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Open Access Journal of Gynecology
ISSN: 2474-9230

Effects of Vitamin D3 Supplementation on Antioxidant Status and Lipid Peroxidation Product in Preeclamptic Women

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Research Article

Volume 4 Issue 1

Received Date: January 14, 2019

Published Date: February 01, 2019

DOI: 10.23880/oajg-16000169

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Abstract

Background: Oxidative stress plays a causative role in the pathophysiology of preeclampsia. This study aimed at assessing the effects of vitamin D supplementation on the antioxidant status and lipid peroxidation product of preeclamptic women.

Methods: Ninety women between ages of 18 and 35 were recruited at 22weeks gestation from antenatal Clinic in Obstetrics and Gynecology Department of University College Hospital Ibadan, and Adeoyo Maternity Clinic, Yemetu, Nigeria. 30 normotensive pregnant women were grouped into Group A, and 60 preeclamptic women randomly grouped into Group B and Group C. Group C was given 1000IU/day of Vitamin D3 for 8weeks after recruitment at 22 weeks. Serum concentration of antioxidants were done by standard methods at 22 weeks, 30 weeks after supplementation and postpartum in all groups. They were followed up 3-7days postpartum, and obstetric data collected. Statistical analysis was done by using Statistical Package for Social sciences (SPSS) soft version 17.0.

Results: There was no significant difference ($p>0.05$) in gestational age at delivery, weight of fetus between the three groups, while there was a significant increase ($p<0.05$) in BMI, systolic and diastolic blood pressure in group B and C. The level of Malonaldehyde (MDA) was significantly higher ($p<0.05$), while SOD, GPX and catalase were lower in the preeclamptic groups at 2nd trimester when compared with control. After supplementation the MDA levels reduced significantly ($p<0.05$), while SOD, GPX and catalase increased significantly ($p<0.05$) in 3rd trimester and postpartumly in the supplemented group when compared with non-supplemented group. Vitamin C levels were not statistically different ($p>0.05$) at 2nd, 3rd trimester and postpartum, while Vit. E was significantly reduced ($p<0.05$) at the 3rd trimester in the control group. The level of Vit. E was significantly increased ($p<0.05$), while Vit. C level was not statistically different ($p>0.05$) at 2nd trimester in the PE groups when compared with control. After supplementation, a significant increase ($p<0.05$) occurred in Vit. E, while Vit. C level was not statistically different ($p>0.05$) when compared with the non-supplemented PE group.

Conclusion: Vitamin D supplementation is important in improving the antioxidant status in Preeclampsia.

Keywords: Preeclampsia; Vitamin D; Antioxidants; Blood Pressure; Lipid Peroxidation

Abbreviations: PE: Preeclampsia; ROS: Reactive Oxygen Species; GPx: Glutathione Peroxidase; SOD: Superoxide Dismutase; CAT: Catalase; MDA: Malondialdehyde; NADP: nicotinamide adenine dinucleotide phosphate; AGEs: advanced glycation end products; GCl: glutamate-cysteine ligase; GR: glutathione reductase.

Introduction

Preeclampsia (PE) is defined as gestational hypertension of at least 140/90 mmHg on two separate occasions ≥4 hours apart accompanied by significant proteinuria of at least 300 mg in a 24-hour collection of urine, or a urine dipstick result of 1+ or greater, arising de novo after the 20th week of gestation in a previously normotensive woman and resolving completely by the 6th postpartum week [1]. If left untreated; it progresses to eclampsia, which refers to the development of grand mal seizures in a woman with preeclampsia, in the absence of other neurologic conditions that could account for the seizure. Preeclampsia is a characteristic multisystem disorder of pregnancy that affects between 2-8% of pregnancies [2,3].

Due to metabolic changes and low grade inflammation, pregnancy is a condition of increased susceptibility to oxidative stress .Several organs in pregnancy show increased basal oxygen consumption and changes in substrate energy use resulting in increased mitochondrial mass and production of reactive oxygen species (ROS), this is further aggravated in PE. Although the cause of preeclampsia remains largely unknown, the occurrence of oxidative stress is a feature of this maternal syndrome. Oxidative stresses have been shown to play a causative factor in the pathophysiology of preeclampsia. Free radicals have emerged as the likely promoters of maternal vascular malfunction [4]. Strong evidence exists that oxidative stress plays a pivotal role in the pathology of PE [5]. The generation of ROS is enhanced by increased placental mitochondrial activity and the increased placental generation of the radical superoxide [6,7].

The main source of ROS initiating the pathophysiological events in PE appears to be the placenta [8]. PE is associated with abnormal trophoblast differentiation and invasion, resulting in an altered vascular remodeling of spiral arteries which also contribute to placental perfusion and ischemia. Abnormal vascular development of the blood vessels in the preeclamptic placenta leads to reduced placental perfusion and hypoxia which is by itself a potent stimulus for ROS formation [9], results in vasoconstriction of spiral artery which release free radicals and trigger oxidative stress [10]. Insufficient antioxidant capacity leads to oxidative stress and subsequently oxidative injury may occur in both the maternal and placental compartments [11]. Placental oxidative stress has been proposed as a promoter of lipid peroxidation, and endothelial cell dysfunction associated with preeclampsia [12]. Endothelial function has a pivotal role in health of cardiovascular system. Oxidative stress alters many functions of the endothelium, modulation of vasomotor tone and inactivation of nitric oxide by ROS [13]. Lipid peroxidation has also been proposed to play an etiopathological role in various vascular complications of pregnancy, such as intrauterine growth restriction and preeclampsia.

Enzymatic antioxidants work by breaking down and removing free radicals. The antioxidant enzymes convert dangerous oxidative products to hydrogen peroxide (H_2O_2) and then to water, in a multi-step process. Non-enzymatic antioxidants work by interrupting free radical chain reactions. Examples of the non-enzymatic antioxidants are vitamin C, vitamin E. While the enzymatic antioxidants are glutathione peroxidase (GPx), superoxide dismutase (SOD), catalase [14].

Glutathione peroxidase (GPx) is a selenium-containing antioxidant enzyme that effectively reduces H2O2 and lipid peroxides to water and lipid alcohols, respectively, and in turn oxidizes glutathione to glutathione disulfide. Reduced glutathione plays a major role in the regulation of the intracellular redox state of vascular cells by providing reducing equivalents for many biochemical pathways. Superoxide dismutase (SOD) is the first detoxification enzyme and most powerful antioxidant in the cell. It is an important endogenous antioxidant enzyme that acts as a component of first line defense system against reactive oxygen species (ROS). It catalyzes the dismutation of two molecules of superoxide anion to hydrogen peroxide (H_2O_2) and molecular oxygen (O_2), consequently rendering the potentially harmful superoxide anion less hazardous. Catalase (CAT) is a common antioxidant enzyme present almost in all living

tissues that utilize oxygen. The enzyme uses either iron or manganese as a cofactor and catalyzes the degradation or reduction of hydrogen peroxide (H_2O_2) to water and molecular oxygen, consequently completing the detoxification process imitated by SOD [15]. It is abundant in cells, where it continuously scouts for hydrogen peroxide molecules. CAT is highly efficient; it can break down millions of hydrogen peroxide molecules in one second. The enzyme is located primarily in the peroxisomes but absent in mitochondria of mammalian cells. CAT also reacts efficiently with hydrogen donors such as methanol, ethanol, formic acid, or phenols with peroxidase activity. These antioxidants are very important in pregnancy because they play a significant role in preventing oxidative stress.

Lipid peroxidation can be described generally as a process in which oxidants such as free radicals attack lipids containing carbon-carbon double bond(s), especially polyunsaturated fatty acids (PUFAs) that involve hydrogen abstraction from a carbon, with oxygen insertion resulting in lipid peroxyl radicals and hydroperoxides . Lipid peroxidation or reaction of oxygen with unsaturated lipids produces a wide variety of oxidation products, one of which is malondialdehyde (MDA); a main primary product of lipid peroxidation. In preeclamptic women, it was found that MDA levels correlate with the severity of the disease and a good indicator of lipid peroxidation and oxidative stress levels [8].

Lipid peroxidation has been proposed to play an etiopathological role in various vascular complications of pregnancy, such as intrauterine growth restriction and preeclampsia. Increased lipid peroxidation leads to the consumption of antioxidants which leads to reduction in levels of nonenzymatic antioxidants such as Vitamins A, C, and E, erythrocyte thiol, and glutathione as well as enzymatic antioxidants such as glutathione peroxidase and superoxide dismutase.

Vitamin E (α-tocopherol) is an efficient lipid soluble antioxidant that functions as a 'chain breaker' during lipid peroxidation in cell membranes and various lipid particles including low-density lipoprotein (LDL). It functions to intercept lipid peroxyl radicals ($LOO^{\cdot}$) and to terminate the lipid peroxidation chain reactions. Vitamin E exerts antioxidant effects by scavenging lipid peroxyl radical's in vivo as well as in vitro systems.

Vitamin C or ascorbic acid, is a water-soluble free radical scavenger, it regenerates vitamin E in cell membranes in combination with GSH or compounds capable of donating reducing equivalents [16]. It has been observed that ROS are increased, and the levels of several detoxifying enzymes are reduced in preeclampsia.

Previous studies have linked vitamin D insufficiency to increased risk of preeclampsia. Vitamin D insufficiency was observed in preeclamptic women in south western Nigeria in a pivotal study [17]. Also, some supplementation studies observed that vitamin D supplementation in preeclampsia might help ameliorate the complications associated with preeclampsia and also improve pregnancy outcome. This link might be as a result of the effect of vitamin D on antioxidant status in preeclampsia. Supplementation studies on this topic are few in Nigeria and there is paucity of knowledge. Therefore this study aimed at investigating the effects of vitamin D supplementation on enzymatic and nonenzymatic antioxidants in Nigerian women with preeclampsia.

Methodology

Study Design

This is an interventional study in which subjects were recruited from Antenatal Clinic in Obstetrics and Gynecology Department of University College Hospital and Ekiti State Teaching Hospital. Ninety subjects were enrolled, 30 healthy pregnant women (Group A) and 30 nulliparious women with singleton pregnancies with preeclampsia (Group B) and 30 preeclamptic women were chosen randomly into Group C to be given vitamin D supplements for 8weeks.They were between the ages of 18 and 35years. Blood pressure, weight, were measured and body mass index calculated in each of the subjects at 22weeks of pregnancy, using a standard analog sphygmomanometer, weighing balance and meter rule respectively.

Sample Collection

Informed consent form was duly signed and questionnaires on sociodemographic information, medical history, health behavior, diets and lifestyle were issued to the subjects. Group C was placed on 1000IU of Vitamin D3 for 8 weeks and blood samples were collected after supplementation and postpartumly. Blood samples were also collected from Group A and B at baseline (22 weeks), after 8weeks and postpartumly. 10mls of venous blood was collected from each participant at 22 weeks, 30weeks and 3 to 7 days after delivery. The blood sample was dispensed into plain bottle, blood was allowed to clot, centrifuged and serum separated for analysis of antioxidants.

Biochemical Assessment

- Serum Glutathione activity was estimated by Colorimetric method as described by Wendel A, et al. [18].
- Superoxide Dismutase (SOD) was evaluated by spectrophotometric method as described by Kuthan H, et al. [19].
- Serum Catalase was assessed by using colorimetric method as described by Sinha AK, et al. [20].
- Malonaldehyde (MDA) was determined by Thiobarbituric acid reactive substances (TBARS) method as described by Sharma JB, et al. [21].
- Plasma Vitamin E was quantified by Spectrophotometric method as described by Rutkowski M, et al. [22].
- Plasma Vitamin C was quantified by Spectrophotometric method as described by Rutkowski M, et al. [22].

Statistical Analysis

Data obtained from this study was subjected to statistical analysis using SPSS version 17.0. The results obtained was grouped and expressed as mean ± Standard Deviation (SD). One way analysis of variance (ANOVA) was used to compare variables across the groups. Students T-test was used to compare variables between two groups. Significant difference set at $P<0.05$.

Results

The mean age of the normotensive and preeclamptic women were not statistically different.($P>0.05$),while the systolic blood pressure, diastolic blood pressure and BMI of the preeclamptic groups(Group B and C) were significantly higher than the normotensive group ($P<0.05$).

Variables	Control (n=30)	PE without Suppliment (n=30)	PE without Suppliment (n=30)
Age	33.1 ±2.4^a	32.4±2.3^a	32.9±3.1^a
Systolic Blood Pressure	118±6.5^b	150.8±12.5^c	149.7±8.4^c
Diastolic Blood Pressure	80.3 ±4.6^a	91.9±13.2^b	90.9±9.9^b
Body Mass Index(BMI)	24.1± 1.4^a	31.2±3.2^b	30.7±3.8^b

Values of the same subscript within the same column are not statistically different at ($P>0.05$) between the control and case group, while values with different subscripts are significantly different at ($P<0.05$).

Table 1: Baseline Characteristics of Normotensive pregnant women (Group A), Preeclamptic women without supplement (Group B), Preeclamptic women on supplement (Group C).

Parameters		Control (n=30)	PE without Suppliment (n=30)	PE without Suppliment (n=30)
SOD(u/ml)	2nd trimester	3.01±1.09^a	1.94±1.06^b	1.84±1.89^b
	3rd trimester	2.64±2.0 ^{a}	1.44±2.06^b	2.81±2.3^c
	Postpartum	3.20±1.6^a	2.00±0.98^b	3.07±1.62^c
GPX(IU/gHB)	2nd trimester	26.4±2.09^a	16.5±2.60^b	15.9±2.9^b
	3rd trimester	23.8±4.0^a	15.14±2.6^b	21.6±5.8^a
	Postpartum	21.8±4.6^a	16.6±2.7^b	21.9±3.2^a
Catalase(umol/mg)	2nd trimester	104.5±8.5^a	92.4±18.0^b	93.3±13.0^b
	3rd trimester	100.3±8.3^a	91.1±10.6^b	106.5±10.6^a
	Postpartum	109.9±10.0^a	101.2±10.4^b	112.15±11.29^a
MDA(mmol)	2nd trimester	2.42±1.2^a	5.14±1.8^b	5.78±1.6^b
	3rd trimester	2.96±2.6^a	6.20±3.1^b	3.25±0.8^c
	Postpartum	2.82±1.8^a	7.36±1.8^b	3.29±0.9^c

Table 2: Maternal levels of Enzymatic Antioxidants and MDA in Normotensive pregnant women (Group A), Preeclamptic women without supplement (Group B), Preeclamptic women on supplement (Group C).

Values of the same subscript within the same column are not statistically different at ($p>0.05$) between control and the case groups, while values with different subscript are significantly different at ($p<0.05$).

MDA=Malonaldehyde, SOD= Superoxide Dismutase, GPX=Glutathione Peroxidase

The level of MDA was significantly higher ($p<0.05$), while SOD, GPX and catalase were lower in the

preeclamptic groups at 2nd trimester when compared with control. After supplementation the MDA levels reduced significantly ($p<0.05$), while SOD, GPX and catalase increased significantly ($p<0.05$). In 3rd trimester and postpartumly in the supplemented group when compared with non-supplemented group.

Parameters		Control (n=30)	PE without Supplement (n=30)	PE without Supplement (n=30)
Vit. C(mg/dl)	2nd trimester	1.72 ± 0.6[a]	1.21±0.59[a]	1.42±0.38[a]
	3rd trimester	1.70± 0.47[a]	1.36±0.43[a]	1.44±0.28[a]
	Postpartum	1.83±0.50[a]	1.47±0.6[a]	1.49±0.49[a]
Vit. E(umol/L)	2nd trimester	18.64±5.5[a]	10.29±3.7[b]	11.18±3.23[b]
	3rd trimester	11.60±3.33[b]	8.49±3.3[b]	15.78±4.7[a]
	Postpartum	16.46±4.59[a]	10.16±3.6[b]	18.63±5.3[a]

Table 3: Maternal levels of Non-enzymatic Antioxidants in Normotensive pregnant women (Group A), Preeclamptic women without supplement (Group B), Preeclamptic women on supplement (Group C).

Discussion and Conclusion

In this study, the levels of SOD, GPX and catalase were lower, while MDA was significantly higher at the second and third trimester in the preeclamptic groups when compared with control. This is in accordance with the work of Anjum Sayyed, et al. & Chamy VM, et al. [23,24]. SOD is an important antioxidant enzyme, which is capable of preventing excessive superoxide accumulation and may contribute to the continuation of pregnancy. A significantly reduced SOD activity in preeclampsia may be due to increased attack of free radicals and thus low production of SOD [23].

Also, low levels of Glutathione peroxidase (GP) and Catalase observed in this study is similar to the work of Funai EF, et al. [25]. Low GP level and catalase caused by imbalance between lipid peroxidation and antioxidants will release free radicals that lead to endothelial dysfunction and cell damage. This condition might contribute to excessive maternal inflammatory response and the occurrence of thrombotic occlusion resulting in chronic hypoxia and poor placenta reoxygenation during pregnancy and initiate the onset of severe preeclampsia. The increased lipid peroxidation product (MDA) leads to the consumption of antioxidants, cumulative evidence has shown that in preeclampsia, there is an increase in lipid peroxidation and a decrease in antioxidants protection leading to oxidative stress [26]. MDA may mediate disturbance of the maternal vascular endothelium. These products may inhibit prostacyclin synthesis and stimulate smooth muscle contraction resulting in widespread vasospasm, a prominent feature of preeclampsia [26].

The reduced serum level of vitamin E, in preeclamptic women as reported in this study is consistent with the work of Bargale B, et al. [27]. Decrease in vitamin E in preeclampsia could be due to its increased consumption to counteract free radical mediated changes and also due to decreased absorption from gut as a result of vasoconstriction in preeclampsia. Several studies have demonstrated decreased serum levels of vitamin C in preeclamptic patients [28]. Reduced ascorbate is quite effective in protecting plasma lipids and susceptible molecules from peroxidation. Plasma ascorbate level decreases gradually throughout normal pregnancy, and decreases more in preeclampsia. However, in this present study, there was no statistical difference in vit. C levels in all groups. This might be due to increased intake of citrus fruit by pregnant women as typical of Nigerian women.

There was significant decrease in serum malondialdehyde levels and increase in antioxidant status following Vitamin D supplementation in preeclamptic women after 20weeks gestation. This demonstrates the antioxidant action of Vitamin D, and this is in agreement with results of the randomized controlled trial by Foroozanfard F, et al. [29]. In that study, Vitamin D supplementation at doses of 50,000 IU/week for 8 weeks produced significant decrease in malondialdehyde level by 0.1 µmol/L and increase in total antioxidant status by 22.5 mmol/L in Vitamin D deficient women with polycystic ovary syndrome [29]. Another randomized controlled study in patients with nonalcoholic fatty liver disease showed that supplementation with 50,000 IU of Vitamin D3 every 14 days for 4 months produced significant decrease in serum malondialdehyde by 2.09 ng/ml and an increase in total antioxidant status by 270 µmol/L) [30]. Disruption in the expression of the enzymes as CYP27B1, enzyme-activating vitamin D trophoblast cells; 25-hydroxylase (CYP2R1); and 24-hydroxylase (CYP24A1) in the placenta of women with PE can be considered the main causes for the relation of PE with vitamin D and lipid peroxidation metabolites such as MDA

and lipid peroxides in pregnancy [31,32]. Lin et al. reported that vitamin D plays a vital role in reducing redox stress via ending the lipid peroxidation chain reaction [33]. Vitamin D may influence oxidative stress through its effects on immune functions. Cytokines have a regulatory influence on circulating SOD, and vitamin D may upregulate superoxide dismutase through regulation of cytokines [34]. The antioxidant properties of vitamin D is attributed to decreased lipid peroxidation, suppressed gene expression of nicotinamide adenine dinucleotide phosphate(NADP) enzyme and inhibiting accumulation of the advanced glycation end products (AGEs) in the aortic tissue [35]. According to the literature, Vitamin D could enhance the pathway of ROS removal, by increasing the intracellular pool of reduced glutathione, partially through upstream regulation of glutamate-cysteine ligase (GCL) and glutathione reductase (GR) genes expression [36]. GCL is a key enzyme that is involved in synthesis of GSH. Furthermore, Sardar, et al. [37] proposed that this vitamin is an antioxidant as a result of an increase in hepatic GSH amounts in rats that have gotten cholecalciferol. 1,25-dihydroxycholecalciferol could also be a direct antioxidant of membrane, via stabilizing and protecting membrane from lipid peroxidation through relations with their hydrophobic parts.

Conclusion and Recommendation

Vitamin D is important in improving the antioxidant status in preeclampsia, thereby preventing oxidative stress and decreasing the production of lipid peroxidation products that can worsen endothelial dysfunction and cell damage associated with PE. Vitamin D is just not a fat soluble vitamin but an effective antioxidant and should be administered routinely to pregnant women and women at high risk of developing preeclampsia.

Acknowledgement

The authors acknowledge the contribution of the staff of the Department of Biochemistry and Science Laboratory Technology of Ekiti State University. Ado Ekiti, Ekiti State, Nigeria.

Ethical Approval

Ethical clearance was given by Joint Ethical Committee of the College of Medicine and the University College Hospital Ibadan, and Oyo State Ethical committee, Nigeria.

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