Journal of Steroid Biochemistry and Molecular Biology 180 (2018) 51–64

Contents lists available at ScienceDirect

Journal of Steroid Biochemistry and Molecular Biology

journal homepage: www.elsevier.com/locate/jsbmb

Review

Impact of vitamin D on pregnancy-related disorders and on offspring outcome

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ARTICLE INFO

Keywords:
Vitamin D deficiency
Free vitamin D
Vitamin D binding protein
Epigenetics
DNA methylation
Single nucleotide polymorphism
Preeclampsia
Gestational diabetes mellitus
Small for gestational age
Long term health

ABSTRACT

Observational studies from all over the world continue to find high prevalence rates of vitamin D insufficiency and deficiency in many populations, including pregnant women. Beyond its classical function as a regulator of calcium and phosphate metabolism, vitamin D elicits numerous effects in the human body. Current evidence highlights a vital role of vitamin D in mammalian gestation. During pregnancy, adaptations in maternal vitamin D metabolism lead to a physiologic increase of vitamin D levels, mainly because of an increased renal production, although other potential sources like the placenta are being discussed. A sufficient supply of mother and child with calcium and vitamin D during pregnancy ensures a healthy bone development of the fetus, whereas lack of either of these nutrients can lead to the development of rickets in the child. Moreover, vitamin D insufficiency during pregnancy has consistently been associated with adverse maternal and neonatal pregnancy outcomes. In multitudinous studies, low maternal vitamin D status was associated with a higher risk for preeclampsia, gestational diabetes mellitus and other gestational diseases. Likewise, several negative consequences for the fetus have been reported, including fetal growth restriction, increased risk of preterm birth and a changed susceptibility for later-life diseases. However, study results are diverging and causality has not been proven so far. Meta-analyses on the relationship between maternal vitamin D status and pregnancy outcomes revealed a wide heterogeneity of studied populations and the applied methodology in vitamin D assessment. Until today, clinical guidelines for supplementation cannot be based on high-quality evidence and it is not clear if the required intake for pregnant women differs from non-pregnant women. Long-term safety data of vitamin D supplementation in pregnant women has not been established and overdosing of vitamin D might have unfavorable effects, especially in mothers and newborns with mutations of genes involved in vitamin D metabolism. Reliable data from large observational and interventional randomized control trials are urgently needed as a basis for any detailed and safe recommendations for supplementation in the general population and, most importantly, in pregnant women. This is of utmost importance, as ensuring a sufficient vitamin D-supply of mother and child implies a great potential for the prevention of birth complications and development of diseases.

1. Introduction

A high prevalence of vitamin D deficiency has become of growing concern for scientists and societies worldwide because of potential adverse effects on human health. Importantly, pregnant women and their children display high-risk groups for vitamin D deficiency and should therefore especially be in the focus of research.

This review summarizes background information on vitamin D deficiency in the general population and in pregnant women. At first, a general overview of vitamin D biochemistry and physiology is given.

Abbreviations: 1,25(OH)$_2$D, 1,25-dihydroxy vitamin D$_2$/1,25-dihydroxyvitaminD$_3$; 25OHD, 25-hydroxyvitamin D$_2$/25-hydroxyvitamin D$_3$; Calcitriol, 1,25-dihydroxyvitamin D$_3$; CYP, cytochrome P450 enzyme; CYP24A1, 25-hydroxy vitaminD-24-hydroxylase; CYP27B1, 1α-hydroxylase; FGF-23, fibroblast growth factor 23; LC–MS/MS, liquid chromatography coupled to tandem mass spectrometry; PTH, parathyroid hormone; RMP, Reference Measurement Procedures; RXR, retinoid x receptor; SGA, small for gestational age; SNP, single nucleotide polymorphisms; DBP, vitamin D-binding protein; VDR, vitamin D receptor

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https://doi.org/10.1016/j.jsbmb.2017.11.008
Received 30 August 2017; Received in revised form 15 November 2017; Accepted 20 November 2017
Available online 21 November 2017
0960-0760/

Biological steps of the formation of active vitamin D are explained and different metabolites and enzymes of the vitamin D family and their possible actions are presented. In the following, data from clinical studies on deficiency prevalence in different populations are summarized. The second part of the review concentrates on vitamin D and pregnancy. It points out what is known about the physiologic role of vitamin D during pregnancy so far, and what still has to be investigated in the future. This is followed by a summary of studies on the prevalence of vitamin D deficiency in pregnant women and studies on the association of maternal vitamin D status and pregnancy outcomes. Current data on possible adverse effects of vitamin D deficiency on maternal and fetal outcomes like preeclampsia, gestational diabetes, and birth weight and the respective dietary guidelines are discussed. Additionally, epigenetic and genetic factors which might influence maternal and neonatal vitamin D status and challenges for measuring vitamin D are mentioned and in a final conclusion, important open questions and areas for future research are addressed.

1.1. Biochemistry and physiology of vitamin D

Vitamin D is a general term for several related metabolites belonging to the vitamin D family. Because of diverse bioactive effects and a structural resemblance to steroid hormones, vitamin D is rather a hormone than a vitamin. It is a key nutrient which plays a major role in various metabolic processes in the human body, especially in calcium and phosphate homeostasis and bone metabolism [1]. Even though it is not a vitamin in the classical sense of the definition, specific amounts are required for many biological processes. Although vitamin D can be obtained from dietary intake, it is less available from food than other nutrients. Only a few foods are suitable sources, including fatty fish species, egg, beef and fish liver oils [1]. The major source in humans is the skin, where vitamin D is photochemically synthesized from a steroid precursor. Upon irradiation with ultraviolet light, pro-vitamin D_3 (7-dehydrocholesterol) turns into pre-vitamin D3 which then is converted to vitamin D3 (cholecalciferol). In plants, vitamin D2 (ergocalciferol) is synthesized in a comparable manner upon exposure to ultraviolet light out of the pro-vitamin D_2 (ergosterol) [2]. Humans can metabolize both vitaminD_2 and D_3 but vitamin D_2 is distinctively less potent than vitamin D_3 and de novo synthesis in the skin is only possible for vitamin D_3. VitaminD_3 leaves the skin through small capillaries and enters the circulation. In the blood, it binds with high affinity to the vitamin D-binding protein (DBP) and only a small fraction is carried by albumin and lipoprotein. When absorbed from the intestine and released into the blood stream, dietary vitamin D_3 also binds to DBP. Either form of the vitamin D bound to DBP is then transported to the liver where it undergoes a first hydroxylation to 25-hydroxyvitamin D_2 respective 25-hydroxyvitamin D_3 (25OHD). This metabolite is not particularly active, but it is the major circulating form of vitamin D. Notably, its concentration in the serum accounts as the most reliable marker to assess the vitamin D status [1]. The conversion to 25OHD by the 25-hydroxylases CYP27A1, CYP2R1 and other cytochrome P450 (CYP) enzymes is not highly regulated nor a rate limiting step [3]. The half-life of this relatively stable molecule is about two to three weeks [1,4]. In a next step, 25OHD bound to DBP is transported to the kidney where it binds to a cell surface receptor for DBP in the epithelial cells of the proximal tubule. Via the transmembrane protein megalin, the renal uptake for the concomitant hydroxylation of 25OHD in the cell is prepared [5]. This second hydroxylation is a crucial and highly controlled step in which the precursor 25OHD is turned into the functional, hormonally active forms 1,25-dihydroxy vitamin D_2 respective 1,25-dihydroxy vitamin D_3 ($1,25(OH)_2D$), also known as calcitriol. The responsible cytochrome P450 enzyme for the conversion is 1α-hydroxylase (CYP27B1). In the kidney, 1α-hydroxylase is regulated by a number of factors including parathyroid hormone (PTH), serum calcium, phosphate, and by $1,25(OH)_2D$ itself. The biological actions of $1,25(OH)_2D$ are mediated by its binding to the vitamin D receptor (VDR) followed by a conformational change of the receptor that allows an obligate heterodimerization with the retinoid x receptor (RXR). The VDR/RXR complex is then able to bind vitamin D responsive elements in the promoter region of hormone sensitive genes, thus regulating their transcription and the respective protein biosynthesis [6].

Serum levels of $1,25(OH)_2D$ are also controlled by a cytochrome P450 enzyme, the 25-hydroxyvitamin D-24- hydroxylase (CYP24A1). It is able to convert both, 25OHD and $1,25(OH)_2D$, into biologically inactive and water soluble metabolites, including 24,25-dihydroxyvitamin D and calcitroic acid [7]. $1,25(OH)_2D$ is crucial for the maintenance of physiological serum calcium and phosphate levels as well as for bone growth and bone remodeling. $1,25(OH)_2D$ increases the intestinal absorption of calcium and phosphorous and inhibits the secretion of parathyroid hormone. It facilitates renal tubular reabsorption of calcium and mobilizes calcium and phosphate from the bone [7]. Low $1,25(OH)_2D$ serum concentrations activate the parathyroid glands and a subsequent increase in PTH, in turn, stimulates renal 1α-hydroxylase activity in the kidney. Via an enhanced conversion of 25OHD to $1,25(OH)_2D$, serum calcium and phosphate levels are restored. Another important regulator of vitamin D metabolism is fibroblast growth factor 23 (FGF-23). In concert with the transmembrane protein Klotho, FGF-23 balances concentration of $1,25(OH)_2D$ via a negative feedback loop [8,9].

The VDR has been found to be expressed in a variety of tissues and CYP24A1 is present in all cells containing the VDR. Thus, organs like pancreas, breast, skin, lung, intestine, prostate and others are able to generate $1,25(OH)_2D$ in a tissue-specific, auto-, and paracrine manner [10]. This locally produced $1,25(OH)_2D$ apparently does not influence the concentration of circulatory $1,25(OH)_2D$ and it does not depend so much on other calcium homeostasis regulators like PTH and calcium levels. Available levels of the substrate 25OHD seem to be more important though. In fact, higher concentrations of 25OHD are required for sufficient local production of $1,25(OH)_2D$ in non-renal tissues compared to the requirements in the kidney [10,11]. Besides the classical impact on genes of mineral homeostasis, vitamin D allows a very selective control of genes involved in processes in skeletal muscle, skin, the cardiovascular system, glucose metabolism, and components of the immune system [7]. This multitude of biological processes influenced by the vitamin D metabolism underlines its important role in health and disease prevention. Fig. 1 gives an overview of the biologically relevant steps in the vitamin D metabolism.

1.2. Vitamin D deficiency – prevalence in the general population

It has long been known that sustained vitamin D deficiency in children is associated with the development of rickets in the developing bone [12]. In adults, vitamin D deficiency classically is known for its manifestation as osteomalacia [13], osteoporosis [14], and fractures [15]. Such impairments in bone metabolism can be prevented or at least mitigated by adequate vitamin D and calcium supplementation [16]. More recently, a considerable amount of literature has been published on the association of vitamin D insufficiency with different diseases. Inverse associations with low serum levels of 25OHD have been observed for cardiovascular disease [17], multiple scleroses [18], chronic infections, autoimmune diseases [19], different types of cancer [20], and diabetes [21] in various studies. A systematic review and meta-analysis of observational cohorts and randomized intervention studies from 2014 investigated vitamin D status and risk of death due to cardiovascular disease, cancer, and other causes. It revealed that most of the studies, while indeed showing an inverse association of circulating 25OHD with cause specific death, did not give evidence for causality. Moreover, the meta-analysis found that supplementation with vitamin D reduced all-cause mortality only in a subpopulation of older adults [22].

Despite conflicting study results, a putative link between different diseases and vitamin D status is of crucial interest because vitamin D