ORIGINAL ARTICLE PEER REVIEWED | OPEN ACCESS

Maternal serum adiponectin, leptin and adiponectin-leptin ratio as possible biomarkers of preeclampsia

Linda Ahenkorah Fondjo, Enoch Appiah Adu Gyamfi, William K. B. A. Owiredu, Cornelius Archer Turpin, Daniel Asante Mante, Enoch Odame Anto

ABSTRACT

Aims: Preeclampsia is associated with significant maternal and perinatal morbidity and mortality, yet biomarkers for the condition have not been fully elucidated. As such, diagnosis of the condition in Ghana is based on blood pressure and urine protein measurement. The aim of this study was to compare the levels of adiponectin, leptin and the adiponectin-leptin ratio between normotensive pregnancy and preeclampsia. Materials and Methods: 60 normotensive pregnant women and 60 preeclamptic women were recruited for this case-control study. Social and clinical information were obtained from all the participants. Maternal serum adiponectin and leptin were quantified using immunoassays. Differences in measured variables between groups were assessed with unpaired student's t-test; and associations among variables were described with Pearson's correlation coefficients. Results: Adiponectin levels (p=0.001), leptin levels (p=0.010) and the adiponectin-leptin ratio (p=0.001) were higher in preeclampsia than in normotensive pregnancy. There was a significant inverse correlation between adiponectin and leptin in the normotensive controls (r=-0.768, p=0.002) but this relationship was attenuated in preeclampsia (r=-0.290, p=0.052). Conclusion: Levels of adiponectin, leptin and the adiponectin-leptin ratio were elevated in the preeclamptic women and could serve as biomarkers for the diagnosis of preeclampsia.

Keywords: Adiponectin, Adiponectin-leptin ratio, Biomarkers, Body mass index, Leptin, Preeclampsia

How to cite this article

Fondjo LA, Gyamfi EAA, Owiredu WKBA, Turpin CA, Mante DA, Anto EO. Maternal serum adiponectin, leptin and adiponectin-leptin ratio as possible biomarkers of preeclampsia. Edorium J Gynecol Obstet 2016;2:41–47.

Article ID: 100013G06LF2016

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doi:10.5348/G06-2016-13-OA-7

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Received: 28 July 2016
Accepted: 12 October 2016
Published: 01 November 2016

INTRODUCTION

Preeclampsia is a pregnancy-specific syndrome characterized by hypertension and significant proteinuria. It affects 2–8% of pregnancies globally, and is associated with substantial maternal and fetal morbidity and mortality [1]. To date, the pathogenesis and pathophysiology of preeclampsia remains elusive, although several theories–comprising immunological, genetic, hematological and environmental factors–have

been proposed. All these factors are believed to result in endothelial dysfunction, inflammation and angiogenesis, which are evident in preeclampsia [1, 2]. Since adiponectin and leptin – plasma proteins partly produced by the placenta [3] have been found to play roles in endothelial dysfunction, inflammation, angiogenesis and proteinuria, it has been hypothesized that these adipokines may play roles in the development of preeclampsia [1, 2]. If they are involved in the pathogenesis of preeclampsia, then their levels in preeclampsia and normotensive pregnancy may differ, thus serving as biomarkers and possible therapeutic targets for the diagnosis and treatment of preeclampsia respectively. Nonetheless, studies in this area have been inadequate and reports have been conflicting.

While some studies have reported higher levels of adiponectin [4] and leptin [5] in preeclampsia, compared to normotensive pregnancy, others have reported differently [6–8]. Furthermore, not many of these studies have been conducted in Africa and for that matter Ghana. It is, therefore, evident that the levels of these markers- adiponectin, leptin and the adiponectin-leptin ratio in normotensive pregnancy and preeclampsia need additional investigation in the Ghanaian population. We hypothesize a priori that adiponectin, leptin and the adiponectin-leptin can serve as biomarkers for preeclampsia. This study thus aimed at comparing the levels of adiponectin, leptin and the adiponectin-leptin ratio between normotensive pregnancy and pregnancy complicated with preeclampsia.

MATERIALS AND METHODS

Study Site and Design

This case-control study was conducted at the Manhyia Government Hospital, a secondary healthcare facility in the Ashanti Region of Ghana between the periods of January 2014 to March 2014.

Ethical Considerations

The study was approved by the Committee on Human Research Publications and Ethics of the School of Medical Sciences, Kwame Nkrumah University of Science and Technology as well as the Institutional Review Board of the Hospital. Participation was voluntary and informed consent was obtained from each study participant.

Eligibility Criteria

Inclusion criteria were third trimester pregnant women above 18 years and with first trimester body mass indices greater than 18.5 kg/m^2 but less than 30.0 kg/m^2; with or without hypertension (cases and controls respectively). Normotensive pregnant women without dipstick (reagent strip) proteinuria were enrolled as controls. While pregnant women with multiple pregnancy, pre-gestational hypertension, renal disease, diabetes, cancers were excluded from the study.

Study Population

Sixty normotensive pregnant women were enrolled as controls and sixty maternal age, gestational age and body mass index matched drug-naive preeclamptic women were enrolled in the study as cases. Pregnant women with high blood pressure (≥ 140/90 mmHg) on two occasions, at least four hours apart, with visible dipstick proteinuria (≥ "+"), were categorized as preeclampsia [9]. The diagnosis of preeclampsia was done by qualified obstetrician/gynecologist. Clinical information and biological samples were collected from participants soon after recruitment.

Anthropometric Measurement

The participants stood on a Camry weight balance (Zhongshan Camry Electronic Co. Ltd, Guangdong, China) after they had removed their shoes and any other heavy clothing. Their weights were recorded to the nearest 0.1 kg; and their heights were measured to the nearest whole number with a stadiometer. Each participant stood with heels, buttocks and shoulders resting lightly against the backing board so that the Frankfort plane was horizontal. All the measurements were converted to the SI units. That is; kilogram (kg) for weight and metre (m) for height. Body mass index (BMI) for each participant was calculated as weight (kg)/height (m^2) [10].

Blood Pressure Measurement

Each participant was asked to sit down comfortably, extend the left arm on a table and then relax for 10 minutes. Mercury sphygmomanometer and a stethoscope was used by trained personnel to measure the systolic blood pressure and diastolic blood pressure of each participant. Measurements were taken from the left arm in accordance with the recommendations of the American Heart Association [11]. Duplicate measurements were taken after each participant had had a 5–10 minute-rest interval between successive measurements. The mean values of the duplicate measurements were then computed and recorded as the blood pressure.

Collection, Preservation and Biochemical Analysis of the Blood Samples

About 5 ml of venous blood samples were collected from each participant and introduced into serum separator tubes. The blood samples were then centrifuged and aliquots of the serum pipetted into CryoPure tubes, and stored at -80^{o}C in a refrigerator. Total serum adiponectin and leptin were quantified in the serum with the quantikine® human adiponectin immunoassay method and the quantikine® human leptin immunoassay method respectively (R&D systems, USA), according to the manufactures' instructions.

Collection, Preservation and Biochemical Analysis of the Urine Samples

Each participant was provided with clean dry, wide mouth, leak proof containers for urine sample. About 5 ml of urine were collected from each participant. The samples that contained visible precipitates were centrifuged to obtain clear specimens. Urine protein was determined using the dipstick semi-quantitative method (CYBOW™ DFI Co Ltd, Gimhae-City, Republic of Korea). Proteinuria in respondents with preeclampsia was defined as the presence of urinary protein in concentrations ≥ "+", using the semi-quantitative color scale on the urine reagent dipstick [9].

Statistical Analysis

Differences in measured variables between groups were assessed with unpaired Student's t-test and associations among variables were described with Pearson's correlation coefficients. One-way ANOVA was used to compare multiple groups. Two-tailed tests were used for all analysis, and significance was assessed at a p-value<0.05. Statistical computations were made using SPSS (version 20) (SPSS Inc, Chicago, IL, USA).

RESULTS

The entire study population comprised of 60 normotensive pregnant women and 60 women with preeclampsia. As given in Table 1, in both the normotensive pregnancy and preeclampsia most of the respondents were within the age range 18–23 years. All the participants had had formal education and there was significant between group differences in educational status. The majority of the participants were employed in the informal sector. None of the normotensive pregnant women were single, whereas 17% of the women with preeclampsia were unmarried, marital status also showed significant between group differences. While the prevalence of gravidity differed significantly between the normotensive and the preeclamptic women, the opposite held true for the prevalence of parity between the two groups. Although, most of the respondents, however, were nulliparas.

Table 1: Distribution of socio-demographic and obstetric parameters among the studied participants

Parameters	Normotensive women	Preeclampsia	p-value
	N=60	N=60	
Ages (years)			0.6704
18–23	29 (48%)	31 (52%)	
24–29	15 (25%)	11 (18%)	
30–36	16 (27%)	18 (30%)	
Educational status			**0.0243**
University Graduates	21(35%)	18 (30%)	
SHS Graduates	10(17%)	23 (38%)	
JHS Graduates	29(48%)	19 (32%)	
Occupational Status			0.6186
Formal	1 (2%)	3(5%)	
Informal	59(98%)	57(95%)	
Marital status			**0.0013**
Single	0 (0%)	10 (17%)	
Married	60(100%)	50 (83%)	
Divorcee	0 (0%)	0 (0%)	
Gravidity			**0.0045**
Nulligravida	-	-	
Primigravida	35(58%)	50(83%)	
Multigravida	25 (42%)	10 (17%)	
Parity			0.3679
Nulliparas	35 (58%)	40 (67%)	
Primiparas	15 (25%)	15(25%)	
Multiparas	10 (17%)	5 (8%)	

Abbreviations: Results are expressed as: actual values (percentages); JHS Junior High School, SHS Senior High School, Data in boldface indicate statistical significance.

Table 2 gives that the normotensive pregnant women and the preeclamptic women had comparable ages (p = 0.322), comparable gestational ages (p = 0.490) and comparable body mass indices (p = 0.534). As expected the preeclamptic women had higher systolic blood pressures (p=0.001) and diastolic blood pressures (p = 0.010). Adiponectin levels (p = 0.001), leptin levels (p = 0.010) and adiponectin-leptin ratios (p = 0.001) was higher in the women with preeclampsia as compared to the normotensive pregnant women.

Table 3 gives the correlation among adiponectin, leptin and blood pressure in the normotensive pregnant women and the preeclamptic women. Among the normotensive pregnant women, adiponectin correlated inversely with leptin (p = 0.002), body mass index (p = 0.001), systolic blood pressure (p = 0.003) and diastolic blood pressure (p = 0.024); but all these relationships, except for body mass index, were blunted among the preeclamptic women (p > 0.05). Leptin correlated positively with body mass index (p = 0.021), systolic blood pressure (p = 0.040) and diastolic blood pressure (p = 0.031) among the normotensive pregnant women.

Among the preeclamptic women, there was a strong linear relationship between leptin and systolic blood pressure (p = 0.001) and diastolic blood pressure (p = 0.010). Among the normotensive pregnant women, the adiponectin-leptin ratio correlated inversely with body mass index (p = 0.022), systolic blood pressure (p = 0.031) and diastolic blood pressure (p = 0.023). Among the preeclamptic women, similar inverse correlation were observed between the adiponectin-leptin ratio and body mass index (p = 0.004), systolic blood pressure (p = 0.011) and diastolic blood pressure (p = 0.021).

DISCUSSION

It has been observed from this study that an inverse relationship exists between adiponectin and leptin in the normotensive pregnant women but not in the preeclamptic

Table 2: Adiponectin, leptin and the adiponectin-leptin ratio compared between normotensive pregnancy and preeclampsia

Parameter	Normotensive pregnant women N=60	Preeclamptic women N=60	p-value
Age (years)	27.12±5.92	28.11±4.98	0.322
Gestational Age (weeks)	34.41±3.103	35.15±2.00	0.490
BMI (kg/m²)	26.77±3.00	26.56 ± 3.10	0.534
Adiponectin (µg/ml)	4.14 ± 0.91	12.27 ± 3.22	**0.001**
Leptin (ng/ml)	13.36 ±3.11	18.22 ± 2.01	**0.010**
Adiponectin-leptin ratio	0.30 ± 0.10	0.66 ± 0.10	**0.001**
SBP (mmHg)	115.85 ±8.70	150.21±7.11	**0.001**
DBP (mmHg)	73.82 ±7.95	99.12 ± 9.00	**0.010**

Abbreviations: BMI Body Mass Index, SBP Systolic Blood Pressure, DBP Diastolic Blood Pressure

†N Sample size, Data mean±standard deviation, Data in boldface indicate statistical significance.

Table 3: Pearson correlations among adiponectin, leptin, adiponectin-leptin ratio, body mass index and blood pressure of the normotensive and the preeclamptic women

Parameter	Normotensive pregnant women		Preeclamptic women	
	r	p-value	r	p-value
Adiponectin and Leptin	-0.768	0.002	-0.290	0.052
Adiponectin and BMI	-0.723	0.001	-0.521	0.003
Adiponectin and SBP	-0.410	0.003	-0.320	0.053
Adiponectin and DBP	-0.490	0.024	-0.440	0.055
Leptin and BMI	0.800	0.021	0.700	0.002
Leptin and SBP	0.499	0.040	0.578	0.001
Leptin and DBP	0.300	0.031	0.601	0.010
Adiponectin-leptin ratio and BMI	-0.589	0.022	-0.429	0.004
Adiponectin-leptin ratio and SBP	-0.432	0.031	-0.241	0.011
Adiponectin-leptin ratio and DBP	-0.331	0.023	-0.332	0.021

r = Correlation Coefficient

women. This therefore suggests that adiponectin and leptin levels are possibly altered by preeclampsia. The results of this study also indicate that adiponectin levels are significantly elevated in preeclampsia as compared to normotensive pregnancy, with the preeclamptic levels being approximately three times the normotensive pregnancy levels. Studies conducted by Abd-Alaleem et al. and Khosrowbeygi et al. are in consonance with the findings of this present study [4, 12]. However, studies conducted by authors contradict the findings of this study [6, 7, 13]. While Hendler et al., [6] observed that the levels of adiponectin in normotensive pregnancy and preeclampsia are comparable, and Mazaki-Tovi et al. and Ouyang et al. observed significantly lower levels of adiponectin in preeclampsia than in normotensive pregnancy [7, 13]. Several reasons could account for the higher levels of adiponectin in preeclampsia –which is characterized by hypertension, proteinuria, inflammation and endothelial dysfunction [2, 14].

Overproduction of angiotensin II of the Renin-Angiotensin System (RAS) is linked to hypertension [15] and since it has been established that adiponectin antagonises the production of angiotensin II [16], it could be stated that hyperadiponectinaemia during preeclampsia is a possible feedback mechanism to antagonize angiotensin II production so as to control hypertension [17]. A study conducted by Sharma et al., [18] revealed that the expression of adiponectin receptor 1 (AdipoR1) in podocytes helps adiponectin to increase adenosine monophosphate kinase (AMPK) phosphorylation in podocytes to regulate kidney function against proteinuria. These investigators then concluded that adiponectin has a positive effect on the kidney, and that a fall in adiponectin levels may predispose to proteinuria, and a rise in adiponectin levels may be protective against proteinuria [18]. This indicates that elevation in the levels of adiponectin is, probably, part of the body's physiological mechanism that acts to forestall the development of proteinuria associated with preeclampsia. This assertion is supported by the findings of Hendler et al., [6] which indicated that alterations in renal function and an on-going adiponectin synthesis in adipose tissues might result in a rise in adiponectin levels. According to Tan et al., [19], adiponectin receptors are also expressed in human endothelial cells; so adiponectin binds to those receptors to regulate endothelial nitric oxide synthase (eNOS) activity which results in increased nitric oxide production in human aortic endothelial cells to offset endothelial dysfunction [20]. Since the endothelium plays a role in inflammation [21], protecting it from dysfunctional effects, will, in a way, control inflammatory processes. As posited by Robinson et al., [22], adiponectin exerts an anti-inflammatory effect through activation of all of its receptors by having direct actions on inflammatory cells and nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), and interacting with tumor necrosis factor alpha (TNF-α) [22]. This, therefore, indicates that hyperadiponectinaemia during preeclampsia is a step to restoring the integrity of the endothelium, and counteracting the inflammatory processes. All these positive feedback reactions of increasing adiponectin levels to annul the pathology, then possibly result in adiponectin resistance [23]. The above stated roles of adiponectin in preeclampsia depicts that a rise in the levels of adiponectin in preeclampsia, as observed in this study, could be suggestive of the body's physiological mechanism of antagonizing the pathophysiological progression of preeclampsia.

Also, in this study, the levels of leptin were observed to be significantly higher in the preeclamptic women than in the normal pregnant women. The report of this study is in concordance with the reports of Mumtaz et al., [5], but in divergence with the reports of Martinez-Abundis et al. [24] and Laml et al. [8]. While Martinez-Abundis et al. [24] observed that serum leptin levels are comparable between normal pregnancy and preeclampsia, and so concluded that leptin cannot be used as a biomarker for preeclampsia, Laml et al. [8] observed decreased levels of leptin in preeclampsia.

The positive correlation between leptin and blood pressure in the normal pregnant women, and the increase in strength of this positive correlation in preeclampsia suggests that the pathophysiological progression of preeclampsia may involve hyperleptinaemia. The finding that angiotensin II stimulates leptin production [25], and that higher leptin levels can cause hypertension [26], proteinuria and endothelial dysfunction [27], together with the finding that leptin plays a vital role during inflammation [28], may justify the higher levels of leptin seen in the preeclamptic women. Thus, unlike adiponectin, the rise of leptin levels during preeclampsia may not indicate a feedback mechanism to rectify the pathology but, rather, a pathophysiological mechanism to exacerbate the pathology.

In this study, adiponectin-leptin ratio was two times higher in the preeclamptic women than in the normotensive pregnant women (100% increment). This suggest that during preeclampsia, the physiological mechanisms that underlie the secretion and circulation of adiponectin and leptin are altered, and that a transient increase in adiponectin-leptin ratio at any gestational age may be predictive of preeclampsia, and about 100% rise may indicate a preeclamptic state.

CONCLUSION

The levels of adiponectin, leptin and the adiponectin-leptin ratio are elevated in preeclampsia. This indicates that they could serve as biomarkers for preeclampsia, and that determination of their levels could be integrated into the routine obstetric investigations that form the basis of antenatal care to help in early diagnosis of preeclampsia.

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Acknowledgements
The authors are thankful to the staff and clients of the Obstetric and Gyneacology Department of Manhyia Government Hospital, Kumasi Ghana.

Author Contributions
Linda Ahenkorah Fondjo – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Critical revision of the article, Final approval of the version to be published
Enoch Appiah Adu Gyamfi – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Critical revision of the article, Final approval of the version to be published
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Daniel Asante Mante – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Critical revision of the article, Final approval of the version to be published
Enoch Odame Anto – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Critical revision of the article, Final approval of the version to be published

Guarantor
The corresponding author is the guarantor of submission.

Conflict of Interest
Authors declare no conflict of interest.

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