***CORR* Insights®: Does Vitamin D Improve Osteoarthritis of the Knee: A Randomized Controlled Pilot Trial**

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Where Are We Now?

The increased prevalence of osteoarthritis in Western countries is due, in part, to an aging and gradually more obese population. Obesity is a major risk factor for knee and to a lesser extent, hip osteoarthritis. The rates of disease are rising faster than can be explained by aging and obesity. This increase may be ascribed to sports-related injury or an unwillingness of patients to accept even modest joint pain that in the past probably did not trigger medical care [7]. Rates of knee replacement are rising rapidly. Effective nonsurgical treatments are desperately needed, but no treatments for osteoarthritis have been consistently shown to slow the course of disease, and there are few symptom

modifying treatments considered effective — most, like exercise treatment, come with compliance issues.

Vitamin D has promise as treatment for osteoarthritis, especially among those who are vitamin D deficient. Vitamin D receptors are present on chondrocytes, the cells within cartilage. Through these receptors, vitamin D may regulate matrix metalloproteinases [8]. Vitamin D deficiency inhibits bone remodeling, which may affect the bone changes that evolve with osteoarthritis. Also, deficiency may augment pain sensitivity [4] and contribute to muscle weakness.

With this background, epidemiologic cohort studies [3, 5] examined the relationship of blood levels of 25-OH vitamin D, the major storage form of the vitamin, to osteoarthritis. While the initial studies suggested that vitamin D deficiency accelerated osteoarthritis disease progression [5], a later study [3] showed mixed or even negative results.

This CORR Insights® is a commentary on the article “Does Vitamin D Improve Osteoarthritis of the Knee: A Randomized Controlled Pilot Trial” by Sanghi and colleagues available at: DOI: [10.1007/s11999-013-3201-6](https://doi.org/10.1007/s11999-013-3201-6).

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Where Do We Need to Go?

The study by Sanghi and colleagues reported the results of a trial of vitamin D supplementation in persons with painful knee osteoarthritis who were also vitamin D deficient (defined as serum levels ≤ 50 nmol/L (equivalent to ≤ 20 ng/ml)). They randomized these patients to capsules of 60,000 IU vitamin D versus placebo capsules and followed them for a year. The results showed that vitamin D supplementation relieved pain significantly compared to placebo. The effect on pain was substantial with an effect size of > 0.5 (to put this in context, this effect size is larger than the pain relieving effect of NSAID for osteoarthritis, and approaches that of the short term effect of an intraarticular steroid injection [1]). However, the substantial

difference in pain change between active and placebo group was driven in large part by the increased pain seen in the placebo group. If pain had not worsened in this group, it is doubtful that the difference between the pain change in the active and placebo groups would have reached statistical significance. Sanghi and colleagues did not supply data determining whether vitamin D supplementation had effects on structures within the knee.

Given the inconsistent but promising findings of epidemiologic studies and the importance of understanding the effect of vitamin D on osteoarthritis, McAlindon and colleagues [6] carried out a 2-year randomized trial evaluating 2000 IU vitamin D daily versus placebo in persons with painful knee osteoarthritis. This well done study showed no effect of vitamin D supplements on either pain severity or MRI assessed quantitative cartilage loss. However, there were several aspects of the design and results of the study that raise questions about the findings. First, all subjects with osteoarthritis, except those on large vitamin D supplements, were recruited into the study, and many of them were not vitamin D deficient and may not have needed supplements. Second, even though the results for pain reduction did not reach statistical significance, the trial may have been too small ($n = 146$) to show a small effect of vitamin D supplements on pain. In fact, the authors found a small effect of vitamin D on pain reduction. When they carried out a post hoc analysis of those in the study who actually started the trial vitamin D deficient, the effect of vitamin D on pain reduction was much larger (effect size 0.4, larger than effects of NSAIDs on pain reduction in osteoarthritis [2]). Therefore, the effects of vitamin D supplementation on osteoarthritis findings in persons with vitamin D deficiency were not definitively answered by this study. We need additional trials testing vitamin D especially in those who are vitamin D deficient to address whether vitamin D improves pain or delays structural damage in osteoarthritis. Since vitamin D may target bone, the trials should include bone endpoints including bone marrow lesions on MRI.

How Do We Get There?

Despite the accumulated evidence from these trials, the effects of vitamin D on osteoarthritis remain uncertain. Fortunately, other large scale trials of vitamin D in osteoarthritis are under way, potentially providing a more

comprehensive picture of vitamin D's effects on disease. In the meantime, clinicians must grapple with management issues in patients with osteoarthritis. Vitamin D deficiency (using the same thresholds for 25-OH vitamin D as in the trial by Sanghi et al.) is common, and this deficiency has negative effects on bone, and perhaps a variety of other tissues. Since it may also have negative effects on osteoarthritis, it makes sense to screen for D deficiency by checking a serum 25-OH vitamin D level in patients with osteoarthritis. If deficiency is present, supplementation with D is needed. The trial by Sanghi and colleagues suggests that D supplementation may diminish knee pain in those with osteoarthritis, and given conflicting findings on this matter in other studies, the results of this trial need to be corroborated.

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