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Pharmacological Role of Vitamin D Supplementation in the Prevention of Diabetes and Gestational Diabetes

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Abstract

Diabetes is a disorder of carbohydrate metabolism that requires immediate changes in lifestyle. Gestational diabetes (GDM) is defined as carbohydrate intolerance that begins or is first recognized during pregnancy, in both the conditions vitamin D play an important role in supporting pathogenesis. Vitamin D is regulated in the form of 25OHD from kidney to intestine and to the blood. Vitamin D and pro drug can protect against complications of diabetes like kidney failure, vision loss, hypertension and heart attack. Vitamin D receptors are present in both pancreatic beta-cells and immune cells. Beside its classical role as the major regulator for calcium absorption, it mediates the activity of beta-cell calcium-dependent endopeptidases promotes conversion of proinsulin to insulin and increases insulin output. In peripheral insulin target tissues, it enhances insulin action via regulation of the calcium pool. Its deficiency impairs insulin secretion and induces glucose intolerance. Vitamin D supplementation has shown to reduce the risk of developing type2 diabetes. Vitamin D intake is essential for maternal health and prevention of adverse outcomes. Circulating 25OHD concentrations reflect vitamin D status, and the normal range is between ~32 ng/ml and ~80 ng/ml, with values below ~32 ng/ml defined as deficient.

Keywords: Diabetes; Vitamin D; Gestational Diabetes; T2D

Abbreviations

1,25(OH)2D: 1α,25-dihydroxyvitamin D; 25OHD: 25-hydroxyvitamin D; CYP24A1: 24- hydroxylase; CYP27B1: 1α-hydroxylase; CAMP: Cathelicidin Antimicrobial Peptide; DBD: DNA Binding Domain; Th1: T helper 1; Th2: T helper 2; TLR: Toll like Receptor; TGF-α: Tumor Growth Factor-alpha; TNF-α: Tumor Necrosis Factor-alpha; DBP: Vitamin D Binding Protein (Gc-globulin); VDR: Vitamin D Receptor

Introduction

Gestational diabetes mellitus (GDM) usually reveals itself in the latter half of pregnancy and it is identified by carbohydrate intolerance of variable severity [1]. Recently, vitamin D has sparked widespread interest in the pathogenesis and prevention of diabetes. As the major regulator for calcium homeostasis, vitamin D directly and or indirectly improves insulin exocytosis via activating calcium-dependent endopeptidases. Vitamin D also improves glucose tolerance. Vitamin D could also prevent type 2 diabetes through its role as an efficient antioxidant. Gestational diabetes mellitus (GDM) is defined as glucose intolerance occurring in or is detected during pregnancy. The pathophysiology of GDM parallels that of T2DM in many aspects, including insulin resistance and relative insulin insufficiency. Women with previous GDM are at increased risk for developing T2DM in their later life [2]. Therefore, vitamin D deficiency may also play a role in the pathogenesis of GDM. Vitamin D deficiency has reappeared as an important public health problem in developed and developing countries, and vitamin D deficiency during pregnancy is becoming increasingly common. In recent studies in the United States (US), Canada, Australia, Iran, Sweden, and Pakistan, 24%-95.8% of pregnant women were deficient and 54%-100% were insufficient for vitamin D, with a general trend towards increased prevalence of vitamin D deficiency or insufficiency in women with darker skin pigmentation or who regularly wear veils. Serum 25OHD levels were negatively correlated with fasting glucose and insulin level [3]. Furthermore, maternal plasma 25OHD concentration sin early pregnancy were reported to be associated with an increased risk of GDM, but no significant association between 25OHD levels and GDM risk was observed in an Indian population. Results from these studies point towards an inverse association between vitamin D status and the risk of hyperglycemia or insulin resistance, but are inconclusive. The present study was designed to evaluate the association between serum vitamin D deficiency and the risk for GDM in pregnant women.

Vitamin D deficiency during pregnancy is common in many parts of the world, and there is a very strong relationship between vitamin deficiency D and multiple potential adverse pregnancy outcomes. However, the role and metabolism of vitamin D in the pregnant state is not well known or understood [3]. Despite the reported high prevalence of deficiency and the possible consequences, the desired optimal level needed for pregnant women in their body and the amount of vitamin D intake required to maintain adequate levels is not very well documented [4].

The vitamin D stores in the infant start with transplacental transfer of 25(OH)D in early pregnancy from mother to fetus [5]. It is very obvious that maintaining optimum vitamin D nutrition during pregnancy is essential for prevention of hypovitaminosis D in the fetus and vitamin D deficiency at birth and in early infancy [5]. In recent years, the prevalence of vitamin D deficiency has increased, and the incidence of low vitamin D status has risen in the developing world and in the UK and other developed countries [4,5]. There is a high prevalence of vitamin D deficiency in pregnant women from non-Western countries in Northern Europe, and vitamin D deficiency during pregnancy is an ongoing epidemic. At present, there is not enough evidence to evaluate the effectiveness of vitamin D in pregnancy, and therefore vitamin D supplementation is not

routinely offered to all pregnant women. Many studies have investigated vitamin D deficiency in pregnancy in different ethnic minority groups and the method of supplementation. There is evidence that an immediate dose is as effective as a daily dose, with no adverse effects for vitamin D supplementation.

Natural Vitamin D by itself has no hormonal activity. To become biologically active, vitamin D needs two successive hydroxylation in the liver (at carbon 25) and in the kidney (at a position of carbon 1). In the liver vitamin D is hydroxylated at carbon 25 to 25-hydroxy vitamin D (25(OH) D) (vitamin D2). Circulating 25(OH)D concentrations are considered an indicator of vitamin D status. In the kidneys, 25-hydroxy vitamin D (25(OH) D) (vitamin D2) is converted to an activated (1,25-dihydroxy vitamin D; 1,25(OH)2D) (vitamin D3). This is the biologically active form of vitamin D [6]. The production of 1,25(OH)2D3 in the kidney is regulated by several factors, particularly by levels of parathyroid hormone, although kidney 1α-hydroxylase is also subject to direct negative feedback inhibition by 1,25(OH)2D3. The proximal renal tubule is the principal site of 1α-hydroxylation, although high levels of 1α-hydroxylase mRNA have also been found in human keratinocytes, dendritic cells and macrophages. Another hydroxylation enzyme, 24-hydroxylase, initiates the catabolic cascade of 25-hydroxy vitamin D3 and 1,25(OH)2D3. In the circulation, all metabolites of vitamin D are bound to a carrier protein known as vitamin D-binding protein (DBP) [7].

Vitamin D Structure and its Mode of Actions

Vitamin D, or calciferol, is a group of lipid soluble substance with a four-ringed cholesterol backbone. Human obtained Vitamin D from exposure to Sunlight, their diet and from dietary supplement. Ultraviolet light convert provitamin D to vitamin D3 (cholecalciferol) in the skin and afterwards Vitamin D3 was bounded by vitamin D binding proteins (DBP) and transported via blood to target organs for metabolism and activity. Vitamin D hydroxylate to form 25-hydroxy-vitamin-D (25OHD) in the liver. Hydroxylation of 25-hydroxy-vitamin- D to 1, 25-dihydroxy-vitamin D occurs in the mitochondria of the proximal tubules of the kidney. This form of vitamin D (1,25(OH)2-vitamin D) is the physiologically active form. The renal production of 1,25-dihydroxy-vitamin D is regulated by plasma parathyroid hormone and serum calcium and phosphorus levels. Vitamin D increases calcium and phosphorus absorption from the gut and reabsorption from the kidneys and increases plasma concentration of these elements. As such, the main effect of vitamin D is maintenance of mineral homeostasis and regulation of bone remodeling.

Vitamin D deficiency is defined when the level of 25- Hydroxyvitamin D is less than 20 ng/ml (50 nmol/l). Level of 25-29 ng/ml can be considered to indicate a relative insufficiency of vitamin D and a level of 30 ng/ml or more indicate sufficient vitamin D. Vitamin D intoxication is observed when serum level of 25-hydroxyvitamin D are greater than 150 ng/ml [6-7]. Vitamin D deficiency or resistance is caused by different mechanisms including reduced of vitamin D access due to insufficient dietary vitamin D, fat malabsorptive disorders, and/or lack of photoisomerization, Impaired hydroxylation of vitamin D by the liver and kidney to produce 25-OH vitamin and 1,25(OH)2-vitamin D respectively and end organ insensitivity to vitamin D metabolites.

Correlation between Vitamin D and Glucose

Insulin stimulates glucose metabolism in its target tissues via recruitment of transporters from a large intracellular pool to the plasma membrane. The functional activity of these transporters has been shown to be impaired in diabetes [8]. As vitamin D modulates insulin secretion, it is reasonable that vitamin D deficiency may in part contribute to the altered expression of these transporters. Although the role of vitamin D in diabetes is well recognized, its relation to glucose transport is not well studied. Consuelo et al. [9] observed the effect of vitamin D on glucose transport in adipocytes in non-diabetic and streptozotocin induced diabetic rats. Treatment with 1,25 D3 to non-diabetic rats did not alter basal and insulin stimulated glucose transport in adipocytes from these animals. The treatment with vitamin D to streptozotocin induced diabetic rats, improved the decreased basal glucose transport by 107% and the insulin stimulated glucose transport in adipocytes by 71% from these diabetic animals. The Possible mechanism is likely to be the indirect effect of vitamin D. Vitamin D contributes to normalization of extracellular calcium ensuring normal intracellular calcium pool as elevated intracellular calcium impairs insulin receptor phosphorylation leading to impaired insulin signal transduction and decreased GLUT-4 activity. Peeyush et al. [16] examined the effect of vitamin D supplementation on preventing the altered expression of GLUT-3 in STZ-induced diabetic rats leading to imbalanced glucose transport in the neurons of cerebellum. They observed that treatment with vitamin D and insulin stabilized the glucose transport mechanism mediated through GLUT-3 in the cerebellum. They concluded that supplementation with vitamin D to STZ-induced diabetic rats has beneficial effects in reducing the alterations in GLUT-3 and imbalanced glucose utilization in cerebellum. However large, well-controlled, randomized studies are required to define the relationship between vitamin D and glucose transport.

Effects of Vitamin D in Diabetic Complications

Effect on kidney

Over time, hyperglycemia can have a damaging effect on the kidneys. Zhang et al. reported that the prodrug vitamin D analogue, doxercalciferol (1a(OH) D2), may protect kidneys in mice with diabetic nephropathy. This result suggests that vitamin D might be useful and preventative for the kidneys. The NHANES survey found that 25(OH)D levels were significantly lower in persons with severely decreased glomerular filtration rate when compared with healthy individuals. In addition, persons with higher levels of 25(OH)D had decreased glucose homeostasis model assessment of insulin resistance (HOMA-IR), but 25(OH)D levels did not correlate with b-cell function (also estimated by HOMA) [10]. In a cross-sectional analysis of the 2001 to 2006 nNHANES study, diabetic patients with nephropathy had a high prevalence of vitamin D deficiency and insufficiency. This finding may be worrisome, as recent work by Wolf et al. [18] suggested that vitamin D deficiency in hemodialysis patients was associated with increased mortality risks. Of note, an independent association between vitamin D deficiency and insufficiency with the presence of diabetic nephropathy was seen. Given these findings, the improvement of the vitamin D status or pharmacologic intervention with vitamin D analogues for the prevention or treatment of renal failure needs further study.

Effect on eyes

Although not a sudden process, subjects with diabetes face a very real threat of vision loss, including blindness (diabetic retinopathy). Diabetes also increases the risk of developing cataracts (clouding of the eyes lenses) and glaucoma (damage to the optic nerves). In T2D patients, severity of retinopathy was inversely correlated with serum 1,25(OH)2D3 levels [11]. Age-related macular degeneration (AMD) occurs when the macula, the area at the back of the retina that produces the sharpest vision, deteriorates over time. AMD is the most common cause of blindness among individuals older than 50 years. Levels of serum vitamin D were inversely associated with early AMD. These data suggest that vitamin D supplementation might have a beneficial effect on eye health.

Effect on heart

As many as 65% of diabetic patients will eventually die of heart failure or stroke. A wealth of recent data suggests a central role of the vitamin

D endocrine system on blood pressure regulation and cardiovascular health. For this important topic, recent reviews discussing a potential link between low 25(OH)D levels and cardiovascular disease and the possible mechanisms mediating it have been published [12]. Here it was summarized that severe vitamin D deficiency or resistance caused hypertension in animal models. In addition, mild vitamin D deficiency was associated with higher blood pressure in Caucasians, Hispanics, and African Americans. In recent years, Pilz and colleagues have demonstrated a clear association between low levels of 25(OH)D as well as of 1,25(OH)2D with prevalent myocardial dysfunction, deaths due to heart failure, and sudden cardiac death. In the Multi-Ethnic Study of Atherosclerosis, low 25(OH)D levels were linked to increased risk for developing incident coronary artery calcification. Also, direct effects of vitamin D on the cardiovascular system may be involved. Because various tissues such as cardiomyocytes, vascular smooth muscle cells, and endothelial cells express the VDR and vitamin D affects inflammation as well as cellular proliferation and differentiation, vitamin D may lower the risk of developing cardiovascular disease. A recent meta-analysis of 18 independent randomized controlled trials for vitamin D, including 57,311 participants, described that intake of regular vitamin D supplements (from 300 IU to 2000 IU) was associated with reduced mortality risk (relative risk 0.93; 95% CI, 0.87–0.99). Interventional trials are warranted to elucidate whether vitamin D replenishment is useful for prevention or treatment of cardiovascular diseases and other health outcomes

Effect on nerves

Neuropathy is a common complication in diabetic patients, with a hallmark of sensory neuropathy being the loss of sensation in feet, a risk factor for limb amputation. Recently, diabetic neuropathy has been linked with low levels of 25(OH)D [13]. In this study, a total of (only) 51 patients with T2D (all vitamin D insufficient) with typical neuropathic pain were included and given vitamin D3 treatment (mean dose, approximately 2000 IU). Serum concentrations of 25(OH)D increased from 18 to 30 ng/mL, and the intervention was associated with significant pain reduction. Whether vitamin D can be useful as therapeutic application for neuropathic pain needs to be elucidated in adequately powered prospective clinical studies. Diabetes also increases the risk of Alzheimer disease and vascular dementia. There is ample biologic evidence to support a role for vitamin D in neuroprotection and reducing inflammation, and moreover to put forward a role for vitamin D in brain development and function. Whether vitamin D can reduce the risk of diseases linked to dementia, such as vascular and metabolic diseases like diabetes, needs further investigation.

Effect on bones

Large cross-sectional studies have indicated that patients with T2D have significantly increased risk of bone fractures, predominantly hip fractures [14]. This group of patients frequently displayed loss of vision caused by diabetic eye disease, peripheral neuropathy, arterial hypertension, orthostatic hypotonia, and ischemic disease of the brain, heart, and lower extremities—conditions that predispose to falls. Lately, frequently used drugs in T2D (thiazolidinediones) have been implicated in an increase in bone fractures. Implication of the vitamin D system in this issue is unlikely, but data are scarce. The ADOPT (A Diabetes Outcome Progression Trial) group recently reported slightly reduced vitamin D levels in rosiglitazone-treated patients compared with metformin-treated patients. Moreover, as vitamin D exerts a direct action on skeletal muscle function, it was suggested that T2D patients might benefit from eliminating unfavorable diet and environmental factors, such as low physical action and low vitamin D intake. Several meta-analyses of randomized controlled trials showed that vitamin D supplementation (>400 IU/d) reduces the risk of nonvertebral fractures by 20% and hip fractures by 18% [15]. These studies also pointed out that vitamin D deficiency is common in patients with hip fractures, and truly contributes to the risk of fracture.

Vitamin D in Pregnancy

Important changes occur in the maternal concentration of vitamin D and in calcium metabolism during pregnancy. Calcium is transported from the mother to the fetus through the placenta. In rats, the placenta transports 25(OH)2D and 24,25(OH)2D but not 1,25(OH)2D [25]. Although transplacental transport has not been studied in humans, vitamin D passage from the mother to the fetus would be facilitated by serum concentrations of 1,25(OH)2D being higher in the maternal compared to the fetal circulations [16]. Synthesis in the kidney of 1,25(OH)2D increases during pregnancy. In addition, the deciduas and placenta generate a large amount of 1,25(OH)2D by CYP27B1 enzyme activity [17]. Moreover, specific methylation of the placental CYP24A1 represses transcription of this gene. Production thus exceeds clearance and 1,25(OH)2D levels increase, being two-fold higher in serum of women in the third trimester of pregnancy than in non-pregnant or post-partum women [18]. The synthesis, metabolism and function of vitamin D compounds during pregnancy are complex. The human endometrial decidua makes 1,25(OH)2D and 24,25(OH)2D and the placenta synthesizes 24,25OH2D [17]. Notably, the 24,25(OH)2D synthesized by the placenta accumulates in bone [19] and may be involved in ossification of the fetal skeleton.

Although the sheep fetus can synthesize 24,25(OH)D from 25OH and the 24 hydroxylase enzyme is expressed in the fetal kidney [20] the sheep fetus cannot produce 1,25(OH)2D, as renal 1 hydroxylase activity is suppressed in this relatively hypercalcemic and hyperphosphatemic environment. 24,25(OH)2D is the major form of vitamin D in the fetal lamb and this metabolite, instead of 1,25(OH)2D, may promote calcium absorption by the placenta and enhance skeletal ossification, without increasing fetal blood calcium concentrations or urinary excretion of calcium. If the sheep placenta produces 1,25(OH)2D, as does the human placenta, increased calcium absorption by the maternal gut may be enhanced to meet the increasing demands of the fetus for calcium through gestation. 1,25(OH)2D and CYP27B1 play a role in the autocrine and paracrine immunomodulatory networks prominent during gestation [21]. 1,25(OH)2D affects decidual dendritic cells and macrophages, which in turn interact in the maternal-fetal interface to stimulate T-regulatory cells [22]. 1,25(OH)2D also inhibits the release of Th1 cytokines and increases release of Th2 cytokines, as discussed in section 3.1, and Th2 cytokines thus dominate at implantation.

This modulation of the immune system may prevent rejection of the implanted embryo. 1,25(OH)2D also aids in the transformation of endometrial cells into decidual cells and increases expression of HOXA10 a gene important for embryo implantation and myeloid differentiation in early pregnancy [23]. Established as the chorioallantoic placenta at the end of the first trimester, villous tissues secrete multiple hormones that maintain pregnancy and regulate placental physiology. In human syncytiotrophoblasts, the VDR, CYP27B1, CYP24A1 and 1,25(OH)2D, in an autocrine manner, combine to regulate the expression of human chorionic gonadotropin (hCG), human placental lactogen (hPL), estradiol and progesterone [24-26]. Collectively, the data suggest that 1,25(OH)2D aids implantation and maintains normal pregnancy, supports fetal growth through delivery of calcium, controls secretion of multiple placental hormones, and limits production of proinflammatory cytokines.

Vitamin D deficiency and gestational diabetes

Data about vitamin D as a risk factor for GDM is spare. Pregnant women with diabetes are known to be more vitamin D deficient compared with normal pregnant women [27]. Intravenous administration of vitamin D to pregnant women with gestational diabetes transiently decreases fasting glucose; however, the level of insulin also decreases [28]. Vitamin D deficiency was associated with a 2.66-fold increase in

GDM risk and each 5 ng/ml decrease in 25-hydroxy D concentrations was related to a 1.29 fold increase in GDM risk [29]. Another study demonstrated that the serum concentration of vitamin D during 24-28 weeks of pregnancy in gestational diabetes was lower than normal groups [30]. Women with GDM had a 2.66 fold increased risk of vitamin D deficiency (25-hydroxy D<15 ng/ml) compared with control group [31]. Maternal hypovitaminosis was reported in diabetic pregnancies in Spain and fasting glycaemia decreased with vitamin D supplementation [32]. Vitamin D, insulin and proinsulin were measured at 30 weeks gestation in another study. Some study demonstrated that vitamin D insufficiency is common in mothers but is not associated with gestational diabetes. There was no association between maternal 25(OH)D and gestational diabetes. In this study mothers with hypovitaminosis D, higher 25(OH)D concentrations were associated with lower 30-min glucose concentrations and higher fasting proinsulin concentrations . Clifton-Bligh et al. showed mean serum 25(OH)D concentration in pregnant women was negatively correlated with fasting plasma glucose, fasting insulin and insulin resistance as calculated by homeostasis model assessment. The association between fasting glucose and log-transformed 25OHD concentration was of borderline significance after accounting for ethnicity, age and body mass index in multivariate analyses. The odds ratio of gestational diabetes in women with 25OHD < 50 nmol/L did not reach statistical significance (1.92, 95% confidence interval 0.89-4.17) [33]. In another study total prevalence of vitamin D deficiency (<25 nmol/L) was 70.6% in pregnant women. Prevalence of severe vitamin D deficiency (<12.5) in GDM patients was higher than in normoglycaemic pregnancies. These results show that a positive correlation of 25(OH) vitamin D concentrations with insulin sensitivity and vitamin D deficiency could be a confirmative sign of insulin resistance [34]. Several studies suggest that vitamin D supplementation in children reduces the risk of type 1 diabetes. Increasing vitamin D intake during pregnancy reduces the development of islet auto antibodies in offspring. In Finland, 10,366 children who were given 2000 IU of vitamin D3 per day during their first year of life were followed for 31 years. The risk of type 1 diabetes was reduced by approximately 80% (relative risk, 0.22; 95% CI, 0.05 to 0.89). Among children with vitamin D deficiency, the risk was increased by approximately 200% (relative risk, 3.0; 95% CI, 1.0 to 9.0). In another study, vitamin D deficiency increased insulin resistance, decreased insulin production, and was associated with the metabolic syndrome [35]. Another study demonstrated that a combined daily intake of 1200 mg of calcium and 800 IU of vitamin D lowered the risk of type 2 diabetes by 33% (relative risk, 0.67; 95% CI, 0.49 to 0.90) as compared with a daily intake of less than 600 mg of calcium and less than 400 IU of vitamin D [36]. 4000 IU vitamin D was administrated for 6 months to women with vitamin D less than 50 nm/Land median serum 25(OH)D3 increased significantly and insulin resistance and fasting insulin decreased [37]. In summary the result of different studies show high prevalence of vitamin D deficiency in pregnant women and most of these findings demonstrated the relationship between vitamin D status and glucose tolerance in pregnancy.

Vitamin D effects during pregnancy

The human placenta expresses all components for vitamin D signaling, including the VDR, RXR, CYP27B1 and CYP24A1. In agreement with these findings, cultured primary human syncytiotrophoblasts and decidual cells produce 1,25(OH)2D and secrete the active form into the culture medium [38]. Increased levels of 1,25(OH)2D reduces transcription of CYP27B1 in primary human cytotrophoblasts and syncytiotrophoblasts but transcription of CYP24A1 increases [39]. Antagonists of VDR can block the 1,25(OH)2D induced increase in CYP24A1 levels, suggesting the effect is mediated by ligand-bound VDR [39]. Insulin-like growth factor I (IGF-I), a key regulator of fetal growth, stimulates hydroxylation of 25OHD in a dose-dependent manner in cultured placental cells [40]. In the 3A human trophoblast cell line, unlike in macrophages, CYP27A1 expression is not increased by TLR2 binding ligand. 1,25(OH)2D inhibits expression of cytokines, such as granulocyte macrophage colony stimulating factor 2 (GMCSF-2), TNF-α, IL-6, and increases expression of CAMP in primary cultured human decidual cells and cytotrophoblasts [41]. Importantly, when the 3A trophoblast cell line was exposed to *E. coli*, vitamin D treatment resulted in a lower rate of infection and reduced cell death, likely because of the increased CAMP levels [40]. This finding suggests vitamin D supplementation may reduce infection during pregnancy.

Maternal effects of vitamin D

Vitamin D intake is essential for maternal health and prevention of adverse outcomes. Circulating 25OHD concentrations reflect vitamin D status, and the normal range is between ~32 ng/mL and ~80 ng/mL, with values below ~32 ng/mL defined as deficient [42]. Pregnancy does not exacerbate hypocalcaemia and secondary hyperparathyroidism in people with pre-existing vitamin D deficiency. However, vitamin D deficiency during pregnancy is associated with the nonclassical actions of this hormone, being linked with preeclampsia insulin resistance, and gestational diabetes mellitus. Notably, vitamin D deficiency during pregnancy is of epidemic proportions, present in ~20– 85% of women, depending on country of residence and other factors. Preeclampsia, as identified by new onset hypertension and proteinuria during pregnancy, is a serious disorder affecting 5–8% of pregnancies, and is alleviated only by delivery of the placenta. Preeclampsia rates are elevated during winter months, when sunlight-dependent 25OHD production is reduced [43], and vitamin D deficiency increases the risk of preeclampsia. Vitamin D supplementation reduces preeclampsia risk, compared to unsupplemented controls [44]. Preeclampsia is associated with low circulating levels of IGF-I and 1,25(OH)2D and, in vitro, IGF-1 increases 1,25(OH)2D production by primary human syncytiotrophoblasts from placentas from normal pregnancies but not from preeclamptic pregnancies . Furthermore, trophoblasts isolated from the placentas of preeclamptic women have only one-tenth the CYP27B1 enzyme activity of trophoblasts from uncomplicated pregnancies. Although the role of vitamin D in preeclampsia is unclear [45], one hypothesis is that low vitamin D levels impair the normal Th1 to Th2 cytokine balance, with higher Th1 cytokine expression adversely affecting the immunological tolerance of embryo implantation. Insulin resistance, glucose intolerance, and diabetes are correlated with deficits in vitamin D. 1,25(OH)2D regulates insulin secretion by pancreatic β-cells and thereby affects circulating glucose levels [22]. As expected, low concentration of 25OHD is a risk factor for glucose intolerance while higher serum concentrations of 25OHD correlate with improved insulin sensitivity. Vitamin D deficiency during early pregnancy significantly increases the risk for gestational diabetes in later pregnancy. Vitamin D may influence the course of infectious diseases during pregnancy. In limited studies, low vitamin D levels in HIV-positive pregnant women were correlated with increased mortality and mother-to-child HIV transmission and a polymorphism in the VDR gene is correlated with the frequency of HIV-to-AIDS progression. Low 25OHD levels are correlated with increased bacterial vaginosis in the first trimester and bacterial vaginosis is more prevalent in black women. Indeed, black women typically have lower serum 25OHD concentrations and have a six-fold higher chance of vitamin D deficiency, compared with white women [45]. Vitamin D effects on the immune system, cytokines, and antibacterial peptides likely regulate the bacterial flora.

Serum 25OHD levels are inversely related to primary cesarean section in nulliparous women, an unexpected and unexplained maternal outcome recently identified. The risk was four-fold higher in women with serum 25OHD level below 37.5 nM/L (15ng/mL) controlling for multiple confounding factors. VDR and 1,25(OH)2D normally increase

skeletal muscle function. Conversely, vitamin D deficiency results in proximal muscle weakness and lower extremity muscle function, perhaps contributing to the risk for cesarean section. Adequate maternal vitamin D levels are also important for fetal and child health. Inadequate vitamin D intake during pregnancy is associated with low infant birth weight in populations at risk for adverse outcomes. Maternal vitamin D deficiency also has been associated with craniotabes, a softening of skull bones that is one of the earliest signs of vitamin D deficiency, in a case study with neonatal seizures of a hypocalcemic infant and with impaired skeletal development in utero. Recent retrospective studies found a significant and previously undetected association of maternal vitamin D deficiency with rickets-associated infant heart failure and with acute lower respiratory tract infection, a serious complication often associated with sepsis without clinical signs of rickets. Interestingly, vitamin D deficiency during pregnancy is also associated with risks of health problems later in childhood, including improper bone development at 9 yrs of age, asthma, schizophrenia and type I diabetes.

Conclusion

In summary, there is consistent evidence supporting that vitamin D status is related to and is important to regulate some pathways related to type 2 diabetes developments. We have described the multiple effects of vitamin D in human health. The classical and nonclassical pathways of this hormone affect calcium metabolism, the immune system, cell proliferation and differentiation, infection, and cancer. The enzymes encoded by the CYP27B1 and CYP24A1 genes are local regulators of levels of 1,25(OH)2D, which binds the VDR to induce both the genomic and non-genomic responses. Importantly, vitamin D analogs offer new potentials for treatments of a variety of diseases and disorders. Furthermore, genetic polymorphisms studies are also important in order to identify groups that are more susceptible to vitamin D deficiency and to developing type 2 diabetes in the population. The investigation into the effects of vitamin D supplementation analogs will contribute to an improvement in human health generally and mothers and children specifically. Role of vitamin D supplementation is forwarding to be a boon for diabetic conditions.

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References

1. Sicree R, Shaw J, Zimmet P (2006) Prevalence and projections. In: Diabetes Atlas. 3rd ed. Brussels, Belgium: International Diabetes Federation, 16-104.
2. Tuorkey MJ, Abdul-Aziz KK (2010) Strategies for diabetes and pathways of vitamin D. Diabetes Metab Syn Clin Res Rev 4: 101-110.
3. Bodnar LM, Catov JM, Simhan HN, Holick MF, Powers RW, et al. (2011) Maternal vitamin D deficiency increases the risk of preeclampsia. J Clin Endocrinol Metab 92: 3517–22.
4. Yorifuji J, Yorifuji T, Tachibana K, Nagai S, Kawai M, et al. (2008) Craniotabes in normal newborns: the earliest sign of subclinical vitamin D deficiency. J Clin Endocrinol Metab 93: 1784–1788.
5. Metzger BE, Coustan DR (1998) Summary and recommendations of the Fourth International Workshop-Conference on Gestational Diabetes Mellitus. The Organizing Committee. Diabetes Care. 1998 Aug 21, 2: B161-167.
6. Hunt KJ, Schuller KL (2007) The increasing prevalence of diabetes in pregnancy. Obstet Gynecol Clin North Am. 34: 173-199.
7. Snijder MB, van Dam RM, Visser M, Deeg DJ, Dekker JM, et al. (2005). Adiposity in relation to vitamin D status and parathyroid hormone levels: a population-based study in older men and women. J Clin Endocrinol Metab 90: 4119-23.
8. Ford ES, Ajani UA, McGuire LC, Liu S (2005) Concentrations of serum vitamin D and the metabolic syndrome among U.S. adults. Diabetes Care: 28: 1228-1230.
9. Norman AW, Frankel JB, Heldt AM, Grodsky GM (2011) Vitamin D deficiency inhibits pancreatic insulin secretion. Science 109: 823- 825.
10. Forouhi NG, Luan J, Cooper A, Boucher BJ, Wareham NJ (2008) Baseline serum 25-hydroxy vitamin d is predictive of future glycemic status and insulin resistance: the Medical Research Council Ely Prospective Study 1990-2000. Diabetes 57: 2619-2625.
11. Bodnar LM, Catov JM, Roberts JM, Simhan HN (2007) Prepregnancy obesity predicts poor vitamin D status in mothers and their neonates. J Nutr 137: 2437-2442.
12. Mathieu C, Gysemans C (2006) Vitamin D and diabetes. Diabetol 22: 187-193.
13. Alvarez JA, Ashraf A (2010) Role of vitamin d in insulin secretion and insulin sensitivity for glucose homeostasis. Int J Endocrinol 2010: 351385.
14. Dawson-Hughes B, Heaney RP, Holick MF, Lips P, Meunier PJ, et al. (2012) Estimates of optimal vitamin D status .Osteoporos Int 16: 713-716.
15. Karnieli E, Armoni M (2009) Regulation of glucose transporters in diabetes. Horm Res 33: 99-104.
16. Calle C, Maestro B, Garcia-Arencibia M (2008) Genomic actions of 1,25-dihydroxyvitamin D3 on insulin receptor gene expression, insulin receptor number and insulin activity in the kidney, liver and adipose tissue of streptozotocin- induced diabetic rats. BMC Mol Biol 9: 65.
17. Peeyush KT, Savitha B, Sherin A, Anju TR, Jes P, Paulose CS (2010) Cholinergic, dopaminergic and insulin receptors gene expression in the cerebellum of streptozotocin-induced diabetic rats: functional regulation with Vitamin D3 supplementation. Pharmacol Biochem Behav 95: 216-222.
18. Moses RG, Mackay MT (2004) Gestational diabetes: Is there a relationship between leg length and glucose tolerance? Diabetes Care 27: 1033-1035.
19. Zhang C, Qiu C, Hu FB, David RM, van Dam RM, et al. (2008) Maternal plasma 25-hydroxyvitamin d concentrations and the risk for gestational diabetes mellitus. PLoS ONE 3: e3753.
20. Heaney RP, Davies KM, Chen TC, Holick MF, Barger-Lux MJ, et al. (2003) Human serum 25-hydroxycholecalciferol response to extended oral dosing with cholecalciferol. Am J Clin Nutr 77: 204-210.
21. Li W, Green TJ, Innis SM, Barr SI, Whiting SJ, et al. (2011) Suboptimal vitamin D levels in pregnant women despite supplement use. Can J Public Health 102: 308-312.
22. Widness JA, Teramo KA, Clemons GK, Voutilainen P, Stenman UH, et al. (2012). Direct relationship of antepartum glucose control and foetal erythropoietin in human type 1 diabetic pregnancy. Diabetologia 9: 75-79.
23. Shaat N, Karlsson E, Lernmark A, Ivarsson S, Lynch K, et al. (2013) Common variants in MODY genes increase the risk of gestational diabetes mellitus. Diabetologia 49: 1545-51.
24. Ben-Haroush A, Yogev Y, Hod M (2004) Epidemiology of gestational diabetes and its association with Type 2 diabetes. Diabet Med 21: 103-113.
25. Buchanan TA, Xiang A, Kjos SL, Watanabe R (2007) What is gestational diabetes? Diabetes Care 2: 105-111.
26. Noff D, Edelstein S (1987) Vitamin D and its hydroxylated metabolites in the rat. Placental and lacteal transport, subsequent metabolic pathways and tissue distribution. Horm Res 9: 292–300.
27. Johnson DD, Wagner CL, Hulsey TC, McNeil RB, Ebeling M, et al. (2011) Vitamin D deficiency and insufficiency is common during pregnancy. Am J Perinatol 28: 7-12.

28. Weisman Y, Harell A, Edelstein S, David M, Spirer Z, et al. (2009) 1 alpha, 25-Dihydroxyvitamin D3 and 24,25-dihydroxyvitamin D3 in vitro synthesis by human decidua and placenta. Nature 281: 317–319.

29. Teale GR, Cunningham CE (2010) Vitamin D deficiency is common among pregnant women in rural Victoria. Aust N Z J Obstet Gynaecol 50: 259-261.

30. Kooh SW, Vieth R (2008) 25-hydroxyvitamin D metabolism in the sheep fetus and lamb. Pediatric Res 14: 360-363.

31. Zehnder D, Evans KN, Kilby MD, Bulmer JN, Innes BA, et al. (2002) The ontogeny of 25- hydroxyvitamin D3 1alpha-hydroxylase expression in human placenta and decidua. Am J Pathol 161: 105–114.

32. Gregori S, Casorati M, Amuchastegui S, Smiroldo S, Davalli AM, et al. (2001) Regulatory T cells induced by 1 alpha,25-dihydroxyvitamin D3 and mycophenolate mofetil treatment mediate transplantation tolerance. J Immunol 167: 1945–1953.

33. Wallace AM, Gibson S, de la Hunty A, Lamberg-Allardt C, Ashwell M (2010) Measurement of 25-hydroxyvitamin D in the clinical laboratory: current procedures, performance characteristics and limitations. Steroids 75: 477-488.

34. Barrera D, Avila E, Hernández G, Méndez I, González L, et al. (2008) Calcitriol affects hCG gene transcription in cultured human syncytiotrophoblasts. Reprod Biol Endocrinol 6: 3.

35. Stephanou A, Ross R, Handwerger S (2012) Regulation of human placental lactogen expression by 1,25- dihydroxyvitamin D3. Endocrinology 135: 2651–2656.

36. Barrera D, Avila E, Hernández G, Halhali A, Biruete B, et al. (2007) Estradiol and progesterone synthesis in human placenta is stimulated by calcitriol. J Steroid Biochem Mol Biol 103: 529–532.

37. Bikle DD (1992) Clinical counterpoint: vitamin D: new actions, new analogs, new therapeutic potential. Endoc Rev 13: 765-784.

38. Rudnicki PM, Molsted-Pedersen L (2009) Effect of 1, 25 dihydroxycholecalciferol on glucose metabolism in gestational diabetes mellitus. Diabetologia 40: 40-44.

39. Zhang C, Qiu C, Hu FB, David RM, Van Dam RM, et al. (2008) Maternal plasma 25-hydroxyvitamin D concentrations and the risk for gestational diabetes mellitus. PLoS One 3: e3753.

40. Maghbooli Z, Hossein nezhad A, Karimi F, Shafaei AR, Larijani B (2008) Correlation between vitamin D3 deficiency and insulin resistance in pregnancy. Diabetes metab res rev 24: 27-32 .

41. Soheilykhah S, Mohammadi M, Mojibian M, Rahimi-Saghand S, Rashidi M, et al. (2009) Maternal serum adiponectin concentration in gestational diabetes. Gynecol Endocrinol 25: 593-596.

42. Farrant HJW, Krishnaveni GV, Hill JC, Boucher BJ, Fisher DJ, et al. (2008) Vitamin D insufficiency is common in Indian mothers but is not associated with gestational diabetes or variation in newborn size. Eur J clin nutr 63: 646-652.

43. Clifton Bligh RJ, McElduff P, McElduff A (2008) Maternal vitamin D deficiency, ethnicity and gestational diabetes. Diabet med 25: 678-684.

44. Maghbooli Z, Hossein-nezhad A, Rahmani M, Shafaei AR, Larijani B (2007) Relationship between leptin concentration and insulin resistance. Horm metab res 39: 903-907.

45. Chiu KC, Chu A, Go VLW, Saad MF (2004) Hypovitaminosis D is associated with insulin resistance and cell dysfunction. Am J Clin Nutr 79: 820.