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Role of Oxidative Stress in Preeclampsia in Egyptian Women

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Abstract: Preeclampsia remains a frequent and potentially dangerous complication of pregnancy. Preeclampsia (PE) is a multisystem, pregnancy-specific disorder and one of the main causes of fetal and maternal mortality. The cause remains largely unknown, but oxidative stress and a generalized inflammatory state are features of the maternal syndrome. The placenta appears to be the principal source of free radical synthesis but maternal leukocytes and the maternal endothelium are also likely contributors. The aim of this study was to evaluate oxidative stress markers such SOD, GSH, GPx and MDA as well as lipid profile in preeclampsia patient. Egyptian pregnant women (100) were selected for the study which was recruited from Mansoura University Main Hospital, Department of Obstetrics and Gynecology and also 100 normotensive pregnant women were collected. Classified into two groups; patient group with gestational mean age 28.96±6.9 weeks, and gestational age 32.4±3.4 weeks (majority were severe imposed PE) and control group. Our result shows that superoxide dismutase activity and reduced glutathione levels were decreased in preeclamptic women (89.18±19.7 and 0.11±0.08, respectively) when compared to normotensive ones (243.5±23.15 and 1.73±0.365, respectively). On the other hand, malondialdehyde and glutathione peroxidase levels were increased in preeclamptic patient group (0.55±0.11 and 498.56±53.3, respectively) when compared with normalized pregnant ones (0.49±0.25 and 303.22±71.59, respectively). Our finding concluded that preeclampsia pathogenesis is arising from major cascade of oxidative stress that results from the imbalance between oxidant and antioxidant

Keywords: *Preeclampsia, Pregnancy, oxidative stress, Hypertensio*

1. Introduction:

Preeclampsia affects between 0.4% and 2.8% of all pregnancies in developed countries and many more in developing countries, leading to as many as 8 370 000 cases worldwide per year. This common disorder, which is more prevalent in first pregnancies, is associated with the highest maternal and fetal morbidity and mortality of all pregnancy complications, with >90% of the most serious outcomes occurring in developing countries **[1, 2]**.Mostly women suffer from PE in their 1st pregnancy and the risk is higher if it is a twin pregnancy **[3]**. Usually, preeclamptic pregnant women is diagnosed at 20 weeks of gestation with high blood pressure **[4, 5].** One of the important risk factor for PE is placental oxidative stress which arise due to a deficiency in minerals, high rate of oxygen consumption leading to placental hypoxia, endothelial dysfunction and high level of reactive oxygen species **[6]**. The incidence of low concentration of free radicals in healthy pregnant is due to the neutralization mechanism by active defense

system of antioxidant molecules including superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx) **[7]**. Preeclamptic women have an increased level of malondialdehyde (MDA), lipid peroxidation product, compared with healthy pregnant women **[8, 9]**. In fact vascular endothelial cell dysfunction occurs as a consequence of increased lipid peroxides products in preeclamptic women. on the other hand, other studies failed to prove the relationship between lipid peroxidation level and endothelial dysfunction in early or late preeclampsia **[10]**. In this study, we examined the role of the imbalance between oxidants and antioxidants in a population of Egyptian women.

3. Subject and methods

3.1. Sample preparation

This study was performed on 100 women diagnosed with PE. Patients have blood pressure >140/90 mmHg and proteinuria>0.3 g in the 3rd trimester of pregnancy. The study included 100 healthy pregnant women for the comparison. The samples were collected from December 2019 to August 2020 in Mansoura University Main hospital from Department of Obstetrics and Gynecology according to the ethical standards of Institutional Research Board (IRB), Faculty of Medicine, Mansoura University. Each participant signed the informed consent. Any patients with past or present medical disorder associated or not associated with pregnancy were excluded from the study.

3.2. Blood sampling

Five milliliters of blood were collected by vein puncture from all participants. Each collected blood sample was either dispensed into EDTA-tubes for molecular studies or allowed to collect for collection of serum after centrifugation for oxidative stress parameters measurement.

3.3. Oxidative stress parameters:

Malondialdehyde (MDA) was estimated according to the method of **[11]**. Superoxide dismutase (SOD) activity was estimated according to the method of **[12, 13]**. Glutathione peroxidase (GPx) activity was determined by the nonenzymatic method **[14]**. Glutathione peroxidase activity can be decreased by negative feedback from excess substrate or from damage by oxidative modification. Glutathione reductase (GSH) activity was measured according to the method of Goldberg et. al., **[15]**.

3.4. Statistical analysis

Statistical analysis was performed using SPSS version 25. The genotype distributions of mutation, the frequency of heterozygous and homozygous were compared between patients and controls using Pearson's Chi-square test. The P value of <0.05 was regarded as significant.

4. Results

The current study represents a clinical trial including about 100 preeclampsia patients and 100 control volunteers from Mansoura University Hospital between 2019- 2020. The present results show descriptive data of all studied quantitative parameters in control subjects compared to cases of preeclampsia.

1 shows that the activity of SOD in preeclampsia (PE) patients was diminished **(89.18±19.7)** than the activity of healthy controls **(243.5±23.15)**, so there is a strong statically significant difference between patients group and control group as regards SOD, where P=0.0001. Additionally, GSH level in PE patients was decreased than that of healthy controls, where Mean ± SD were (0.11±0.08) and (1.73±0.365) of patients and controls respectively, so there is a strong statically significant difference between patients group and control group as regards GSH where P=0.0001. On the other hand the serum level of MDA in patients group was higher than that of control group, where Mean ± SD of patient and controls were (0.55±0.11) and (0.49±0.25) respectively, so there is a statically significant difference between patients group and control group as regards MDA where P=0.03.Also GPX level in patients group was higher than that of control group, where Mean ± SD of patients and controls were (498.56±53.3) and (303.22±71.59) respectively, so there is a strong statically significant difference between patients group and control group as regard GPx, where P=0.0001

Table1: Comparison of antioxidants and lipid peroxidation in preeclampsia patients group and control groups

	Control (n=100)	Patients (n=140)	P value
	Mean ± SD	Mean ± SD	
SOD (U/mL)	243.5±23.15	89.18±19.7	**0.0001******
GSH (ng/mL)	1.73±0.365	0.11±0.08	**0.0001******
MDA (nmol/mL)	0.49±0.25	0.55±0.11	**0.03***
GPx (U/mL)	303.22±71.59	498.56±53.3	**0.0001******

*P = probability, *P≤0.05 = significant, **P≤0.01 = very significant, ***P≤0.001 = highly significant, ****P≤0.0001 = strong significant, n= number of cases, SOD=Superoxide dismutase, GSH=Reduced Glutathione, MDA= Malondialdehyde, GPx= Glutathione peroxidase. Data were expressed as Mean ±SD. Results were obtained using independent t-test.*It is worth mentioning that, there are many correlations between biochemical oxidative stress and clinical parameters as illustrated in the Figures(2-5) where SOD has a positive correlations with age, HB, and serum albumin within groups indicated that high levels of the antioxidants increases with advanced age to neutralize more stress from free radicals and lipid peroxidation products, also high levels was

found of the antioxidant activity with HB to fight the hemoglobin susceptibility to oxidation by the action of reactive oxygen species and lipid peroxidation products specially with anemia patients as PE patients, also high levels of SOD with serum albumin may be due to that human serum albumin (HAS) nanoparticle encapsulating plasmid encoding Cu-, Zn-SOD that illustrated high levels of HAS with high levels of the antioxidant activity, while SOD activity was found to decrease with RBG measurements and liver enzyme as SGPT, also the antioxidant activity decreases strongly with high blood pressure in both SBP and DBP as with the hypertension disease as PE. Similarly, with GSH where high levels of the antioxidant activity were found with high levels of HB, serum albumin and also high levels were found with advanced age too, while the antioxidant activity was found to decrease with RBG, SBP, DBP and SGPT.

On the other hand, high levels of MDA were found with advanced age, SBP, DBP and SGPT, while lower levels of MDA were found with RBG, HB and serum albumin. Finally, GPx activity was found to increase with SBP, DBP and RBG, while the antioxidant activity decreases with age, HB, SGPT and serum albumin.

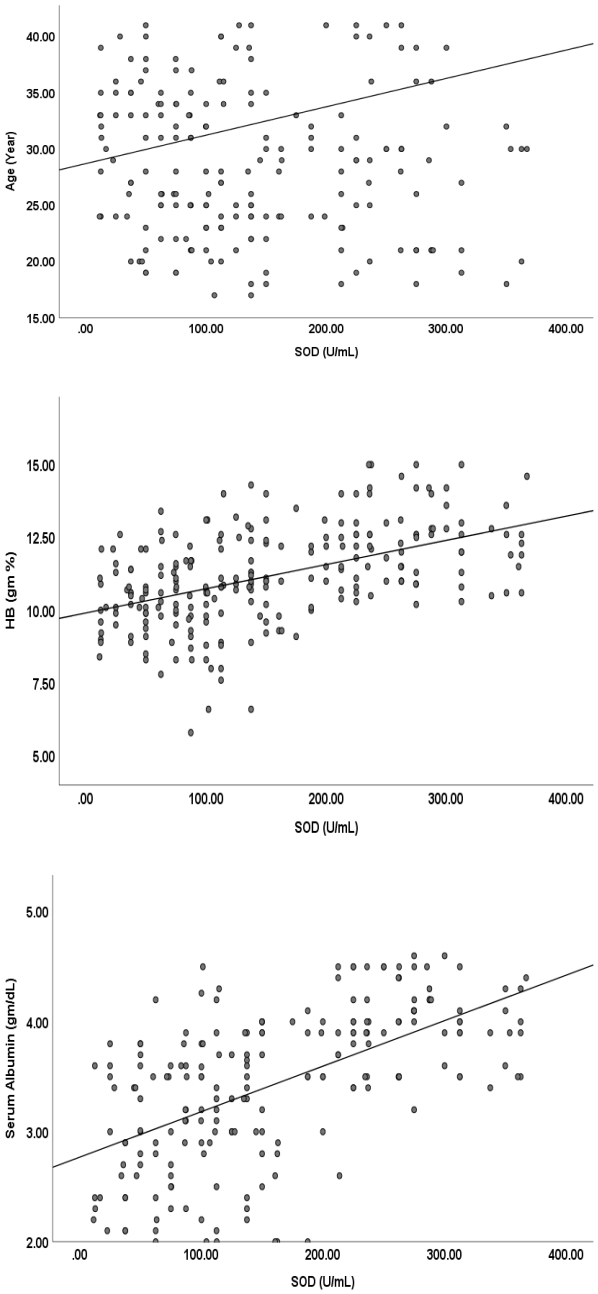

Fig 1: SOD as regard age, HB, serum albumin, where there are positive correlations.

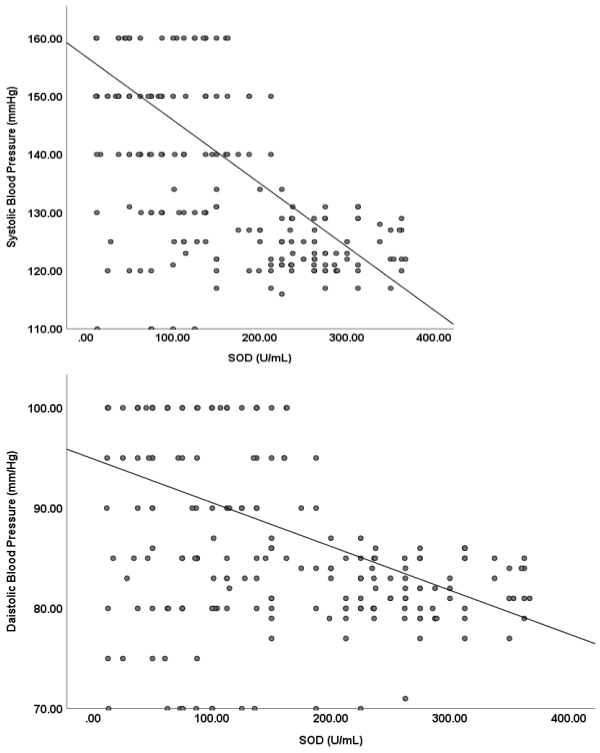

Fig 2: SOD as regard SBP and DBP, where there are negative correlations.

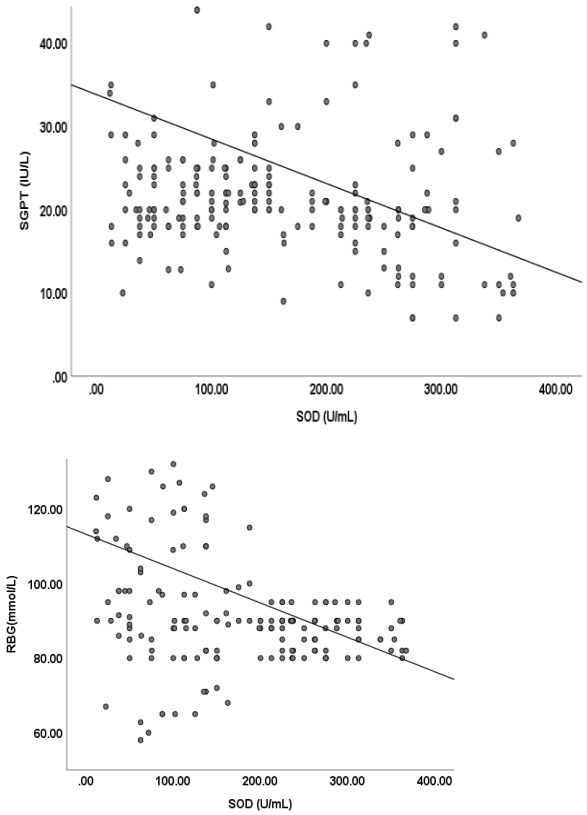

Fig 3: SOD as regard SGPT and RBG, where there are negative correlations.

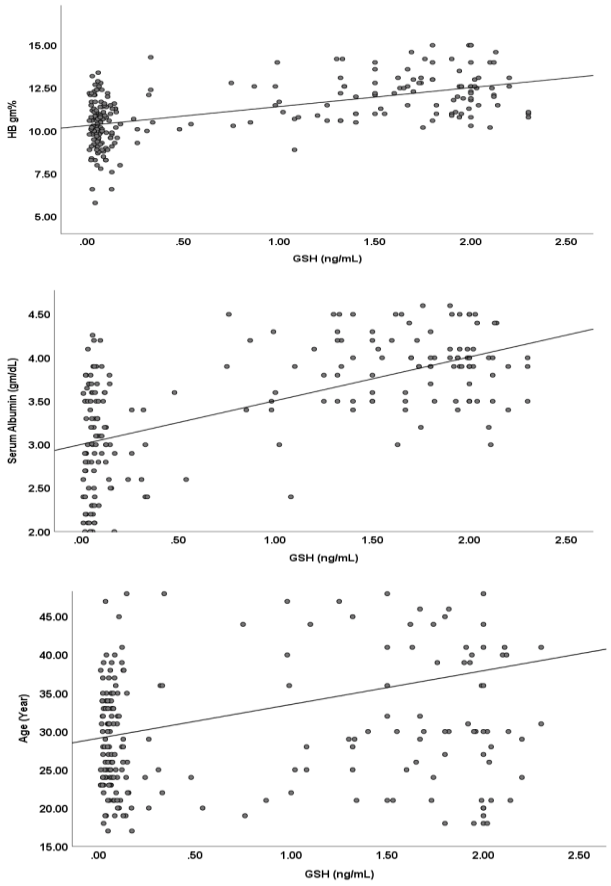

Fig 4: GSH as regard age, HB and serum albumin, where there are positive correlations.

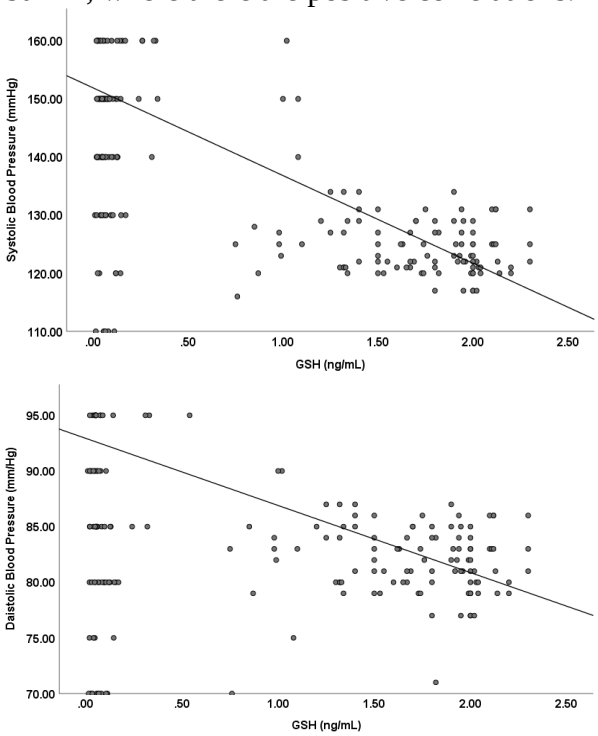

Fig 5: GSH as regard SBP and DBP, where there are negative correlations.

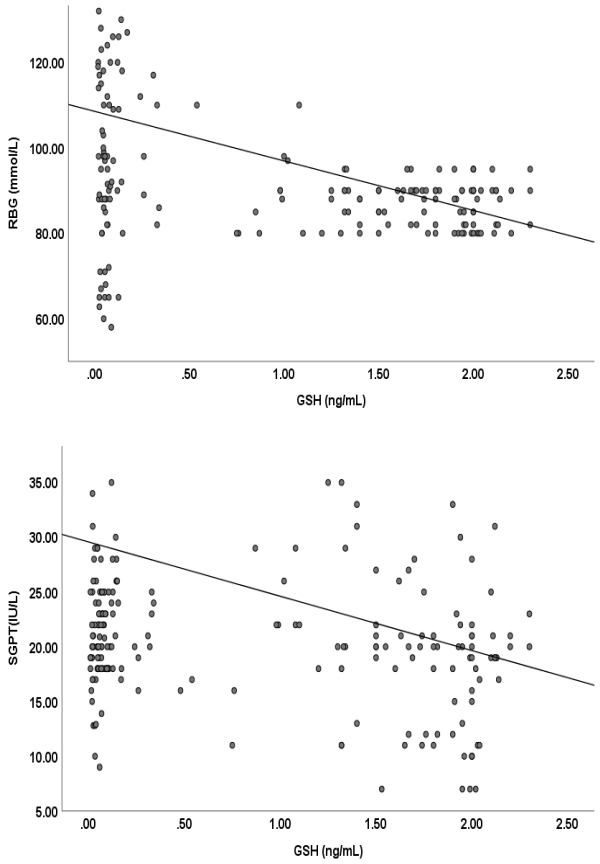

Fig 6: GSH as regard RBG and SGPT, where there are negative correlations.

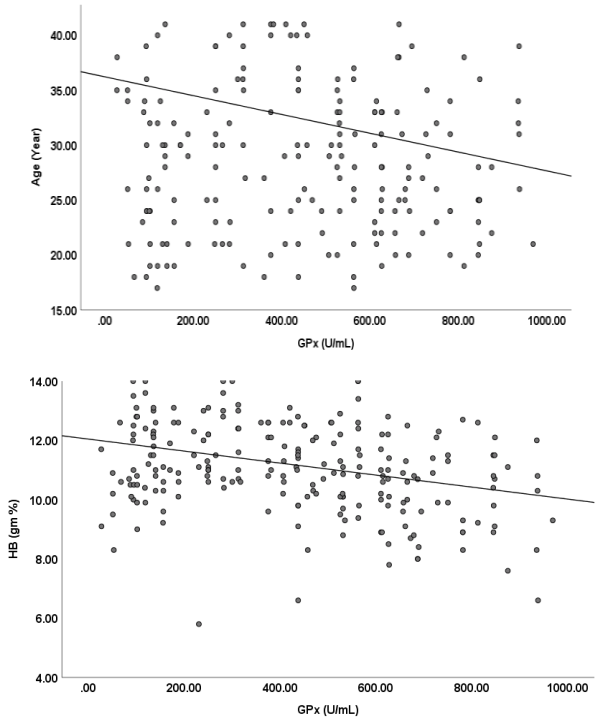

Fig 7: GPX as regard age and HB, where there are negative correlations.

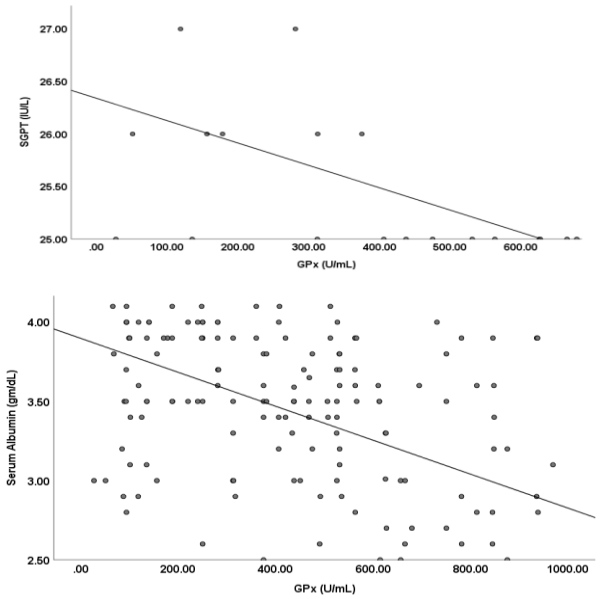

Fig 8: GPX as regard SGPT and serum albumin, where there are negative correlations.

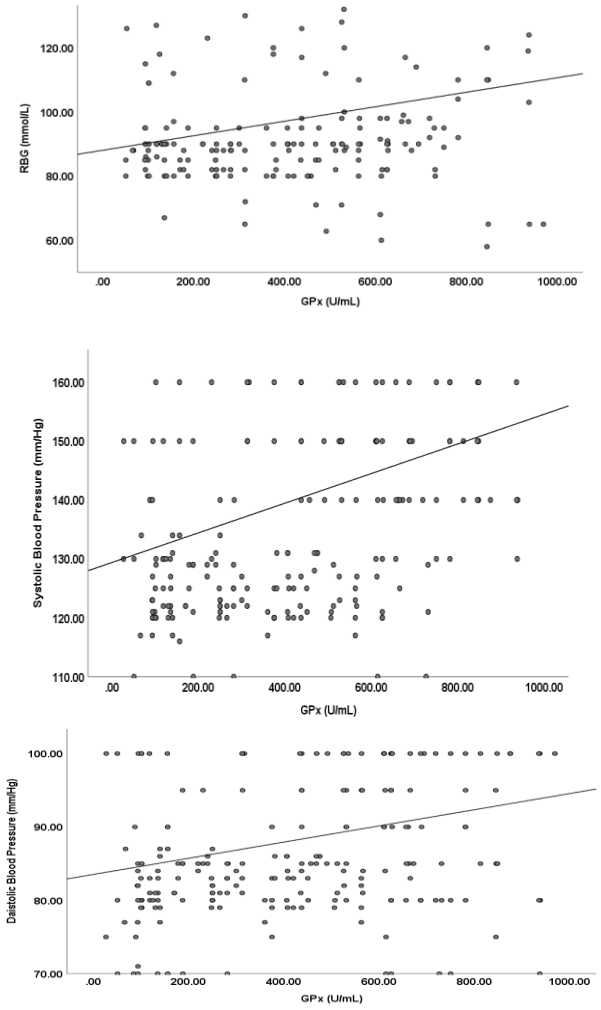

Fig 9: GPX as regard RBG, SBP and DBP, where there are positive correlations.

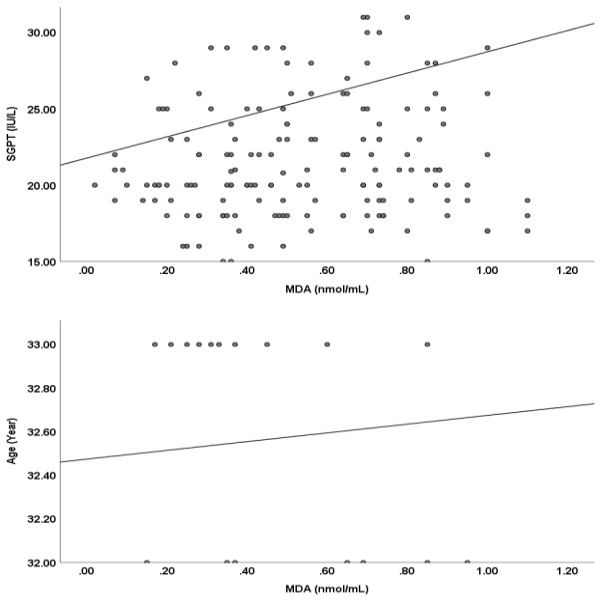

Fig10: MDA as regard age and SGPT, where there are positive correlations.

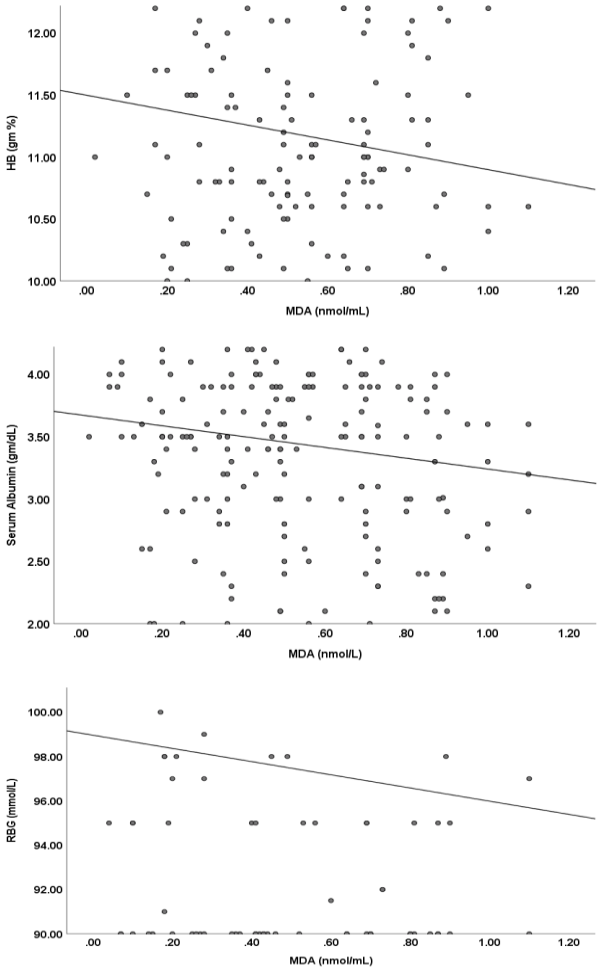

Fig 11: MDA as regard RBG, HB and serum albumin, where there are negative correlations.

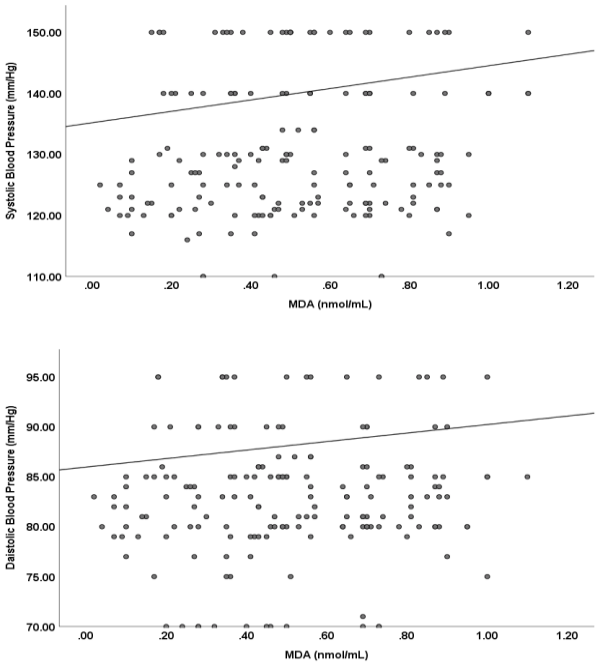

Fig 12: MDA as regard SBP and DBP**,** where there are positive correlations *but there are negative correlations with HB, Serum albumin, age and SGPT.*

5. Discussion

Preeclampsia is a complex disorder involving the role of multiple genes related to placental pathophysiology. The imbalance between oxidants as well as antioxidants is a condition called oxidative stress that involved in the pathogenesis of PE **[16, 17]**. Normally, in normal healthy pregnant women oxidative stress occurs compared with non-pregnant women, but over production of reactive free radicals occur in preeclamptic women. Additionally, the imbalance between antioxidants defense system and oxidative stress leads to an increased lipid peroxidation in preeclampsia. In our study, an increased level of MDA was observed. However, increased lipid peroxidation products were noticed in both normal pregnancy as well as preeclampsia as contrast to non-pregnant women **[18, 19]**. In numerous studies, preeclamptic women have a high significant level of antioxidant amount, while other studies **[20]** have found a low significant level of total antioxidant amount. In this current study, significant decrease in total antioxidant capacities were found, in spite of significant increase in total peroxide and oxidative stress end products.

Several contradictory studies found significantly higher SOD activity in preeclamptic women but other studies found significantly lower SOD activity **[21-23]** . Generally, our study indicated that SOD activity was lower in preeclamptic women. It was earlier found that plasma and placental SOD level is negatively correlated with the increased diastolic blood pressure of preeclamptic women. Lipid peroxidation that results from the increase in superoxide concentrations, caused by the deficiency of superoxide dismutase, in presence of iron , lipid peroxidation products was observed **[24]**. Our study confirmed a significant increase in GPx activity in preeclamptic women compared to normal pregnant women. In spite of this, a few studies found significantly lower GPx activity in preeclamptic women. GPx activity is measured in blood samples in another study that showed that the hazard and severity of preeclampsia is increased with the decrease in GPx activity **[25]**. Additionally, the endothelium damage that caused by free radical attack is reduced by the capability of GPx activity *via* decomposition of hydrogen peroxide as well as organic hydroperoxides such lipid and phospholipid hydroperoxides using GSH. Catalase enzymatic activity cleaves H_2O_2, this enzymatic action gets rid of the harmful effects of reactive oxidants. In cooperation glutathione peroxidase as well as catalase are dispensed in red blood cells and plasma. It is observed that in preeclamptic women there is an increase in catalase as well as GPx activities, illustrates H_2O_2 decomposition by these enzymes. Furthermore, increased activities of these enzymes help to attenuate the increased oxidative stress and provide a compensatory mechanism in order to avoid additional damage occurs through reactive radicals or other toxins. Contrary to glutathione peroxidase, in preeclamptic women GSH concentration in blood was significantly decreased than that of normal pregnant women. This finding is due to the consumption of GSH by the increased GPx activity. In preeclamptic women, reduced GSH level could be related with restricted or general oxidative stress increase on this group **[26]**.

Our study shows that there is a strong statically significant difference in both systolic blood pressure and diastolic blood pressure between patients compared to control where (P= 0.000), that illustrates high blood pressure that is generated specially during the severe stages of the PE disease. Underlying medical conditions such as chronic hypertension, gestational diabetes, urinary tract infection is found to be associated with increased risk of pre-eclampsia**.** Elevated cardiac output and increased systematic vascular resistance in hypertension is suspected to lead to endothelial cell dysfunction. Our results concluded that Preeclampsia development by inflammatory and oxidative in the placenta among Egyptian women

6. References

1. Villar K, Say L, Gulmezoglu AM, Meraldi M, Lindheimer MD, Betran AP, (2000) et al. Eclampsia and pre-eclampsia: a health problem for years. Pre-eclampsia. 2000;189:207.
2. Ghulmiyyah L, Sibai B, (2012)editors. Maternal mortality from preeclampsia/eclampsia 2012: Elsevier.
3. Walker JJ. Pre-eclampsia. (2000) The Lancet.;356(9237):1260-5.
4. Hutcheon JA, Lisonkova S, (2011) Joseph KS. Epidemiology of pre-eclampsia and the other hypertensive disorders of pregnancy. Best Practice & Research Clinical Obstetrics & Gynaecology.;**25(4)**:391-403.
5. Powe CE, Levine RJ, Karumanchi SA. Preeclampsia, (2011)a disease of the maternal endothelium: the role of antiangiogenic factors and implications for later cardiovascular disease. Circulation.;**123(24)**:2856-69.
6. Guerby P, Tasta O, Swiader A, Pont F, Bujold E, Parant O, et al. (2021) Role of oxidative stress in the dysfunction of the placental endothelial nitric oxide synthase in preeclampsia. Redox Biol.;40:101861-.
7. Vaka R, Deer E, LaMarca B. .(2022)Is Mitochondrial Oxidative Stress a Viable Therapeutic Target in Preeclampsia? Antioxidants;**11(2)**:210.
8. Zejnullahu VA, Zejnullahu VA, (2021)

Kosumi E. The role of oxidative stress in patients with recurrent pregnancy loss: a review. Reprod Health.;**18(1)**:207-.
9. Piotr Surmiak, Wojnarowicz O, (2022) Szymkowiak M. Malondialdehyde and Neutrophil Gelatinase-Associated Lipocalin as Markers of Oxidative Stress in Small for Gestational Age Newborns from Hypertensive and Preeclamptic Pregnancies. BioMed Research International.;2022:1-7.
10. Llurba E, Gratacós E, Martín-Gallán P, Cabero L, Dominguez C. A comprehensive (2004) study of oxidative stress and antioxidant status in preeclampsia and normal pregnancy. Free Radical Biology and Medicine.;**37(4)**:557-70.
11. Marcus S, Chandrakala M, Nadiger H. Lipid peroxidation and ethanol toxicity in rat liver: (1988) Effect of vitamin E deficiency and supplementation. Medical Science Research.;**16(16):**879-80.
12. Hartz JW, Funakoshi S, Deutsch HF. (1973) The levels of superoxide dismutase and catalase in human tissues as determined immunochemically. Clinica Chimica Acta.;**46(2)**:125-32.
13. Jacques PF, Chylack LT, McGandy RB, Hartz SC. (1988) Antioxidant status in persons with and without senile cataract. Archives of Ophthalmology.;**106(3):**337-40.
14. Paglia DE, Valentine WN. (1967) Studies on the quantitative and qualitative characterization of erythrocyte glutathione peroxidase. The *Journal of laboratory and clinical medicine*.;**70(1)**:158-69.
15. Spooner RJ, Delides A, Goldberg DM. (1981);Heat stability and kinetic properties of human serum glutathione reductase activity in various disease states. Biochemical medicine. **26(2)**:239-48.
16. Bosco C, Díaz E, Gutiérrez R, González J, Parra-Cordero M, Rodrigo R, et al. A (2015) putative role for telocytes in placental barrier impairment during preeclampsia. Medical Hypotheses.;**84(1)**:72-7.
17. Bosco Becerra C, Díaz Guerra E, Gutierrez Rojas R, González Montero J, Parra Cordero M, Ramón Rodrigo Salinas R, et al. (2016) Placental Hypoxia Developed During Preeclampsia Induces Telocytes Apoptosis in Chorionic Villi Affecting The Maternal-Fetus Metabolic Exchange. Current Stem Cell Research & Therapy.;**11(5)**:420-5.
18. Wang Y, Walsh SW, Guo J, Zhang J. Maternal levels of prostacyclin, thromboxane, (1991) vitamin E, and lipid peroxides throughout normal pregnancy. American *Journal of Obstetrics and Gynecology*.;**165(6)**:1690-4.
19. Wendy, Phoswa, Khaliq OP. (2021)The Role of Oxidative Stress in Hypertensive Disorders of Pregnancy (Preeclampsia, Gestational Hypertension) and Metabolic Disorder of Pregnancy (Gestational Diabetes Mellitus). Oxidative Medicine and Cellular Longevity.;2021.
20. Shaarawy M, Aref A, Emad Salem M, Sheiba M. (1998) Radical-scavenging antioxidants in pre-eclampsia and eclampsia. International *Journal of Gynecology & Obstetrics*.;**60(2)**:123-8.
21. Kharb S. (2011);Extracellular superoxide dismutase levels in preeclampsia. Mediterranean *Journal of Nutrition and Metabolism.* **5(1):**53-5.
22. Negi R, Pande D, Karki K, Kumar A, Khanna RS, Khanna HD. (2012)Trace elements and antioxidant enzymes associated with oxidative stress in the pre-eclamptic/eclamptic mothers during fetal circulation. Clinical Nutrition.;**31(6)**:946-50.
23. Pimentel AML, Pereira NR, Costa CA, Mann GE, Cordeiro VSC, de Moura RS, et al. (2013)L-arginine-nitric oxide pathway and oxidative stress in plasma and platelets of patients with pre-eclampsia. Hypertension Research.;**36(9)**:783-8.
24. Radi R, Beckman JS, Bush KM, Freeman BA. (1991) Peroxynitrite-induced membrane lipid peroxidation: The cytotoxic potential of superoxide and nitric oxide. Archives of Biochemistry and Biophysics.;**288(2)**:481-7.

25. Chamy VM, Lepe J, CatalÁN Á, Retamal D, Escobar JA, Madrid EM. (2006) Oxidative stress is closely related to clinical severity of pre-eclampsia. Biological Research.;**39(2).**

26. Dekker GA, Sibai BM. (1998) Etiology and pathogenesis of preeclampsia: Current concepts. American *Journal of Obstetrics and Gynecology*.;1**79(5)**:1359-75.