REVIEW ARTICLE

The Role of Vitamin D Supplementation in Preventing Osteoporosis as Complication among Patients with Systemic Lupus Erythematosus: A Systematic Review of Clinical Trials

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ABSTRACT

The development of systemic lupus erythematosus activity is negatively correlated with serum vitamin D levels and can complicate to osteoporosis. This systematic review aimed to synthesize the role of vitamin D supplementation in preventing osteoporosis among patients with systemic lupus erythematosus. Literature search in ScienceDirect, ProQuest journals, Scopus and SAGE journals. Studies met the following criteria were included: clinical trials reporting vitamin D use in patients with systemic lupus erythemathosus and osteoporosis. The intervention was patients receiving vitamin D. The control group was patients that did not receive vitamin D. The outcome was osteoporosis. The result show that of the 180 studies retrieved, 7 met inclusion criteria. Vitamin D supplementation increased level of 25OHD, and trabecular count. It was also associated with 13.4% reduced incidence of osteoporosis. Vitamin D supplementation was not associated with bone turnover marker. Effects on BMD, vitamin D supplementation reported a significant decrease in volumetric BMD in one study, significant increased in 2 studies, but there is study reported results that BMD did not change significantly. This systematic review demonstrated that vitamin D supplementation may prevent osteoporosis in patients with systemic lupus erythematosus through mechanisms associated with increased trabecular count and BMD but further research is needed to clarify the results.

Keywords: Vitamin D, SLE, Osteoporosis, BMD, Bones

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INTRODUCTION

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease of unknown cause and can affect all organs and tissues (1). SLE can have an impact on damage to various organs such as cardiovascular, respiratory system, skin, musculoskeletal, kidney, hematology, and neuropsychiatry (2). The development and activity of SLE disease are exacerbated by various factors, including genetics, environment, physical and hormonal stress (1). Globally, the incidence of SLE is about 1.5 to 11 cases per 100,000 population in one year, and the global prevalence is around 13 to 7,713.5 per 100,000 population (3). The prevalence of SLE in Indonesia reaches 1,250,000 cases with an average incidence of new cases of SLE in hospitals in Indonesia of 10.5% (4).

Vitamin D plays an important role in the pathogenesis of SLE because it has anti-proliferative effects and controls the development of the cell cycle (5). Vitamin D regulates several genes involved in innate and adaptive immunity through its immunomodulatory effects, which include downregulation of Th1 immune responses, modulating dendritic cell differentiation, reducing activated B cell proliferation, upregulating T cells and maintaining the innate immune response. Vitamin D can inhibit the production of alpha interferon which plays a role in the pathogenesis of SLE (6). Vitamin D deficiency is thought to be an environmental trigger of disease onset and contributes to increased SLE activity. Further, patients with SLE are prone to vitamin D deficiency due to photosensitivity, which tends to behave in avoiding

sunlight (7). One of the effects of vitamin D deficiency in SLE is osteoporosis (6).

In a study in Italy, the incidence of osteoporosis in SLE patients was 42% (8). Patients with SLE show the occurrence of decreased bone mineral density (BMD) and fractured bone fragility compared to the healthy population (9). This happens because SLE patients experience photosensitivity, which tends to behave in avoiding sunlight so that they are increasingly experiencing vitamin D deficiency (10).

There is a role for vitamin D in osteoporosis where vitamin D is involved in bone growth and bone remodeling by osteoblasts and osteoclasts, and vitamin D deficiency (<50 nmol/L) can accelerate bone turnover, bone loss, and osteoporotic fractures (11). However, various studies report different results regarding the effect of vitamin D supplementation on osteoporosis biomarkers in SLE patients. Al Kushi et al. reported that vitamin D supplementation increased BMD, but the opposite result was reported by Burt et al. that supplementation increases BMD (12, 13). Meanwhile, Tedeschi et al. reported no significant effect of vitamin D supplementation with bone turnover markers (9).

This study aims to conduct a systematic review of the effects of vitamin D supplementation on osteoporosis in SLE patients. The existence of evidences on the role of vitamin D supplementation in reducing the risk of osteoporosis implicates clinical practice on primary prevention of osteoporosis among patients with SLE.

METHODS

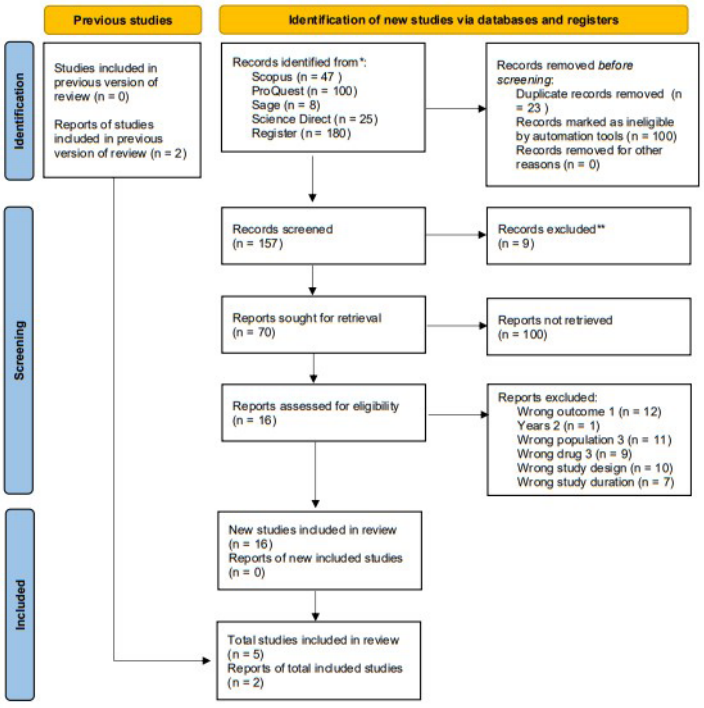
This systematic review followed the Preferred Reporting Items For Systematic Reviews and Meta-Analysis (PRISMA) guideline.

Search strategy and study selection

We performed a systematic literature search from ScienceDirect, ProQuest journals, Scopus and SAGE journals for "Vitamin D" AND "systemic lupus erythematosus OR Lupus". The search of literature was carried out in February 2022. Then it is saved in the form of "RIS" from each journal and entered into the Rayyan. id application for further selection using Mendeley.

Inclusion and exclusion criteria

Studies that met the following criteria were included: clinical trials reporting vitamin D use in patients with SLE and osteoporosis, studies published in english. Studies that met one of the following criteria were excluded: (1) wrong outcome: outcome is not a biomarker of osteoporosis; (2) wrong population: animal model and cell or tissue; (3) wrong drug: intervention not using vitamin D; and wrong study design: observational studies, review article, editorial/commentaries, abstracts, letters, and case reports. Language restriction was imposed and the year of publication is not limited due to limited research, see in Figure 1 and Supplement Figure.



Picture 1. PRISMA 2020

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71 doi: 10.1136/bmj.n71 http://www.prisma-statement.org/

Fig. 1: PRISMA Flowchart research study selection process.

Intervention and outcome

The intervention group was patients receiving vitamin D supplementation. The control group was patients that did not receive vitamin D supplementation. The outcome was osteoporosis as measured by osteoporosis biomarkers such as BMD, trabecular count and bone turnover. The effect estimate was reported as mean levels of BMD, trabecular count and bone turnover as osteoporosis biomarkers. This is because there has been no direct study of the effect of vitamin D supplementation on osteoporosis.

Data extraction

Two independent authors performed data extraction of the eligible studies using standardized extraction form for the first author, study design, location of the study, inclusion criteria, sample size, age, sex, comorbidities, medication use, and the osteoporosis in the intervention and control groups. Discrepancies during data extraction were resolved by discussion.

Risk of bias assessment

The Cochrane quality assessment tool was used to assess bias for each study included in the current meta-analysis. The tool contains seven domains including randomization, allocation concealment, reporting bias, performance bias, detection bias, bias bias, and other source bias. Each domain was assigned a "high risk" score if the study consisted of methodological defects that might have distorted the results, a "low risk" score if the defect was deemed ineffective and a "unclear risk" score if the information was insufficient to determine impact. If a trial has "low risk" for all domains, it is labeled as a high-quality study with a very low risk of bias.

Statistical analysis

Mean differences in changes in osteoporosis biomarkers, comparing the vitamin D supplementation group and the control group, were used to obtain an overall effect size. When the mean change was not reported, we calculated it taking into account the change in outcome during the intervention. We also converted standard error (SE), 95% confidence interval (CI), and interquartile range (IQR) to SD using the relevant formulas. To obtain an overall effect size, we applied a random effects model taking into account inter-study variation. Heterogeneity was determined by I2 statistic. I2 values >50% as significant inter-study heterogeneity. The results of the meta-analysis are presented in the form of a forest plot that shows the average difference that has been adjusted for the subject or standardized mean differences (SMD). Forest plot was performed using JASP. SMD = 0.05 means that threre is no difference significantly between groups.

RESULT

Baseline characteristics

There were 7 studies consisting 180 study in this systematic review. The selection process is described in PRISMA flowchart as illustrated in Figure 1. Characteristics of the included studies can be seen in Table I.

Vitamin D supplementation and osteoporosis

Vitamin D supplementation was associated with increased trabecular count, and decreased incidence of osteoporosis. One study reported that vitamin D supplementation did not cause changes in BMD, two study reported increase significantly and one study reported reduce volumetric BMD. Vitamin D supplementation had no significant effect on bone turnover biomarker levels.

Publication bias

The risk of bias assessment using cochrane quality assessment tool can be seen in Figure 2 and Figure 3. The included studies were considered to be of less than acceptable quality a low risk of bias overall. The detected potential bias may interfere with the results obtained. All studies were classified as clear on missing outcome data. Nearly 40% of the studies were classified as unclear for the selection of the reported result.

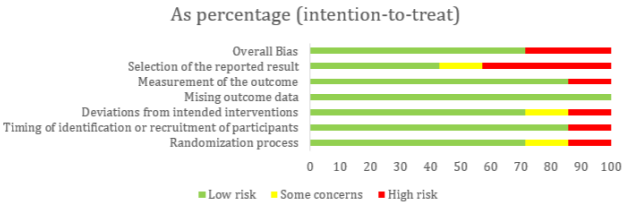


Fig. 2: Risk of bias across studies.

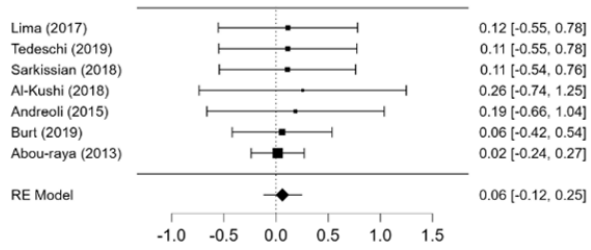


Fig. 3: Forrest plot.

Effect vitamin D on biomarker for osteoporosis

Data on the direct effect of vitamin D supplementation on osteoporosis exist in only one study. A total of 7 studies studied the effect of vitamin D supplementation on osteoporosis biomarkers. The four studies were studies using a comparison group, by comparing the group of SLE patients with vitamin D supplementation and the control group. The results obtained SMD

Table I: Summary of effects of vitamin D supplementation on osteoporosis in SLE patients

Study group	Intervention	Results	Reference
40 female SLE patients Mean age 18.7 years in Brazil	Intervention: 50,000 IU/week vitamin D Control: identical placebo tablet 6 months	Vitamin D supplementation was significantly associated with increased level of 25OHD and trabecular count, but not with BMD.	(10)
81 male and female SLE patients aged 20-70 years in Egypt	Intervention: 1,400 IU vitamin D and 1,250 mg calcium carbonate tablets per day Control: not receive supplementation 6 months	Vitamin D supplementation was significantly associated with increased BMD and decreased incidence of osteoporosis, but not with bone turnover marker (osteocalcin and CTX).	(12)
42 postmenopausal women with SLE in USA	Intervention: Four regimen groups: • 200–800 IU daily • 1,000–2,000 IU daily • 50,000 IU weekly • 500,000 IU monthly Control: not receive supplementation 6 months	Vitamin D supplementation was not significantly associated with bone turnover marker (osteocalcin and CTX).	(14)
43 male and female SLE patients aged 29.5–45.0 in USA	Intervention: Vitamin D 2000 IU/day or 4000 IU/day obtained serum 25(OH)D ≥30 ng/mL Control: Vitamin D 2000 IU/day or 4000 IU/day obtained serum 25(OH)D <30 ng/mL 12 weeks	Vitamin D supplementation was not significantly associated with bone turnover marker.	(9)
34 premenopausal women aged 19-44 years in Italy	Standard: Vitamin D 25,000/month Intensive: Vitamin D 300,000 UI at baseline and 50,000 UI/month as maintenance for 24 months	Serum vitamin D levels increased significantly after supplementation Bone turnover marker has not changed significantly	(15)
267 SLE patient in Egypt	Intervention: Vitamin D 2000 IU/day Control: identical placebo tablet 12 months	Vitamin D supplementation was not significantly associated with bone turnover marker.	(16)
311 adults in Canada	Intervention: Vitamin D 4000 IU/day or 10.000 IU/day Control: 400 IU/day 3 years	BMD significant lower in high dosage vitamin D	(13)

value of 0.06, which means that there is no significant difference between groups in average. Thus, osteoporosis biomarkers (BMD, trabecular count and bone turnover) were not significantly differences between vitamin D supplementation group and control (0.06; 95% CI -0.120–250) (Figure 3). The I2 statistic showed no significant heterogeneity across studies with I2 = 0%.

Vitamin D Levels in SLE Patients

Vitamin D deficiency is stated as a risk factor for SLE (8). A retrospective cohort study in Jeddah of 95 patients showed that SLE patients had significantly lower 25(OH) D levels than non-SLE patients. In addition, SLE patients have high anti-dsDNA levels and low serum C3 and C4 levels (23). A cross-sectional study in 60 SLE patients showed that 25(OH)D levels were significantly lower in SLE patients (17.6 ± 6.9 ng/mL) compared to controls (79.0 ± 28.7 ng/mL) (8). In an Australian study, vitamin D deficiency (<40 nmol/L) was present in 27.7% of SLE patients. Low vitamin D levels are associated with high SLE disease activity (24). A meta-analysis study showed that there was a significant difference in serum vitamin D levels with healthy controls where all SLE patients showed very low vitamin D levels (25).

Vitamin D levels in SLE patients vary according to geographic location (24). SLE patients without vitamin D supplementation or on corticosteroid, hydroxychloroquine, or immunosuppressant treatment in South America, Africa, and Asia, and patients living below 37° latitude are at high risk of developing serum vitamin D deficiency during winter (25).

Research in Egypt also showed that vitamin D levels were significantly lower than healthy controls, where vitamin D levels were significantly associated with the FokI VDR polymorphism. BsmI polymorphisms are significantly associated with fever, mucosal ulcers, and neuropsychiatric impairment (26). Serum vitamin D was also found to be significantly lower in patients with active SLE according to SLEDAI compared with inactive SLE patients. Vitamin D deficiency is commonly found in SLE patients, especially in the activity phase of SLE and nephritis. Low serum vitamin D levels in SLE patients are closely associated with the development of malar rash, mucocutaneous and lupus nephritis. Thus, vitamin D deficiency is not only a risk factor for SLE activity but also a risk factor for nephritis in SLE patients (5). Vitamin D supplementation with regular monitoring can be considered as a health management of SLE that can reduce the incidence of SLE and prevent nephritis in SLE patients (25; 5).

The Role of Vitamin D in the Occurrence of SLE

Vitamin D plays an important role in the pathogenesis of SLE because it has anti-proliferative effects and controls the development of the cell cycle (25). Vitamin D regulates several genes involved in innate and adaptive immunity so that plays a role in SLE

through its immunomodulatory effects, which include downregulation of Th1 immune responses, modulating dendritic cell differentiation, reducing activated B cell proliferation, upregulating T cells, and maintaining the innate immune response. Vitamin D can inhibit the production of interferon-alpha which plays a role in the etiology and pathogenesis of SLE (6). Vitamin D deficiency is thought to be an environmental trigger of disease onset and contributes to increased SLE activity. SLE patients are prone to vitamin D deficiency due to photosensitivity, which tends to behave in avoiding sunlight (7).

Relationship of Vitamin D and Immune Response

Vitamin D has various actions through interactions with vitamin D receptors. Vitamin D has an important role in the regulation of the immune response because the expression and distribution of vitamin D receptors are mostly found in immune cells such as macrophages, peripheral lymphocytes, dendritic cells, monocytes, T cells, and B cells, and natural killer cells. In addition, vitamin D also plays a role in cell differentiation and proliferation. FokI located in exon 2, BsmI located in intron 8, TaqI, and ApaI located in exon 9 and intron 9 Polymorphisms were the most studied vitamin D receptor (26).

The relationship between vitamin D and the immune response has been described by (21) especially related to vitamin D function in immune cells in the form of dendritic cells, macrophages, or monocytes, T cells, and B cells. Dendritic cells trigger an adaptive immune response which is an antigen-presenting cell to T cells. Vitamin D can reduce costimulatory molecules such as CD40, CD80, and CD86, and regulation of MHC class II expressed on dendritic cells results in T cell activation. Vitamin D also suppresses the production of dendritic cell cytokines, in particular, interleukin (IL)-12, which affects the differentiation of helper T cells into Th1 cells, and IL-23, which affect helper T cell differentiation. to Th17 cells. Macrophages or monocytes produce inflammatory cytokines to protect against infection. Infectious components are recognized by receptors expressed on the surface of monocytes and macrophages, thereby increasing the expression of vitamin D and CYP27B1 receptors. 25-hydroxyvitamin D is metabolized by CYP27B1 to the active form of vitamin D, 1,25-dihydroxy vitamin D. Inside cells, 1,25D binds to vitamin D receptors present in the cytosol or nucleus (21).

The vitamin D receptor is activated to form a heterodimer with the retinoid-X receptor. Heterodimers bind to DNA and induce the production of antibiotic peptides that destroy viral and bacterial cell membranes or by activating antibiotic signaling cascades in infected cells. T cells interact with antigen-presenting dendritic cells to induce an antigen-specific immune response. 1,25D suppresses the differentiation and proliferation of CD4-positive T cells through cytokine secretion and reduces Th1-type differentiation and secretion of inflammatory cytokines (IL-2, IFNγ, and TNF-α), and promotes Th2-type differentiation and secretion of anti-inflammatory cytokines (IL-4). , IL-5 and IL-10) and inhibits the secretion of Th17-associated cytokines (IL-17, IFNγ, IL-21, and IL-22). B cells stimulate the production of autoantibodies, express vitamin D receptors and CYP27B1 about their role in autoimmune diseases. 1,25D has been shown to suppress the differentiation of naive B cells or maturation into memory B and plasma cells (21).

Immune System and Bone Metabolism in SLE Patients

The interaction between the immune system and bone has been studied. Helper T cells that produce IL-17 (TH17) induce the ligand-receptor activator NF-κB (RANKL) which via activated T cell nucleus factor (NFAT)c1 can stimulate osteoclast differentiation. The immune system and skeleton share signaling molecules, cytokines, membrane receptors, and transcription factors. Immune cells are also maintained in the bone marrow thereby providing space for reciprocal interactions (27).

A study reported that female SLE patients without glucocorticoids had lower markers of bone formation and higher markers of bone resorption than normal controls. The 25(OH)D of female SLE patients without glucocorticoids was lower than that of normal people. Elderly women with SLE have a higher risk of osteoporosis than healthy controls (17). In SLE patients with lupus nephritis, which is the main clinical manifestation of SLE, it indicates intense inflammatory activity indicating decreased osteoprotegerin (OPG) immunostaining, and increased RANKL expression. The OPG/RANKL system is associated with increased bone resorption in SLE patients that is regulated by cytokines. The OPG/RANKL system, composed of members of the TNF superfamily, is the final signaling pathway involved in modulating bone resorption. RANKL is a transmembrane protein produced by osteoblastic lineage cells and activated T cells (28).

The binding of RANKL to its specific receptor RANK stimulates osteoclast formation, differentiation, fusion, activation, and survival resulting in increased bone resorption and loss (28). Similar results are described by (22) that SLE patients may pose a risk of osteoporosis as a result of cytokines, such as IL-1, IL-6, IL-11, TNFα, and vitamin D3 that stimulate RANKL and OPG activation.

Osteoporosis in SLE Patients

Osteoporosis is one of the complications of SLE (29). The prevalence of osteoporosis in women aged 50-80 years in Indonesia is 23% (4). In a study in Indonesia, the prevalence of osteoporosis in SLE was 4.3% (30). In a study of 155 female SLE patients in Korea, osteoporosis was 15.0%. Risk factors for osteoporosis in SLE patients are related to nephritis and cumulative dose

of glucocorticoids (29). A cohort study of 25 SLE patients in America found that 36% had osteoporosis (31). The results of a meta-analysis regarding the frequency and risk factors for decreased bone mineral density (BMD) showed a 45% reduction in BMD and a 13% incidence of osteoporosis in SLE patients. The prevalence of osteoporosis increases with age (32).

Osteoporosis can be measured based on BMD and several bone turnover regulators such as RANKL, osteoprotegerin, dickkopf-1 (DDK-1), and sclerostin (33). Osteoporosis is a preventable condition associated with SLE patients (34). This cased inhibiting the development of permanent internal organ damage in SLE. Osteoporosis develops due to a decrease in the number or function of osteoclasts and osteoblasts. Cytokines play a role in maintaining a balance between bone resorption and bone formation so that the pathological level of proinflammatory cytokines in SLE may be a key mechanism for the development of osteoporosis. Levels of IL-6, telopeptide C-terminal type I collagen, and osteocalcin and decreased serum estradiol levels were found to be independent predictors of impaired BMD in SLE women (35).

Vitamin D Status and Osteoporosis of SLE Patients

One of the risk factors for osteoporosis in SLE patients is vitamin D deficiency (34). The deficiency of vitamin D is associated with bone resorption. In addition, it is also related to the role of cytokines in bone metabolism (36). A study on school-age children showed that there is a negative relationship between 25(OH)D and β-crosslaps which are markers of bone resorption (37).

Vitamin D deficiency and low BMD occur in SLE patients where vitamin D levels, BMD, and T scores are obtained significantly different results between SLE patients and healthy individuals(38). Long-standing vitamin D deficiency/insufficiency is considered a risk factor for osteoporosis. When the serum 25(OH)D level is less than 30 ng/mL there is a decrease in serum ionized calcium and an increase in serum parathyroid hormone secondary to decreased intestinal calcium absorption. Increased serum parathyroid hormone induces activation and differentiation of osteoclasts resulting in increased bone resorption activity by removing both osteoid and mineral bone matrix (39).

Effects of Vitamin D Supplementation in Preventing Osteoporosis in SLE Patients

Osteoporosis is an irreversible complication of SLE. Vitamin D insufficiency and deficiency both play an important role in reducing BMD. Persistent bone mineral resorption and re-deposition, or bone remodeling is the pathophysiology of osteoporosis (40). It is therefore important to study, monitor, prevent and treat bone metabolic disorders in SLE patients (40).

Vitamin D supplementation is recommended to prevent osteoporosis in SLE, but there is no consensus on the optimal dose and level of vitamin D for bone health in SLE 41). The importance of vitamin D supplementation in SLE patients is related to the low levels of vitamin D in SLE patients and there is supporting evidence that there is a strong association between a serum 25(OH)D level of about 40-60 ng/mL with reduced mortality and the risk of developing several chronic diseases including bone disease. This is because vitamin D regulates calcium and phosphate metabolism and maintains a healthy mineral framework (39). Research on vitamin D supplementation in SLE patients to the incidence of osteoporosis is very limited. Some of these studies are summarized in Table.

Al-Kushi et al., 2018 conducted a study on the effect of vitamin D and calcium supplementation on bone mineral density, disease activity, and related immune markers in SLE patients in both men and women with the results that vitamin D and calcium supplementation significantly increased bone mineral density in SLE patients with vitamin D deficiency, but vitamin D supplementation did not significantly attenuate disease activity or immune markers (11). An initial regimen of 300,000 UI vitamin D followed by 50,000 UI monthly is safe and effective in achieving serum vitamin D levels of 30 ng/ml in the majority of SLE patients. However, this regimen was not significantly different from the vitamin D regimen of 25,000 IU per month on SLE disease activity (14).

The relationship between vitamin D supplementation and bone turnover markers has been investigated by (13) with the result that bone turnover markers were not significantly different in patients stratified by serum vitamin D level with a cut-off of 30 ng/mL after vitamin D supplementation. This result can be explained because SLE disease activity has a direct effect on bone formation, but no effect on bone turnover. bone resorption due to the inflammatory suppressive effect of glucocorticoids that inhibit cytokine-induced osteoclast activity. Another study also showed that changes in bone turnover markers were not significantly different in the group with vitamin D supplementation and healthy controls (13). Vitamin D supplementation did not significantly affect changes in bone turnover markers over 12 weeks in SLE patients (42). Long-term supplementation of vitamin D (400-1200 IU) and calcium (1-1.5 g) may have a better effect on BMD in postmenopausal osteoporosis women (6). Further investigation with higher doses of vitamin D and a longer period is recommended to normalize vitamin levels as an effort to control SLE (11).

Bone turnover markers are not used for the diagnosis of osteoporosis and do not improve the prediction of bone loss or fracture. Very high concentrations of bone turnover markers indicate a secondary cause of high bone turnover (eg, bone metastases or multiple myeloma). In people with osteoporosis, bone turnover markers are useful for assessing response to anabolic

and antiresorptive therapy, for assessing adherence to therapy, or for suggesting possible secondary osteoporosis (18). Meanwhile, (1) reported that vitamin D supplementation was carried out to achieve vitamin D 25(OH) levels of 40 ng/ml. In addition, the effect of supplementation is also influenced by adequate dosage and adherence to therapy (1). Besides that, there is concern about the potential dangers of calcium and vitamin D supplementation concerning cardiovascular risk (19). Various factors such as behavior and lifestyle, age, light exposure, BMI, physical activity, season, and smoking can affect serum 25(OH)D levels which should also be considered in researching the effects of vitamin D supplementation (16)

Role of Vitamin D in Osteoporosis in SLE Patients

Vitamin D should be administered to all SLE patients with insufficiency or deficiency to provide an immunomodulatory and antifibrotic effect. The immunomodulatory properties of vitamin D are mediated by vitamin D3 receptors on monocytes, dendritic cells, T cells, and B cells as well as in skin, blood vessels, and other tissues (1; 21). Vitamin D downregulates Th1 immune responses, modulates dendritic cell differentiation, reduces activated B cell proliferation, upregulates T cells, and maintains innate immune responses (6). The regulation of the immune response stimulates the activation of RANKL and OPG which are related to the bone metabolism system (43). In addition, serum vitamin D status is useful for maintaining serum calcium and phosphorus levels to maintain various metabolic functions, transcriptional regulation, and bone metabolism (44).

Vitamin D has phosphatemic and calcemic effects by altering the expression of several genes in the small intestine, kidney, and bone. Vitamin D supplementation (1,25(OH)2D) can activate vitamin D receptors thereby increasing intestinal calcium and phosphate absorption, renal tubular calcium reabsorption, and calcium mobilization from bone. Increased intestinal absorption of calcium and phosphate is useful for maintaining sufficient calcium-phosphate products that crystallize in the collagen matrix resulting in passive bone mineralization. Vitamin D forms the endocrine system together with parathyroid hormone and fibroblast growth factor 23 (FGF23) which are useful in calcium and phosphate homeostasis and normal bone growth and mineralization (39).

DISCUSSION

This study showed that there was no significant difference in the mean of osteoporosis biomarkers between the vitamin D intervention group and the control group. Various parameters of osteoporosis were measured in this study including BMD, trabecular count and bone turnover. Compared to the healthy population, patients with SLE were more frequently having decreased BMD and fractured bone fragility (11). This is due to photosensitivity among patients with SLE so they tend to behave avoiding sunlight, resulting in prone to vitamin D deficiency (6).

Vitamin D supplementation can impact on increase serum vitamin D levels, but not on bone turnover parameters. Studies demonstrated different results on association between vitamin D supplementation and BMD. Al-Kushi et al. conducted a study on the effect of vitamin D and calcium supplementation on bone mineral density, disease activity, and related immune markers in SLE patients. The study revealed that vitamin D and calcium supplementation was significantly associated with increased BMD in SLE patients with vitamin D deficiency, but not with disease activity attenuation or immune markers (9). In addition, bone turnover markers was reported to be unable to used for the diagnosis of osteoporosis and do not improve the prediction of bone loss or fracture. Significant high concentrations of bone turnover markers indicate a secondary cause of high bone turnover (for example, bone metastases or multiple myeloma) (10, 14, 17, 18).

In people with osteoporosis, bone turnover markers are useful for assessing response to anabolic and antiresorptive therapy, for assessing adherence to therapy, or for suggesting possible secondary osteoporosis (19). Meanwhile, Fava and Petri reported that vitamin D supplementation was carried out to achieve vitamin D 25(OH) levels of 40 ng/ml. In addition, the effect of supplementation is also influenced by adequate dosage and adherence to therapy (1). Various factors, including behavior and lifestyle, age, light exposure, BMI, physical activity, season, and smoking can affect serum 25(OH)D levels which should also be considered in researching the effects of vitamin D supplementation (17). In addition, there is concern about the potential harm of calcium and vitamin D supplementation about cardiovascular risk (20).

Osteoporosis develops due to a decrease in the number or function of osteoclasts and osteoblasts. Cytokines play a role in maintaining a balance between bone resorption and bone formation so that the pathological level of proinflammatory cytokines in SLE may be a key mechanism for the development of osteoporosis. Levels of IL-6, telopeptide C-terminal type I collagen, and osteocalcin and decreased serum estradiol levels were found to be independent predictors of impaired BMD in SLE women (21). However, the results of this study confirmed that vitamin D supplementation had no significant effect on BMD.

The mechanism of effect of vitamin D supplementation in SLE is explained that vitamin D provide immunomodulatory and antifibrotic effects. The immunomodulatory properties of vitamin D are mediated by vitamin D3 receptors on monocytes,

dendritic cells, T cells, and B cells as well as in skin, blood vessels, and other tissues (1, 22). Vitamin D downregulates Th1 immune responses, modulates dendritic cell differentiation, reduces activated B cell proliferation, upregulates T cells, and maintains innate immune responses (6). The regulation of the immune response stimulates the activation of RANKL and OPG which are related to the bone metabolism system (23). In addition, serum vitamin D status is useful for maintaining serum calcium and phosphorus levels to maintain various metabolic functions, transcriptional regulation, and bone metabolism (17, 24).

Vitamin D has phosphatemic and calcemic effects by altering the expression of several genes in the small intestine, kidney, and bone. Supplementation of vitamin D (1,25(OH)2D) can activate vitamin D receptors thereby increasing intestinal absorption of calcium and phosphate, reabsorption of calcium in the renal tubules, and mobilization of calcium from bone. Increased intestinal absorption of calcium and phosphate is useful for maintaining sufficient calcium-phosphate products that crystallize in the collagen matrix resulting in passive bone mineralization. Vitamin D forms the endocrine system together with parathyroid hormone and fibroblast growth factor 23 (FGF23) which are useful in calcium and phosphate homeostasis and normal bone growth and mineralization (25).

The limitation of the study was limited clinical research on the relationship between vitamin D supplementation and biomarkers of osteoporosis with different parameter for measurement osteoporosis. In addition, various factors including the use of glucocorticoids, lifestyle, age, light exposure, BMI, physical activity, season and smoking, can affect serum vitamin D levels which must also be taken into account as confounding variables in the studies.

CONCLUSION

Based on the explanation above, it can be concluded that there is no significant difference in the mean of osteoporosis biomarkers between the vitamin D intervention group and the control group. The results of SMD values showed that there is no significant difference between groups. Bone turnover markers are useful for assessing response to anabolic and antiresorptive therapy in assessing adherence to therapy in prevention secondary osteoporosis.Vitamin D supplementation can have an impact significantly on increasing serum vitamin D levels, trabecular count, and BMD but not on bone turnover parameters. Further studies are urgently needed to confirm the effect of vitamin D supplementation in preventing osteoporosis in SLE patients.

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