Vitamin D and rheumatic diseases

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INTRODUCTION

Besides the well-known effects of vitamin D on the skeleton and on phosphorus and calcium metabolism, unsurprisingly it has also shown to have some extra-skeletal effects and in particular in numerous metabolic, degenerative, inflammatory and autoimmune rheumatic diseases. This is justified by at least four main aspects:

1) the presence of vitamin D receptors in various tissues other than bone cells, such as cartilages, sinoviocytes and muscle cells;
2) the role of vitamin D in the control of the transcription of genes involved in rheumatic diseases;
3) the evidence that vitamin D has multiple endocrine effects not only on calcium homeostasis;
4) the activation of vitamin D not only in the kidney, but also in monocyte-macrophage and lymphocytic cell lines and in some epithelial cells with additional intracrine and paracrine effects.

The aim of this review is to summarize the latest evidence concerning the relationship between vitamin D and the most relevant rheumatic diseases.

VITAMIN D AND OSTEOPOOROSIS

It has long been known that vitamin D plays an important role in the regulation of phosphorus, calcium and skeletal metabolism. Hence vitamin D deficiency may cause rickets in children and osteomalacia in adults and can contribute to the pathogenesis of osteoporosis. Over the last year new evidence has emerged of the relationship between vitamin D deficiency and the risk of osteoporosis and fractures (1-4). This is of particular interest, since fractures place a huge burden on healthcare services (5). A recent meta-analysis has demonstrated that patients with the bb-genotype of vitamin D receptor gene BsmI polymorphism...
have statistically-significant slightly lower frequency of fracture (6). Furthermore in the past some studies demonstrated a strong correlation between bone mineral density (BMD) and some polymorphisms of this gene (7-9).

It has long been known that both calcium uptake and the level of vitamin D affect BMD. A recent study has shown that the former is more important than the latter, because a low calcium intake has detrimental effects only in patients with vitamin D deficiency (10). BMD loss is affected by the level of vitamin D, as confirmed by a recent prospective study in elderly male patients. In particular, in the group of over 75s, low levels of 25(OH)D (<20 ng/mL) have shown to correlate with a faster BMD loss (11).

Vitamin D also correlates with other bone features, besides BMD. A positive correlation has been reported between 25OH-vitamin D and some indices of bone quality, such as cortical thickness and axial and polar strength strain indices (12). Vitamin D deficiency also increases both the induction and the propagation of micro-cracks in the bone tissue (13).

Recent studies have highlighted the effects of vitamin D supplementation on BMD and other determinants of bone resistance and fractures. A Finnish study in women aged between 65 and 71 has shown that supplementation with 800 UI of vitamin D plus 1g of calcium was associated with a significant increase in total body and femur BMD. This improvement was reasonably more significant in patients with a good level of compliance (14).

Unsurprisingly vitamin D supplementation proves useful only in patients with hypovitaminosis D, as demonstrated by a recent Cochrane meta-analysis which has reported an increase in BMD after vitamin D supplementation only in young patients with low vitamin D levels (15). Recent studies have also demonstrated that vitamin D and calcium supplementation have some limited effects on some geometrical features of the bones, other than BMD, that correlate with bone resistance. In particular a structural analysis of the femur in a sub-group of female patients investigated in the Women’s Health initiative trial has shown that calcium plus vitamin D supplementation preserves BMD better than placebo and can increase the cross-sectional area and the section modulus of the femur neck, which are geometrical properties inversely correlated with the risk of hip fracture (16).

However the most important aspect of vitamin D supplementation is its capacity of reducing the risk of fracture. A recent meta-analysis has demonstrated a significant reduction of hip (-30%) and non-vertebral fractures (-14%) in patients treated with vitamin D (800 UI/die or more) (17). This supplementation strategy led to vitamin D serum levels higher than 20-24 ng/mL (i.e. 50-60 nmol/L).

However the administration of a daily dose of vitamin D can pose problems in terms of compliance, which on the contrary is an essential pre-requisite for its efficacy. It is likely that the same effects can be achieved with weekly or monthly doses, which may lead to the same serum levels of 25 OHD, provided adequate equivalent doses are administered (18, 19). In some cases a supplementation with a vitamin D bolus may also be justified, even though recent studies have unexpectedly reported an increased incidence of falls and fractures in women over 70 years treated with a 500,000 UI vitamin D bolus (20). This increase appeared to be more marked in the first 3 months after the bolus supplementation. However the population enrolled in this study included subjects with normal serum vitamin D levels, therefore such results may not be applicable to the Italian elderly population that is well-known to be affected by widespread hypovitaminosis D. A possible explanation for this unexpected increase in the incidence of falls may be paradoxically found in the potential extra-skeletal benefits of vitamin D, since they may allow elderly patients to have a more active life and consequently become more prone to falls. Another possible explanation may lie in the increase in bone turnover after non physiological peaks of serum levels of 25OHD and 1-25(OH2)D, as was observed after a supplementation of boluses of 300,000
UI or more (21, 22). There is also further evidence of negative effects of vitamin D boluses in fracture prevention strategies, which however show significant limits and uncertain interpretations. For example an unexpected increase in hip fracture risk was reported after intramuscular administration of an annual bolus of 300,000 UI of vitamin D (23). However this result is questionable, since the subjects enrolled in the study had no vitamin D deficiency (the median 25OHD serum level was 56 ng/mL at baseline). Also, as expected, the intramuscular administration, in particular of vitamin D2, could neither increase significantly serum levels of 25OHD, nor decrease PTH levels. Also an oral supplementation of 100,000 UI of vitamin D2 every 4 months did not prove to correlate with a significant reduction in the incidence of fractures, probably because it involved low doses administered also in this case to subjects with no deficient serum levels (median serum 25OHD concentration of 54 nmol/L in the control group) (24).

In any case the supplementation of high doses of vitamin D appears to be appropriate and is also recommended by the guidelines of the Italian Society of Osteoporosis, Mineral Metabolism and Skeletal Diseases (Società Italiana dell’Osteoporosi, del Metabolismo Minerale e delle Malattie dello Schieltro, SIOMMMS) for the treatment of vitamin D deficiency, provided adequate maintenance doses are administered subsequently on a daily, weekly or monthly basis (27, 28).

Furthermore the results of a previous study (29) were confirmed by a recent study, which has reported that an inadequate supplementation in patients with vitamin D deficiency is a risk factor for fractures during oral bisphophonate therapy (30).

### VITAMIN D AND MYOPATHIES

As regards the possible effects of vitamin D on muscles, it should be noted that vitamin D receptors (VDR) are known to be present on muscle cells and their expression tends to decrease with aging (31). There is also recent evidence of non-receptor-mediated effects of vitamin D on muscle cells (32).

Myocytes contain mRNA for 25OHD-1-alpha-hydroxylase, which suggests a local independent conversion of 25OHD into 1-25OHD (33). It has also long been known that vitamin D stimulates the production of muscle proteins and can activate calcium transport in the sarcoplasmic reticulum, which is essential for muscular contraction. Patients with vitamin D deficiency have often shown signs of myopathies of the proximal muscles of the limbs (i.e. difficulty in standing up from a chair, functional deficit in raising arms over their head), sarcopenia and reduction of muscular strength with associated balance disorders that cause an increase in the risk of falls and fractures, especially in elderly patients.

A correlation between hypovitaminosis D and the risk of frailty syndromes (sarcopenia, weakness, exhaustion, slowness, low physical activity levels) has been recently observed (34), even though a similar correlation has also been unexpectedly observed with high vitamin D serum levels, which however is a very rare finding in elderly patients. It has also been observed that the level of vitamin D influences functional recovery following hip fractures (35). Patients with 25OHD levels higher than 25 nmol/L (or 9 ng/mL) reported a better physical performance and were at lower risk of falling. Also mortality after hip fracture was lower in patients treated with vitamin D after hip fracture (36).

An association between hypovitaminosis D and a subsequent decline in physical performance has been recently confirmed in particular in women (37). The timed up-and-go test (i.e. the amount of time it takes to stand up from a chair, walk 3 meters, and return to the sitting position) and the timed chair standing test (i.e. the participants are seated on a straight-backed chair with their
arms folded across their chests and are asked to stand up and sit down as quickly as possible for five times without stopping or using their arms) were significantly decreased after 2.5 years, in particular in women with vitamin D levels in the lowest quartile. In another study in 739 elderly women a positive correlation has been observed between 25OHD serum levels and fast walking speed (38). A recent study has shown that vitamin D deficiency significantly correlates with functional limitations and functional decline (39). Furthermore an association has also been demonstrated between some genetic polymorphisms of VDR and the risk of falling. In particular this risk appears significantly greater in subjects carrying the B allele of Bsm1 polymorphism (40). This increased risk may be due to worst balance or muscular strength, which are present in patients carrying the B allele of Bsm1 polymorphism of VDR (41). Is there any evidence that vitamin D supplementation can increase muscular strength? A recent randomized and controlled clinical trial has reported that a daily administration of 1000 UI of vitamin D to elderly women improves muscular function in the subset with the weakest and slowest patients (42). Two more studies have also recently reported an improvement in muscular performance after vitamin D administration (43, 44). A specific meta-analysis has demonstrated a trend close to statistical significance of the relationship between vitamin D supplementation and functional indices in the proximal muscles of lower limbs (45). As expected statistical significance has been largely obtained in subjects with a more severe deficiency, i.e. with 25OHD levels <25 nmol/L.

The role of hypovitaminosis D-related myopathies in causing falls in elderly patients has been confirmed by the reduction in falls reported after the administration of adequate doses of vitamin D. Risk reduction close to the limit of statistical significance one year after the beginning of supplementation has been recently confirmed at 2 years (46) and has also been documented, especially if associated with calcium supplementation, in 3 recent meta-analyses (47-49). In particular a specific Cochrane meta-analysis has confirmed that vitamin D plus calcium supplementation leads to a 29% reduction in the incidence of falls, as compared with calcium supplementation alone (47). The lack of statistical significance associated with vitamin D supplementation alone may be due to the type of vitamin D used (D2 instead of D3) and to an insufficient dose (100,000 UI/3 months). It’s actually well-known that the longer the interval between the doses, the higher the cumulative dose must be as compared with the daily dose (19). Therefore a dose of 100,000 UI/3 months does not correspond to 1100 UI/day, as stated by the authors. In another meta-analysis (50) it was observed that doses of at least 800 UI/day (or equivalent weekly or monthly dosages) are needed to obtain a significant reduction of the risk of falling and to reach serum levels of 25OHD >60 nmol/L, which can be more easily obtained using vitamin D3, as is well-known. Also low 25OHD levels have been recently observed in patients affected by inflammatory idiopathic myopathies (51), even though in this group it is very easy to expect a causal relationship in which hypovitaminosis D is the consequence.

**VITAMIN D AND RHEUMATOID ARTHRITIS**

A correlation between the prevalence of rheumatoid arthritis (RA) and latitude has been described to confirm a potential association between hypovitaminosis D and the risk of RA (52). It has been observed that subjects with a higher vitamin D intake have a lower risk of developing RA (53), despite this finding has not been confirmed by subsequent studies (54, 55). The discrepancy between these studies may be attributable to a low accuracy in assessing vitamin D levels, which was estimated in both studies on the basis of food intake that is known to account only for 10–20% of endogenous vitamin D. Recently a negative correlation between ultraviolet-B (UV-B) light exposure and the risk of developing
Vitamin D and rheumatic diseases

RA has actually been observed. However, this may not be assessed in younger patients, because of a more widespread use of sun block creams (Fig. 1) (56). Indirect evidence of a possible role of vitamin D in the etiopathogenesis of RA may derive from the correlation between genetic polymorphism of VDR and the risk of developing RA. It has been actually reported that the polymorphisms of FokI gene (allele B) for VDR are associated with an increased incidence of RA in both the Caucasian American population (OR 1.5, 95% CI 1.16-1.95, P=0.002) (57) and the North American native population (58). The most accurate approach to investigate any correlation between vitamin D and RA is to assess directly the level of 25OHD in the serum. A study (59) reported an increased prevalence of vitamin D deficiency in patients affected by undifferentiated arthritis, which however was not confirmed by further evidence (60). Also no correlation has been found between levels of 25OHD and levels of rheumatoid factor and anti-cyclic citrullinated peptide antibodies (61).

We have recently conducted a multi-centric study on a wide Italian population that has demonstrated widespread vitamin D deficiency in patients affected by RA (62, 63). We have observed that most RA patients have low serum levels of 25OHD and also that current supplementation schemes with 400-800 UI/die of vitamin D is insufficient (Fig. 2) (62). This problem is also present in southern Italy, although in these regions sun exposure is greater due to more favorable latitude (64).

Some studies have also described an inverse correlation between disease activity and low levels of 25OHD (62, 65, 66), although it has not been confirmed by other studies (67, 68). It is not actually clear if hypovitaminosis D in patients with active RA is simply a consequence of the associated disability, leading in particular to reduced sun exposure, or it directly contributes itself to inflammation and disability. We have observed a positive correlation between vitamin D levels and the probability of remission or good response to therapy and a negative correlation with disease activity and disability (Fig. 3) (62, 64). These

Figure 1 - UVB exposure and risk of developing rheumatoid arthritis in Nurses’ Health Studies (NHS). Modified from: Arkema et al., 2013 (56).
results have also been confirmed after being adjusted for the main determinants of 25OHD serum levels (sun exposure, BMI and age). Therefore this may actually show that vitamin D has a role in controlling disease activity and in reducing the ensuing disability. As to a potential correlation between the typical bone complications of RA, erosion and vitamin D, we have also recently observed that a relevant independent risk factor is not so much the serum level of 25OHD, but an absolute or relative

Figure 2 - Prevalence of vitamin D deficiency (25OHD serum levels <20 or 30 ng/mL) in rheumatoid arthritis patients (pts) supplemented or not supplemented with vitamin D. Modified from: Rossini et al., 2010 (62).

Figure 3 - Correlations between 25OHD serum levels, health assessment questionnaire disability index (HAQ) and disease activity score 28 (DAS28) in rheumatoid arthritis patients. Modified from: Rossini et al., 2013 (64).
secondary hyperparathyroidism (69). This is also consistent with the recent observation of an increased progression of erosions, if the disease onset occurs in winter or in spring (70), which are marked by the lowest serum level of 25 OHD and highest levels of parathyroid hormone.

Another potential bias in the studies on the correlation between 25OHD levels and the disease activity is the reported reduction of 25OHD levels during inflammation (71, 72). However it has also been observed that low levels of 25OHD do not increase with a reduction in the inflammation indicators and clinical remission after treatment with adalimumab (73) or rituximab (74).

Although in patients affected by RA vitamin D supplementation may have a rationale which goes beyond the mere prevention of osteoporosis (27), there are only a few trials that have actually demonstrated its benefits, also because of the ethical issues arising from the need to have a control group of subjects at risk of vitamin D deficiency to whom no supplementation should be administered.

Two studies have demonstrated a positive role of vitamin D in determining immunological modification that may have a favorable effect in patients affected by RA (75, 76).

A study conducted in India has documented that the association between disease-modifying antirheumatic drugs (DMARDs) and calcitriol plus calcium may have positive effects in patients with recent RA if compared with the association of DMARDs and calcium without calcitriol (77). Lastly an Israeli climatherapy study has found a correlation between sun exposure and the ensuing increase in serum levels of 25OHD, and the improvement of disease activity in patients with rheumatic diseases, including RA (78).

VITAMIN D AND SYSTEMIC LUPUS ERYTHEMATOSUS

Since sun exposure in patients with systemic lupus erythematosus (SLE) is a possible risk factor for disease reactivation, it’s not surprising that hypovitaminosis D is very common in these patients. Most studies are cross-sectional, therefore limited by the indefinable cause-effect relationship, have found lower levels of 25OHD in patients with SLE than in controls (79-86). It should also be noted that, unlike healthy individuals, SLE patients have abnormal serum levels of 25OHD also in summer (83).

It has been observed that on average 25OHD levels are lower in Afro-american women (known to have a high incidence of SLE) than in those living in Sierra Leone, where SLE incidence is low, thus supporting an etiopathogenetic role of hypovitaminosis D in SLE (87).

This may seem contrary to the lack of evidence of a correlation between food vitamin D intake and the risk of developing SLE (54, 55), but it’s known that the dietary intake accounts only for a small portion of the vitamin D level. Furthermore the accuracy of these studies is poor since they have not taken into account sun exposure or serum levels of 25OHD.

The potential role of vitamin D deficiency in the etiopathogenesis and the clinical manifestation of SLE is corroborated by its correlations with VDR polymorphism (88). For example the Asian population has shown a correlation between the B allele of BsmI polymorphism and the risk of developing SLE (OR 3.58, 95% CI: 1.41-9.13, P=0.007) (89). However this finding has not been confirmed in the Caucasian population (90, 91).

It has also been observed that low levels of vitamin D are associated with an increased risk of anti-nuclear antibody (ANA) positivity, lymphocyte B activation and interferon-α activity (92). Other investigators have observed that the levels of anti-native DNA antibodies, anti-smith antibodies and immunoglobulin G increase as 25OHD decreases (93). Like in RA, also in SLE, there is evidence of a negative correlation between vitamin D levels and disease activity (93-99), also in pediatric patients (100-102).

A Canadian study has demonstrated that
the total dose of steroids is associated with lower serum levels of 25OHD on average, thus suggesting a correlation between these levels and greater disease activity (99). In particular a negative correlation has been described between low vitamin D and a clinical indicator of SLE named SLE disease activity inventory (SLEDAI). As shown by an in vitro study, this correlation may be mediated by the effects of vitamin D on the differentiation and maturation of dendritic cells, which would become reversible by adding calcitriol (103). Additionally it has been observed that the reactivation of this disease can be triggered by significant seasonal drops in vitamin D levels (104).

Obviously such a correlation between vitamin D and disease activity may be explained also by a reduction of vitamin D, which is a negative acute phase marker, caused by inflammation (71), but this hypothesis would not clarify the seasonal trend. Some studies have reported no correlation between serum levels of 25OHD and SLEDAI (105-106), but between vitamin D and fatigue (105), that is not considered a symptom in SLEDAI. Therefore this index may not be the most appropriate indicator to assess disease activity. Clinical factors, such as post-menopausal status, pericarditis, neuropsychiatric disorders and deep vein thrombosis, have demonstrated to predict low levels of 25OHD in SLE (93).

Like in RA, also in SLE the strong rationale for supplementation with a low-cost product such as vitamin D has led for ethical and economic reasons to conduct only two observational studies (105, 107), which incidentally contradict each other, and one RCT of vitamin D supplementation in SLE, which has investigated a 50,000 UI weekly dose plus a 400 UI daily dose of vitamin D in patients with SLE and hypovitaminosis D (25OHD<40 ng/mL) (108). It has been observed that an increase of 20 ng/mL in 25OHD serum levels is associated with a 21% reduction in the risk of having a high disease activity index and a 15% reduction in the likelihood of having a clinically relevant proteinuria.

### VITAMIN D AND ANTI-PHOSPHOLIPID SYNDROME

Also patients affected by anti-phospholipid syndrome have a higher prevalence of hypovitaminosis D than in healthy controls, except for springtime, when levels of 25OHD tend to be low in all groups (109). A very interesting finding is the correlation between hypovitaminosis D and risk of thrombosis, which may be attributable to the proven capacity of vitamin D of inhibiting the expression of the anti-β2GPI-mediated tissue factor (110).

### VITAMIN D AND SYSTEMIC VASCULITIS

It has been known that the antineutrophil cytoplasmatic antibody (ANCA)-associated vasculitis, in particular granulomatous polyangiitis, have a higher prevalence in northern countries, that is thought to be attributable to low sun exposure and then low vitamin D synthesis (111).

### VITAMIN D AND SYSTEMIC SCLEROSIS

Many studies have demonstrated a widespread hypovitaminosis D in patients affected by systemic sclerosis (112-117). Like in other diseases, low 25OHD levels may simply be caused by a limited sun exposure of these patients. The correlations between disease activity and its various clinical manifestations appear to be variable and occasionally absent, probably because of the heterogeneity of populations investigated (115-117). Furthermore the typical skin manifestations of this disease may reduce the synthesis of vitamin D and affect the other clinical manifestations in case the deficiency of this vitamin played a pathogenic role.

There is only one small double-blind RCT that has explored the effect of vitamin D supplementation on the disease activity and has found no significant differences
between the systemic sclerosis group and placebo (118).

■ VITAMIN D AND BEHÇET’S DISEASE

Two studies (119, 120) have found a high prevalence of hypovitaminosis D in patients affected by Behçet’s disease, which, according to one of them (120), is associated to a higher disease. The FokI F allele (F/F genotype) of a VDR gene has been demonstrated to be significantly associated with the risk of developing Behçet’s disease, in particular with its typical vascular manifestations (121).

■ VITAMIN D AND PSORIATIC ARTHRITIS

Despite some exceptions attributable to better environmental conditions in terms of sun exposure (122), also patients with psoriatic arthritis (PsA) have shown on average low levels of vitamin D (123-125). Some studies have also identified a correlation with the disease activity (123). Furthermore it has been confirmed that, also in these patients, obesity (123, 125), a well-known risk factor for vitamin D deficiency, takes on a particular meaning both in terms of susceptibility to develop this disease and to show a weaker response to treatment (126). According to some small open-label studies, the treatment with 1,25-dihydroxyvitamin D3 or alphacalcidol would seem to have significant clinical and immunological effects in patients with PsA (127, 128).

■ VITAMIN D AND SPONDYLOARTHRITIS

Although no association between hypovitaminosis D and spondyloarthritis (SA) has been found, some studies have demonstrated a negative association between some disease activity indices and serum levels of 25OHD (129) and 1-25OHD (130). In addition no significant association has been found between the susceptibility to SA and vitamin D binding protein polymorphisms, but some haplotypes are associated with a higher risk of uveitis and a lower risk of peripheral arthritis (131). A proteomic study has found a correlation between a vitamin D metabolite and the disease activity, even though the cause-effect relationship is not yet well-understood (132).

■ VITAMIN D AND FIBROMYALGIA

Some studies (133-137) have observed an association, which is still poorly un-

Figure 4 - Risk of chronic widespread pain in patients with vitamin D deficiency. Modified from: Atherton et al., 2009 (133).
derstood, between low vitamin D levels and the risk of fibromyalgia and chronic diffuse pain (Fig. 4) (133). Nevertheless the very limited number of studies which have investigated the effects of vitamin D supplementation on chronic diffused muscular-skeletal pain have not reported any convincing benefit (138, 139).

VITAMIN D AND OSTEOARTHRITIS

An additional problem in the assessment of vitamin D levels in case of osteoarthritis is correlated with the variability of the diagnostic indicator considered. A large study conducted in Italy has found unexpectedly a correlation between low vitamin D levels and the risk of suffering from spondylosis-related low back pain, even after a multivariate adjustment (Fig. 5) (140).

The main studies on the potential role of polymorphisms of VDRs in patients affected by osteoarthritis have yielded conflicting results (141-145). Some studies have explored the correlation between vitamin D levels and the severity or progression of the disease. It has been observed that male patients with hypovitaminosis D have a double risk of having radiographic

![Figure 5 - Risk of chronic low back pain in patients with vitamin D deficiency. Modified from: Hicks et al., 2008 (140).](image)

![Figure 6 - Risk of hip osteoarthritis in patients with vitamin D deficiency. Modified from: Chaganti et al., 2010 (146).](image)
evidence of coxarthrosis (Fig. 6) (146). In an 8 years-prospective study it has been demonstrated that patients with hip osteoarthritis and low levels of 25OHD have an increased risk of joint space narrowing, but not of developing osteophytes (147). It has also been demonstrated that the knee cartilage volume, determined by nuclear magnetic resonance in female patients with knee osteoarthritis, is positively correlated with 25OHD levels, both at the baseline and prospectively (148).

Since vitamin D receptors are present on chondrocytes, hypovitaminosis D may reduce cartilage resistance to stress and therefore may play a role in the pathogenesis of osteoarthritis. In a prospective study conducted in Rotterdam, it has been observed that 25OHD levels were negatively associated with radiographic signs of osteoarthritis only in patients with low BMD (149). The risk of progression of osteoarthritis was eight-fold greater in patients in the lowest tertile of 25OHD levels compared with patients in the highest tertile, despite a very wide interval of confidence (149).

On the contrary in the Framingham Osteoarthritis Study and in the Boston Osteoarthritis of the Knee Study, no significant correlation has been observed between basal vitamin D levels and further risk of joint space narrowing (150). In a study conducted in UK an increased risk of suffering from knee pain has been found in patients with serum levels of 25OHD in the lowest tertile (151).

Pain in patients with knee osteoarthritis seems actually to correlate with 25OHD levels (152). It has recently been reported that a moderate vitamin D deficiency can predicts the development or worsening of knee or hip pain after 2-5 years (153). However a recent RCT of vitamin D supplementation (2000 UI/die or more in order to reach serum levels of at least 36 ng/mL) in patients with osteoarthritis has shown no improvement either in terms of symptoms or disease progression (154). Unfortunately this result is biased because most patients enrolled in this RCT had no vitamin D deficiency.

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Vitamin D and rheumatic diseases


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