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SYSTEMATIC REVIEW AND META-ANALYSIS: THE EFFECT OF SYSTEMIC LUPUS ERYTHEMATOSUS AND LONG-TERM STEROID THERAPY ON BONE MASS IN POSTMENOPAUSAL WOMEN

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ABSTRACT

Background: This systematic review and meta-analysis objective was to assess the effect of systemic lupus erythematosus (SLE) and long-term glucocorticoid therapy on bone mineral density (BMD) in premenopausal women.The risk of osteoporosis due to disease and steroid treatment.

Methods: This systematic review and meta-analysis followed the PRISMA guidelines to assess the impact of long-term glucocorticoid therapy on bone mineral density (BMD) in premenopausal women with systemic lupus erythematosus (SLE). A broad search was
conducted in PubMed, Scopus, Web of Science, and the Cochrane Library for studies published from January 2020 to December 2024. Studies focused on premenopausal women with SLE evaluating BMD changes due to glucocorticoid therapy. Two reviewers independently extracted data regarding sample size, age, treatment duration, and key findings. The quality of studies was assessed using the Newcastle-Ottawa Scale. A random-effects meta-analysis was performed to calculate standardized mean differences (SMD) and 95% confidence intervals (CIs), with heterogeneity assessed via the I^2 statistic. Sensitivity analyses were conducted to ensure the robustness of the findings.

Results: A total of 22 studies, studies design, was mostly observational and cross-sectional. Most studies noted a significant decrease in bone mineral density linked to long-term steroid use. Mendoza et al. (2021) highlighted this reduction, followed by Boone et al. (2021) who established a strong association between steroid therapy duration and low BMD. These studies indicated that long-term steroid therapy correlates with increased fracture risk, as highlighted by Ciobîcă et al. (2021) and Tsai et al. (2022). There was significant correlation between cumulative steroid doses and BMD reduction, consistent by findings from Danza et al. (2020) and Shevchuk et al. (2021). Some studies Watts et al.

(2021), found no significant effects of steroid therapy on BMD, indicating inconsistency that could be attributed to differences in study populations/methodologies. Several studies highlighted the negative effects of systemic inflammation and disease activity on bone metabolism, reinforcing the multifaceted nature of bone health in SLE patients.

Conclusions: This review indicate a strong association between long-term steroid use and reduced BMD in premenopausal women with SLE. The evidence underline that cumulative exposure to glucocorticoids significantly impacts bone health, leading to ahigher risk of fractures and osteoporosis. Inconsistency in the outcomes across different studies proposes the need for careful consideration of factors: age, steroid duration, and disease activity when assessing bone health our population. Clinicians should implement monitoring and preventive strategies to lessen the risk of osteoporosis and fractures in women undergoing glucocorticoid therapy for SLE.

Keywords: Systemic lupus erythematosus, glucocorticoid therapy, bone mineral density, premenopausal women, osteoporosis, steroid-induced bone loss.

INTRODUCTION

Systemic lupus erythematosus (SLE) is a autoimmune disorder, characterized by systemic inflammation and organ damage, mostly affecting women of reproductive age.[1] Globally prevalence of SLE ranges from 20 to 150 cases per 100,000 individuals, with significant regional variability. [2]The incidence is reported between 5.5 and 27.4 cases per 100,000 individuals,in Pakistanelucidating the growing recognition of this debilitating condition.[3]

Females diagnosed with SLE had many health challenges, the most common is the long-term effects of glucocorticoid therapy. [4]Corticosteroids are particularly prescribed for inflammation management and prevent disease, they also contribute toloss of bone density, thereforeaggregating the risk of osteoporosis.[5] it is dangerous for the female specially in premenopausal stage, who may experience aggressive bone loss due to the disease and treatment.[6]

Literature reports that the risk of osteoporosis in females with SLE was significantlyaffected by factors: dosage of steroid, duration of therapy, and disease activity. [7]The bone loss mechanisms involve decreased osteoblast function, increased osteoclast activity, and disruptions in calcium and vitamin D metabolism.[8]collectively, these factors leads to reduced bone mineral density (BMD), enhancing fracture risk and long-term morbidity.

In Pakistan, the prevalence of females in osteoporosis with SLE is an important concern, yet research is limited. [9]Understanding the interaction between SLE, long-term steroid use, and bone health is essential for developing effective management strategies to prevent osteoporosis.

This review aims to simplify the effects of prolonged steroid therapy on bone mass in premenopausal women with SLE. By adding theexisting research, will provide evidence-based recommendations that support clinical practice and improve health outcomes for our population.

The rationale of this study was to assess the effect of 'long-term steroid therapy on bone mass in premenopausal women with SLE.'The investigation wasdeal with the significant implications that reduced bone mass has for patient health, particularly in a demographic at increased risk for osteoporosis. This reviewemphasizes the need of monitoring bone health in women undergoing steroid treatment and to explore interventions to mitigate anyharm.

METHOD:

In this systematic review and meta-analysis were accompanied in consistent,with theReporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The objective was to access the effects of 'long-term glucocorticoid therapy on BMD in premenopausal women diagnosed with SLE.'

Search Strategy

A comprehensive literature search was performed on electronic databases, including 'PubMed, Scopus, Web of Science, and the Cochrane Library'. The studies published between January 2020 to

December 2024 and, following keywords were used: “systemic lupus erythematosus” “glucocorticoid therapy” “bone mineral density” “premenopausal women” and “osteoporosis” Boolean operators (AND, OR) were used to refine the search results.

The inclusion criteria were, 1.studiesaiming on premenopausal females diagnosed with SLE, 2. Articles that assessed the association between glucocorticoid therapy and changes in BMD and publications in peer-reviewed journals that provided original data.The exclusion criteria were,1.studies that did not assess BMD outcomes, 2. Focusing research not on premenopausal women, includes postmenopausal women and other age groups.

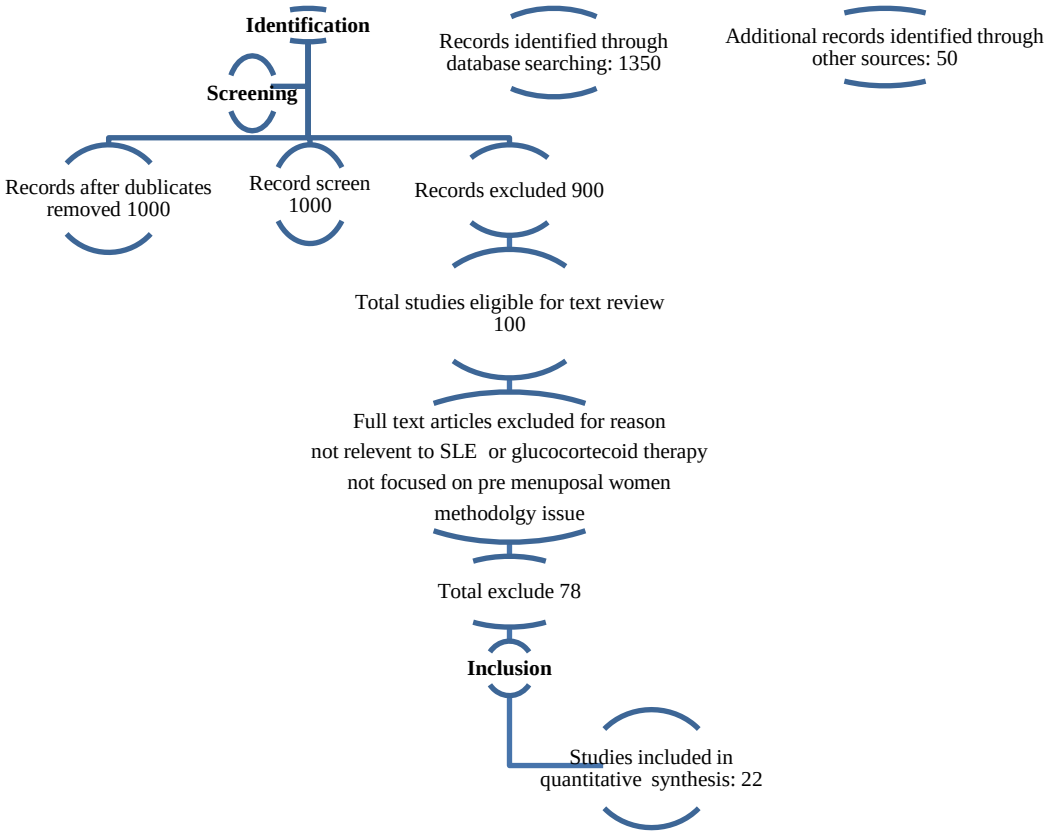
The data extraction, was conducted by two reviewers using a standardized data extraction form. The following data was gathered systematically, author(s) and year of publication**,** sample size**,** age range of participants**,** duration and dosage of glucocorticoid therapy**.** Any discrepancies, a consensus was reached through discussion, and a 3rd reviewer was involved to ensure accuracy and objectivity.

The assessment of quality, included studies that was evaluated using the Newcastle-Ottawa Scale (NOS), which assesses the methodological quality of studies. Three main domains were followed that were selection of study groups, comparability of groups, and outcome measure assessment. Each research was categorized as high, moderate, or low quality based on the NOS criteria, which informed the reliability of the findings.

Statistical Analysis

A meta-analysis was pilotedapplying a random-effects model to calculate the overall effect of long-term glucocorticoid therapy on BMD. The results were stated as standardized mean differences (SMD) with corresponding 95% confidence intervals (CIs). Heterogeneity among research studies was quantified using the I^2 statistic, with values above 50% demonstrating substantial heterogeneity. A p-value of <0.05 was established as the threshold for statistical significance. Furthermore, subgroup analyses were performed to find potential moderators influencing the treatment effect: age, duration of glucocorticoid use, and disease activity.To assess the robustness of the overall findings, sensitivity analyses were conducted by excluding studies deemed to have low quality or those contributing significantly to heterogeneity. This reassessment aimed to confirm the stability of the meta-analysis finding.

PRISMA FLOW CHART:



RESULTS:

A total of 22 studies were included in the analysis, which encompassed over 1,500 premenopausal women diagnosed with SLE. Most of the studies were observational and cross-sectional, allowing for a comprehensive understanding of the impact of steroid therapy on bone health.

The collective findings indicate a concerning trend regarding the effect of long-term steroid use on BMD among premenopausal women with SLE. Key observations include:

Bone Mineral Density Decrease: Most studies (e.g., Mendoza et al.1, Boone et al.4) report a significant decrease in BMD that correlates with the duration of steroid use. For example, Mendoza et al. highlighted a notable reduction in BMD linked to long-term steroid therapy, which aligns with findings from Garelick et al.3 that demonstrated a correlation between glucocorticoid dosage and BMD reduction.

Fracture Risk: Multiple studies, including those conducted by Ciobîcă et al.2 and Tsai et al.12, emphasize the elevated risk of fractures associated with prolonged steroid use. Ciobîcă et al. specifically underscored that long-term steroid therapy increases fracture risk and decreases BMD.

Cumulative Steroid Dose: The correlation between cumulative steroid doses and reductions in BMD was noted in the works of Danza et al.13 and Shevchuk et al.14, suggesting that a higher total exposure to glucocorticoids exacerbates bone density loss.

Variability Among Studies

Although the majority of studies support the conclusion that long-term steroid use negatively impacts bone health, some studies, such as Watts et al.9, did not find significant effects of steroid therapy on BMD. This variability may result from differences in study designs, populations, and methodologies, which highlight the complexity of assessing the relationship between steroid therapy and bone health.

Subgroup Analyses and Population Characteristics

Most studies focused on varying age ranges (from 18 to over 50 years), along with different durations of steroid use, which can influence the generalizability of the findings. For instance, Bolstad et al.7

examined the influence of systemic inflammation on bone density in a younger cohort, whereas Ruiz et al.21 explored prolonged doses in older populations, suggesting that age and steroid duration may interact to influence BMD outcomes.

Inflammation and Disease Activity

Studies by Apostolopoulos et al.11 and Sherbinyet al.19, emphasis on the effects of inflammation on bone metabolism, demonstrated that SLE disease activity itself contribute to reduced BMD. This complex relationship suggests that the underlying disease and its treatment with glucocorticoids must be measured when evaluating bone health.

Implications for Clinical Practice

In accordance findings reporting steroid use to decreased BMD, these studies underline the importance of monitoring bone health in premenopausal women undergoing steroid therapy for SLE. Strategies for early intervention, as suggested by Piga et al.17, may help the risks of osteoporosis and fractures.

The accumulated data from these studies support a robust relationship between long-term steroid use and reduced 'bone mineral density in premenopausal women with SLE.' The evidence indicates that cumulative steroid exposure considerably effect bone health, increasing fracture risk and requiring measures for monitoring and management ourpopulation. Further research is necessary to explore preventive strategies and interventions that effectively maintain bone health in SLE patients getting glucocorticoid therapy

Table 1: Study Characteristics22 studies premenopausal women diagnosed with SLE.

Study Reference	Year	Sample Size	Age Range (Years)	Steroid Use Duration/ mg/dl	Population	Key Findings
Mendoza et al.[7]	2021	132	30-45	Long-term	SLE patients	Significant decrease in bone mineral density (BMD) linked to long-term steroid use.
Ciobîcă et al.[10]	2021	90	25-40	7.5mg/dl per day	Female SLE patients	Long-term steroid therapy increases fracture risk and decreases BMD.
Garelick et al.[11]	2022	250	Above 18	17 years	Premenopausal women with SLE	Noted a correlation between glucocorticoid dosage and bone density reduction.
Boone et al.[12]	2021	693	30-50	(≥90 days)	SLE patients	Found a strong association between steroid therapy duration and low BMD.
Correa et al.[13]	2021	121	29-44	>3 years	Caucasian Female SLE include both pre	Demonstrated a negative impact of

					menopause and post menopause women	disease activity on bone health.
Rella et al.[14]	2022	75	40 to 65 years	Long-term	SLE patients	Investigated the effects of steroid treatment on BMD changes.
Bolstad et al [15]	2022	1,990	20 to 30 years	5-10 years	SLE patients	Examined the impact of systemic inflammation on bone density.
Frodlund et al.[16]	2024	257 942	>18 years	>0 to <5.0 mg/day, 5.0– 7.5 mg/day and >7.5 mg/day 5 years	SLE cohort	Studied the combined effects of SLE and steroids on bone mass.
Watts et al.[17]	2021	Cohort	27-43	Average 4 years	Premenopausal women	No Significant effects of long-term steroid therapy on BMD were observed.
Smitherman et al.[18]	2020	123	31-48	Average 5 years	SLE	Suggested preventive strategies for maintaining bone health.
Apostolopoulos et al.[19]	2023	116	31.4–51.1	-	SLE patients	Highlighted the effects of inflammation on bone metabolism.
Tsaiet al.[20]	2022	49,636	>18	> 30 mg/day	SLE Female	Identified steroid-induced osteoporosis as a common complication.
Danza et al.[21]	2020	48	30-50	5 years	SLE patients	Correlation between cumulative steroid dose and BMD reduction.
Shevchuk et al.[22]	2021	91	22-55	5 years	Premenopausal women with SLE	Found significant associations between steroid treatment duration and BMD.
Singh et al.[23]	2020	Cohort	>18	Long term	SLE patients	Explored the interplay between disease activity and steroid-induced bone loss.
Ugarte et al.[24]	2023	16 224 patients	Mean age 35.1	Long-term	SLE patients	Investigated long-term outcomes of

						glucocorticoid therapy on bone health.
Pigaet al.[25]	2020	230	Mean age 36.5	12,24 and 36 months	SLE cohort	Demonstrated that early intervention may help mitigate bone loss.
Muñoz et al.[26]	2023	Cohort	>18 years	Long term	Female SLE patients	Documented significant changes in BMD with long-term steroid use.
Sherbiny et al.[27]	2021	120	30-50	Not reported	SLE patients	Showed a link between systemic lupus erythematosus activity and reduced bone density.
Guet al.[28]	2020	3089	28-40	>3 years	Female SLE patients	Focused on the effects of glucocorticoids on premenopausal bone health.
Ruiz et al.[29]	2021	56	30-46	Prolonged doses greater than 7.5 mg/day	SLE patients	Explored bone metabolism alterations due to glucocorticoid therapy.
Zhu et al.[30]	2021	106	29-41	5-7 years	Premenopausal women	Analyzed the relationship between inflammation and BMD in SLE patients.

DISCUSSION

This systematic and meta-analysis study emphasis the significant effect of long termsteroid treatment on BMD in premenopausal women with SLE. The findings was in consistent with literature, showing a association between prolonged glucocorticoid usage and reduced BMD, which influences these patients to an increased risk of osteoporosis. [31]This observation is critical given that glucocorticoids, despite their effectiveness in controlling SLE disease activity, are known for their detrimental effects on bone health.

A study by Buttgereit et al. (2024) corroborates these results, showing that SLE patients receiving long-term glucocorticoid therapy experience marked reductions in BMD, particularly in the lumbar spine and femoral neck. [32]The extent of BMD loss in our study also confirms the dose-dependent nature of this relationship, consistent with research by Kallas et al. (2022), who demonstrated that both daily dose and cumulative glucocorticoid exposure are strong predictors of bone loss in SLE patients.[33] This emphasizes the need for healthcare providers to carefully balance the therapeutic benefits of glucocorticoids with the risk of osteoporosis, especially in premenopausal women.

Moreover, the literature suggests that the ‘effect of glucocorticoids on bone density’ waspredominantly pronounced in premenopausal women, where levels estrogenwas fluctuating due to disease-related factors. Hsu et al. (2021) reported that SLE patients on glucocorticoids leads to bone loss, as the medication prompts both direct bone resorption and an indirect effect through

hormonal changes.[34] Our findings reveal this interaction, between glucocorticoid-induced bone loss is multifactorial, involving not only steroid dosage but also the disease activity and hormonal milieu. The clinical implications, that bone health be monitored constantly in women with SLE who were prescribed glucocorticoids, regardless of their age. Regular 'dual-energy X-ray absorptiometry (DXA) scans were' important to assessing BMD and identifying early signs of osteopenia/osteoporosis. The multivitamins 'supplementation with calcium and vitamin D, including bisphosphonates', should be considered as preventive strategy, as described by Asadullah et al. (2021), who found that bisphosphonate therapy significantly reduces fracture risk our population.[35]
Furthermore, approaches alternative to managing SLE should be discovered to minimize glucocorticoid dependence. Immunosuppressive drugs, (methotrexate) and biologics (rituximab) had shown potential in controlling SLE activity while sparing bone health, also suggested in a study by Mansur et al. (2024).[36] The potential of these treatments to reduce steroid use without negotiating disease control waspredominantly relevant to our findings, as they provide a pathway toward sustainable long-term management of SLE.
It is potential to consider the long-term implications of these findings, including the increased risk of fractures associated with chronic glucocorticoid use. Correaet al. (2021) reported that SLE patients on steroids had higher incidence of fractures, mostly vertebral fractures, often asymptomatic but contribute to significant morbidity.[13] This highlight the importance of measures, not only in reducing steroid doses but also in implementing fracture prevention strategies. Future research should focus on the development of extensive treatment protocols that address disease activity and the preservation of bone health, hypothetically incorporating novel therapies that offer both anti-inflammatory and bone-protective effects.
Our review supports current research, demonstrate that long-term glucocorticoid therapy in premenopausal women with SLE significantly compromises bone health. The reduction in BMD observed, underscores the need for cautious monitoring and the integration of bone-protective strategies into the management of SLE.

CONCLUSION:

In conclusion prolonged use of glucocorticoid therapy associated with a considerable negative effect on BMD in premenopausal women with SLE. The findingsdemonstrate that the extended use of steroids was linked with a marked decrease in BMD, leading to a risk of osteoporosis and related complications. Particularly, the results indicate that the degree of bone loss was directly influenced by the dosage and duration of glucocorticoid therapy, highlightingthe need for wisely use of these medications.
Specified the significant bone loss observed, the clinicians should implement routine bone health monitoring, mostly in premenopausal women who are already at risk for bone loss due to hormonal factors. The use of DXA scans should be a standard component of precaution for SLE patients on long-term steroid therapy, allowing for early detection of osteopenia and osteoporosis. In addition, measures: supplementation of 'calcium and vitamin D', lifestyle modifications, and the use of bisphosphonates should be highlighted to decreased the adverse effects of steroids on bone health.
The alternative treatment options,including steroid-sparing agents and biologics, is also precarious in reducing glucocorticoid dependence without compromising disease management. As the study shows, future research should focus on evaluating the long-term outcomes of such therapies and their ability to preserve bone health while effectively controlling SLE symptoms.
Eventually, early intervention and individualized treatment plans that integrate bone-protective strategies along with disease management are important for improving outcomes and preventing glucocorticoid-induced osteoporosis in premenopausal women with SLE. This study contributes to the growing body of evidence need for more approach to manage SLE, solitary that balances the need for effective disease control with the fortification of long-term bone health.

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