VITAMIN D
UpDates

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EDITORIAL

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Dear Colleagues,
The tissues that make up bones and skeletal muscles are intimately interconnected from a biomechanical standpoint, and it has been hypothesised that vitamin D may be considered a "director" molecule of the inter-tissue cross-talk that governs the structural and functional efficiency of the musculoskeletal system. In this issue you will find an update on the relationship between vitamin D deficiency and osteosarcopenia, and specifically on the mechanisms through which it seems that vitamin D influences muscle strength.
Muscles also have receptors for vitamin D. In animal studies it has been observed that their deletion leads to sarcopenia and muscle function deficits [1]. Furthermore, for some time now, it has been known that a condition of severe vitamin D deficiency can manifest in severe muscle weakness, especially among the proximal muscles, and thus in an increased risk of falls. Nevertheless, it is still being vigorously debated whether vitamin D supplementation in community-dwelling elderly adults will lead to an increase in muscle strength and reduce the risk of falls, or whether over-supplementation may exacerbate these outcomes.
Though a 2014 meta-analysis concluded that vitamin D supplementation improved muscle strength [2], this was not confirmed by two more recent meta-analyses [3,4]. Two recent meta-analysis studies, included in this issue's bibliography, found no significant reduction in the risk of falls and fractures with vitamin D supplementation [5,6]. Instead, two earlier meta-analysis studies showed that the risk of falls in deficient subjects was significantly reduced, but not, understandably, in non-deficient subjects [7,8]. Still, two recent RCTs [9,10], including the VITAL Study, observed no effect on the risk of falls, even though the participants were largely vitamin D deficient! On the other hand, as you may recall, the administration of a 500,000 IU vitamin D bolus, moreover largely among non-deficient subjects, was seen to be associated with an increased risk of falls after three months [11]. In addition, two other studies showed an increased risk of falls in those participants who achieved high serum 25(OH)D levels [12,13], whilst in the STOP-IT trial, a "U-curve" in the relationship between serum 25(OH)D levels and the risk of falls was observed, which indicated that a concentration of between 20 and 40 ng/mL could be viewed as optimal [14]. It is likely that the differences in the vitamin D status and the clinical profiles of the subjects receiving treatment (e.g. muscle performance, body mass index and comorbidities), the treatment schedule variability and the lack of well-defined primary endpoints could justify this discordance in results and thus generate an unfortunate level of uncertainty and confusion.
The other article in this issue has been dedicated to the possible anti-inflammatory role of vitamin D. The regulation of inflammation and cytokine expression is of crucial importance not only for many inflammatory diseases but also in view of the recent "inflammaging" hypothesis, which states that with increasing age there seems to in fact be a shift towards a pro-inflammatory state that would create and maintain a chronic basic state of inflammation, which would result in organ damage and progression towards various chronic diseases typical of ageing (e.g. rheumatological, metabolic, cardiovascular and cancerous conditions). That be-

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ing the case, it has recently been observed that elderly people with vitamin D deficiency have higher levels of C-reactive protein in their blood [15]. Just a few and sometimes discordant studies have evaluated the effect of cholecalciferol administration on inflammatory status, particularly among deficient subjects, whilst bias has often limited the interpretation of these studies, especially when considering pathological conditions. In a group of young, healthy subjects who were vitamin D-deficient, we have recently observed that cholecalciferol supplementation brought about a progressive reduction in the levels of IL-6 and IL-17 [16], two key cytokines in the pathogenesis of rheumatoid arthritis and spondyloarthritis, respectively. Therefore, vitamin D deficiency could accelerate inflammaging whilst increasing the risk or progression of inflammatory diseases or reduce response to their treatment.
What are your thoughts?
Happy reading!

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