ABSTRACT

Objective. To review the relationships between vitamin D status and systemic lupus erythematosus (SLE) concerning immunological, clinical aspects and possible effects of supplementation in disease modulation.

Methods. The literature was reviewed up to January 2017 for studies regarding the epidemiology, pathogenesis, immunological aspects, clinical implications and supplementation strategies. The focus was mainly on studies with implications on every day clinical practice.

Results. Vitamin D interacts with immune system mechanisms, therefore, it may be involved in the pathogenesis of autoimmune diseases. The literature is concordant on vitamin D insufficiency being endemic in SLE patients. Data on the correlation between SLE disease activity and circulating levels of vitamin D are controversial, as well as those related to the immunomodulatory effects of vitamin D supplementation. Novel areas of study are the relationship between constitutional symptoms and cognitive involvement of SLE and hypovitaminosis D, and the possible role of vitamin D in the formation of the atherosclerotic plaque, opening new avenues for the modulation of the cardiovascular risk.

Conclusion. Future studies are needed to fully understand the relationship between hypovitaminosis D and different aspects of SLE. The most challenging topic will be to clarify supplementation strategies with vitamin D analogues that can be effective in modulating disease activity.

Introduction

Historically, the role of 1,25-dihydroxy-vitamin D has been well recognised in the context of bone metabolism, but in more recent time, “non-classical actions” of vitamin D have been described for multiple health outcomes, in particular its intracrine effects on the immune function and cancer prevention (1). The discovery that also immune cells possess the vitamin D receptor (VDR) suggested that vitamin D may have a key role in mediating the communication between the innate and adaptive pathways of the immune system (1). Hypovitaminosis D has been described in an increasing number of autoimmune diseases, including type 1 diabetes mellitus (2, 3), multiple sclerosis (4), rheumatoid arthritis (5) and systemic lupus erythematosus (SLE) (6). The role of vitamin D in the pathogenesis of SLE is reported in a number of lines of evidence (7, 8) and growing data are available in the literature about its role in SLE development, modulation of activity and disease course and possible effects of supplementation in SLE treatment. Recent reviews of the literature (9, 10) on the epidemiology of vitamin D insufficiency and the strategies of supplementation in SLE patients highlighted that no conclusive data are available on the relationship between vitamin D levels and SLE disease activity and about the effectiveness of supplementation in terms of immunomodulation (11). This lack of agreement is probably due to the large number of variables involved in Vitamin D metabolism, the different methodological approach, and the relatively small number of clinical trials.

Vitamin D (1,25(OH)₂D₃) and autoimmunity

The main source of vitamin D in humans is the endogenous synthesis in the skin from 7-dehydrocholesterol cholesterol as response to sun exposure and ultraviolet radiation. Other two subsequent steps, one in the liver and one in the proximal tubules of the
kidney, generate the 1,25 dihydroxycholecalciferol 1,25(OH)2D3 (calcitriol), the major final active dihydroxylated metabolite of vitamin D precursor [25(OH)D3] (12, 13). 1,25(OH)2D3 is considered a steroid hormone (D hormone), due to its origin from cholesterol and its immunomodulatory activity, like glucocorticoids (14). Only recently, vitamin D has received increased attention for its non-skeletal activities (immunomodulatory), especially in presence of several chronic autoimmune diseases (1).

In fact, 1,25(OH)2D3 like other steroid hormones (glucocorticoids or gonadal hormone) exerts its action on the immune system by the interaction with a nuclear receptor (VDR). The complex 1,25(OH)2D3-VDR heterodimerises with the retinoid receptor (RXR) and binds to vitamin D response elements (VDRs) in the promotor region of target genes; this mechanism modulate, cellular growth, proliferation and apoptosis among others functions, in non-skeletal tissues (15-17).

In particular, the antiproliferative effect of vitamin D is not fully know, but certainly vitamin D regulates the growth of normal and neoplastic cells and also cycle progression (18). A recent study found that vitamin D decrease the expression of Fasl and Bax and increase expression of Bel-2, a molecule with antiapoptotic function. The antiapoptotic and antiproliferative effects of vitamin D are partially due to the cell cycle arrest in G1 (19).

In the inflammatory processes, the up-regulation of proinflammatory genes and the down-regulation of anti-inflammatory genes are regulated by signal transducers or transcription factors that translate the signal cascade into gene transcription; MAP kinases such as p38 are among transducers of inflammatory signals (20). Interestingly, data are reported about the interaction between VDR/RXR and MAP kinase signalling. In this case 1,25(OH)2D3 (also called calcitriol) acts by inhibiting p 38 Map Kinase in the monocytes by the activation of MAPK phosphatase-1(MAPK-1) which dephosphorylates and reduces p38 activation. Another interesting target is NFAT (Nuclear factor of activated T-cells), a transcription factor leads to the activation of proinflammatory genes such as IL-2 and cyclooxygenase-2(COX-2) (20). The VDR gene may present different polymorphisms that influence its function and as a consequence vitamin D serum concentration can be different among individuals. Some of these polymorphisms (for example FokI, BsmI and TaqI) predispose to autoimmune disorders; a recent meta-analysis, for example, showed an association of FokI variant with increased risk to develop rheumatoid arthritis (RA) in European people while the TaqI variant is linked to systemic involvement and worse prognosis in SLE. The 25(OH)D serum concentration required to maintain non-calcicemic functions of vitamin D are not completely understood (21). Several lines of evidence show that a high prevalence of vitamin D deficiency in the general population has been linked to an increased risk of autoimmune diseases such as multiple sclerosis, diabetes, RA, SLE (22). Considering that the synthesis of vitamin D depends in sunshine body exposure, vitamin D availability is related to sunlight exposure and showed an association with sign and symptoms of autoimmune diseases (25). This observation emerged from the reports that people living near the equator are at decreased risk of developing autoimmune conditions. Moreover, an increased prevalence of RA seems more common in northern European countries compared to the southern ones and vitamin D serum levels and disease activity in RA are regulated with a circannual rhythm and more severe disease activity in the winter (17, 25).

**Vitamin D (1,25(OH)2D3) and systemic lupus erythematosus**

In SLE, the inflammatory milieu drives the development of T cells into the proinflammatory pathways, defective function of Tregs with hyperactivity of Th cells, and survival and activation of autoreactive B cells that produce autoantibodies (6). In addition, alterations in apoptosis and decreased elimination of autoreactive lymphocytes could influence the loss of self-tolerance. Some works showed an elevated apoptosis in of SLE lymphocytes, and Treg are particularly sensible to apoptosis mechanisms (26).

Patients with SLE showed also multiple additional risk factors for the induction of vitamin D deficiency, which in turn seems to further influence the disease severity. Particularly, the reduced sun exposure due to photosensitivity, the use of photo-protection, the alteration of renal vitamin D metabolism, as well as dark skin are all further explanations for vitamin D insufficiency (27).

As a matter of fact, the literature reports the prevalence of vitamin D insufficiency (between 20 and 30 ng/ml) to be between 38-96% in SLE patients and the prevalence of vitamin D deficiency (less than 20 ng/ml) to be between 8-30% (28).

Recent investigations reported also the relationship between vitamin D concentrations and SLE disease activity, suggesting that vitamin D deficiency during wintertime can be a risk factor for disease flare (29). These observations represent the basis to test the possible therapeutic role of cholecalciferol in clinical practice as modulator of the immune system in SLE (30). Of note, vitamin D is a key factor able to influence both innate and adaptive immunity, in particular potentiating the innate immune response but suppressing adaptive immunity by acting on B lymphocytes, B cell homeostasis and Ig production (13).

Regarding the innate immunity, calcitriol enhances first line response against different pathogens by acting on antigen presenting cells (APC) (31). By using intracellular mechanisms inside monocytes/macrophages/keratinocytes, such as activation of the lalpha-hydroxylase (CYP27B1), 1,25(OH)2D3 can even stimulate the synthesis of antimicrobial peptides such as cathelicidins, which contribute to bacterial killing (13).
Concerning the adaptive immunity, 1,25(OH)2D3 seems to have a direct effects on both T cells and B cells. Selectively, calcitriol downregulates TH1 response and inflammatory cytokines production such as IL-2 and interferon gamma (INF gamma) through a direct effect of 1,25(OH)2D3/VDR complex on IL-2 and IFN gamma transcription (32). In contrast, calcitriol, like glucocorticoids, enhances the production of cytokines associated with Th2 cells and induces Treg that are involved into a sort of “switch off” of the inflammatory reaction (32).

Previous investigations suggested some beneficial effects of vitamin D in SLE both by increasing the number of Treg and by an anti-proliferative effect on B cells differentiation and autoantibody production (33). Finally, vitamin D serum concentrations in SLE patients showed a negative correlation with clinical disease activity and anti dsDNA titre (34).

Vitamin D status: which metabolite can we measure and which is the adequate target for circulating levels?

25-Hydroxy vitamin D is the metabolite currently evaluated because it is considered the most accurate biomarker of serum vitamin D levels since it derives from cutaneous synthesis and dietary intake. Several assays for vitamin D measurement are available but they carry methodological limitations most of which are attributable to the molecule itself. In fact, 25 (OH) vitamin D is probably the most hydrophobic compound measured by protein binding assay (PBA), which constitutes either competitive BPA or radioimmunossay. Currently, a general consensus exists on some key points that should be summarised as follows: first of all, choose an assay that measures both 25 (OH)D2 and 25 (OH)D3 and, if it is not possible to separate the two compounds, indicate the sum of the two compounds. Moreover, it is important to participate to an external quality assessment scheme that provides materials commutable to patients specimens, and report appropriate levels for vitamin D deficiency and toxicity in addition to reference levels obtain in well-selected reference subjects (14).

There is some consensus regarding optimal vitamin D levels to prevent endocrine disease, although there is variability regarding the definition of “deficiency” or adequate vitamin D status. On the other hand there is no consensus on the target concentration of vitamin D needed to achieve “non-classical” vitamin D beneficial effects. International scientific societies such as the Institute of Medicine (IOM) (35, 36) and The National Osteoporosis Society (37) have defined cut-off for concentrations of vitamin D but studies were conducted on the healthy population and no data are available regarding the optimal levels of vitamin D in patients with chronic diseases.

Epidemiology of hypovitaminosis D: focus on SLE

Vitamin D deficiency is highly prevalent worldwide, involving both healthy and ill subjects, and it particularly affects patients with rheumatic diseases (14). In the National Health and Nutrition Examination Survey (NHANES) 2005 to 2006, 41.6% of adult participants (≥20 years) had 25-hydroxyvitamin D (25[OH]D) levels below 20 ng/mL (50 nmol/L) (38) and the prevalence of low vitamin D levels may be increasing globally (39). Multivariate analysis showed that being from a non-white race, not college educated, obese, having low high-density lipoprotein (HDL) cholesterol, poor health, and no daily milk consumption were significantly and independently associated with low vitamin D levels.

In a review of vitamin D levels in different regions of the world, vitamin D levels below 30 ng/mL were prevalent in every studied region, and low vitamin D levels (<10 ng/mL) were more common in South Asia and the Middle East than in other regions (40). Some SLE patients may develop renal involvement during the follow-up and the 1-hydroxylation of vitamin D into its active form may be lost or significantly reduced in advanced renal disease. Sumethkul et al. (41) found that active SLE patients with lupus nephritis had significantly lower vitamin D levels than the other groups, suggesting that nephritis is a significant predictor of vitamin D deficiency in SLE. Medications used for treatment of SLE may also influence vitamin D status. Data...
on hydroxychloroquine (HCQ) are still controversial: some authors found lower vitamin D levels in patients treated with HCQ (42) although other studies found opposite results or did not observe any association (43, 44). Chronic corticosteroid use reduces intestinal absorption and accelerates the catabolism of 25(OH)D and 1,25(OH)2D through an increase in 24a-hydroxylase activity (45, 46). Also genetic factors may affect vitamin D status and in particular the genetic variants of two genes encoding key enzyme regulators of endogenous production of 25-hydroxyvitamin D have been studied. Polymorphic variants in these two genes result in differential efficiencies in synthesising 25-hydroxyvitamin D (47).

Moreover the wide variation in the rates of vitamin D deficiency relates to many environmental factors such as latitude, cigarette smoking, working environment (outdoor vs. in-door) season at the time of blood sample and ethnicity.

**Vitamin D, gender and sex hormones**

Sex hormones are thought to be crucial for SLE regulation, in fact the disease mostly affects women at child bearing age with a female: male ratio 8-15:1, suggesting some association between oestrogen levels and the disease itself. Oestrogen and prolactin affect maturation and selection of autoreactive B cells, behaving then as immune-stimulators. Moreover, men with SLE show as well elevated serum levels of oestrogens. In this context, could be explain the beneficial effects of vitamin D, which by decreasing aromatase expression reduces oestrogen peripheral synthesis (48).

**Vitamin D and cardiovascular risk factors in SLE**

SLE patients have a 7.5 to 17.0-fold excess risk of developing cardiovascular (CV) disease compared with general population even after adjusting for Framingham risk factors. Morbidity and mortality remain higher in SLE patients than in general population, with CV disease being major cause of death (49). In particular a recent study by Watad et al. (50) shows that SLE is associated with ischaemic heart disease (OR 3.77, 5% confidence interval 3.34–4.26). Both traditional and non-traditional risk factors of CV disease may play a role in SLE patients, and it has been suggested that also vitamin D may be involved.

Different studies analysed the relationship between low levels of vitamin D and cardiovascular events in SLE patients. The association between hypertension and low vitamin D levels seems to be mediated by the effects of vitamin D on the renin angiotensin system (51). The association between low vitamin D levels and CV risk factors in SLE patients was reported by different studies. Besides hypertension, risk factors include insulin resistance, dyslipidaemia, LDL cholesterol, body mass index (52, 6, 53).

Other studies observed that there was an association between vitamin D deficiency and increased aortic stiffness (53, 54) while it seems that patients with higher vitamin D levels had a better endothelial function measured with flow-mediated dilatation (55) and vitamin D deficiency resulted in impaired endothelium-dependent vasorelaxation and decreases in neoangiogenesis (56). In particular calcitriol appeared to be able to ameliorate the ability of myeloid angiogenic cells in restoring damaged vessels and endothelial damage by decreasing Neutrophil Extracellular Traps (NETs) activity (57, 58). In contrast, other authors (59-61) found that 25(OH)D levels were not associated with any subclinical measure of atherosclerosis. Hence, the relationship between vitamin D and cardiovascular diseases among lupus patients remains controversial. Nonetheless, encouraging vitamin D supplementation in SLE patients can be part of the strategy in reducing CV risk, such the minimisation of the use of steroids (62).

**Vitamin D and SLE clinical activity**

Although experimental data support the potential benefits of vitamin D on SLE disease activity, the reviews of the literature on this topic reveal that available data are still controversial, even if most studies have shown an association of 25 (OH) D deficiency with increased SLE disease activity (6). However, data analysis is arduous because of the heterogeneity of the different variables (9, 10, 28; 63).

Tables I and II show the studies supporting or not an association between vitamin D deficiency and/or insufficient and SLE disease activity according to different scores. Tables were modified and updated to January 2017 starting from the table presented in a recent review (27).

**Vitamin D and other SLE features/manifestations**

**Vitamin D and cognitive function**

Vitamin D exerts marked effects on immune and neural cells. These non-classical actions of vitamin D have gradually gained a renewed attention since it has been shown that diminished levels of vitamin D induce immune-mediated symptoms in animal models of autoimmune diseases and is a risk factor for various brain diseases (81). In fact there is a link between low vitamin D levels and impaired brain function, given that 25 (OH) D crosses the blood-brain barrier to reach VDRs which are present on neurons and glial cells of the central nervous system (CNS). In the CNS, the conversion of 25 (OH) D into the active form takes place, qualifying vitamin D as neurosteroid. Based on these assumptions, a recent study looked at the relationship between vitamin D and cognitive dysfunction (82) in SLE patients. The authors concluded that deficiency of 25 (OH) D3 independently predicted worse cognitive function in SLE patients. The association between 25 (OH) D3 deficiency and cognitive impairment in SLE is novel and further prospective studies are needed to clarify if SLE patients with hypovitaminosis D are more likely to experience cognitive dysfunction and the role of vitamin D supplementation in prevention of such neurological impairment.

**Vitamin D, fatigue and sleep disorders**

Fatigue is a common disabling symptom complained by more than 50% of patients with SLE (83). Ruiz Irastorza et al. (84) and Lima et al. (85) demon-
Table I. Studies supporting an association between vitamin D deficiency and/or insufficiency and disease activity. SLE disease activity was assessed with SELENA-SLEDAI if not otherwise specified.

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Country</th>
<th>Other conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gao et al. [64]</td>
<td>2016</td>
<td>China</td>
<td>Severe deficiency increases the risk of moderate to severe disease activity but not for organ damage</td>
</tr>
<tr>
<td>Abaza et al. [65]</td>
<td>2016</td>
<td>Egypt</td>
<td>Association also with SLICC and fatigue</td>
</tr>
<tr>
<td>Dall’Ara et al. [29]</td>
<td>2015</td>
<td>Italy</td>
<td>Association between winter SLE flare and vitamin D insufficiency</td>
</tr>
<tr>
<td>Yap et al. [10]</td>
<td>2015</td>
<td>Australia</td>
<td></td>
</tr>
<tr>
<td>Schoindre et al. [66]</td>
<td>2014</td>
<td>France</td>
<td></td>
</tr>
<tr>
<td>Mandal et al. [67]</td>
<td>2014</td>
<td>India</td>
<td></td>
</tr>
<tr>
<td>McGhie et al. [68]</td>
<td>2014</td>
<td>Jamaica</td>
<td>BILAG scale used</td>
</tr>
<tr>
<td>Lertratanakul et al. [69]</td>
<td>2014</td>
<td>North America, Europe and Asia</td>
<td></td>
</tr>
<tr>
<td>Emerah et al. [70]</td>
<td>2013</td>
<td>Egypt</td>
<td></td>
</tr>
</tbody>
</table>


Table II. Studies opposing an association between vitamin D deficiency and/or insufficiency and disease activity. SLE disease activity was assessed with SELENA-SLEDAI if not otherwise specified.

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Country</th>
<th>Other conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Garcia-Carrasco et al. [71]</td>
<td>2016</td>
<td>Mexico</td>
<td>MEX-SLEDAI</td>
</tr>
<tr>
<td>Shahin et al. [72]</td>
<td>2016</td>
<td>Egypt</td>
<td>Correlation with thrombocytopenia</td>
</tr>
<tr>
<td>Salman Monte et al. [73]</td>
<td>2016</td>
<td>Spain</td>
<td>Correlation with fatigue and more use of corticosteroids</td>
</tr>
<tr>
<td>Garf Ke et al. [74]</td>
<td>2015</td>
<td>Egypt</td>
<td>Juvenile-onset SLE</td>
</tr>
<tr>
<td>Miskovic et al. [75]</td>
<td>2015</td>
<td>Serbia</td>
<td></td>
</tr>
<tr>
<td>Simioni et al. [76]</td>
<td>2015</td>
<td>Brazil</td>
<td>Association between leukopenia and vitamin D deficiency</td>
</tr>
<tr>
<td>Souza et al. [77]</td>
<td>2014</td>
<td>Brazil</td>
<td></td>
</tr>
<tr>
<td>Attar et al. [78]</td>
<td>2014</td>
<td>Saudi Arabia</td>
<td>SLEDAI-2K scale was used</td>
</tr>
<tr>
<td>Sahebari et al. [63]</td>
<td>2014</td>
<td>Iran</td>
<td>Also includes a systemic review in which intervening variables to this relationship were found: medications (hydroxychloroquine, steroids, and vitamin D supplements), BMI, renal function, and proteinuria</td>
</tr>
<tr>
<td>Squance et al. [79]</td>
<td>2014</td>
<td>Australia</td>
<td>Measured in self-reported flares</td>
</tr>
<tr>
<td>Chaiamnuay et al. [80]</td>
<td>2013</td>
<td>Thailand</td>
<td>MEX-SLEDAI</td>
</tr>
</tbody>
</table>


Vitamin D and bone health
Vitamin D is a key regulator of calcium and phosphate stores in the human body, in fact it increases their absorption from intestine by 30/40% to 80% respectively. Therefore vitamin D deficiency may influence calcium status and bone health of SLE patients. Watad et al. (89) in their study examined the relationship between hypocalcaemic events, total serum calcium and vitamin D levels in SLE patients and they found that SLE patients are at higher risk for hypocalcaemic events than general population. Specific changes in vitamin D and calcium homeostasis in SLE patients may be responsible for the severity of symptoms, therefore these data support the need for both calcium and vitamin D supplements in SLE patients in order to prevent not only osteoporosis, but also events of hypocalcaemia. Guo et al. (90) in their recent study concluded that SLE disease activity itself directly contributed to the development of SLE-associated osteopenia and osteoporosis. In fact this study revealed negative correlations between osteocalcin (marker of bone formation) and SLEDAI, ds-DNA antibody and β-crosslaps (collagen degradation products as markers of bone resorption), while a positive correlation was observed between osteocalcin and C3, C4, 25-OH vitamin D, lumbar and hip bone mineral density. Moreover it is well known that osteoporosis and fractures give the major contribute

strated that vitamin D supplementation may have beneficial effects on fatigue in SLE patients. Salman Monte et al. (73) in their recently published study concluded that non-supplemented female SLE patients showed more fatigue and received more oral corticosteroids than those with normal levels of vitamin D. Nevertheless, a review (86) on this topic concluded that evidence regarding

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to damage in SLE patients, being symptomatic fractures reported in 6–42% of patients since SLE diagnosis (91). Vitamin D deficiency is one of the major risk factors, in addition to persistent disease activity, glucocorticoid use, renal insufficiency, premature menopause and physical inactivity as the results of pain and fatigue. Vitamin D supplementation is indicated for both prevention and treatment of osteoporosis in SLE patients and in particular Edens and colleagues (92) recommended a daily oral dose of cholecalciferol between 800 and 2000 UI to maintain serum levels above the target of 30 ng/ml.

**Vitamin D supplementation in SLE**

Vitamin D supplementation is part of good clinical practice in patients with rheumatic disease for the prevention of osteoporosis especially in winter time. What is not completely clear is how to adjust supplementation in order to gain immunomodulatory effects of vitamin D. The purpose of the interventional studies reported in Table III was to answer these questions, but results are not conclusive. The analysis of the available studies is quite difficult for different reasons. First of all, the studies are not homogeneous in terms of number of enrolled patients, type and duration of the supplementation and for different endpoints.

Cholecalciferol (vitamin D3) was the compound used in the majority of the studies because of its availability in most countries. The use of ergocalciferol (vitamin D2) was limited to America and it should be kept in mind that it is cleared more quickly and has lower tissue bioavailability. Schedules (daily, weekly, monthly) and dosages of supplementation were also different. All the regimens allowed to increase vitamin D serum levels, and in the majority of the studies more than half of the treated patients achieved sufficient values (Table III).

Concerning the relationship between vitamin D supplementation and SLE disease activity, two randomised double blind placebo controlled trial (93, 85) and a cohort study (94) found that supplementation is able to reduce disease activity, while other two cohort studies failed to observe any significant variation (95, 84). Schedules and dosages were highly variable across these studies. SLE serology does not seem to be affected by vitamin D supplementation (95) given both with an intensive or a standard regimen, while higher dose (7) was able to reduce anti-DNA antibodies. Some authors demonstrated that vitamin D supplementation may have a role in reduction of inflammatory-haemostatic markers (96) and in decreasing urine protein-to-creatinine ratio (94).

Immunological effects of vitamin D have been underline in different studies (7, 30): after supplementation there is an enhancement of regulatory T cells, with an increase of naïve CD4T cells, decrease Th1 and Th17 cells with a higher production of Th2 cytokines. Also B compartment appear to be modulated by vitamin D, in fact supplementation induced a decrease of memory B cells. Recently Aranow et al. (93) published the results of randomised double blind, placebo controlled trial concluding that vitamin D3 supplementation up to 4000 IU day failed to diminish the IFN-alpha signature. Another important issue analysed by these interventional studies is safety of vitamin D supplementation. Vitamin D toxicity is possible although rare, and the main complications are hypercalcaemia and hypercalciuria. Globally, the dosages used in these studies appeared to be safe, and the incidence of hypercalcemia ranged from 0.002% (94) to a maximum 2% (96); none of these studies described an increased occurrence of lithiasis. In conclusion, supplementation is needed first of all for the prevention of glucocorticoid induced osteoporosis with possible immunomodulatory effects that remain to be fully established. Current vitamin D supplementation strategies are not sufficient in rising serum levels of vitamin D in every patient, therefore a treat-to-target approach could be a possible solution. For this reason an initial measurement of serum levels of vitamin D should be done for each patients. As a general rule, 100 IU/day of vitamin D intake is needed to increase 1 ng/ml of serum25 (OH)D, which takes about 3 months to became stable once supplementation is started (97).

**Vitamin D insufficiency: predictors and biomarkers**

In clinical practice it would be useful to have demographic, clinical and serological predictors of hypovitaminosis D. It is well known that use of sunscreen and sun avoidance have been shown to be predictors of low serum levels of 25 (OH)D in SLE patients (98), but it would be better to have more specific parameters.

In a study of 177 SLE patients post-menopausal versus pre-menopausal status, pericarditis, neuropsychiatric disease and deep-vein thrombosis were identified as predictors of lower serum levels of 25(OH)D. Furthermore, disease activity score was inversely related to 25(OH)D status, and markers such as anti-dsDNA antibodies, anti-Smith antibodies and IgG increased with decreasing serum 25(OH)D status (99). These serological variables are probably the most useful for clinicians as surrogate biomarkers of low levels of vitamin D. Another interesting data, but with a lower impact in practice, is that patients with insufficient 25(OH)D had higher levels of IL-6 and higher prevalence of haematuria (77). Different studies analysed the association between low vitamin D levels and interferon IFN signature. A study performed in India showed a positive correlation between IFN levels and the severity of disease manifestations (67); a similar correlation was also shown by Schneider et al. (28) but the latter failed to demonstrated an association between vitamin D levels and patient cytokine profile. Recently Shahin et al. (72) found that hypovitaminosis D contributes to ANA antibody production and that it is associated with high serum levels of IL-23 and IL-17; thus they may trigger the inflammatory process in SLE. A recent multicentre study in RA (100), based on patient reported outcomes (PRO), showed a relationship between vitamin D deficiency/insufficiency and related clinical aspects.

**Conclusions**

Further investigations are needed to better understand the relationship between vitamin D deficiency and clinical consequences in SLE patients. The most chal-
<table>
<thead>
<tr>
<th>Author (reference)</th>
<th>Type of study</th>
<th>Number of enrolled patients</th>
<th>Type of supplementation</th>
<th>Main findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ruiz-Irastorza et al. (2010)</td>
<td>Longitudinal observational study (84)</td>
<td>80</td>
<td>Oral cholecalciferol 600–800 IU/day for 24 months</td>
<td>Beneficial effect on fatigue; no significant correlations were seen in SLEDAI or SDI values. Vitamin D supplementation was not associated with changes in urinary protein-to-creatinine ratio, no cases of hypercalcemia;</td>
</tr>
<tr>
<td>Terrier et al. (2012) (7)</td>
<td>Prospective longitudinal study</td>
<td>20</td>
<td>Oral cholecalciferol 100,000 IU/week during 4 weeks</td>
<td>Increase in regulatory T cells, decrease in pro-inflammatory cytokines, decrease in anti-DNA antibodies, no cases of hypercalcemia;</td>
</tr>
<tr>
<td>Petri et al. (2013) (94)</td>
<td>Prospective cohort</td>
<td>1006</td>
<td>Oral cholecalciferol 50,000 IU weekly + 200 U calcium/vitamin D twice daily</td>
<td>20 U increase in the 25(OH)D level was associated with a 0.22 decrease of SELENA-SLEDAI and 2% decrease in urine protein-to-creatinine ratio; no cases of hypercalcemia;</td>
</tr>
<tr>
<td>Abou-Raya et al. (2013)</td>
<td>Randomised double blind, placebo controlled trial (96)</td>
<td>267</td>
<td>Oral cholecalciferol 2000 IU/day</td>
<td>Lower Vit.D levels correlated with higher disease activity and haemostatic markers. Increase in 25(OH)D levels after 12 months is associated with improvement in inflammatory-haemostatic markers; no cases of hypercalcemia;</td>
</tr>
<tr>
<td>Andreoli et al. (2015) (95)</td>
<td>Two-year-long prospective study with a cross-over design</td>
<td>34</td>
<td>Oral cholecalciferol 300,000 IU initially, followed by 50,000 IU monthly (850,000 annually)</td>
<td>Intensive regimen significantly raised vitamin D serum levels. No significant differences in disease activity, or SLE parameters; slight hypercalciuria; no cases of hypercalcemia;</td>
</tr>
<tr>
<td>Piantoni et al. (2015) (30)</td>
<td>Prospective study with a cross-over design</td>
<td>34</td>
<td>Oral cholecalciferol 5000 IU week</td>
<td>Intensive regimen with a long-term monthly treatment with vitamin D in SLE patients; an enhancement in T-reg cells and the production of Th2 cytokines; no cases of hypercalcemia;</td>
</tr>
<tr>
<td>Lima et al. (2016) (85)</td>
<td>Randomised double blind, placebo controlled trial</td>
<td>40</td>
<td>Cholecalciferol 5000 IU week or placebo</td>
<td>After a long-term monthly supplementation with vitamin D, disease activity and fatigue improved in those who received vitamin D; no cases of hypercalcemia;</td>
</tr>
<tr>
<td>Aranow et al. (2015) (93)</td>
<td>Randomised double blind, placebo controlled trial</td>
<td>57</td>
<td>Vitamin D3 2,000 IU/day or 4,000 IU weekly</td>
<td>Vitamin D3 supplementation up to 4,000 IU daily was safe and effective in decreasing disease activity and improving fatigue; no cases of hypercalcemia;</td>
</tr>
</tbody>
</table>

**Table III.** Prospective studies reporting the effects of vitamin D supplementation in SLE patients. The column “objectives” contains the items that were expected to be modified by vitamin D supplementation.

- Assessment of safety: including the occurrence of hypercalcemia, hyperphosphoremia or lithiasis; PBMCs peripheral blood mononuclear cells; JoSLE juvenile-onset SLE; IFN-alpha: alpha interferon; SLEDAI systemic lupus erythematosus disease activity index, SDI rheumatology damage index.
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