Vitamin D on Skeletal Muscle Dysfunction with COPD

Subjects: Others

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Skeletal muscle dysfunction is frequently associated with chronic obstructive pulmonary disease (COPD), which is characterized by a permanent airflow limitation, with a worsening respiratory disorder during disease evolution. COPD is a progressive lung disease, characterized by an irreversible airflow limitation. In COPD, the pathophysiological changes related to the chronic inflammatory state affect oxidant–antioxidant balance, which is one of the main mechanisms accompanying extra-pulmonary comorbidity such as muscle wasting. Muscle impairment is characterized by alterations on muscle fiber architecture, contractile protein integrity, and mitochondrial dysfunction. Vitamin D deficiency affects oxidative stress and mitochondrial function influencing disease course through an effect on muscle function in COPD patients.

Keywords: vitamin D ; COPD ; muscle weakness ; mitochondria

1. Introduction

Chronic obstructive pulmonary disease (COPD) is a progressive lung disease, characterized by an irreversible airflow limitation [1]. The airway alterations characterizing COPD are obstructive bronchiolitis due to chronic inflammation of peripheral airways and lung parenchyma and emphysema due to the collapse of the alveolar walls and expansion of alveoli. Patients with severe COPD often exhibit overlapping pathologies such as bronchiectasis, lung cancer, hypertension, cardiovascular disease, diabetes mellitus, and osteoporosis [2]. Extra-pulmonary comorbidities also include skeletal muscle dysfunctions. Airflow limitation in patients with COPD decreases the systemic oxygen supply, producing a decline in the aerobic capacity of the type I muscle fibers with a consequent reduction in muscle endurance and a further increase in physical fatigue [3]. Moreover, systemic oxidative stress in patients with severe COPD reduces lower-extremity muscle strength, impairing the functional capacity of locomotor muscles and the ability to perform normal daily activities, such as walking or upright standing. In peripheral skeletal muscles of COPD patients, enzymatic changes and mitochondrial abnormalities have been found [4]. Other muscular abnormalities include a gradual decline of the cross-sectional area, and modifications in the structure of the type of fibers switching from slow-oxidative to fast-glycolytic fiber type [4][5]. As the disease progresses, in many patients, skeletal muscle dysfunction can turn into sarcopenia or cachexia, both of which have been associated with further increased disease severity and mortality risk [6]. Some studies have suggested the importance of optimal vitamin D status on respiratory function, underlining that vitamin D deficiency (VDD) might represent a marker of disease severity [7]. Meta-analysis studies indicate that VDD is directly associated with a more severe disease and with an increased rate of exacerbations and hospitalization [8][9]. Moreover, it has been reported that vitamin D status is linked with muscle strength outcomes [10]. VDD eliciting mitochondrial dysfunction, adenosine triphosphate (ATP) depletion, enhancement of reactive oxygen species (ROS), and oxidative damage leads to muscle atrophy and compromised muscle function [11]. However, several investigations showed that vitamin D supplementation recovers lung function, reduces exacerbations, and improves inspiratory muscle strength and maximal oxygen uptake [12] [13]. It also improves physical performance, maximal voluntary ventilation, and inspiratory pressure [14].

2. Mechanisms Mediating Muscular Wasting in COPD Patients

In developed countries, most COPD cases are due to cigarette smoking, biomass smoke, and additional environmental pollutants [1]. Carbon monoxide and nicotine damage the endothelium of blood vessels, allowing the adhesion and accumulation of fat in the blood. As a consequence, blood circulation gradually degenerates, and insufficient oxygenation depletes cellular metabolism releasing minor, macro-, and micronutrients to the cells. Altered pulmonary ventilatory mechanics in patients with COPD can further reduce the systemic oxygen supply, producing a decrease in the aerobic cellular metabolism and muscle strength, increasing physical fatigue [15]. Less oxygen distribution to skeletal muscle tissue generates peripheral muscle dysfunction, characterized by reduced muscle strength and subsequent diminished exercise propensity in COPD. Peripheral fatigue leads to progressive muscle disuse with crucial muscle fiber transformations. As muscle activation reduces, the typical tonic activation of the slow motor units, innervating type I fibers,

changes into a more intermittent discharge, with significant modification of cellular functions. In fact, a prolonged period of phasic activity applied to oxidative myofibers normally induces oxidative enzymatic reduction, mitochondrial abnormalities, and an increase in myosin heavy chains. As a result, there is a transformation of type I muscle fibers into fatigable type IIx fast-twitch glycolytic fibers [15]. These muscle fiber shifts further increase muscle fatigability, leading to the spiral of progressive inactive lifestyles degenerating into muscle weakness and atrophy [16]. In COPD patients, the impairment in lower limb muscle groups leads to deficits in biomechanical constraints; the balance is altered by anticipatory postural adjustments and motor task transitions [17][18]. Along with adaptations to reduced postural control, they also have slower walking speed with a reduced step length and increased time spent in double support [19]. Muscle dysfunctions in COPD patients are paralleled by the reduction in passive viscoelastic tension produced by the muscular articular system [20]. This finding suggests that disuse may also affect the passive components included in muscles and joints, contributing to the severe motor task alterations associated with COPD linked to muscle dysfunctions [21]. In addition to decreased physical activity, other causes facilitate muscle wasting in COPD including systemic inflammation, oxidative stress, hypoxia, and nutritional depletion [22]. Muscle dysfunction frequently occurs before disease development. This can be considered an index of mortality rate in patients with COPD not negligible compared to lung function [23].

3. Vitamin D Metabolism and Biological Function in the Muscle

Vitamin D is a fat-soluble steroid prohormone crucial for calcium homeostasis and bone metabolism [24]. To become active, vitamin D is subjected to two hydroxylation reactions that take place principally in the liver and kidneys [25]. 1α,25$(OH)_2$ D3 plasma level is regulated by CYP24A1 (cytochrome P450 family 24 subfamily A member 1) and CYP27B1 (cytochrome P450 family 27 subfamily B member 1). The excess 1α,25$(OH)_2$ D3 is regulated by the CYP24A1 enzyme which inactivates the hormone in 24,25-Dihydroxycholecalciferol (1α,24,25$(OH)_3$ D3). Conversely, CYP27B1 allows the conversion of 25(OH)D in 1α,25$(OH)_2$ D3 [25]. This conversion occurs mostly in the kidney and in all those cells/tissues expressing the CYP27B1 including homeostatic skeletal muscle fibers, in both C2C12 myoblasts and whole mouse muscle [26]. CYP27B1 is an important regulator of the calcium and phosphate homeostatic systems. It is induced by the parathyroid hormone (PTH), low Ca^{2+}, and low PO_4^{3-} levels [27]. 1,25$(OH)_2$D synthesis is induced by the parathyroid hormone (PTH), whereas calcium decreasing PTH directs negative feedback from 1,25$(OH)_2$D to PTH [28].

The active metabolite 1,25$(OH)_2$D modulates the expression of many genes by binding to its nuclear receptor, the vitamin D receptor (VDR) exerting diverse biological effects through genomic and non-genomic activities [29]. Moreover, the vitamin d/VDR complex binding the retinoid X receptor (RXR) forms a VDR-RXR heterodimer which, interacting with genomic vitamin D response elements (VDREs), regulates gene transcription [29]. In humans, the vitamin D system has been shown to be present more in precursor cells than in adult skeletal muscle [30]. Much evidence in the last few decades indicates that vitamin D is involved in skeletal muscle development and regeneration [25]. Moreover, VDR expressed in skeletal muscle induces the synthesis of muscle protein and is required to maintain muscle volume [31]. The addition of 1,25$(OH)_2$D to C2C12 myoblasts increases VDR expression, decreases cell proliferation, and promotes myogenic differentiation [32]. The binding of vitamin D to VDR stimulates the intracellular uptake of the inorganic phosphates that are used for producing energy-rich phosphate compounds essential for sustaining muscle contractility [33]. Vitamin D and VDR have an important impact on skeletal muscle function. Subsequently to muscle damage, the moderate expression of VDR and CYP27B1 observed in homeostatic conditions increases significantly. 1,25$(OH)_2$D induces the expression of myoblast determination protein 1 (MyoD1) and consequently inhibits myostatin in a time-dependent manner. Furthermore, vitamin D modulates forkhead box O (FOXO) 3 and Notch signaling pathways promoting myoblast self-renewal and sustains the satellite stem cell pool [30].

4. Vitamin D Deficiency and Muscle Weakness

Serum 25(OH)D concentration is related to vitamin D exposure and absorption. Therefore, VDD in humans is estimated as serum levels of this metabolite [34]. Serum 25(OH)D < 30 nmol/L (12 ng/mL) is defined as VDD, while 25(OH)D concentrations between 30 and 50 nmol/L (12–20 ng/mL) are categorized as vitamin D insufficiency [29]. At 25(OH)D levels above 30 ng/mL, there are optimum musculoskeletal benefits. A significant association of VDD with muscle dysfunction has been demonstrated [35]. In older adults, plasma 25(OH)D concentrations < 25 nmol/L are associated with significantly lower grip strength [36].

Much evidence suggests that vitamin D supplementation improves muscle strength, although in the different studies conducted up to date, there are different methodological differences such as the characteristics of the participants, the duration, and dosage of supplementation. In a study performed in young adults, which included subjects with a vitamin D status varying from insufficient to optimal, it observed that in those with higher baseline 25(OH)D concentrations, the muscle strength following an intense endurance exercise was recovered [37].

In a meta-analysis study including young participants with 25(OH)D concentrations < 25 nmol/L, vitamin D supplementation ranging from 4000 to 60,000 IU per week strengthened both upper and lower body strength [38].

In a biopsy sample, VDD was found to be linked to skeletal muscle dysfunction and mainly related to type II muscle fiber atrophy [39]. VDR knockout mice (VDRKO) show muscle weakness, muscle fiber atrophy, and hypernuclearity, as well as VDR deletion, generating alterations in muscle function and strength [40][41]. VDRKO exhibited smaller muscle mass and weaker grip strength when compared with controls [42]. Moreover, they showed reduced diameter muscle fibers and an abnormal expression of myogenic transcription factors with respect to wild-type mice, suggesting a physiological role of VDR through temporal down-regulation of myogenic transcription factors [43]. Humans with VDD are often affected by skeletal muscle weakness and myopathy; however, they promptly react to treatment with vitamin D3 [32]. As a consequence of VDD, a pronounced weakness in the proximal muscle becomes evident, which leads to widespread muscle pain and waddling gait [44]. Vitamin D3 supplementation improves muscle strength in humans. Meta-analyses of randomized clinical trials in the general population reported that vitamin D supplementation exerts beneficial effects on muscle strength and physical abilities [45][46]. These improvements are higher in subjects with severe VDD at baseline [47]. Nevertheless, scientific opinions on the relationships between vitamin D status and muscle function in COPD patients are controversial.

5. Role of Vitamin D in Anti-Oxidative Mechanisms Implicated in Muscular Wasting in COPD Patients

Vitamin D regulates calcium (Ca^{2+}) homeostasis in skeletal muscle. Ca^{2+} is an important component in muscle energy metabolism contributing to the interaction between cytosol and mitochondria [48]. Ca^{2+} and ROS are the main secondary messengers involved in numerous cellular signaling pathways. Mitochondria influence both ROS and Ca^{2+} homeostasis and transfer signaling [49]. The compromised Ca^{2+} protecting role of dysfunctional mitochondria generates an increase in the intracellular level of Ca^{2+}. Thus, VDD may cause mitochondria's insufficient Ca^{2+} uptake generating the perturbations of cellular metabolic homeostasis [11]. 1α,25$(OH)_2D_3$, the most active form of vitamin D3, is crucial in muscle regeneration, in the regulation of skeletal muscle tone and contraction, as well as in the preservation against muscle damage [11]. VDD modifies muscle contraction kinetics reducing Ca^{2+} reuptake into the sarcoplasmic reticulum, thus leading to a perpetuation of the relaxation phase of muscle contraction. Moreover, VDD increases the cytotoxicity mediated by ROS and is associated with failure in mitochondrial respiration [50]. Therefore, VDD may contribute to exacerbating the damage of muscle and atrophy for the excess mitochondrial ROS production [11], oxidative impairment, and ATP reduction. In several clinical models, muscle atrophy and deficits in muscle strength at low 25(OH)D concentrations (<50 nmol/L) levels have been reported [51]. In muscle, one of the wasting reasons results from a disproportion in the protein degradation and synthesis rates [19]. VDD influences protein synthesis and degradation. The foremost known proteolytic pathways in the skeletal muscle are the ATP-ubiquitin-dependent system, the lysosomal system, and the cytosolic calcium-activated system [52]. The ATP-ubiquitin-dependent system is the only one dependent on vitamin D [52]. In skeletal muscle cells, the treatment with 1α,25$(OH)_2D_3$ induces an increment of oxygen consumption rate (OCR) and the generation of ATP [45]. In addition, vitamin D status mediates changes in skeletal muscle mitochondrial dynamics, pyruvate dehydrogenase phosphorylation, and expression of nuclear genes encoding mitochondrial proteins, and influences skeletal muscle performance [53]. Nevertheless, direct treatment of isolated mitochondria with 1α,25$(OH)_2D_3$ fails to increase OCR, showing that the effects of 1α,25$(OH)_2D_3$ on OCR might be VDR-dependent or by other extra-mitochondrial biochemical events (**Figure 1**) [51]. Therefore, vitamin D is beneficial in the treatment of muscle weakness once metabolized to 1α,25$(OH)_2$ D_3 [45]. This process may occur when VDD and high PTH levels drive the rapid metabolism of 25$(OH)D_3$ to 1α,25$(OH)_2D_3$. A treatment with cholecalciferol in VDD humans increases the mitochondrial oxidative phosphorylation rate [51]. Furthermore, VDD affects alterations in antioxidant enzyme activities [11]. In skeletal muscle, VDD also impacts on nitrosative stress, lipid and protein peroxidation, and reduced activities of the antioxidant enzymes [11][51]. C2C12 cell lines treated with 1,25(OH)D showed a decrease in ROS synthesis, lipid and protein oxidation, protein ubiquitination, intracellular damage, muscle proteolysis, and atrophy markers, and an increase in glutathione peroxidase (GPx) and superoxide dismutase (SOD) activities and markers of mitochondrial biogenesis in paraspinal muscle [52]. Optimal levels of ROS are used for signal transduction by skeletal muscle cells following damage. While exaggerated production of ROS by disabling defensive antioxidant systems, it damages muscle integrity [51]. Treatments of hyperoxia-exposed animals with 1,25(OH)2D3 cause a significant increase in body weight and reduced hyperoxia-induced lung injury [54]. Experimental studies on mice show that 12 months' VDD decreases anaerobic capacity and lean mass, and promotes a trend towards smaller fast-twitch fiber cross-sectional area and gait disturbance, resulting in sarcopenia. Additionally, VDD mice displayed an increase in atrophy-associated atrogin-1 gene expression and differential expression of muscle-regulation-associated miR-26a compared to control mice [55]. This finding strongly confirms that VDD impacts muscular deterioration. Indeed, vitamin-D-treated rats displayed a reduction in both oxidative stress and tissue damage after full

exercise [55]. These data corroborate the notion that vitamin D controls mitochondrial function and oxidative stress in skeletal muscle. In several experimental models, vitamin D analogues exert a protective effect on skeletal muscle and cells experiencing oxidative stress [56]. The explanation of the mechanism by which vitamin D regulates oxidative stress may be dependent on its influence in the regulation of mitochondrial dynamics and function. Pulmonary VDR and Nrf-2 are reduced in COPD patients [57] (Figure 1). Nrf-2 is an important transcription factor that mediates antioxidant defense pathways [58]. Pulmonary Nrf-2 downregulation causes failure of the antioxidant defense system, impairment of pulmonary epithelial cells, and promotes the onset of COPD [57]. Vitamin D supplementation activates VDR [59] and induces the Nrf2-Keap1 antioxidant pathway [58] (**Table 1**).

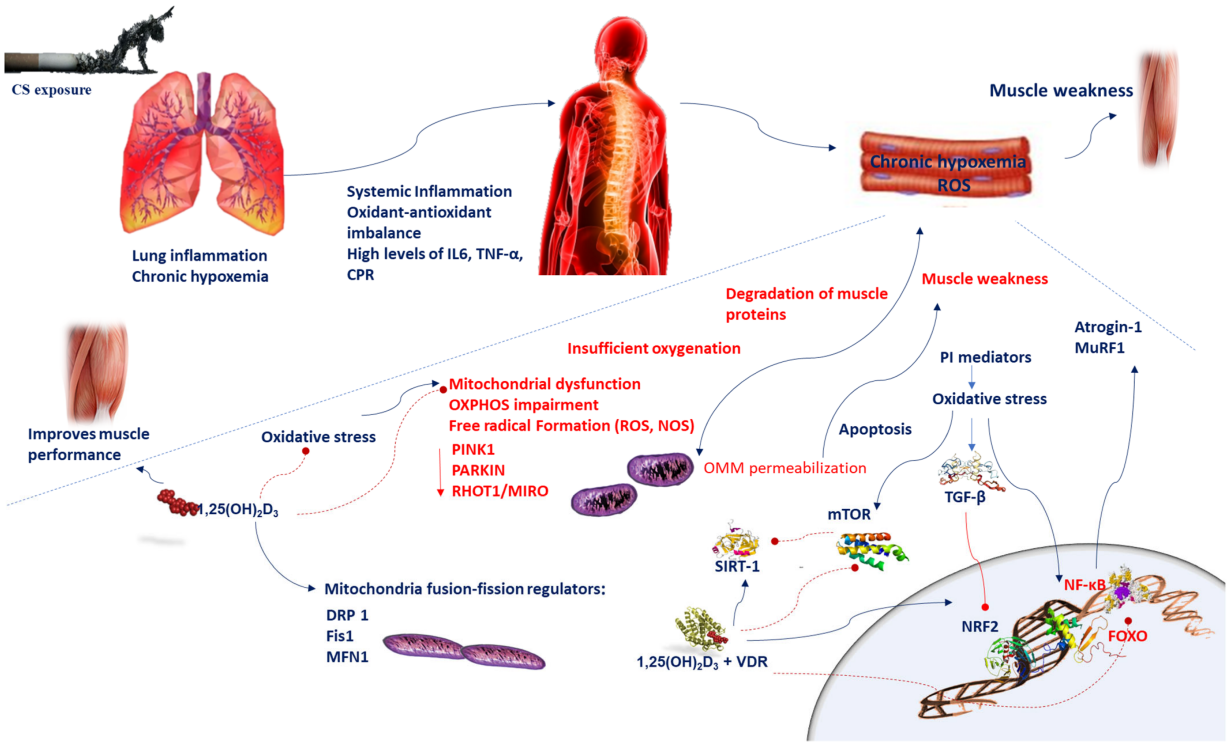

Figure 1. Chronic hypoxemia contributes to inflammation, which generates mitochondrial dysfunction, impairments in mitochondrial turnover, and oxidant–antioxidant imbalance. Reduced respiration causes insufficient oxygenation and mitochondrial dysfunction, which in turn leads to alteration of mitochondrial OXPHOS and increases ROS levels. A disproportionate stimulation of fission induces mitochondrial dysfunction. Reduction in the mitochondrial fusion factor OPA1 impairs the mitochondrial network and promotes apoptosis. Blockade of fission Fis1 or Drp1 inhibits mitochondrial fragmentation. Oxidative stress triggers the TGF-β signaling pathway, which induces inhibitory effect on Nrf2, which in turn inhibits endogenous antioxidants. Oxidative stress induces cellular senescence via FOXO transcription factors and decreases SIRT-1 expression and enzyme activity; ROS activate the PI3K-mTOR pathway. Vitamin D supplementation prevents the mitochondrial dysfunction and oxidative stress by setting MFN1/2, OPA1, and Drp1 expression. Oxidative stress activates NF-κB and FOXO pathways which influences muscle wasting in COPD patients. Vitamin D and VDR represses NF-κB and modulates the post-translational modification and function of FoxO proteins. The beneficial effects of SIRT-1 on mitochondrial function are regulated by vitamin D, which acts by increasing SIRT-1 formation. Abbreviations: CPR = C-reactive protein; Drp1 = dynamin-related protein 1; 1,25(OH)2D3 = 1,25-dihydroxyvitamin D3; Fis1 = fission protein 1; FOXO = forkhead box O; IL-6 = interleukin-6; MFN1/2 = mitofusin-1/2; mTOR = mammalian target of rapamycin; MuRF1 = muscle-specific RING finger protein 1;NOS = nitrogen species; Nrf2 = nuclear factor erythroid 2-related factor 2; NF-κB = nuclear factor kappa; OPA1 = optic atrophy protein 1; OXPHOS = oxidative phosphorylation; PI3K = phosphatidylinositol-3-kinase; ROS = reactive oxygen species; RHOT-1/MIRO = Ras homolog family member T-1; TGF-β = transforming growth factor-beta; TNF-α = tumor necrosis-alpha; sirtuin-1 = SIRT-1; VDR = vitamin D receptor.

Table 1. Possible vitamin D linked mechanisms involved in mitochondrial function.

Experimental Data	Model	Sample Size	Tissue	Approach	Reference
Evaluation of oxygen consumption, biogenesis, dynamics, and nuclear genes encoding variations.	Human	//	Muscle biopsies. Primary human skeletal muscle cells.	Supplementation of 1α,25-Dihydroxyvitamin D3 (10-8 M) for 48 h. VDR expression in human muscle cells and skeletal muscle homogenates. Effect of 1α,25(OH)$_2$D mitochondrial oxygen consumption and in expression of: mitochondrial proteins that alter mitochondrial fusion; proteins associated with mitochondrial fission; phosphorylated pyruvate dehydrogenase and pyruvate dehydrogenase kinase 4; genes encoding mitochondrial proteins; and genes encoding cellular signaling and growth-regulatory pathways in adult human skeletal muscle cells. Knockdown of VDR with silencing RNA in skeletal muscle cells to detect the effects of 1α,25(OH)$_2$D$_3$ on OCR.	[45]
Assessment of oxidative and nitrosative stress parameters.	Rat	//	Fasting blood samples analysis. C2C12 cell culture.	Supplementation of 1,25(OH)2D3 (1 nM and 10 nM) for 24 h. Effect of VDD in muscle oxidative stress in a rat model. Pre/post treatment of C2C12 muscle cells with vitamin D offers protection against oxidative stress induced muscle proteolysis. VDD increase in activities of the glutathione-dependent enzymes and decrease in SOD and catalase enzymes in the rat muscle. Pre/post treatment of C2C12 muscle cells with vitamin D correct total protein degradation, 20S proteasomal enzyme activity, muscle atrophy gene markers and expression of proteasome subunit genes induced by oxidative stress.	[51]
Serum and lung tissue analysis.	Human	180 COPD patients	Human lung tissues and serum samples of COPD.	Level of pulmonary VDR-positive nuclei between COPD patients and control subjects Correlations of pulmonary function with pulmonary DJ-1, Nrf-2 and VDR in COPD patients.	[57]
Antioxidant and antiaging effects of 1,25Dihydroxyvitamin D by activation of Nrf2-antioxidant signaling and inactivation of p16/p53-senescence signaling.	Mouse	120	Skin, lung, liver, kidney, and spleen.	Two different supplementation: thrice weekly of 2.2 IU vitamin D/g or 1,25(OH)2D3 (1 µg/kg) until death. Effects of a high-calcium/phosphate diet, of 1,25(OH)$_2$D$_3$, and of antioxidant supplementation on lifespan, body weight, skin morphology; on oxidative stress, DNA damage, protein expression of oncogenes and tumor suppressive genes; and on cell proliferation and senescence in 1α(OH)ase$^{-/-}$ mice.	[58]
Improvement in parameters of mitochondrial function in vitamin-D-deficient individuals after vitamin D supplementation.	Human	12 subjects with severe vitamin D deficiency	Serum samples	Effect of cholecalciferol therapy (20 000 IU supplementation on alternate days for 10–12 weeks) in muscle mitochondrial maximal oxidative phosphorylation after exercise in symptomatic, vitamin-D-deficient individuals.	[60]

Experimental Data	Model	Sample Size	Tissue	Approach	Reference
FOXO1 activation in the skeletal muscle of global VDR-null mice.	**Mouse**		**$VDR^{-/-}$ mice administered a diet enriched with calcium and phosphorus; $SMVDR^{-/-}$ mice generated by crossing $VDR^{loxp/loxp}$ mice with mice with muscle-specific Cre recombinase expression under the control of the myosin light chain 1f (MLC 1f) genomic locus; C2C12 muscle cells.**	**Treatment of C2C12 muscle cells with 1,25-dihydroxyvitamin D (100 nM for 48 h) to detect FOXO1 expression, nuclear translocation, and activity. Evaluation of FOXO1 activation in knockdown VDR mice.**	[61]
Effect of vitamin D supplementation on oxidative stress.	**Mouse**	**Eight mice for each experimental group.**	**Adipocyte cell culture model**	**Supplementation of cholecalciferol (67 IU VD/kg daily for last 8 weeks) to detect the effects of $1,25(OH)_2D_3$ supplementation in NOX4, Nrf2 SIRT-1 expression, ROS production, NF-κB and AMPK phosphorylation.**	[62]

Abbreviations: VDR = vitamin D receptor; $1α,25(OH)_2D$ = 1α,25-Dihydroxyvitamin D; RNA = ribonucleic acid; 1,25(OH)2D3 = 1,25-dihydroxyvitamin D3; OCR = oxygen consumption rate; VDD = vitamin D deficiency; SOD = Superoxide dismutase; Nrf2 = nuclear factor erythroid 2-related factor 2; 1α(OH)ase = 1α-hydroxylase enzyme; FOXO1 = forkhead box O1; SMVDR = skeletal muscle-specific VDR; NOX4 = NADPH Oxidase 4; SIRT-1 = sirtuin-1; ROS = reactive oxygen species; NF-κB = nuclear factor kappa; AMPK = AMP-activated protein kinase.

These data highlight the value of vitamin D for a suitable redox equilibrium and underline how vitamin D analogues' administration stimulates muscle mitochondrial health during oxidative stress.

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