Afr. J. Med. Med. Sci. (2018) 47, 141-146

Serum adiponectin levels in normotensive and pre-eclamptic women at the University College Hospital, Ibadan, Nigeria

OM Akinpelu, FA Bello, OA Awolude, CO Adetayo, BO Akinwunmi and AA Odukogbe

Department of Obstetrics and Gynaecology, College of Medicine, University of Ibadan, Ibadan, Nigeria

Abstract

Background: Adiponectin is a hormone produced mainly by adipocytes. The levels of adiponectin are inversely related to insulin resistance, hypertension and obesity. Physiological insulin resistance is exaggerated in pre-eclamptic women. The objective of the present study was therefore to compare serum adiponectin levels in pre-eclamptic patients and normotensive patients.

Methods: This prospective study was conducted among one hundred and twenty women. Purposive sampling technique was used to select all consenting participants, consisting of sixty pre-eclamptic patients as cases and sixty normotensive pregnant women at comparable gestational age as control. Concentration of serum adiponectin was measured by using enzyme linked immunosorbent assay (ELISA) method.

Results: Serum levels of adiponectin were significantly higher in the pre-eclampticgroup(p<0.001). Body mass index was also significantly higher in women with pre eclampsia (p<0.01).In the pre-eclamptic patients, serum levels of adiponectin showed a weak negative correlation with BMI (r= -0.16, p= 0.22) and no correlation was found in normotensive patients.

Conclusion: This study showed a clear distinction in the serum adiponectin concentration between pre-eclamptic and normotensive pregnant women. The impact of BMI on serum adiponectin in both groups also differs. Therefore, serum adiponectin may be useful in predicting pre-eclampsia.

Keywords:*Serum adiponectin, Normotensive, pre-eclamptic, UCH, Pregnant woman*

Résumé

Contexte: Adiponectine est une hormone produite principalement par les adipocytes. Les niveaux d'adiponectine sont inversement liés à la résistance à l'insuline, à l'hypertension et à l'obésité. La résistance à l'insuline physiologique est exagérée chez les femmes pré-éclamptiques. L'objectif de la présente étude était donc de comparer les taux sériques d'adiponectine chez des patientes pré-éclamptiques et des patientes normo-tendues.

Méthodes: Cette étude prospective a été menée auprès de cent vingt femmes. La technique d'échantillonnage raisonné a été utilisée pour sélectionner tous les participants consentants, consistant soixante patientes pré-éclamptiques en tant que cas et soixante femmes enceintes normo-tendues à un âge gestationnel comparable en tant que témoin. La concentration d'adiponectine sérique a été mesurée en utilisant la méthode ELISA.

Résultats: Les taux sériques d'adiponectine étaient significativement plus élevés dans le groupe pré-éclamptique (p<0,001). L'indice de masse corporelle était également significativement plus élevé chez les femmes pré-éclamptiques (p <0,01). Chez les patientes pré-éclamptiques, les taux sériques d'adiponectine présentaient une faible corrélation négative avec l'IMC (r = -0,16 ; p = 0,22) et aucune corrélation chez les patientes normo-tendues.

Conclusion: Cette étude a montré une nette distinction dans la concentration sérique d'adiponectine entre les femmes enceintes pré-éclamptiques et normo-tendues. L'impact de l'IMC sur l'adiponectine sérique dans les deux groupes diffère également. Par conséquent, l'adiponectine sérique peut être utile pour prédire la pré-éclampsie.

Mots clés: *Sérum adiponectine, normo-tendus, pré-éclampsie, UCH, femme enceinte*

Introduction

Pre-eclampsia, one of the biggest causes of maternal and perinatal mortality and morbidity is a pregnancy complication which is associated with hypertension [1].Women with pre-eclampsia are at a higher risk of developing pulmonary edema, coagulation defects, blindness, cerebral hemorrhage, hepatic and/or renal failure, seizures and later in life, cardiovascular diseases while newborn babies of pre-eclamptic patients tend to be premature and are more prone to be small for gestational age [2,3].

The global estimate of complications of pregnancies due to pre-eclampsia is between 2 and 10% [2]. The World Health Organisation (WHO)

Correspondence: Dr. O.M. Akinpelu, Department of Obstetrics and Gynaecology, College of Medicine, University of Ibadan, Ibadan, Nigeria. E-mail:o_akinpelu@yahoo.com

reported that in developing countries,the incidence of pre-eclampsia is seven times higher than in developed countries[4].Various studies in Nigeria have revealed the prevalence of pre-eclampsia to be between 0.3% and 3.3% [5,6,7]. Many conditions have been linked to pre-eclampsia, including prior hypertension and insulin-dependent diabetes mellitus [8, 9]. The risk of pre-eclampsia is higher in primigravid women and it increases with greater interval between pregnancies, age greater than 40 years, pre-pregnancy obesity and pre-existing hypertension [9].

The etiology of pre-eclampsia remains obscure at the present [10]. In spite of the fact that researchers in the last century could not reveal the etiology of pre-eclampsia, much improvement was made in comprehending the pathophysiological changes related with its development [11]. Many hypotheses about etiology and pathogenesis of pre-eclampsia have been reported and they relate to angiogenesis, inflammation and endothelial dysfunction [11]. Adiponectin, a specific adipocyte-derived hormone has been thought to enhance insulin sensitivity, restrict atherogenesis and vascular inflammation [11].It has been suggested that adiponectin plays an important role in regulating metabolic adaptation during pregnancy as well as pathophysiology of pre-eclampsia [12]. Ali & Hassan concluded that insulin resistance indices correspond with circulating maternal adiponectin concentrations during pregnancy and that pre-eclampsia is linked with alterations in maternal adiponectin concentrations [12]. Several studies have reported elevated serum levels of adiponectin in pre-eclamptic women compared to normotensive women [11-16]. In contrast to this finding, some other studies have revealed decreased levels of serum adiponectin in women with pre-eclampsia [12]. Ramsey *et al* discovered that "serum adiponectin levels in the third trimester are higher in women with pre-eclampsia compared with controls". The reason for this elevation was stated to be due to exaggerated non-specific adipolysis and feedback mechanism to improve insulin sensitivity [17, 18]. Fasshauer *et al* also confirmed this finding in their study [18].

The relationship of adiponectin concentrations with BMI has also been examined by various researchers. For instance, one study attempting to determine "maternal serum levels of adiponectin in pre-eclampsia" found out that serum levels of adiponectin of pre-eclamptic patients revealed a significant negative correlation with BMI prior to pregnancy and third trimester [11].This finding has also been confirmed by Nien *et.al* [19].

There is no published research work done in Nigeria to determine serum levels of adiponectin, hence the need for this study. An understanding of the impact of pre-eclampsia on serum adiponectin levels in pregnancy will help to determine the usefulness of the protein as a valuable screening test for patients at risk, especially in our environment. This study therefore aimed to compare serum adiponectin levels between normotensive and pre-eclamptic women attending antenatal clinic at the University College Hospital, Ibadan.

Materials and method

This prospective case- control study was conducted at the University College Hospital, Ibadan, which is a tertiary health institution with eight hundred and fifty bed spaces. It is located in Ibadan, the capital of Oyo State. Its Obstetrics and Gynaecology department provides specialist care for antenatal, intrapartum and post natal patients. It is a study centre for many research works on pre-eclampsia.

One hundred and twenty pregnant women participated in the study. Purposive sampling technique was used to select all consenting participants. Sixty pre-eclamptic patients were cases while the other sixty were healthy normotensive patients at comparable gestational age served as the control group. Inclusion criteria were:Women diagnosed to have pre-eclampsia as cases and healthy normotensive pregnant women at a comparable gestational age as controls. Exclusion criteria included women with molar gestation, chronic hypertension, cardiac disease, Human Immunodeficiency Virus (HIV), renal disease, liver disease, diabetes mellitus, sickle cell disease and non-consenting patients. The diagnosis of pre-eclampsia was made using American College Of Obstetrician and Gynaecologists'(ACOG) guidelines [10].A proforma, designed based on existing literature findings, was used to collect patients' information and clinico-laboratory findings including maternal and gestational age, parity, height, weight, body mass index (BMI), blood pressure (BP), urinalysis, serum total adiponectin and high molecular weight adiponectin levels, maternal outcome(Glasgow coma scale score, need for intensive care unit, development of eclampsia and HELLP syndrome) and infant outcome (birth weight, Apgar score, need for admission into neonatal intensive care unit). Measurement of severity of the disease (mild or severe pre-eclampsia) was determined by the mean arterial blood pressure. The blood pressure was measured using a desk-type mercury sphygmomanometer with big cuff

(ACCOSON, Essex, England) calibrated in mmHg. The Korotkoff phase V (disappearance of sound) was used as the diastolic blood pressure. The mean arterial pressure (MAP) was calculated as DBP + (SBP - DBP)/3 mmHg.[SBP= Systolic blood pressure and DBP= Diastolic blood pressure]

The concentrations of adiponectin were measured using commercially available Human Adiponectinenzyme-linked immunosorbent assay (ELISA) by Biovendor®, Brno, Czech Republic. The procedures for the measurement were performed based on the instructions by the manufacturer.To measure the total Adiponectin concentrations,the sample was pre-treated with Sample Pretreatment Buffer (Citrate buffer + Sodium Dodecyl Sulphate [SDS]) which reduces multimeric adiponectin to dimers. Subsequent measurements by the ELISA quantified the amount of all multimers of adiponectin in the sample.

BMI was classified as normal (18.5-24.9)kg/m^2, overweight (25.0-30.0) kg/m^2 and >30kg/m^2 was regarded as obesity. Normal range of serum adiponectin is between 3.58 and 9.68µg/ml according to kit's manufacturer's manual. Apgar scores between 0 and 6 were considered to be low while 7 and above were considered normal.

All collected data were analysed using the Statistical Package for the Social Sciences (SPSS) version 17. The difference in mean serum adiponectin levels of the two groups was statistically tested using the Student t- test.

Spearman correlation coefficient was used to find a correlation between adiponectin and blood pressure, serum adiponectin and BMI. Level of significance was set at $p<0.05$.

Results

Table 1 shows the socio-demographic and clinical characteristics of normotensive and pre-eclamptic pregnant women. The mean ages of normotensive and pre-eclamptic pregnant women were similar. In the pre-eclampsia group, significant shorter length of gestation at delivery was observed ($p<0.0001$). Mean serum level of adiponectin and BMI was significantly higher in the pre-eclamptic group compared to normotensives ($p<0.01$).

The association between serum adiponectin levels and signs of severe pre-eclampsia among pre-eclamptic women is shown in Table 2. In the pre-eclamptic group, only four subjects developed seizures; out of these, three (75%) had significantly high levels of serum adiponectin ($p=0.02$). Development of headache was significantly associated with high serum adiponectin level

Table 1: Socio-demographic and clinical characeristics of normotensive and pre-eclamptic pregnant women

Variable	Normotensive (n=60)	Pre-eclamptic (n=60)	P-value
Age (years)	30.8±3.9	31.1 ±4.8	0.66
GA at delivery	38.55 ±1.11	36.93±2.84	<0.0001
SystolicBP	109.4 ±9.6	160.3 ±18.3	<0.0001
DiastolicBP	67.0 ±7.9	102.3±12.9	<0.0001
BMI	27.5 ±4.3	30.1 ±4.7	<0.01
Adiponectin (µg/ml)	6.3 ±1.8	9.9 ±5.4	<0.001

Table 2: Association between serum adiponectin levels and signs of severe pre-eclampsiaamong pre-eclamptic women

Variables	Serum adiponectin			
	Normal(%)	Abnormal(%)	Chi Square	p-value
Development of eclampsia (Seizures)				
Yes	1(25.0)	3(75.0)	5.83	0.02
No	90(77.6)	26(22.4)		
Development of headaches				
Yes	11(52.4)	10(47.6)	7.64	<0.01
No	80 (80.8)	19(19.2)		
Vomiting				
Yes	4(66.7)	2(33.3)	0.29	0.59
No	87(76.3)	27(23.7)		
Development of blurring of Vision				
Yes	3(75.0)	1(25.0)	0.002	0.97
No	88(75.9)	28(24.1)		
Development of epigastric pain				
Yes	5(50.0)	5(50.0)	3.97	0.05
No	86(78.2)	24(21.8)		

(p<0.01). Other severe pre-eclampsia symptoms such as vomiting (p=0.59) and epigastric pain(p=0.05) were associated with elevated serum adiponectin levels, but not significantly.

Table 4 shows serum adiponectin levels and neonatal outcomes in pre-eclamptic and normotensive women. There were more babies in the pre-eclamptic group with low Apgar scores. In

Table 3: Relationship between BMI and serum adiponectin levels

BMI	Normotensive	Pre-eclamptic	T	p- value
Normal BMI (n=26)	6.2±1.8*	10.6±4.9*	-3.27	<0.01
Overweight (n=94)	6.4±1.9*	9.7±5.5*	-3.98	<0.0001

**mean+ SD serum adiponectin (in µg/ml)*

Table 4: Serum adiponectin levels and neonatal outcome among pre-eclamptic women

	n	Serum Adiponectin Normotensive (Mean±SD)	n	Serum Adiponectin Pre-eclamptic (Mean±SD)	p- value
Apgar score					
Low	6	6.6±2.4	46	10.0±5.4	0.02
Normal	54	6.3±1.8	14	9.4±5.8	0.07
Birthweight					
Low	4	7.2±1.0	22	10.6±6.1	0.03
Normal	56	6.3±1.9	38	9.4±5.0	<0.01
Need for SCBU admission					
Yes	0	0	16	9.9±6.7	-
No	60	4.4±0.3	44	10.7±5.5	<0.001
Neonatal condition at birth					
Alive	6	6.3±1.8	54	9.5±5.1	<0.01
Dead	00	0	6	11.5±6.6	-

Table 3 reveals relationship between BMI, blood pressure and serum adiponectin levels. Mean serum adiponectin was significantly higher in pre-eclamptic overweight women (p<0.0001). Similarly, among women with normal weight, the mean serum adiponectin level was significantly higher in the pre-eclamptic group (p<0.01). The relationship of adiponectin concentrations with BMI was further explored. In the pre-eclamptic patients, serum levels of adiponectin showed a weak negative correlation with BMI (r= -0.16, p= 0.22). In the normal pregnant women, no correlation was found between serum levels of adiponectin and BMI.

Also, a negative correlation of serum adiponectin levels with diastolic blood pressure (r=0.82, p=0.06) was observed and a positive correlation with systolic blood pressure (r=0.30, p<0.01) was found.

the pre-eclamptic group, the participants whose babies had low apgar scores had higher mean serum adiponectin levels (p=0.02). In the same vein, mothers of babies with low birthweight in the pre-eclamptic group had higher mean serum adiponectin compared to those with low birthweight in the normotensive group. All six neonates that died were in the pre-eclamptic group.

Discussion

The findings from the current study suggest that serum adiponectin levels are higher in pre-eclamptic pregnancy. This is also in line with results from studies by Ramsay *et al* [17]. Nien *et al* [19], and Naruse *et al* [21] where these researchers indicated that plasma adiponectin concentrations were especially increased in women with pre-eclampsia compared with normotensive pregnant women. Ali and Hassan also confirmed that the most significant

finding of their study was an obvious increase in serum levels of adiponectin in women with pre-eclampsia when compared with pregnant women without pre-eclampsia [12]. Faussher *et al*, concluded that increased adiponectin serum levels in pre-eclamptic patients are positively associated with renal dysfunction [18], although this does not correlate with the creatinine levels of the women in their study which were within the normal range.Some of the authors likewise suggested that generation of adiponectin is increased due to physiological reaction by adipocytes in pre-eclamptic women to restrict atherogenesis and resultant vascular inflammation and also to enhance insulin sensitivity. However, contrary to these results, some other researchers have observed that pre-eclamptic women have reduced serum adiponectin concentrations than those of normal healthy pregnant women [12,16,18]. Some in the later group such as Mazaki-Tovi *et al* proposed that high and low levels of serum adiponectin in pre-eclamptic patients compared to normotensive pregnant women infers that adiponectin assumes a regulatory role in vascular and metabolic complications of pregnancy [22]. In the current study, serum levels were significantly associated with development of eclampsia.

Nienet al's study found out that adiponectin levels of normal pregnant women correlate negatively with BMI [19]. Dissimilar to their study, the findings from the present study have revealed a weak positive relationship between serum adiponectin level and BMI in the normotensive women, and very weak negative correlation in pre-eclamptic women [19]. This may be explained by the fact that BMI in pregnancy is impacted by the weight of the fetus, placenta and amniotic fluid and by plasma volume: this infers that maternal weight does not precisely reflect fat stores [27].

This study has shown a negative correlation of serum adiponectin levels with diastolic blood pressure and positive correlation with systolic blood pressure in normal healthy pregnant women. This is contrary to findings of Li *et al* where the authors reported a negative correlation between adiponectin and blood pressure in normotensive patients [25]. The authors concluded that this effect may be mediated through inflammatory pathway or lipid metabolism [25]. Abnormal serum adiponectin levels were found more in patients with signs of severe pre-eclampsia. This corroborates our earlier finding of higher mean adiponectin concentrations in pre-eclamptic patients.

Dalamangal *et al.*, in their case-control study, found that women in the pre-eclamptic group had a lower mean gestational age at delivery and smaller birth weights when compared with normal pregnant women [26].This finding was additionally affirmed in the current study. This may be partly explained by the fact that pre-eclamptic women may be delivered early to limit the progression of the disease.

Adiponectin levels were significantly higher in association with poor neonatal outcome (low birth weight and poor Apgar scores) in pre-eclamptic mothers. This again may highlight the usefulness of adiponectin in predicting poor outcomes of pregnancy.

The results of this study must be interpreted with caution as the findings may not be generalizable due to the small sample size. It would also have been desirable to take sequential samples to determine when Adiponectin levels begin to rise in pre-eclampsia and thus determine whether it can predict pre-eclampsia (rather than just be an association). The earlier gestational age at which normotensive women were recruited could be a confounder in the interpretation of results. Non-use of re-pregnancy body weight can be described as a limitation for the study.

Conclusion

This study revealed that there is a clear distinction in the serum adiponectin concentration between pre-eclamptic and normotensive pregnant women. The impact of BMI on serum adiponectin in both groups differs. Elevated serum adiponectin is associated with progression to eclampsia and poor neonatal outcome. Further longitudinal research is required to study these associations and to determine the usefulness of adiponectin as a predictor of severe pre-eclampsia, its progression and to determine the implications of weight loss on adiponectin and pregnancy outcome in pre-eclampsia.

References

1. Fact sheet on hypertension and pregnancy (2013). Geneva, World Health Organisation. Available at www.paho.org/hipertension/wp.../2013/04/WHD2013-factsheet. Accessed on 8th of November, 2015.
2. Sibai B, Dekker G and Kupferminc M. Pre-eclampsia. Lancet. 2005; 365:785–799.
3. Roberts JM and Cooper DW. Pathogenesis and genetics of pre eclampsia. Lancet. 2001; 357:53–56.
4. WHO, Make every mother and child count, in the World Health Report 2005, World Health Organization, Geneva, Switzerland, 2005.

5. Itam IH and Ekabua JE. Socio-demographic determinants of eclampsia in Calabar; A ten year review. Mary Slessor Journal of Medicine 2003;3:72-74.
6. Kooffreh ME, Ekott M and Ekpoudom DO. The prevalence of pre-eclampsia among pregnant women in the University of Calabar Teaching Hospital, Calabar. Saudi Journal for Health Sciences 2014; 3:133-136.
7. Ugwu EO, Dim CC, Okonkwo CD and Nwankwo TO. Maternal and perinatal outcome of severe pre-eclampsia in Enugu, Nigeria after introduction of magnesium Sulphate. Nigeria Journal of Clinical Practice 2011; 14:4: 418-421.
8. National Institute for Health and Care Excellence (NICE). Hypertension in pregnancy: the management of hypertensive disorders during pregnancy. NICE CG 107. National Institute for Health and Clinical Excellence; Manchester, UK: 2010.
9. Fred AE, Louise C K and Fergus P M. Risk factors and effective management of pre-eclampsia. Integrated blood pressure control2015; 8: 7-12
10. American College of Obstetricians and Gynecologists. ACOG practice bulletin: Diagnosis and management of pre eclampsia and eclampsia. Obstetrics & Gynecology. 2002; 99(1):159-167.
11. Mandy J B. A Historical Overview of Pre-eclampsia-Eclampsia. Journal of Obstetric, Gynecologic and Neonatal nursing. 2010; 39(5): 510-518.
12. Ali K and Hassan A. Maternal Serum Levels of Adiponectin in Pre-eclampsia. Journal of Ayub Medical College, Abbottabad 2009; 21:79-82.
13. Mazaki-Tovi S, Romero R, Vaisbuch E, *et al.* Maternal serum adiponectinmultimer in pregnancy. Journal of Perinatal Medicine. 2009; 37: 4:349-363.
14. Nakatsukasa H, Masuyama H, Takamoto N, and Hiramatsu Y. Circulating leptin and angiogenic factors in pre eclampsia patients. Endocrine Journal 2008; 55:565–573.
15. Lu D, Yang X, Wu Y, *et al.* Serum adiponectin, leptin and soluble leptin receptor in pre-eclampsia. International Journal of Gynecology and Obstetrics 2006:95:121-126.
16. Takemura Y, Osuga Y, Koga K, *et al.* Selective increase in high molecular weight adiponectin concentration in serum of women with pre eclampsia. Journal of Reproductive Immunology 2007; 73:60-65.
17. Ramsay J.E., Jamieson N., Greer I.A. and Sattar N. Paradoxical elevation in adiponectin concentrations in women with pre eclampsia. Hypertension. 2003; 42:891–894.
18. Fasshauer M., Waldeyer T. and Seeger J. Circulating high-molecular-weight adiponectin is upregulated in pre eclampsia and is related to insulin sensitivity and renal function. European Journal of Endocrinology. 2008; 158:197–201.
19. Nien JK, Mazaki-Tovi S, Romero R, *et al.* Adiponectin in severe pre eclampsia. Journal of Perinatal Medicine. 2007;35:503–512.
20. Abd-Alaleem DI, Attiaa KI, Khalefa AA and Ahmad RA. Serum Adiponectin levels in women with pre eclampsia. Eastern Mediterranean Health Journal. 2011: 17: 575-581.
21. Naruse K, Yamasaki M, Umekage H, *et al.* Peripheral blood concentrations of adiponectin, an adipocyte -specific plasma protein, in normal pregnancy and pre eclampsia. Journal of Reproductive Immunology. 2005; 65:65-75.
22. Mazaki-Tovi S, Kanety H and Sivan E. Adiponectin and human pregnancy. Current Diabetes Report. 2005; 5:278–281.
23. Mazaki-Tovi S, Kanety H, Pariente C, *et al.* Maternal serum adiponectin levels during human pregnancy. Journal of Perinatology. 2007; 27:77–81.
24. Suwaki N, Masuyama H, Nakatsukasa H, *et al.* Hypoadiponectinemia and circulating angiogenic factors in overweight patients complicated with pre-eclampsia. American Journal Obstetrics and Gynecology. 2006; 195: 1687-1692.
25. Li J, Miller EJ, Ninomiya-Tsuji J, *et al.* AMP-activated protein kinase activates p38 mitogen-activated protein kinase by increasing recruitment of p38 MAPK to TAB1 in the ischemic heart. Circulation Research, 2005, 97:872 –879.
26. Dalamaga M, Srinivas SK, Elovitz MA, *et al.* "Serum adiponectin and leptin in relation to risk for pre eclampsia: results from a large case-control study." Metabolism, 2011; 60(11): 1539-1544
27. Ozkan S, Erel CT, Madazli R and Aydinli K. Serum leptin levels in hypertensive disorders of pregnancy. European Journal of Obstetrics and Gynecology and Reproductive Biology, 2005, 120:158-163.