | 19.2 ± 1.8  | 27.0 ± 1.8  | 26.3 ± 1.3      | 27.7 ± 1.7  | <0.001     |

A-FABP4, Adipocyte-fatty acid binding protein 4; CAD, coronary artery disease; HDL-C, high density lipoprotein cholesterol; hsCRP, high sensitive C-reactive protein; LDL-C, low density lipoprotein cholesterol; Non-CAD, there is no CAD; SS, syntax score; (Low SS, syntax score ≤ 22; Intermediate SS, syntax score = 23–32; High SS, syntax score ≥ 33); All values are expressed as the mean ± standard deviation, p-value threshold is set at < 0.17.

Table 3: Comparisons of inter-group and intra-group adiponectin and A-FABP4 concentrations according to status for diabetes mellitus, with significance assessed by p-value.

| Variables             | Non-CAD     | Low SS      | Intermediate SS | High SS | p-Value (inter-group) |
|-----------------------|-------------|-------------|-----------------|---------|------------------------|
| Adiponectin (mg/L) (SD) |            |             |                 |         |                        |
| N-DM                  | 8.69 ± 2.16 | 8.44 ± 1.98 | 8.56 ± 1.86     | 8.81 ± 2.34 | –                      |
| DM                    | 6.16 ± 1.36 | 6.37 ± 1.95 | 5.58 ± 0.95     | 5.77 ± 1.75 | –                      |
| p-Value (intra-group) | 0.001       | 0.005       | <0.001          | <0.001  |                        |
| A-FABP4 (μg/L) (SD)   |             |             |                 |         |                        |
| N-DM                  | 18.9 ± 1.9  | 26.4 ± 1.6  | 26.0 ± 1.4      | 27.2 ± 1.9 | –                      |
| DM                    | 20.3 ± 1.3  | 28.6 ± 1.4  | 27.1 ± 0.6      | 28.7 ± 0.7 | –                      |
| p-Value (intra-group) | 0.027       | <0.001      | 0.021           | 0.015   |                        |
| Adiponectin in patient with DM | 6.16 ± 1.36 | 6.37 ± 1.95 | 5.58 ± 0.95     | 5.77 ± 1.75 | 0.622       |
| A-FABP4 in patient with DM | 20.3 ± 1.3  | 28.6 ± 1.4  | 27.1 ± 0.6      | 28.7 ± 0.7 | <0.001     |

All values are expressed as the mean ± standard deviation. p < 0.05 is set as the significance level.

Adverse cardiac event(s) (MACE; defined ‘as a composite of death, MI or any repeat revascularization’ in patients undergoing either PCI or CABG for multivessel involvement) [27]. At the end of our study, a correlation between the patient groups’ SSs with adiponectin and A-FABP4 concentrations could not be found. Our results are like those of some of the studies that have been conducted previously, in which no association was observed between adiponectin concentrations and coronary heart disease (CHD) events. However, our results differ from those of other previous studies that reported that high adiponectin concentrations in the circulation may be associated with an increased risk of CHD recurrence and all-cause/CVD mortality [19] and that CAD patients might have a lower concentration of adiponectin [28].

Our data have once again demonstrated that A-FABP4 concentrations of the groups with CAD are significantly different from the A-FABP4 concentrations of a control group [29] but the situation is different for adiponectin. Adiponectin concentrations of the groups with CAD are not significantly different from the control group. In some experimental studies, it was demonstrated that adiponectin displays insulin-sensitizing, anti-inflammatory, anti-thrombotic, anti-atherogenic and cardioprotective
properties. The concentration of adiponectin is decreased in patients with DM and CAD. On the other hand, other CAD-related studies are inconsistent with the aforementioned observations, and some previous meta-analysis studies failed to demonstrate this effect [26]. In fact, some studies reported, surprisingly, that high adiponectin concentrations are associated with increased risk of recurrent cardiovascular events [30] and mortality in patients with myocardial infarction [31] and heart failure [32]. Therefore, it may be difficult to use adiponectin for individual patients to predict risk of cardiovascular disease or mortality.

In terms of the effect of DM, adiponectin concentrations of DM subjects in all groups were found to be lower than those of the N-DM subjects. According to the inter-group comparisons made, there was no difference detected between the non-CAD group with DM and any of the three-vessel stable CAD groups with DM. This result suggests that low adiponectin concentrations could be caused by the presence of DM, not of CAD. Similarly, in most of the studies conducted in the past, lower adiponectin concentrations were found in DM patients [33]. For all of the groups, when the intra-group A-FABP4 concentrations were compared according to the presence or absence of DM, A-FABP4 concentrations of the DM subjects were found to be higher than those of the N-DM patients. In the inter-group comparison, it was seen that the A-FABP4 concentrations of all of the three-vessel stable CAD groups with DM were higher than those of the non-CAD group with DM. According to this result, it was concluded that the increase in A-FABP4 concentration was influenced not only by DM, but was also affected simultaneously by CAD. In a previous study, it was found that concentration of A-FABP4 was higher in multi-vessel CAD patients than those of non-CAD and/or one vessel CAD as well as DM patients which have higher concentration of A-FABP4 than non-DM patients [34, 35]. Moreover, it was determined a negative correlation between the adiponectin and A-FABP4 concentrations in the non-CAD group with DM in accordance with our study results revealing that the adiponectin levels of the DM subjects are lower while A-FABP4 concentrations of the DM subjects are higher than those of the N-DM patients in the non-CAD group.

In our study, we did not detect an association between adiponectin or A-FABP4 concentrations and the coronary lesion complexity of the three-vessel stable CAD groups. However, unlike adiponectin, the mean A-FABP4 concentrations of all patient groups were higher than the control group’s mean A-FABP4 concentration. In other studies, A-FABP4 concentrations were reported to be higher in multi-vessel CAD patients and closely related to the development of atherosclerosis in humans. Adiponectin and A-FABP4 concentrations of the male subjects were found to be lower than those of the female subjects. Similar results had also been obtained in earlier studies [11, 33]. HsCRP has been reported to be an acute phase reactant and inflammation marker associated with cardiovascular (CV) risk [36]. In this study, the level of hsCRP showed a negative correlation with the adiponectin concentration and a positive correlation with the A-FABP4 in all study groups. This result supports the roles of adiponectin and A-FABP4 in inflammation and is consistent with results obtained in other studies [1, 37]. Associations were found between BMI and A-FABP4 concentrations (positive correlation) and with adiponectin concentrations (negative correlation). In addition, there was negative correlation between adiponectin and TGs in the three-vessel stable CAD groups, consistent with the results of previous studies [38–40]. Moreover, hsCRP, BMI, glucose and LDL-C were determined to be independent risk factors in terms of coronary lesion complexity.

In some of the studies, it was reported that the adiponectin concentration is particularly affected by gender, age, BMI, glucose, TC, LDL-C, DM and use of drugs such as statins, whereas A-FABP4 concentration is affected by gender, age, obesity, high blood pressure, DM and use of drugs such as aspirin, statins and antihypertensives. The characteristics—including age, gender, BMI, fasting blood glucose, TC, LDL-C, use of drugs, presence of DM and HT of the patients involved in this study, were similar among all groups.

We think that the contradictory results among the studies conducted on adiponectin concentrations in multi-vessel CAD may originate from the adiponectin having different molecular structures and/or from the uncertainties related to the active form of adiponectin in the circulation. As a matter of fact, previous studies reported that HMW adiponectin may be the active form of this protein. On the other hand, a different study proposed that HMW adiponectin represented a precursor pool that can be activated, with the cleaved form, i.e. LMW adiponectin, being responsible for the effect on AMP kinase activity. In summary, biological activities among these isoforms are controversial. Moreover, in one study, patients with ACS were reported to have significantly lower plasma levels of adiponectin than those with stable CAD. According to this result, the absence of ACS patients in our group could also be another factor.

In contrast to the adiponectin results, all the studies, including ours, have demonstrated similar results with respect to A-FABP4 concentrations. We think that the
agreement among these studies may reflect the fact that A-FABP4's structure is more homogenous than adiponectin's structure.

Thus, we concluded that there was no correlation between the coronary lesion complexities in three-vessel stable CAD subjects with adiponectin and A-FABP4 concentrations. In addition, we also determined that the adiponectin concentrations correlate with DM, but not with three-vessel stable CAD. However, we found that A-FABP4 concentrations were in correlation with both DM and three-vessel stable CAD and were much higher in the patients having both diseases together, that is, both three-vessel stable CAD and DM. The correlation between adiponectin and A-FABP4 with hsCRP shows that these two analytes are related with inflammation.

To set forth the limitations of our study, we can primarily say that it was neither a study containing large patient groups nor carried out as a multi-center study. Additionally, we think that a prospectively designed study should include ACS subjects in addition to the stable CAD subjects; in such a study, the correlation between the SS, adiponectin and A-FABP4 and the predictive values in terms of MACE could be examined. Finally, it is especially important that future adiponectin-related studies are designed in a way that allows one to evaluate the effects of the various molecular forms of adiponectin.

In conclusion, for the three-vessel stable CAD subjects, no correlation could be found between the coronary lesion complexity and the adiponectin and A-FABP4 concentrations. In addition, adiponectin was only correlated with DM, not with stable CAD. Also, A-FABP4 was concluded to be correlated with both DM and stable CAD and to be at a higher concentration in three-vessel stable CAD subjects with DM. More studies should be performed to accumulate additional data on this subject.

Acknowledgments: As the authors of this study, we are grateful to the staff in the Department of Biochemistry of Haseki Hospital and in the Department of Cardiology of Kosuyolu Hospital.

Conflict of interest statement: The authors declare that there are no conflicts of interest regarding the publication of this paper.

References

1. Dursunoglu D, Goksoy H, Ozturk MS, Rota S. Relationship between CRP, adiponectin and gensini score in the patients with coronary artery disease. Anatol J Cardiol 2011;11:195–220.
2. Sahan C, Sozmen K, Doganay S, Unal B. The assessment of changes in cardiovascular diseases trend in Turkey. Turk J Public Health 2015;13:62–80.
3. Golia E, Limongelli G, Natale F. Adipose tissue and vascular inflammation in coronary artery disease. World J Cardiol 2014;6:539–54.
4. Madjid M, Fatemi O. Components of the complete blood count as risk predictors for coronary heart disease. Tex Heart J 2013;40:17–29.
5. Kershaw EE, Flier JS. Adipose tissue as an endocrine organ. J Clin Endocrinol Metab 2004;89:2548–56.
6. Ouchi N, Parker JL, Lugus JJ, Walsh K. Adipokines in inflammation and metabolic disease. Nat Rev Immunol 2011;11:85–97.
7. Tilg H, Moschen AR. Adipokytokines: mediators linking adipose tissue, inflammation and immunity. Nat Rev Immunol 2006;6:772–83.
8. Rajala MW, Scherer PE. Minireview. The adipocyte – at the crossroads of energy homeostasis, inflammation, and atherosclerosis. Endocrinology 2003;144:3765–73.
9. Ahima RS, Flier JS. Adipose tissue as an endocrine organ. Trends Endocrin Met 2000;11:327–32.
10. Jin J, Peng DQ, Yuan SG, Zhao SP, Ning XH, Wang SH, et al. Serum adiponectin fatty acid binding proteins and adiponectin in patients with coronary artery disease: the significance of A-FABP/adiponectin ratio. Chin Clin Acta 2010;411:1761–5.
11. Aso Y, Yamamoto R, Wakabayashi S, Uchida T, Takayanagi K, Takebayashi K, et al. Comparison of serum high-molecular weight (HMW) adiponectin with total adiponectin concentrations in type 2 diabetic patients with coronary artery disease using a novel enzyme-linked immunosorbent assay to detect HMW adiponectin. Diabetes 2006;55:1954–60.
12. Pajvani UB, Du X, Combs TP, Berg AH, Rajala MW, Schulthess T, et al. Structure-function studies of the adipocyte-secreted hormone Acrp30/adiponectin: implications for metabolic regulation and bioactivity. J Biol Chem 2003;278:9073–85.
13. Tsao TS, Tomas E, Murrey HE, Hug C, Lee DH, Ruderman NB, et al. Role of disulfide bonds in Acrp30/adiponectin structure and signaling specificity: different oligomers activate different signal transduction pathways. J Biol Chem 2003;278:810–7.
14. Waki H, Yamauchi T, Kamon J, Ito Y, Uchida S, Kita S, et al. Impaired multimerization of human adiponectin mutants associated with diabetes: molecular structure and multimer formation of adiponectin. J Biol Chem 2003;278:40352–63.
15. Yoo HJ, Choi KM. Adipokines as a novel link between obesity and atherosclerosis. World J Diabetes 2014;5:357–63.
16. Miyoshi T, Onoue G, Hirohata A, Hirohata S, Usui S, Hina K, et al. Serum adipocyte fatty acid-binding protein is independently associated with coronary atherosclerotic burden measured by intravascular ultrasound. Atherosclerosis 2010;211:164–9.
17. Maeda K, Cao H, Kono K, Gorgun CZ, Furuhashi M, Uysal KT, et al. Adipocyte/macrophage fatty acid binding proteins control integrated metabolic responses in obesity and diabetes. Cell Metab 2005;1:107–19.
18. Boord JB, Fazio S, Linton MF. Cytoplasmic fatty acid-binding proteins: emerging roles in metabolism and atherosclerosis. Curr Opin Lipidol 2002;13:141–7.
19. Fisman EZ, Tenenbaum A. Adiponectin: a manifold therapeutic target for metabolic syndrome, diabetes, and coronary disease? Cardiovasc Diabetol 2014;13:103.
20. Huang CL, Wu YW, Wu CC, Lin L, Wu YC, Hsu PY, et al. Association between serum adipocyte fatty-acid binding protein concentrations, left ventricular function and myocardial perfusion abnormalities in patients with coronary artery disease. Cardiovasc Diabetol 2013;12:105.

21. Kajiya M, Miyoshi T, Doi M, Usui S, Iwamoto M, Takeda K, et al. Serum adipocyte fatty-acid-binding protein is independently associated with complex coronary lesions in patients with stable coronary artery disease. Heart Vessels 2013;28:696–703.

22. Sianos G, Morel MA, Kappetein AP, Morice MC, Colombo A, Dawkins K, et al. The syntax score: an angiographic tool grading the complexity of coronary artery disease. EuroIntervention 2005;1:219–27.

23. Leaman DM, Brower RW, Meester GT, Serruys P, Van Den BM. Coronary artery atherosclerosis: severity of the disease, severity of angina pectoris and compromised left ventricular function. Circulation 1981;63:285–99.

24. Pijls NH, Van Schaardenburgh P, Manoharan G, Boersma E, Bech JW, van’t Veer M, et al. Percutaneous coronary intervention of functionally nonsignificant stenosis: 5 year follow-up of the DEFER study. J Am Coll Cardiol 2007;49:2105–11.

25. Poulin F, Rinfret S, Gobeil F. Potential shift from coronary bypass surgery to percutaneous coronary intervention for multivessel disease and its economic impact in the drug-eluting stent era. Can J Cardiol 2007;23:1139–45.

26. Hascoet S, Elbaz M, Bongard V, Bouisset F, Verdier C, Vindis C, et al. Adiponectin and long-term mortality in coronary artery disease patients and controls. Arterioscler Throm Vasc Biol 2013;33:19–29.

27. Nam CW, Fearon W. Role of the functional syntax score in evaluating multivessel coronary artery disease. Interv Cardiol 2011;3:695–704.

28. Ferrarezi DA, Cheurfa N, Reis AF, Fumeron F, Velho G. Adiponectin gene and cardiovascular risk in type 2 diabetic patients: a review of evidences. Arq Bras Endocrinol 2007;52:153–9.

29. Sook LE, Park SS, Kim E, Sook YY, Ahn HY, Park CY, et al. Association between adiponectin levels and coronary heart disease and mortality: a systematic review and meta-analysis. Int J Epidemiol 2013;42:1029–39.

30. Wilson SR, Sabatine MS, Wiviott SD, Ray KF, De Lemos JA, Zhou S, et al. Assessment of adiponectin and the risk of recurrent cardiovascular events in patients presenting with an acute coronary syndrome: observations from the pravastatin or atorvastatin evaluation and infection trial-thrombolysis in myocardial infarction. Am Heart J 2011;161:1147–55.

31. Lindberg S, Pedersen SH, Magelvang R, Bjerre M, Frystyk J, Flyvbjerg A, et al. Usefulness of adiponectin as a predictor of all cause mortality in patients with ST-segment elevation myocardial infarction treated with primary percutaneous coronary intervention. Am J Cardiol 2012;109:492–6.

32. Kistorp C, Faber J, Galatius S, Gustafsson F, Frystyk J, Flyvbjerg A, et al. Plasma adiponectin, body mass index, and mortality in patients with chronic heart failure. Circulation 2005;112:1756–62.

33. Klis MZ, Kasznicki J, Kosmalski M, Smigielski J, Dzwoski J. Adiponectin plasma concentration, type 2 diabetes mellitus, cardiovascular diseases and features of metabolic syndrome. Diabetologia Doświadczalna i Kliniczna 2009;9:81–7.

34. Bao Y, Lu Z, Zhou M, Li H, Wang Y, Gao M, et al. Serum levels of adipocyte fatty acid-binding protein are associated with the severity of coronary artery disease in Chinese women. PLoS One 2011;6:e19115.

35. Rhee EJ, Lee WY, Park CY, Oh KW, Kim BJ, Sung KC, et al. The association of serum fatty acid-binding protein with coronary artery disease in Korean adults. Eur J Endocrinol 2009;160:165–72.

36. Habib SS, A Al Masri A. Relationship of high sensitivity C-reactive protein with presence and severity of coronary artery disease. Pak J Med Sci 2013;29:1425–9.

37. Hung CS, Wu YW, Huang JY, Hsu PY, Chen MF. Evaluation of circulating adipokines and abdominal obesity as predictors of significant myocardial ischemia using gated single-photon emission computed tomography. PLoS One 2014;9:e87710.

38. Okauchi Y, Kishida K, Funahashi T, Noguchi M, Ogawa T, Ryo M, et al. Changes in serum adiponectin concentrations correlate with changes in BMI, waist circumference, and estimated visceral fat area in middle-aged general population. Diabetes Care 2009;32:e122.

39. Terra X, Quintero Y, Auguet T, Porras JA, Hernández M, Sabench F, et al. FABP4 is associated with inflammatory markers and metabolic syndrome in morbidity obese women. Eur J Endocrinol 2011;164:539–47.

40. Cpmp M, Havel PJ, Utzschneider KM, Carr DB, Sinha MK, Boyko EJ, et al. Relationship of adiponectin to body fat distribution, insulin sensitivity and plasma lipoproteins: evidence for independent roles of age and sex. Diabetologia 2003 46:459–69.