Vitamin D: a Review of its Effects on Epigenetics and Gene Regulation

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Abstract
Vitamin D is a secosteroid hormone with known beneficial effects on several body systems other than the musculoskeletal system. Both 25 dihydroxy vitamin D [25(OH)2D] and its active hormonal form, 1,25-dihydroxyvitamin D [1,25(OH)2D] are essential for human physiological functions, including damping down inflammation and the excessive intracellular oxidative stresses. In the present study we set out to review all available literature on vitamin D and the role it plays in epigenetics and gene regulation. We searched the PubMed/Medline electronic database for studies published in the English language up to January 2020. The Medical Subject Headings (MeSH) database was searched with the keywords ‘vitamin D’, ‘DNA methylation’, ‘nutritional supplements’, ‘epigenome’ and ‘pregnancy’. Observational studies, supplementation studies, and meta-analyses dealing with the effect of vitamin D on epigenetics and gene regulation were included in the review. The obtained information from the databases such as PubMed, Google Scholar, and ResearchGate was analysed and summarized.

We found that hypovitaminosis D increases the incidence and severity of several age-related common diseases such as the oxidative stress-associated metabolic disorders. These include obesity, insulin resistance, type 2 diabetes, hypertension, pregnancy complications, memory disorders, osteoporosis, autoimmune diseases, certain cancers, and systemic inflammatory diseases. New understandings of vitamin D-related advances in metabolomics, transcriptomics, epigenetics, in relation to its ability to control oxidative stress in conjunction with micronutrients, vitamins, and antioxidants, following normalization of serum 25(OH)D and tissue 1,25(OH)2D concentrations, are likely to promise better cost-effective clinical outcomes in humans.

There is a strong reciprocity between the vitamin D system and epigenetic mechanisms. The vitamin D system is, on the one hand regulated by epigenetic mechanisms and, on the other hand, is involved in regulating epigenetic events.

Keywords
DNA methylation, epigenome, nutritional supplements, pregnancy, vitamin D

INTRODUCTION
Vitamin D is a critical nutrient that is, apart from some limited supply from diet and supplement use, mainly obtained from the biosynthesis within the human body in response to the exposure of solar ultraviolet B radiation. Vitamin D is a micronutrient that is metabolized into a multifunctional secosteroid hormone that is essential for human health. Globally, its deficiency is a major public health problem affecting all ages and ethnic groups; it has surpassed iron deficiency as the most common nutritional deficiency in the world.

Vitamin D metabolism and functions are modulated by many factors. Accumulating evidence supports biological
associations of vitamin D with disease risk reduction and improved physical and mental functions.

Epigenetic mechanisms play a crucial role in regulating gene expression. The main mechanisms involve methylation of DNA and covalent modifications of histones by methylation, acetylation, phosphorylation, or ubiquitination. The complex interplay of different epigenetic mechanisms is mediated by enzymes acting in the nucleus. Modifications in DNA methylation are performed mainly by DNA methyltransferases (DNMTs) and ten-eleven translocases (TETs), while a plethora of enzymes, such as histone acetyltransferases (HATs), histone deacetylases (HDACs), histone methyltransferases (HMTs), and histone demethylases (HDMs) regulate covalent histone modifications. In many diseases, such as cancer, the epigenetic regulatory system is often disturbed.

The field is rapidly advancing, including the knowledge of the physiology of vitamin D receptor (VDR) interactions and the biology and metabolism of vitamin D and their effects on vitamin D axis and gene polymorphisms. Vitamin D receptor is a member of the steroid nuclear receptor superfamily. The effect of liganded VDR depends on the epigenetic landscape of the target gene.

Genome wide analysis in the human leukemia cell line THP-1 showed that VDR binds mainly at loci of open chromatin. Upon treatment with the VDR ligand 1,25-dihydroxyvitamin D3 (1,25-D3), chromatin accessibility further increases in more than 30% of these loci. The mechanism of action of the liganded VDR is dependent on binding and action of histone acetyltransferases and histone methyltransferases. It has been shown that co-treatment of cells with 1,25-D3, and histone deacetylase or DNA methyltransferase inhibitors often have synergistic effects.

Hypovitaminosis D increases the incidence and severity of several age-related common diseases such as metabolic disorders that are linked to oxidative stress. These include obesity, insulin resistance, type 2 diabetes, hypertension, pregnancy complications, memory disorders, osteoporosis, autoimmun diseases, certain cancers, and systemic inflammatory diseases.

Vitamin D deficiency during pregnancy has been associated with some adverse neonatal outcomes as well as an increased risk of late pregnancy complications.

**Vitamin D and gene regulation**

The effect of nutrition on the methylation equilibrium of the genome is already accepted as one of the mechanisms preventing either promoter hyper- or global hypomethylation. Several nutrients are renowned for their impact on DNA methylation, such as folic acid, vitamin B, green tea, and alcohol. The effect of vitamin D is currently under debate.

Primary epigenetic effects of vitamin D are linked to histone modifications, mainly acetylation. The VDR/RXR dimer interacts with HATs to induce transcriptional activation. Several studies have suggested that vitamin D may affect also DNA methylation. A recent study associated severe vitamin D deficiency with methylation changes in leukocyte DNA, although the observed differences were relatively small. This study suggested that subjects with vitamin D deficiency were more likely to show reduced synthesis and increased catabolism of active vitamin D. Whether this was the cause of the vitamin D deficiency or the consequence thereof is not clear and needs further studies.

The vitamin D system has pleiotropic functions and regulates approximately 3% of the human genome. To maintain balance, a strict regulation of the vitamin D system genes is of utmost importance. The main role of liganded VDR in tissues not involved in calcium homeostasis is to control expression of genes that regulate cell proliferation, differentiation, and apoptosis. One major limitation in the therapeutic exploitation of these effects is the resistance of cancer cells to 1,25-D3. Epigenetic corruption of VDR signalling is suggested to be one of the mechanisms that leads to reduced responsiveness to 1,25-D3 actions. This can be caused by promoter methylation of key vitamin D system genes or by skewed accumulation of VDR-associated co-repressors, preferentially at promoters of anti-proliferative target genes.

Expression of the vitamin D degrading and metabolizing enzymes is regulated through binding of 1,25-D3-ligated VDR to vitamin D responsive elements (VDRs). However, the major regulators of 1,25-D3, levels and signalling CYP2R1, CYP24A1, CYP27B1, and VDR, “the vitamin D tool” genes, are prone to epigenetic regulation. CpG islands span the promoters of CYP2R1, CYP24A1, and VDR, while a CpG island is located within the CYP27B1 gene locus.

Epigenetic mechanisms influence cancer genesis, growth, dissemination, and aging phenomena. For example, the epigenetic modifications of VDR–1,25(OH)2D effects can be mediated through complex processes involving CYP27A1 and CYP27B1 and via the vitamin D-catabolizing enzyme CYP24. These actions can be favourably influenced by modifications of VDREs across the genome modulated by both histone acetylases and deacetylases. Epigenetic regulation of vitamin D metabolism influences several physiological mechanisms and modulate outcomes of some human diseases. Example of diseases include adenocarcinoma of the lung, specific gene mutations in Asians with advanced non-small cell lung cancer, and genetic alterations in the effectiveness of systemic therapy for lung cancer induced by cigarette smoking. In severely obese children, low 25(OH)D concentrations are associated with increased markers of oxidative and nitrosative stress, inflammation, and endothelial over-activation. CYP27B1-mediated target tissue production of 1,25(OH) D is critically important for the paracrine and autocrine functions of calcitriol to obtain the full biological potential of vitamin D. Taken together, the benefits of having adequate serum 25(OH)D concentrations and maintaining vitamin D repletion in the long run and considering the overall health benefits of vitamin D, there is an urgent need.
to create national policies to combat hypovitaminosis D. The savings derived from reducing the risks and severity of infectious and parasitic diseases alone would pay off the cost of this public health approach. This can be achieved through targeting to raise the population serum 25(OH)D concentration, leading to a tangible positive impact on humans and on the economy.

Molecular and genetic studies confirm that vitamin D also modulates risks of several other human diseases, including autoimmune disorders such as multiple sclerosis. Although the predominant cause of cancer is modulation of the underlying metabolic abnormalities through genes, such as p53 and c-myc modifying the metastatic risks, the responsiveness to therapy is in part determined by epigenetic modifications of genes. Tumor-related key metabolic abnormalities include imbalance between glucose fermentation and oxidative phosphorylation (under aerobic and anaerobic conditions – the Warburg effect); dysregulation of metabolic enzymes, such as pyruvate kinase, fumarate hydratase, and succinate dehydrogenase; isocitrate dehydrogenase mutations; and alterations of gene expression levels linked to tumorigenesis that are influenced by the vitamin D status. Examples related to activity of the vitamin D axis include epigenetic changes that affect the expression of the CYP24A1 gene and VDR polymorphisms. Although epigenetic enhancement can occur through methylation and repression by histone-modifications of DNA, vitamin D markedly influences the regulation of cell replication. This substantiates targeting of CYP24A1 to optimize the expression of the CYP24A1 gene and VDR polymorphisms. Although epigenetic enhancement can occur through methylation and repression by histone-modifications of DNA, vitamin D markedly influences the regulation of cell replication. In addition, gene activation following the interaction of 1,25(OH)2D with VDR is important for mitochondrial integrity and respiration, and many other physiological activities. Moreover, the vitamin D signalling pathway plays a central role in protecting cells from elevated mitochondrial respiration and associated damage and overproduction of reactive oxygen species (ROS), which can lead to cellular and DNA damage.

**Immunomodulatory effects on vitamin D**

The effects of vitamin D on the production and action of several cytokines has been extensively investigated in recent years. In this connection, deficiency of vitamin D has been associated with several autoimmune diseases, including rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), antiphospholipid syndrome (APS), Hashimoto thyroiditis (HT), and multiple sclerosis (MS). Research has shown that autoimmune diseases have a significant prevalence within the female population, and women with autoimmune disorders are at a higher risk for adverse pregnancy outcomes. Provocatively, dysregulation of T cells plays a crucial role in the pathogenesis of autoimmunity, and adverse pregnancy outcomes where these pathologies are also associated with vitamin D deficiency.

The expression of vitamin D receptor in immune cells has highlighted an interesting role of vitamin D in immunity. Today a compelling body of experimental evidence indicates that vitamin D plays a fundamental role in regulating both innate and adaptive immune systems. Vitamin D displays a local immune effect via intracellular vitamin D receptors, that are known to be present in monocytes/macrophages, T cells, B cells, natural killer cells, and dendritic cells. After binding to its receptor VDR (a member of nuclear receptor superfamily), vitamin D forms a heterodimer with retinoid X receptor (RXR). This complex engages vitamin D Response Element and recruits activators and enzymes with histone acetylation activity. Therefore, the structural changes in chromatin induced by this complex result in the regulation of targeted gene.

**Vitamin D and autoimmunity**

Autoimmune diseases are characterized by self-tissue destruction via the adaptive immune responses which evade immune regulation. Vitamin D regulates the differentiation and activity of CD4+ T cells, resulting in a more balanced Th1/Th2 response that limits development of self-reactive T cells preventing inflammation and autoimmunity.

Vitamin D modulates adaptive immune cell functions explaining the significant association between vitamin D deficiency and autoimmune diseases, such as rheumatoid arthritis, systemic lupus erythematosus, antiphospholipid syndrome, Hashimoto's thyroiditis, and multiple sclerosis.

**The role of vitamin D in pregnancy**

The concentration of 25(OH)D is relatively constant throughout pregnancy. The mother is the only source of vitamin D for the foetus. Vitamin D concentrations in the umbilical cord are usually 60%–89% of the values in the mother's blood. The active form of vitamin D does not cross the placenta. However, its concentrations in the mother's blood are doubled in pregnancy, probably because of its production in foetal tissues and placenta. The concentration of 1,25(OH)2D is determined by the activity of the enzymes 1α-hydroxylase and 24-hydroxylase. 1α-hydroxylase is a product of the gene CYP27B1 which is expressed in the kidneys, decidua and placenta during pregnancy. On the other hand, 24-hydroxylase is an enzyme responsible for the production of less potent vitamin D metabolites and is a product of the gene CYP24A1. The rise in the concentration of 1,25(OH)2D during pregnancy could be due to the methylation of catabolic gene CYP24A1. As shown by Novakovic et al., the methylation of CYP24A1 gene promoter could cause the decreased activity of this gene and consequently the decreased activity of 24-hydroxylase. The increased concentration of 1,25(OH)2D could also be caused by increased concentrations of calcitonin during pregnan-
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Cy. Calcitonin increases the activity of 1α-hydroxylase and thus the production of 1,25(OH)2D irrespective of serum calcium concentration. Consequently, the intestinal calcium absorption increases. Despite a 100% increase in 1,25(OH)2D concentration the serum calcium concentration in the mother remains constant. Another important change during pregnancy is a rise in the concentration of vitamin D-binding-protein. The circulating form of vitamin D is bound to vitamin D-binding-protein which is filtered in the glomeruli of the kidneys and then reabsorbed in the proximal tubules. Vitamin D-binding-protein could have a role in the function and metabolism of vitamin D during pregnancy. It has a higher affinity to 25(OH)D than to 1,25(OH)2D and thus plays an important role in maintaining 25(OH)D as it promotes the reabsorption of 25(OH)D from the glomerular filtrate. The compound 1,25(OH)2D as the active form of vitamin D has non-genomic and genomic effects through its action on vitamin D receptor. The non-genomic effects occur quickly and include the activation of ion channels with the change of electrical state of the cell and protein kinase activation. On the other hand, the genomic effects which include the modulation of gene expression take more time. The abnormalities of the action of vitamin D receptor could manifest in signs and symptoms of vitamin D deficiency. During pregnancy, this may present as gestational diabetes, pre-eclampsia, preterm birth or miscarriage in early stages of pregnancy.

Several studies underscore the role of vitamin D in conception, placentation, progression of pregnancy and pregnancy outcomes including the offspring’s health. Vitamin D deficiency is common in women of reproductive age. A recent cohort study performed in Norway pregnant women from different ethnic groups showed hypovitaminosis D. Circulating vitamin D levels (<25 nmol/L) were found during pregnancy in women from South Asia (45%), Middle East (40%) and Sub-Saharan Africa (26%). Hypovitaminosis D is a risk factor for infertility and several adverse pregnancy outcomes. Furthermore, pre-pregnancy vitamin D levels higher than 75 nmol/L were associated with increased likelihood of pregnancy, reduced pregnancy loss and increased number of live births.

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CONCLUSIONS

The aim of this review was to present the findings of different kinds of studies on vitamin D and role on epigenetics and gene regulation. There is a strong reciprocity between the vitamin D system and epigenetic mechanisms. The vitamin D system is, on the one hand regulated by epigenetic mechanisms and, on the other hand, is involved in regulating epigenetic events. Vitamin D deficiency during pregnancy has been associated with some adverse neonatal outcomes as well as an increased risk of late pregnancy complications. The impact of vitamin D in the maintenance of the normal epigenetic landscape underlines the central role of this hormone in physiology.
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Витамин D: обзор его влияния на эпигенетику и регуляцию генов

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Резюме

Витамин D является секостероидным гормоном с некоторыми полезными эффектами на нескольких систем организма, кроме костно-мышечной системы. И 25 дигидроксивитамин D [25 (OH)2D], и его активная гормональная форма – 1,25 дигидроксивитамин D [1,25 (OH)2D] необходимы для физиологических функций человека, включая подавление воспаления и чрезмерный внутриклеточный окислительный стресс. В настоящем исследовании мы стремились изучить всю доступную литературу о витамине D и его роли в эпигенетике и регуляции генов. Мы провели поиск в электронной базе данных PubMed / Medline на предмет исследований, опубликованных на английском языке до января 2020 года. База данных MeSH была проанализирована с использованием ключевых слов «витамин D», «метилирование ДНК», «пищевые добавки», «эпигеном» и «беременность». Обзор включал обзорные исследования, исследования с добавками и метаанализы, посвящённые влиянию витамина D на эпигенетику и регуляцию генов. Информация, полученная из баз данных PubMed, Google Scholar и ResearchGate, была проанализирована и обобщена.

Мы обнаружили, что гиповитаминоз витамина D увеличивает частоту и тяжесть ряда распространённых возрастных заболеваний, таких как метаболические нарушения, связанные с окислительным стрессом. К ним относятся ожирение, инсулинорезистентность, диабет 2 типа, гипертония, осложнения беременности, нарушение памяти, остеопороз, аутоиммунные заболевания, некоторые виды рака и системные воспалительные заболевания. Достижения в новом понимании витамина D в метаболомике, транскриптомике, эпигенетике в отношении его способности контролировать окислительный стресс в сочетании с питательными микроэлементами, витаминами и антиоксидантами после нормализации концентрации 25 (OH)D в сыворотке крови и концентрации 1,25(OH)2D в тканях по всей вероятности приведут к лучшим и более экономичным клиническим результатам у людей.

Между системой витамина D и эпигенетическими механизмами существует тесная взаимосвязь. Система витамина D, с одной стороны, регулируется эпигенетическими механизмами, а с другой стороны, участвует в регуляции эпигенетической активности.

Ключевые слова

метилирование ДНК, эпигеном, пищевые добавки, беременность, витамин D