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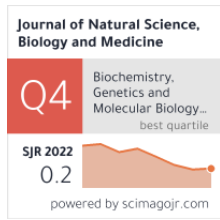
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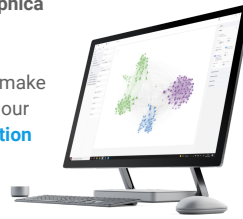
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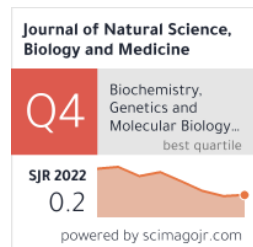
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Effects of Vitamin D on Muscle Mass Regulation: Potential Treatment in Patients with Sarcopenia

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Abstract

Many studies have revealed that vitamin D is required in the cellular metabolism of skeletal muscles. It acts in the genomic pathway, particularly in the mTOR signalling pathway, namely IGF-I-Akt-FOXO pathway. Vitamin D also acts in the ATP-dependent ubiquitin-proteasome pathway, a major proteolytic pathway, affecting mitochondrial function. In older adults, vitamin D deficiency is quite common leading to decrease in muscle mass and strength and increase in frailty incidence. Sarcopenia enhances the risk of physical limitation, reduces life quality and independence and increases mortality. Because of its burden, the potential treatment is required to improve the muscle strength. Based on previous studies, vitamin D supplementation has advantageous effects on sarcopenia. These effects include increase in muscle strength and suppression in the process of muscle atrophy. However, the precise role of vitamin D supplementation in preventing and treating sarcopenia is still being explored. Further interventional investigations are required to prove the effectiveness of vitamin D supplementation on skeletal muscle. Moreover, determining the optimum level of this vitamin to preserve muscle mass and strength in older adults requires further investigation.

Keywords: aging, mTOR, sarcopenia, vitamin D

INTRODUCTION

Sarcopenia is a syndrome defined by gradual and complete loss of skeletal muscle mass and decline in its strength. This condition develops slowly over a span of several decades. The disorder enhances the risk of physical limitation, reduces the quality of life and independence and also increases mortality.^[1-3] This condition is estimated as an unavoidable part of advancing age.^[3,4] Some studies have revealed that vitamin D level not only correlates with muscle mass and strength but also the physical performance in the elderly.^[5,6] Some have reported that the decline of muscle mass and strength is independently linked with serum vitamin D levels.^[2,6-8] The baseline of vitamin D is lower in men than in women and is relevant to decline in muscle strength because it might be related to physical activity, disease burden and renal impairment.^[6,9] The elderly with low level of vitamin D are at higher risk of developing this disorder. Besides sarcopenia, they are more prone to develop other geriatric-related problems, such as frailty and falls.^[5] Vitamin D supplementation improves age-related deterioration of muscles^[2,5,8,10] and reduces the risk of falls.^[7]

Based on previous studies, vitamin D supplementation has advantageous effects on sarcopenia i.e. increase in muscle strength and decrease in muscle atrophy, however, it is still controversial. The precise function of vitamin D in preventing and treating sarcopenia, especially its role in the mTOR pathway, is still under investigation.

SARCOPENIA

Sarcopenia is a multifactorial disease recognized by decreased physical activity, reduced caloric intake, altered muscle metabolism and developed progressive fibrosis. In addition, prolonged inflammatory conditions, oxidative stress and neuromuscular junction degeneration are also the causative factors of this disease.^[1-5,7,11] The main risk factor for sarcopenia in middle age is the

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lack of physical activity with decreased muscle fiber. Gradually, muscle fiber loss starts at the age of 50 years until it reaches a loss of about 50% by the age of 80. These conditions can also be seen in athletes.^[1,3,8] The decrease in muscle mass occurs at the rate of about 0.8% per year in the fourth decade and reaches at about 15% decrease per decade following the sixth decade.^[10]

Sarcopenia is commonly found in older adults with decreased regulation of protein synthesis and inadequate caloric and protein intake to maintain muscle mass.^[1,3] Food consumption is reduced by 25% at the age of 40-70 years with a significant reduction in the quality of food as well.³ Decreased protein intake and low vitamin D levels are indicated by diminished muscle mass and strength.^[1,7] Other than this, lack of physical activity is also known to contribute to sarcopenia. Reduction in muscle fiber and strength are more evident in patients having sedentary lifestyle than those who are physically active.^[1,3,6] Physical exercise synergized with protein and essential amino acid consumption can slowdown the decline in age-related muscle mass and its strength.^[6]

With increasing age, the concentration of some hormones (growth hormone, insulin-like growth factors, testosterone, thyroid hormone) decreases, leading to muscle mass and strength deterioration. Critical muscle loss is often because of decrease in hormonal anabolism and increase of catabolic signalling mediated by pro-inflammatory cytokines.^[3] Some of these inflammatory markers and their associated factors are tumor necrosis factor-alpha (TNF-), interleukin-6 (IL-6) and C-reactive protein (CRP). The age-related inflammation is usually low-grade, continuous, and systemic and it also contributes to tissue degeneration. It occurs due to decreased immunity or exposure to lifelong antigenic provocations, leading to the rise of reactive oxygen species (ROS) and tissue injury. This is followed by release of cytokines which contribute to sarcopenia through the ubiquitin-protease system. Disruption in ed these cytokine-signalling pathways promote inflammatory conditions and drive sarcopenia pathogenesis. This condition results in anabolic resistance, indicating that physiological protein synthesis of skeletal muscle in older adults is below muscle maintenance level.^[1]

Histologically, sarcopenic conditions affect the type II muscle fibers in conjunction with the decreased amount, size, (of the muscle) and mitochondria number.^[1] In humans, satellite cell content decreases with age especially in the type II muscle fibers. These cells have an essential role in the renewal, restoration and hypertrophy of the fibers. The loss of satellite cells is related to the sarcopenia process, impaired muscle adaptive response to anabolic stimuli, or both.^[12] Type II muscle fibers which are required during high-intensity anaerobic activity, provoke fast muscle contraction rate. There are two main sub-

types of these muscle cells; type IIA are an intermediate between type I, a slow-twitch with aerobic metabolism, and type II, while type IIB are fast-twitch glycolytic characterized by high power and low endurance. Type II muscle fibers are essential for the elderly, athletes and young adults.^[6]

The European Working Group on Sarcopenia in Older People (EWGSOP2) revised the initial definition of sarcopenia based on scientific and clinical indications. The latest consensus has three critical points. First, the main sarcopenia characteristic focuses on muscle strength weakness which is evaluated by the grip strength test (cut-off point <27 kg for men and <16 kg for women). In case of the chair-standing test time, the cut-off point is >15 seconds for five times in both sexes. Diagnosis is confirmed by the low muscle mass, measured by appendicular muscle mass with a cut-off point <20kg for men and <15kg for women. Additionally, severe sarcopenia is identified by the low physical performance, which is evaluated by a gait speed test having a cut-off point < 0.8 meters per second. Second, the clinical algorithms used to diagnose, confirm and determine the severity of sarcopenia are updated. Last, the measurement indicators for identifying and defining sarcopenia with different cut-off points are provided.^[1,6,13]

Sarcopenia evaluation needs objective measurement of muscle strength and mass. The methods used to measure muscle strength include grip strength and chair-standing tests, while muscle mass is measured through calf circumference, bioimpedance analysis (BIA) and dual-energy X-ray absorptiometry (DXA). BIA and DXA are suggested to be the gold standard due to their accuracy and universal availability. They are also the only radiological tools which accept borderline values for diagnosing sarcopenia. EWGSOP2 suggested using magnetic resonance imaging (MRI) and computed tomography (CT), however, both these tools are insensitive or non-specific for assessing this disease.^[1,13] In addition, profit is reported that measuring muscle mass through deuterated creatinine is more reliable and correlates better with physical activity.^[1]

Because of the various evaluation methods, cut-off points and standards, diagnosis sarcopenia can be challenging. Significant variations in the prevalence of sarcopenia such as community-dwelling, hospitalization and home nursing make it challenging to promote preventive practices or therapeutic protocols and demand a focused and individual-centred approach.^[1]

VITAMIN D

In humans, vitamin D production mainly occurs in skin under radiance ultraviolet light as the foremost pathway and provides 80% to 100% of the body's requirements.

[2,10] Vitamin D functions in calcium homeostasis by regulating intestinal calcium absorption and maintaining serum calcium and phosphate concentrations.^[14] Some factors can affect the rate of vitamin D synthesis such as season, latitude, sun exposure, using sunscreen and clothes, ethnicity, skin pigmentation and age. The liver converts cholesterol vitamin D precursor i.e. 7-dehydrocholesterol or pro-vitamin D. When exposed to solar radiation, it is converted into pre-vitamin D which through thermic isomerization, is converted to vitamin D, returning vitamin D-binding protein to the liver. The hydroxyl group adheres to the carbon atom 25 in 25-hydroxyvitamin D or calcidiol which is released into the circulation and undergoes activation in the kidney. In the kidney, 1-alpha-hydroxylase converts calcidiol into its active form i.e. calcitriol which is administered to various tissues, including skeletal muscle.^[6,10,15]

The two main forms of vitamin D are ergocalciferol (vitamin D₂), which comes from plants and cholecalciferol (vitamin D₃), which comes from animals. Liver, fish liver oil, fatty fish such as salmon and tuna, eggs and any fortified foods such as milk, cereals and juices are sources of vitamin D₃ whereas ergocalciferol can be obtained from mushrooms like shitake.^[2,6,10,15]

Administering the optimal vitamin D concentration for the benefits of muscle metabolism and regeneration is still challenging. Maintaining bone health and modulating immunity requires different levels of serum vitamin D. According to bone-centered guidelines, a calcidiol target is 20ng/ml (50nmol/L) and recommended dose of vitamin D supplementation varies from 400 to 800 IU depending on age.^[10]

The role of vitamin D in muscle was first explained by the discovery of vitamin D receptor (VDR), which was first detected in intestinal cells and then detected in many body cells, including skeletal muscle cells.^[7,10,14] The presence of VDR in many tissues indicates an association between vitamin D and various disorders such as obesity, insulin resistance, metabolic syndrome, type II diabetes mellitus, cardiovascular risk, Alzheimer's disease, depression and cancer.^[14] Vitamin D works by binding its active form to the VDR and this vitamin D signalling through VDR regulates myoblast proliferation and differentiation.^[2] The VDR expression is found higher in satellite cells than mature muscle fibers, however, it constantly varies over life. With age, VDR expression decreases which possibly contributes to diminished muscle strength. The role of vitamin D is crucial in the early stages of muscle growth and becomes less critical in muscle physiology at an older age.^[6,10]

Low vitamin D levels correlate with low physical performance; specifically, serum levels <10 ng/mL in older adults exhibit poorer performance than others.^[6] Low

levels of this vitamin in the elderly are also correlated with an enhanced incidence of frailty.^[7]

VITAMIN D SIGNALLING IN ANABOLIC AND CATABOLIC PATHWAYS

Vitamin D plays an important role in skeletal muscle cell metabolism that regulates calcium homeostasis as an indispensable constituent in the cytosol and mitochondria interplay.^[14] Through its active metabolite activity, vitamin D maintains the balance of calcium and phosphorous. So, vitamin D is essential in regulating and contracting skeletal muscles.^[14,16]

The three main proteolytic pathways regulating skeletal muscle atrophy are the ATP-ubiquitin-dependent system, the lysosomal system and the cytosolic calcium-activated system. Some studies showed increased expression of the enzyme E2-ubiquitin conjugate and two muscle-specific E3 ligases in vitamin D-deficient muscle. In addition, the expression of muscle atrophy F-box-protein (MaFbx) and muscle ring finger protein (MuRF1) was also found doubled in vitamin D-deficient muscle. These proteins provide specific substrates in the ATP-dependent ubiquitin-proteasome pathway (UPP) and are believed to be responsible for significant intracellular proteolysis in the muscle atrophy progression. On the other hand, several studies have revealed that muscle wasting due to vitamin D deficiency do not change the activity of lysosomal enzymes and calpain.^[14,16,17]

Signalling pathways involved in vitamin D action in muscles also demand steroid receptor coactivator complexes (Src) and non-receptor tyrosine kinases for activating mitogen-activated protein kinase (MAPK) in various tissue organs. Another study showed that non-receptor tyrosine kinase and Src activation coincided with the interaction between Src kinase and 1,25(OH)₂D₃-induced VDR in chicken muscle cells. Activated Src is needed to activate vitamin D-dependent extracellular signal-regulated kinases 1 and 2 (ERK1/2) and p38 MAPK in skeletal muscle myoblasts. MAPK signaling is essential for maintaining skeletal muscle mass because inhibition of this signaling cascade drives muscle atrophy. In particular, inhibited ERK1/2 signaling would provoke myotube atrophy, up-regulate atrophic markers of MaFbx and MuRF and down-regulate phosphorylation of protein kinase B (PKB/Akt) with its downstream kinases. Akt and its downstream signaling cascade simultaneously increase protein synthesis and decrease protein breakdown to regulate muscle hypertrophy. The activation of Akt induced by calcitriol in skeletal muscle myoblasts is also mediated by Src.^[14,16]

Signalling of ERK mediated by IGF-I contributes to muscle hypertrophy. Several studies showed that IGF-I triggers the expression and activity of hydroxylase-1 al-

pha to produce $1\alpha,25(\text{OH})_2\text{D}_3$ in the kidney, causing an increase in the level of $1,25(\text{OH})_2\text{D}_3$ in the blood. On the other hand, serum levels of IGF-I are increased with vitamin D administration in adults. Activated IGF-I causes a hypertrophic or a supportive impact on muscle fibers and their function. During endurance training, IGF-I signalling induces anabolism through the IGF-I-Akt-FOXO pathway.^[14,16] Akt regulates protein metabolism through the IGF-I-Akt-FOXO pathway, specifically through mammalian target of rapamycin (mTOR) for synthesis and transcription of the forkhead box O (FOXO) family.^[14,16] One of the downstream effectors of Akt and mTOR is identified to be a significant regulator of cell growth and a fundamental sensor of nutrient state.^[18] FOXO is a significant regulator of the ubiquitin-proteasome system that regulates muscle-specific E3 ligases directly. FOXO3, a member of FOXO, suppresses protein synthesis, whereas Akt suppresses protein breakdown to anabolic effect.^[14,16,17,19]

Based on the evidence that low energy can increase the FOXO1 gene expression, mice with FOXO1 overexpression in genetically modified skeletal muscle develop muscle atrophy.^[15] After vitamin D intervention, enhanced VDR signalling represses the expression, activity and nuclear translocation of FOXO1 which mediates VDR-null signaling in skeletal muscle and promotes muscle atrophy development.^[14,16] Thus, vitamin D might repress the activity of atrophy-associated transcription factors.

Activation of mTOR occurs due to vitamin D-dependent suppression of FOXO1 through the serine/threonine kinase which belongs to protein kinase family phosphatidylinositol-3-kinase (PI3K). Besides mediating protein synthesis and cell growth, mTOR kinase primarily regulates cellular metabolism, protein synthesis and cell turnover. These kinases have two types of complexes i.e. mTORC1, which is adhered to the Raptor protein and mTORC2, which is adhered to the Rictor protein. Modulation of mTOR activity due to pharmacological and genetic interventions significantly increases muscle size and function.^[4,17,20,21] In addition, several studies have shown mTORC1 to signal protein breakdown to regulate increased protein synthesis. Autophagic flux during catabolic conditions in skeletal muscle is principally regulated by the transcription factor FOXO, whereas autophagy under basal states is modulated by mTORC1.^[4,21]

VITAMIN D DEFICIENCY AND MUSCLE MASS

Vitamin D deficiency in the elderly is common and discovered worldwide for several causes including decreased skin synthesis, limited daily sun exposure, limited outdoor activities and reduced vitamin D intake. In addition, numerous conditions such as chronic renal fail-

ure, hepatic impairment or gastrointestinal malabsorption are also the reasons of deficiency of this vitamin.^[2,6,10,15] Recent guidelines state concentrations $<30\text{ng/mL}$ as vitamin D insufficiency and $<20\text{ ng/mL}$ as vitamin D deficiency.^[2,10,14,15]

The action of vitamin D is mediated by binding its active form to the VDR to increase muscle fiber size. The number of VDR in muscle tissue is reduced by advancing age, followed by a poor functional response to vitamin D leading to a decline in muscle mass and strength.^[6,10] A study reported smaller muscle fiber in VDR-null mice as compared to wild-type mice. The same study also reported quicker waste of muscle mass in VDR-null mice at eight weeks of age than wild-type mice. It suggests a role for the center and trophic functions of the VDR in muscle fibers.^[2,6]

Research in rats reported that vitamin D deficiency for twelve months induces the features of sarcopenia including inadequate anaerobic capacity, lower lean mass, less fiber cross-sectional area tendency and impaired gait. Another investigation on vitamin D-deficient mice showed enhanced atrophy-associated atropine-1 expression and differential miR-26a-associated expression of muscle regulation. These studies suggest association between vitamin D insufficiency or deficiency and muscle atrophy however, the related mechanisms require further study.^[14]

Prolonged vitamin D deficiency likely provokes VDR ablation and reactive oxygen species (ROS) formation and disrupt mitochondrial function, ultimately leading to muscle atrophy.^[14,16] Besides regulating mitochondrial dynamics and function, vitamin D may also directly evoke mitochondrial ROS. The link between VDR and ROS signalling and antioxidants are complex. Vitamin D deficiency enhances ROS-mediated cytotoxicity which significantly causes oxidative stress in skeletal muscle. At normal level, ROS is essential for skeletal muscle signalling after cell injury, but it can be destructive to the muscle itself at an excessive level. In skeletal muscles having vitamin D deficiency, lipid and protein oxidation increases, and antioxidant enzyme activities are disturbed.^[22] Although the exact mechanism regarding vitamin D regulating oxidative stress is unexplained,^[14,16] yet, some studies have confirmed that vitamin D manages oxidative capacity through binding of activated vitamin D to the VDR in skeletal muscle.^[22,23]

A study showed that vitamin D could induce peroxisome proliferator-activated receptor-gamma coactivator (PGC-1 α) synthesis due to ROS generation in muscle. The oxygen consumption rate of skeletal muscle cells increases following vitamin D treatment, proving that vitamin D controls mitochondrial oxygen consumption and dynamics^[15] and mitochondrial enzyme

function.^[8] Therefore, vitamin D is thought to reduce muscle atrophy by improving mitochondrial function.^[16] In addition to its function in mitochondrial biogenesis, increased PGC-1 α prevents the transcriptional activity of FOXO3a.^[1,14,16,17] Thus, vitamin D activity in skeletal muscle can be through the IGF-1/Akt/FOXO3 pathway or PGC-1 α and FOXO3a independently.^[16]

A study reported a decrease in ATP production of mitochondria in VDR-knockdown C2C12 myoblasts. It supports the hypothesis that lack of vitamin D signaling at the VDR may lower ATP availability. Another study showed that difficulty in muscle regeneration is due to the loss of mitochondrial capacity.^[22,23]

Studies of VDR ablation suggest that vitamin D regulates oxidative capacity independently of any changes in mitochondrial density and electron transport system (ETS) protein abundance. ETS is a protein complex in the inner membrane of mitochondria which is involved in oxidative phosphorylation. A study showed that VDR-knockdown in C2C12 myotubes increases optic atrophy 1 (OPA1) abundance, which is suggested to be a compensatory mechanism to recover mitochondrial function decline due to vitamin D deficiency.^[22,23] OPA1 mediates the inner membrane fusion of mitochondria, resulting in more giant mitochondria and increasing its oxidative capacity. Interestingly, a study showed an in-

crease in OPA1 expression after vitamin D supplementation in vitamin D deficient mice with statin-induced myopathy. The same results were also observed in human skeletal muscle cells treated with vitamin D.^[22]

Several studies revealed that treating vitamin D deficiency using cholecalciferol increases the maximal rate of mitochondrial oxidative phosphorylation as measured by ³¹P-NMR spectroscopy.^[8,14] The rate of oxidative phosphorylation depends on various factors including mitochondrial amount and components, oxidative enzyme content and vascular supply of substrate and oxygen.^[14] Several studies also reported that treating vitamin D deficiency with 3,200 IU/day five times a week of vitamin D supplementation would improve myopathy symptoms and repair mitochondrial fatigue in skeletal muscle in low back pain. There is increased activation of citrate synthase, a quantitative enzyme marker in the intact mitochondria, approximately 40% higher in the paraspinal muscle after supplementation. Moreover, the increased protein content of PGC-1 α , a transcriptional coactivator, is also observed.^[14,16] Other than this, the oxygen consumption rate of skeletal muscle cells increases following vitamin D treatment, proving its role in controlling mitochondrial oxygen consumption and dynamics^[15] and mitochondrial enzyme function.^[8] Therefore, vitamin D is thought to reduce muscle atrophy by improving mitochondrial function.^[16]

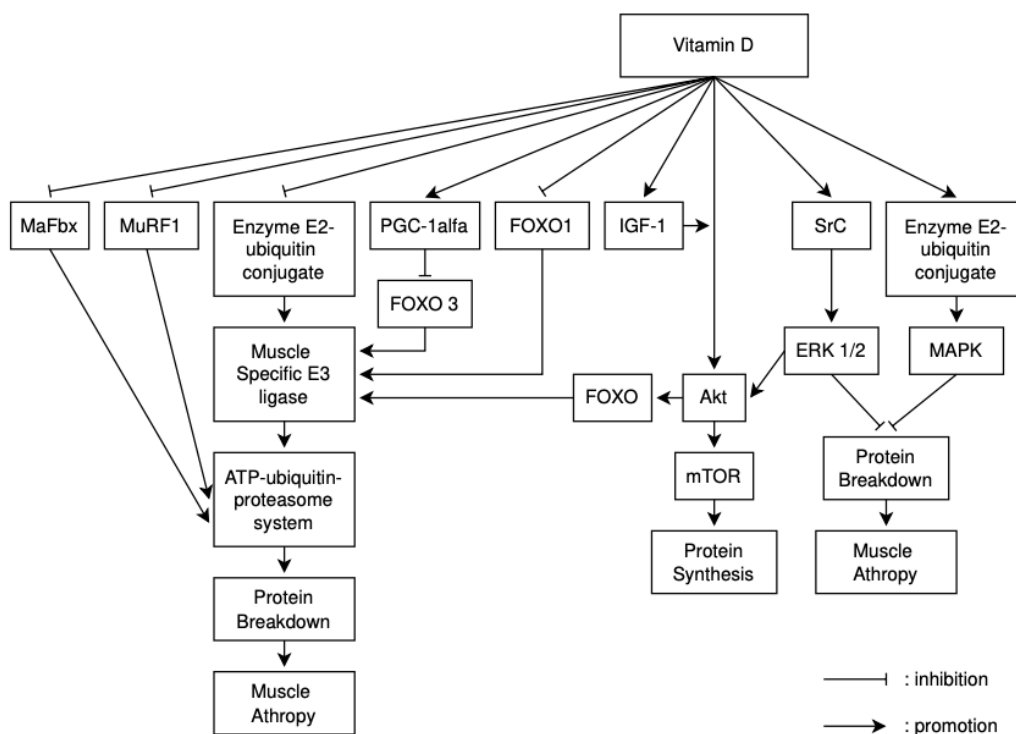


Figure 1. Role of vitamin D in anabolic and catabolic pathways.

CONCLUSION

Vitamin D is involved in anabolic and catabolic processes in skeletal muscle cells. Vitamin D supplementation has advantageous effects in sarcopenia, such as rise in muscle strength and decrease in the process of muscle atrophy. However, the precise function of vitamin D supplementation in preventing and treating sarcopenia is yet under examination. Further interventional investigations are required to prove effectiveness of vitamin D supplementation on skeletal muscle. Determining its optimum level to preserve muscle mass and strength to support physical function in older adults requires further investigation. Considering that vitamin D deficiency is experienced in older adults with its biological impact on skeletal muscle metabolism, clinicians are advised to evaluate its levels in sarcopenic patients. The clinicians should decide to start oral supplementation for any elderly with vitamin D deficiency.

AUTHOR CONTRIBUTION

Novira Widajanti was involved in the conception and design, drafting of the manuscript and writing the manuscript to the final paper. Usman Hadi was involved in drafting the manuscript, revision and final approval. Soebagijo Adi Soelistijo was involved in the revision and final approval of the manuscript.

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CONFLICT OF INTEREST

The authors have no conflict of interest to declare.

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