VITAMIN D AND TISSULAR EXPRESSION OF VITAMIN D RECEPTOR IN OBESITY

Raluca Haliga¹, F. Zugun-Eloae², T. Oboroceanu¹, A. Pînzariu¹, Veronica Mocanu¹
University of Medicine and Pharmacy “Grigore T. Popa”-Iasi
Faculty of Medicine
Department of Morpho-functional Sciences
* Corresponding author. E-mail: pinzariu_alin@yahoo.com

VITAMIN D AND TISSULAR EXPRESSION OF VITAMIN D RECEPTOR IN OBESITY (Abstract): Vitamin D (VitD), a lipid-soluble hormone, is able to regulate the transcription of many genes through vitamin D receptor (vitD receptor - VDR). It has been shown that VitD deficiency is associated with obesity, characterized by a low degree inflammatory state, which contribute to the pathogeny of metabolic syndrome and type 2 diabetes mellitus. VitD deficiency is a public health problem, at the same time the global prevalence of obesity and cardiovascular diseases is continuously growing. Evidence from recent studies on animal models suggest that VitD or VDR deficiency promotes cardiomyocyte hypertrophy, which can be one of the mechanisms for increasing cardiovascular risk. The heart is one of the target organs of action for VitD, because VDR is expressed in cardiomyocytes. Also, previous in vitro studies have shown that VitD is able to inhibit the production of monocyte chemotactic factors (MCP-1) and other pro-inflammatory mediators in human preadipocytes and mature adipocytes. Inflammation is an important factor in the pathogenesis of atherosclerosis. In obesity there are not known data about correlations between plasma levels of VitD and VDR expression in the subcutaneous fat tissue, epicardial visceral adipose tissue, and in particular in myocardium. Also, there are still no studies to test VDR expression in myocardial cells and to investigate the results of dietary VitD supplementation on the expression of VDR in the epicardial adipose tissue and myocardium. Keywords: OBESITY, HEART, INFLAMMATION, VITAMIN D RECEPTOR.

VITAMIN D – MORE THAN A CALCIUM REGULATOR

It has been established in time the vital role of vitamin D (VitD) in the regulation of calcium and phosphate homeostasis, a key nutrient for maintaining the health of the musculoskeletal system (1). VitD deficiency is a public health problem. Humans obtain vitD either from exposure to sunlight or dietary intake, both whole food and supplementation (2).

The circulating form of Vit D is 25-hydroxycholecalciferol (25OHD) and the most active form is 1α,25-dihydroxyvitamin D (1α,25(OH)₂D) or calcitriol. The enzymes responsible for the activation to 1α,25(OH)₂D are vitamin D-25-hydroxylase (25-OHase) and 25-
hydroxyvitamin D-1α-hydroxylase (1α-OHase or CYP27B1). Calcitriol is further degraded by 24-hydroxylase CYP24A1.

The worldwide prevalence of obesity has nearly doubled between 1980 and 2008. According to World Health Organization, in 2008, 10% of men and 14% of women in the world were obese (BMI ≥30 kg/m2), compared with 5% for men and 8% for women in 1980, and the prevalence is rapidly increasing. As a group, obese individuals have decreased levels of circulating 25(OH)D, and, according to a recently published meta-analyses, are at a 35% higher risk for vitD deficiency across all age ranges (1). While actually recommended daily dietary supplementation of vitD are at least 600 IU for healthy adults aged 19–70 (2), and 800 IU/d for those over 70 years old, these doses reflect adequate intake for maximal bone health and muscle function, but for obese populations may be necessary at least two to three times more vitD (1,3).

Recent experimental and human studies demonstrated an inverse correlation between adiposity and the level of VitD. VitD deficiency has been showed to be closely associated with obesity, which is a chronic, low-grade inflammatory state, and contribute to the pathogenesis of insulin resistance, metabolic syndrome, and type 2 diabetes mellitus (1).

VitD, a fat-soluble hormone, is able to regulate the transcription of many genes through vitD receptor (VDR) (4). The VDR functions in cells such as osteoblasts, skin keratinocytes, macrophages, and epithelial cells and modulates the action of 1,25-(OH)2D, and in turn controls transcription of several genes (1). Adipose tissue is recognized as a target for VitD actions. In particular, adipocytes may be directly involved in the local synthesis and degradation of calcitriol, which is able to affect adipocyte biology by modulating preadipocyte differentiation, lipid accumulation and mobilization and also adipokine production (4). There are contradictory data in the literature regarding the expression of VDR in subcutaneous or visceral adipose tissues.

Muscle fat infiltration can be the result of aberrant trans differentiation of myogenic precursor cells into adipocytes, resulting in the formation of fat within the intermuscular space. Recent studies demonstrated that myogenic precursor cells have the potential to transdifferentiate towards the adipogenic lineage (5) and VitD has potent effects on both adipogenesis and myogenesis (6). Muscle fat infiltration has been shown to have a direct consequence on muscle strength and functionality, but it is also a key independent risk factor for metabolic diseases, such as insulin resistance, obesity and diabetes mellitus (3).

In rats, adipose tissue has been shown to sequester more vitamin D for significantly longer periods of time than other major tissues or organs. In humans, central adiposity in obese states is a key marker of metabolic syndrome, which, along with type 2 diabetes mellitus, has been identified to be associated with vitD deficiency. VitD deficiency may also be associated with lipid synthesis via action of the VDR. VitD and VDR also regulate de novo adipogenesis since VDR has been shown to be expressed in preadipocytes (1).

Recent studies reported that calcitriol induces genomic effects, leading to the synthesis of new proteins that affect muscle cell contractility, proliferation and differen-
Furthermore, mice lacking the vitamin D receptor showed a skeletal muscle phenotype with smaller and variable muscle fibers and persistence of immature muscle gene expression during adult life, suggesting a role of VitD in muscle development (8).

VitD deficiency can lead to myopathy, characterized by muscle hypotonia, weakness and atrophy of skeletal muscle. Muscle biopsies from VitD-deficient adults demonstrated enlarged interfibrillar spaces, fibrosis and loss of type II fiber complement (7). There was also found an increase in fat infiltration within the muscles (9), similar effects being observed in elderly individuals, where progressive loss in muscle mass and strength are seen at the onset of sarcopenia, associated with an increase in fat deposition within the tissue. Sarcopenia consists of a deterioration in muscles quantity and quality, a gradual slowing of movement, a decline in strength and power, and an increased risk of falls and fall-related injuries (10).

VITAMIN D, CARDIOVASCULAR SYSTEM AND INFLAMMATION

Cardiovascular diseases (CVD) are the most common causes of morbidity and remain the most important cause of death. Recent observational and prospective studies have shown an association between VitD deficiency and hypertension, diabetes mellitus, metabolic syndrome, coronary and peripheral arterial disease (PAD), and heart failure. Vit D has been shown to exert many biological activities, including reduction in blood pressure through down regulation of renine-angiotensin system (RAS), enhancement in insulin secretion and insulin sensitivity (11), protection against angiogenesis and regulation of cellular differentiation and proliferation through locally-formed calcitriol in tissues (12).

VitD deficiency has been also shown to impair endothelial function, which may be a supplementary contributing factor to increased CVD risk (1). Recent studies suggested that serum 25(OH)D levels were inversely associated with coronary lesion severity established by coronary angiography, but not with arterial stiffness or peripheral arterial disease (12).

Epicardial adipose tissue (EAT) (epicardial fat) is a metabolically active visceral adipose tissue, which may locally interact with myocardium and coronary arteries through secretion of various adipokines and cytokines. Recent reports indicated that EAT accumulation may be a risk factor for coronary artery disease (CAD) and alterations in EAT biology, such as increased thickness, elevated inflammatory infiltrate and cytokine production, have been observed in CAD patients (6). The secretion of various epicardial inflammatory adipokines, including tumor necrosis factor alpha (TNF-α), interleukin-6 (IL-6), adiponectin, and monocyte chemoattractant protein-1 (MCP-1), contribute to an inflammatory milieu and play a significant role in the development and progression of atherosclerosis. Subjects with coronary artery disease (CAD) had elevated inflammatory infiltrates in EAT (13).

Evidence from studies on animal models suggest that vitamin D or VitD receptor (VDR) deficiency promotes cardiac hypertrophy, which might be also one of the mechanisms for increased cardiovascular risk (13). Thus, a recent experimental study revealed that VitD deficiency was associated with cardiomyocyte hypertrophy in
hypercholesterolemic miniswine and significantly decreased expression of VDR was found in ventricular cardiomyocytes of vitD-deficient swine (13). The heart is believed to be one of the target organ of vitD, because VDR is expressed in cardiomyocytes (14).

In addition to its well-known role as a regulator of calcium homeostasis and bone metabolism, vitamin D may exert other different functions. In particular, due to its ability to modulate T-lymphocyte proliferation and function, vitamin D exert immune-regulatory effects and suppress the production of inflammatory cytokines, thus being recognized as a potential anti-inflammatory molecule. Previous in vitro studies showed that vitD is able to down-regulate the expression of pro-inflammatory mediators in human monocytes stimulated with interferon and to inhibit the production of MCP-1 and other pro-inflammatory mediators in human preadipocytes and mature adipocytes (6).

In human adipose tissue, there are few studies which investigated the potential anti-inflammatory role of vitamin D. One study demonstrated that, as 25OHD level decreases, local EAT expression of both VDR and proinflammatory cytokines increases (13). In condition of plasma 25OHD deficiency, local vitamin D metabolism seemed to be suppressed and associated to an increased production of inflammatory mediators. It was also observed an increased expression of VDR associated to reduced plasma 25OHD level, as well as to increased EAT inflammation (15).

In conclusion, besides the vital role of vitamin D in maintaining the health of the musculoskeletal system, studies showed that VitD deficiency has been closely associated with obesity, induced an increase in fat infiltration within the muscles and cardiomyocyte hypertrophy, and significantly increased proinflammatory cytokines. It is not yet known which are the correlations between the plasmatic level of VitD and expression of VDR in subcutaneous adipose tissue, visceral epicardial adipose tissue and especially in myocardium in obesity. There are no studies which tested the expression of VDR in the myocardial cells and to investigate and correlate the results of diet supplementation with VitD on VDR expression in the visceral epicardial adipose tissue and myocardium.

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