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ROLE OF FIBROBLAST GROWTH FACTOR-21 IN WOMEN WITH PRE-ECLAMPSIA

By

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ABSTRACT

Background: Pre-eclampsia (PE) is a pregnancy-specific syndrome and one of the main causes of maternal, fetal, and neonatal mortality. Fibroblast growth factor (FGF)-21 was introduced as a biomarker for detection of several diseases.

Objective: Evaluation of serum levels of the adipokine fibroblast growth factor-21 in patients with mild and severe preeclampsia and its correlation with other biochemical markers lipid profile and hemoglobin, in addition to blood pressure (systolic and diastolic), maternal and gestational ages.

Patients and methods: Eighty patients were included in this study divided into three groups: Group 1: twenty healthy pregnant women, group 2: thirty patients with mild preeclampsia, and group 3: thirty patients with severe preeclampsia. All groups were subjected to history, clinical examination, blood pressure measurement as well as estimation of hemoglobin, serum triglycerides, total cholesterol,HDL cholesterol and fibroblast growth factor 21.

Results: FGF 21 in severe group increased by 102.7 % and 58.6 % than control and mild groups respectively. No significant correlation between FGF 21 and each of TG, LDL/C, systolic and diastolic blood pressure in mild group. There was a significant positive correlation between fibroblast growth factor 21 (FGF21), TG, HDL/C, systolic blood pressure in severe group, and negative correlation with LDL/C.

Conclusions: Maternal FGF-21 serum concentration significantly increased in severe pre-eclampsia than mild and normal pregnancy.

Key words: Fibroblast growth factor 21, preeclampsia, lipid profile, blood pressure.

INTRODUCTION

Pre-eclampsia is a pregnancy-specific syndrome that affects 3-5% of pregnancies and is traditionally diagnosed when a pregnant woman presents with increased blood pressure and proteinuria **(Ananth et al., 2013).**It is one of the main causes of maternal, fetal, and neonatal mortality, especially in low-and middle-income countries **(Saleem et al., 2014).**The acute clinical importance of pre-eclampsia lies in its relation to maternal and neonatal mortality and morbidity. When left untreated, pregnant women with pre-eclampsia have severe complications such as eclampsia, liver rupture, stroke, pulmonary edema, or kidney failure, which can all be lethal **(Souza et al., 2013).**

Pre-eclampsia is also related to fetal growth restriction and preterm birth, either spontaneous or through iatrogenic

delivery. Children born to mothers with pre-eclampsia have an increased risk of bronchopulmonary dysplasia and cerebral palsy, caused by preterm birth and being small for gestational age **(Strand et al., 2013).** In women with pre-eclampsia, placental antiangiogenic factors are up regulated and disrupt the maternal endothelium, leading to an antiangiogenic state that can result in clinical signs of pre-eclampsia **(Ben et al., 2016).**

Since PE shares various risk factors with the metabolic syndrome, it is of major interest to elucidate whether adipokines influencing glucose and lipid metabolism, as well as vascular disease, are dysregulated in and contribute to PE and its complications **(Stepan et al., 2013).** One of the adipokines that could be involved in placental metabolism is fibroblast growth factor 21.Fibroblast growth factors (FGFs) are signaling proteins of ~150– 300 amino acids with diverse biological functions mainly in development and metabolism. The human/mouse FGF family comprises FGF1–FGF23. However, as mouse FGF15 and human FGF19 are orthologs, they are usually referred to as FGF15/19 **(Itoh and Ornitz, 2011).**

Fibroblast growth factor 21 (FGF21), a metabolic hormone predominantly produced by the liver, is also expressed in adipocytes and the pancreas. It regulates glucose and lipid metabolism through pleiotropic actions in these tissues and the brain. In mice, fasting leads to increased PPAR-a mediated expression of FGF21 in the liver where it stimulates gluconeogenesis, fatty acid oxidation, and ketogenesis, as an adaptive response to fasting and starvation **(Woo et al., 2013).**

Since the placenta synthesizes FGF21, it has been hypothesized that it could be involved in the regulation of placental metabolism, which may affect infant growth and development through differential expression of nutrient receptors and transporters. In the placenta of women with an uncomplicated pregnancy or gestational diabetesmellitus, there was a positive correlation between the gene expression levels of PPARα and FGF21 and a tendency for a positive correlation between PPARγ and FGF21 **(Dekker Nitert et al., 2014).**

The present study aimed to evaluate serum levels of the adipokine fibroblast growth factor-21 in patients with mild and severe preeclampsia and to evaluate its correlation with other biochemical markers: lipid profile and hemoglobin, and also to evaluate its correlation with blood pressure (systolic and diastolic), maternal and gestational age.

PATIENTS AND METHODS

This study was conducted on 80 pregnant women selected from Obstetrics and Gynecology Clinics and Department in Al-Zahra'a University Hospital. Inclusion criteria were singleton pregnancy, gestational age (24-40 week gestation), mild preeclampsia with blood pressure ≥140/80 mm of Hg and <160/110 mm of Hg with age ranged between 20-35 years, severe preeclampsia with blood pressure over 160/110 mm of Hg with age range between (22-35) years. Exclusion criteria were multiple pregnancies, associated medical disorders affecting

blood pressure (chronic renal disease, thyroid disease, long standing diabetes) and chronic hypertension with pregnancy.

Those pregnant women were classified into three groups: Control group: Twenty normotensive pregnant women (free from any medical disorders), mild pre-eclampsia: Thirty women with mild preeclampsia, and severe preeclampsia: Thirty women with severe preeclampsia. This study protocol was approved by the hospitals ethical committee. An informed consent was obtained from the patients prior to their enrollment in this study. All subjects were subjected to detailed history, general and obstetric examinations.

Venous blood samples were obtained after 12-14 h fasting by vein puncture from each subject. The blood sample was left to coagulate adequately before centrifugation at 3000 rpm for 10 minutes followed by serum separation, and aliquots of serum samples were stored at -20 °C until the time of assay. Serum triglycerides (TG) and total cholesterol (TC) concentrations were measured by an enzymatic colorimetric method using kits provided by spinreact chemicals, ?Spain? **(Kaplan, 1984 and Natio and Kaplan, 1984).**

Serum low density lipoprotein cholesterol (LDL-C)was estimated using Friedwald equation **(Friedwald, et al., 1972).** Serum high-density lipoprotein cholesterol (HDL-C) was measured by differential precipitation enzymatic colorimetric method using kits provided by spin react chemicals **(Naito and Kaplan, 1984)**, ?Spain?. Hemoglobin concentration was measured by light deflection method. Fibroblast growth factor-21 was measured by quantitive sandwich enzyme immunoassay technique using kits provided by assaypro LLC Charles ?USA? **(Schmidt et al., 2012) .**

Statistical methods: Statistical package of Graph pad prism 7 was used for analysis of data.Data were summarized as mean ± SD. Comparison between groups was carried out using one way analysis of variance (ANOVA).If F values were significant, Tukey-Kramer multiple comparison test was used.Pearson's correlation was also done to examine the correlation between parameters. P-value was considered significant if $P \leq 0.05$ at confidence interval 95%. Pearson's correlation was also done to examine the correlation between parameters.

RESULTS

Regarding fibroblast growth factor-21, severe group showed marked elevation to reach almost 2-folds that of control group, and 1.5 folds of mild group**.**In relation to lipid profile, the mean serum levels of TC of severe group significantly increased by 6.9 % and 16.7% than that of control and mild group respectively. In addition, the mean serum levels of triglycerides of severe group significantly increased to reach 119.8 % and 68.7% that of control and mild group respectively **(Table 1).**

Table (1): Fibroblast growth factor 21, hemoglobin and lipid profile in control, mild and severe groups (Mean ±SD).

Groups / Variables	Control group	Mildpreeclampsia group	Severe preeclampsia group	P value
FGF21	0.36±0.334	0.46±0.395	(ab) 0.73±0.40	0.0023
Triglycerides (mg/dl)	174.2±26.25	227±32.50	(ab) 383±156.1	<0.0001
TC (mg/dl)	273.3±43.54	250.2±41.18	(ab) 292.2±49.27	<0.0001
LDL-C (mg/dl)	165.8±35.67	173.6±39.75	175.8±62.11	0.767
HDL-C (mg/dl)	36.51±13.07	32.11±8.157	37.78±10.99	0.107
Hb (gm/dl)	10.72±0.88	10.23±1.09	10.18±1.0	0.145

a: Significant difference from control group.
b: Significant difference from mild group.

Regarding the systolic and diastolic blood pressure of severe group significantly increased by 17.2 % and 16.4 % respectively than that of mild group, and increased by 55 % and 48.5 % respectively than that of control group. Also, systolic and diastolic blood pressure of mild group increased by 32.3 % and 27.6 respectively than that of control group **(Table 2).**

Table (2): Systolic, diastolic blood pressure and gestational age in control, mild and severe groups (Mean ±SD).

Groups / Variables	Control group	Mild preeclampsia group	Severe preeclampsia group	P value
Systolic BPmm/Hg	109±10.21	(a) 144.2±5.27	(ab) 169±7.92	<0.0001
Diastolic BPmm/Hg	72.50±7.86	(a) 92.50±6.263	(ab) 107.7±7.54	<0.0001
Gestational age (weak)	34.77±4.65	35.68±4.124	35.79±1.50	0.572

a: significant difference from control group.
b:significant difference from mild group.

Significant positive correlation between fibroblast growth factor-21 (FGF-21) and each of TG, HDL/C, and systolic blood pressure were observed in severe preeclampsia. However, there was significant negative correlation between fibroblast growth factor-21 and LDL/C in severe preeclampsia group **(Table 3).**

Table (3): Correlation between fibroblast growth factor-21 (FGF21) and TG, HDL/C, LDL/C and systolic blood pressure in severe group.

Parameters / Variables	Correlation coefficient	FGF21
TG (mg/dl)	r	0.4066
	p	0.0258*
TC (mg/dl)	r	0.07
	p	0.72
HDL-C (mg/dl)	r	0.3778
	p	0.0396*
LDL-C (mg/dl)	r	-0.5438
	p	0.0019**
Hb (gm/dl)	r	0.13
	p	0.50
SBP (mm/Hg)	r	0.4032
	p	0.0272*
DBP(mm/Hg)	r	0.05
	p	0.81
Gestational age (weak)	r	0.12
	p	0.51
Maternal age (year)	r	0.16
	p	0.39

DISCUSSION

This study investigated whether serum Fibroblast growth factor 21 (FGF21) concentration differed in mild and severe preeclampsia as compared to normal pregnancy and its correlation with other biochemical markers (lipid profile and Hb) also to evaluate its correlation with blood pressure (systolic and diastolic), maternal and gestational age to assess if PE affects these levels.

In the current study we measure FGF-21 concentration to know whether levels of maternal FGF-21 are increased during mild and sever preeclampsia. The studied groups showed a statistically significant difference in Fibroblast growth factor 21 (FGF-21) concentration between control and severe and mild and severe groups, also showed no significant difference between control and mild groups.

Also, in the current study, we demonstrated that maternal serum concentrations of the adipokine fibroblast growth factor-21 (FGF21) in severe preeclampsia group significantly increased to reach almost two folds than that of healthy, age-matched control group. This results were in agree with **Stepan et al. (2013) and Dekker Nitert et al. (2014)** who found that FGF-21 levels increased in preeclampsia to reach almost 3-folds increase in PE patients as compared to healthy, age-matched control in study conducted on one hundred and two women with PE and normal pregnancy their age range was between 18 and 40 years. However this finding disagree with **Dekker Nitert et al. (2015)** who stated that no significant changes in FGF-21 concentrations in late onset preeclampsia.

The physiological significance of increased FGF-21 in PE remains unclear so far **(Stepan et al., 2013).**FGF-21 improves glucose tolerance and lipid metabolism **(Lundasen et al., 2007).** Taking these findings into consideration, it is tempting to speculate that increased FGF-21 concentrations in PE might be a compensatory mechanism to diminish the adverse vascular and metabolic effects of the disease. Alternatively, FGF-21 resistance (a phenomenon reminiscent of hyperinsulinemia and insulin resistance) might be found in PE similar to the FGF-21-resistant state seen in obesity **(Fisher et al., 2010).**

No significant difference in mean total cholesterol concentration of the mild preeclamptic group compared to that of control pregnant group was observed. However, there was significant difference between severe preeclamptic group when compared with that in control and mild groups.This results was in accordance with the findings reported by **Siddiqull (2014).**

In our study, TG concentration significantly elevated in mild and severe preeclampsia as compared to control group. This result came in agreement with **Mittal et al.(2014)** who found significant difference in TG concentration between control , mild and severe groups.

Siddiqull (2014) reported that in the pathogenesis of preeclampsia, the initiating event has been postulated to be the reduced placental perfusion that leads to widespread dysfunction of the maternal vascular endothelium by mechanisms that are not well defined **(Gilbert et al., 2008).**Increased serum triglyceride levels leads to its increased endothelial accumulation, which may result in endothelial dysfunction in pregnancy Increased triglycerides in preeclampsia are likely to be deposited in uterine spiral arteries and contributed to the endothelial dysfunction, both directly and indirectly through generation of small dense LDL **(Siddiqull, 2014).**

Also, **Omorogiuwa and Ozor (2015)** reported that the principle modulator of this hypertriglyceridemia is estrogen as

pregnancy is associated with hyperestrogenemia. Estrogen induces hepatic biosynthesis of endogenous triglycerides, which is carried by VLDL**.** This process may be modulated by hyperinsulinemia found in pregnancy**.**

Also, in this study, levels of HDL/C, LDL/C were not significantly different in the three groups. This is in a part agreement with **Stepan et al. (2013)** who found no significant difference in HDL/C concentration between control and preeclamptic women, and in a part agreement with **Mittal et al. (2014)** who found that no significant difference between LDL/C and HDL/C concentration between control, mild and severe preeclamptic women.

Also, in this study, there were significant positive correlations between fibroblast growth factor-21 (FGF-21) and each of TG, HDL/C, and systolic blood pressure were observed in severe preeclampsia group. On the other hand, there was significant negative correlation between FGF-21 and LDL/C in severe preeclampsia group. This result also was in agreement with **Stepan et al. (2013).** However , no correlation between FGF 21 and each of maternal age, hemoglobin concentration, total cholesterol, HDL/C and fetus age were found in severe group.Also no significant correlation between fibroblast growth factor-21 (FGF-21) and each of lipid profile, hemoglobin, gestational age, systolic and diastolic blood pressure in mild preeclampsia group.

CONCLUSION

Maternal FGF-21 serum concentrations significantly increased in preeclampsia and it could be used as an important biomarker for the early diagnosis of preeclampsia. Also, abnormal lipid profile may have value to be used as screening markers in early stages of pregnancy for the development of pre-eclampsia later.

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دور عامل نمو الخلايا الليفية -٢١ لدي النساء المصابات بتسمم الحمل

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خلفية البحث: يعتبر تسمم الحمل متلازمة خاصة بالحمل وأحد الأسباب الرئيسية لوفيات الأمهات والأجنة والأطفال حديثي الولادة. وقُدم عامل نمو الخلايا الليفية -٢١ كعلامة بيولوجية للكشف عن العديد من الأمراض.

الهدف من البحث: تقييم مستويات المصل لعامل نمو الخلايا الليفية أديبوكين -٢١ في المرضى الذين يعانون من تسمم الحمل متوسط الشدة والشديد، وعلاقته مع العلامات البيوكيميائية الأخرى مثل مستوي الدهون ومستوي الهيموجلوبين ، بالإضافة إلى ضغط الدم (الإنقباضي والإنبساطي) وعمر الأم وعمر الحمل.

المرضي وطرق البحث: اشتملت هذه الدراسة علي ثمانين مريضة مقسمة إلى ثلاثة مجموعات: مجموعة ١: ٢٠ من النساء الحوامل الأصحاء، ومجموعة ٢: ٣٠ من المرضى الذين يعانون من تسمم الحمل متوسط الشدة، ومجموعة ٣: ٣٠ من المرضى الذين يعانون من تسمم الحمل الشديد. وقد تعرضت جميع المجموعات للتاريخ والفحص السريري، وقياس ضغط الدم، وكذلك تقدير الهيموجلوبين، ومستوي الدهون وعامل نمو الخلايا الليفية ٢١.

النتائج: ازداد عامل نمو الخلايا الليفية-٢١ في مجموعة مرضي تسمم الحمل الشديد بنسبة ١٠٢,٧٪ و ٥٨,٦٪ عن المجموعة الضابطة ومجموعة مرضي تسمم الحمل متوسط الشدة علي التوالي. بينما لا توجد علاقة بينه وبين كل من الدهون الثلاثية و البروتين الدهني منخفض الكثافة وضغط الدم الإنقباضي والإنبساطي في مجموعة مرضي تسمم الحمل متوسط الشدة. و كان هناك ارتباط إيجابيا كبير بين عامل نمو الخلايا الليفية -٢١ وكل من الدهون الثلاثية والبروتين الدهني عالي الكثافة، وضغط الدم الإنقباضي والإنبساطي في مجموعة مرضي تسمم الحمل الشديد. وإرتبط عامل نمو الخلايا الليفية سلبيا مع البروتين الدهني منخفض الكثافة.

الخلاصة : يزداد مستوي عامل نمو الخلايا الليفية -٢١ في مصل الدم الخاص بالأم زيادة كبيرة في تسمم الحمل الشديد عن ذلك الخاص بالمجموعة الضابطة. ومجموعة مرضي تسمم الحمل متوسط الشدة.