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Role of vitamin D in Pain, Muscle Strength and Falls

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There is growing evidence that vitamin D plays a role in pain, muscle strength and falls. This issue reviews recent evidence pertaining to this association.

Vitamin D has received remarkable attention in recent years. Vitamin D from sunshine, food or supplements is automatically metabolized by the liver to 25-hydroxyvitamin D [25(OH)D]. The more vitamin D is taken into the body, the higher the serum 25(OH)D concentration. While the classic actions of vitamin D are related to the handling of calcium, it is now known that 25(OH)D is a substrate used by tissues throughout the body to produce a local signaling molecule. It happens that the local signaling molecule is 1,25-dihydroxyvitamin D [1,25(OH)2D] which is the same molecule as the hormone produced and secreted by the kidney in response to a need to stimulate the active absorption of calcium from the gut.

The role of serum 25(OH)D is often the most difficult part of vitamin D nutrition for people to understand, because by itself, the molecule is inactive. The effect that an improved 25(OH)D supply has on the human body is for the most part, hidden inside the tissues that use it to produce 1,25(OH)2D. The vitamin D system is both similar to, and different from the steroid hormone system. Vitamin D is a cholesterol-like molecule, and its metabolites are lipid soluble. Many of the basic rules of metabolism are different for vitamin D. This is because 25(OH)D circulates at nano-molar concentrations, while cholesterol circulates at milli-molar concentrations – a million-fold difference. The enzymes of the vitamin D system behave like factories that are working below capacity because a lack of raw material (25(OH)D). As a result, the amount of 25(OH)D available to cells plays a major role in health, because availability affects the ability of many different tissues throughout the body to produce 1,25(OH)2D. In contrast, the enzymes producing steroid hormones behave like factories at full capacity, and with raw material (cholesterol) present in huge excess; hence, regulation of steroid hormones is more straight-forward than regulation of 1,25(OH)2D.

PAIN AND NEUROMUSCULAR FEATURES OF VITAMIN D ACTION

Severely impaired muscle function is the first, and often the only sign of vitamin D-deficiency. It generally occurs before bone disease develops. Full correction of the myopathy may require six months from the time vitamin D nutrition is implemented¹.

Vitamin D deficiency probably needs to be relatively severe (serum 25(OH)D <30 nmol/L) before it will reliably cause impaired neuromuscular function

and osteomalacia. The mechanism of the effect at muscle is thought to involve the interaction of 1,25(OH)2D with its nuclear receptor in muscle cells. This improves muscle function, and it increases the relative number and size of type II (fast twitch) muscle fibers^{2,3}. Vitamin D also increases the ATP-dependent uptake of calcium by intracellular organelles and across the plasma membrane of muscle cells⁴. Calcium release from intracellular stores is necessary for muscle contraction and diminution of stored calcium available for release to the intracellular fluid of muscle cells and can account for the muscle weakness of vitamin D deficiency⁴.

Deficiency of vitamin D is characterized by neuromuscular pain and myopathy. Pediatricians have classically described infants with rickets as having “weak floppy crying baby syndrome”. These infants cry because of neuro-muscular pain when picked up. Vitamin D deficiency is a treatable part of the differential diagnosis of the syndrome.

In adults, vitamin D deficiency is also a part of the differential diagnosis of vague pain syndromes. The myopathy of vitamin D deficiency is often misdiagnosed as a nonspecific rheumatic disease, a psycho-neurotic disorder, or fibromyalgia¹. The effect is related both to the muscle per se, as well as to a reduction in motor-nerve conduction velocities⁵. It is important to understand that the decline in muscle strength occurs so gradually that by that time patients complain of muscle weakness, they may already be impaired in terms of ability to walk or to rise unaided from a sitting position. The muscles affected by osteomalacic myopathy have a characteristic proximal distribution. As a result, walking is characterized by a “waddling” gait, and the thigh muscles may be too weak to support the rising from a chair without help from the arms, to press down on the knees.

The nature of osteomalacic pain and muscle weakness is often vague and can lead to misdiagnosis. However, there is nothing to be lost and only a potential cure to be gained by providing these patients with a vitamin D supplement. If a diagnosis is required, this can be achieved by measuring the serum 25(OH)D concentration. A concentration below 25 nmol/L will be consistent with myopathy.

RICKETS, OSTEOMALACIA AND OSTEOPOROSIS

Rickets and osteomalacia are the classic Vitamin D

deficiency diseases. These are the result of inadequate availability of calcium. When the intake of calcium is marginal (less than 300 mg/day in adults) then a greater supply of vitamin D is needed to improve the efficiency of calcium absorption from the diet⁶. A lack of calcium makes it impossible to mineralize osteoid, the protein matrix of bone. In infants and children, this impaired mineralization manifests itself as rickets. With rickets, intact stretches of bone are soft and unmineralized, and with weight they bend, resulting in the classic image of bowed legs. In adults, the same rickets-like disease is called osteomalacia, which manifests itself as pixel-like areas of unmineralized osteoid distributed in many discrete areas throughout the skeleton. Bone mineral density measurements cannot distinguish between the vitamin D deficiency disease, osteomalacia, and the long-term loss of bone, osteoporosis. It is important to note that osteomalacia is curable, whereas osteoporosis is only treatable to the extent that effort is made to prevent further loss of bone. When patients with osteomalacia are treated with calcium and vitamin D, there will be an initial gain in bone density as the hungry bone osteomalacia takes up calcium.

The distinction between osteomalacia and osteoporosis is not always clear-cut, because they can both be present in the same person. Hence, calcium and vitamin D repletion can be particularly beneficial in a patient with a low bone density because drugs designed to treat osteoporosis per se will not cure osteomalacia. The prolonged inability to mineralize the bone protein matrix of osteomalacia will eventually result in the porous bone of osteomalacia. These osteopenic diseases are not so much distinct entities, as part of a continuum of disease progression⁷.

FALLS AND OSTEOPOROSIS FRACTURE

More than 90% of fractures in older people occur as a result of falls⁸. If balance can be improved either because of muscle function or neuromuscular conduction, this will prevent falls. In the event of a fall, stronger muscles protect the bone. Together, these lower the incidence of osteoporotic fractures independent of any direct effect on bone. Indeed, those elderly people most prone to falling exhibit weaker quadriceps muscles, slower functional performance, slower reaction times and impaired balance compared with healthy age-matched subjects⁹. Moreover, each of these muscle measurements is statistically related to low serum

25(OH)D concentrations (< 30 nmol/L)⁹. However, these are cross-sectional relationships, and it is difficult to discern cause and effect. Is it truly vitamin D status that improves muscle function, or does better muscle function result in more outdoor activity and with that, higher vitamin D status?

There are at least three ways through which calcium and vitamin D might lower fracture rates: bone density could increase, bone quality could be improved, neuromuscular function could be improved to reduce the number of falls or could be improved to help protect bone in case of a fall.

META-ANALYSES

When clinical trials are pooled together for a meta-analysis, the combination of vitamin D and calcium is associated with moderately improved bone density at the hip and spine, and with fewer fractures¹⁰. Clinical trial results are not so consistent when it comes to falls. It is impossible to distinguish whether vitamin D alone or calcium alone could reliably produce the fracture related benefits, because practically all clinical trials have combined 800 IU vitamin D3 with 1,000–1,200 mg calcium daily. However, if the focus is solely on the effect of vitamin D on lowering an older person's risk of falling, then it appears that the calcium requirement may not be as high as that needed for maximizing the bone effect (i.e. >512 mg Calcium/day)¹¹.

There is only one large-scale clinical trial in which vitamin D was administered without calcium at a dose over 400 IU/day. In that, reports of fractures were reduced by about 25% but there was no difference in the rate of falls between placebo and the vitamin D-treated group¹². The lack of an effect of vitamin D on falls should not be surprising for a study performed on subjects not at increased risk of inadvertent falls.

The University of Ottawa-based evidence review by Cranney et al. is the most rigorous attempt to date at reviewing the role of vitamin D for bone health¹⁰. They concluded that vitamin D together with calcium improves bone density, and that the combination lowers the risk of fractures in studies involving institutionalized elderly, with less positive data for those living in the community. It is worth bearing in mind that the greater treatment efficacy in institutionalized elderly is at least partly accounted for by

the greater degree of compliance to the treatment protocol that is almost certainly ensured by professional caregivers. The same meta-analysis went on to address the effect of vitamin D on rates of falls, but the authors could not come to a conclusion.

An earlier meta-analysis by Bischoff-Ferrari et al. did come to the strong conclusion that vitamin D with calcium does prevent falls¹¹. It is of course frustrating when different high-level meta-analyses end up with different conclusions. The difference between University of Ottawa and the Bischoff-Ferrari perspectives lies largely in their selection of studies for inclusion. The University of Ottawa meta-analysis was less restrictive as to which studies were included for its pooled analysis, and thus, more of what was included were clinical trials that were negative.

ADHERENCE/COMPLIANCE TO CALCIUM AND VITAMIN D

It has become ever more clear that the clinical efficacy of any therapy or preventive measure depends upon adherence¹³⁻¹⁵. The risk-reduction for fractures demonstrated in clinical trials correlates strongly with the compliance of study participants¹⁵. The longer the trial, the poorer compliance becomes, and the ability to demonstrate efficacy declines¹⁴. Unfortunately, even though calcium and vitamin D are safe and inexpensive, adherence to them is shockingly poor among osteoporosis patients in Canada. The vast majority of osteoporosis

patients who were surveyed after being treated for hip fracture had discontinued calcium and vitamin D within 12 months¹⁶. Volunteers for clinical trials are presumably relatively well motivated, and even in those people, the compliance rate (proportion of subjects taking 80% of doses) to calcium and vitamin D is commonly 50-60% in larger clinical trials^{14,17,18}. The main reasons for discontinuation were GI symptoms or difficulty taking tablets¹⁷.

Practical strategies need to be implemented to help adults stay adherent to either calcium, vitamin D, or better yet, to both. Vitamin D supplementation has been so strongly tied to calcium supplementation that it is common for patients to discontinue both at the same time¹⁶. If the supply of calcium is decreased, then patients require more, not less, vitamin D^{6,19}. More attention needs to be paid to offering alternative approaches to each nutrient separately. For example, less pill-like calcium supplements, such as chewable formats, may be more tolerable for patients. And for vitamin D, the pharmacology is well suited for intermittent dosing. Bischoff-Ferrari has suggested that patients may be more adherent to vitamin D supplementation if the dosing frequency could be reduced from daily to higher intermittent doses (e.g. 100,000 IU every 4 months¹⁵). One way or the other, there is much to be gained from encouraging patients to take vitamin D supplements.

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