Evaluation of Serum Levels of the Adipokines Chemerin and Resistin in Preeclampsia

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Abstract: Objectives: the aim of this study was to determine serum chemerin and resistin levels in preeclamptic patients as well as healthy pregnant women, and to evaluate the association of serum chemerin with markers of severity of preeclampsia and other metabolic parameters. **Methods.** In the current study, the serum concentrations of both chemerin and resistin were measured by enzyme linked immunosorbent assay (ELISA) in control and preeclampsia patients during pregnancy (Control: n=30, preeclampsia: n=29). Furthermore, the association between chemerin and markers of adiposity [weight, body mass index (BMI) and resistin], glycolipid metabolism [lipid profile, fasting insulin, and HOMA-IR] as well as markers of severity of preeclampsia [blood pressure (BP), uric acid (UA) and lactate dehydrogenase (LDH)] were studied in pregnant patients. **Results.** Both median maternal chemerin and resistin concentrations were significantly elevated in preeclampsia patients (249.5 [range: 123.1–366.9] µg/l) as compared to controls (204.8 [138.5– 280.8] µg/l) (p=0.001). Serum chemerin level was higher in severe group when compared to the mild pre-eclamptic group. By multiple linear regression analysis SBP and UA were independently associated with serum chemerin levels, when the data were adjusted for preeclampsia triglycerides (TGs) still independently associated with serum chemerin levels in multiple regression analysis. **Conclusions.** Serum chemerin and resistin concentrations were significantly increased in preeclampsia relative to normal pregnancy. Moreover, serum chemirin was significantly up-regulated in severe preeclampsia, and was independently associated with marker of severity and dyslipidemia.

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1. Introduction

Pre-eclampsia is a common multisystem pregnancy disorder in which diagnosis is based on hypertension and proteinuria, affecting 3–5% of all pregnancies. Pre-eclampsia generally occurs de novo in late pregnancy, and severe cases constitute a serious problem to the mother and the fetus [1]. This disorder is a major cause of prenatal and maternal morbidity and mortality worldwide, and associated with an increased risk of cardiovascular disease and type II diabetes later in life for the mother [2]. for materno-fetal safety it is better to understand preeclampsia, and to develop accurate screening, preventive and treatment strategies. Some previous studies have indicated that preeclampsia is associated with endothelial dysfunction, metabolic abnormality, inflammatory state and atherosclerosis, however the etiology of this disease remains elusive and multiple factors are implicated in pathogenesis of preeclampsia [3]. Many authors have demonstrated that– dysregulation of Adipocyte-secreted factors – so-called adipokines such as leptin, resistin and chemerin —might play an important role in the pathogenesis of preeclampsia, because of their role in insulin resistance, lipid metabolism, atherosclerosis, and low-grade systemic inflammation, therefore, it is reasonable to suppose that adipokines may directly or indirectly influence the function of endothelial cells [4]. Resistin is also known as adipose tissue-specific secretory factor, is a hormone that is secreted primarily by human adipocytes and mononuclear cells and is probably associated with insulin resistance. Resistin is expressed in the human placenta and has been postulated to play a role in regulating energy metabolism in pregnancy. Studies investigating maternal serum or plasma resistin levels in pathological pregnancies, including PE, however, the changes in serum resistin levels in normal pregnancy and in the setting of pre-eclampsia are far from understood [26]. Chemerin is a recently identified adipocytokine that acts through the G proteincoupled receptor chemokine-like receptor 1 (CMKLR1). It is expressed mainly by plasmacytoid dendritic cells, macrophages, natural killer cells, and adipocytes, promoting the recruitment of these cells to lymphoid organs and sites of injury [5]. Circulating concentrations of chemerin are altered in inflammatory states [3,6,7], and are significantly correlated with dyslipidemia and hypertension, both characteristic features of metabolic syndrome. Moreover, chemerin is a potent angiogenic factor and induces gelatinolytic activity of endothelial cells [7], in addition chemerin is involved in the regulation of adipose tissue insulin sensitivity [8]. In current study, we determine whether serum chemerin and resistin were elevated in preclamptic patients and whether these adipokines levels differ between patients with

severe preeclampsia and those with mild preeclampsia. The association between maternal serum chemerin concentration and clinical and biochemical parameters of the study subjects was also assessed.

2. Subjects and Methods:

Study population:-

The study protocol was approved by the local Ethics Committee of Umm AlQura University, and all participants gave informed consent. Fifty nine pregnant women were enrolled in this study, they were recruited from the Department of Obstetrics & Gynecology of AL-NOOR and HERRA Hospital, Makkah, Saudi Arabia. They were categorized as Group I: included pregnant Women with preeclampsia (n= 29). Group II: Control healthy-pregnant group (n= 30), both groups were matched for age, gestational age. Preeclampsia was defined according to criteria recommended by guidelines of the American College of Obstetricians and Gynecologists (ACOG) as gestational hypertension >140 systolic mmHg and >90 diastolic mmHg on at least two occasions, at least 6 hrs apart accompanied by proteinuria (≥1+ by dipstick or ≥0.3 g/24 hrs) occurring after 20th weeks in pregnant women who were previously normotensive [9]. The preeclampsia group was sub-classified into 2 groups, mild preeclampsia (n=19) and severe preeclampsia (n=10) . Severe pre-eclampsia was diagnosed if one or more of the following criteria were present: blood pressure of 160/ 110 mmHg or higher, excretion of 5 g or more of protein in a 24-hrs urine sample or a urine dipstick showing 3 or 4 in a random urine sample, oliguria of less than 500 ml in 24 hrs, pulmonary edema or cyanosis, visual or cerebral disturbance, impaired liver function, thrombocytopenia and HELLP syndrome. Patients with preeclampsia who were not met criteria of severe preeclampsia were diagnosed with mild preeclampsia [10]. Exclusion criteria include: All were non current or ex smokers participants, cardiovascular, chronic liver disease [11], chronic kidney disease and renal failure [12].

Sample collection

Five milliliters of venous blood were collected after 12 hours fasting under complete aseptic precautions and divided into two portions: one contained sodium fluoride, centrifuged and plasma separated for determination of fasting blood glucose. The second one was allowed to clot in plain test tubes, centrifuged (at 1500 xg for 15 minutes). The separated serum was divided into 3 aliquots, were stored at -20ºC for subsequent assay of both uric acid, lactate dehydrogenase (LDH) and lipid profile, the other 2 aliquots for ELISA assay of insulin, resistin and chemerin.

Methods:

All participants were subjected to:-

(a) A certain detailed questioner involves (personal, medical, family history), through general and abdominal examination ,arterial blood pressure and body mass index (BMI) were recorded Body mass index was calculated according to the equation: BMI = [(Weight)/ (Height) ^{2}]. Ultrasonographic examination was conducted to confirm the gestational age, and to exclude the presence of fetal congenital abnormalities.

(b) Analysis of routine biochemical markers: plasma glucose, total cholesterol (TC)**, triglycerides** (TGs), **High density lipoprotein cholesterol** (HDL-C), Uric acid (UA) and Lactate dehydrogenase (LDH) were analysed using Automated (Cobas c 111/ applying UV assay method and enzymatic colorimetric method **[13, 14, 15, 16,17, 18]**) **Low density lipoprotein cholesterol (**LDL-C) value was calculated according to "Friedewald equation": LDL-C = Total cholesterol-(HDL-C+TG/5) This equation was applied provided that serum TG level is <400 mg/dL **[19]**

(c) ELISA assay of Insulin: maternal insulin concentrations were measured using a commercially available enzyme-linked immunosorbent assay (ELISA) kit supplied by (DRG, GmbH, Germany). According to the manufacture instructions [20]. **The homeostasis model assessment-insulin resistance index (HOMA-IR):** It was calculated using the equation: HOMA-IR = fasting glucose (mg/dL). Fasting insulin (µU/mL)/ 405 The cutoff point to define insulin resistance corresponds to HOMA-IR ≥ 3.8 **[21]**. (d) **Resistin:** maternal resistin concentrations were measured using a commercially available enzyme-linked immunosorbent assay (ELISA) kit supplied by (Catalogue no.ER1001-1-ASSAY PRO). According to the manufacture instructions. Concentrations of the unknown diluted samples were determined using the instructed standard curve and then multiplied by the dilution factor(1:5) to get the actual amount of resistin in the original serum [22]. **(e) Chemerin:** Chemerin concentrations were measured using a commercially available enzyme-linked immunosorbent assay (ELISA) kit supplied by (Biovender GmbH, Im Neuenheimer Feld 583, D-69120 Heidelberg, Germany), according to the manufacture instructions . Concentrations of the unknown diluted samples were determined using this the instructed standard curve and then multiplied by the dilution factor (1:100) to get the actual amount of chemerin in the original serum [23].

Statistical analysis:- Statistical analysis was done using SPSS software, version 16, Echosoft Corporation, USA. Descriptive statistics in the form of mean±SD were calculated for parametric data. On the other hand, non parametric data were expressed as median and interquartile range (25-75th percentile). The Kolmogorov-Smirnov test was

done to determine the distribution of data. Between group comparisons were done using the Student's t test in case of normally distributed data, and Mann-Whitney-U test was used in case of skewed data. The correlation between the variables were analysed using pearson ′s correlation (for normally distributed data), Spearrman's rank correlation (not- normally distributed data). To adjust the effects of covariates and identify independent relationships, multiple linear regression analyses were performed. *p* values <0.05 were considered significant, whereas *p* values <0.01 were considered highly significant.

3. Results:-

Demographic and clinical characters are summarized in (table 1). Systolic (SBP) (P=0.001) and diastolic (DBP) (P= 0.001) blood pressure, were significantly elevated in patients with preeclampsia as compared to controls

Table1:- demographic and clinical character of studied groups

Parameters		Healthy pregnant Control (n=30) (Means ± SD)	Preeclampsia (n=29) (Means ± SD)	*P* value and significance
Age (years)		31.96±5.27	34.37±5.79	0.1 NS
Gage (weeks)		33.76±3.29	32.68±4.88	0.3 NS
Parity		1.7±0.46	1.79±0.41	0.4 NS
BP	SBP	117.47±7.37	147.9±26.03	0.001 HS
	DBP	80.16±8.1	91.24±12.5	0.001 HS
BMI		29.36±2.69	30.46±1.3	0.051

GA: gestational age- BP: blood pressure SB: systolic blood pressure DBP: diastolic blood pressure

Regarding Glycometabolic parameters (FBG, F insulin) there were non-statistically significant difference in preeclamptic group as compared to healthy pregnancy control (P=0.068, P=0.27), accordingly HOMA-IR was non-significantly differ in preeclamptic group as compared to healthy pregnancy control (P=0.54), with regard to lipid profiles TGs are significantly higher in preeclamsia as compared to normal pregnancy (P=0.002). Although T. chol, LDLC were increased and HDLc were decreased in preeclampsia compared to healthy pregnant women the difference was non statistically significant (P=0.29, 0.6, 0.68 respectively). (Table 2)

Table 2: laboratory parameters and chemerin of studied groups

Parameters	healthy pregnant Control		Preeclampsia		*P*-value and significance
	Means ± SD	Median (25-75th percentile)	Means ± SD	Median (25-75th percentile)	
FBG (mg/dl)	96.3±12.35	98 (87.25-107.75)	90.44±13.97	90 (79-105.5)	0.068 NS
F insulin (uU/ml)	15.63±11.38	15 (7-20)	19.86±15.90	15 (11-28.5)	0.27 NS
HOMA-IR	3.99±2.82	3.85 (2.57-4)	4.44±4.02	4 (2.2-5.65)	0.54 NS
TC(mg/dl)	200.25±55.99	227.8 (154.8-240.25)	208.93±37.94	185.7 (181.65-236.6)	0.29 NS
TG (mg/dl)	183.96±50.69	160 (144-237.6)	229.94±59.77	223.7 (206.7-276.3)	0.002 HS
HDLc(mg/dl)	45.28±13.93	50.8 (32.6-58.5)	44.93±16.82	45.9 (27-56)	0.68 NS
LDLc(mg/dl)	118.16±44.14	123 (77.8-151.23)	122.61±34.71	113.7 (92.85-143.1)	0.6 NS
UA (mg/dl)	3.94±1.28	3.8 (2.97-4.15)	6.34±2.6	6.5 (3.55-9.5)	0.001 HS
LDH (U/L)	226.87±100.59	176 (160-281)	370.34±206.23	296 (245-415)	0.001 HS
Resistin (ng/ml)	38.06±31.26	29 (13.1-47.37)	61.98±32.26	75 (34-96.5)	0.013 S
Chemerin (ng/ml)	174.4±29.17	177 (148.75-196.25)	349.9±147.92	375 (168.5-530)	0.001 HS

FBG: fasting blood glucose HOMA-IR: homeostasis model assessment HDLc: high density lipoprotein cholesterol. LDLc: low density lipoprotein cholesterol TGs; triglycerides TC: total cholesterol LDH: lactate dehydrogenase

Markers of severity (UA and LDH) were significantly higher in preeclampsia compared to healthy pregnant women (p=0.001) (table 2). Moreover, the patients with severe preeclampsia had the highest serum levels UA, LDH (p= 0.001, 0.002). Furthermore, glycolipid parameters F insulin, TG were significantly higher in severe preeclampsia as compared to mild cases (p=0.04, 0.024) (table 3). Serum resistin was significantly higher in preeclampsia as compared to healthy pregnant control, however no significant difference between mild and severe cases regarding it.

Table 3: laboratory markers in mild and severe preeclampsia

Parameters	Mild preeclampsia (n=19)		Severe preeclampsia (n=10)		*p*-value and significance
	Means ± SD	Median (25-75th percentile)	Means ± SD	Median (25-75th percentile)	
Finsulin uU/ml	17.89±18.69	15 (11-15)	23.6±8.01	28(12-29)	0.04 S
HOMA-IR	4.35±4.85	31 (2.3-4)	4.62±1.76	5.3(2.1-6)	0.19 NS
T chol mg/dl	214.95±42	209 (185.7-241.8)	197.51±26.99	181.7(179.5-236.6)	0.17 NS
TG mg/dl	213.17±62.69	209.6 (166.4-259)	261.81±39.14	276.3(206.7-297.6)	0.024 S
HDLc mg/dl	48.3±18.02	47.7 (30.3-62)	38.55±12.73	36.5(27-56)	0.21 NS
LDLc mg/dl	128.09±39.03	111 (97.6-170.6)	112.2±22.7	113.7(83.4-139)	0.6 NS
UA mg/dl	512.63±2.18	4.8 (3.3-6.8)	8.66±1.65	9.5(6.4-9.8)	0.001 HS
LDH U/L	267.3±78.72	246 (222-312)	566±234.55	707(296-758)	0.002 HS
Resistin ng/ml	63.94±30.64	75 (40-99)	58.25±36.57	75(17-96.5)	0.35 NS

FBG: fasting blood glucose HOMA-IR: homeostasis model assessment LDH: lactate dehydrogenase HDLc: high density lipoprotein cholesterol. LDLc: low density lipoprotein cholesterol TGs; triglycerides TC: total cholesterol

Serum chemerin concentrations were significantly increased in subjects with preeclampsia as compared to healthy pregnant. Moreover, maternal serum chemerin was significantly higher for severe preeclampsia as compared to mild preeclampsia and healthy pregnant (Figure1).

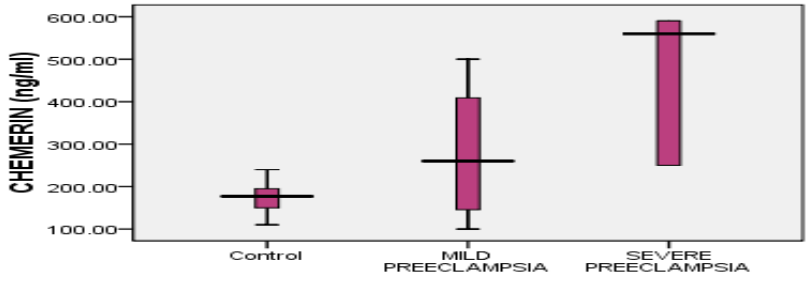
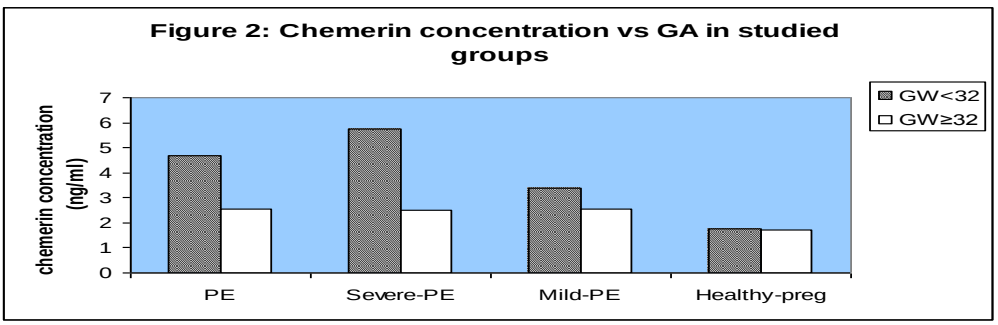


Figure 1: Chemerin concentration in healthy pregnant control and patients with preeclampsia

Table 4: Chemerin in mild and severe preeclampsia

Parameters	Mild preeclampsia		Severe preeclampsia		*p*-value and significance
	Means ± SD	Median (25-75th percentile)	Means ± SD	Median (25-75th percentile)	
Chemerin (ng/ml)	281.95±144.54	260 (135-433)	479±158.56	560(250-590)	0.002 HS

Each of the studied groups (all patients with preeclampsia, severe preeclampsia, mild preeclampsia and healthy pregnant control) were divided according to GA into 2 groups GA<32W and GA≥ 32 W, serum chemerin levels were significantly higher in gestational age (GA)<32W compared to GA≥ 32 W in both total and severe preeclampsia. However, chemerin levels were non significantly different in subjects with GA<32W compared to GA≥ 32 W among control and mild preeclampsia (Figure 2).



Bivariate analysis in the 59 pregnant women revealed significant positive correlation between maternal serum chemerin and BP{ SBP (r=0.768,*p*=0.001) DBP (r=0.583, *p*=0.001)}, weight (r=0.45, *p* =0.001), TG (r=0.32, *p* =0.012), LDH(r=0.34, *p* =0.008) and uric acid(r=0.6, *p* =0.001) and significant negative correlation with GA (r= -0.551, *P=0*.001). Also, in 29 preeclampsia a significant positive correlation between maternal serum chemerin and both F insulin (r = 0.43, *P=0.02*) and HOMAIR(r=0.43, *p* =0.019) (Table 5). While, resistin was significantly positively correlated with SBP(r=0.25, p=0.047), LDH(r=0.35, p=0.005) and GA(r=.44, p=0.001), in contrast resistin was negatively correlated with parity(r=-0.35, p=0.005) (Table 6)

Table 5: correlation of chemerin with all parameters in study subjects

Variables		Bivariate correlation			
		Studied groups		Preeclampsia group	
		r	*p* -value	r	*p* -value
Age		0.13	0.34 NS	-0.03	0.86 NS
G age		-0.55	0.001 HS	-0.71	0.001 HS
Parity		-0.06	0.84 NS	-0.15	0.42 NS
Weight		0.45	0.001 HS	-0.005	0.78 NS
BP	SBP	0.768	0.001 HS	0.66	0.001 HS
	DBP	0.575	0.001 HS	0.47	0.009 HS
F insulin		0.09	0.47 NS	0.43	0.02 S
HOMA-IR		0.08	0.54 NS	0.43	0.019 S
Resistin		0.07	0.57 NS	-0.20	0.28 NS
Total chol		0.2	0.12 NS	- 0.21	0.25 NS
Triglycerides		0.32	0.012 S	0.45	0.014 S
HDLc		0.06	0.64 NS	-0.22	0.24 NS
LDLc		0.2	0.11 NS	0.03	0.86 NS
UA		0.6	0.001 HS	0.81	0.001 HS
LDH		0.34	0.008 HS	0.25	0.18 NS

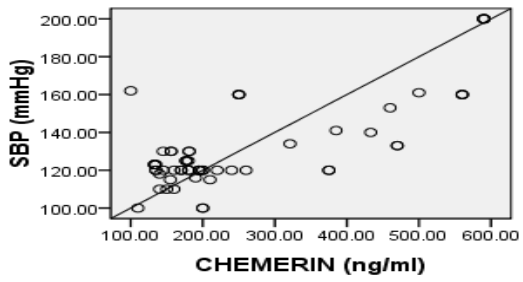


Figure 3: Correlation between serum chemerin and SBP in studied groups

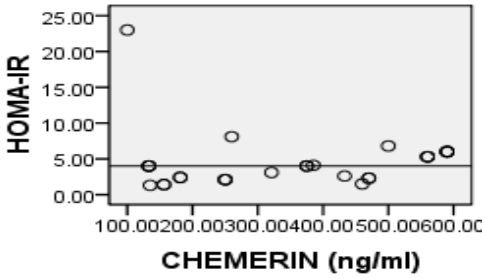


Figure 4: correlation between serum chemerin and HOMA-IR in preeclampsia

Table 6: correlation of serum resistin with all parameters in study subjects

Variables		*Studied groups*	
		r	*p* -value
Age		-0.15	0.23 NS
G age		0.44	0.001 HS
Parity		-0.35	0.005 HS
Weight		0.17	0.18 NS
BP	SBP	0.25	0.047 S
	DBP	0.11	0.39 NS
F insulin		-0.08	0.53 NS
HOMA-IR		-0.07	0.59 NS
Total chol		0.09	0.46 NS
Triglycerides		-0.09	0.45 NS
HDLc		0.22	0.08 NS
LDLc		0.08	0.53 NS
UA		0.06	0.64 NS
LDH		0.35	0.005 HS
Chemerin		0.07	0.57 Ns

In multiple linear regression analysis only SBP and UA were independently associated with chemerin (dependant variable) among all cases (adjusted R square= 0.738, F=33.7 p <0.001) regarding resistin only LDH and GA were independently associated with resistin (adjusted R square=0.4 F=10 , p =0.001)

Table 7: Multiple linear regression between chemerin (dependant variable) and both clinical and biochemical parameters

Independent variable	βeta	p value
SBP	0.607	0.000
DBP	-0.2	0.07
UA	0.49	0.000
LDH	-0.05	0.5
GA	0.15	0.053

The association between chemerin serum concentrations (dependant factor) on one hand and TG (independent variables) on the other hand persisted in multiple linear regression analysis after adjustment for preeclampsia (β=0.4& p =0.021). Thus TGs are independent factor of chemerin.

4. Discussion:

Previous studies have indicated that preeclampsia is associated with endothelial dysfunction, a hypercoagulable state, metabolic abnormalities, an inflammatory response and atherosclerosis [24]. The etiology of these conditions remains elusive and multiple factors are implicated in pathogenesis of preeclampsia. Recently, increasing evidence has supported the diverse role of several so-called adipokines such as leptin, adiponectin, free fatty acid (FFA) and resistin in the pathogenesis of preeclampsia. Resistin is a novel peptide hormone that is specifically secreted by human adipocytes and mononuclear cells [26]. Our study reveled a marked elevation of maternal serum resistin levels in women with preeclampsia compared to healthy pregnant control women. This comes in accordance with **Haugen *et al.* and Seol *et al.* [25,26],** they demonstrated that Serum resistin levels were significantly elevated in women with preeclampsia compared to normal pregnant women. Although the exact function of resistin in the pathophysiology of preeclampsia remains unclear, the elevated serum resistin levels might be associated with exaggerated insulin resistance via the extensive systemic inflammatory response in preeclampsia. Extensive systemic inflammation is a well known characteristic of preeclampsia, and monocyte activation is one of the associated features of systemic inflammation. Monocytes may be the source of the increased serum resistin concentrations in preeclampsia. Increased resistin can not be explained through placental gene expression of resistin as it was found to be unaltered and , resistin mRNA levels in abdominal subcutaneous adipose tissues were similar between women with preeclampsia and normal pregnant women. **Sonagra *et al.* [27],** who reported that increased levels of both UA and LDH are seen as the disease severity increases, and significant positive correlation of these parameters with systolic and diastolic blood pressure in preeclampsia cases and estimation of serum LDH and UA at regular interval may give insight to ongoing disease progression and organ damage. They may prove to be a useful tool to predict the maternal and fetal complications even at an earlier stage of the disease. These results go hand in hand with our results which demonstrated that the mean serum triglycerides, serum UA and LDH were significantly higher in preeclampsia group when compared to healthy gestational age-matched control group. Women with pre-eclampsia are more likely than normotensive pregnant women to experience metabolic disturbances, such as obesity, hypertension, dyslipidemia, insulin resistance, systemic inflammation and impaired fibrinolysis, Demirci et al [28] reported alterations in the triglycerides concentrations early in the pregnancies of women who later develop pre-eclampsia. High concentrations of circulating triglyceride-rich lipoproteins may induce endothelial dysfunction through the generation of small dense LDL sub fractions, which have been found to be oxidized more readily than their larger counterparts. It was indicated that small dense LDL fractions had a greater capacity to stimulate the thromboxane synthesis by endothelial cells and an increase in intracellular calcium in vascular smooth muscle, which might be relevant to vasospasm in pre-eclampsia [29]. A previous study demonstrated that serum chemerin levels correlated with body fat, glucose and lipid metabolism, inflammation and hypertension, suggesting that this adipokine plays a role in the pathophysiology of metabolic syndrome [30].Our study revealed that maternal serum chemerin levels were significantly higher in preeclampsia group when compared to healthy gestational age-matched controls group. Moreover, patients with severe preeclampsia had significantly higher serum chemerin concentration as compared to patients with mild preeclampsia and healthy pregnant women. This is in agreement with **Stepan *et al.* [31],** they proved that maternal serum levels of the adipokine chemerin were significantly up-

regulated in preeclampsia patients as compared to healthy pregnant women. Also, they demonstrate that chemerin serum levels are significantly increased in pregnancy independent of preeclampsia as compared to non-pregnant subjects. Based on these findings, it can be hypothesized that a certain level of chemerin is required for or associated with normal pregnancy but further elevated chemerin levels could be a marker for and/or contributor to preeclampsia. Moreover, **Duan *et al.*** [32], found that all cases developed PE, irrespective of its severity, showed significantly higher maternal serum chemerin compared to levels estimated in control group, in addition patients with severe preeclampsia had higher chemerin concentration than either mild preeclampsia or healthy pregnant women. These findings pointed to an association between chemerin serum levels and the development of PE. In support of such assumption, there was a highly significant positive correlation between serum levels of maternal chemerin and estimated (SBP, DBP, UA and LDH), which are markers of severity. Moreover, by multiple regression analysis only SBP and UA were independently associated with chemerin among all cases. These results concerning blood pressure were in agreement with studies by **Stejskal *et al.*** **Bozaoglu *et al.*** **and Kaur *et al***. [33,34, 7]. They revealed that chemerin serum levels correlated positively with systolic and diastolic blood pressure. Chemerin may also be a novel regulator of blood pressure because of good correlations with both systolic and diastolic pressure. This hypothesis is supported by the fact that chemerin is highly expressed in the kidney, a key site of blood pressure regulation. Chemerin is an inducer of endothelial angiogenesis factors as kininogens, which proteolytic product is the vasoactive peptide bradykinin. Moreover, among patients with preeclampsia, but not in normal pregnant women, the serum chemerin was significantly higher in gestaional age <32weeks as compared to gestational age ≥32 weeks, this is supported in our work by a significantly negative correlation between serum chemerin with gestational age at blood collection (at the time of diagnosis of preeclampsia). Thus, the earlier the diagnosis, the higher was the maternal plasma chemerin concentrations. This is pertinent since the timing of the diagnosis of preeclampsia is an important index of severity. The physiological significance of increased maternal serum chemerin in preeclampsia remains to be elucidated, a significant positive correlations between chemerin and adiposity (body weight) was recorded amoung studied groups, this comes in line with ***Shin et al.*, *Yoo et al.*** and ***Yan et al.***[35,36,37]. They proved that serum chemerin levels were significantly increased in obese individuals compared with lean controls and circulating chemerin levels had a significant positive correlation with the body mass index, waist circumference, abdominal visceral fat area, ***Ernst et al.*** [38] stated that chemokine-like receptor 1 (CMKLR1 (-/-)) mice had lower food consumption, total body mass, and percent body fat compared with wild-type controls ***Blüher et al.***[39]. proved that insulin is tightly correspond to changes in body weight, with the trend to go to the opposite direction during the weight loss phase and downregulation of glucose transporter-4 (GLUT4) in adipose tissue is an important feature of insulin resistance. Moreover, significant positive correlation between serum chemerin and glycolipid metabolism {fasting insulin, HOMA-IR (in preeclampsia), In agreement with these in vitro findings **Sell *et al.*** [40] reported that chemerin induces insulin resistance in human skeletal muscle cells at the level of insulin receptor substrate and glycogen synthase kinase 3 phosphorylation, Chemerin konkout reduces the expression of genes involved in glucose and lipid metabolism, such as perilipin, GLU4, adiponectin and leptin are resulted in reduced basal lipolysis and phosphdiasterase inhibitor-stimulated lipolysis rates. **Ernst *et al.*** [30] reported that an administration of chemerin in rodents impairs glucose tolerance, lowers serum insulin levels, and decreases basal glucose uptake in diabetic mice *in vivo*. Furthermore, TGs remain independently associated with circulating chemerin in multiple linear regression analysis adjusted for preeclampsia, this result is in accordance with **Bozaoglu *et al.*** [41] who reported that significant and positive correlation between circulating chemerin levels and TG independent of age, gender, and BMI , **Stepan *et al.*** and **Duan *et al.*** [31,32] reported that maternal chemerin serum concentrations are significantly increased in preeclampsia and independently associated with markers of dyslipidemia. It was documented that multiple factors such as obesity, insulin resistance and dyslipidemia are implicated in pathogenesis of preeclampsia. Altered lipids, especially increased FFAs and increased TGs, may have an important role in the endothelial cell dysfunction seen in pre-eclampsia. Our data demonstrate that circulating TGs was markedly elevated in women with pre-eclampsia, moreover, TGs were significantly increased in severe preeclampsia as compared to both mild cases and healthy pregnant women. We speculated that dyslipidemia may have an important role in the pathophysiology of Preeclampsia. **Lei Q *et al.*** [3] indicates that pre-eclamptic women have higher circulating TG. Although. The interplay between dyslipidemia and insulin sensitivity in pre-eclampsia may be regulated by other factors, such as placental hormones. Another explanation for association between chemerin and preeclampsia, Widespread maternal endothelial dysfunction is the vital factor for preeclampsia, inevitably and sensitively

influencing the glomerular dynamics and renal function. [12] Chemerin is shown to be associated with inflammation which is involved in the pathogenesis of diabetic nephropathy. **Pfau *et al.*** and **Rutkowski *et al.*** [42,43] demonstrated Significant negative correlation between the change of serum chemerin concentration and the change of eGFR, as well as the significant positive correlation between the change of serum chemerin concentration and the change of serum creatinine suggest that serum chemerin is affected by renal function. Thus serum chemerin may reflect the degree of renal affection in these pre-eclamptic women. In conclusions, our results demonstrate that both maternal serum chemerin and resistin levels are significantly increased in preeclampsia and serum chemerin levels are up-regulated especially in severe preeclampsia. Moreover chemerin is independently associated with markers of severity of preeclampsia and dyslipidemia, indicating that chemerin could be a novel marker of preeclampsia. Further studies are needed to demonstrate whether increased chemerin is causally linked to preeclampsia and by which mechanisms circulating chemerin potentially influences metabolic and vascular health in humans.

References:-

1 Bonney EA. Preeclampsia: a view through the danger model. J Reprod Immunol. (2007): 76; 68.
2 Kajantie E, Eriksson JG, Osmond C, Thornburg K, Barker DJ. Pre-eclampsia is associated with increased risk of stroke in the adult offspring: the Helsinki birth cohort study. Stroke. (2009): 40; 1176–1180.
3 Lei Q, Lv LJ, Zhang BY, Wen JY, Lin XH. Anti-partum and post-partum markers of metabolic syndrome in preeclampsia. J Hum Hypertension. (2011):25;11-7.
4 Chudek J, Wiecek A. Adipose tissue, inflammation and endothelial dysfunction. Pharmacol Rep (2006): 58; 81–88.
5 Bozaoglu K, Bolton, McMillan, Zimmet, Jowett, Collier, Walder, Segal. Chemerin is a novel adipokine associated with obesity and metabolic syndrome. Endocrinology. (2007): 148; 4687–94.
6 Roh SG, Song, Choi, Katoh, Wittamer, Parmentier, Sasaki. Chemerin—a new adipokine that modulates adipogenesis via its own receptor. Biochem Biophys Res Commun. (2007): 362; 1013–8.
7 Kaur J, Adya R, Tan BK, Chen J, Randeva HS. Identification of chemerin receptor (Chem R23) in human endothelial angiogenesis. Biochem Biophys Res Commun. (2010): 391; 1762-8.
8 Lehrke M, Becker A, Greif M, Stark R, Laubender RP, von Ziegler F, Lebherz C, Tittus J, Reiser M, Becker C, Goke B, Leber AW, Parhofer KG, Broedl UC. Chemerin is associated with markers of inflammation and components of the metabolic syndrome but does not predict coronary atherosclerosis. Eur. J. Endocrinol. (2009) : 161; 339–344
9 National high blood pressure education program working group on high blood pressure in pregnancy. Report of the national high blood pressure education program working group on high blood pressure in pregnancy. Am J Obstet Gynecol. (2000): 183;S1–S22.
10 ACOG Committee on obstetric practice. ACOG practice bulletin. Diagnosis and management of preeclampsia and eclampsia. Int J Gynaecol Obstet. (2002):77; 67-75.
11 Marra, F. and Bertolani , C. Adipokines in liver diseases. Hepatology(2009): 50(3); 957–969.
12 Hu W and Feng P. Elevated serum chemerin concentrations are associated with renal dysfunction in type 2 diabetic patients. Diabetes Res Clin Pract. (2011): 91(2); 159-63.
13 James J. C.l, Nancy, S., and Arthur L. B. A colorimetric serum glucose determination using hexokinase and glucose-6-phosphate dehydrogenase. Biochemical Medicine. (1970): 4(2); 171-180.
14 Allain, C. C., L. S. Poon, C. S. G. Chain, W. Richmond, and P. C. Fu. Enzymatic determination of the serum cholesterol. Clin. Chem. (1974): 20; 470–475.
15 Buccolo G and David H. Quantitative determination of serum triglycerides by the use of enzymes clin. Chem. (1973): 19; 476.
16 Assman G.; Schriewer H.; Schmitz G. and Hagele E.O. Quantification of high density lipoprotein cholesterol by precipitation with phosphotungestic acid/MgC12. Clin. Chem. (1983): 29; 2026-2027.
17 Trinder, P. ann. Enzymatic determination of uric acid in serum Clin. Biochem. (1969): 6; 24.
18 Amador E, Dorfman LE, Wacker WE. Serum Lactate dehydrogenase activity, an analytical assay of current assay. Clin. Chem. (1963): 9;391-399.
19 Friedwald W.T.; Levy R.I. and Fridrickson D.S. Estimation of the concentration of lowdenisty lipoprotein cholesterol in plasma without use of the preparative ultracentrifugation. Clin. Chem. (1972):18; 449-501.
20 Judzewitsch, R. G., Pfeifer, M. A., Best, J. D., Beard J. C., Halter, J. B. and Porte D. Jr. Chronic Chlorpropamide therapy of noninsulin-dependent diabetes augments basal and stimulated insulin secretion by increasing islet sensitivity to glucose. J. Clin. End. and Metab. (1982): 55; 321-328.
21 Shirai K. Obesity as the core of the metabolic syndrome and the management of coronary heart disease. Curr. Med. Res. Opin. (2004): 20(3); 295-304.
22 Schaffler A, Buchler C, Muller-Lander U, et al. Identification of variables influencing resistin serum levels in patients with type 1 and type 2 diabetes mellitus. (2004): 36(10); 702-7.
23 Roh S, Song SH, Choi KC, Katoh K, Wittamer V, Parmentier M, Sasaki S. Chemerin – A new adipokine that modulates adipogenesis via its own receptor. Biochem. and Biophys. Research Comm. (2007): 362; 1013-1018.
24 Craici I, Wanger S, Garovic VD. Preeclampsia and future cardiovascular risk: formal risk factor or failed stress test Ther Adv Cardiovascular Diseases. (2008): 2; 249-59.
25 Haugen F, Ranheim T, Harsem NK, Lips E, Staff AC, Drevon CA. Increased plasma levels of adipokines in preeclampsia: relationship to placenta

and adipose tissue gene expression. Am J Physiol Endocrinol Metab. (2006): 290; E326–333.
26 Seol HJ, Oh MJ, Yeo MK, Kim A, Lee ES and Kim HJ. Comparison of Serum Levels and the Placental Expression of Resistin Between Patients with Preeclampsia and Normal Pregnant Women. Hypertension in Pregnancy. (2010): 29; 310–317.
27 Sonagra AD, Dattatreya. K2, and Murthy D.S. Serum ldh, alp and uric acid in hypertensive disorders of pregnancy. International Journal of Pharmacy and Biological Sciences. (2012): 2(3); 201-209
28 Demirci O, Tug- rul A, Dolgun N, Sözen H and Eren S. Serum lipids level assessed in early pregnancy and risk of pre-eclampsia. J. Obstet. Gynaecol. Res. (2011): 37; 1427–1432.
29 Ray JG, Diamond P, Singh G, Bell CM. Brief overview of maternal triglycerides as a risk factor for preeclampsia. BJOG. (2006): 113; 379–386.
30 Ernest MC and Sinal CJ. Chemerin: at the crossroads of inflammation and obesity. Trends in Endocrinology and Metabolism. (2010): 21; 34-45.
31 Stepan H, Philipp A, Roth I , Kralisch S, Jank A, Schaarschmidt W, Lössner U, Kratzsch J, Blüher M, Stumvoll M and Fasshauer M. Serum levels of the adipokine chemerin are increased in preeclampsia during and 6 months after pregnancy. Regulatory Peptides. (2011): 168; 69–72.
32 Duan DM, Niu JM, Lei Q, Lin XH and Chen X. Serum levels of adipokine chemerin in preeclampsia. Journal of Prienatal Med. (2012): 40; 121-127.
33 Stejskal D.; Karpisek M.; Hanulova Z. and Svestak M. Chemerin is an independent marker of the metabolic syndrome in a Caucasian population a pilot study. Biomed. Pap. (2008):152(2) ;217-221.
34 Bozaoglu K, Curran JE, Stocker CJ, Zaibi MS, Segal D, Konstantopoulos N, Morrison S, Carless M, Dyer TD, Cole SA, Goring HH, Moses EK and Walder K. Chemerin, a novel adipokine in the regulation of angiogenesis. J Clin Endocrinol Metab. (2010): 95(5); 2476-85.
35 Shin HY, Lee DC, Chu SH, Jeon JY, Lee MK, Im JA, Lee JW. Chemerin levels are positively correlated with abdominal visceral fat accumulation. Clin Endocrinol. (2011)
36 Yan Q, Zhang Y, Hong J, Gu W, Dai M, Shi J, Zhai Y, Wang W, Li X, Ning G. The association of serum chemerin level with risk of coronary artery disease in Chinese adults. Endocrine. (2012): 41(2);281-8.
37 Yoo HJ, Choi HY, Yang SJ, Kim HY, Seo JA, Kim SG, Kim NH, Choi KM, Choi DS, Baik SH. Circulating chemerin level is independently correlated with arterial stiffness. J Atheroscler Thromb. (2012):19(1); 59-66
38 Ernst M.C, Haidl I.D, Zúñiga L.A, Dranse H.J, Rourke J.L, Zabel BA, Butcher E.C, Sinal CJ. Disruption of the chemokine-like receptor-1 (CMKLR1) gene is associated with reduced adiposity and glucose intolerance. Endocrinology. (2012):153(2); 672-82.
39 Blüher M, Rudich A, Klöting N, Golan R, Henkin Y, Rubin E, Schwarzfuchs D, Gepner Y, Stampfer MJ,Fiedler M, Thiery J, Stumvoll M and Shai I. Two patterns of adipokine and other biomarker dynamics in a long-term weight loss intervention. Diabetes Care. (2012): 35 (2); 342-9.
40 Sell H, Laurencikiene J, Taube A, Eckardt K, Cramer A and Horrighs. Chemerin is a novel adipocyte-derived factor inducing insulin resistance in primary human skeletal muscle cell. Diabeties. (2009): 58; 2731-40.
41 Bozaoglu K.; Segal D., Shields K., Cummings, N., Curran, J, Comuzzie, A., Mahaney, M., Rainwater, D., VandeBerg, J., MacCluer, J., Collier, G. and Jowett, J. Chemerin is associated with metabolic syndrome phenotypes in a Mexican- American population, The Journal of Clinical Endocrinology & Metabolism. (2009): 94 (8); 3085-3088.
42 Pfau D, Stepan, Kratzsch, Verlohren, Verlohren, Drynda, Lossner, Bluher, Stumvoll, Fasshauer. Circulating Levels of the Adipokine Chemerin in Gestational Diabetes Mellitus. Horm Res Paediatr. (2010): 74; 56–61.
43 Rutkowski P, Sledzinski T, Zielinska H, Lizakowski S, Goyke E, Swierczynski E et al. Decrease of serum chemerin concentration in patients with end stage renal disease after successful kidney transplantation. Regulatory Peptides. (2012): 173; 55–59.