KASPRZAK, Małgorzata, KUŁAGA, Monika, KASPRZAK, Anna, SZOSTAK, Barbara, WIELGOSZ-BIAŁA, Sylwia, GRZYBEK, Monika, MAZUR-LESIŃSKA, Diana, WILCZYŃSKA, Barbara, TYSZKIEWICZ, Krzysztof and ŁOZOWSKI, Borys. Pleiotropic effect of vitamin D and supplementation. Journal of Education, Health and Sport. 2025;79:57873. eISSN 2391-8306.
https://doi.org/10.12775/JEHS.2025.79.57873
https://apcz.umk.pl/JEHS/article/view/57873

The journal has had 40 points in Minister of Science and Higher Education of Poland parametric evaluation. Annex to the announcement of the Minister of Education and Science of 05.01.2024 No. 32318. Has a Journal's Unique Identifier: 201159. Scientific disciplines assigned: Physical culture sciences (Field of medical and health sciences); Health Sciences (Field of medical and health sciences).
Punkty Ministerialne 40 punktów. Załącznik do komunikatu Ministra Nauki i Szkolnictwa Wyższego z dnia 05.01.2024 Lp. 32318. Posiada Unikatowy Identyfikator Czasopisma: 201159. Przypisane dyscypliny naukowe: Nauki o kulturze fizycznej (Dziedzina nauk medycznych i nauk o zdrowiu); Nauki o zdrowiu (Dziedzina nauk medycznych i nauk o zdrowiu).
The authors declare that there is no conflict of interests regarding the publication of this paper.
Received: 16.01.2025. Revised: 01.03.2025. Accepted: 01.03.2025. Published: 03.03.2025.

Pleiotropic effect of vitamin D and supplementation

Małgorzata Kasprzak

Cardinal Stefan Wyszyński Provincial Hospital in Lublin, 20-718 Lublin, Poland, al. Kraśnicka 100

malgorzata.m.kasprzak@gmail.com

https://orcid.org/0009-0007-3791-1632

Monika Kułaga

Cardinal Stefan Wyszyński Provincial Hospital in Lublin, 20-718 Lublin, Poland, al. Kraśnicka 100

monikakulaga93@gmail.com

https://orcid.org/0009-0001-3949-2124

Anna Kasprzak

Cardinal Stefan Wyszyński Provincial Hospital in Lublin, 20-718 Lublin, Poland, al. Kraśnicka 100

a.kasprzak93@wp.pl

https://orcid.org/0009-0002-1491-245X

Barbara Szostak
Cardinal Stefan Wyszyński Provincial Hospital in Lublin, 20-718 Lublin, Poland, al. Kraśnicka 100
barbara.szostak02@gmail.com
https://orcid.org/0009-0000-8035-7584

Sylwia Wielgosz-Biała
Cardinal Stefan Wyszyński Provincial Hospital in Lublin, 20-718 Lublin, Poland, al. Kraśnicka 100
sylwia.wielgosz@o2.pl
https://orcid.org/0009-0003-0567-5998

Monika Grzybek
Cardinal Stefan Wyszyński Provincial Hospital in Lublin, 20-718 Lublin, Poland, al. Kraśnicka 100
monika.c@vp.pl
https://orcid.org/0009-0003-2246-800X

Diana Mazur-Lesińska
Cardinal Stefan Wyszyński Provincial Hospital in Lublin, 20-718 Lublin, Poland, al. Kraśnicka 100
diana_mazur@wp.pl
https://orcid.org/0009-0000-2489-9100

Barbara Wilczyńska
University Children's Hospital in Lublin, 20-093 Lublin, Poland, ul. Profesora Antoniego Gębali 6
b.machulska@interia.pl
https://orcid.org/0009-0001-4939-7550

Krzysztof Tyszkiewicz
Cardinal Stefan Wyszyński Provincial Hospital in Lublin, 20-718 Lublin, Poland, al. Kraśnicka 100
tyszkiewicz.krzysztof@wp.pl
https://orcid.org/0009-0005-0208-2286

Borys Łozowski
University Clinical Hospital No. 4 in Lublin, 20-954 Lublin, Poland, ul. Doktora Kazimierza Jaczewskiego 8,
borys.lozowski@gmail.com
https://orcid.org/0000-0002-1990-040X

ABSTRACT

Introduction and purpose

Calcitriol is the active form of vitamin D. It belongs to the family of hormones that are transcription factors for target protein genes. It is involved in many signalling pathways in cells, which is associated with its various essential functions in the body. It is synthesised in skin exposed to sunlight. It can be delivered to the body as food or supplemented, too. In the skin, exposed to ultraviolet rays (UVB), cholecalciferol is produced. Cholecalciferol can be supplemented to prevent vitamin D deficiency or to treat diseases. Cholecalciferol supplementation may not be effective in people with severe kidney diseases. The aim of this paper is to review broad effects of vitamin D and recent knowledge about the supplementation.

Materials and methods

To write this article, data bases such as PubMed and Google Scholar were searched using the following terms: vitamin D, calcitriol, vitamin D deficiency, hypervitaminosis D, vitamin D supplementation.

Description of the state of knowledge

The 25-hydroxycholecalciferol (calcidiol) - 25(OH)D concentration is considered the best indicator of vitamin D level in the human body. There is no clinical reason for screening the concentration of the mentioned marker in the general population. The assessment of 25(OH)D serum level is, however, justified in risk groups. The optimal concentration is 30 - 50 ng/ml 25(OH)D. A serum calcidiol concentration in the range of 0 - 20 ng/ml is considered vitamin D deficiency. Both vitamin D deficiency and hypervitaminosis can be harmful. The recent guidelines of the Endocrine Society indicate the potential benefits of vitamin D supplementation in certain groups of patients.

Summary

Calcitriol as the active form of vitamin D is involved in many physiological processes in cells, which assist in crucial functions of the human body. The main source of this vitamin is the dermal synthesis. Additionally, food ingredients may deliver vitamin D to the body. Cholecalciferol can be supplemented to prevent vitamin D deficiency or to treat diseases connected with an insufficient level of vitamin D. Recent studies demonstrate rules of supplementation which is limited to determined in research populations.

Keywords: vitamin D, calcitriol, vitamin D hormone, vitamin D deficiency, hypervitaminosis D, vitamin D supplementation

Introduction

Calcitriol (1,25(OH)2D3), the active form of vitamin D, belongs to the family of hormones that are transcription factors for target protein genes. It is involved in many signalling pathways in cells, which is associated with its various functions in the body [1]. It is produced in skin during exposure to sunlight. Additionally, food or supplementation may be sources of this vitamin. Dermal synthesis of cholecalciferol is possible due to exposure to ultraviolet light B (UVB), then it undergoes hydroxylation, first in the liver to calcifediol (25(OH)D) and then in the kidneys to calcitriol [2,3]. Cholecalciferol can be supplemented to prevent vitamin D deficiency or to treat diseases such as rickets. Furthermore, it is used in familial hypophosphatemia, hypoparathyroidism and Fanconi syndrome. Vitamin D supplementation may not be effective in people with severe kidney diseases [4,5].

Hypovitaminosis D

Vitamin D deficiency is an essential and widespread health issue worldwide. Regardless of age, the lack of sufficient amount of vitamin D in the human body poses a risk of numerous diseases and negative health outcomes. Hypovitaminosis D affects the general population regardless of race, latitudinal position, gender and age [6]. Patients at risk of vitamin D deficiency include those with metabolic syndrome, obesity, hyperlipemia, type 2 diabetes mellitus. People affected by arterial hypertension or ischaemic heart disease, some

autoimmune diseases (rheumatoid arthritis, Hashimoto's thyroiditis, type 1 diabetes mellitus) are prone to hypovitaminosis D. Allergic diseases (asthma, atopic dermatitis) as well as kidney and liver conditions - i.e. liver failure, metabolic associated steatotic liver disease (MASLD), kidney failure, nephrolithiasis - may also lead to vitamin D deficiency. Patients with digestive and absorption disorders, calcium-phosphate metabolism disorders and those chronically treated with glucocorticosteroids, steroid synthesis inhibiting drugs - ketoconazole and anticonvulsant or antiretroviral drugs, are more susceptible to vitamin D deficiency [7, 8]. A decreased intake of vitamin D-containing products and low sun exposure can result in a deficiency of this vitamin in the human body. Impaired absorption and abnormalities that interfere with the formation of its biologically active metabolites can also produce hypovitaminosis D [9]. As vitamin D plays an invaluable role in calcium-phosphate homeostasis, it is crucial for mineralised tissues and organs, especially bones and teeth. Vitamin D deficiency may reveal as rickets in the paediatric population, with bone deformities of varying severity, impaired mineralisation and reduced bone mass. In children, adolescents and adults, after growth cartilage overgrowth, vitamin D deficiency can demonstrate as bone softening (osteomalacia), an osteoporotic fracture tendency, neurological impairment, and immune system dysfunction. In all age groups, hypovitaminosis D can induce bone pain of variable degrees of severity, particularly in the lower extremities, and rise the susceptibility to bone fractures. Advanced stage of rickets and osteomalacia can be life-threatening disorders [10, 11].

Hypervitaminosis D

Physiologically, hypervitaminosis D is an infrequent condition. It can occur in patients with hypersensitivity to vitamin D. The excess of vitamin D in the human body may be due to the presence of mutations in the genes responsible for its metabolism [12]. It may be attributed to many disorders, such as Williams syndrome or mutations in enzyme-coding genes such as CYP24A1 responsible for vitamin D catabolism. Overexposure to sunlight does not trigger vitamin D intoxication. When produced in excessive amount in physiological situations, vitamin D is then broken down to its inactive metabolites [13]. The clinical manifestations of hypervitaminosis D are combined with elevated serum calcium concentrations. They may manifest as polyuria, constipation, vomiting, weakness, difficulty concentrating, drowsiness [14]. Although an exogenous supply of vitamin D in excessive amounts may be harmful to the body. In the United Kingdom it was reported that vitamin D overfortification of infant

formula may contribute to following adverse effects: hypercalcaemia, failure to thrive, abnormal facies, learning difficulties, and nephrocalcinosis. Currently, there is an increasing tendency for hipervitaminosis D associated with both intentional and inadvertent administration of large doses of vitamin D. The link between the amount of vitamin D delivered to the body in exogenous form and the resulting marker level, its metabolite - serum 25-hydroxyvitamin D (25(OH)D) concentrations is unpredictable, thus the severity of the effects of vitamin D toxicity varies between individuals. Research suggests that nephrocalcinosis can occur at a 25(OH)D level lower than what is generally considered to be toxic [13].

Mechanism of action

The fundamental role of vitamin D in the human body is the homeostasis of calcium and phosphate metabolism. This is the calcemic action of vitamin D. It involves the three main effector organs, i.e. the intestines, the bones and the kidneys. The active form of vitamin D triggers an increased synthesis of calcium-binding protein in the intestines and a rise in calcium absorption; in the bones, a release of calcium and phosphate (in hypocalcaemia); and in the kidneys, by means of parathormone (PTH), a reabsorption of calcium [15].The primary procalcaemic action of calcitriol is the inhibition of PTH secretion by the parathyroid glands both directly and indirectly. This action results in an increase in serum calcium and phosphate concentrations. Vitamin D also impacts the RANK/RANKL (Receptor Activator of NF-kB/Receptor Activator of NF-kB Ligand) system, which is a component of osteoclastogenesis in bone metabolism. This stimulates bone resorption, releasing calcium and phosphate from the skeleton. By influencing calcium and phosphate metabolism, the vitamin is of greatest significance for mineral-rich tissues and organs, such as bones and teeth. Vitamin D activity in effector tissues is caused by genomic and non-genomic effects. The active form of vitamin D binds in many tissues to the nuclear receptor – vitamin D receptor (VDR), thereby initiating genomic action. Thus, calcitriol is involved in the regulation of several hundred genes in the human genome. Non-genomic actions are triggered by responses mediated by the vitamin D membrane receptor, which activates intracellular metabolic pathways that modulate actions resulting from gene expression [16]. The pleiotropic effects of vitamin D have been linked to the presence of VDR and 25-hydroxyvitamin D 1-alpha-hydroxylase in many tissues of the body, allowing extra-renal synthesis of the active form of vitamin D. It is proved that calcitriol is involved in numerous physiological processes [17]. The active form of vitamin D

exhibits strong immunomodulatory effects. The high content of VDR in cells of the immune system, especially in macrophages, dendritic cells, T and B lymphocytes, is connected to the essential role of this vitamin in immune processes, in the course of acute and chronic inflammatory reactions and autoimmune diseases. In the immune system, vitamin D induces cell proliferation and differentiation, modulates lymphocyte activity, the ratio of Th1 and Th2 lymphocytes. It also participates in the synthesis of many mediators of the immune system - enhances the production of bactericidal cathelicidin and beta-defensin, reduces the concentration of pro-inflammatory cytokines (IL-1, TNF-alpha), while increasing the concentration of anti-inflammatory cytokines (IL-4, IL-5, IL-10) [18-22]. It promotes apoptosis of cancer cells and inhibits their proliferation. The active form of vitamin D is also involved in reducing renin secretion, thereby reducing the action of the renin-angiotensin-aldosterone system. It inhibits the fibrosis process in the kidneys [23,24]. In the cardiovascular system, it is also responsible for the inhibition of angiogenesis and has a beneficial effect on calcification processes in blood vessels [25]. Calcitriol has a supportive influence on the nervous system through stimulation of neurotrophic factors. The involvement of 25(OH)D in endocrine, autocrine and paracrine pathways appears to be crucial in reducing the risk of cancer, autoimmune diseases, asthma, cardiovascular disease, stroke, type 2 diabetes, systemic lupus erythematosus (SLE), Alzheimer's disease, neurocognitive disorders [24,25]. In addition, 25(OH)D reduces the incidence of recurrent infections. In the skeletal system, it decreases the risk of falls, osteoporosis and fractures, rickets and osteomalacia. An anabolic effect on skeletal muscle has also been suggested. Furthermore, vitamin D may have an impact on reducing the risk of perinatal complications. Additionally, a reduction in overall mortality is possible [26].

Sources

It is essential to remember that the primary source of vitamin D is the dermal synthesis (80%) by means of ultraviolet-B (UVB) radiation (wavelength 290–315 nm). Pre-vitamin D may be synthesised from cholesterol-like precursor (7-dehydrocholesterol) in skin epidermal cells after UVB radiation, which may isomerise to vitamin D3. Although, both vitamin D3 and D2 are biologically inactive. In the human body they may be converted enzymatically into their active forms. Firstly, it is processed (25-hydroxylation) in the liver to 25(OH)D (calcidiol), the main circulating form of vitamin D. Subsequently, it is transformed in the kidney through 1-alpha-hydroxylation to its most active form, 1,25(OH)2D (calcitriol). This process is driven

by parathyroid hormone (PTH) and other mediators, including hypophosphatemia and growth hormone. Although there are dietary sources of vitamin D, these are not able to meet the human body's need for this vitamin. Vitamin D is found in food in small amounts, basically in animal products as cholecalciferol (vitamin D3) (fish and fish preparations, fats, meat and meat preparations, egg yolk, cheese) and as ergocalciferol (vitamin D2) in plant products, mushrooms and yeast. In animal derived products, there is a correlation between the food's fat content, the fodder the animals have been fed, the food's exposure to UVB light, and the vitamin D content in food. The main dietary sources of vitamin D (vitamin D3) include the flesh of some fish (such as wild trout, wild pacific salmon, wild tuna and wild mackerel) and fish liver oils. The vitamin D content depends on the origin of food delivered to the body. It should be considered that the vitamin D3 content is usually higher in wild, rather than farmed animals. Moreover, vitamin D may be found in fortified foods. The process of fortification is defined as supplementing food with required nutrients for their health benefits and in order to prevent diseases. Thus, producers add vitamin D2 and vitamin D3 to foods. It is more advantageous to enrich products with 25(OH)D3 than vitamin D2 and D3, since it is more rapidly effective in correcting nutritional deficiency [27-28].

Supplementation

According to recent studies, the Endocrine Society guidelines indicate the potential benefits of vitamin D supplementation in certain populations. It may be beneficial in the population of children, people aged 75 years and older, pregnant women and adults with pre-diabetes. Previous recommendations were based almost exclusively on observational studies. Currently, it is acknowledged that children and adolescents ages 1-18 may be prevented from rickets due to empiric vitamin D supplementation. Furthermore, vitamin D while supplemented in these populations may improve the activity of the immune system which results in reduction of the risk of respiratory tract infections. The daily intake of vitamin D in the clinical trials has been estimated to be approxiamtely 1200 IU. Additionally, in the general population ages 75 years and older supplementation of vitamin D is potentailly beneficial in view of reduction of the risk of mortality. Vitamin D may be delivered to the body in various formulations such as fortified foods, vitamin preparations rich in vitamin D or daily dosage of a vitamin D supplement. When it comes to the form of vitamin D supplied to the body, there is the advantage of daily, lower-dose vitamin D over non-daily, higher doses. The population of pregnant women may benefit from empiric vitamin D supplementation in terms of potential

decrease in risk of preeclampsia, intra-uterine mortality, preterm birth, small for gestational age birth, and neonatal mortality. Another group of patients for whom supplementation of vitamin D can be advantageous includes adults with high-risk prediabetes. The risk of progression to diabetes may be diminished through empiric intake of vitamin D as well as lifestyle modification. In populations mentioned above there is no need for routine 25(OH)D testing according to guidelines. In the general adult population younger than age 74 years, the Endocrine Society's guideline suggests against empiric vitamin D supplementation. According to analysed research it is enough to deliver to the body the Dietary Reference Intakes (DRIs) established by the Institute of Medicine's (IOM). Adults in this age group should follow the Recommended Daily Allowance established by the IOM (600 IU daily for those younger than 70 years; 800 IU daily for those older than 70 years). In the general adult population younger than age 74 years, there is no need for routine 25(OH)D testing. This recommendation relates to generally healthy adults who do not otherwise have established indications for 25(OH)D testing (e.g., hypocalcemia) [29-30].

Conclusion

The active form of vitamin D3 is a very crucial compound in the regulation of the metabolism of cells and tissues belonging to various systems in the human body. An indicator of its presence in serum is the 25(OH)D concentration. Clinically relevant is vitamin D deficiency. Its excess represents marginal cases. Vitamin D is involved in calcium-phosphate homeostasis. It exhibits pleiotropic effects, with a particular focus on the immune system. The main source in the body is dermal synthesis; a minor part is vitamin D supplied with food, especially of animal origin. It is significant to be able to supplement vitamin D, mainly in the form of cholecalciferol, both for the prevention and treatment of vitamin D deficiency and hypovitaminosis-related diseases.

Author's contribution

Conceptualization: Małgorzata Kasprzak

Methodology: Monika Kułaga

Software: Anna Kasprzak and Sylwia Wielgosz-Biała

Check: Monika Grzybek, Barbara Wilczyńska and Borys Łozowski

Formal analysis: Barbara Szostak and Anna Kasprzak

Investigation: Monika Kułaga and Diana Mazur-Lesińska
Resources: Monika Kułaga and Anna Kasprzak
Data curation: Monika Kułaga and Sylwia Wielgosz-Biala
Writing - rough preparation: Borys Łozowski, Krzysztof Tyszkiewicz
Writing - review and editing: Diana Mazur-Lesińska and Monika Grzybek
Visualization: Barbara Wilczyńska
Supervision: Monika Kułaga
Project administration: Małgorzata Kasprzak
Receiving funding: Barbara Wilczyńska and Anna Kasprzak
All authors have read and agreed with the published version of the manuscript.

Funding Statement
The study did not receive any special funding.

Institutional Review Board Statement
Not applicable.

Informed Consent Statement
Not applicable.

Acknowledgments
Not applicable.

Conflict of Interest Statement
Ther

AI Statement
Assisted Generative Intelligence was not used in writing the manuscript.

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