

Review Article

Effect of vitamin D on Becker muscular dystrophy: A review

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Abstract

The correlation between Becker muscular dystrophy (BMD) and vitamin D has long been known, since vitamin D controls bone turnover which occurs in this disease. Thus, vitamin D is beneficial to some extent to BMD patients due to the fact that it has long been known to play an important part in bone metabolism. According to recent studies which suggest association between vitamin D and multiple diseases involving multiple organs, vitamin D may alleviate the pathophysiology of BMD. This review focuses on the benefits of vitamin D to BMD patients through alleviation of the pathophysiology and complications of the disease.

Keywords: *Becker muscular dystrophy, Cardiomyopathy, Vitamin D*

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INTRODUCTION

Becker muscular dystrophy (BMD) is a genetic disorder caused by a mutation in dystrophin gene, resulting in synthesis of a defective dystrophin protein in the muscle. This disease is named after the German doctor, Peter Email Becker, who first described this variant of BMD [1-3]. Dystrophin performs a major structural role because it links the internal cytoskeleton to the extracellular matrix. The N-terminal amino acid of dystrophin binds to actin, while the C-terminal amino acid binds to dystrophin-associated protein complex (DAPC) which consists of dystroglycans, sarcoglycans, integrins and caveolins. Dystrophin-associated protein complex (DAPC) is destabilized when dystrophin is absent, leading to diminished levels of the

member protein. This in turn leads to progressive fiber damage and membrane leakage [4-6]. The muscles affected by this disease are skeletal muscle, cardiac muscle and respiratory muscle. The decline in cardiac muscle in these patients may surpass decline in skeletal muscle, and death from cardiomyopathy often occurs before the age of 60 [7-9]. The role of vitamin D in bone metabolism has for long been recognized. However, recent studies have suggested the involvement of vitamin D in many skeletal diseases.

This review was carried out to summarize the pathophysiology of BMD and effect of vitamin D on the disease, based on recent studies.

Pathophysiology of dystrophin-deficient skeletal muscle

Muscle damage is the first step in the pathophysiology of dystrophin-deficient muscle which finally leads to pathological processes such as loss of calcium homeostasis, chronic inflammatory response, and ultimately fibrosis. Thus, two defects occur in dystrophin-deficient muscle which may lead to muscle damage: fragility and leakiness of cell membrane (due to a defect in dystrophin gene) which render the muscle highly susceptible to mechanical stress and ischemia [7]. Three different isoforms of nitric oxide synthase (NOS) are generated by three genes in skeletal muscle. These genes are neuronal NOS (nNOS or NOS1 which is the predominant form of NOS in skeletal muscle fibers and an isoenzyme form of nNOS; inducible NOS (iNOS or NOS2) which is present in small amounts in healthy muscle tissue, but in muscular dystrophy, there are increases in iNOS in skeletal muscle (SM) as a result of presence of inflammatory cells rich in the isoenzyme; and endothelial NOS (eNO or NOS3). In SM, eNOS is derived mostly from cells of the endothelium.

Ischemia in dystrophin-deficient skeletal muscle is caused by several factors viz:

(a) *Deficiency of nNOS*: The nitric oxide (NO) produced by nNOS is very important for increasing local blood flow to meet metabolic load of contracting muscle, especially during exercise. Thus, lack of nNOS leads to functional ischemia [5,10,11].

(b) *Deficiency of eNOS*: As mentioned previously, SM eNOS is present mainly in vasculature endothelium. The NO produced by eNOS is necessary for regulation of vascular tone and blood flow. Consequently, any defect in NO production by this enzyme may result in ischemia. Indeed, it has been reported that eNOS level is reduced in dystrophin-deficient patients [12]. After muscle damage, a number of pathological processes occur which finally lead to fibrosis as a result of increased calcium level in dystrophin-deficient muscle due to leakiness of cell membranes, an important factor in the pathophysiology of cell death [7,13]. The increased calcium levels induce proteolysis due to activation of calcium-dependent proteases such as skeletal muscle-specific calpains and activation of calcium channel, ultimately leading to muscle degeneration [7,14]. Moreover, chronic inflammation results from oxidative damage which occurs as a consequence of impaired calcium homeostasis [15] and inflammation/fibrosis which occur due to continuous muscle

degeneration and damage, as in muscular dystrophy. Chronic inflammation ultimately leads to fibrotic lesions characterized by massive deposition of collagen, resulting in permanent scar formation that impairs tissue function. Injury to muscles lacking dystrophin provokes a 'cytokine storm'. Cytokines [e.g. tumor necrosis factor alpha (TNF α), interleukin (IL)-1 and IL-4] are major mediators of inflammatory responses involved in tissue lesions [13,16,17]. These damages include pathophysiological changes that can occur in dystrophin-deficient muscle (skeletal muscle) which ultimately decrease the strength of the muscle. The pathophysiological processes involved in dystrophin deficiency are summarized in Figure 1.

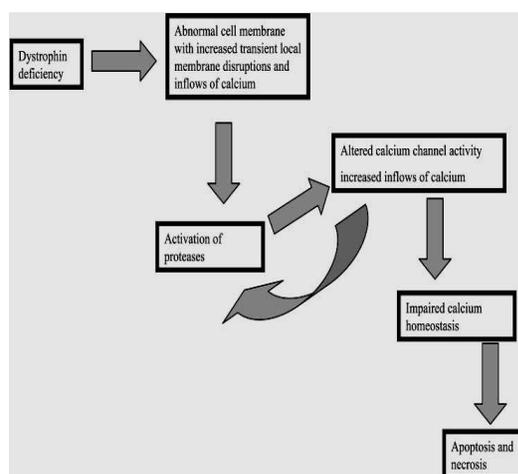


Figure 1: Pathophysiology of dystrophin deficiency

Immune cells involved in inflammation of dystrophin deficient skeletal muscle

The immune cells involved in inflammation in skeletal muscle in BMD are:

Macrophages: The key cells associated with damaged muscle tissue are tissue-resident macrophages and blood-derived monocytes which arise from invasion of the injury site (they also differentiate into macrophages). These macrophages perform the function of removing muscle tissue debris, apart from regulating muscle regrowth through cytokine release [18,19]. There are two types of macrophages in regenerating muscles after injury, and they are involved in opposing functions i.e. pro-inflammatory and anti-inflammatory macrophages. The pro-inflammatory type comprise macrophages or classically activated (M1) macrophages which are implicated in acute inflammatory processes due to exposure to T-helper1 cytokines (INF- γ and TNF α) and LPS. The M1 macrophages appear in early stages of

muscle injury with recruited monocytes, and are involved in antigen presentation, phagocytosis of dead tissue components, and secretion of inflammation-inducing cytokines (tumor necrosis factor- α and interleukins). Moreover, M1 macrophages secrete iNOS which catalyzes the conversion of L-arginine substrate to NO used for destroying pathogenic organisms. In contrast, activated M2 macrophages consist of sub-types which perform varied functions. The M2a sub-type is linked to tissue repair and fibrotic lesions, while the M2c sub-type is thought to inhibit inflammation since it suppresses M1 macrophages. In addition, M2c enhances the viability of cells outside the bone marrow. Therefore, M2 macrophages are associated with the initial phases of muscle damage, prior to presence of M2c sub-type, while the M2a sub-type dominates at the later phases [16].

T lymphocytes: These are the other cells in the immune system which are involved in muscle repair and fibrosis. They can differentiate into different functional types: CD4+ T helper-1 cells produce interferon- γ , TNF α , IL-12 and IL-20 which enhance cell-mediated immunity. These cytokines exert fibrosis-suppressing effects. On the hand, CD4+ T helper (Th)2 cells secrete IL-4, IL-5, IL-6 and IL-13 which induce fibrosis. The Th1 and Th2 cytokines are mutually antagonistic in their functions. Changes in this mutual relationship are reflected in either pathogenesis of fibrosis or suppression of same [20]. In addition, the other inflammatory cells involved in dystrophic muscle fiber wasting are mast cells, eosinophils, and neutrophils. However, the role of these cells in BMD is not clear, although research data indicate that they are significant factors in pathogenesis of the disease [21].

Pathophysiology of dystrophin-deficient cardiac muscle

In addition to skeletal muscle involvement in BMD, myocardial involvement also occurs, resulting in dilated cardiomyopathy (DCM). Studies have shown DCM, a progressive disease linked to heart failure and ventricular arrhythmias, results in high degree of morbidity and mortality [22,23]. The main pathophysiological changes involved in cardiac muscle fibrosis are similar to some extent to what occurs in skeletal muscle. Impairments in membrane stability, as well as impaired resistance to mechanical stress and ischemia which nearly resemble what occurs in skeletal muscle due to dysfunctional dystrophin protein, lead to cardiomyocyte damage. These changes lead to a sequence of events which result in fibrosis. The pro-fibrotic changes are increased

calcium influx as a result of fragility and susceptibility of the sarcolemma to damage from muscle contractions, which finally leads to death of cardiomyocytes; and membrane-destructive proteolysis due to calcium-induced activation of calpains, a group of proteases, resulting even in more calcium influx. Sustained Ca²⁺ overload results in cardiomyocyte necrosis [24-26]. Moreover, it leads to oxidative damage due to impairment of mitochondrial function and raised levels of damaging free radicals, both of which ultimately lead to cell death [15]. When cardiomyocytes are damaged, inflammation occurs due to migration of macrophages to remove lesioned cells and rubble. This results in fibrosis due to invasion of the damaged area by fibroblasts which then form a scar tissue. Fibrosis results in inflexible scar tissue, thereby decreasing the contractility of heart muscle. The fibrotic region gradually stretches, becomes thinner and loses contractility, leading to dilated cardiomyopathy [16,24].

Vitamin D

Vitamin D is a fat-soluble vitamin that exists in two forms: ergocalciferol or vitamin D2 and cholecalciferol or vitamin D3. Vitamin D2 is present in plants and some fish, while vitamin D3 is synthesized in the skin from 7-dehydrocholesterol on exposure to sunlight (ultraviolet B rays) [27-29]. Vitamin D in its native form is not biologically active. Vitamin D from diet (ergocalciferol) and skin (cholecalciferol) are transported in the blood by circulating vitamin D-binding globulin to the liver where it is converted to 25-OHvitamin D (25-OHD), the main circulating metabolite of vitamin D which has low biological activity. In the kidneys, 25-OHD is hydroxylated by the enzyme 1 α -hydroxylase to 1,25-diOH vitamin D [1,25(OH)2D], the active form of the vitamin [30-32].

Functions of vitamin D

Vitamin D is important for maintenance of adequate serum levels of calcium and phosphorus necessary for formation and sustenance of strong bones [33]. The binding of 1,25-(OH) 2D to its receptor (VDR) enhances the absorption of Ca in the intestine up to 40 %, and enhances that of phosphorus to about 80 % [34]. Vitamin D receptor (VDR) is present in osteoblasts. Vitamin D deficiency impacts the skeletal muscle, and results either in rickets or osteomalacia, depending on age [35-37]. The discovery of the presence of VDR in various other sites such as cardiomyocytes, pancreas, immune cells, brain and other sites suggests that

the vitamin has effects on other systems apart from musculoskeletal system [38-40].

Vitamin D and Becker muscular dystrophy

Vitamin D may play a role in mitigating BMD in skeletal and cardiac muscles. As mentioned previously, ischemia is one of the pathophysiological features of BMD in skeletal and cardiac muscles. Ischemia arises from lack of eNOS. The endothelial cells contain VDR which express 1-alpha-hydroxylase that enables the endothelial cells carry out the conversion of 25-OHD to 1,25 (OH)₂D which controls the expression of NOS in endothelial cells, thereby enhancing the production of NO [41]. Thus, administration of vitamin D to BMD patients may alleviate ischemia which occurs in skeletal and cardiac muscles, especially in patients suffering from vitamin D deficiency. Moreover, vitamin D may mitigate oxidative damage that occurs in BMD due to the fact vitamin D suppresses the generation of superoxide anion, thereby inhibiting ROS and oxidative stress [42,43].

In chronic inflammation which leads to fibrosis, an important step in the pathophysiology of BMD in skeletal and cardiac muscles, the expressions of cytochrome p450 27B1 and VDR genes by macrophages and T lymphocytes are markedly upregulated. This suggests that vitamin D may target the immune/inflammation system via regulation of expressions inflammatory cytokines and suppression of pro-inflammatory cells [44, 34]. Thus, vitamin D may be beneficial to BMD patients.

CONCLUDING REMARKS

There is need for further studies on the mitigating influence of vitamin D on BMD. Although recent studies indicate that vitamin D is critical in the pathophysiology of other diseases beyond its critical function in maintenance of calcium homeostasis, there is still limited knowledge about the relationship between vitamin D and BMD. Thus, further studies are needed to get more detailed information on how vitamin D may help BMD patients to maintain muscle mass and strength and decrease cardiac complications associated with the disease.

DECLARATIONS

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Conflict of interest

No conflict of interest is associated with this work.

Contribution of authors

I declare that this work was done by the author named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by the authors. The author read and approved the final manuscript.

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