Adiponectin levels in serum of women with pre-eclampsia

D.I. Abd-Alaleem,1 K.I. Attiaa,1 A.A. Khalefa1 and R.A. Ahmad2

ABSTRACT Adiponectin has profound insulin-sensitizing, anti-inflammatory and anti-atherogenic effects. However, reports of the role of adiponectin in pre-eclampsia are conflicting. This study in Egypt investigated the association between serum adiponectin levels and pre-eclampsia and between adiponectin levels and some clinical and hormonal parameters. A sample of 60 pregnant women in the third trimester were divided into 3 equal groups: normal pregnancy, mild pre-eclampsia and severe pre-eclampsia. Serum adiponectin levels in pre-eclamptic women were significantly higher than in normal pregnant women and the increase was more marked in cases of severe pre-eclampsia. There was a significant negative correlation between adiponectin levels and arterial blood pressure in all groups. However, there was no correlation between serum adiponectin and proteinuria or estradiol and progesterone levels. The results support the theory that adiponectin might be part of a feedback mechanism improving insulin sensitivity and cardiovascular health in pre-eclamptic patients.

Taux sériques d’adiponectine chez les femmes souffrant de prééclampsie

RÉSUMÉ L’adiponectine a de profonds effets insulino-sensibilisants, anti-inflammatoires et antiatherogènes. Toutefois, les résultats des études sur le rôle de l’adiponectine dans la prééclampsie sont discordants. La présente étude en Égypte a recherché l’association entre les taux sériques d’adiponectine et la prééclampsie et entre les taux d’adiponectine et certains paramètres cliniques et hormonaux. Un échantillon de 60 femmes enceintes au troisième trimestre de grossesse a été constitué, lesquelles ont été réparties en trois groupes comptant un nombre égal de participantes : grossesse normale, prééclampsie légère et prééclampsie sévère. Les taux sériques d’adiponectine chez les femmes prééclamptiques étaient nettement supérieurs à ceux des femmes ayant une grossesse normale et l’augmentation était plus marquée dans les cas de prééclampsie sévère. Les taux d’adiponectine étaient fortement et négativement corrélés à la pression artérielle dans tous les groupes. Cependant, aucune corrélation n’a été trouvée entre l’adiponectine sérique et les taux de protéinurie ou d’estradiol et de progesterone. Les résultats appuient la théorie selon laquelle l’adiponectine pourrait jouer un rôle dans le mécanisme de rétroaction qui contribue à l’amélioration de la sensibilité à l’insuline et la santé cardio-vasculaire des patientes prééclamptiques.

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Introduction

Pre-eclampsia, which occurs in about 5% of pregnancies and results in substantial maternal and neonatal morbidity and mortality, is a pregnancy-specific syndrome of reduced organ perfusion secondary to vasoconstriction and endothelial activation [1,2]. It is characterized by hypertension and proteinuria.

The syndrome is usually associated with maternal obesity and shares common features with obesity, e.g. hypertension, glucose intolerance, insulin resistance [3] and hyperlipidaemia [4]. Several studies have therefore focused on the relation between pre-eclampsia and hormones secreted by adipocytes [5–7]. Adiponectin is an adipocyte-derived plasma protein [8] that is believed to be involved mainly in the regulation of insulin resistance and glucose homeostasis [9]. Experimental and clinical studies have indicated that low plasma levels of adiponectin are associated with obesity-related metabolic disorders and abnormal vascular reactivity [17–24], suggesting that adiponectin may play a role in the syndrome. However, reports about the levels of adiponectin in pre-eclampsia are conflicting. The present study in Egypt was therefore designed to examine the association between serum adiponectin levels and pre-eclampsia and to detect any correlation between serum levels of this hormone and some clinical and hormonal parameters.

Methods

Sample

A sample of 60 pregnant women in the third trimester of pregnancy were recruited from the outpatient clinics and inpatient department of obstetrics and gynaecology at Zagazig University hospitals, Zagazig, Egypt during the period August 2007 to April 2008. Women targeted were: 20–35 years old, single pregnancy, 20 weeks or more gestational age.

Consent was obtained from each patient after full explanation of the objectives and procedures of the study. Women included in this study were divided into the following groups: normal pregnancy (n = 20), mild pre-eclampsia (n = 20) and severe pre-eclampsia (n = 20). The normal pregnancy (n = 20) and mild pre-eclampsia groups had no medical disorders and normal routine laboratory investigations.

Patients were defined according to criteria established by the Royal College of Obstetricians and Gynaecologists (RCOG) [25]. All women in the normal group were healthy, normotensive and had single gestation. Moreover, this insulin resistance is increased in pregnancies complicated with pre-eclampsia [16].

The evidence that adiponectin interacts with many risk factors of pre-eclampsia, e.g. insulin resistance, inflammatory disorders and abnormal vascular reactivity [17–24], suggests that adiponectin may play a role in the syndrome. However, reports about the levels of adiponectin in pre-eclampsia are conflicting. The present study in Egypt was therefore designed to examine the association between serum adiponectin levels and pre-eclampsia and to detect any correlation between serum levels of this hormone and some clinical and hormonal parameters.

or vomiting, abnormal liver enzymes (aspartamine or alanine aminotransferase rising to above 70 IU/L), signs of clonus, HELLP syndrome [haemolytic anaemia/ elevated liver enzymes/low platelet count] and papilloedema.

All the women included in the study were taking a multivitamin supplement with iron, and none was receiving antihypertensive medications or exogenously administered hormones. None of the participants had any history of hypertension or diabetes.

Data collection

All pre-eclamptic pregnant women were hospitalized, while for the normal pregnant group samples were collected during routine antenatal visits. In all groups gestational age was derived from the last menstrual period and was corrected according to transabdominal and/or transvaginal ultrasonography if needed.

In all groups blood pressure was recorded, body weight and height were measured and body mass index (BMI) was calculated by using the formula of kg/m² [26]. Blood pressure was measured with the patients in a seated position and with the cuff of the sphygmomanometer at the level of the heart.

A urine sample was taken and proteinuria was determined according to the method of Dilena et al. [27]. A venous blood sample was withdrawn at 09.00 hours following overnight fasting and with the woman in the resting position. Samples were taken into standard serum tubes, allowed to clot, then serum was separated by centrifugation and stored at –60 °C until assayed. The following hormonal assays were carried out: serum adiponectin level according to Arita et al. [10]; serum estradiol level according to Tietz [28]; and serum progesterone level according to Tietz [28].
Statistical analysis

Data are presented as mean and standard error of the mean (SE). Statistical significance was determined by 1-way analysis of variance (ANOVA) test. *P* values less than 0.05 were considered to be statistically significant. The correlations between the parameters were analysed using Spearman rank correlation. SPSS for Windows, version 10.0 was used for statistical analysis.

Results

Serum adiponectin

Table 1 shows the serum adiponectin levels in the 3 study groups. In the mild and severe pre-eclamptic women, the mean serum adiponectin levels [18.8 (SE 0.7) µg/mL and 22.2 (SE 0.7) µg/mL respectively] were significantly higher than that of normal pregnant women [8.5 (SE 0.6) µg/mL] (*P* < 0.001). Moreover, the mean values in cases of severe pre-eclampsia were significantly higher when compared with those of mild pre-eclampsia (*P* < 0.01).

BMI

Table 2 shows the BMI of the 3 studied groups. The mean values of BMI in the women with normal pregnancy, mild pre-eclampsia and severe pre-eclampsia [32.2 (SE 0.5) kg/m², 33.7 (SE 0.7) kg/m² and 33.8 (SE 0.6) kg/m² respectively] showed no significant difference between the groups (*P* > 0.05).

Hormone assays

Table 3 shows the serum levels of estradiol and progesterone in the 3 studied groups. There were no significant difference in estradiol levels between the groups; the mean values in normal pregnancy, mild pre-eclampsia and severe pre-eclampsia were 33.0 (SE 1.4) ng/mL, 33.2 (SE 1.4) ng/mL and 33.0 (SE 1.8) ng/mL respectively (*P* > 0.05). There were also no significant difference in progesterone levels between the groups; mean values were 105.6 (SE 2.8) ng/mL, 105.3 (SE 2.9) ng/mL and 106.9 (SE 2.9) ng/mL respectively in normal pregnancy, mild pre-eclampsia and severe pre-eclampsia (*P* > 0.05).

Correlations of serum adiponectin levels and blood pressure

Figures 1 shows that there were negative correlations between serum adiponectin levels and systolic and diastolic blood pressure respectively in all the 3 groups: *r* = −0.96 and −0.92 (*P* < 0.001) in the normal pregnancy group (Figure 1a); *r* = −0.94 and −0.84 (*P* < 0.001) in the mild pre-eclampsia group (Figure 1b); and *r* = −0.98 and −0.95 (*P* < 0.001) in the severe pre-eclampsia group (Figure 1c).

Discussion

Our results revealed that serum adiponectin levels were significantly higher in the women with eclampsia in comparison with normal pregnant women who had similar gestational age and BMI. The difference was more marked in cases of severe pre-eclampsia than of mild pre-eclampsia. However, there were no significant differences between the groups in either serum estradiol or progesterone levels.

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Table 1: Serum adiponectin levels in the 3 study groups of pregnant women

<table>
<thead>
<tr>
<th>Group</th>
<th>Serum adiponectin level (µg/mL)</th>
<th>Mean (SE)</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal pregnancy (n = 20)</td>
<td></td>
<td>8.5 (0.6)</td>
<td>4.5–13.3</td>
</tr>
</tbody>
</table>
| Mild pre-eclampsia (n = 20)|                             | 18.8 (0.7)
| Severe pre-eclampsia (n = 20)|                           | 22.2 (0.7) |

*P* < 0.001 versus normal group; *P* < 0.01 versus mild pre-eclampsia group. SE = standard error.

Table 2: Body mass index (BMI) in the 3 study groups of pregnant women

<table>
<thead>
<tr>
<th>Group</th>
<th>BMI (kg/m²)</th>
<th>Mean (SE)</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal pregnancy (n = 20)</td>
<td></td>
<td>32.2 (0.5)</td>
<td>27.7–35.1</td>
</tr>
<tr>
<td>Mild pre-eclampsia (n = 20)</td>
<td></td>
<td>33.7 (0.7)</td>
<td></td>
</tr>
<tr>
<td>Severe pre-eclampsia (n = 20)</td>
<td></td>
<td>33.8 (0.6)</td>
<td></td>
</tr>
</tbody>
</table>

Not significant versus normal group; Not significant versus mild pre-eclampsia group. SE = standard error.

Table 3: Serum levels of estradiol and progesterone in the 3 study groups of pregnant women

<table>
<thead>
<tr>
<th>Group</th>
<th>Estradiol (ng/mL)</th>
<th>Progesterone (ng/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SE)</td>
<td>Range</td>
</tr>
<tr>
<td>Normal pregnancy (n = 20)</td>
<td>33.0 (1.4)</td>
<td>23.3–42.3</td>
</tr>
<tr>
<td>Mild pre-eclampsia (n = 20)</td>
<td>33.2 (1.4)</td>
<td>23.0–43.2</td>
</tr>
<tr>
<td>Severe pre-eclampsia (n = 20)</td>
<td>33.0 (1.8)</td>
<td>24.4–43.0</td>
</tr>
</tbody>
</table>

*Not significant versus normal group; Not significant versus mild pre-eclampsia group. SE = standard error.*
Our results are supported by those of Davis et al. who reported a significant increase in adiponectin in pre-eclamptic women without any significant changes in serum levels of estrogen, progesterone or human chorionic gonadotrophin [29]. The results are also in line with the findings of D’Anna et al. who reported increases in the levels of adiponectin during the third trimester in pre-eclamptic patients [30].

Several mechanisms to explain the elevation of adiponectin levels in pre-eclampsia have been proposed. It may be secondary to exaggerated non-specific adipocyte lipolysis or a physiological response to enhance fat utilization and attenuated endothelial damage [31]. Other factors that may cause the elevation of plasma adiponectin concentrations in pre-eclampsia include adiponectin resistance [32], alterations in renal function and ongoing adiponectin synthesis in adipose tissues [35].

Serum adiponectin levels did not correlate with BMI, proteinuria, estradiol or progesterone levels in any group. On the other hand, there was a significant negative correlation between serum levels of adiponectin and both systolic and diastolic blood pressure in the pre-eclamptic group.

Our finding that adiponectin levels did not correlate with maternal BMI is in line with the study of Herse et al. [33]. This can be explained by the evidence that BMI in pregnancy does not accurately reflect fat stores because maternal weight is influenced by the weight of the fetus, placenta and amnions and by plasma volume [34]. However, Hendler et al. concluded that women with severe pre-eclampsia and BMI > 25 kg/m² have decreased serum adiponectin levels, while normal weight women with pre-eclampsia have increased adiponectin levels [35]. They suggested that the increased adiponectin in normal weight pre-eclamptic women may represent the normal physiological feedback response, but that this mechanism might not function properly in overweight and obese pre-eclamptic woman because of increased adiponectin levels and insulin resistance, suggesting that decreased adiponectin levels may play a role in the pathophysiology of pre-eclampsia.

It is reported that the second half of pregnancy is a state of physiological insulin resistance, which is characterized by hyperinsulinaemia, glucose intolerance and lipid abnormalities [36–41]. This state of insulin resistance is exacerbated in pre-eclampsia, together with enhanced systemic inflammatory reactivity and endothelial dysfunction. At the same time, the circulating levels of both adiponectin and leptin are elevated in pre-eclampsia with the enhancement of insulin sensitivity [15,36–40].

When the pathological characteristics of pre-eclampsia and the changes in adiponectin and leptin levels are considered together, it is clear that the elevation of serum adiponectin and leptin is paradoxical and may play an important role in the pathophysiology of pre-eclampsia. This concept was supported by Fasshauer et al., who reported increased serum levels of adiponectin in pre-eclamptic patients which were positively associated with markers of insulin sensitivity in those patients. They concluded that adiponectin might be part of a physiological feedback mechanism improving insulin sensitivity and cardiovascular health in pre-eclamptic patients [42].

In the present study serum adiponectin levels showed a significant negative correlation with both systolic and diastolic blood pressure in all groups. This finding is in line with that of Li et al. who reported a negative correlation between adiponectin and blood pressure in normotensive populations [43]. Moreover, Ouchi et al. concluded that this effect may be mediated via inflammatory pathway or lipid metabolism [44]. Adiponectin has been shown to have pro-angiogenic, anti-atherogenic and anti-inflammatory functions in the endothelium [45]. Moreover, hypoadiponectinaemia is associated with impaired endothelium-dependent vasodilatation and reduced blood flow [23], and is an independent risk factor for hypertension [44]. These data suggest that adiponectin might maintain endothelial function and its deficiency might lead to endothelial dysfunction/hypertension. Thus, the elevation of circulating adiponectin might be a physiological response to the endothelial dysfunction caused by angiogenic factors derived from the placenta in pre-eclamptic women [46,47]. Taken together, these findings indicate that adiponectin has a role, either direct or indirect in the regulation and integrity of the vascular system.
On the other hand, our results contradict those of other investigators who reported decreased adiponectin levels in pre-eclamptic women in comparison with normotensive pregnant women; they also suggested that this decrease may contribute to the pathophysiology of pre-eclampsia [48–51]. Ouyang et al. found reduced adiponectin levels in pre-eclamptic women, especially in severe cases [52]. This contradictory may relate to differences in body fat, insulin sensitivity or haemoconcentration in the study populations.

In conclusion, adiponectin was markedly increased in case of pre-eclampsia, especially in severe cases, and there was a negative correlation.
between adiponectin levels and blood pressure, but no correlation between adiponectin levels and BMI, proteinuria, estradiol or progesterone levels. From a preventive and therapeutic perspective, understanding the mechanisms involved in the regulation of adiponectin levels in pre-eclampsia may allow the design of a new class of agents to combat many risk factors in this disease such as hypertension and endothelial dysfunction.

References


