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Risks associated with preeclampsia: possible mechanisms

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ABSTRACT

Findings have shown that low serum 25-hydroxy vitamin D level is a possible risk factor for incidence of preeclampsia during pregnancy. Vitamin D has important effects on multiple biological pathways, including angiogenesis. Some studies have shown that vitamin D deficiency is highly prevalent among women suffering from preeclampsia, influencing immune modulation and vascular function. Evidence has shown that an imbalance of pro-antigenic and anti-angiogenic proteins can be considered as a possible etiological factor in the development of preeclampsia. Besides, there is a series of studies linking the renin–angiotensin aldosterone system (RAAS) with preeclampsia. In this article, we review the current studies evaluating the association between maternal vitamin D status and vascular health, metabolism, placental immune function and the risk of preeclampsia. We provided evidence of the different factor involved in the metabolism of vitamin D and vitamin D receptor (VDR) expression, gene regulations, immune function, and chronic disease when vitamin D is used optimally.

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Introduction

Preeclampsia is defined by hypertension and proteinuria during pregnancy (1). It is diagnosed based on the blood pressure of 140/90 mmHg or more in two stages with the urinary protein of 300 mg/day or higher, after 20 weeks of gestation (2). About 2–8 percent of primigravida women suffer from preeclampsia (3). Worldwide, 25 percent of maternal deaths are related to preeclampsia (4). Vitamin D deficiency (VDD) is considered as a high risk factor for preeclampsia, and on the other hand the prevalence of VDD is between 20 and 40 percent in pregnant women (5). Preeclampsia is not only associated with pregnancy-related complications such as preterm birth, but is also related to female mortality due to cardiovascular complications twenty years after pregnancy (6). In this paper, we review the possible mechanisms related to VDD and manifestation of preeclampsia.

We performed a literature search from January 1970 to November 2015 using PubMed/Medline, Scopus, Web of Science, and Google Scholar. The search terms were “Preeclampsia” plus “angiogenic factors”, ” VEGF ”, ” SFlt-1”, ” inflammation ”, ”genetic”, ”Rennin-angiotensin system”, and ”vitamin D deficiency”. Moreover, we selected arti¬cles that evaluated the epigenetic mechanisms of preeclampsia during pregnancy.

Literature review

Incidence and risk factors for preeclampsia

Preeclampsia usually affects young and nulliparous women. There is a higher risk of developing

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preeclampsia superimposed on chronic hypertension in older women. Furthermore, the prevalence rates and ethnicity influence risk for preeclampsia; other risk factors are anti-phospholipid antibodies, diabetes, body mass index (BMI) greater than or equal to 25, first pregnancy, family history of preeclampsia, twin pregnancies, the genetic predisposition, environmental, social, and economic factors, multiple pregnancies, maternal age of 35 years or over, and race (7-10). Preeclampsia is a two-stage disease, the first step involves insufficient implantation of the placenta in early pregnancy, and the second stage involves events leading to activation of systemic endothelial response and clinical symptoms in the third trimester of pregnancy (11). It seems that inadequate placental blood flow causes increased release of substances that stimulate endothelium and play significant role in the occurrence and severity of this disease (12). There is a progressive relation between weight and risk of preeclampsia. The rate is variable between 4.3% in women with a BMI below 20 to 13.3% in women with a BMI over 35; in women who are pregnant with twins, the incidence of high blood pressure is 13% (13). Smoking has harmful consequences during pregnancy, but it reduces the risk of preeclampsia (14). In women who have fetuses with trisomy 13, the incidence of preeclampsia is 30–40%.(15); these women also have high serum levels of anti-angiogenic soluble Fms-like tyrosine kinase-1 (sFlt-1), which is known to be located on the chromosome13 and 3 (15).

Vitamin D status in blood pressure

Vitamin D is associated with the pathophysiology of structural conditions such as hypertension and kidney disease. Hormonal mechanisms regulate blood pressure and diabetes. Vitamin D is known to negatively regulate the renin-angiotensin system (RAS) (16, 17). The main source of human vitamin D is endogenous production in the skin by the effect of sunlight. This process takes place in two stages: the first one occurs in the deep layers of the dermis, where the conversion of 7-dehydrocholesterol to pre-vitamin D occurs (18). Secondly, there is a chemical isomerization depending on the body temperature, where vitamin D converts slowly and gradually to vitamin D3, which is highly dependent on circulating vitamin D binding protein (DBP). After reaching the skin capillary network, vitamin D is transported to the liver by DBP, beginning its metabolic transformation (18). Sufficient maternal vitamin D level is necessary for neonatal health; in addition, maternal VDD increases the risk of fetal rickets (19, 20). The results show that by supplementation of vitamin D (containing 900 IU/D) during pregnancy, the risk of preeclampsia decreased by 32% (95% CI, 11-47%). Epidemiological studies show relationship between vitamin D and lower incidence of the hypertension in pregnancy (21). By measurement of serum 25-hydroxyvitamin D (25 [OH] D), vitamin D status will be considered as follows (22):

21–29 ng/ml (52.5–72.5 nmol/L): vitamin D inadequacy

< 20 ng/ml (< 50 nmol/L): vitamin D deficiency

Serum parathyroid hormone (PTH) levels may be helpful in the diagnosis of VDD. PTH level is often increased in patients with vitamin D inadequacy. The people most at risk for VDD may have osteoporosis, malabsorption syndrome, dark skin, obesity (body mass index> 30 kg/m2), and metabolic disorders (22).

Soluble Fms-like tyrosine kinase-1 (sFlt-1 or sVEGFR-1)

Recent studies confirm the hypothesis that placental anti-angiogenesis factors are only in part responsible for the clinical manifestation of preeclampsia. Soluble Flt-1, (the soluble form of vascular endothelial growth factor (VEGF) receptor 1) and endoglin, transforming growth factor beta (TGF-B) receptor, placenta-derived soluble endoglin (sEng), is secreted by the placenta, and mobilized in the maternal blood weeks before preeclampsia (23-25). These factors may lead to endothelial dysfunction and endothelium-dependent vasodilation and proteinuria. Several days after delivery, sFlt-1 levels normalize simultaneously with reduction in proteinuria and blood pressure (26,27). SVEGFR1 is a protein called sFlt-1, which acts as an antagonist of fetal growth factor and VEGF. Increased level of sFlt-1 in preeclampsia is associated with decreased levels of VEGF and placental growth factor (PLGF) (28-30). All signs of preeclampsia including proteinuria, hypertension, and glomerular endothelial inflammation can also be observed in non-pregnant rats that were treated with sFlt-1 (30-32). Also, findings suggested that a 24% decrease in the levels of VEGF in non-pregnant mice causes glomerular endothelial, inflammation, and proteinuria (30,33). It seems that due to increased levels of sFlt-1 in preeclampsia, VEGF signaling is reduced in the kidneys, which causes inflammation of the endothelium and proteinuria (34). Moreover, sFlt-1 by binding to VEGF and PLGF inhibits their angiogenic effects (28,35). Possibly, inadequate placenta blood flow causes the inflammatory response, including release of tumor necrosis factor alpha (TNF-α) (36). The cause of sFlt-1 overproduction in preeclampsia is unknown. Lately, it has been suggested that angiotensin II type 1 (AT) receptor autoantibodies lead to increased levels of sFlt-1. As a result, immunoglobulin G (IgG) from women

with preeclampsia motivates the synthesis and release of sFlt-1 through AT1 receptor activation in human trophoblast cells and placental villous explants (36-38). Siddiqui et al., showed that the angiotensin II type I receptor agonistic autoantibody (AT1-AA) levels in preeclampsia are proportional to disease severity. Antibody levels were also detected in 30% of healthy pregnant women, which were five times less than women with preeclampsia (39). Hypoxia increased sFlt-1 (from 207.1 ± 78.98 to 559.3 ± 43.06) placental secretion in the preeclampsia(PE) and vitamin D supplementation meaningfully reduced sFlt-1 serum levels in the PE placentas (40). Studies show that the model containing both 25 (OH) D and sFlt-1 / PLGF ratio best prognosticated severe preeclampsia. It shows the odd's ratio estimates, 95% confidence intervals (CIs) and P-values less than 0.05 for this model. After adjusting for the confounders, the 25 (OH) D and sFlt-1 / PLGF ratios were highly significant independent predictors of severe preeclampsia (both P <0.001) (41).

Rennin-angiotensin system (RAS) ratio in the diagnosis of vitamin D deficiency and preeclampsia

The rennin-angiotensin system (RAS) has an essential role in regulating blood pressure and maintaining internal stability (42). The RAS is a body monitor of blood pressure (4). Angiotensin (AGT) breaks angiotensin 1 by the effect of the renin enzyme. Angiotensin 1 is bound to the converter on the endothelial cells, which converts it to angiotensin 2. Angiotensin 2 is a strong vascular retractor that causes an increase in blood pressure (42). Angiotensin has two forms, the oxide and retractor. The oxide form AGT produces disulfide bridges causing structural changes in the molecule's structure, which connects it to renin, consequently, facilitating the release of angiotensin 1. The ratio of oxide AGT to reduced AGT is nearly 40 to 60 in healthy pregnant women, which changes in the preeclampsia patients, consequently the amount of reduced AGT and oxide AGT is more active. This can lead to increased blood pressure in preeclampsia women (38). An increase in the expression of RAS, the AT1 receptor, leads to enhanced oxidative stress and endothelial dysfunction (27,43). The expression of renin mRNA has been recognized in macrophages, fetal membrane, and vascular smooth muscle cells (44). In addition, the AT1 was observed in villous trophoblasts and local extravillous (45,46). An important proposed mechanism of the relation between vitamin D and blood pressure includes vitamin D-mediated inhibition of the RAS (2,37). Nevertheless, studies on vitamin D receptor- deficient mice showed an increase in renin gene expression followed by overproduction of AGT II (2). Vitamin D affects vascular endothelial and smooth muscle function (47,48). Also, vitamin D receptor (VDR) agonists negatively regulate renin expression (49). Treatment of obese mice with 1α-hydroxy vitamin D2 reduced proteinuria, angiotensin II type 1 receptors ,renin expression, inflammation, plasma renin activity, blood pressure and myocardial hypertrophy (50-52).

Genetics

Preeclampsia is a complex genetic disorder, and numerous genes determine the risk of preeclampsia (59,60). So far, more than 70 candidate genes associated with preeclampsia have been studied (61). CYP27B1 is the key enzyme in the transformation of 25 (OH) D3 to 1, 25 (OH) 2D3. The data from cell culture studies show that the hypoxia/oxidative stress down-regulates CYP2R1 expression, while increased CYP27B1 could be an operational response to the oxidative stress. The conquering expression of CYP27B1 in the endothelium vessel indicates that vessel endothelium can be an origin of maternal embryonic 1, 25 (OH) 2D3, and decreased CYP27B1 expression in vascular endothelium may describe the levels of 1, 25 (OH) 2D3 as a component in maternal preeclampsia (62). VDR is expressed in placental trophoblast of normotensive and pre-eclamptic pregnant women. Trophoblastic cell expression of vitamin D binding protein (VDBP), 25-hydroxylase (CYP2R1), CYP27B1, 24-hydroxylase (CYP24A1), and VDR in reproductive tissues such as placentas . Along with CYP2R1, CYP27B1 and CYP24A1, VDR regulates key target autocrine signaling within trophoblasts. Protein expressions of CYP2R1, VDBP and VDR are reduced, but CYP27B1 and CYP24A1 expressions are increased, in preeclamptic compared with normotensive placentas (30,65-67). Oxidative stress can lead to exposed vitamin D homeostasis in placental trophoblasts in preeclampsia (69).

Inflammation

At the end of pregnancy, there is a strong dependency between the immune factors and preeclampsia. In the woman whose genital tracts are exposed to fertility procedures of the sperm and ovule donor, the risk of preeclampsia increases three-fold. A partner-particular immune incompatibility might be associated (53). VDR is a family of the steroid hormone receptors, which has been found in active T-lymphocytes and B-lymphocytes and macrophage/monocyte and hence, vitamin D plays significant role as an immune system regulator by linking active (OH) to VDR (54, 55). Vitamin D influences the balance of T helper1 (Th1)/ T helper2 (Th2), with a negative impact on the Th1 and positive effect on the Th2 cells. In fact, it re-

duces the production of Th1 cytokines and induces Th2 cytokines. It seems that the high production of 1, 25(OH) 2D in the placenta has an effect on microbial factors. In vitro studies have shown that 25 (OH) D and 1.25(OH)2D can increase cathelicidin (antimicrobial protein) in the decidual and embryo trophoblast. VDD increases the incidence of bacterial vaginitis in the first trimester of pregnancy (1). The activity of inflammatory cytokines is a part of the response to the microbial invasion and this activity disrupts the uterine relaxation. Factors such as interleukin-1 (IL-1), interleukin-6 (IL-6), and TNF-α are increased in amniotic fluid and in the serum of pregnant women (56). Natural pregnancy is needed to coordinate enough responses between the antimicrobial and anti- inflammatory responses, and vitamin D is required for regulating these replies (56). In vessels of preeclamptic patients, there was significantly increased activity of neutrophils; perhaps syncytiotrophoblast microparticles (STMPs) stimulate systemic inflammation, resulting in activation of leukocytes and binding neutrophils to the endothelium. After entering the vascular wall, neutrophils cause the release of cytokines such as TNF-α and damage the vessels (57). On the other hand, it seems that VDD causes an increase in TNF-α IL-6 and interferon-γ (58). The placenta is an important cytokine producer during pregnancy (58). In cultured human trophoblast, calcitriol inhibited production of cytokines such as TNF-α (59). Finally, VDD increases levels of TNF-α, which increases the inflammatory cytokines such as interferon-gamma and interleukin-6 (59).

VEGF status in pathogenesis of preeclampsia and vitamin D

VEGF and PLGF affect the process of angiogenesis, with VEGF being the more important factor. These two factors facilitate trophoblastic invasion in the maternal spiral artery and so spread the angiogenesis process (30,60). VEGF is the most important factor involved in the growth and survival of the vascular endothelial cells, and is reduced in preeclamptic patients (31). VEGF acts as an important regulator of angiogenesis, cell proliferation, and differentiation. It prevents cellular apoptosis and increases the production of nitric oxide and associated vascular permeability (61,62). VEGF has three types of tyrosine kinase receptors including VEGF R1 (Flt-1), VEGF R2 (KDR/Flk-1), and VEGF R3 (Flt-4). The VEGF-R1 also called sFlt-1 binds to VEGF and involves in angiogenesis (63,64). The matrix metalloproteinases (MMPs) are a family of proteolytic enzymes capable of breaking down the extracellular proteins (65,66). The MMPs are zinc and calcium-dependent enzymes that have essential roles in mechanisms such as angiogenesis and vascular remodeling by degrading extracellular matrix proteins (67). MMPs are implicated in the vascular dysfunction associated with preeclampsia (68,69), and blocking the VDR or VEGF signaling pathway causes reduced vascular-like structures and increases pro-MMP-2 activity. It seems that vitamin D increases the expression of VEGF (70). Pro-MMP-2 plays an important role in vascularization (71), and it inhibits reduced VEGF gene expression(72); while VEGF increases the activity of MMPs and decreases MMP inhibitors such as tissue inhibitors of metalloproteinases-1 (TIMP-1) and tissue inhibitors of metalloproteinases-2 (TIMP-2) (73). Thus, it seems that the effect of vitamin D on pro-MMP-2 also increases the expression of the VEGF gene (70). Studies have shown that VDR directly binds to response elements from the promoter region of VEGF gene in smooth muscle cells. These results could explain the beneficial effects of vitamin D in improving endothelial cell function through VEGF-dependent pathways (74). VEGF is one of the most important factors for the growth and survival of endothelial cells that its serum levels is reduced in patients with preeclampsia (75). Therefore, local or systemic increases of VEGF in the presence of vitamin D can improve endothelial function and thus improve the symptoms of preeclampsia (70).

Conclusion

VDD is associated with an increased risk of preeclampsia. Many studies show that the use of vitamin D supplements is associated with reduced risk of preeclampsia during pregnancy. Although, at present, grave consequences of changing environmental regulations and genetic or epigenetic homeostasis of vitamin D are known, screening patients at risk for VDD including obese people, blacks and individuals with malabsorption seems necessary. In addition, further studies are necessary to determine vitamin D requirements during pregnancy.

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Conflict of Interest

The authors declare no conflict of interest.

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