Inflammatory Rheumatic Disorders

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Despite their beneficial effects, the effects of vitamin supplementation on RA activity, if any, seem to be limited. Evidence on their efficacy on SpA or PsA activity is lacking. However, folic acid supplementation should be suggested to prevent methotrexate-related side effects, and vitamin D should be given to patients with vitamin D deficiency to prevent musculo-skeletal complications.

Inflammatory Rheumatic Disorders Oral Vitamin Supplementation

1. Introduction

Patients with inflammatory rheumatic diseases (IRD) are seeking natural and safe alternatives to complement their conventional anti-rheumatic therapies. Vitamins are over-the-counter supplements which might be attractive for patients as complementary medicines.

The family of vitamins is composed of various organic molecules with diverse chemical structure and biological function. Vitamin D was identified quite early as a putative candidate complementary treatment of rheumatoid arthritis (RA). Vitamin D is a hormone produced in the skin in the presence of UVB but can also be provided by dietary sources. Its immunomodulatory effects have been known for nearly three decades, and it has been shown that 1,25-dihydroxyvitamin D3 (or calcitriol, the biologically active metabolite of vitamin D) acts via the intracellular vitamin D receptor (VDR). VDR is ubiquitously present and specifically on the cells of the immune system [1]. Globally, 1,25-dihydroxyvitamin D3 inhibits pro-inflammatory Th1 and Th17 responses and promotes Th2 and T-reg responses, leading to regulation of the immune response of T effector cells [2][3][4], mechanisms that may be involved in the pathogenesis of RA. Moreover, 1,25-dihydroxyvitamin D3 prevented the development of arthritis and blocked its progression in a collagen-induced arthritis mouse model [5]. Oral vitamin D supplementation is available under vitamin D3 (cholecalciferol), or activated forms such as calcitriol, alphacalcidol or 22-oxa-1-alpha, 25-dihydroxy vitamin D3 (22-oxa-calcitriol), which has less hypercalcaemic activity than calcitriol.

Vitamin E is a major fat-soluble antioxidant present in plasma. As oxygen free radicals may play a role in the genesis and persistence of proliferative and destructive synovitis in RA [6], vitamin E might, therefore, restore a normal pool of reactive oxygen species scavengers and modulate eicosanoic acid production, via the action of tocopherol.

Vitamin K has been shown to inhibit the proliferation of fibroblast-like synoviocytes and the development of arthritis in mice [7] and is also important for bone metabolism [8].

Folic acid supplementation in IRD is widely used to reduce toxicity of methotrexate-related toxicity [9].

2. Efficacy of Oral Vitamin Supplementation in Inflammatory Rheumatic Disorders

There were only a few randomized controlled trials which investigated the efficacy of vitamin supplementation only on RA. Thus, there might be not enough evidence to properly determine the efficacy of vitamin supplementation on RA symptoms and recurrence.

Regarding vitamin E, only two studies evaluated the benefit of vitamin E supplementation with contradictory results. While there were no differences compared with placebo regarding SJC, TJC, DAS-28 in both studies, results were different for VAS pain, where Edmonds et al. found a benefit in vitamin E supplementation. The reduction in VAS pain was, however, not clinically relevant. Both studies were conducted at different time periods (1997 and 2008) with different treatments, and assessed two different regimens of vitamin E, which can partially explain those results. Nevertheless, pooling both studies in our meta-analysis led to no differences regarding VAS pain. Thus, the effect of vitamin E, if any, seems to be limited, and the evidence is too weak to recommend this supplementation for RA patients.

Regarding vitamin K supplementation, with only one study which did not find any statistically significant differences in DAS-28 reduction compared with placebo, the evidence is also too limited to recommend this supplementation.

Regarding folic acid supplementation, randomized controlled studies evaluated the efficacy in both reducing RA activity and preventing methotrexate-related adverse effects with different regimens. In those studies, there were no difference regarding DAS-28 reduction, joint indices for tenderness and swelling. However, patients with folic acid supplementation had lower methotrexate-related toxicity. Thus, while there might be no benefit of folic acid supplementation in RA patients not treated with methotrexate, folic acid should be given to patients treated with methotrexate to prevent its side effects, as stated in current treatment guidelines [9][10].

Finally, vitamin D supplementation has been assessed in two different situations: first, among RA patients in remission, for whom the risk of recurrence was evaluated in a previously published meta-analyses showing an insignificant reduction in recurrence rates; second, among active RA patients, to evaluate the benefit of this supplementation in reducing RA activity and symptoms. Regarding DAS-28 reduction, while none of the studies showed a benefit in vitamin D supplementation, the meta-analysis of the two studies (Hansen and Salesi) performed by Franco et al. [11] and ours assessing DAS-28 found no significant effect of vitamin D on DAS-28 reduction. Of note, both Franco's and our meta-analyses were performed comparing the absolute values of DAS28 at follow-up between intervention and control group, rather than variations of DAS28 in the two groups, as these data were not available. As DAS-28 was relatively similar at baseline between the two groups, we believe that this method is acceptable. Regarding VAS pain, our meta-analysis did not show any significant effect of vitamin D. Nevertheless, studies assessing vitamin D supplementation are highly heterogeneous, and several factors could partly explain those discrepancies. Indeed, different vitamin D regimens were evaluated, and inclusion criteria

varied across studies (patients in remission or active RA; vitamin D deficiency [12][13][14] or not), which makes comparisons across studies difficult. In addition, only three studies evaluated 25-OH vitamin D levels before and after supplementation, and the increase in vitamin D levels was often limited, thus vitamin D supplementation might not be sufficient to provide any anti-inflammatory effect. Thus, if any, the effect of vitamin D on RA flares and RA activity seems to be limited. Evidence is currently lacking to recommend a systematic supplementation for this goal. However, as vitamin D deficiency is extremely frequent among the general population and RA patients, and is associated with an increased osteopenia and osteoporosis risk, especially within women and older patients with RA, patients with vitamin D deficiency should be supplemented for this specific aim [15][16]. Physicians may, however, be aware of potential side effects of vitamin D supplementation, including hypercalcemia and hypercalciuria [17].

3. Conclusions

Few studies assessed the benefit of vitamin supplementation on RA activity and recurrence rate. Evidence is currently lacking to recommend any vitamin supplementation to control disease activity, and further well-conducted RCTs are needed to complete our knowledge on this topic. Data regarding SpA or PsA are lacking.

However, folic acid supplementation should be suggested to prevent methotrexate-related side effects, and vitamin D should be given to patients with vitamin D deficiency to prevent musculo-skeletal complications and in case of glucocorticoid treatment, as recommended in international guidelines for the prevention and treatment of glucocorticoid-induced osteoporosis [18][19].

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