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Vitamin D in Prevention of Preeclampsia

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Abstract
The present study aimed to analyse the relation between vitamin D and preeclampsia. 120 pregnant females with a single ton pregnancy (healthy/preeclamptic) were selected and their body mass index was determined. They were further divided into four groups; normotensive patients with body mass index<25 kg/m2 (Group-I, N=30'CONTROL'), normotensive patients with body mass index>25 kg/m2 (Group-II, N=30), preeclamptic patients with body mass index<25 kg/m2 (Group-III, N=30), and preeclamptic patients with body mass index>25 kg/m2 (Group-IV, N=30). Their serum 25 OH D levels were analysed. Through the analysis, preeclamptic patients showed significantly reduced serum levels of vitamin D and a positive association between low vitamin D levels and preeclampsia was observed.
Keywords: *Hypertension; Preeclampsia; 25 OHD; Vitamin D; Body Mass Index.*

Introduction

Preeclampsia (PE) is a pregnancy-specific hypertensive disorder which usually occurs after 20 weeks of gestation. Classically, PE is defined by the occurrence of *new-onset hypertension* and *new-onset proteinuria*; Hypertension, defined as either a systolic blood pressure ≥ 140 mm Hg, a diastolic blood pressure ≥ 90 mm Hg, or both with at least two determinations for diagnosis of blood pressure at least 4 hours apart (although in severe hypertension, the time interval can be reduced even under minutes). Proteinuria is diagnosed with excretion of ≥ 300mg protein in the urine sample of 24-hour excretion or the ratio of measured protein to creatinine in a single voided urine is ≥ 3.0 mg/dl with, qualitative dipstick readings of 1+[(1)].

However, some women experience an absence of proteinuria, therefore there has been a revision on the diagnostic criterions for PE, as now being

defined with the involvement of multisystem etiologies. For a legitimate diagnosis certain multi systemic signs are taken under review including, thrombocytopenia (platelet count less than 100,000/microliter), impaired liver function (elevated blood levels of liver transaminases to twice the normal concentration), the new development of renal insufficiency (elevated serum creatinine greater than 1.1 mg/dl or a doubling of serum creatinine in the absence of other renal disease), pulmonary edema, or new-onset cerebral or visual disturbances are taken into consideration for the diagnosis of PE[(1)].

The incidence of PE ranges between 8-10% in India while 2-10%of pregnancies worldwide[(2)]. The complications of PE include Eclampsia, Disseminated Intravascular Coagulation (DIC) and the *Haemolytic anaemia-Elevated Liver enzymes-Low Platelets* (HELLP)- syndrome. Risks to the foetus include Intrauterine Growth Restriction (IUGR) and foetal death.Studies have shown that insufficient intake of vitamin D, calcium, magnesium, selenium,vitaminA and vitamin C, has a role in immunomodulation and impaired placentaldevelopment[(3)(4)]. In a study conducted by Benachi A. et al, it was found that women with vitamin D sufficiency during the 1st and 3rd trimesters had a significantly lower risk of PE[(5)] and that Vitamin-supplementations can reduce the onset of PE[(6)].

The objectives of the present study were:

1. To measure the concentration of 25-hydroxyvitamin D (25 OH D), from the withdrawn blood sample.
2. To record anthropometric data of the PE patients.
3. To confirm an association between PE and vitaminD levels.

Methods

A total of 120 antenatal patients were included in the study. Their blood pressure was measured on the left arm using mercury column sphygmomanometer; the individual was made comfortable and seated back in rest at least for five minutes in their chair before measurement. Covering 2/3rd of the arm, 1 inch above the cubital line, 3 subsequent readings were taken and their average was calculated. Their anthropometric data were also recorded and thereafter, were divided into four groups.

1. Group I (control): 30 normotensive and non-overweight (BMI<25kg/m^2)/non-obese subjects.
2. Group II: 30 normotensive and overweight/ obese subjects (BMI>30kg/m^2).
3. Group III : 30 preeclamptic and non-overweight/non-obese subjects
4. Group IV: 30 preeclamptic and overweight/obese subjects.

Patients were screened for vitamin D deficiencyusing the Chemiluminescence immunoassay method (CLIA) and the levels were expressed in 'ng/ml' (deficiency <30 ng/ml).

Statistical analysis was performed by the Statistical Package for the Social Sciences (SPSS) program for Windows, version 17.0. Continuous variables were presented as Mean ± SD. For all statistical tests, a p-value less than 0.05 was taken to indicate a significant difference.

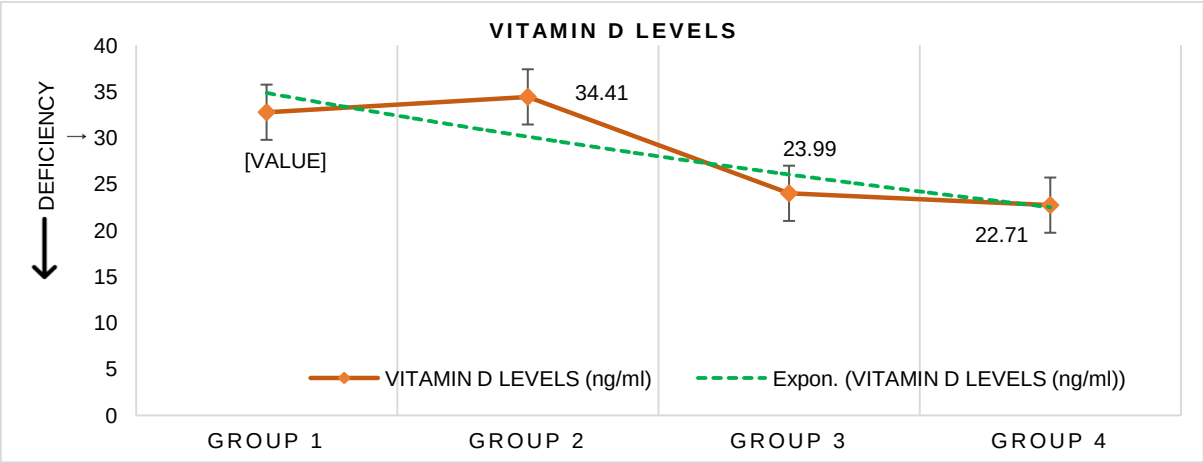
Results

In the present study, we found a positive association between serum deficiency of vitamin D and PE. It was observed that *Group-I* & *Group-II* had normal serum levels of vitamin D. While the patients under the *Group-III* and *Group-IV* showed a serum deficiency of vitamin D **(**Table 1) (Figure 1).

Table 1: Comparison of Vitamin D levels in different groups.

Characteristic variables		Group-I; N=20 CONTROL	Group-II; N=20	Group-III; N=20	Group-IV; N=20
Vitamin D (ng/ml)	Mean	32.747	34.408	23.991	22.713
	SD	8.721	7.802	7.328	5.970
	Mean difference	------	-1.661	8.756	10.034
	Std. error	------	2.136	2.079	1.930
	p-Value	------	0.969	0.001	0.000

Figure 1: Vitamin D levels in different groups.



Discussion

Preeclampsia is a hypertensive disorder of pregnancy, comprising of its own serious complications, including eclampsia. This study aimed to assess whether vitamin D could be associated with the pathological factors contributing towards the hypertensive disorder as vitamin D deficiency have often been linked to certain maternal and foetal morbidities and co-morbidities by different studies conducted in the past decade, also being recognized as a matter of public health concern lately.

In general, PE has been hypothesised as a two-stage disorder. In stage-1, there occurs an impaired remodelling of the spiral artery due to the trophoblastic invasion on walls of the uterus, producing placental ischemia and an increase in oxidative stress leading to decreased uteroplacental perfusion followed by stage-2 in which, there occurs severe endothelial damage, further aggravating the oxidative stress. In a study conducted by Robert JM et al. reveals the presence of numerous infarcts in placental arterioles with significant sclerotic narrowing of preeclamptic patients[7].

Vitamin D is a known antioxidant and is debated for its role in downregulation of some of the known etiological factors of the PE. Vitamin D is proved to induce Vascular Endothelial Growth Factor (VEGF) release and also increase the release and activity of Pro-Matrix Metalloproteinase (pro-MMP-2)[8] thus promoting angiogenesis, and which is otherwise unregulated in the placenta of preeclamptic pregnancies as explained above. Vitamin D is released by endothelial cells[9] and causes vascular smooth muscle cell proliferation[10]. Vitamin D supplementations have been shown to reverse endothelial dysfunction in PE (11) possibly via increased VEGF release[12].

In PE, *soluble fms–like tyrosine kinase* 1 (sFlt-1) seems to be a key mediator in the development of PE. Gilbert JS and Makris A et al. in their studies have associated uteroplacental hypoperfusion with elevated levels of sFlt-1leading to PE.[13][14]. In a study conducted by Maynard *et al.* it was observed that levels of sFlt-1were increased in the

circulation of preeclamptic women. sFlt-1 is an analogue of VEGF receptor fms–like tyrosine kinase 1. When the levels of sFlt-1 are abnormally increased, it competitively binds to VEGF and placental growth factor (PlGF), thus antagonizing their binding to cell surface receptor fms–like tyrosine kinase 1 (VEGF receptor 1) creating an angiogenic imbalance leading to increased chances of endothelial damages[15].

Vitamin D supplementation reduces endothelial dysfunction by decreasing apoptosis and increasing Nitric Oxide (NO) production, as well as reduced the expression of sFlt-1 in Reduced Uterine Perfusion Pressure (RUPP) modelled rats. Vitamin D supplementation also decreased the activity of caspase-3 in RUPP rats thereby, alleviating PE characteristic symptoms[16].

Another important etiological factor of PE includes NO, which is a potent vasodilator, the levels of which are found deranged in PE. NO deficiency causes impaired spiral artery remodelling and PE-characteristic uteroplacental changes in pregnant mice[17]. NO deficiency has also been shown to correlate with derangements seen in PE, including hypertension and proteinuria[18].

Vitamin D is a known immunomodulator, as it decreases the anti-angiogenic factors, including reducing the production of γ-Interferon (IF-γ) and Interleukin-2 (IL-2)[19], Tumor Necrosis Factor-α (TNF-α), and Interleukin-6 (IL-6) secretions[20]. In a study conducted by Martinez-Miguel P et. al. demonstrated that active vitamin D increases NO production in endothelial cells, as well as increases the activity of Endothelin-Converting Enzyme-1 (ECE-1) and Endothelial-Nitric Oxide Synthase (eNOS)[21].

Although, there are other proximal pathways of sFlt-1 induction, including downregulation of levels of Heme Oxygenase (HO). The HO enzyme degrades heme into carbon monoxide (CO) which is a vasodilator. In states of hypoxia and ischemia, levels of HO increases, thus leading to increased expression of CO resulting in decreased perfusion pressure in placenta[22-24]. In a study by McCaig D. et al. shows defective trophoblastic invasion which is characteristic of PE due to decreased HO levels[25]. Various studies have been conducted which proves that in patients with PE, there are decreased levels of HO[26-32]. Further, in a study by Cudmore M. et al. demonstrated that HO1 pathways inhibits Flt-1 release[33].

Further, haemodynamic dysregulation and its association with Renin-Angiotensin System (RAS) has also been contemplated in PE. Studies have shown that in preeclamptic women, levels of serum angiotensin I, angiotensin II and aldosterone are reduced as compared to normotensive women, and moreover, active renin levels and autoantibodies to angiotensin type 1 receptor (AT1-AAs) are increased[34-36]. In a study conducted by Dechend *et al.* discovered that AT1-AAs causes an increase in levels of Reactive Oxygen Species (ROS), NADPH oxidase and NK-*κ*B in preeclamptic women[37]. Further, in studies conducted by Zhou CC. et al. demonstrated that AT1-AA induces sFlt-1 release via calcineurin pathway and also by TNF-*α* induction and reducing HO levels during gestation[38][39]. AT1-AA also induces production of endothelin, which is a vasoconstrictor, thus leading towards the hypertension characteristic in PE[40].

According to Roth CL. Et al., there is a decreased expression of HO-1 in vitamin D deficient obese rats[41], as well as it is proven by Oermann E. et al. that vitamin D causes upregulation of HO-1 levels[42]. Further, in a study conducted by Faulkner JL et al. have demonstrated that vitamin D supplementation downregulates release and activity of AT1-AA[36].

Thus, it can be presumed that upon several etiological factors responsible for the possible prevalence of the hypertensive disorder, mere sufficient levels of vitamin D can come as a boon for its prevention. But, it should be acknowledged that for a better understanding of the effects of vitamin D levels on the prevalence of PE, more human-based trials are required to establish a direct association between the parameter and the disease. Further, the right levels of vitamin D

supplementation during gestation remains unknown, therefore, it can be suggestive of planning of more studies on investigation of a right dose of vitamin D supplement.

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