INTERRELATIONSHIP BETWEEN PATHOPHYSIOLOGICAL MECHANISMS OF VITAMIN D DEFICIT AND CHRONIC OBSTRUCTIVE PULMONARY DISEASE

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INTERRELATIONSHIP BETWEEN PATHOPHYSIOLOGICAL MECHANISMS OF VITAMIN D DEFICIT AND CHRONIC OBSTRUCTIVE PULMONARY DISEASE (Abstract): Several similarities have reported between patients with suboptimal level of vitamin D and patients with Chronic Obstructive Pulmonary Disease (COPD): both conditions are more prevalent after the 6th decade and are associated with impaired defense mechanisms, with skeletal muscles dysfunction and with an early ageing process. We have reviewed the literature concerning the interrelationship between the main pathophysiological processes of both conditions, in order to emphasize the influence of vitamin D deficit on COPD development and evolution. Epidemiological, clinical and experimental data supporting this association are presented. We concluded that the identification of common pathophysiological mechanisms for the vitamin D deficiency and COPD substantiates the hypothesis of the involvement of this hormone in the chronic obstructive pulmonary disease. Keywords: VITAMIN D, COPD, PATHOPHYSIOLOGICAL MECHANISMS.

Vitamin D is well-known for its essential role in bone metabolism. Nevertheless, the perspective on vitamin D has changed significantly over the past years and new actions have been described. The activation of vitamin D takes place in the tissues which express 1-α-hydroxylase (CYP27B1), an enzyme that is present, beside other localizations in the pulmonary cells, striated muscles (including the respiratory muscles), endothelium and in the cells involved in the processes of specific and non-specific defense (1). Several similarities have been noticed between adults with suboptimal level of vitamin D and Chronic Obstructive Pulmonary Disease (COPD). Both conditions mostly affect adults over 60 years old. The suboptimal level of vitamin D has 59 % prevalence in Romania, with a peak in elderly females (2).
tain risk groups, such as people with osteoporosis, the level can reach over 80% (3). The estimated prevalence of COPD in Romania is 8.3% and is higher in males aged over 60 (4). The level of vitamin D has seasonal variation and reaches its peak in the cold season, when there are also the most frequent exacerbations of COPD. A recent meta-analysis showed that low levels of vitamin D correlate with the COPD severity (6) and is associated with a decrease of the ventilatory function, irrespective of other factors (5).

**IMPAIRMENT OF THE DEFENSE MECHANISMS**

Impairment of the non-specific inflammatory response is a classical pathophysiological mechanism of COPD, which relates to the chronic inhalation of irritants that activates the pattern recognition receptors, such as Toll-like receptors and increases the transcription nuclear factor κB (NF-κB) and of the mitogen-activated protein kinases (MAPK) in the pulmonary neutrophils and macrophages. The chronic inflammatory processes and the oxidative stress lead to mucus hypersecretion, destruction of the elastin fibers and fibrosis.

Vitamin D suppresses in macrophages the formation of inflamasome by preventing the activation of the TLR-NF-κB pathway by the bacterial endotoxins. It also increases the IL10 production by enhancing transcription and via a calcium-dependent mechanism (7, 8). Vitamin D inhibits the maturation of dendritic cells, which modulates the function of T helper cells (Th), increasing the efficiency of the defense mechanism. Therefore, in vitamin D deficit, there is an impairment of the nonspecific host defense with increase of the inflammatory processes and a decrease of the reparatory, limitative ones. Vitamin D (1,25-dihydroxyvitamin D3) receptors (VDR) complex translocate in the nucleus, inducing the expression of cathelicidin, an antimicrobial and anti-inflammatory peptide. Cathelicidin is expressed in cells involved in the primary line of defense (keratinocytes, leukocytes, monocytes, neutrophils) as well as in T and B or NK cells.

In macrophages, the activation of Toll-like receptors up regulates the expression of VDR and of the genes expressing 25(OH)D3-1α-hydroxylases, inducing the expression of cathelicidin and the intracellular destruction of Mycobacterium tuberculosis (9, 10). In aseptic inflammation, cathelicidin plays a role in chemokine expression, stimulates angiogenesis and apoptosis and favors wound healing (10). Therefore, the chronic bacterial colonization and the decrease of the defense ability against pathogens through an impairment of the macrophage and neutrophils function in COPD patients could be magnified by the low level of cathelicidin secondary to vitamin D deficiency.

The actual mechanism of the specific immunity activation in COPD is not known. An exacerbated immune activation is noted, along with the increase in the number of T lymphocytes (L) and BL in the lungs. Lymphocytes organize themselves in lymphoid follicles, with the increase of the number and the activation of dendritic cells, which induces a predominantly differentiation in Th1 type. This increases the level of TNF-α, IL-1β, and IL-6, cytokines with pro-inflammatory effect, of the TGF-β and other growth factors for fibroblasts. These processes end up with the fibrosis of the small airways and a permanent inflammatory infiltrate of monocytes and Th1 cells. Vitamin D suppresses
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both the proliferation and the secretion of pro-inflammatory Th1 cytokines: IL2, IFNγ, TNFα and promotes the synthesis of anti-inflammatory cytokines by Th2 lymphocytes (IL3, IL4, IL5, IL10) (10, 11, 12). As consequence, in vitamin D deficit, the pathogenic mechanisms of COPD, previously described, are favored (fig. 1).

**Fig. 1.** Defense mechanism impairment in vitamin D deficit and COPD

**THE DYSFUNCTION OF THE RESPIRATORY MUSCLES**

The respiratory muscles are made up of 2 very thin muscle layers located in the intercostal space and by the diaphragm; the contraction of the later one ensures 70% of the ventilation/minute. In COPD, hyperinflation causes the flattening of the diaphragm and reduces the contraction force by altering its radius; hyperinflation also changes the normal relationship between the ends of the myosin fibers and the actin filaments and decreases the pressure generated for the same tension developed within (13). As an adaptation to permanent overload, type II fibers in the respiratory muscles change into type I fibers (14, 15), increasing the diaphragm resistance to fatigue but decreasing its ability to generate contraction force. In COPD, there is also a reduction in number and length of sarcomeres that moves the curve tension length to the left, as an adaptation to a lesser inspiratory extension determined by hyperinflation. However, reduction of the number of sarcomeres will end up reducing the force of muscle contraction. The respiratory muscles have to work 10 – 14 times more in COPD patients, as compared to healthy people, due to the chronic hypoxemia (16) and the adaptive phenomena described so far become inefficient. Even in moderate forms of COPD, the force of the inspiratory muscles is more severely
reduced than that of the expiratory ones; this is associated with a decrease of the proximal muscle force in the peripheral muscles (17). The long-term effects of COPD on respiratory muscle are muscle atrophy, changes in titin structure and an increase of sarcomere susceptibility to the harmful action of external factors (18).

Vitamin D has a regulatory role in muscle development and in the contraction force, increasing the transcription of myosin and of other calcium binding proteins. The association between the vitamin D deficiency and the proximal myopathy is clinically demonstrated by the improvement of muscular force after the administration of vitamin D to adults with a deficit of this vitamin. The preferential atrophy of type II muscle fibers may occur in the vitamin D deficiency with a similar effect to the one found in age-related sarcopenia and COPD (19) and it is reversible after vitamin D administration (20). The interaction of vitamin D with VDR stimulates adenylate cyclase, phospholipase C, D and A2 and increases the MAPK signal and inositol 3 phosphates (IP3). The intracellular calcium rises by influx through calcium voltage-dependent channels activated by protein kinase A and by release from endoplasmic reticulum system IP3. The MAPK and Akt signal influences cell development, mitosis and differentiation of the myoblasts. Vitamin D deficiency will trigger a reduction of the contraction force through calcium deficit and impaired muscle fibers formation (21) and a decrease of the phosphate transport into the muscle cell, essential for ATP and protein synthesis.

Vitamin D releases the arachidonic acid from the phosphatidylcholine bound to the cell membrane. This polyunsaturated fatty acid modulates the insulin receptors and the glucose uptake (22, 23). Reduction of glucose transport in muscle cell under low level of vitamin D condition has major metabolic implications and reduces the ATP production, contributing to the reduction of the contraction force (fig. 2).

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**Fig. 2.** Reduction of the contraction force of the respiratory muscles in vitamin D deficit
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**THE PREMATURE AGEING PROCESS OF THE CELLS IN THE BRONCHIAL MUCOSA**

Forced expiratory volume in one second (FEV₁) normally decreases with age from a peak reached around 25 years old. Patients with COPD present an accelerated yearly decrease of FEV₁, generally fewer than 60% of the value corresponding to age (24). Subjects who reach a maximum of initial FEV₁ lower than the medium one may develop symptoms even if no other risk factors are present, through the normal age reduction of the pulmonary function. Genetic factors, reduced physical activity during childhood/adolescence, treatment with glucocorticoids and malnutrition are other possible causes of low initial maximum FEV₁.

The premature ageing process in COPD is related to the reduction of the expression of sirtuins compared to the age. Oxidative stress, characteristic for the chronic inflammation in COPD, blocks sirtuins activity. Vitamin D also affects both the acetylation of histones and the methylation of the DNA. The VDR/RXR complex, in the absence of 1.25-D₃, can bind to co-repressors which attract histone-deacetylases. By binding of vitamin D to VDR, the co-repressors are replaced by co-activators as histone acetyl transferases; these might lead to similar effects with the decrease or blockage of the sirtuins.

The decrease of autophagy and the increase of mitophagy contribute to premature ageing of the respiratory mucosa in COPD. The mitophagy, enhanced by many compounds from the cigarette smoke, has the opposing effect to autophagy, triggering apoptosis. Vitamin D takes part in the regulation of autophagy through calcium, PI3k, the expression of beclin-1 (25, 26) and of cathelicidin (27). In the absence of vitamin D, the physiologic processes of autophagy are reduced and the cell destruction phenomena are emphasized (25, 26).

The level of vitamin D decreases after the 6th decade. A conclusion regarding the preventive effect of vitamin D on the ageing of bronchial cells in COPD, although conceivable, has not yet enough scientific proofs.

**CONCLUSIONS**

We concluded that the vitamin D and COPD relationship is very complex. Since the epidemiologic and experimental data support the relationship between vitamin D deficiency and COPD, it is expected that future research will bring important insights in the understanding of these processes. The identification of common pathophysiological mechanisms for the vitamin D deficiency and COPD substantiates the hypothesis of the involvement of this hormone in the chronic obstructive pulmonary disease.

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