Zinc-alpha 2-glycoprotein serum level in Egyptian females with preeclampsia and eclampsia

Original Article

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ABSTRACT

Objective: The aim of this study was to measure serum zinc-α2-glycoprotein (ZAG) in pregnant Egyptian females with preeclampsia and eclampsia and to correlate its levels to biochemical measures of kidney function, lipid and glucose metabolism.

Study Design: It was a retrospective study.

Patients and Methods: This study measured ZAG levels by enzyme linked immunosorbent assay (ELISA) in pregnant females with preeclampsia (PE) (no. = 40) and eclampsia (no.=20) and were compared to healthy gestational age-matched subjects (no.=20). In addition, the association of ZAG with kidney function, lipid and glucose metabolism was studied.

Results: Significant difference was detected on comparing the different groups regarding ZAG levels (*p = 0.001*). Furthermore, ZAG was positively correlated to systolic blood pressure, urinary protein, fasting insulin and HOMA-IR. After adjusting for other parameters,the association between ZAG and SBP, urinary protein, serum insulin and HOMA-IR remained significant by multivariate linear regression analysis.

Conclusion: The study noted that maternal ZAG serum levels are significantly increased in PE.

Key Words: Adipokines, eclampsia, preeclampsia, ZAG

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INTRODUCTION

Preeclampsia (PE) and eclampsia are serious complications that occur in pregnancy. Preeclampsia is characterized by hypertension and/or proteinuria after 20 weeks of gestation. Eclampsia is known as onset of tonic clonic seizures in a preeclamptic woman. [1-4]. As a result of a preeclamptic pregnancy, the mother and her newborn have an increased future risk for cardiovascular and metabolic diseases. PE and metabolic syndrome have some similar risk factors such as obesity and insulin resistance (IR). [2, 3]. The pathogenesis of PE is thought to result from the imbalance between proangiogenic factors such as vascular endothelial growth factor as well as placental growth factor and anti-angiogenic factors such as soluble fms-like tyrosine kinase 1 [2, 5-8]. In addition, adipocyte-secreted factors (adipokines) have a majorrole in the PE pathogenesis [2]. Adipose tissue is recognized as an endocrine organ producing adipokines such as adiponectin, leptin, tumour necrosis factor α (TNF-α), chemerin and zinc-α 2-glycoprotein (ZAG)[9-13]. Adipokines act in an autocrine/paracrine manner and/or as endocrine signals to regulateenergy expenditure, appetiteand other processes such as inflammation, angiogenesis and insulin sensitivity [13-17]. They also keep the vascular homeostasis by acting on endothelial cells. Thus, altered production of these adipokines results in the structural and functional changes in the vessels by vascular smooth muscle cell proliferation and endothelial dysfunction [18-19]. ZAG is considered as 41 kDa soluble glycoprotein which has been found first in plasma. The name of ZAG is derived from its ability to precipitate with zinc and from its electrophoretic migration in the region of α2- globulins. [20-22] ZAG is a lipid mobilizing adipokine which significantly decreases fat mass by inhibiting lipogenesis and inducing lipolysis via a cyclic AMP-mediated system and through interaction with the β3- adrenoreceptor [13,23-25]. It is regulated by and regulates hormones influencing glucose tolerance. It was proved that ZAG level is correlated significantly with glucose metabolism, fasting insulin, and HOMA-IR [22]. Recently, it was found that patients with hypertension have lower ZAG levels suggesting the role of ZAG in vascular homeostasis [18]. Renal clearance plays a role

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in ZAG catabolism. It was suggested that ZAG may be involved in the pathogenesis of obesity and obesity related metabolic disease; including hypertension and diabetes mellitus which represent important metabolic syndrome components [14-20]. Based on the above mentioned data, it was proposed that ZAG may have a role in the pathogenesis of PE and its complications [2].

PATIENTS AND METHODS

Eighty pregnant females were recruited from the Obstetrics and Preeclampsia Units of Obstetrics and Gynecology Department at El-Shatby Maternity University Hospital. This study had been approved by the Ethics Committee of Alexandria Universityand a written consent was taken from each patient. Patients were divided into 3 groups; twenty pregnant females with mild preeclampsia, twenty pregnant females with severe preeclampsia, twenty pregnant females with eclampsia and twenty healthy gestational age-matched pregnant females were included as controls. PE was defined as systolic $\geq$ 140 mmHg or $\geq$ 90 mmHg diastolic blood pressure in combination with proteinuria in pregnant female with normal blood pressure before 20 weeks gestation. [4] Patients with chronic hypertension, renal diseases, diabetes mellitus, endocrine diseases or chronic disease were excluded. Data for medical history, last menstrual period date, gravidity, parity and age were recorded. Blood samples were drained by venipuncture. Complete blood countwas assessed on a 3 part differential automated cell counter. Sysmex and routine chemistry investigations; fasting glucose, serum cholesterol, serum triglycerides, serum creatinine and liver function tests were performed by standard laboratory methods using Dimension RxLautoanalyzer. Estimated glomerular filtration rate (eGFR) was calculated by the Modification of Diet in Renal Disease (MDRD) study equation. [26] Serum for ELISA assays (ZAG and insulin) was aliquoted and stored frozen at -20°C. Fasting insulin was determined by a commercially available ELISA (EIA-2935, DRG International, USA). Insulin sensitivity was assessed by homeostasis model assessment of insulin resistance (HOMA-IR). [27] ZAG was determined by a commercially available ELISA (BMS2201, eBioscience, Austria).

STATISTICAL ANALYSIS

Data were fed to the computer and analyzed using IBM SPSS software package version 20.0. (Armonk, NY: IBM Corp). Qualitative data were described using number and percentage. The Kolmogorov-Smirnov test was performed to verify the normality of distribution. Quantitative data were described using range (minimum and maximum), mean, standard deviation and median. Significance of the obtained results was judged at the 5% level. Spearman coefficient was used to correlate between two distributed abnormally quantitative variables.

RESULTS

There was statistically significant difference between thestudied groups and the normal pregnant females as regards LMP, systolic and diastolic blood pressure, platelets count, protein creatinine ratio, serum creatinine, liver function tests, triglycerides levels, fasting insulin levels, fasting serum glucose and HOMA-IR. Nosignificant difference was detected between the studied groups regarding age, parity, gravidity and cholesterol levels. Tables (1 - 8).

Table 1 : Comparison between the different studied groups according to descriptive data

Obstetrics data	Control (n = 20)	Mild PE (n = 20)	Severe PE (n = 20)	Eclampsia (n = 20)	Test of Sig.	p
	No. %	No. %	No. %	No. %		
Age (years) Min. – Max. Mean ± SD. Mean ± SD.	19.0 – 42.0 28.65 ± 5.0 28.50	23.0 – 38.0 28.55 ± 3.87 27.50	16.0 – 40.0 29.80 ± 5.85 30.0	19.0 – 37.0 31.0 ± 5.08 33.0	1.057	0.372
LMP (weeks) Min. – Max. Mean ± SD. Median	28.50 36.20 ± 3.64 38.0	29.0 – 37.0 33.10 ± 2.17 33.50	27.0 – 36.0 31.80 ± 2.35 32.50	27.0 – 35.0 30.85 ± 2.11 31.0	F = 15.572*	*< 0.001**
pControl		*0.002**	*< 0.001**	*< 0.001**		
Sig. bet. grps.		$p_1 = 0.410$, $p_2 = 0.042$*, $p_3 = 0.668$				

Parity Nulliparous Multiparous	5 15	25.0 75.0	7 13	35.0 65.0	11 9	55.0 45.0	7 13	35.0 65.0	$\chi^2 = 4.053$	0.256
Gravidity Primigravida Multigravida	3 17	15.0 85.0	7 13	35.0 65.0	11 9	55.0 45.0	7 13	35.0 65.0	$\chi^2 = 7.033$	0.071
Min. – Max. Median	1.0 – 6.0 2.50		1.0 – 5.0 2.0		1.0 – 6.0 1.0		1.0 – 5.0 2.0		H = 6.014	0.111

χ^2, p: χ^2 and p values for Chi square test for comparing between the different groups
F,p: F and p values for ANOVA test, Sig. bet. grps was done using Post Hoc Test (Tukey)
H,p: H and p values for Kruskal Wallis test
pControl: p value for comparing between control and each other group
p1: p value for comparing between mild and severe
p2: p value for comparing between mild and eclampsia
p3: p value for comparing between severe and eclampsia
*: Statistically significant at $p \leq 0.05$

Table 2 : Comparison between the different studied groups according to blood pressure

Blood pressure (mmHg)	Control (n = 20)	Severity Mild PE (n = 20)	Severe PE (n = 20)	Eclampsia (n = 20)	F	p
Systolic (mmHg) Min. – Max. Mean ± SD. Median	100.0 – 130.0 117.5 ± 9.67 120.0	140.0 – 160.0 149.5 ± 7.59 150.0	160.0 – 200.0 167.3 ± 10.19 162.5	140.0 – 170.0 155.0 ± 7.61 160.0	115.094*	< 0.001*
pControl		*< 0.001**	*< 0.001**	*< 0.001**		
Sig. bet. grps.		p1 < 0.001*, p2 = 0.210, p3 < 0.001*				
Diastolic (mmHg) Min. – Max. Mean ± SD. Median	60.0 – 80.0 72.50 ± 7.16 70.0	90.0 – 100.0 94.0 ± 5.03 90.0	110.0 – 120.0 111.8 ± 3.35 110.0	100.0 – 115.0 104.8 ± 5.73 100.0	194.627*	*< 0.001**
pControl		*< 0.001**	*< 0.001**	*< 0.001**		
Sig. bet. grps.		p1 < 0.001*, p2 < 0.001*, p3 = 0.001*				

Table 3 : Comparison between the different studied groups according to CBC

	Control (n = 20)	Severity Mild PE (n = 20)	Severe PE (n = 20)	Eclampsia (n = 20)	F	p
Haemoglobin (g/dl) Min. – Max. Mean ± SD. Median	9.0 – 12.0 10.13 ± 1.06 10.0	8.40 – 11.0 9.73 ± 0.84 9.95	8.50 – 11.0 9.75 ± 0.70 9.80	8.80 – 11.0 9.65 ± 0.69 9.60	1.293	0.283
WBCs(/µl) Min. – Max. Mean ± SD. Median	4000 – 11000 7520 ± 2169.79 8000	4300 – 11000 7440 ± 1919.54 7500	5300 – 11500 7715 ± 1912.36 7800	4000 – 12100 7265 ± 2446.54 7050	0.155	0.926
Platelets (×103/µl) Min. – Max. Mean ± SD. Median	155.0 – 320.0 203.8 ± 43.70 188.5	120.0 – 250.0 173.8 ± 32.75 170.5	90.0 – 127.0 107.4 ± 9.89 104.5	92.0 – 138.0 113.2 ± 12.77 111.0	54.463*	*< 0.001**
pControl		*0.007**	*< 0.001**	*< 0.001**		
Sig. bet. grps.		p1 < 0.001*, p2 < 0.001*, p3 = 0.919				

Table 4 : Comparison between the different studied groups according to urinary protein, urinary creatinine and PCR

	Control (n = 20)	Severity			H	p
		Mild PE (n = 20)	Severe PE (n = 20)	Eclampsia (n = 20)		
Urinary protein (mg/dl) Min. – Max. Mean ± SD. Median	2.0 – 23.0 8.71 ± 8.11 4.0	10.0 – 230.0 54.25 ± 47.96 37.50	55.0 – 340.0 178.3 ± 90.78 173.0	11.0 – 831.0 143.6 ± 180.1 94.0	55.033*	*< 0.001**
pControl		*< 0.001**	*< 0.001**	*< 0.001**		
Sig. bet. grps.		p1 < 0.001*, p2 = 0.002*, p3 = 0.030*				
Urinary creatinine (mg/dl) Min. – Max. Mean ± SD. Median	42.81 – 334.1 107.7 ± 63.47 96.56	24.02 – 167.3 87.81 ± 38.63 70.97	11.0 – 69.53 33.36 ± 15.24 33.10	12.46 – 136.5 29.99 ± 29.40 18.01	45.442*	*< 0.001**
pControl		0.372	*< 0.001**	*< 0.001**		
Sig. bet. grps.		*p1 < 0.001*, p2 < 0.001*, p3 = 0.074*				
PCR (mg/g) Min. – Max. Mean ± SD. Median	11.30 – 169.0 79.07 ± 51.85 68.05	314.3 – 1892.2 622.7 ± 419.5 414.3	2038.0 – 10757.0 6065.6 ± 2879.3 5399.6	881.4 – 7275.0 4095.3 ± 1795.7 3719.8	67.047*	*< 0.001**
pControl		*< 0.001**	*< 0.001**	*< 0.001**		
Sig. bet. grps.		*p1 < 0.001*, p2 < 0.001*, p3 = 0.051*				

Table 5 : Comparison between the different studied groups according to serum creatinine and eGFR

	Control (n = 20)	Severity			F	p
		Mild PE (n = 20)	Severe PE (n = 20)	Eclampsia (n = 20)		
Serum creatinine (mg/dl) Min. – Max. Mean ± SD. Median	0.36 – 0.60 0.46 ± 0.05 0.47	0.69 – 1.23 0.88 ± 0.14 0.88	1.08 – 2.79 1.74 ± 0.54 1.63	1.83 – 5.91 3.35 ± 1.18 2.94	77.174*	*< 0.001**
pControl		0.190	*< 0.001**	*< 0.001**		
Sig. bet. grps.		*p1 < 0.001*, p2 <0 .001*, p3 < 0.001**				
eGFR (ml/min/1.73m²) Min. – Max. Mean ± SD. Median	123.9 – 216.2 163.5 ± 22.42 161.7	52.38 – 100.3 78.85 ± 13.47 78.21	19.31 – 59.17 38.34 ± 12.11 36.94	8.59 – 35.56 18.30 ± 6.96 18.08	375.974*	*< 0.001**
pControl		*< 0.001**	*< 0.001**	*< 0.001**		
Sig. bet. grps.		*p1 < 0.001*, p2 < 0.001*, p3 < 0.001**				

Table 6 : Comparison between the different studied groups according to lipid profile

Lipid profile	Control (n = 20)	Severity			Test of Sig.	p
		Mild PE (n = 20)	Severe PE (n = 20)	Eclampsia (n = 20)		
Triglycerides (mg/dl)						
Min. – Max.	50.0 – 245.0	114.0 – 400.0	100.0 – 385.0	137.0 – 343.0	H = 16.707*	*0.001**
Mean ± SD.	159.45 ± 43.29	218.10 ± 91.66	235.70 ± 65.38	226.35 ± 60.10		
Median	169.50	179.0	217.0	206.50		
pControl		0.104	*< 0.001**	*0.001**		
Sig. bet. grps.		p1 = 0.234, p2 = 0.402, p3 = 0.588				
Cholesterol (mg/dl)						
Min. – Max.	80.0 – 278.0	140.0 – 292.0	123.0 – 291.0	150.0 – 287.0	F = 0.754	0.524
Mean ± SD.	211.75 ± 42.75	211.70 ± 40.63	217.35 ± 50.55	197.15 ± 43.54		
Median	217.50	217.50	224.0	179.50		

Table 7 : Comparison between the different studied groups according to liver function (ALT, AST)

Liver function	Control (n = 20)	Severity			F	p
		Mild PE (n = 20)	Severe PE (n = 20)	Eclampsia (n = 20)		
AST(IU/L)						
Min. – Max.	18.0 – 37.0	18.0 – 43.0	40.0 – 71.0	40.0 – 73.0	81.100*	*< 0.001**
Mean ± SD.	24.10 ± 5.60	29.05 ± 7.69	52.45 ± 7.20	54.60 ± 10.06		
Median	22.0	28.0	50.50	52.50		
pControl		0.195	*< 0.001**	*< 0.001**		
Sig. bet. grps.		*p1 < 0.001*, p2 < 0.001**, p3 = 0.820				
ALT (IU/L)						
Min. – Max.	17.0 – 28.0	17.0 – 30.0	30.0 – 49.0	33.0 – 46.0	115.722*	*< 0.001**
Mean ± SD.	20.55 ± 2.76	23.50 ± 4.44	39.45 ± 4.98	38.75 ± 4.01		
Median	20.0	22.50	39.50	38.50		
pControl		0.117	*< 0.001**	*< 0.001**		
Sig. bet. grps.		*p1 < 0.001*, p2 < 0.001**, p3 = 0.950				

Table 8 : Comparison between the different studied groups according to fasting serum glucose, fasting serum insulin and HOMA-IR

	Control (n = 20)	Mild PE (n = 20)	Severe PE (n = 20)	Eclampsia (n = 20)	Test of Sig.	p
Fasting serum glucose (mg/dl)						
Min. – Max.	60.0 – 89.0	68.0 – 147.0	78.0 – 185.0	98.0 – 181.0	F = 29.301*	*< 0.001**
Mean ± SD.	72.20 ± 7.92	103.2 ± 21.69	125.1 ± 34.45	134.9 ± 19.72		
Median	71.0	95.50	117.0	132.0		
pControl		*< 0.001**	*< 0.001**	*< 0.001**		
Sig. bet. grps.		p1 = 0.018*, p2 < 0.001*, p3 = 0.530				
Fasting serum insulin(µIU/mL)						
Min. – Max.	6.20 – 34.07	6.20 – 45.40	8.19 – 97.35	6.30 – 54.09	H = 26.666*	*< 0.001**
Mean ± SD.	13.69 ± 8.56	24.15 ± 13.20	36.73 ± 28.17	10.69 ± 10.45		
Median	11.14	23.79	24.79	7.55		
pControl		*0.007**	*0.001**	0.198		
Sig. bet. grps.		p1 = 0.234, p2 = 0.003*, p3 < 0.001*				
HOMA-IR						
Min. – Max.	0.96 – 5.46	1.09 – 13.40	2.50 – 38.30	2.30 – 16.43	H = 32.494*	*< 0.001**
Mean ± SD.	2.31 ± 1.27	6.17 ± 3.83	12.81 ± 12.17	3.42 ± 3.11		
Median	2.15	5.45	7.05	2.51		
pControl		*< 0.001**	*< 0.001**	*0.026**		
Sig. bet. grps.		p1 = 0.133, p2 = *0.010*, p3 < 0.001**				

Statistically significant difference was detected on comparing the different groups regarding ZAG levels in the serum (*p = 0.001*). Table 9 and Figure 1. A positive correlation was found between ZAG and systolic blood pressure (r = 0.305, *p = 0.018*), urinary protein (r = 0.316, *p = 0.014*), fasting insulin (r = 0.303, *p = 0.019*) and HOMA-IR (r = 0.261, *p = 0.044*) in the patients group by univariate correlation.Table (11). In the patients group,the association between ZAG and SBP (β = 0.354, *p = 0.013*), urinary protein (β = 0.310, *p = 0.014*), serum insulin (β=1.259, p=0.005) and HOMA-IR (β=-1.189, p=0.013) remained significant after adjusting for other parameters by multivariate linear regression analysis. Table (11).

Regarding the performance of ZAG for diagnosing preeclampsia/eclampsia, ROC curve analysis showed that at a cut off >146.1 µg/ml, ZAG had a diagnostic sensitivity of 75.0% and a specificity of 60.0%. Figure (2), Table (12)

Table 9 : Comparison between the different studied groups according to ZAG

	Control (n = 20)	Mild PE (n = 20)	Severe PE (n = 20)	Eclampsia (n = 20)	F	p
ZAG(µg/ml)						
Min. – Max.	75.9 – 160.4	87.8 – 157.6	133.3 – 166.8	59.2 – 157.6	*6.065**	*0.001**
Mean ± SD.	126.7 ± 31.6	146.5 ± 14.1	151.3 ± 7.3	126.7 ± 31.1		
Median	144.6	148.3	149.9	142.3		
pControl		*0.047**	*0.008**	1.000		
Sig. bet. grps.		p1 = 0.916, p2 = 0.046*, p3 = 0.008*				

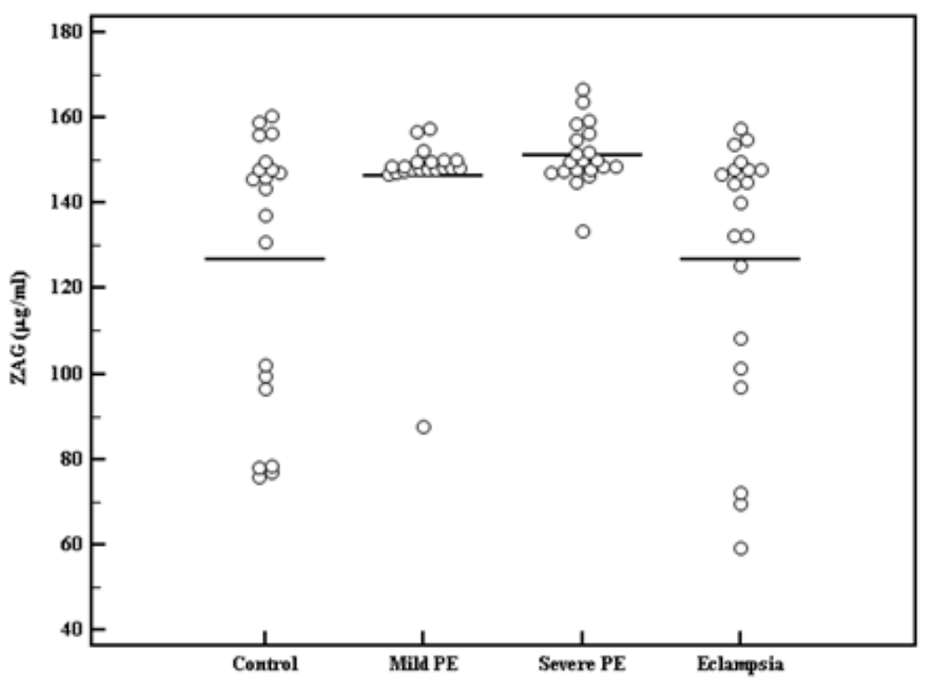

Fig. 1 : Comparison between the different studied groups according to ZAG

Table 10 : Univariate correlation between ZAG (µg/ml) and different parameters

	ZAG (µg/ml)					
	Total sample (n = 80)		Patients (n = 60)		Control (n = 20)	
	r	p	r	p	r	p
Age (years)	0.109	0.334	0.106	0.421	0.052	0.828
LMP (weeks)	-0.046	0.683	0.122	0.353	0.117	0.623
Gravidity	-0.010	0.929	0.074	0.573	-0.046	0.848
Systolic blood pressure (mmHg)	0.291*	0.009*	0.305*	0.018*	-0.226	0.337
Diastolic blood pressure (mmHg)	0.195	0.083	0.021	0.874	-0.193	0.415
Urinary protein (mg/dl)	0.332*	0.003*	0.316*	0.014*	0.533	0.016*
Urinary creatinine (mg/dl)	-0.099	0.382	-0.088	0.501	0.178	0.453
Serum Creatinine (mg/dl)	0.008	0.941	-0.185	0.156	-0.104	0.662
eGFR (ml/min/1.73m²)	-0.145	0.200	0.235	0.071	0.041	0.863
Triglycerides (mg/dl)	0.153	0.177	0.147	0.263	-0.256	0.276
Total cholesterol (mg/dl)	0.011	0.921	0.087	0.507	-0.139	0.560
Fasting serum glucose (mg/dl)	0.101	0.372	-0.072	0.586	-0.267	0.254
Fasting serum insulin (µIU/mL)	0.286*	0.010*	0.303*	0.019*	0.084	0.724
HOMA-IR	0.264*	0.018*	0.261*	0.044*	0.048	0.841

r : Pearson coefficient
*: Statistically significant at $p \leq 0.05$

Table 11 : Multivariate linear regression analysis for ZAG (µg/ml) in patients group

	Beta	t	p
Systolic blood pressure (mmHg)	0.354	2.553*	0.013*
Urinary protein (mg/dl)	0.310	2.548*	0.014*
Serum insulin (µIU/mL)	1.259	2.892*	0.005*
HOMA IR	-1.189	2.558*	0.013*

Beta: Standardized Coefficients

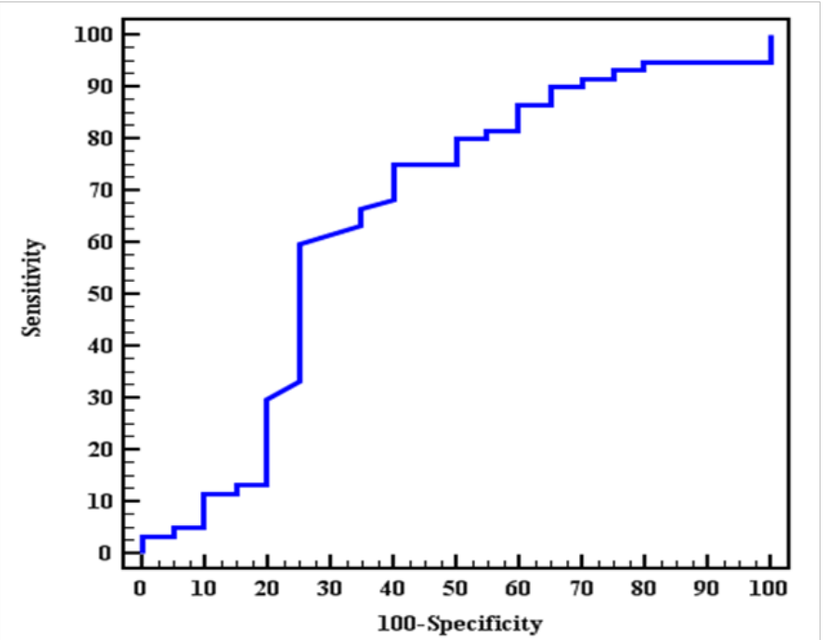

Fig. 2 : ROC curve for ZAG (µg/ml) to diagnose patients from control

Table 12 : Agreement (sensitivity, specificity) for ZAG (µg/ml) to diagnose patientsfrom control

	AUC	p	95 % C.I		Cut off	Sensitivity	Specificity	PPV	NPV
			LL	UL					
ZAG (µg/ml)	0.655*	0.039*	0.500	0.809	> 146.1	75.0	60.0	84.9	44.4

DISCUSSION

In our study, maternal ZAG was significantly increased in mild and severe preeclampsia subjects as compared to healthy pregnant controls. The results may be attributed to that systemic endothelial dysfunction occurs in preeclampsia which affects glomerular epithelial cells and causes renal injury. Renal degradation contributes to ZAG clearance and elimination. Therefore, renal impairment may result in elevation of ZAG concentration.[28]

In agreement with these findings, Stepan H *et al.* found that the median ZAG was 1.4-fold higher in preeclamptic patients when compared to controls. This is in accordance with the hypothesis that adipokines such as ZAG may have a role in preeclampsia pathogenesis and its complications.[2]

Furthermore, the current study found a positive correlation between circulating ZAG on one hand and SBP, urinary protein, fasting insulin and HOMA-IR on the other hand in the patients group. The association remained significant after adjusting for other parameters that may affect levels of ZAG in patients.

However, Stepan H. and his colleagues [2] reported that ZAG was positively associated only with SBP, DBP, creatinine and TG. No correlation between circulating ZAG and fasting glucose, fasting insulin as well as HOMA-IR and age was found. Only serum creatinine remained a strong independent predictor of ZAG concentrations in multiple regression analysis. These results had pointed out that ZAG depended on kidney function and that renal elimination was a major route by which physiologic ZAG serum levels are maintained.

The results were supported by other researchers, who suggested that increased ZAG concentration in CKD patients and chronic hemodialysis patients could be attributed to decreased GFR and/or tubular reabsorption which in turn decreases the renal degradation of ZAG.[28-30]

Also, Leal V *et al.* [31] found that ZAG was significantly increased in regular hemodialysis patients

when compared to controls. In addition, markers of inflammation, interleukin-6 and CRP were increased in patients on hemodialysis. It has been proposed that ZAG is an adipokine with anti-inflammatory properties. Thus, elevation of ZAG levels might be linked to oxidative stress and inflammation occurred in renal patients on hemodialysis and might reflect resolution of the pro-inflammatory process.[32]

In contrast with this study, Zhu H *et al.*[18] reported lower ZAG levels in hypertensive subjects with normal kidney function compared to controls. The median ZAG levels were 21.6% lower in hypertensive subjects. They concluded that ZAG may have a role in blood pressure control and that the lower ZAG levels in hypertensive subjects was related to blood pressure but not to renal function. The different change trend of ZAG concentrations in preeclampsia and hypertensive patients may be explained by the different pathogenesis of these two diseases.

Yang M *et al.*[22] reported significantly lower levels of ZAG in newly diagnosed diabetes mellitus (DM) patients or impaired glucose tolerance (IGT) compared with controls with normal glucose tolerance. HOMA-IR was independently related with serum ZAG. Also, obese or overweight individuals had significantly decreased ZAG concentrations than lean individuals. In addition, they found that ZAG mRNA expression and ZAG protein were down-regulated in adipose tissues from newly diagnosed DM patients compared with controls. A negative correlation was noted between ZAG level and dyslipidemia, adiposity, glucose metabolism, fasting insulin as well as HOMA-IR. These findings suggested that circulating ZAG might be linked to obesity and insulin resistance through its interaction with β3-adrenoreceptors and stimulating lipolysis suggesting a role in the regulation of lipid metabolism and insulin sensitivity. So, it could be used as a novel biomarker for insulin resistance syndrome and DM.[33,34]

However, Xu L *et al.*[35] reported that the diabetic patients with higher ZAG concentrations had decreased eGFR than those with low ZAG concentrations. This result suggested that serum ZAG concentrations were increased in T2DM patients complicated by diabetic nephropathy which is a microvascular complication that leads to slow deterioration of the kidneys and finally to end-stage renal disease. ZAG was found to be negatively correlated with eGFR in diabetic patients.

Moreover, Marrades M. *et al.*[23] revealed that the expression of gene of ZAG was decreased in adipose tissue of obese subjects compared to lean subjects. These results suggested that ZAG might play a major role in the regulation of adipose tissue metabolism. The down regulation of ZAG gene in obese subjects could be the cause of an impairment of lipid-mobilization, increasing the possibility that ZAG might be a candidate gene in the control of body weight and obesity related disorders.

On the other hand, Yeung D *et al.*[36] found that obese individuals had significantly increased ZAG concentrations than lean individuals. Furthermore, significantly higher ZAG levels were observed in patients with dyslipidemia, hypertension and type 2 DM. In addition, ZAG correlated positively with diastolic blood pressure, fasting insulin, insulin resistance indices and parameters of adiposity. These findings suggested that the elevation of ZAG in subjects with obesity might be a compensatory up-regulation to counteract the metabolic stress imposed by obesity. Also, it is possible that obesity may cause resistance to ZAG actions leading to its compensatory up regulation. The authors concluded that circulating ZAG might play a regulatory role in obesity-related metabolic syndrome and metabolism of lipid.

In contrast, Stejskal D *et al.*[37] reported that ZAG level did not differentiate healthy subjects from subjects with metabolic syndrome. This might be explained by the influence of hormonal interactions, food intake or energy balance on ZAG level or might result from the fact that ZAG is secreted in various tissues and fluids of the body. These findings corroborated those of other authors who noted that the difference between obese subjects with high insulin resistance and those with low insulin resistance regarding ZAG was not significant. These results suggested that ZAG might be closely linked mainly to obesity and its expression might be related to its important role in the modulation of lipid metabolism.[33]

CONCLUSION

In the current study, it was proved that the concentrations of maternal circulating ZAG are significantly elevated in pregnancies complicated by PE. The results suggested that ZAG might have a role in the development of preeclampsia and could be served as a promising predictor marker for PE diagnosis.

CONFLICT OF INTEREST

There are no conflicts of interest

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