

Relationship between leptin and lipids during pre-eclampsia

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Abstract

Objective: To assess the relation between serum leptin levels and lipid profile in women with pre-eclampsia and to evaluate their atherogenic role in the pathophysiology of pre-eclampsia.

Methods: This was a comparative cross-sectional study, carried out in the Department of Physiology, Basic Medical Sciences Institute, Jinnah Postgraduate Medical Centre (JPMC), in collaboration with the department of Gynaecology and Obstetrics, JPMC. For this purpose 45 primigravidas with normal pregnancy and 45 primigravidas with pre-eclamptic pregnancy were selected who were in their third trimester. All the subjects were of the same maternal age, gestational age, height and weight. Serum leptin levels were determined by immunoenzymometric assay and total lipid profile was determined by enzymatic colorimetric method.

Results: The study included 90 patients, divided into two groups of whom 45 were diagnosed as pre-eclampsia and 45 were controls. All the variables of the lipid profile of pre-eclamptic patients, were found to be significantly elevated as compared to controls. The total lipid profile was also compared to the severity of pre-eclampsia and total cholesterol was found to be significantly raised ($p < 0.01$) in severe pre-eclampsia when compared to mild. On correlating serum leptin with lipid profile, again total cholesterol was found to be significantly high ($p < 0.05$) in pre-eclamptic group compared to controls.

Conclusion: This study concluded that serum leptin levels during pre-eclampsia are strongly associated with total cholesterol whereas association with other variables is insignificant. With severity of pre-eclampsia when leptin level rises, total cholesterol also rises. These changes may be the result of oxidative stress and may contribute to atherogenesis and pathogenesis of pre-eclampsia (JPMA 60:432; 2010).

Introduction

The discovery of leptin at the end of 1994 opened up a new perspective to study the role of adipocyte derived factors in energy balance homeostasis.¹ Leptin is a product of Ob/Ob gene, containing 167 amino acids and circulates in blood at low levels (5-15ng/ml) in lean subjects.² It decreases food intake via its cognate receptors (Ob-R) in the hypothalamus. In addition leptin activates sympathetic nervous system and increases energy expenditure. The leptin thus decreases body weight and adiposity as a novel messenger of energy metabolism.³ Leptin not only functions as an "adipostat" to signal the status of body energy stores to the brain (and perhaps other tissues) but also functions as a sensor of energy balance.⁴ Leptin is synthesized and secreted from white adipocytes into blood and is transported into the brain via a saturable system.⁵ Leptin travels to brain where it acts to cause the stimulation or inhibition of neurotransmitter such as neuropeptide Y (NPY), which acts to inhibit food intake and stimulate thermogenesis and physical activity.⁴ Leptin receptors outside CNS affect various peripheral functions such as glucose and lipid metabolism, insulin sensitivity, haematopoiesis, angiogenesis and blood pressure.³

Pre-eclampsia (PE) is a hypertensive disorder which develops in late pregnancy and is usually associated with placental hypoxia and dysfunction.⁶ In PE there is development

of hypertension and proteinuria after week 20 in a woman with previously normal blood pressure.⁷ Maternal circulating leptin concentration is significantly higher in pregnancies complicated by PE than gestational age matched controls.⁸ Anim-Nyame(2000),⁹ in a longitudinal study have shown that biochemical maternal hyperleptinaemia pre-dates the development of PE and the clinical onset of which is associated with significant further rise in maternal leptin concentration. The physiological role maternal leptin during pregnancy remains enigmatic. Pregnancy is a hypermetabolic state with an increase in maternal body fat and weight and an alteration in neuroendocrine milieu.¹⁰

All the above mentioned studies were done mostly in the western population and do not obviate the need for establishing normal physiology and pathophysiology in our population as geographic, racial and ethnic factors significantly affect the dynamics of every process in the normal and diseased human body.

Therefore the present study was designed to assess the relationship between leptin and lipids in women with P.E and to determine their atherogenic role in the pathogenesis of P.E.

Subjects and Methods

This study was carried out in the department of

Physiology, Basic Medical Sciences Institute, JPMC, in collaboration with the department of Gynaecology and Obstetrics, JPMC.

The study included 90 pregnant women of age ranging between 16-32 years and gestational age between 28-38 weeks. All the subjects were briefed about the nature of the study and an informed consent was taken.

Inclusion Criteria: Forty five normotensive women with singleton pregnancies without any previous history of hospitalization or any medical complication were taken as control.

Forty five obstetric patients with singleton pregnancies, diagnosed as having pre-eclampsia according to ISSHP(International society for the study of hypertension) when they presented with blood pressure $\geq 140/90$ mmHg on 2 separate occasions 4 hours apart or a single recording of a diastolic blood pressure of 110mmHg in association with proteinuria $\geq 2+$ on dipstick testing, formed the study group.

Exclusion Criteria: Pre-existing chronic hypertension; Pre-existing diabetes; Gestational diabetes; Diseases involving kidneys; Diseases involving liver; Known history of any peripheral vascular disease; Twin pregnancy and Smoking or any drug addiction.

All the subjects included in the study were primigravidas with same maternal age, gestational age, height and weight. A detailed general physical examination was done and history was taken.

The arterial blood pressure in the brachial artery was measured by using a simple mercury sphygmomanometer on right arm in a comfortable sitting position after 10 minutes of rest. Blood pressure was measured using both palpatory and auscultatory methods. The reported values represent the mean of two readings taken at 5 minutes interval.

The blood samples were collected under strict aseptic measures. Each sample was labelled with patient's name and identification number. Samples were analyzed in one run at the end of the study. Serum leptin was determine by immunoenzymometric assay and lipid profile was determined by enzymatic colorimetric method.

Mild and severe pre-edampsia was categorized according to the recommendations of the American College of Obstetrics and Gynaecology (ACOG 2002).¹¹

Pre-edampsia is considered mild when the blood pressure is $\geq 140/90$ mmHg and proteinuria is 300mg in 24 hours or 1+ or 2+ on dipstick analysis.

Severe pre-edampsia includes anyone of the following: BP $\geq 160/110$ mmHg on two occasions, 6 hours apart, 5 gm proteins in 24 hours urine or 3+ or 4+ on semi quantitative assay, oliguria or urine less than 500 ml in 24 hours, cerebral or visual disturbances, pulmonary oedema or cyanosis, right upper quadrant tenderness, foetal growth restriction, thrombocytopenia and impaired live function tests.

Data analysis was done on computer package SPSS (Statistical Package for Social Sciences) version 10.0. The Statistical significance of difference between the mean values of two groups was evaluated by the student's "t" test. The difference in the mean values of the two groups was regarded as statistically significant, if the P-Value was less than 0.05 and it was taken as highly significant, if P-Value was less than 0.001. Correlation Coefficient was detected using Pearson Coefficient of Correlation SPSS-10.0 For data feeding, the computer package Microsoft Excel was used.

Results

The study included 90 pregnant women. Of these 45 women had uncomplicated pregnancies and 45 were diagnosed as PE. The pre-eclamptic group was again divided according to the severity of the disease into patients with mild PE (n=28) and patients with severe PE (n=17). Maternal serum leptin levels were significantly higher in pre-eclamptic group, 62.1 ± 23.8 ng/ml than in control group, 26.8 ± 6.47 ng/ml ($p < 0.001$).

Table-1 shows the comparison of the lipid profile variables between the controls and pre-eclamptic group of patients along with the severe and mild PE cases.

LDL cholesterol was significantly higher in PE group compared to controls ($P < 0.05$). Total serum cholesterol was also significantly raised in the severe PE group compared to mild PE ($p < 0.01$).

Table-1: Fasting triglyceride, total cholesterol, high density lipoprotein, low density lipoprotein and very low density lipoprotein in normal pregnant women (controls) & in pre-eclampsics & also according to severity of pre-eclampsia. (All the values are expressed in Mean \pm S.D)

Lipid profile	Group A Control (n=45) Mean \pm S.D	GroupB Pre-eclamptic (n=45) Mean \pm S.D	Pre-eclampsics Severe (n=17) Mean \pm S.D	Pre-eclampsics Mild (n=28) Mean \pm S.D
Triglycerides (mg/dl)	186.3 \pm 20.9	245 \pm 53.5***	253 \pm 41.8	239 \pm 59.5
Total cholesterol (mg/dl)	209 \pm 13.6	238 \pm 28.8***	254 \pm 31.9**	228 \pm 22.2
HDL-cholesterol (mg/dl)	35.4 \pm 2.7	32.8 \pm 3.40***	32.3 \pm 2.4	33.2 \pm 3.8
LDL-cholesterol (mg/dl)	148.4 \pm 13.6	162.1 \pm 24.8*	172 \pm 27.2	156 \pm 21.8
VLDL-cholesterol (mg/dl)	36.8 \pm 4.8	50.1 \pm 11.1***	51 \pm 8.34	50 \pm 12.60

n= Number of subjects. *P < 0.05 when compared to control. **P < 0.01. ***P < 0.001

Table-2: Correlation between lipid profile vs serum leptin in normal pregnant women (controls) and in pre-eclampsics.

Lipid profile	Group A (Control) (n=45)	Group B (Pre-eclamptic) (n=45)
	Serum leptin	Serum leptin
Triglycerides (mg/dl)	r =0.06	r=0.10
Total cholesterol (mg/dl)	r =-0.05	r =0.34*
HDL-cholesterol (mg/dl)	r =-0.22	r=0.11
LDL-cholesterol (mg/dl)	r =-0.12	r =0.09
VLDL-cholesterol (mg/dl)	r =-0.02	r=0.16

*P < 0.05 statistically significant.

On correlating serum lipid profile with serum leptin in pre-eclampsics, a significant positive correlation ($r=0.34$) ($P<0.05$) was found between serum leptin and total cholesterol (Table-2).

Discussion

P.E is characterized by profound lipid abnormalities,¹² P.E and atherosclerosis are both endothelial diseases with an important involvement of lipid-mediated oxidative damage, and their lipid profiles are remarkably similar.¹³⁻¹⁵ Our findings revealed that there was a significant increase in serum levels of triglycerides, total cholesterol, LDL-cholesterol, VLDL-cholesterol in pre-eclamptic women when compared to controls. Serum levels of HDL-cholesterol were significantly decreased when compared to normotensive pregnant women. These findings are in agreement with the findings of Kocyigit,¹⁶ Bayhan et al,¹² JG Ray et al,¹⁷ Ziaei et al.¹⁸ On comparing lipid variables according to the severity of P.E, no statistical significant difference was found between mild and severe group except for total cholesterol which was significant in severe P.E as compared to the mild group. Hypertensive subjects frequently have higher cholesterol levels than normotensive subjects. A positive relationship between serum cholesterol level and blood pressure has been reported in many epidemiological studies.¹⁹

Information concerning relations between serum leptin concentration and the levels of serum lipids are limited²⁰ although the hormone is produced by adipocytes and in most cases reflect the fat content. To evaluate this, we calculated the correlation between serum leptin and lipid profile.

In our population we found a significant positive correlation between serum leptin and total cholesterol but the correlation with other lipid fractions was found to be non-significant.

The association of serum leptin concentration with serum lipids has been inconsistent and in a study conducted by Hallikainen,²¹ was found that high serum leptin concentration was associated with high cholesterol synthesis and low cholesterol absorption but not with serum lipids. Leptin has been associated with atherosclerosis and has been shown to interfere with

lipoprotein profiles.²² Leptin levels during P.E were associated with atherogenic lipid profiles which may contribute to increased risk of cardiovascular disease that has been linked to hyperleptinaemia.

These alterations may be the result of oxidative stress, thus affecting abnormal lipid profile and atherogenesis. Serum leptin has been suggested to be involved in the proatherogenic process by increasing oxidative stress²³ and leptin has been reported to induce oxidative stress in cultured endothelial cells.²⁴ Our results positively showed that changes in serum leptin level could contribute to lipid metabolism alterations in patients with P.E which might be related to proatherogenic process and increases the cardiovascular risk.

Conclusion

From this comparative cross-sectional study, it is concluded that Leptin levels during P.E are strongly associated with total serum cholesterol whereas relation with other lipid variables is not significant. On comparing different lipid variables according to severity of P.E, a relationship was found between severe P.E, leptin and total cholesterol. During P.E when leptin level rises with severity, total cholesterol also rises which may contribute to the elevated cardiovascular risk that has been linked to hyperleptinaemia.

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