Review

Vitamin D and systemic lupus erythematous: a review of immunological and clinical aspects

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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-dihydroxyvitamin 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 ($1,25(OH)_2D_3$) 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 dihydroxy-cholecalciferol $1,25(OH)_2D_3$ (calcitriol), the major final active dihydroxylated metabolite of vitamin D precursor [25(OH)D)] (12, 13).

$1,25(OH)_2D_3$ 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 autoimmmune diseases (1).

In fact, $1,25(OH)_2D_3$ 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 $1.25(OH)_2D_3$-VDR heterodimerises with the retinoid receptor (RXR) and binds to vitamin D response elements (VDREs) in the promotor region of target genes; this mechanism modulate, cellular growth, proliferation and apoptosis among others functions, in non-calcaemic 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 Bcl-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 $1,25(OH)_2D_3$ (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-calcaemic 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 80–90% by the sunlight body exposure (23) low levels of vitamin D have been reported for healthy subject particularly in the Northern climate (17). However, in the recent years, probably due to changes in lifestyle, also in sunny areas healthy subjects seem to have low levels of vitamin D (24).

Interestingly, the different seasonal 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 ($1,25(OH)_2D_3$) 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 flares (29). These observations represent the basis to test the possible therapeutical 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 intracrine mechanisms inside monocytes/macrophages/keratinocytes, such as activation of the 1alpha-hydroxylase (CYP27B1), $1,25(OH)_2D_3$ can even stimulate the synthesis of antimicrobial peptides such as cathelicidins, which contribute to bacterial killing (13).

Concerning the adaptive immunity, $1,25(OH)_2D_3$ 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 $1,25(OH)_2D_3$/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).

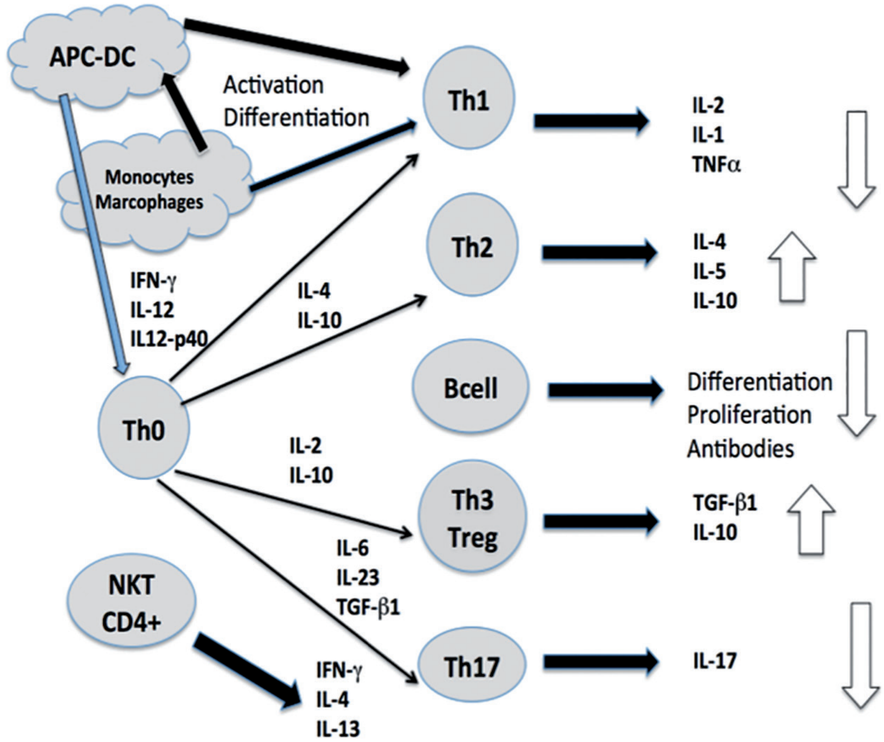

Fig. 1. Vitamin D and immune response: suppression of adaptive immunity and enhancement of innate immunity.

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 radioimmunoassay. 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 oestrogenes. 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 insufficiency 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) D3 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) D3 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.

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

SELENA-SLEDAI: Safety of Estrogen in Lupus Erythematosus National Assessment- Systemic Lupus Erythematosus Disease Activity Index; BILAG: British Isles Lupus Assessment Group.

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.

Study	Year	Country	Other conclusions
Garcia-Carrasco *et al*. [71]	2016	Mexico	MEX-SLEDAI
Shahin *et al*. [72]	2016	Egypt	Correlation with thrombocytopenia
Salman Monte *et al*. [73]	2016	Spain	Correlation with fatigue and more use of corticosteroids
Garf Ke *et al*. [74]	2015	Egypt	Juvenile-onset SLE
Miskovic *et al*. [75]	2015	Serbia	
Simioni *et al*. [76]	2015	Brazil	Association between leukopenia and vitamin D deficiency
Souza *et al*. [77]	2014	Brazil	
Attar *et al*. [78]	2014	Saudi Arabia	SLEDAI-2K scale was used
Sahebari *et al*. [63]	2014	Iran	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
Squance *et al*. [79]	2014	Australia	Measured in self-reported flares
Chaiamnuay *et al*. [80]	2013	Thailand	MEX-SLEDAI

SELENA-SLEDAI: Safety of Estrogen in Lupus Erythematosus National Assessment- Systemic Lupus Erythematosus Disease Activity Index; SLEDAI-2K: Systemic Lupus Erythematosus Disease Activity Index-2000; MEX-SLEDAI: Mexican version, Systemic Lupus Erythematosus Disease Activity Index; BMI: body mass index.

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 the association between vitamin D and fatigue remains inconsistent since supplementation studies failed to improve fatigue in SLE patients. Sleep disorders can occur in more than half of the patients with SLE and in the majority of the studies an association between sleep disorders and disease activity, pain and fatigue has been reported (87).

To our knowledge, only one study investigated a possible connection between low vitamin D levels and sleep alterations. Gholamrezaei *et al*. (88) found a role for vitamin D in sleep quality of SLE patients, and this association remained significant independently of demographic, diseases and psychological-related factors as well as season of assessment.

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 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 hypercalcaemia 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 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.

Author (reference)	Type of study	Number of enrolled patients	Objectives	Type of supplementation	Main findings
Ruiz Irastorza *et al*. (2010) (84)	Longitudinal observational study	80	- Variation in disease activity, organ damage, and fatigue	Oral cholecalciferol 600–800 IU day for 24 months	Beneficial effect on fatigue, no significant correlations were seen in SLEDAI or SDI values. Side effects: not reported
Terrier *et al*. (2012) (7)	Prospective study	20	- assessment of safety parameters - Variation in T cell and B cell homeostasis - Variation in cytokines and gene expression profiles in PBMCs - Variation in disease activity	Oral cholecalciferol 100,000 IU/week during 4weeks	Increase of naive CD4 T cells Increase in regulatory T cells Decrease Th1 and Th17 cells Decrease memory B cells Decrease anti-DNA antibodies → no cases of hypercalcaemia
Petri *et al*. (2013) (94)	Prospective cohort	1006	- Variation in disease activity	50,000 IU of ergocalciferol weekly+ 200 U calcium/vitamin D twice daily	A 20-U increase in the 25(OH)D level was associated with decrease of 0.22 of SELENA-SLEDAI and 2% decrease in urine protein-to-creatinine ratio → hypercalcaemia 0,002%
Abou-Raya *et al*. (2013) (96)	Randomised double blind, Placebo controlled trial	267	- Variation in inflammatory and haemostatic markers - Variation in disease activity	Oral cholecalciferol 2000 IU/day or placebo	Lower Vit.D levels correlated with higher disease activity Increase in 25(OH)D levels after 12 months is associated with improvement in inflammatory-haemostatic markers → hypercalcaemia 2%
Andreoli *et al*. (2015) (95)	Two-year-long prospective study with a cross-over design	34	- Variation on 25-OH vit.D levels, on disease activity and on serological SLE parameters - Assessment of safety parameters	Oral cholecalciferol Intensive Regimen: 300,000 IU initial bolus followed by 50,000 IU monthly (850,000 annually) Standard Regimen: 25,000 IU monthly (300,000 annually) for 12 months Regimens switched in the second year	Intensive regimen significantly raised vitamin D serum levels. No significant differences in disease activity, or SLE serology → no cases of hypercalcaemia; three cases of transitory slight hypercalciuria
Piantoni *et al*. (2015) (30)	Prospective study with a cross-over design	34	- Variation on the circulating numbers of T-cells and on cytokine production	Oral cholecalciferol Intensive Regimen: 300,000 IU initial bolus followed by 50,000 IU monthly (850,000 annually) Standard Regimen: 25,000 IU monthly (300,000 annually) for 12 months Regimens switched in the second year	After a long-term monthly treatment with vitamin D in SLE patients, an enhancement of T-reg cells and the production of Th2 cytokines should be expected. → no cases of hypercalceamia
Lima *et al*. (2016) (85)	Randomised double blind, placebo controlled trial	40 JoSLE	- Variation in disease activity and fatigue	Cholecalciferol 5000 IU week or placebo	Cholecalciferol supplementation for 24 weeks was effective in decreasing disease activity and improving fatigue in JoSLE patients. → no cases of hypercalcaemia
Aranow *et al*. (2015) (93)	Randomised double blind, placebo controlled trial	57	- Variation on the expression of IFN-alpha-inducible genes - Variation in the IFN-alpha signature response	Vitamin D3 2,000 IU/day or 4,000/day IU or placebo	Vitamin D3 supplementation up to4,000 IU daily was safe and well-tolerated but failed to diminish the IFN-alpha signature → no cases of hypercalcaemia

Assessment of safety: including the occurrence of hypercalcaemia, 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.

lenging task will be to optimise supplementation strategies, including the use of non-hypercalcaemic vitamin D analogues that could be directly effective in modulating disease activity. In everyday clinical practice it would be useful to monitor serum vitamin D and calcium levels in order to correctly replete the patients. Since hypercalcaemia and hyperphosphataemia have been reported only for very high doses of vitamin D (over 50,000 IU per day), SLE patients could be given more generous doses as compared to the current practice, aiming at exploiting the immunomodulatory properties of vitamin D.

References

1. ADORINI L, PENNA G: Control of autoimmune diseases by the vitamin D endocrine system. *Nat Clin Pract Rheumatol* 2008; 4: 404-12.
2. DANKERS W, COLIN EM, VAN HAMBURG JP, LUBBERTS E: Vitamin D in autoimmunity: molecular mechanisms and therapeutic potential. *Front Immunol* 2017; 20: 7-697.
3. MATHIEU C: Vitamin D and diabetes: Where do we stand? *Diabetes Res Clin Pract* 2015; 108:201-9.
4. NIINO M, MIYAZAKI Y: Vitamin D in multiple sclerosis. *Brain Nerve* 2015; 67: 1429-33.
5. JEFFERY LE, RAZA K, HEWISON M: Vitamin D in rheumatoid arthritis-towards clinical application. *Nat Rev Rheumatol* 2016; 12: 201-10.
6. YAP KS, MORAND EF: Vitamin D and systemic lupus erythematosus: continued evolution. *Int J Rheum Dis* 2015; 18: 242-9.
7. TERRIER B, DERIAN N, SCHOINDRE Y *et al.*: Restoration of regulatory and effector T cell balance and B cell homeostasis in systemic lupus erythematosus patients through vitamin D supplementation. *Arthritis Res Ther* 2012; 14: R221.
8. RITTERHOUSE LL, CROWE SR, NIEWOLD TB *et al.*: Vitamin D deficiency is associated with an increased autoimmune response in healthy individuals and in patients with systemic lupus erythematosus. *Ann Rheum Dis* 2011; 70: 1569-74.
9. YAP KS, SAHEBARI M, NABAVI N, SALEHI M: Correlation between serum 25(OH)D values and lupus disease activity: An original article and a systematic review with meta-analysis focusing on serum VitD confounders. *Lupus* 2014; 23: 1164-77.
10. IRURETAGOYENA M, HIRIGOYEN D, NAVES R, BURGOS PI: Immune response modulation by vitamin D: role in systemic lupus erythematosus. *Front Immunol* 2015; 12: 6-513.
11. DURCAN L, PETRI M: Immunomodulators in SLE: Clinical evidence and immunologic actions. *J Autoimmun* 2016; 74: 73-84.
12. SASANO H, MIKI Y, NAGASAKI S, SUZUKI T: In situ estrogen production and its regulation in human breast carcinoma: from endocrinology to intracrinology. *Pathol Int* 2009; 59: 777-89.
13. CUTOLO M, PIZZORNI C, SULLI A: Vitamin D endocrine system involvement in autoimmune rheumatic diseases. *Autoimmun Rev* 2011; 11: 84-7.
14. CUTOLO M, PLEBANI M, SHOENFELD Y, ADORINI L, TINCANI A: Vitamin D endocrine system and the immune response in rheumatic diseases. *Vitam Horm* 2011; 86: 327-51.
15. PLUDOWSKI P, HOLICK MF, PILZ S *et al.*: Vitamin D effects on musculoskeletal health, immunity, autoimmunity, cardiovascular disease, cancer, fertility, pregnancy, dementia and mortality-a review of recent evidence. *Autoimmun Rev* 2013; 12: 976-89.
16. HOLICK MF: Vitamin D: a millennium perspective. *J Cell Biochem* 2003; 88: 296-307.
17. CUTOLO M, OTSA K, LAAS K *et al.*: Circannual vitamin D serum levels and disease activity in rheumatoid arthritis: Northern versus Southern Europe. *Clin Exp Rheumatol* 2006; 24: 702-4.
18. CUTOLO M: The challenges of using vitamin D in cancer prevention and prognosis. *Isr Med Assoc J* 2012; 14: 637-9.
19. TABASI N, RASTIN M, MAHMOUDI M *et al.*: Influence of vitamin D on cell cycle, apoptosis, and some apoptosis related molecules in systemic lupus erythematosus. *Iran J Basic Med Sci* 2015; 18: 1107-11.
20. WÖBKE TK, SORG BL, STEINHILBER D: Vitamin D in inflammatory diseases. *Frontiers in physiology* 2014; 2; 5-244.
21. BRODER AR, TOBIN JN, PUTTERMAN C: Disease-specific definitions of vitamin D deficiency need to be established in autoimmuneand non-autoimmune chronic diseases: a retrospective comparison of three chronic diseases. *Arthritis Res Ther* 2010; 12: R191.
22. HOLICK MF: Vitamin D deficiency. *N Engl J Med* 2007; 357: 266-81.
23. MONTICIELO OA, TEIXEIRA TDE M, CHIES JA, BRENOL JC, XAVIER RM: Vitamin D and polymorphisms of VDR gene in patients with systemic lupus erythematosus. *Clin Rheumatol* 2012; 31: 1411-21.
24. OREN Y, SHAPIRA Y, AGMON-LEVIN N *et al.*: Vitamin D insufficiency in a sunny environment: a demographic and seasonal analysis. *Isr Med Assoc* 2010; 12: 1-6.
25. CUTOLO M, OTSA K, UPRUS M, PAOLINO S, SERIOLO B: Vitamin D in rheumatoid arthritis. *Auto Immun Rev* 2007; 7: 59-64.
26. DHIR V, SINGH AP, AGGARWAL A, NAIK S, MISRA R: Increased T-lymphocyte apoptosis in lupus correlates with disease activity and may be responsible for reduced T-cell frequency: a cross-sectional and longitudinal study. Lupus 2009; 18: 785-91.
27. AZRIELANT S, SHOENFELD Y: Eppur Si Muove: vitamin D is essential in preventing and modulating SLE. *Lupus* 2016; 25: 563-72.
28. SCHNEIDER L, DOS SANTOS AS, SANTOS M, DA SILVA CHAKR RM, MONTICIELO OA: Vitamin D and systemic lupus erythematosus: state of the art. *Clin Rheumatol* 2014; 33: 1033-8.
29. DALL'ARA F, ANDREOLI L, PIVA N *et al.*: Winter lupus flares are associated with low vitamin D levels in a retrospective longitudinal study of Italian adult patients. *Clin Exp Rheumatol* 2015; 33: 153-8.
30. PIANTONI S, ANDREOLI L, SCARSI M *et al.*: Phenotype modifications of T-cells and their shift toward a Th2 response in patients with systemic lupus erythematosus supplemented with different monthly regimens of vitamin D. *Lupus* 2015; 24: 490-8.
31. GAUZZI MC, PURIFICATO C, DONATO K *et al.*: Suppressive effect of 1alpha,25-dihydroxyvitamin D3 on type I IFN-mediated monocyte differentiation into dendritic cells: impairment of functional activities and chemotaxis. *J Immunol* 2005; 174: 270-6.
32. CANTORNA MT: Mechanism underlying the effect of vitamin D. *Proc Nutr Soc* 2010; 69: 286-89.
33. CHEN S, SIMS GP, CHEN XX *et al.*: Modulatory effects of 1,25-dihydroxyvitamin D3 on human B cell differentiation. *J Immunol* 2007; 179: 1634-47.
34. CUTOLO M, PAOLINO S, SULLI A, SMITH V, PIZZORNI C, SERIOLO B: Vitamin D, steroid hormones, and autoimmunity. *Ann N Y Acad Sci* 2014; 1317: 39-46.
35. ROSEN CJ, GALLAGHER JC: The 2011 IOM report on vitamin D and calcium requirements for North America: clinica limplications for providers treating patients with low bone mineral density. *J Clin Densitom* 2011; 14: 79-84.
36. ROSS AC, MANSON JE, ABRAMS SA *et al.*: The 2011 report on dietary reference intakes for calcium and vitamin D from the Institute of Medicine: what clinicians need to know. *J Clin Endocrinol Metab* 2011 96: 53-8.
37. ASPRAY TJ, BOWRING C, FRASER W *et al.*: National osteoporosis society vitamin D guideline summary. *Age Ageing* 2014; 43: 592-5.
38. FORREST KY, STUHLDREHER WL: Prevalence and correlates of vitamin D deficiency in US adults. *Nutr Res* 2011; 31: 48-54.
39. MITHAL A, WAHL DA, BONJOUR JP *et al.*: IOF Committee of Scientific Advisors (CSA) Nutrition Working Group. Global vitamin D status and determinants of hypovitaminosis D. *Osteoporos Int* 2009; 20: 1807-20.
40. YETLEY EA: Assessing the vitamin D status of the US population. *Am J Clin Nutr* 2008; 88-558.
41. SUMETHKUL K, BOONYARATAVEJ S, KITUMNUAYPONG T *et al.*: The predictive factors of low serum 25-hydroxyvitamin D and vitamin D deficiency in patients with systemic lupus erythematosus. *Rheumatol Int* 2012; 33: 1461-7.
42. O'LEARY TJ, JONES G, YIP A, LOHNES D, COHANIM M, YENDT ER: The effects of chloroquine on serum 1, 25-dihydroxyvitamin D and calcium metabolism in sarcoidosis. *N Engl J Med* 1986; 315: 727-30.
43. RUIZ-IRASTORZA G, EGURBIDE MV, OLIVARES N, MARTINEZ-BERRIOTXOA A, AGUIRRE C: Vitamin D deficiency in systemic lupus erythematosus: prevalence, predictors and clinical consequences. *Rheumatology* 2008; 47: 920-3.
44. TOLOZA S, COLE D, GLADMAN D, IBANEZ D, UROWITZ M: Vitamin D insufficiency in

a large female SLE cohort. *Lupus* 2010; 19: 13-9.
45. KAMEN DL: Vitamin D in lupus – new kid on the block? *Bull NYU Hosp Jt Dis* 2009; 68: 218-22.
46. AKENO N, MATSUNUMA A, MAEDA T, KAWANE T, HORIUCHI N: Regulation of vitamin D-1alpha-hydroxylase and -24-hydroxylase expression by dexamethasone in mouse kidney. *J Endocrinol* 2000; 164: 339-48.
47. GITTOES NJ: Vitamin D -what is normal according to latest research and how should we deal with it? *Clin Med* (Lond) 2015; 15: 54-7.
48. VASILE M, CORINALDESI C, ANTINOZZI C, CRESCIOLI C: Vitamin D in autoimmune rheumatic diseases: A view inside gender differences. *Pharmacol Res* 2017; 117: 228-41.
49. BENVENUTI F, GATTO M, LAROSA M, IACCARINO L, PUNZI L, DORIA A: Cardiovascular risk factors, burden of disease and preventive strategies in patients with systemic lupus erythematosus: a literature review. *Expert Opin Drug Saf* 2015; 14: 1373-85.
50. WATAD A, ABU MUCH A, BRACCO D *et al.*: Association between ischemic heart disease and systemic lupus erythematosus-a large case-control study. *Immunol Res* 2017; 65: 459-63.
51. TOMASCHITZ A, PILZ S, RITZ E *et al.*: Independent association between 1,25-dihydroxyvitamin D, 25-hydroxyvitamin D and the renin-angiotensin system. The Ludwigshafen Risk and Cardiovascular Health (LURIC) study. *Clin Chim Acta* 2010; 411: 1354-60.
52. SAKTHISWARY R, RAYMOND AA: The clinical significance of vitamin D in systemic lupus erythematosus: A systematic review. *PLoS One* 2013; 8: 1-6.
53. SABIO JM, VARGAS-HITOS JA, MARTINEZ-BORDONADO J *et al.*: Association between low 25-hydroxyvitamin D, insulin resistance and arterial stiffness in non-diabetic women with systemic lupus erythematosus. *Lupus* 2015; 24: 155-63.
54. REYNOLDS JA, HAQUE S, BERRY JL *et al.*: 25-Hydroxyvitamin D deficiency is associated with increased aortic stiffness in patients with systemic lupus erythematosus. *Rheumatology* 2012; 51: 544-51.
55. KAMEN DL, OATES JC: A pilot study to determine if vitamin D repletion improves endothelial function in lupus patients. *Am J Med Sci* 2015; 350: 302-7.
56. REYNOLDS JA, ROSENBERG AZ, SMITH CK *et al.*: Brief Report: Vitamin D deficiency is associated with endothelial dysfunction and increases type i interferon gene expression in a murine model of systemic lupus erythematosus. *Arthritis Rheumatol* 2016; 68: 2929-35.
57. REYNOLDS J, RAY D, ALEXANDER MY, BRUCE I: Role of vitamin D in endothelial function and endothelial repair in clinically stable systemic lupus erythematosus. *Lancet* 2015; 26; 385 Suppl. 1: S83.
58. HANDONO K, SIDARTA YO, PRADANA BA *et al.*: Vitamin D prevents endothelial damage induced by increased neutrophil extracellular traps formation in patients with systemic lupus erythematosus. *Acta Med Indones* 2014; 46: 189-98.
59. KIANI AN, FANG H, MAGDER LS, PETRI M: Vitamin D deficiency does not predict progression of coronary artery calcium, carotid intima-media thickness or high-sensitivity C-reactive protein in systemic lupus erythematosus. *Rheumatology* (Oxford) 2013; 52: 2071-6.
60. JUNG JY, KOH BR, BAE CB, KIM HA, SUH CH: Carotid subclinical atherosclerosis is associated with disease activity but not vitamin D in Korean systemic lupus erythematosus. *Lupus* 2014; 23: 1517-22.
61. STOJAN G, PETRI M: Atherosclerosis in systemic lupus erythematosus. *J Cardiovasc Pharmacol* 2013; 62: 255-62.
62. IACCARINO L, BETTIO S, ZEN M *et al.*: Premature coronary heart disease in SLE: Can we prevent progression? *Lupus* 2013; 22: 1232-42.
63. SAHEBARI M, NABAVI N, SALEHI M: Correlation between serum 25(OH)D values and lupus disease activity: An original article and a systematic review with meta-analysis focusing on serum VitD confounders. *Lupus* 2014; 23: 1164-77.
64. GAO CC, LIU SY, WU ZZ *et al.*: Severe vitamin D deficiency increases the risk for moderate to severe disease activity in Chinese patients with SLE. *Lupus* 2016; 25: 1224-9.
65. ABAZA NM, EL-MALLAH RM, SHAABAN A *et al.*: Vitamin D deficiency in Egyptian systemic lupus erythematosus patients: how prevalent and does it impact disease activity? *Integr Med Insights* 2016; 11: 27-33.
66. SCHOINDRE Y, JALLOULI M, TANGUY ML *et al.*: Lower vitamin D levels are associated with higher systemic lupus erythematosus activity, but not predictive of disease flare-up. *Lupus Sci Med* 2014; 7: 1.
67. MANDAL M, TRIPATHY R, PANDA AK *et al.*: Vitamin D levels in Indian systemic lupus erythematosus patients: Association with disease activity index and interferon alpha. *Arthritis Res Ther* 2014; 16: R49.
68. MCGHIE TK, DECEULAER K, WALTERS CA, SOYIBO A, LEE MG: Vitamin D levels in Jamaican patients with systemic lupus erythematosus. *Lupus* 2014; 23: 1092-96.
69. LERTRATANAKUL A, WU P, DYER A *et al.*: 25-Hydroxyvitamin D and cardiovascular disease in patients with systemic lupus erythematosus: Data from a large international inception cohort. *Arthritis Care Res* (Hoboken) 2014; 66: 1167-76.
70. EMERAH AA, EL-SHAL AS: Role of vitamin D receptor gene polymorphisms and serum 25-hydroxyvitamin D level in Egyptian female patients with systemic lupus erythematosus. *Mol Biol Rep* 2013; 40: 6151-62.
71. GARCÍA-CARRASCO M, MENDOZA-PINTO C, AYÓN-AGUILAR J *et al.*: Serum levels of vitamin D in systemic lupus erythematosus patients (SLE) and their relationship with disease activity: longitudinal study. *Gac Med Mex* 2016; 152 2: 32-7.
72. SHAHIN D, EL-FARAHATY RM, HOUSSEN ME *et al.*: Serum 25-OH vitamin D level in treatment-naïve systemic lupus erythematosus patients: Relation to disease activity, IL-23 and IL-17. *Lupus* 2017; 26: 917-26
73. SALMAN-MONTE TC, TORRENTE-SEGARRA V, ALMIRALL M, CORZO P, MOJAL S, CARBONELL-ABELLÓ J: Prevalence and predictors of vitamin D insufficiency in supplemented and non-supplemented women with systemic lupus erythematosus in the Mediterranean region. *Rheumatol Int* 2016; 36: 975-85.
74. GARF KE, MARZOUK H, FARAG Y, RASHEED L, GARF AE: Vitamin D status in Egyptian patients with juvenile-onset systemic lupus erythematosus. *Rheumatol Int* 2015; 35 9: 1535-40.
75. MISKOVIC R, PLAVSIC A, RASKOVIC S, JOVICIC Z, BOLPACIC J: Vitamin D status in patients with systemic lupus erythematosus in Serbia: correlation with disease activity and clinical manifestations. *Open Access Maced J Med Sci* 2015 15; 3: 256-61.
76. SIMIONI JA, HEIMOVSKI F, SKARE TL *et al.*: On lupus, vitamin D and leukopenia. *Rev Bras Reumatol* 2016; 56: 206-11.
77. DE SOUZA VA, BASTOS MG, FERNANDES NM *et al.*: Association of hypovitaminosis D with systemic lupus erythematosus and inflammation. *J Bras Nefrol* 2014; 36: 430-6.
78. ATTAR SM, SIDDIQUI AM: Vitamin D deficiency in patients with systemic lupus erythematosus. *Oman Med J* 2013; 28: 42-47.
79. SQUANCE ML, REEVES GE, TRAN HA: Vitamin D levels are associated with expression of SLE, but not flare frequency. *Int J Rheumatol* 2014; 2014: 1-10.
80. CHAIAMNUAY S, CHAILURKIT LO, NARONGROEKNAWIN P, ASAVATANABODEE P, LAOHAJAROENSOMBAT S, CHAIAMNUAY P: Current daily glucocorticoid use and serum creatinine levels are associated with lower 25(OH) vitamin D levels in Thai patients with systemic lupus erythematosus. *J Clin Rheumatol* 2013; 19: 121-5.
81. FERNANDES DE ABREU DA, EYLES D, FÉRON F: Vitamin D, a neuro-immunomodulator: implications for neurodegenerative and autoimmune diseases. *Psychoneuroendocrinology* 2009; 34: 265-77.
82. TAY SH, HO CS, HO RC, MAK A: 25-Hydroxyvitamin D3 deficiency independently predicts cognitive impairment in patients with systemic lupus erythematosus. *PLoS One* 2015; 10: e0144149.
83. SCHMEDING A, SCHNEIDER M: Fatigue, health-related quality of life and other patient-reported outcomes in systemic lupus erythematosus. *Best Pract Res Clin Rheumatol* 2013; 27: 363-75.
84. RUIZ-IRASTORZA G, GORDO S, OLIVARES N, EGURBIDE MV, AGUIRRE C: Changes in vitamin D levels in patients with systemic lupus erythematosus: effects on fatigue, disease activity, and damage. *Arthritis Care Res* (Hoboken) 2010; 62: 1160-5.
85. LIMA GL, PAUPITZ J, AIKAWA NE, TAKAYAMA L, BONFA E, PEREIRA RM: Vitamin D supplementation in adolescents and young adults with juvenile systemic lupus erythematosus for improvement in disease activity and fatigue scores: a randomized, double-blind, placebo-controlled trial. *Arthritis Care Res* (Hoboken) 2016; 68: 91-8.
86. YUEN HK, CUNNINGHAM MA: Optimal management of fatigue in patients with systemic lupus erythematosus: a systematic review. *Ther Clin Risk Manag* 2014; 10: 775-86.

87. PALAGINI L, MAURI M, FARAGUNA U *et al.*: Insomnia symptoms, perceived stress and coping strategies in patients with systemic lupus erythematosus. *Lupus* 2016; 19: 101-7.
88. GHOLAMREZAEI A, BONAKDAR ZS, MIRBAGHER L, HOSSEINI N: Sleep disorders in systemic lupus erythematosus. Does vitamin D play a role? *Lupus* 2014; 23: 1054-8.
89. WATAD A, TIOSANO S, AZRIELANT S *et al.*: Low levels of calcium or vitamin D - which is more important in systemic lupus erythematosus patients? An extensive data analysis. *Clin Exp Rheumatol* 2017; 35: 108-112.
90. GUO Q, FAN P, LUO J *et al.*: Assessment of bone mineral density and bone metabolism in young male adults recently diagnosed with systemic lupus erythematosus in China. *Lupus* 2017; 26: 289-93.
91. BULTINK IE, LEMS WF: Lupus and fractures. *Curr Opin Rheumatol* 2016; 28: 426-32.
92. EDENS C, ROBINSON AB: Systemic lupus erythematosus, bone health, and osteoporosis. *Curr Opin Endocrinol Diabetes Obes* 2015; 22: 422-31.
93. ARANOW C, KAMEN DL, DALL'ERA M *et al.*: Randomized, double-blind, placebo-controlled trial of the effect of vitamin D3 on the interferon signature in patients with systemic lupus erythematosus. *Arthritis Rheumatol* 2015; 67: 1848-57.
94. PETRI M, BELLO KJ, FANG H, MAGDER LS: Vitamin D in systemic lupus erythematosus: modest association with disease activity and the urine protein-to-creatinine ratio. *Arthritis Rheum* 2013; 65: 1865-71.
95. ANDREOLI L, DALL'ARA F, PIANTONI S *et al.*: A 24-month prospective study on the efficacy and safety of two different monthly regimens of vitamin D supplementation in pre-menopausal women with systemic lupus erythematosus. *Lupus* 2015; 24: 499-506.
96. ABOU-RAYA A, ABOU-RAYA S, HELMII M: The effect of vitamin D supplementation on inflammatory and hemostatic markers and disease activity in patients with systemic lupus erythematosus: a randomized placebo-controlled trial. *J Rheumatol* 2013; 40: 265-72.
97. HOLLIS BW: Editorial: The determination of circulating 25- hydroxyvitamin D: no easy task. *J Clin Endocrinol Metab* 2004; 89: 3149-51.
98. CUSACK C, DANBY C, FALLON JC *et al.*: Photoprotective behaviour and sunscreen use: impact on vitamin D levels in cutaneous lupus erythematosus. *Photodermatol Photoimmunol Photomed* 2008; 24: 260-7.
99. SZODORAY P, TARR T, BAZSO A, POOR G, SZEGEDI G, KISS E: The immunopathological role of vitamin D in patients with SLE: data from a single centre registry in Hungary. *Scand J Rheumatol* 2011; 40:122-6.
100. VOJINOVIC J, TINCANI A, SULLI A *et al.*: European multicentre pilot survey to assess vitamin D status in rheumatoid arthritis patients and early development of a new Patient Reported Outcome questionnaire (D-PRO). *Autoimmun Rev* 2017; 16: 548-54.