Investigating vitamin D as a performance enhancer

A Systems-Based Investigation into Vitamin D and Skeletal Muscle Repair, Regeneration and Hypertrophy

Introduction

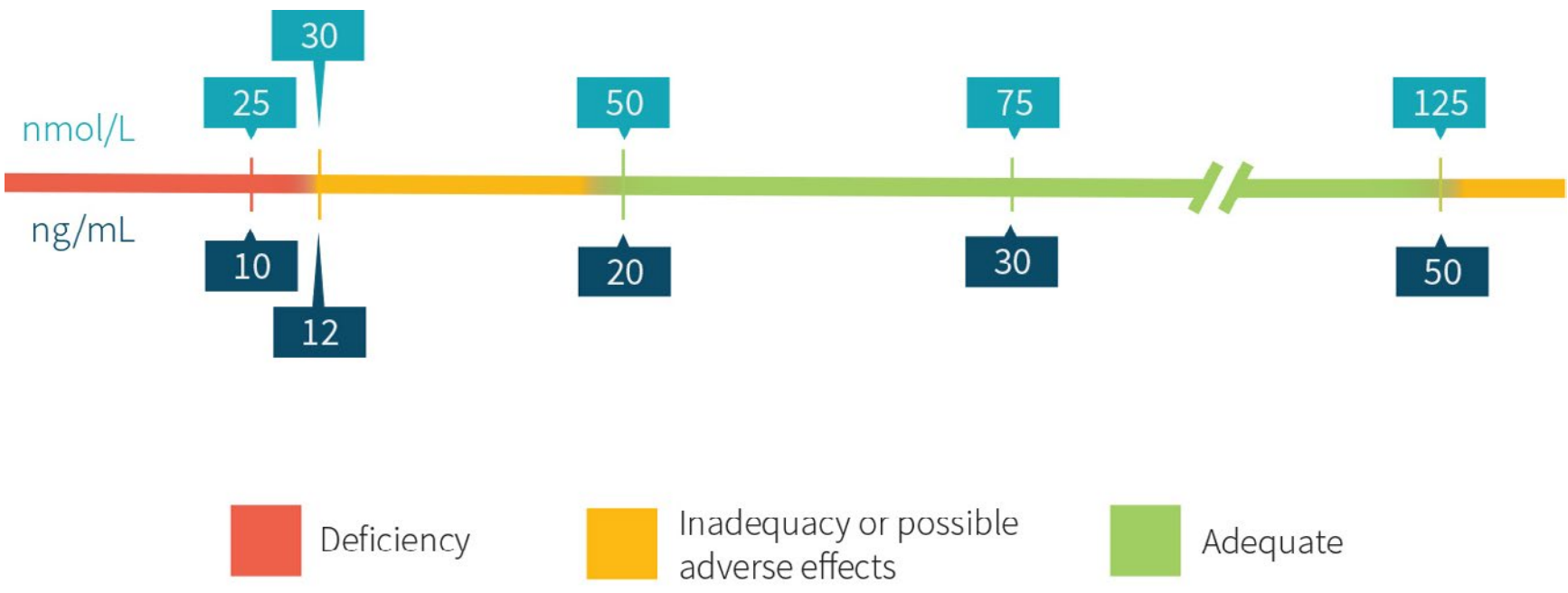
Why is Vitamin D such a popular supplement, among both researchers and the general public? One reason is that it potentially acts on a broad spectrum of health and performance measurements. Researchers have examined the effects of this fat-soluble vitamin on chronic pain, cystic fibrosis, multiple sclerosis, and the risk of cardiovascular disease and mortality (covered in ERD #7).

Many people are not getting enough of this vitamin. Recent estimates have indicated that 37.3% of the world's population may have an inadequate level of vitamin D. The Institute of Medicine has defined blood concentrations between 30 to 50 nmol/L of vitamin D to generally be considered inadequate. Although sometimes defined at different cutoff points, risk of deficiency can be characterized by levels lower than 30 nmol/L, while an adequate, healthy range is usually considered to be between 50 and 125 nmol/L.

We'll be using units of nmol/L throughout this article, although many labs report vitamin D levels in ng/mL. You can see how these two units relate to each other in Figure 1. One possible downstream effect of these inadequacies may be a decrease in the body's ability to regenerate muscle tissue. Researchers have known since 1985 that there are vitamin D_3 receptors on muscle cells, and in the past few years research on vitamin D in the context of boosting performance has become popular. One intervention trial in well-trained athletes showed an improvement in sprint times and vertical jump with supplementation. Further studies have associated higher vitamin D status with a more rapid recovery of skeletal muscle strength after an acute bout of intense exercise.

The growing body of data showing that vitamin D plays an important part in the function of skeletal muscle suggests this vitamin may be a potential ergogenic aid. The fact that vitamin D_3 is a relatively inexpensive and widely-available supplement makes it all the more attractive to athletes. Around 56% of athletes have vitamin D levels of 80 nmol/L or lower, so supplementation could help combat deficiency. Although previous research has indicated vitamin D may help with improved muscle healing, a causal relationship has not yet been firmly established. The study under review looked further into this connection to determine if there is a potential cause-effect relationship between vitamin D and muscle repair, regeneration, and hypertrophy.

Figure 1: Converting nmol/L to ng/mL



Vitamin D plays diverse roles in maintaining health, and has been investigated for beneficial effects on a host of conditions. A developing line of research has looked into the roles this vitamin could play in the context of boosting physical performance. The present study investigated vitamin D to determine how it affects muscle repair, regeneration, and hypertrophy.

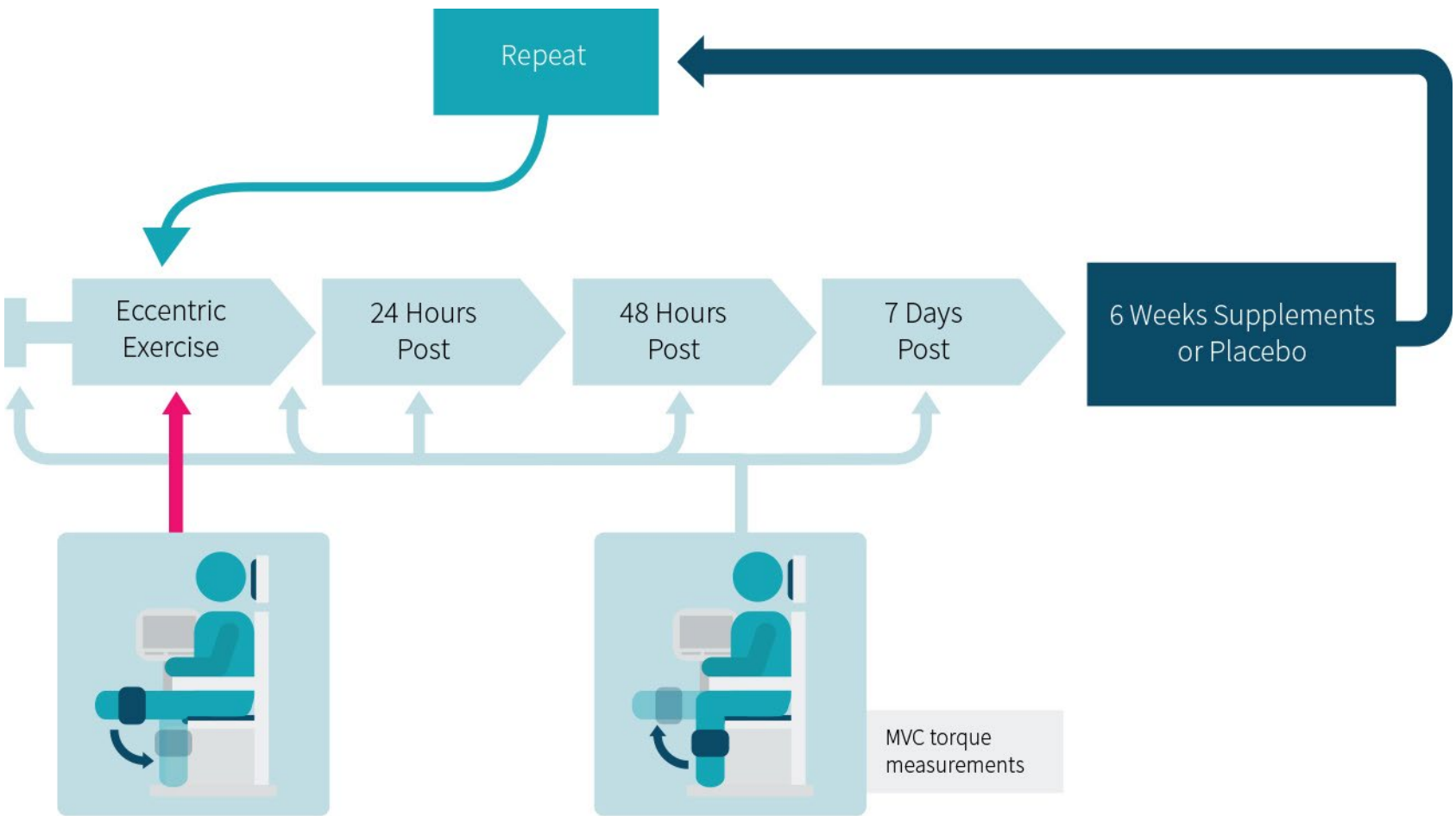
Who and what was studied?

First, the researchers conducted a double blind, randomized controlled trial in humans (in vivo) to investigate the effects of vitamin D on the muscle's ability to recover from exercise-induced damage. The overall study design is shown in Figure 2.

Second, they extracted isolated muscle cells (*in vitro*) from humans that were vitamin D insufficient and exposed them to 1,25-dihydroxyvitamin D (1,25(OH)D), the biologically active form of vitamin D. This was done to identify the aspects of muscle cell regeneration that respond to the supplement. By using a combined *in vivo/in vitro* design, the researchers were able to examine the impact vitamin D had on muscle recovery in humans while also attempting to determine the cellular mechanisms through which the effect might occur. Essentially, the researchers were trying to figure out how vitamin D affects muscle repair and how it does what it does.

Researchers recruited twenty young, physically active, and healthy males for the in vivo study. Baseline vitamin D status was assessed and participants were excluded if they had adequate vitamin D concentrations, defined in this study as greater than 75 nmol/L. All vitamin D blood measurements were analyzed using an analytical chemistry technique considered the gold standard for assessing vitamin D levels (LC-MS/MS). The average vitamin D status of the cohort was 45 nmol/L. Participants were randomized into the control or intervention groups and received six weeks of either supplemental vitamin D3 (4,000 IU/day) or placebo.

Figure 2: Trial design



What's the difference between vitamin D_2 and D_3 ?

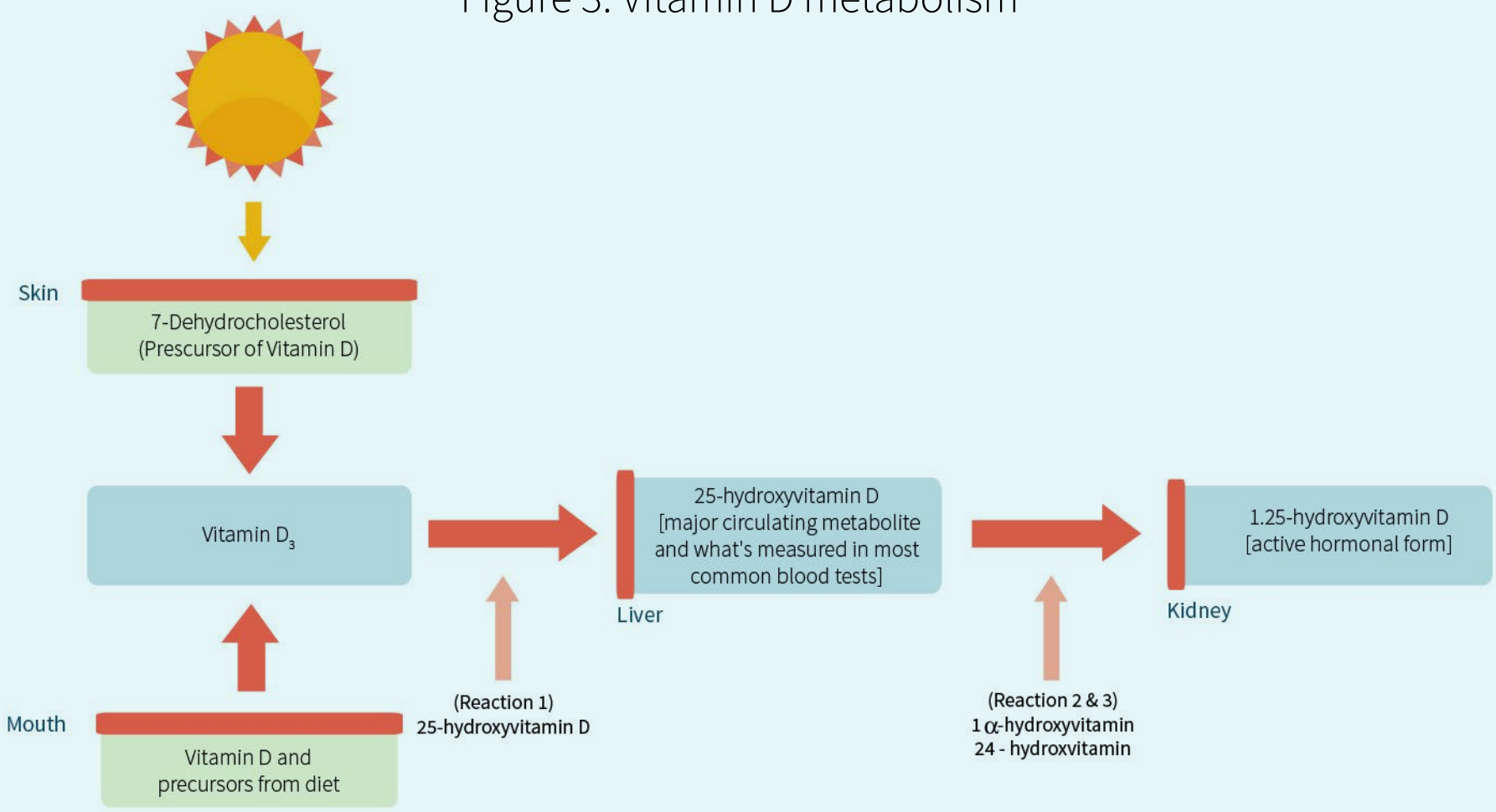
Vitamin D in the diet comes in two forms: D_2 and D_3. D_2 is usually found in fungi, while D3 is found in animal products.

D_2 does not bind well to the human vitamin D receptor, compared to D_3. For that reason, and because it is more easily deactivated and thus remains in an active form for less time, it is generally considered to be a poorer form of the supplement.

An overview of vitamin D metabolism is shown in Figure 3. Vitamin D_2 and D_3 must both undergo further enzymatic reactions before the body can utilize them. They both travel to the liver, where they are converted into 25-hydroxyvitamin D (25(OH)D), the form that is usually measured in blood tests for vitamin D. Vitamin D_3 is more effective at raising this measurement than D_2 is. They are then sent to the kidneys, where the final conversion step occurs. 25(OH)D becomes 1,25-dihydroxyvitamin D (1,25(OH)D), the bioactive hormonal form of the vitamin.

It is this substance that can interact with the vitamin D receptors found throughout tissues in the body. The 1,25(OH)D that is not used by the body gets degraded into inactive forms, with D_2 tending to be deactivated more quickly than D_3 .

Figure 3: Vitamin D metabolism



Adapted from: Dahlquist et al. J Int Soc Sports Nutr. 2015 Aug.

Before the participants began their supplement regimen, baseline muscle recovery measurements were taken. Participants produced a maximal voluntary contraction (MVC) in their right leg prior to and following a series of eccentric exercises. An eccentric contraction is the portion of the exercise during which a muscle is lengthening. For example, the eccentric portion of a bicep curl is when the weight is lowered back down to the rest at the side, thus lengthening the biceps. The eccentric exercises and MVCs were performed on an isokinetic dynamometer, which can measure the amount of torque being produced. A video of this machine in action can be viewed here. MVC torque was then re-measured 24 hours, 48 hours and seven days following the exercise session. This same procedure was repeated following the six weeks of supplementation.

For the *in vitro* study, researchers took muscle biopsies from the quadriceps of fourteen young male volunteers with inadequate levels of vitamin D. The muscle cells were cultured and isolated before the experiment began. To induce muscle damage, a pipette was used to scrape the cells on the culture plate. Once any remaining cell debris had been removed, the muscles cells were exposed to a low (10 nmol/L) or high (100 nmol/L) dose of vitamin D_3, or a control substance. These varying doses were used to determine if the potential responses in muscle repair are dose dependent. Researchers observed the cells at zero and 48 hours, as well as seven and 10 days after the pipette-induced cell damage.

This study was split into two parts: one performed on humans and one on cultured muscle cells. During the human study, researchers administered exercise tests before and after a six-week intervention during which participants either took vitamin D_3 or a placebo. The researchers were attempting to determine if vitamin D plays a role in muscle repair. During the second study, the cultured muscle cells were given varying doses of vitamin D_3 to try and determine the mechanisms through which the vitamin acts on muscle tissue.

What were the findings?

The first, and perhaps most obvious finding, was that there was a significant increase in serum vitamin D in the group receiving the supplement. Concentrations increased by a factor of 2.5, from an inadequate vitamin D status of 45 nmol/L to an adequate status of 115 nmol/L. On the other hand, the placebo group's serum level actually dropped by 26%, from 45 nmol/L to 33 nmol/L.

Two exercises were utilized to test muscle recovery. One where participants produced maximal torque while moving their legs at 60 degrees per second and one at 180 degrees per second. Within the vitamin D group, significant muscle recovery improvements were seen in the 60°/second test and, although a positive trend was observed, no statistically significant results were record-

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ed for the 180°/second test. However, the relationship between higher serum vitamin D levels and the ability of the participants to recover their strength after eccentric exercises (i.e. peak torque) was highly correlated (r^2 = 0.88). No changes in muscle soreness were detected between groups.

The *in vitro* study looked at endpoints like cell migration, which is a key initial step in the muscle repair process. Both the high and low doses significantly enhanced cell migration compared to placebo, but the high dose was superior. The high and low doses also improved migration speed and distance covered, which resulted in more cells moving into the wounded space to repair the damaged tissue. Interestingly, the high dose of vitamin D3 did not perform as well as the low dose when it came to myoblast fusion. Myoblasts are cells that fuse to form myotubes. Myotubes are used to produce various muscle groups required to generate force.

The low treatment group experienced significant improvement in myotube measurements over the control and high vitamin D_3 treatments. Cells exposed to the lower dose also saw increased creatine kinase activity, which helps muscles to function effectively by energizing creatine. Low doses also showed a trend in being able to up-regulate certain gene expressions associated with muscle repair and growth, more so than the high dose.

During the human intervention portion of the trial, higher vitamin D status was positively correlated with the ability of muscles to recover quicker from exercise-induced damage, although statistically significant differences were only seen in one of the two muscle recovery tests. When looking at the results of the muscle cell cultures, the low dose of D_3 appeared to be the most beneficial for muscle fiber repair, improved creatine kinase activity, and up-regulation of gene expressions involved with muscle tissue growth.

What does the study really tell us?

This study illustrates the important role that vitamin D plays in muscle recovery, repair, and regeneration. When serum vitamin D status is brought up from a level of inadequacy, the functional recovery of skeletal muscle occurs more quickly. The cell cultures tested in this study provide a deeper understanding of how this process occurs, namely by illuminating the underlying mechanisms that heal muscle tissue.

Data presented in the study may also provide insight into what might occur if supplemental vitamin D is taken in excess. When tested on the muscle cells, the higher vitamin D dosage suppressed certain aspects of the muscle repair process. Myoblast fusion, creatine kinase activity, and certain gene expressions were not as active as their low dose counterparts by day 10 of the cell culture observations. It is unclear if these same suppressions would happen in vivo and, if so, what dose would be needed to bring about these effects.

While the dosage used in this study (4,000 IU/day) demonstrated a positive effect on muscle repair in people with insufficient levels, it is not known if these effects would continue to improve, level off, or dissipate at higher doses. The safe upper limit established in the United States and Canada is presently set at 4,000 IU/day, but some research suggests that the upper limit could be as high as 10,000 IU/day. However, a dosage of 1,000-2,000 IU/day should be sufficient for most people.

The study did have a few design limitations. A sample size of 20 participants is fairly small, so a larger scale trial is needed to help verify the results of this study. Further studies should include female participants as well. Also, the chosen mode of exercise was highly specific and is not necessarily translatable to everyday activities or training. Future experiments could employ exercise modalities that reflect more real-world scenarios.

Furthermore, the doses of D_3 the muscle cell cultures were exposed to was well above what would be seen in a normal human, making the different doses used in the in vitro and in vivo studies hard to compare. The authors suggest that further research should look into estimating the concentration of D_3 that skeletal muscles are normally exposed to. These discoveries would help researchers design in vitro experiments that are more relevant to real-world concentrations of vitamin D.

People with inadequate serum vitamin D can increase intake to ensure adequate levels, which will likely benefit muscle repair and regeneration. In vitro studies demonstrate that vitamin D is able to enhance these repair mechanisms. Future testing is needed to determine if doses higher than 4,000 IU/day will benefit or potentially attenuate these mechanisms.

The big picture

Views on vitamin D have changed in the past decade. It was previously mostly viewed as a regulator of calcium balance, hence aiding in healthy bone formation. For example, rickets, a bone disorder typically found in children, is caused by insufficient vitamin D intake and can be reversed with supplemental vitamin D. However, research performed over the past decade has shown that many tissues in the body will respond to and function sub-optimally when exposure to vitamin D is limited. Studies have identified over 900 genes that are regulated in part by vitamin D. The biologically active form of vitamin D shares some characteristics with steroids like testosterone. Thus, research looking into these hormone properties has led scientists to investigate vitamin D as a potential ergogenic aid. Specifically, the potential ability of vitamin D to assist in rapid muscle recovery, which would be of particular interest to athletes.

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The authors point out that this research has raised new questions about populations susceptible to muscle damage and vitamin D inadequacy, such as the elderly. A more senior population may experience a diminished capacity to regenerate muscle when vitamin D levels are not sufficient. Higher levels of supplementation may aid in reversing some of these processes.

Previous *in vitro* studies conducted on human cells have shown promise in the use of vitamin D to aid in muscle recovery times. An animal study, performed on rats, echoed these findings and demonstrated enhanced recovery with the supplement. Besides the current study, one additional study has investigated vitamin D's muscle recovery effects in humans. Baker et al. examined 28 healthy active males with adequate vitamin D levels. After baseline measurements were recorded, 4,000 IU daily of vitamin D or placebo was administered for 35 days. The post-test results showed both enhanced recovery time and a decrease in biomarkers of muscle damage in the vitamin D group.

The combined results of the muscle cell tests, animal studies, and experiments performed in humans have built a strong case for the need to ensure adequate vitamin D status for optimal physical performance. However, the research looking into supplementation in females is lacking, as both of the two human intervention trials recruited only fit healthy males.

While typically viewed as the vitamin that aids in bone formation, vitamin D's role in the body has been shown to be wide ranging. An emerging body of evidence has demonstrated that inadequate levels of vitamin D can lead to decreases in muscular performance and increased recovery times. Athletes and the elderly in particular may want to monitor their vitamin D status. Future trials should look to investigate these effects in females, as the present research has been conducted solely in healthy, fit males.

Frequently asked questions

Supplementation vs. Food vs. Sunlight: How should I get my vitamin D?

There are many options to ensure adequate intake of vitamin D. Vitamin D comes in two flavors: D_3, mostly found in animals, and D_2, the form typically seen in non-animal sources. Certain high vitamin D foods can be used to help defend against vitamin deficiency. Fish like halibut, salmon, trout, mackerel, and sturgeon are abundant sources of vitamin D_3. Other good options may include eggs, certain fortified cereals, and fortified dairy products. Sources of D_2 include many varieties of mushrooms, such as portabella and shiitake, and fortified soymilk.

Sometimes food may not be enough. In these cases, a moderate supplemental dose of 1,000 to 2,000 IU/day of D_3 may suffice for most people, although at-risk populations such as those who cover their skin extensively or who have very dark pigmentation could warrant higher doses. Studies have shown 100 IU of additional vitamin D per day can be expected to increase levels by about 2.5 nmol/L on average. So, a person with a starting vitamin D level of 37 nmol/L would need about 1,500 IU/day to bring levels up to 75 nmol/L. Luckily, D_3 tends to be an inexpensive supplement.

The last option is to harness the internal production of vitamin D that occurs after sun exposure. When the skin is exposed to ultraviolet B radiation (UVB), it sets into motion a process that produces biologically active 1,25(OH)D, the form of vitamin D that's useable to our cells. Going outside for five to twenty minutes, two to three times a week, with at least 5% of skin exposed can help generate adequate amounts of D3. Fifteen minutes of UVB exposure during the summer in bathing suit attire (before sunscreen application) can produce 10,000 to 20,000 IU of D_3 in light-skinned individuals, while those with darker skin need much longer exposure times. However, as UV radiation from the sun or tanning beds is a known carcinogen that plays a role in the development of skin cancer (especially in those with very fair skin), limiting exposure of unprotected skin to sunlight would be prudent for some people. Many factors can affect these sunlight-driven synthesis rates though, such as higher altitudes, cloudy climate, thick ozone layers, and skin pigmentation.

What should I know?

The results of this trial demonstrate that low levels of vitamin D can easily be elevated to a healthy range via supplementation, and that this may benefit muscle repair and recovery.

The next step in progressing this line of research would be to try and replicate these results using a larger sample size, while ideally including female participants. If you believe you may have low vitamin D, get your 25(OH)D levels assessed by your doctor before adding a D_3 supplement, as it can interact with some medications. ◆

Oh Vitamin D, what can't you do? The answer: quite a lot actually … although this particular study was promising for a subset of the population. To discuss the rich area in between panaceas and snake oil, head over the to the ERD Facebook forum.