

NON CLASSICAL FUNCTION OF VITAMIN D – INFLUENCE ON REPRODUCTIVE HEALTH, PUBERTY AND FERTILITY



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INTRODUCTION

In the past few years a growing interest in vitamin D can be observed in the clinical trials and in biomedical literature, due to findings demonstrating a low vitamin D status in the population (Figure 1). The determination of optimal 25(OH)D₃ levels in women during the reproductive period of their life would have a significant public health implications.

Data tells us, that even in Ancient Egypt people knew about the healing effect of the sun, through idolization of their Sun God Amon-Rah, whose rays could make «a single man stronger than a crowd» [1]. In Ancient Greece Herodotus recommended solaria as a cure for «weak and flabby muscles», ancient Olympians were instructed to lie exposed and train under the sun's rays [2].

In the 1922 Mc Collum in the USA followed the sequential alphabetical designations and labeled the new substance «Vitamin D» [3]. For the chemical identification and chemical synthesis of vitamin D, earned A. Windaus the Noble Prize in 1928 [4]. Whereas Huldshinsky, Chick, Hume, Hess, and Weinstock discovered the curative effects of UV light [5].

to be fully active, 25(OH)D₃ must be further converted to 1,25-dihydroxyvitamin D₃ (1,25(OH)₂D₃) via CYP27B1, a mitochondrial enzyme. Additionally, 1,25(OH)₂D₃ negatively regulates its own levels by inducing CYP24, that catabolizes both 1,25(OH)₂D₃ and 25(OH)D₃. The mechanism of action of the active form of 1,25(OH)₂D₃ is similar to that of other steroid hormones and is mediated by its binding to vitamin D receptor (VDR) [5].

Nearly all nucleated cells express the VDR in variable concentrations [5]. The tissue and cell type localization of VDR has been confirmed by binding studies, mRNA in situ hybridization, autoradiography, and protein immunocytochemistry. VDR belongs to a class of nuclear transcription factors [5]. The few cells of tissues that have low or absent VDR expression include red blood cells, mature striated muscle, and some highly differentiated brain cells, such as Purkinje cells of the cerebellum [6]. The VDR is undetectable in nonchordate species and this led to the initial hypothesis that a functional vitamin D endocrine system originated during evolution to allow the accumulation of calcium to build a calcified skeleton [7]. VDR is a member of the superfamily of nuclear hormone receptors, including receptors for steroid and thyroid hormones and retinoic acid [8].

Although the proximal renal tubule is the major source of 1,25(OH)₂D₃ production for the body, the 1α-hydroxylase is also found in a number of extrarenal sites such as immune cells, epithelia of many tissues, bone and parathyroid glands, in which it functions to provide 1,25(OH)₂D₃ for local consumption as an intracrine or paracrine factor [8]. The mechanism of action of the active form of 1,25(OH)₂D₃ is mediated by its binding to VDR, and is similar to that of other steroid hormones. The nonclassic actions of vitamin D can be divided into three general functions: regulation of hormone secretion, regulation of immune function, and regulation of cell proliferation, differentiation and apoptosis.

Vitamin D and its metabolites are transported in the circulation bound to a plasma protein, DBP (vitamin D binding protein), which shares many structural and evolutionary similarities with albumin [5]. In DBP null mice, plasma concentrations of 25(OH)D₃ and 1,25(OH)₂D₃ are extremely low, and their metabolic clearance is markedly increased. DBP is filtered in the glomerulus of the nephron, but it is reabsorbed together with 25(OH)D₃ in the renal tubuli by the bulk car-

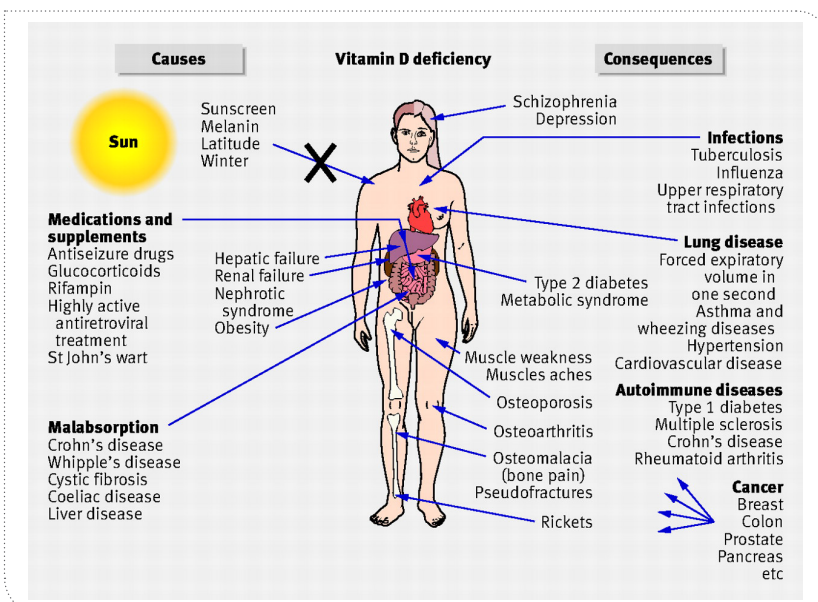


FIGURE 1. TAKE YOUR VITAMINS: HYPOVITAMINOSIS D IN THE DEVELOPING WORLD (Dylan Neel, 2012)

Vitamin D is synthesized in the skin under influence of UV-B light. This is a purely photochemical reaction, where no enzymes are involved. However, the reaction requires a sufficiently large concentration of 7-dehydrocholesterol and UV-B (290-315 nm) light [5]. To be biologically active, vitamin D must be converted to 25(OH)D₃. Lastly,

rier transporter megalin. Megalin-deficient mice cannot reabsorb DBP or 25(OH) D_3 in the nephron and, as a result, develop vitamin D-deficiency rickets [9].

PUBERTY AND FERTILITY

VDR and vitamin D metabolizing enzymes are found in reproductive tissues of women and men. This secosteroid hormone regulates the expression of a large number of genes in reproductive tissues implicating a role for vitamin D in female and male reproduction. VDR regulates gene transcription with different mechanisms, which include interaction with co-activator or co-repressor molecules. Vitamin D_3 has been well-known for its classical function, which is maintaining calcium and phosphorus homeostasis. Regulation of oocyte maturation, follicular development and embryo development are Ca^{2+} -dependent. Vitamin D and calcium repletion predict reproductive success following fertilization [10]. Human and animal data suggest that low vitamin D status in women is associated with impaired fertility, endometriosis, leiomyoma, polycystic ovary syndrome and delayed puberty (Figure 2). The fertility of vitamin D-deficient female rats was decreased by 75% [11]. A possible mechanism may be the direct stimulatory effect of 1,25(OH) $_2D_3$ on the aromatase gene expression in reproductive tissues of female and male mice [12]. Moreover, vitamin D might influence steroidogenesis of sex hormones estradiol and progesterone. VDR expression is dynamically regulated throughout the reproductive cycle, with peak levels observed during gestation and lactation [13, 14].

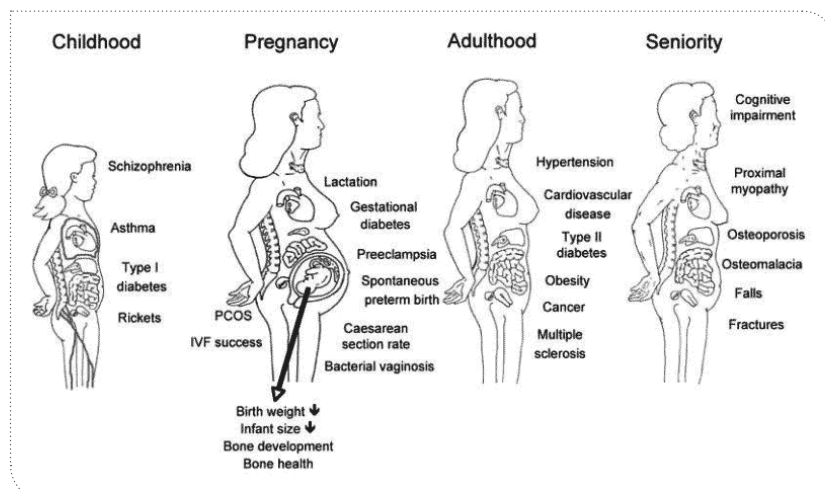
These data all indicate a direct effect of the VDR-vitamin D endocrine system on female and male reproduction.

Dicken et al. [15] have a hypothesis that peripubertal D_3 deficiency disrupts hypothalamo-pituitary-ovarian physiology. The last data suggest that vitamin D_3 is a key regulator of neuroendocrine and ovarian physiology. CYP27B1 and VDR $_2$ are found in the gonads, hypothalamus and pituitary, proposing that the reproductive axis may be regulated by paracrine and autocrine activities of 1,25(OH) $_2D_3$ [16, 17]. Some researches show that vitamin D_3 receptor expression peaks in the hypothalamus during the peripubertal period in rats, suggesting that central vitamin D_3 signaling may be important for pubertal transition [18]. These studies demonstrate that peripubertal vitamin D_3 deficiency delays puberty and causes prolonged estrous cycles, characterized by extended periods of diestrus and reduced frequency of proestrus and estrus in rat. Moreover, estrous cycles can be normalized in young adults by correcting the vitamin D_3 deficiency [15]. Summarizing

these data, we can say, that peripubertal vitamin D_3 deficiency delays pubertal transition by disrupting hypothalamic-pituitary axis physiology. The largest populations with vitamin D_3 deficiency are peripubertal children and reproduction-aged adult females [19, 20]. Puberty depends upon coordinated interactions among all components of the hypothalamic-pituitary-gonadal axis [21]. The onset of puberty is driven by nongonadal events characterized by dynamic changes in glial-neuron interactions [21] and trans-synaptic changes in afferent glutamatergic, kisspeptinergic and GABAergic input into gonadotropin-releasing hormone (GnRH) neurons [22]. In situ hybridization studies localize VDR, CYP27B1, and vitamin D binding protein in the hypothalamus [15]. The presence of VDR and CYP27B1 in the preoptic area of the hypothalamus raises the possibility that vitamin D_3 regulates the activity of GnRH neurons or other hypothalamic neurons important for reproduction [15].



Vitamin D is a hormone which controls nearly 1/3 of human genome and over 200 genes, including those responsible for cell cycle control: proliferation, differentiation, apoptosis



Vitamin D_3 regulates expression of L-type voltage-sensitive calcium channels and nerve growth factor release in the brain [23]. It is possible that vitamin D_3 deficiency disrupts L-type voltage-sensitive calcium channel expression systems, critical for peripubertal GnRH neuronal activation [24]. Some trials suggest that vitamin D_3 deficiency delays first estrus. All these data suggest, that the delayed puberty observed in vitamin D_3 deficient females may reflect primary neuroendocrine dysfunction rather than primary ovarian failure or primary ovarian resistance to gonadotropins [15]. Most ovarian follicles in ovaries of peripubertal vitamin D_3 -deficient females were arrested in the preantral stage. Dicken et al. [15] suggest that peripubertal vitamin D_3 deficiency disrupts hypothalamic-pituitary physiology, resulting in suboptimal exposure to endogenous gonadotropins, arrested follicular development, and estrous cycle irregularities. Therefore, vitamin D_3 deficiency impairs female reproduc-

FIGURE 2. VITAMIN D - ROLES IN WOMEN'S REPRODUCTIVE HEALTH (Grundmann M., Von Versen-Höyneck F., *Reprod. Biol. Endocrinol.*, 2011, 9: 146)

tive function by inducing hypothalamic dysfunction, which secondarily affects pituitary and ovarian physiology [15].

Evidence from observational studies shows higher rates of preeclampsia, preterm birth, bacterial vaginosis and gestational diabetes in women with low vitamin D levels. The regulation of VDR expression is one of the main mechanisms through which target cells respond to calcitriol. Different polymorphisms of this receptor can change the usual mode of functioning. Experimental studies have demonstrated, that the ovary is a target organ for $1,25(\text{OH})_2\text{D}_3$. This active metabolite of vitamin D_3 might play a role in modulating ovarian activity. The results of recent studies implied that VDR genetic variants may impact polycystic ovary syndrome (PCOS) and insulin resistance (IR) in women with PCOS. VDR may influence the acetylation of histones, as well as chromatin remodeling [25]. VDR gene contains 14 exons and is mapped on chromosome 12cen-q12. The function of the TaqI-specific hyper variable polymorphism is unclear. VDR gene variants have been associated to breast cancer risk, prostate cancer progression, colorectal cancer, diabetes, primary hyperparathyroidism, coronary artery disease and PCOS. The findings of Ranjazad et al. [26] demonstrate that there is a significant association between VDR TaqI CC genotype and serum concentrations of luteinizing hormone in women with PCOS. Their data suggest that the CC genotype of VDR TaqI in exon 9 (rs731236) is associated with PCOS. In PCOS women, low 25-hydroxyvitamin D ($25(\text{OH})\text{D}_3$) levels are associated with obesity, metabolic, and endocrine disturbances. Vitamin D_3 supplementation might improve menstrual frequency and metabolic disturbances in those women [27].

Endometrium during the menstrual cycle and early pregnancy is an extrarenal site of vitamin D_3 synthesis and action. In endometriosis patients, the gene encoding for 1α -hydroxylase shows an enhanced expression in ectopic endometrium [28]. Endometriosis risk may also be influenced by vitamin D_3 deficiency. Endometriosis is a disorder characterized by the presence of endometrial tissue outside the uterine cavity. Signs and symptoms vary in severity and include dysmenorrhea, dyspareunia, infertility, dysuria, and dyschezia [29]. Women with endometriosis exhibit changes in cell-mediated immunity, with altered T-helper cell, altered immune surveillance, with depressed cell-mediated immunity and heightened humoral immune response. Vitamin D_3 may influence the development of endometriosis through its immunomodulatory effects. Vitamin D_3 may influence endometriosis through suppression of proinflammatory processes. In vitro studies have demonstrated that $1,25(\text{OH})_2\text{D}_3$ inhibits proliferation of T helper 1 cells [29] and production of interleukin-2 (IL-2) and interferon γ [30] and stimulates development of T helper 2 cells [28].

$1,25(\text{OH})_2\text{D}_3$ is an antitumor agent, that may be a potential nonsurgical therapeutic option for the treatment of uterine leiomyomas [31]. Uterine leiomyomas are the most common benign tumors in women of reproductive age. Treatment with $1,25(\text{OH})_2\text{D}_3$ significantly reduced leiomyoma tumor size in Eker rats. It also reduced leiomyoma size by suppressing cell growth and proliferation-related genes (Pcna, cyclin D1 [Cnd1], Myc, Cdk1, Cdk2, and Cdk4), antiapoptotic genes (Bcl2 and Bcl2l1[Bcl-x]), estrogen and progesterone receptors [31]. $1,25(\text{OH})_2\text{D}_3$ inhibites the

proliferation of human uterine leiomyoma cells by inhibiting catechol-O-methyltransferase, an estrogen-metabolizing enzyme that is overexpressed in human uterine leiomyomas [32]. Halder SK et al [32] demonstrated, that $1,25(\text{OH})_2\text{D}_3$ reduced TGF β 3-induced fibrosis-related gene expressions in leiomyoma cells. Ding L. et al. [33] in their trial observed that $1,25(\text{OH})_2\text{D}_3$ treatment reduced protein expression of collagen type 1 and fibronectin in Eker rat leiomyoma tumors. Summarizing it, may be concerned that $1,25(\text{OH})_2\text{D}_3$ -including therapy is an alternative and nonsurgical treatment option for uterine leiomyoma.

IMMUNOLOGY

The VDR is expressed in most cells of the immune system, including activated CD^{4+} and CD^{8+} T lymphocytes, as well as in antigen-presenting cells (APCs) such as macrophages and dendritic cells (DCs) [34, 35].

1α -hydroxylase or CYP27B1 is also expressed in macrophages, DCs, and even T and B lymphocytes. The 1α -hydroxylase present in immune cells is identical to the renal enzyme, but regulation of its expression and activity is different. Whereas the renal enzyme is under control of calcemic and bone signals, such as PTH and

$1,25(\text{OH})_2\text{D}_3$ itself, but the macrophage enzyme is primarily regulated by immune signals, with interferon gamma (INF- γ) and Toll-like receptor [36]. This explains the massive local production of $1,25(\text{OH})_2\text{D}_3$ by disease-associated macrophages that is seen in patients with granulomatous diseases (sarcoidosis and tuberculosis), and the consequent possible spillover in the general circulation, eventually leading to systemic hypercalcemia [5]. In the last two decades there were made important discoveries: the presence of VDRs in activated human inflammatory cells, the ability of $1,25(\text{OH})_2\text{D}_3$ to inhibit T cell proliferation and the ability of disease activated macrophages to produce $1,25(\text{OH})_2\text{D}_3$. Vitamin D_3 and CYP27B1 play important roles in both innate and adaptive immunity. Vitamin D_3 deficiency is a well-known accompaniment of various infectious diseases such as tuberculosis [37]. $1,25(\text{OH})_2\text{D}_3$ has long been recognized to potentiate the killing of mycobacteria by monocytes. The monocytes, when activated by mycobacterial lipoproteins, express CYP27B1, producing $1,25(\text{OH})_2\text{D}_3$ from circulating $25(\text{OH})\text{D}_3$ and in turn inducing cathelicidin, and antimicrobial peptide that enhances killing of mycobacterium [38]. Vitamin D_3 exerts an inhibitory action on the adaptive immune system. In particular, $1,25(\text{OH})_2\text{D}_3$ suppress proliferation and immunoglobulin production and retards the differentiation of B cell precursors into plasma cells [39]. $1,25(\text{OH})_2\text{D}_3$ inhibits T cell proliferation, T-helper (Th-1) cells capable of producing INF- γ and IL-2 and activating macrophages [39]. In the mid-1800s cod liver oil was used to treat tuberculosis. In the early 1900s heliotherapy was promoted for treating both skin and pulmonary tuberculosis. It was also recognized that young children with rickets had a much higher risk of developing pneumonia and upper respiratory tract infections. Bouillon et al [5] summarized, that $1,25(\text{OH})_2\text{D}_3$ downregulates proinflammatory cytokines and interleukins such as IL-2, IL-4, IL-8, IL-12, tumor necrosis factor α (TNF- α), and INF- γ and upregulates anti-inflammatory interleukins such as IL-10.

Vitamin D signalling pathways in cancer are shown at Figure 3.

DIABETES

Since the early observations in 1980 by Norman et al. [40] showed that pancreatic insulin secretion is inhibited by vitamin D deficiency. Several reports have demonstrated an active role for vitamin D in regulating the function of the endocrine pancreas, especially the insulin-producing beta cells [5]. VDR and calbindin-D 28k are found in pancreatic beta cells, and studies using calbindin-D28k null mice have suggested that calbindin-D28k by regulating intracellular calcium, can modulate depolarization-stimulated insulin release [41]. Calbindin-D28k by buffering calcium, can protect against cytokine mediated destruction of beta-cells [42, 43].

BRAIN

VDR and key enzymes of vitamin D metabolism are expressed in nearly all regions of the rodent brain [44]. The human equivalent of vitamin D effects on early brain development has not been fully explored. The brain not only has a VDR but also a 1α -hydroxylase. $1,25(\text{OH})_2\text{D}_3$ could also act by increasing serotonin levels in the brain. Low levels of 25-OHD in pregnant mothers has been associated with increased risk of schizophrenia of their children [45]. Low vitamin D status is also frequently observed in patients with Alzheimer's disease and schizophrenia and in elderly subjects with cognitive dysfunction [46]. Furthermore $1,25(\text{OH})_2\text{D}_3$ has also been demonstrated to stimulate amyloid- β phagocytosis and clearance by macrophages in Alzheimer patients.

Autism spectrum disorder (ASD) is a complex neurodevelopmental disorder, with multiple genetic and environmental risk factors. Vitamin D deficiency has recently been proposed as a possible environmental risk factor for ASD. Vitamin D has a unique role in brain homeostasis, embryogenesis and neurodevelopment, immunological modulation (including the brain's immune system). Children with ASD had significantly lower serum levels of 25-hydroxy vitamin D than healthy children. Therefore vitamin D deficiency during pregnancy and early childhood may be an environmental trigger for ASD [47, 48].

VITAMIN D AND AGING

Vitamin D plays an important role in the modulation of leucocyte telomere length (LTL), which is a predictor of aging-related disease and decreases with each cell cycle and increased inflammation [49]. The liganded complex $1,25\text{D-VDR-RXR}$ (RXR-retinoid X receptor) binds to vitamin D response elements (VDRE) in the DNA. This complex is involved in regulation of cellular functions, including DNA repair. Vitamin D acts as an inhibitor of the inflammatory response through several pathways. Subsets of leukocytes have receptors for the active form of vitamin D that support the direct effect of vitamin D on these cells, which

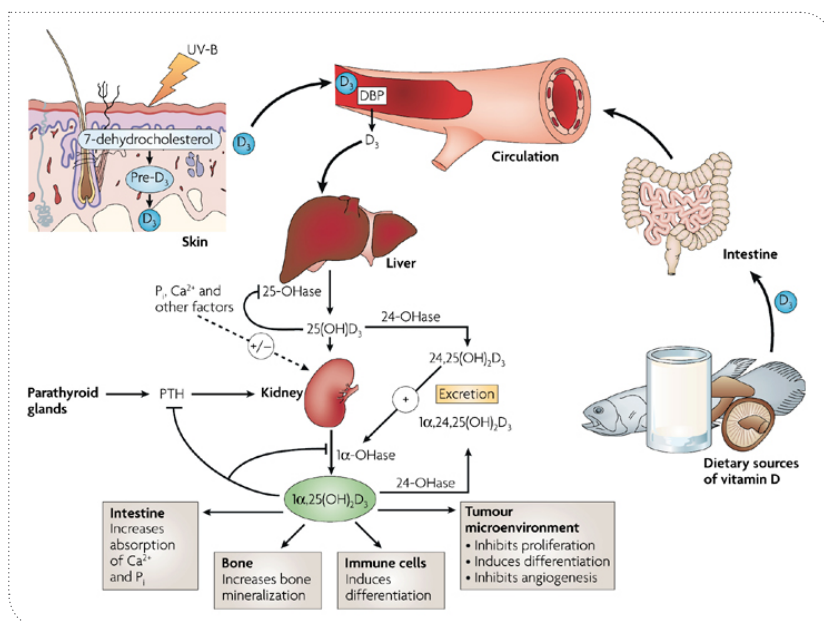


FIGURE 3. VITAMIN D SIGNALING PATHWAYS IN CANCER: POTENTIAL FOR ANTICANCER THERAPEUTICS

(Kristin K. Deeb et al., Nature Reviews Cancer, 2007, 7: 684-700)

explains the connections between vitamin D and autoimmune disease. Furthermore, an inverse relation has been shown between vitamin D concentrations and C-reactive protein (CRP), a marker of inflammation. LTL is relatively short in persons with chronic inflammation, because the inflammatory response entails an increase in leukocyte turnover. Vascular diseases, autoimmune diseases such as lupus and arthritis have been associated with shorter LTL. In the large population of women in the present study, higher serum 25OHD concentrations were associated with longer LTL. Inflammation and oxidative stress are key determinants in the biology of aging [49, 50]. Vitamin D decreases the mediators of systemic inflammation, such as IL-2 and TNF- α . Vitamin D receptors are ubiquitously expressed in T and B lymphocytes, natural killers, monocytes [50].

SUMMARY

Summarizing all these data we can say, that vitamin D has an important public health implications. Vitamin D₃ deficiency is a huge problem for women and men reproduction and fertility. Children, who are vitamin D-deficient are more likely to have delayed puberty, which leads to future reproduction troubles.

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NON CLASSICAL FUNCTION OF VITAMIN D – INFLUENCE ON REPRODUCTIVE HEALTH, PUBERTY AND FERTILITY

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In the past few years, there has been growing appreciation for the many roles of vitamin D and its active metabolites in a large number of tissues. Most tissues in the body, not just those participating in the classic action of vitamin D such as bone, kidney and gut, have receptors (VDR) for the active form of vitamin D – 1,25 dihydroxyvitamin D. The recent data on vitamin D from retrospective, prospective observational studies, case-control and experimental studies confirm the essential role of vitamin D in a variety of physiological functions. Last time there has been growing interest in this substance observed in the scientific researches and biomedical literature, due to findings which demonstrate a vitamin D deficiency status in the population.

This review is an analysis of the association between the vitamin D and the female and male reproduction and fertility. We highlight the latest findings from medical trials on vitamin D during last years. The aim of this article is to understand how vitamin D affects the female and male fertility.

Vitamin D is a hormone which controls nearly 1/3 of human and mice genome, over 200 genes in a human body, including those responsible for cell cycle control: proliferation, differentiation, apoptosis. Apart from basic functions, which are maintaining calcium-phosphoric balance, vitamin D takes active part in process of cell proliferation, epidermal keratinocyte differentiation, immune system stimulation, insulin secretion, brain metabolism, adipocytes function, puberty, reproduction and fertility. The vitamin D receptors (VDR) and vitamin D metabolizing enzymes are found in reproductive tissues of women and men. VDR knockout mice have significant gonadal insufficiency, decreased sperm count and motility, and histological abnormalities of testis, ovary and uterus. Assuming that 30 ng/ml (75 nmol/l) is a lower limit of normal concentration of 25(OH)D₃ in serum, the number of people with vitamin D deficit equals about 1 billion worldwide.

Key words: vitamin D, fertility, puberty, vitamin D receptors, reproductive health.

НЕКЛАСИЧНА ФУНКЦІЯ ВІТАМІНУ D – ВПЛИВ НА РЕПРОДУКТИВНЕ ЗДОРОВ'Я, ПУБЕРТАТ ТА ФЕРТИЛЬНІСТЬ

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За останні кілька років дедалі частіше зустрічаються наукові підтвердження впливу вітаміну D та його активних метаболітів на фізіологію різних органів. Доведено, що більшість тканин організму мають відповідні рецептори (VDR) для активної форми вітаміну D – 1,25 дигідроксिवітаміну D, і не тільки ті, що беруть участь в класичній дії вітаміну D (кістки, нирки і кишківник). Дані ретроспективних, проспективних, випадок-контроль та експериментальних досліджень підтверджують важливу роль вітаміну D в різних фізіологічних функціях. Протягом останнього часу спостерігається зростаючий інтерес до даної субстанції у наукових дослідженнях та біомедичній літературі у зв'язку з висновками, які демонструють статус дефіциту вітаміну D в популяції.

Метою даної статті є аналіз зв'язку вітаміну D з фертильністю та репродуктивною функцією в організмі як жінок, так і чоловіків, з періоду пубертату до зрілого репродуктивного віку. Даний науковий огляд демонструє останні новини медичних досліджень, які підтверджують це.

Вітамін D є гормоном, який контролює 1/3 геному людини та миші, понад 200 генів в організмі людини, в тому числі ті, що відповідають за контроль клітинного циклу: проліферацію, диференціювання, апоптоз. Крім основних функцій, таких як підтримка кальційфосфорного балансу, вітамін D бере активну участь у процесі диференціювання кератиноцитів епідермісу, стимуляції імунної системи, секреції інсуліну, метаболізму головного мозку, функції адипоцитів і фертильності. Рецептори для вітаміну D (VDR) і ферменти, що беруть участь в його метаболізмі, знаходяться в тканинах репродуктивних органів обох статей. VDR-нокаутні миші мають значну гонадну недостатність, зниження кількості сперматозоїдів та їх рухливості, гістологічні аномалії яєчка, яєчників та матки. Якщо припустити, що 30 нг/мл (75 нмоль/л) – нижня межа нормальної концентрації 25(OH)D₃ в сироватці крові, кількість людей з дефіцитом вітаміну D становить майже 1 млрд у всьому світі.

Ключові слова: вітамін D, фертильність, пубертат, рецептор для вітаміну D, репродуктивне здоров'я.