The relation between hypovitaminosis D and IL-6 increase in cases of preeclampsia

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Abstract:

Vitamin D deficiency has been linked to the pathogenesis of preeclampsia. Given the demonstrated antiinflammatory function of vitamin D in multiple organ systems including trophoblast cells and placenta, we hypothesized that vitamin D deficiency contributes to the development of preeclampsia through increased inflammation, as indicated by elevated interleukin (IL)-6 concentrations.

Keywords: Vitamin D, IL-6, preeclampsia.

Introduction:

Vitamin D is a fat-soluble vitamin which belongs to the steroid compounds. The largest source of vitamin D in adults is synthesis from solar radiation; half an hour of sunlight delivers 50 000 iu of vitamin D with white-complexioned skin. Dietary ingestion of vitamin D makes a relatively small contribution to overall vitamin D status as there is little vitamin D that presents naturally in the food supply found in fish-liver oils, fatty fish, mushrooms, egg yolks, and liver. Melanin absorbs ultraviolet B (UVB) from sunlight and lowers cholecalciferol production by at least 90%. Dietary vitamin D is absorbed from the intestine and circulates in plasma bound to vitamin D binding proteins **(1).**

Vitamin D3 is three times more effective than vitamin D2 in increasing vitamin D concentrations and maintaining those levels for a prolonged time **(1).**

One of the most important functions of the kidney is activation of vitamin D. It is synthesized in the epidermis of the skin after UVB exposure or ingested in diet and is transported to the liver by vitamin D-binding protein where it is hydroxylated in the 25 position to yield 25 hydroxyl vitamin D (calcidiol or calcifediol) **(1).**

Exposure to sunlight or dietary intake of vitamin D increases serum levels of 25-hydroxyvitamin D. 25-hydroxyvitamin D constitutes the major circulating form of vitamin D, and it is hydroxylated by the enzyme 1-alpha hydroxylase in the kidney to yield 1,25dihydroxy vitamin D, which is the active form of vitamin D, and this metabolite is responsible for the effect of vitamin D on calcium and phosphorus metabolism, bone health, and regulation of parathyroid function **(2).**

Multiple factors influence the synthesis of vitamin D through the skin such as duration of sun exposure, altitude, season, time of day, pigmentation of the skin, sunscreen use, behavioral habits and diet. The reference values for vitamin D concentrations were recently reviewed, being considered as vitamin D insufficiency values below 20 ng/mL (**3).**

Functions of vitamin D:

Vitamin D is not only a major regulator of calcium, phosphorus, and bone metabolism but also regulates cell growth and differentiation. Vitamin D acts by enhancing intestinal calcium and phosphorus absorption, by stimulating bone calcium mobilization, and by elevating renal reabsorption of calcium in the distal tubules. These functions on bone and possibly kidney, but not intestine, require the parathyroid hormone. As a result of these functions, serum calcium and phosphorus concentrations are increased to supersaturating levels required for the mineralization of bone to prevent rickets, osteomalacia, and hypocalcemic tetany, thus, bone resorption, modeling and remodeling must be considered vitamin D-dependent processes**.** Vitamin D has immunomodulatory and anti-inflammatory effects, and these effects helps glucose metabolism by regulating the release of insulin according to levels of glucose (**4).**

This effect of vitamin D explains the association between maternal vitamin D deficiency in early pregnancy and the increased risk for GDM, and it has been demonstrated in some observational studies. Vitamin D is also associated with non-skeletal roles, including those demonstrated in autoimmune diseases, infectious diseases, metabolic syndrome and its components, cardiovascular diseases, cancers, and all-cause mortality (**4).**

Vitamin D serum level testing:

Examination of plasma calcidiol is the most sensitive vitamin D level test. Calcidiol has a half life of 19-31 days and demonstrates the level of vitamin D acquired from food and synthesized in the skin for several weeks to months. The Endocrine Society found the normal level of calcidiol to be 30-100 ng/mL, with insufficiency occurs at 21-29 mg/mL, and deficiency occurs under 20 ng/mL. Severe deficiency is defined as a 25(OH)D level less than 10 ng/ml (**3).**

Vit D deficiency:

Definition:

Vitamin D deficiency is usually defined as a 25(OH)D level <50 nmol/L (20 ng/ml) and vitamin D insufficiency as a 25(OH) D level of 50–72 nmol/L (20–29 ng/ml). Because an estimated one billion people worldwide suffer from vitamin D deficiency or insufficiency, vitamin D has become an vital focus of current medical research. Vitamin D deficiency is common in northern Europe, especially in females with pigmented skin. Vitamin D deficiency is three times more common in the winter and spring if compared to the summer and autumn in the UK. A cohort study conducted in Brazil evaluated the effect of vitamin D deficiency on neonatal outcomes of pregnant females with GDM. The authors identified that newborns of women with vitamin D deficiency had a significantly increased incidence of hospitalization in critical care units, hypoglycemia, and small size for gestational age. The incidence of prematurity, jaundice, and dystocia of the shoulder were not statistically significant among groups (**4).**

Vitamin D Supplementation:

There has been renewed interest in studying the effects of supplementation with native vitamin D (cholecalciferol) in CKD patients with low 25(OH)D levels and this interest has been fanned by studies that have demonstrated several potential nonskeletal benefits of vitamin D. These benefits include effect of vitamin D on immune system, cardiovascular disease, diabetes, and some cancers

Because of the long life of complex 25(OH)D and DBP (480 h), daily (1000 U D3), weekly or monthly (40,000 U D3) regimens seem efficient for restoring 25(OH)D levels (**4).**

Effect of Native Vitamin D Supplementation on Dialysis Patients:

These effects depend on the vitamin D dosage, the type of vitamin D compounds, the duration of the study, and the studied population. One of the main expected effects is the lowering of serum PTH level. Hence, the results are not always positive. In a meta-analysis, **Meltzer et al.** reported that nutritional vitamin D leads to increased 25(OH)D levels (mean + 24 ng/mL) without any hypercalcemia or hyperphosphatemia and with a decrease in serum PTH level (41% decrease), mostly in dialysis patients-(**4).**

The mean dosage was 50,000 IU weekly during the first month; a lower dosage was used thereafter. **Meltzer et al.** (**4)** reported mildly reduced serum PTH levels after vitamin D supplementation. A decrease in SHPT in dialysis patients after systematic D supplementation during the predialysis period was reported. Novel modified-release calcifediol seems to have significant efficacy in decreasing PTH in CKD patients. A recent randomized controlled trial

(RCT) assessing short-term effects of ergocalciferol, weekly or monthly, during three months, failed to find a significant effect on PTH level.

Zemb et al. (3) reported increased serum 1,25(OH)2D level after cholecalciferol supplementation. **Karakas et al.** confirmed that eight weeks of cholecalciferol improved the percentage of flow-mediated dilatation in dialysis with CKD patients **(5).**

Meltzer et al. (**4)** reported in a RCT that cholecalciferol (50,000 twice weekly) promoted upregulation of CYP27B1 and VDR expression in monocytes and decreased serum IL-6 and C-reactive protein levels. They reported a lack of significant effects of vitamin D supplementation on mortality. Results of vitamin D trials vary for the general population and renal patients. The discrepancies may be due to differences in baseline serum 25(OH)D levels, vitamin D doses and treatment periods, adherence to supplementation, and VDR genetic polymorphisms (**4).**

Vitamin D Toxicity:

Opposite to vitamin D receptor activator (VDRA), nutritional vitamin D compounds are unlikely to induce hypercalcemia using a normal regimen because its 1α-hydroxylase activation is regulated by PTH, FGF-23 and 24-hydroxylase. Therefore, a serum 25(OH)D level up to 100 ng/mL is considered safe. In the general population, daily vitamin D intakes >10,000 IU may be toxic because they lead to DBP saturation with an increase of free serum 25(OH)D. In addition, toxicity has been observed for higher dosages (>40,000 U/day) (**3).**

Meltzer et al. (**4)** reported eight cases of vitamin D intoxication that appear to have been caused by excessive vitamin D fortification of dairy milk with serum 25(OH)D >300 ng/mL. Vitamin D toxicity is increased by higher calcium intake, calcitriol analogs, and adynamic bone disease in dialysis patients. The frequency of this toxicity is not known but appears very rare. Diagnosis mainly includes hypercalcemia with the risk for extraosseous calcification.

Hypercalciuria is not frequently observed because calciuria is very low in CKD and dialysis patients. The native vitamin D compounds' half-life is very long, approximatively two weeks, and toxicity should be treated for weeks. The physiopathology of hypercalcemia includes higher 1,25(OH)2D synthesis, higher intestinal absorption of calcium, and higher calcium release from bone. Close biological monitoring (serum PTH, calcium and phosphate levels), at least in dialysis patients, could prevent vitamin D toxicity (**6).**

Vitamin D2 or D3:

Mitchell et al. (**7)** showed that D2 and D3, given as daily doses, display the same efficiency in increasing serum 25(OH)D levels. Ergocalciferol is mostly used in the United States. In other countries, such as France, cholecalciferol is the standard form, at least for CKD patients. For dialysis patients, we currently use 100,000 IU of oral cholecalciferol monthly(**8).**

Interleukin 6 (IL-6)

The Interleukin 6 (IL-6) gene encodes the classic proinflammatory cytokine IL-6. It is also known as interferon-β2 (IFN-β2), B cell stimulatory factor-2 and hybridoma/plasmacytoma growth factor. IL-6 is a multifunctional cytokine with a central role in many physiological inflammatory and immunological processes**(9).**

Due to its major role in initiation as well as resolving inflammation, deregulation of IL-6 is a mainstay of chronic inflammatory and autoimmune diseases. Additionally, IL-6 has been shown to be implicated in pathogenesis of many human malignancies**(10).**

Therefore, IL-6 controls the intermediary factors that are involved in resolving inflammation. A disruption in this control, for example, by persistent production of IL-6, may thus be crucial at the onset of chronic inflammation. Moreover, by inducing mononuclear cell accumulation, angioproliferation and antiapoptotic functions on T cells, IL-6 contributes to an amplifying loop for chronic inflammatory process**(11).**

The relation between hypovitaminosis D and IL-6 increase in cases of preeclampsia

When a woman presents with new-onset gestational hypertension and proteinuria, a clinical diagnosis of preeclampsia can be made. Preeclampsia can also be diagnosed using ultrasound. The pregnancy-related condition known as preeclampsia is a sickness that affects many body systems. It is a leading cause of disease and mortality in mothers, neonates, and unborn babies, and it affects three to five percent of all pregnancies around the world(**12).**

Even though there have been some recent developments toward a better understanding of the biology of preeclampsia, the illness is still difficult to cure because there is no preventative therapy, and the only effective treatment is delivery, which ends both the pregnancy and the disorder. Even though there have been some recent advancements toward a better understanding of the biology of preeclampsia, the illness is still difficult to cure(**13).**

The pathophysiology of preeclampsia is currently being explained using a model that involves two stages. The initial stage is characterised by a decrease in placental perfusion, which is typically the result of an aberrant trophoblastic invasion. The clinical signs of preeclampsia occur in both the second stage, which is preceded by failed dilatory remodelling of maternal arteries that perfuse the placenta, and in the third stage, which follows the second stage(**14).**

Both the mother and the unborn child could lose their lives as a result of preeclampsia. Initiation and progression of preeclampsia have been attributed to a number of different reasons. These reasons include maternal constitutional characteristics, antiangiogenic factors, endothelial dysfunction, syncytiotrophoblast microparticles (STBM), and inflammatory activation. Some of these factors have been linked to preeclampsia, while others have not. Insufficiency in vitamin D has been found to be associated with an increased risk of developing preeclampsia. This association was made during the process of elucidating the underlying mechanisms that contribute to the development of preeclampsia. The existence of a maternal vitamin D deficit is

associated with a fivefold increase in the chance of preeclampsia when compared with the prevalence of the condition in individuals with normotensive blood pressure(**15).**

One of the well-known functions of vitamin D is that it helps maintain proper levels of phosphorus and calcium in the blood, which is something that may be accomplished with its assistance. On the other hand, it is known to play important parts in a wide variety of cellular responses, some of which may be related to preeclampsia. The way that the body reacts to inflammatory stimuli can be altered by vitamin D outside of the context of pregnancy(**16).**

For example, after hip fracture repair, the levels of IL-6 in the blood of women who are deficient in vitamin D are higher than in women who are not deficient in vitamin D. In human coronary artery endothelial cells, pretreatment with vitamin D results in a significant attenuation of the TNF-induced activation of downstream signalling pathways(**17).**

Not only do human trophoblasts have the ability to produce the active form of vitamin D, which is known as 1,25(OH)2D, but they also have the ability to respond to it. Both the enzyme that is responsible for activating vitamin D, known as 1-hydroxylase (CYP27B1), and the enzyme that is responsible for breaking it down, known as 24-hydroxylase, work together to maintain a steady concentration of 1,25(OH)2D. (CYP24A1) (**18).**

Both of these enzymes are coded for by mRNA that is present in human placenta. Both the decidua and the trophoblast include a protein that is known as a vitamin D receptor (VDR). This protein is what is responsible for mediating the activities of the activated form of 1,25(OH)2D and is found in both the decidua and the trophoblast. Recent studies have shown that the addition of vitamin D to trophoblast cell culture systems can reduce the amount of inflammatory cytokine genes that are transcribed into mRNA (such as TNF, IFN, and IL-6). These inquiries were carried out because of concerns regarding pregnancy(**12).**

In the placenta, immune stimulation with LPS (lipopolysaccharide) promotes the synthesis of VDR and CYP27B1, in addition to cytokines such as IL-6; the up-regulation of IL-6 is further amplified in animals lacking either CYP27B1 or VDR(**18).**

The onset of preeclampsia is in some way linked to a deficiency in vitamin D, which is known to be related with elevated levels of inflammation. This conclusion was reached due to the fact that it has been demonstrated that vitamin D performs an anti-inflammatory activity in a range of organ systems, the placenta and trophoblast cells being one of those organ systems(**12).**

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