THE PUBLISHING HOUSE
OF THE ROMANIAN ACADEMY

MEDICINE
Review article

SUPPLEMENTATION WITH VITAMIN D – NEW OPPORTUNITIES IN OBESITY

Anca-Mihaela PANTEA STOIAN[1] , Cristinel Dumitru BADIU[2], Liliana Florina ANDRONACHE[1], Simona CARNICIU[3], Octavian NEGOIȚĂ[1], Răzvan HAINAROSIE[1,3], Gabriela CIOCA[4] and Silviu Mirel PITURU[1]

[1]"Carol Davila" University, Medicine and Pharmacy Faculty, Hygiene Departament, Bucharest, Romania
[2]"Bagdasar Arseni" Clinical Emergency Hospital, Department of Surgery, Bucharest, Romania
"Carol Davila" University, Medicine and Pharmacy Faculty, Bucharest, Romania
[3]"Prof Dr Dorin Hociota" Institute of Phonoaudiology and Functional ENT Surgery, Bucharest, Romania
[4]"Lucian Blaga" University of Sibiu, Faculty of Medicine, Preclinical Department, Sibiu, Romania
Corresponding author: Anca Mihaela Pantea Stoian, E-mail: ancastoian@yahoo.com

Accepted October 23, 2017

The pandemic incidence of obesity and vitamin D deficiency are real public health problems worldwide. The reversed relationship between obesity and vitamin D deficiency is well-known, while the inflammation of the adipose tissue is the underlying cause of the metabolic syndrome. The action of vitamin D on the adipose tissue via VDR is still a controversial subject, since a series of clinical trials on this topic is now being conducted. The article aims at bringing new information about the relationship between obesity and vitamin D deficiency, possible mechanisms of action, as well as current trends in medical intervention.

Key words: obesity, vitamin D, adipose tissue, supplementation vitamin D.

INTRODUCTION

Vitamin D deficiency is one of the current concerns of healthcare professionals[1]. Vitamin D deficiency could be seen as a pandemic, since 50% of the UK population and 30% of the Romanian population has it. The situation is more severe in the Middle East (90%), but it still does not exceed the incidence in Northern European countries (92%) and Mongolia (98%)[2].

Obesity, in turn, is currently considered a real public health problem worldwide, more specific to developed countries, while the reversed correlation between the BMI > 30 kg/m² and vitamin D deficiency is supported by consistent data in the literature. It is estimated that more than 70% of the US population aged over 60 are overweight or obese,while in Romania, of all people aged 18–79 years, 21.3% are obese and 31.14% overweight, according to the study conducted by the Romanian Association for the Study of Obesity (RASO)[3]. Obesity itself is a significant marker of cardiovascular risks, high blood pressure, metabolic syndrome, diabetes mellitus, osteoarticular degenerative processes and neoplasms. The key element is the subclinical inflammation promoted by obesity, process which could be easily called the underlying cause of chronic pathologies. A series of data in the literature has already established the relationship between obesity and vitamin D deficiency, correlated with an elevated level of the parathyroid hormone (PTH)[1].

Vitamin D or "sun vitamin" is rather a group of liposoluble secosteroid vitamins, which associate 5 forms, out of which only 2 are physiologically important, namely vitamin D_2 (ergocalciferol) and vitamin D_3 (cholecalciferol). The other forms are: vitamin D1: a molecular compound of ergocalciferol with lumisterol, vitamin D_4: 22-dihydroergocalciferol, vitamin D_5: sitocalciferol (derived from 7-dehydrosisterol). They are all insignificantly important to the human body. Vitamin D_3 or colecalciferol, as it is also called, is synthesized from 7-dehydrocolesterol (provitamin D_3), under the action of ultraviolet type B rays (at a wavelength between 290–320 nm, at the integumentary level. Other sources of D_3 synthesis: animal food and supplements based on fish oil or cod liver, while the sources of vitamin D_2 are non-animal, more reduced in biological efficiency.

That is why, the so-called naturally derived supplements of D_2, which derive from yeast and/ or fungi are neither standardized nor efficient[4].

Provitamin D3 isomerized to the form of vitamin D_3, a thermal process by excellence. Both the intensity of UVB and melanin concentration in the skin dictate this process. Vitamin D_3 is converted into 25 (OH) in the liver but also in other sites, by a series of enzymes, out of which the most relevant is CYP2R1. The third step involves the metabolism of 25 form (OH) D to its active form 1,25 (OH) D_3 in the kidney under the action of enzymes CYP27B1 and CYP24 A1, which are very well-controlled in their turn. CYP27B1 is stimulated by the parathyroid hormone (PTH) and inhibited by FGF (the fibroblast growth factor) 23 and the increased concentrations of calcium phosphorus. In contrast, CYP24A1 has an exactly opposite control mechanism. In its turn, 1,25 (OH) D auto-modulates its production directly, but also through PTH inhibition, it stimulates FGF23 and inhibits CYP24A1. The active form binds to specific receptors – vitamin D receptors (VDR), which are found at each tissue level, at genomic binding sites, with hundreds of VDRs which control a series of genes. This is also the reason why vitamin D is involved in a series of biologic processes, many of them which are not fully understood yet. There is a new therapy with calcipotriol and 22-oxacalcitriol to support such findings, which has been recently approved for the treatment of psoriasis, the action of vitamin D-hydroxylase inhibiting the activity of keratinocytes[5]. VDR itself is also a transcription factor which belongs to the family of steroidal hormones and which interacts with its heterodimer – RXR (Retinoid X receptor). Pike and Meyer (2010) define some principles of action of VDR/RXR on the target genome: the number of genomic binding sites of VDR is strictly specific to the respective cells, the predominant active transcription unit is VDR/RXR, the VDR binding sites are exclusive, and the activators which populate the genome are specifically cellular and very active[6]. There is also a non-genomic activity of 1,25 $(OH)_2$ D, on which therapy with vitamin D analogs is based. Such therapies include D_2, α-calcidol, doxercalciferol, calcipotriol used in the treatment of osteoporosis, parathyroidism or psoriasis[7].

This short introduction to vitamin D metabolism actually shows how much it is involved in different pathologies. The main well-known role of vitamin D is that it has a preventative role in osteoporosis and rickets occurrence, if we are to refer to the skeletal system exclusively. Vitamin D has both a direct and indirect effect through VDR on bone development and remodeling. There is still an unresolved problem related to the optimal value at which vitamin D should be in the serum in order to have such benefits. On the other hand, there is a reversed relationship between the circulating level of 25 (OH) D and PTH, the latter being a significant marker for vitamin D deficiency. A series of vitamin D analogs (paricalcitol, doxercalciferol) reduce consistently the PTH level and maintain a satisfactory level of serum calcium, which makes them extremely useful in hyperparathyroidism secondary to renal disease. Associated, this benefit also extends on cardiovascular diseases, decreasing the mortality risk. Consistent data on this matter have been noticed in the study conducted by Duranton (2013)[8]. The mechanism through which such a benefit could be explained is the presence of VDR and CYP27B1 in myoctes and fibroblasts, while 1.25 $(OH)_2$ D inhibits cardiac hypertrophic markers[9]. A series of studies have clearly demonstrated that severe deficiency of vitamin D is associated with cardiovascular diseases, especially cardiomyopathy, thus significantly increasing the cardiovascular risk[10]. It is even suggested that a higher level over 30 ng/ml of 25(OH)D reduces the risk of peripheral vascular disease by 80%[11].

The research in the 1990s also showed the correlation between increased levels of vitamin D and decreased risk of colon, prostate and breast cancer[12], aspects also validated by follow-up studies. Moreover, they also brought into discussion the hypothesis in which vitamin D deficiency is also involved in the occurrence of auto-immune disorders such as type 1 diabetes mellitus, multiple sclerosis, rheumatoid polyarthritis[13, 14]. Interesting data also concern the correlation between vitamin D deficiency and the increased risk of neurocognitive deficits such as depression, schizophrenia, Alzheimer's disease.

THE STATUS OF VITAMIN D AND OBESITY

The association between the low level of 25 (OH) D and obesity is well-known and demonstrated by a series of studies. However, less known is the mechanism of this association. It seems that the major role is played by adipocytes and the occurrence of VDR at this level. Moreover, VDRs are also found at the level of β pancreatic

cells, in both cases. The deficiency of 1,25 (OH) D thus promotes lipogenesis and increases insulin resistance. The insufficient intake of vitamin D, the intense pigmentation of integuments (the black population), older age, the insufficient exposure or under-sun protection, the reduction of the body's ability to synthesize vitamin D, the alteration of intestinal absorption and the metabolic impairment by reducing metabolic activation and increase are some of the suggested mechanisms.

The adipose tissue is not only a storage system, but also a promoter of the secretion of more than 260 proteins and peptides, a real endocrine organ. People with a normal weight have approximately 5 kilos of fat, while the obese >50 kilos, vitamin D being negatively correlated with the overall fat mass[15]. The expansion of the adipose tissue is due to both hyperplasia and hypertrophy of adipose cells. 1,25 OH_2D_3 intervenes in the adipogenetic process at all levels by increasing the expression of adipogenetic markers FABP4, LPL, PPARγ[16]. *In vitro* studies have shown that in 3T3-L1 mice, $1,25(OH)_2D_3$ inhibits adipogenesis by suppressing the expression of C/EBPα and PPARγ, thus seizing RXR[17], but also differentiating preadipocytes. These transcriptional factors induce the expression of more genes which are in connection with lipogenesis, lipolysis and insulin sensitivity, including FABP4 (fatty acid binding protein), LPL (lipoprotein lipase), GLUT4 (glucose transporter) and FASN (fatty acid synthase). The antiadipogenic effect of 1,25 $(OH)_2D_3$ is mediated by WNT/β-catenin, in the sense that it maintains preadipocytes in a pre-differentiated state. The level of expression of β nuclear catenins also suppresses PPARγ factor[18]. $1,25(OH)_2D_3$ at the human adipose level promotes the differentiation of preadipocytes by increasing the expression of adipogenetic markers: $FABP_4$ and LPL[19]. Therefore, $1,25(OH)_2D_3$ plays an important role in adipogenesis, acting at several levels. However, its action is not strictly limited to the differentiation of the adipose tissue, but also on the inflammatory status at this level. Obesity is characterized by a hyperplasic adipose tissue, with a low blood flow at the limit of hypoxia, macrophage infiltration and inflammation, with a higher pro-inflammatory level cytokine (IL-6, IL-8, TNFα, resistin and a low adiponectin secretion). $1,25(OH)_2D_3$ decreases the activity of pro-inflammatory chemokines and cytokines at the adipose tissue level, thus improving the inflammatory state. The action of 1,25 OH_2D_3 on chronic inflammation in the adipose tissue is also due to the inhibitory effect on NF-kB and on the MAPK signaling pathways, aspect which will determine the inhibition of pro-inflammatory transcription factors. However, in-depth studies to prove the physiological relevance and the active optimal level of 1.25 $(OH)_2D_3$ in obese patients to improve inflammation and its complications are still needed.

And yet, the effects of vitamin D do not seem to stop at this level. Recent data in the literature also suggest its implication in the energetic homeostasis of the body, moreover at the level of the adipose tissue. The discovery of VDR at the adipocyte level was a key moment in understanding vitamin D action and its role at this level. In $VDR^{-/-}$ mice, the increase in β-oxidation at the adipose tissue level seems to be mediated by carnitine palmitoyltransferase II (CPTII), which will determine the increase in the basal mechanism, the oxygen consumption and CO_2 production. On the other hand, in these mice, the brown adipose tissue, UCP1, UCP2 and UCP3 are activated and stimulated, thus producing heat[20]. Chang confirms previous research and brings new information on the effect of vitamin D deficiency, in the sense that it is involved in the oxidation of fatty acids, thus increasing the expression of genes at the adipose tissue levels and decreasing mRNA level. It seems to play an interesting role in the activity of AMPK/SIRT1 at the adipocyte level. His conclusion was that vitamin D supplementing could be a likely alternative for the prevention and treatment of obesity, especially the type of vitamin D mediated by AMPK/SIRT1[21].

VITAMIN D SUPPLEMENTATION AND OBESITY

Although these pleiotropic effects of vitamin D are real and beneficial, there is a series of studies that have shown that supplementation with vitamin D in case of obesity does not determine weight loss. However, nutritional intervention in obese/ overweight patients has resulted in improved vitamin D status. Supplementation with vitamin D, in combination with calcium does not seem to have definite effects on the weight, but they can improve the total fat mass and its distribution. Many of the products available in case of supplementation are present in this combination, being recommended when calcium deficiency is also accompanied by vitamin D deficiency.

Determining vitamin D deficiency is a controversial discussion at present. On the one hand, IOM (The Institute of Medicine, United States) defines it at a level below 15 ng/mL. In contrast, in 2011, the American Association of Endocrinologists defines vitamin D deficiency at a value < 20 ng/ml, the insufficiency between 21–29 ng/ml and the optimal level at values higher than 30 ng/ml, thus vitamin D deficiency becomes a pandemic, with 40.4 % of the European population having suboptimal values[21, 24].

Supplementation with vitamin D is based on age and physiological state. However, there is no stratification of the therapy according to race yet, knowing that the black population presents vitamin D deficiency. Supplementation should also take into account the weight, the administration being different in normoponderal people compared to the obese. The initiation of vitamin D treatment may start at 2.5 IU/kg/1ng/ml. In Romania, supplementation in adults is often done with 500, 1000 or 2000 IU, vitamin D_3 derived from fish oil and cod liver.

There are also vitamin D_2 formulas from natural extracts, fungi or yeast, which do not increase efficiently the level of vitamin D. The administration should be monitored every 3 months and the dose adjusted until reaching the optimal level.

CONCLUSIONS

It is obvious that these studies are necessary in order to clearly establish the mechanism of action of vitamin D, but also the serum level at which its pleiotropic effects should occur. Over 116 clinical trials on the relationship between vitamin D and obesity have begun in 2016.

The adipose tissue is not only a deposit for nutrients, but also an endocrine tissue by excellence. Vitamin D is seized at this level, moreover in overweight and obese subjects. In obese, the subclinical inflammatory state increases the risk of chronic diseases, especially the cardio-metabolic ones, tightly correlated with vitamin D deficiency/ insufficiency. On the other hand, a large study which included 33,996 Europeans showed that 25(OH)D is also involved in the metabolism of cholesterol, VLDL-c, triglycerides[24]. The involvement of 1,25 $(OH)_2D_3$ in adipogenesis and inflammation is closely correlated with age and race, more than 30% of the people > 65 years and over 77% of the black population showing vitamin D deficiency[22]. A recent meta-analysis investigated the relationship between the circulating level of 25(OH)D and specific mortality causes and demonstrated that there is a reversed correlation between vitamin D levels and the mortality risk[23]. Under such conditions, it is necessary to assess vitamin D levels in obese/overweight subjects, and therapy is these patients requires supplementation with high doses of vitamin D to reach the optimal level. In the black population, if obesity is also associated, supplementation with vitamin D should reach a level of 4,000 IU/day. Nutritional intervention in obese subjects, by reducing weight excess, improves vitamin D state, while supplementation with calcium has beneficial effects on weight loss. In this context, understanding the mechanism of action of vitamin D, as well as the effects of its insufficiency/ deficiency should help the clinician investigate, monitor vitamin D deficiency and correct it when clinical conditions recommend it.

REFERENCES

1. Simon Vanlint, *Vitamin D and Obesity*, *Nutrients*, **2013**, 5(3), 949–956.
2. Holick M.F., Binkley N.C., Bischoff-Ferrari H.A., *et al*. *Guidelines for preventing and treating vitamin D deficiency and insufficiency revisited*, *J. Clin. Endocrinol. Metab.*, **2012**, 97:1153-8.
3. http://euro-health.ro/sondaj-european-romania-tara-cu-cei-mai-putin-obezi-din-europa.
4. Christakos S., Dhawan P., Verstuyf A., Verlinden L., Carmeliet G., *Vitamin D: Metabolism, Molecular Mechanism of Action, and Pleiotropic Effects*, *Physiol Rev.*, **2016**, 96(1):365–408. doi: 10.1152/physrev.00014.2015.
5. Schuster I., Egger H., Bikle D., Herzig G., Reddy G.S., Stuetz A., Stuetz P., Vorisek G., *Selective inhibition of vitamin D hydroxylases in human keratinocytes*, *Steroids*, **2001**, 66(3–5):409–22.
6. Pike J.W., Meyer M.B., *The vitamin D receptor: new paradigms for the regulation of gene expression by 1,25-dihydroxyvitamin D(3)*, *Endocrinol. Metab. Clin. North Am*., **2010**, 39(2):255–69, table of contents.
7. Jones G., *Vitamin D analogs*, *Endocrinol. Metab. Clin. North Am.*, **2010**, 39(2):447–72, table of contents.
8. *Vitamin D treatment and mortality in chronic kidney disease: a systematic review and meta-analysis*.
9. Chen S., Law C.S., Grigsby C.L., Olsen K., Hong T.T., Zhang Y., Yeghiazarians Y., Gardner D.G., *Cardiomyocyte-specific deletion of the vitamin D receptor gene results in cardiac hypertrophy*, *Circulation*, **2011**, 25, 124(17):1838-47.
10. Gardner D.G., Chen S., Glenn D.J., *Vitamin D and the heart*, *Am. J. Physiol. Regul. Integr. Comp. Physiol*., **2013**, 305(9):R969-77.

11. Melamed M.L., Muntner P., Michos E.D., *et al.*, *Serum 25-hydroxyvitamin D levels and the prevalence of peripheral arterial disease: results from NHANES 2001 to 2004*, *Arterioscler Thromb Vasc Biol*., **2008**, 28:1179-85.
12. Garland C.F., Garland F.C., Gorham E.D., *et al.*, *The role of vitamin D in cancer prevention*, *Am. J. Public Health*, **2006**, 96(2):252-61.
13. Merlino L.A., Curtis J., Mikuls T.R., *et al*., *Iowa Women's Health Study. Vitamin D intake is inversely associated with rheumatoid arthritis*, *Arthritis Rheum*., **2004**, 50(1):72-7.
14. Mohr S.B., Garland C.F., Gorham E.D., *et al.*, *The association between ultraviolet B irradiance, vitamin D status and incidence rates of type 1 diabetes in 51 regions worldwide*, *Diabetologia*, **2008**, 51:1391-8.
15. Ceglia L. *et al*., "Association between body weight and composition and plasma 25-hydroxyvitamin D level in the Diabetes Prevention Program", Eur. J. Nutr., 2017.
16. Shivaprakash Jmutt *et al*., *Vitamin D and adipose tissue-more than storage*, *Frontieres in Physiology*, June 2014.
17. Blumberg, J.M., Tzameli, I., Astapova, I., Lam, F.S., Flier, J.S., and Hollenberg, A.N., *Complex role of the vitamin D receptor and its ligand in adipogenesis in 3T3-L1cells*, *J. Biol. Chem.* **2006**, 281, 11205–11213; doi:10.1074/ jbc.M510343200 ().
18. Lee H., Bae S., and Yoon Y., *Anti-adipogenic effects of 1,25-dihydroxyvitaminD3 are mediated by the maintenance of the wingless-type MMTV integrationsite/beta-catenin pathway*, *Int. J. Mol. Med*, **2012**, 30, 1219–1224; doi: 10.3892/ijmm.2012.1101.
19. Nimitphong, H., Holick, M.F., Fried, S.K., and Lee, M.J., *25-hydroxy vitamin D(3) and 1, 25-dihydroxyvitamin D(3) promotethediffer-entiation of human subcutaneous preadipocytes. PLoSONE*, **2012**, 7:e52171; doi: 10.1371/journal.pone.0052171.
20. Eugene Chang, Yangha Kim, *Vitamin D Insufficiency Exacerbates Adipose Tissue Macrophage Infiltration and Decreases AMPK/SIRT1 Activity in Obese Rats*, *Nutrients* **2017**, 9, 338; doi:10.3390/nu9040338.
21. Sung *et al.*, *High levels of serum vitamin D are associated with a decreased risk of metabolic diseases in both men and women, but an increased risk for coronary artery calcification in Korean men*, *Cardiovasc. Diabetol.*, **2016**, 15, 112; DOI 10.1186/s12933-016-0432-3.
22. Powe, C.E., Karumanchi, S.A., and Thadhani, R., *Vitamin D-binding protein and vitamin D in blacks and whites*, *N. Engl. J. Med.*, **2014**, 370, 880–881. doi: 10.1056/NEJMoa1306357.
23. Chowdhury, R., Kunutsor, S., Vitezova, A., Oliver-Williams, C., Chowdhury, S., Kiefte-de-Jong, J.C., *et al*., *Vitamin D and risk of cause specific death: systematic review and meta-analysis of observational cohort and randomised intervention studies*, *BMJ*, **2014**, 348:g1903; doi:10.1136/bmj.g1903.
24. Wang, T.J., Zhang, F., Richards, J.B., Kestenbaum, B., van Meurs, J.B., Berry, D., *et al*., *Common genetic determinants of vitamin D insufficiency: agenome-wide association study*, *Lancet*, **2010**, 376, 180–188; doi:10.1016/S0140-6736(10)60588-0.