Clinical implications of adiponectin and inflammatory biomarkers in type 2 diabetes mellitus

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Abstract. Objectives: To study the interrelationships of adiponectin, C-reactive protein (CRP) and fibrinogen with each other in T2DM patients with (T2DM-C) and without complications (T2DM-NC) among healthy individuals.

Design and methods: The study comprised of 120 T2DM-C, 59 T2DM-NC patients and 40 healthy volunteers. Biochemical markers were determined in the serum.

Results: Positivity rates of CRP and fibrinogen were significantly increased in T2DM-C as compared to T2DM-NC or controls, whereas adiponectin showed highest level in healthy individuals. Inflammatory biomarkers were inversely correlated with adiponectin ($P < 0.01$). Lipid profiles, kidney functions and BMI, showed positive significant correlation with CRP and fibrinogen but negative correlation with adiponectin. For better detection of T2DM, the combined sensitivity (98.9%) and specificity (92.5%) of fibrinogen and adiponectin was higher than the combined sensitivity and specificity of fibrinogen and CRP or adiponectin and CRP or than that of the biomarkers alone.

Conclusion: Elevated levels of CRP and fibrinogen and reduced level of adiponectin can be used for early diagnosis of T2DM and can predict diabetic complications.

Keywords: Type 2 diabetes mellitus, adiponectin, c-reactive protein, fibrinogen

1. Introduction

The epidemic proportion of people with diabetes is alarming [1]. Type 2 diabetes affects small (microangiopathy) or large vessels (macroangiopathy). Microvascular disease is the hallmark of retinopathy, neuropathy, and nephropathy, whereas macroangiopathy in diabetes is manifested by accelerated atherosclerosis, which affects vital organs (heart and brain) [2]. Therefore, attention has been focused recently on whether

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tein (CRP), a sensitive physiological marker of subclinical systemic inflammation, is associated with hyperglycemia, insulin resistance, and overt T2DM [7]. A study by Takebayashi and colleagues suggested that CRP appeared not to be a discriminatory factor for diabetic complications, although it probably had a pathogenetic role at the level of the vascular endothelium. The role of CRP in diabetic patients in regards to obtaining “value-added” information is therefore, still controversial [8]. Also, Fibrinogen, a plasma protein produced in liver, is regulated by cytokines and is greatly enhanced by the acute phase response to inflammatory processes [9]. It contributes more than other proteins to plasma viscosity in healthy subjects. This contribution is greatly increased in disease states, among them diabetes mellitus. Elevated plasma viscosity is the feature of diabetic blood, which results in greater flow resistance, and a high incidence of certain complications. Long before the biochemical deviation in carbohydrate metabolism is demonstrable, changes occur in the small blood vessels due to elevated viscosity of plasma that are responsible for some of the complications associated with the disease [10].

When T2DM is clinically diagnosed there may already be diabetic complications, [11]. These clinical findings have lead clinicians to the hypothesis that polygenic T2DM is a vascular disease rooted in endothelial genetic defects and occurs as a result of interactions with environmental stressors such as over nutrition, obesity, and under exercise in the metabolic syndrome with hyperglycemia being a late manifestation [12].

The aim of the present study was to explore the association among CRP, fibrinogen and adiponectin in T2DM with and without complications to evaluate their usefulness as screening biomarkers for early prediction of complications in patients with T2DM.

2. Materials and methods

2.1. Study population

This cohort study included 179 with confirmed diagnosis as type 2 diabetes mellitus (T2DM) at the time of blood draw. Based on revised American Diabetes Association diagnostic criteria [13], cases were confirmed if one or more of the following conditions were met: (1) presence of more than 1 classic symptom of hyperglycemia (i.e. polyuria, polydipsia, weight loss with or without polyphagia, and blurred vision) plus either a fasting plasma glucose of 126 mg/dL (7.0 mmol/L) or higher or random plasma glucose 200 mg/dL (11.1 mmol/L) or higher; (2) in the absence of symptoms, 2 or more elevated plasma glucose concentrations (fasting plasma glucose of $\geq 126$ mg/dL [7.0 mmol/L], random plasma glucose $\geq 200$ mg/dL [11.1 mmol/L], or 2-hour plasma glucose $\geq 200$ mg/dL [11.1 mmol/L] during oral glucose tolerance testing); or (3) use of insulin or an oral hypoglycemic agent. Of the diabetic participants; 59 candidates were diabetic mellitus type II without complications, and they were 36 females (mean age $47.4 \pm 9.2$ years; range 29–59 years) and 23 males (mean age $54 \pm 9.3$ years; range 35–63 years) with BMI (BMI; calculated as weight in kilograms divided by the square of height in meters) ranged from 20–35 Kg/m$^2$. Because therapeutic approaches are often very different in the management of patients with diabetes and this significantly influences their vascular complications, we reasoned to include in the present study only subjects not previously treated with vascular medications and with a first diagnosis of type 2 diabetes, thus the remaining 120 diabetic mellitus type 2 candidates were newly diagnosed with diabetic vascular complications [cardiovascular disease 97 (80.8%) such as ischemic heart diseases, hypertension and myocardial infraction.; nephropathy 76 (63.3%); retinopathy 71 (59.2%) and neuropathy 110 (91.7%)], they were examined with Echo-Color Doppler, ophthalmoscopic and fluorangiography, also urinary albumin excretion (UAE) from 24-h urine collection was determined using radial immunodiffusion assay, neuropathy was diagnosed by the presence of abnormal sensation in the extremities. They were categorized according to the gender status into 63 females (mean age $54.2 \pm 8$ years; range 43–70 years) and 57 males (mean age $55.8 \pm 8.3$ years; range 43–81 years) with BMI ranged from 23.8–39 Kg/m$^2$. A group of clinically healthy volunteers ($n = 40$) were enrolled in the study to serve as control group and include 26 females (mean age $49.5 \pm 7.5$ years; range 30–59 years) and 14 males (mean age $51.3 \pm 13$ years; range 29–63 years) with BMI ranged from 20–29 Kg/m$^2$.

2.2. Blood collection and processing

The study was approved by the ethical committee of the University of Alzhraa hospital, and informed consent was obtained from all participants. Venous Blood samples were withdrawn at enrollment after overnight fasting; each sample was divided into three portions: the first was mixed gently with 150 $\mu$L EDTA solution then divided into two tubes; one was centrifuged for
15 min. at 3000 RPM, the supernatant (plasma) was stored in liquid nitrogen until laboratory assay for CRP and adiponectin, the other tube is used immediately to measure glycosylated hemoglobin (Hb)A1c. The second portion was added to 0.2 ml Na citrate 3.2% and mixed gently, then centrifuged and the plasma was separated for immediate estimation of plasma fibrinogen. The third portion was left to clot at room temperature and serum was separated after centrifugation for assessment of lipid profile, kidney function and serum glucose.

Plasma C-reactive protein (CRP) was measured using the US CRP ELISA kit (Diagnostic Systems Laboratories, Inc., Webster, TX) [14]. Plasma adiponectin concentrations were measured by ELISA kit (R&D Systems, Minneapolis, MN) [15]. Hemoglobin (Hb)A1c was measured by chromatographic spectro-photometric ion exchange resin using kit supplied by Biosystems company (S.A, Barcelona, Spain). Assessment of plasma fibrinogen was carried out by modification of the method on system CA analyzer (HITACHI-911TM Roche Diagnostic System, Boheringer Manheim) [16]. Measurement of lipid profile, kidney function and serum glucose was carried out photo-metrically using HITACHI-911TM Autoanalyzer (Roche Diagnostic System, Boheringer Manheim).

2.3. Statistical analysis

The threshold value for optimal sensitivity and specificity was determined by receiver operating characteristics (ROC) curve which was constructed by calculating the true-positive fraction (sensitivity %) and false-positive fraction (100-specificity %) of CRP, fibrinogen, and adiponectin at several cutoff points [17]. The Kruskal-Wallis and Mann-Whitney U non-parametric tests were used for the statistical comparison of the variables between the various groups. The chi-square test was utilized to compare the positivity rates and to study the association between the different variables. Pearson’s correlations were used to test the relationship between variables. The level of significance was determined to be less than 0.05. All analyses were performed using the Statistical Package for the Social Sciences (SPSS software, version 12, Chicago, Illinois).

3. Results

3.1. Clinical characteristics of the study cohort

The clinical characteristics of the controls, diabetic mellitus type 2 with (T2DM-C) and, without (T2DM-NC) complications are shown in (Table 1). Significant difference was observed between all the clinical characteristics among the three investigated groups as well as between T2DM-C as compared to either T2DM-NC or the control groups ($P < 0.0001$). The mean levels of CRP and fibrinogen, were increased 2.07 fold, and 1.28 fold respectively in T2DM-C group as compared to T2DM-NC group and 4.04 fold and 2.5 fold, respectively in T2DM-C group as compared to control group ($P < 0.0001$). While the mean level of CRP and fibrinogen were increased 1.95 fold and 1.97 fold respectively in T2DM-NC group as compared to control group ($P < 0.0001$). On the other hand, adiponectin level was increased 4.45 fold in control group compared to T2DM-C group and 2.6 fold compared to T2DM-NC group. In T2DM-NC group, adiponectin levels were higher 1.69 fold than T2DM-C group ($P < 0.0001$).

3.2. Correlation between biomarkers in type 2 diabetes mellitus group

To assess the associations between biomarkers in T2DM, we calculated Pearson correlation coefficients. Significant positive associations were reported between CRP, fibrinogen and (Hb)A1c, ($R = 0.398, 0.163$), LDL ($R = 0.228, 0.22$), triglyceride ($R = 0.278, 0.329$), urea ($R = 0.194, 0.349$), creatinine ($R = 0.22, 0.242$), fasting ($R = 0.419, 0.338$) and postprandial glucose ($R = 0.391, 0.398$), and BMI ($R = 0.294, 0.256$) respectively at $P < 0.001$, while negative association was detected between CRP, fibrinogen and HDL ($R = -0.305, -0.15$ at $P < 0.001$, respectively). For adiponectin, negative associations were detected between adiponectin and (Hb)A1c, LDL, triglyceride, creatinine, fasting and postprandial glucose, and BMI ($R = -0.275, -0.231, -0.309, -0.174, -0.173, -0.235$, and $-0.282$ respectively at $P < 0.02$), while positive association was detected between adiponectin and HDL ($R = 0.186, P = 0.013$). Moreover, CRP was positively associated with fibrinogen and negatively associated with adiponectin (Fig. 1A-C).

3.3. Positivity rates of CRP, adiponectin, and fibrinogen among different investigated groups

Best cutoff values for CRP, fibrinogen and adiponectin, were calculated using ROC curve as shown in Fig 2. There was statistical difference in the rates of aforementioned biomarkers among the three investigated groups, Table 2.
The other hand, adiponectin was decreased in T2DM patients with CVD, nephropathy and retinopathy. On of T2DMC (Table 3), CRP was increased in T2DM patients with complications (Fig. 3). Among the entire group of T2DMC (Table 3), CRP was increased in T2DM patients with CVD, nephropathy and retinopathy. On the other hand, adiponectin was decreased in T2DM patients with CVD, nephropathy and neuropathy. Fibrinogen showed significant increment in T2DM patients with CVD and nephropathy.

### 3.4. Adiponectin, CRP and fibrinogen among T2DM-C group

According to the studied T2DM patients, 67% (120/179) patients showed complications categorized as follows; 80.8% (97/120) with cardiovascular diseases, 63.3% (76/120) with nephropathy, 91.7% (110/120) with neuropathy, and 59.2% (71/120) with retinopathy. As indicated in Table 3, the three biomarkers of interest were significantly associated with CVD, and nephropathy. Moreover, CRP was associated with retinopathy and adiponectin was associated with neuropathy.

The median percentage change for CRP and fibrinogen in T2DM-C group revealed positive association with different complications. On the other hand, adiponectin revealed negative association with different complications (Fig. 3). Among the entire group of T2DMC (Table 3), CRP was increased in T2DM patients with CVD, nephropathy and retinopathy. On the other hand, adiponectin was decreased in T2DM patients with CVD, nephropathy and neuropathy. Fibrinogen showed significant increment in T2DM patients with CVD and nephropathy.

### 3.5. Combined sensitivity and specificity of investigated biomarkers

Sensitivity and specificity for CRP, fibrinogen and adiponectin as well as their combination were tested for detection of T2DM and T2DM-C, as shown in Table 4. Both sensitivity (93%) and specificity (95%) of fibrinogen were the highest among the other two biomarkers for detection of T2DM. Absolute sensitivity was reached when the three biomarkers were combined although the specificity was decreased. For detection of complications in T2DM patients, CRP revealed the highest sensitivity (95%) and specificity (50.5%) as compared with adiponectin and fibrinogen. Absolute sensitivity was reached when CRP was combined with adiponectin, although the specificity was reduced to 42.9%.

### Table 2

Characteristics by mean (95% CI) for the investigated biomarkers among the different studied groups

<table>
<thead>
<tr>
<th>Biomarkers</th>
<th>Control</th>
<th>T2DM-NC‡</th>
<th>T2DM-C§</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRP (mg/L)</td>
<td>0.75 (0.5–0.9)</td>
<td>1.46 (1.3–1.6)</td>
<td>3.03 (2.78–3.28)</td>
</tr>
<tr>
<td>Fibrinogen (mg/dl)</td>
<td>182 (168–195)</td>
<td>359 (330–353)</td>
<td>461 (427–495)</td>
</tr>
<tr>
<td>Adiponectin (µg/ml)</td>
<td>32.9 (27.8–38)</td>
<td>12.5 (10.3–14.7)</td>
<td>7.4 (6.44–8.44)</td>
</tr>
<tr>
<td>GlyHb(Hb)A1c%</td>
<td>5.3 (5–5.6)</td>
<td>7 (6.4–7.4)</td>
<td>10.8 (10.57–11.1)</td>
</tr>
<tr>
<td>Cholesterol (mg/dl)</td>
<td>155 (147–163)</td>
<td>188 (179–197)</td>
<td>191 (184–197)</td>
</tr>
<tr>
<td>HDL-C (mg/dl)</td>
<td>50.1 (47–51.7)</td>
<td>45.24 (43–47)</td>
<td>33.6 (32.3–34.8)</td>
</tr>
<tr>
<td>LDL-C (mg/dl)</td>
<td>81 (74–88)</td>
<td>80 (75–86)</td>
<td>131 (108–119)</td>
</tr>
<tr>
<td>Triglyceride (mg/dl)</td>
<td>106 (94–118)</td>
<td>107 (97–116)</td>
<td>174 (166–188)</td>
</tr>
<tr>
<td>Urea (mg/dl)</td>
<td>30 (28–31)</td>
<td>29 (28–31)</td>
<td>37 (33–40)</td>
</tr>
<tr>
<td>Creatinine (mg/dl)</td>
<td>0.85 (0.8–0.9)</td>
<td>0.85 (0.8–0.89)</td>
<td>1.1 (1–1.2)</td>
</tr>
<tr>
<td>FBS (mg/dl)</td>
<td>86.6 (84–89)</td>
<td>86 (84–88)</td>
<td>211 (201–222)</td>
</tr>
<tr>
<td>PPS (mg/dl)</td>
<td>99 (95–102)</td>
<td>98.8 (96–101)</td>
<td>301 (283–318)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>22.1 (21.3–22.9)</td>
<td>30.17 (29.5–31)</td>
<td>33.27 (32.8–33.7)</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>124 (115–120)</td>
<td>130 (120–132)</td>
<td>140 (125–145)</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>75 (70–77)</td>
<td>84 (72–88)</td>
<td>101 (80–104)</td>
</tr>
</tbody>
</table>

*Significant P < 0.0001 using Pearson Chi-square test.

### Table 4

Distributions of CRP, adiponectin and fibrinogen among different investigated groups using the cutoff values

<table>
<thead>
<tr>
<th>Investigated groups (no.)</th>
<th>≤ 1.07 mg/L</th>
<th>&gt; 1.07 mg/L</th>
<th>≤ 242 mg/dl</th>
<th>&gt; 242 mg/dl</th>
<th>≤ 14 µg/ml</th>
<th>&gt; 14 µg/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>32 (80%)</td>
<td>8 (20%)</td>
<td>38 (95%)</td>
<td>2 (5%)</td>
<td>6 (15%)</td>
<td>34 (85%)</td>
</tr>
<tr>
<td>T2DM-NC</td>
<td>18 (30.5%)</td>
<td>41 (69.5%)</td>
<td>3 (5.1%)</td>
<td>56 (94.9%)</td>
<td>40 (67.8%)</td>
<td>19 (32.2%)</td>
</tr>
<tr>
<td>T2DM-C</td>
<td>6 (5%)</td>
<td>114 (95%)</td>
<td>8 (6.7%)</td>
<td>112 (93.3%)</td>
<td>105 (87.5%)</td>
<td>15 (12.5%)</td>
</tr>
</tbody>
</table>

The median percentage change for CRP and fibrinogen in T2DM-C group revealed positive association with different complications. On the other hand, adiponectin revealed negative association with different complications (Fig. 3). Among the entire group of T2DMC (Table 3), CRP was increased in T2DM patients with CVD, nephropathy and retinopathy. On the other hand, adiponectin was decreased in T2DM patients with CVD, nephropathy and neuropathy. Fibrinogen showed significant increment in T2DM patients with CVD and nephropathy.
Fig. 1. Linear regression analysis between (1a) CRP and adiponectin, (1b) CRP and fibrinogen and (1c) adiponectin and fibrinogen among T2DM group.
Fig. 2. ROC curve analysis for CRP, fibrinogen and adiponectin to calculate the best cutoff point to discriminate between control and diabetic groups. Open circles denote best cutoff points of CRP (straight line) as 1.07 mg/L [sensitivity = 86.6% and specificity = 80%. Area under the curve (AUC) [SE] = 0.871 [0.034], 95% confidence limits range = 0.805–0.937, \( P < 0.0001 \)], fibrinogen as 242 mg/dl [sensitivity = 93.9% and specificity = 95%. Area under the curve (AUC) [SE] = 0.986 [0.007], 95% confidence limits range = 0.973–0.999, \( P < 0.0001 \)] and adiponectin as 14 (µg/ml) [sensitivity = 81% and specificity = 85%. Area under the curve (AUC) [SE] = 0.922 [0.022], 95% confidence limits range = 0.879–0.964, \( P < 0.0001 \)].

Fig. 3. The median percentage change of the CRP, fibrinogen and adiponectin among the T2DMC as controled for T2DM-NC.
Table 3

<table>
<thead>
<tr>
<th>Complications</th>
<th>CRP (mg/L)</th>
<th>Fibrinogen (mg/dL)</th>
<th>Adiponectin (µg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&gt; 1.07</td>
<td>Mean</td>
<td>&gt; 242</td>
</tr>
<tr>
<td>CVD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>17 (14.9%)</td>
<td>2.26&lt;sup&gt;b&lt;/sup&gt;</td>
<td>19 (17%)&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Positive</td>
<td>97 (85.1%)</td>
<td>3.22</td>
<td>93 (83%)</td>
</tr>
<tr>
<td>Nephropathy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>39 (34.2%)</td>
<td>2.56&lt;sup&gt;b&lt;/sup&gt;</td>
<td>37 (33%)&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Positive</td>
<td>75 (65.8%)</td>
<td>3.31</td>
<td>75 (67%)</td>
</tr>
<tr>
<td>Neuropathy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>10 (8.8%)</td>
<td>2.91</td>
<td>10 (8.9%)</td>
</tr>
<tr>
<td>Positive</td>
<td>104 (91.2%)</td>
<td>3.04</td>
<td>102 (91.1%)</td>
</tr>
<tr>
<td>Retinopathy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>44 (38.6%)</td>
<td>2.67&lt;sup&gt;b&lt;/sup&gt;</td>
<td>45 (40.2%)</td>
</tr>
<tr>
<td>Positive</td>
<td>70 (61.4%)</td>
<td>3.28</td>
<td>67 (59.8%)</td>
</tr>
</tbody>
</table>

Significant *P* < 0.001 using *a*Pearson Chi-square test, and *b*ANOVA test.

Table 4

<table>
<thead>
<tr>
<th>Biomarkers</th>
<th>Detection of T2DM</th>
<th>Detection of T2DM-C</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sensitivity</td>
<td>Specificity</td>
</tr>
<tr>
<td>CRP</td>
<td>86</td>
<td>80</td>
</tr>
<tr>
<td>Fibrinogen</td>
<td>93</td>
<td>95</td>
</tr>
<tr>
<td>Adiponectin</td>
<td>81</td>
<td>85</td>
</tr>
<tr>
<td>CRP + Fibrinogen</td>
<td>98.3</td>
<td>80</td>
</tr>
<tr>
<td>CRP + Adiponectin</td>
<td>98.1</td>
<td>87.1</td>
</tr>
<tr>
<td>Fibrinogen + Adiponectin</td>
<td>98.9</td>
<td>92.5</td>
</tr>
<tr>
<td>CRP + Adiponectin + Fibrinogen</td>
<td>100</td>
<td>67.5</td>
</tr>
</tbody>
</table>

4. Discussion

Diabetes mellitus type 2 (T2DM) is a complex disease with altered expression of many biomarkers, which can be anticipated to interact. It is therefore critical to monitor their changes and their inter-relationships with other risk factors [1].

In the present study, we performed quantitative analysis of CRP, fibrinogen and adiponectin in serum samples from different investigated groups by ELISA to evaluate their usefulness in diagnosis of T2DM as well as early screening of complications associated with T2DM. Accordingly, the levels and positivity (sensitivity) of both inflammatory markers (CRP and fibrinogen) were significantly increased in T2DM-C as compared to T2DM-NC and controls as reported earlier by others [7]. On the other hand, our results were in concordance with Mantozoros and his colleagues [18] as the levels and positivity rates of the circulating adiponectin were lower in T2DM-C as compared to T2DM-NC and controls (*P* < 0.0001). These results indicate that elevation of inflammatory markers and reduced adiponectin levels play an important role not only in the pathophysiology of T2DM but also in the category of complications associated with this type of disease.

Authors investigated the correlation between the aforementioned biomarkers and glycosylated hemoglobin (Hb)A1c, lipid profile, kidney function and BMI. Inflammatory markers were positively correlated with glycosylated hemoglobin (Hb)A1c, fasting and post-prandial glucose, LDL and triglyceride while negatively correlated with HDL. Gorink and his coworkers [19] reported that advanced glycation end products (AGEs) that formed by glycosylated hemoglobin are associated with pathogenesis of diabetic complications through interaction with their receptors (RAGE) which can induce numerous changes linked to inflammation. In addition, increased plasma glucose contributes to the hyperfibrinogenemia of type 2 diabetes [20]. Also, it was previously reported that serum HDL-cholesterol concentrations are associated with triglyceride-rich lipoprotein metabolism and body fat in young healthy men. Therefore, an inverse association between HDL-cholesterol and inflammatory markers found in the present study suggests that low HDL-cholesterol may be related to chronic low-grade inflammation, as well as subtle abnormalities in triglyceride-rich lipoprotein metabolism in young healthy men. Low HDL-cholesterol in low grade inflammation in the present study may be com-
patible with the recent observation that human secreto-
y phospholipase A2, an acute-phase protein, decreased
HDL-cholesterol in response to inflammation [21]. Our
results revealed strong correlation between the level of
the inflammatory markers and BMI in T2DM patients
as previously reported by Kazumi et al. [22] suggest-
ing that obesity may be a state of low grade inflam-
amation as well. This maybe attributed to the fact that
increased synthesis of some cytokines in obese women
lead to increased synthesis of acute – phase reactants
like CRP in liver [23]. Adiponectin, a member of a
new family of obesity-related hormones, the adipocy-
tokines, which is produced solely by white adipose
tissue [24], was negatively correlated with (Hb)A1c,
fasting and postprandial glucose indicating as previ-
ously reported [18] that higher adiponectin levels are
associated with better glycemic control. Moreover, it
was negatively correlated with triglycerides, indicating
that adiponectin may reduce intrahepatic and muscle
triglyceride content through increased muscle fat oxida-
tion and induction of genes which are important in
fatty acid transport and oxidation. Also, its level was
reversed to obesity as measured by BMI, this is may be
due to some of the common polymorphisms in the pro-
moter region, exon and intron 2 and the rare mutations
in exon 3 of the human adiponectin gene [25]. How-
ever, adiponectin was positively correlated with HDL.
These results are in line with report from von Eynatten
et al. [26] who found an association between decreased
post-heparin lipoprotein lipase (LPL) activity and low
plasma adiponectin independent of systemic inflamma-
tion and insulin resistance. Conversely, dramatically
raised levels of LPL activity have been found with in-
creased plasma adiponectin in an animal model. Thus,
adiponectin may directly stimulate the expression of
LPL, which then will result in increased HDL-C levels.

T2DM is the leading cause of new cases of blind-
ness, end-stage renal disease, and increased risk of car-
diovascular disease. Most studies have indicated that
increased risk for these complications can not be ex-
plained solely by conventional risk factors such as dys-
lipidemia, hypertension, and smoking. Therefore, the
diabetic state, per se, confers an increased propensity to
accelerated atherogenesis; however, the precise mech-
anism(s) by which this occurs remain to be elucidated.
Regarding patients with type 2 diabetes, an increased
incidence of cardiovascular diseases has been report-
ed among those with elevated plasma levels for those
markers of inflammation

Preliminarily, we found strong significant correla-
tions between the positivity rates of CRP and fibrino-
gen levels among T2DM-C especially those with CVD
and nephropathy, while only CRP showed parallel as-
association with retinopathy ($P < 0.0001$). These find-
ings could point out, as previously reported, the role
of increased inflammation in the pathogenesis of these
vasculopathies, moreover, confirming that the role of
these two markers of inflammation is complementary.
On the contrary, adiponectin was decreased in T2DM
patients with CVD, nephropathy and neuropathy ($P <
0.0001$). This could be attributed to the presence of
a region of chromosome 3q contains a susceptibility
locus for diabetic nephropathy in patients with type 2
diabetes, and one group evaluated 14 candidate genes
on chromosome q and found the strongest linkage with
a SNP for the promoter of adiponectin [27]. These
findings indicate that adiponectin deficiency accentu-
ates CVD and kidney diseases among T2DM which
indicate that identification of low adiponectin levels
identifies high risk populations [28]. Moreover, the
increased adiponectin levels were increased in T2DM
patients with nephropathy as compared to T2DM-NC
which may result from enhanced filtration through the
damaged kidney [29].

In the current study, the three biomarkers of inter-
est were correlated with each other indicating that adi-
pose tissue synthesizes and secretes adiponectin and
other cytokines. Increased synthesis of these cytokines
in obese subjects leads to insulin resistance in mus-
cle, increased synthesis of acute-phase reactants in the
liver (CRP and fibrinogen), and/or activation of
macrophages in atheromatous plaques, which leads to
an increased incidence of vascular diseases [24]. More-
over, when the median percentage changes of the three
biomarkers were controlled for T2DM-NC, CRP and
fibrinogen were increased while adiponectin was de-
exased among those with complications. These results
suggest that T2DM patients should be treated aggres-
sively and followed closely to prevent future complica-
tions usually associated with T2DM.

The early detection of T2DM would certainly im-
prove the diagnosis and screening of high-risk groups,
such as patients with CVD, nephropathy, neuropa-
thy and retinopathy. This study is among the first
to use combine CRP, fibrinogen and adiponectin in a
joint study as novel biomarkers for T2DM. Fibrinogen
showed both highest sensitivity and specificity as com-
pared to either CRP or adiponectin alone for diagnosing
of T2DM. Among the several combinations, both the
sensitivity (98.9%) and specificity (92.5%) of fibrino-
gen and adiponectin together were higher as compared
to other combinations. Absolute sensitivity was report-
ed when the three biomarkers were combined although the specificity was decreased (67.5%). Intriguingly, absolute sensitivity with a specificity (42.9%); closer to that reported for CRP (50.5%), adiponectin (53.5%) and fibrinogen (41.4%) when tested alone, were observed when CRP and adiponectin where combined. Because recent studies have addressed the importance of therapeutic modulation of these biomarkers in high-risk patients for the prevention of vascular events [14], it also cannot be excluded that an effective primary prevention on the categories of patients with T2DM may take into account the reduction of elevated CRP and fibrinogen as well as elevation of adiponectin levels, thus enable better management of patients. However, beyond the utility of these biomarkers in the prediction of complications in patients with newly diagnosed diabetes, further studies should focus on the prospective analysis of these assays in larger multicentric studies to evaluate the therapeutic implications of these biomarkers.

References


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