Scientific Research Publishing

Modern Research in Inflammation, 2024, 13, 43-57
https://www.scirp.org/journal/mri
ISSN Online: 2169-9690
ISSN Print: 2169-9682

The Intersection of Cutaneous Lupus and Osteonecrosis: Dermatologic Implications for Orthopedic Joint Preservation

Alejandra Sataray-Rodriguez[1], Janae Rasmussen[2], Klaudia Greer[3], Shivam Shah[4], Vivian Liang[5], Laura Palma[6], Kelly Frasier[7], Pedram Razavi[5], Garrett Chin[5]

[1]Reno School of Medicine, University of Nevada, Reno, NV, USA
[2]Valley Consortium for Medical Education, Modesto, CA, USA
[3]Herbert Wertheim College of Medicine, Florida International University, Miami, FL, USA
[4]Health Sciences Center at Shreveport, School of Medicine, Louisiana State University, Shreveport, LA, USA
[5]School of Osteopathic Medicine in Arizona, A.T. Still University, Mesa, AZ, USA
[6]SUNY Upstate Medical University, Syracuse, NY, USA
[7]Department of Dermatology, Northwell Health, New Hyde Park, NY, USA
Email: kellymariefrasier@gmail.com

How to cite this paper: Sataray-Rodriguez, A., Rasmussen, J., Greer, K., Shah, S., Liang, V., Palma, L., Frasier, K., Razavi, P. and Chin, G. (2024) The Intersection of Cutaneous Lupus and Osteonecrosis: Dermatologic Implications for Orthopedic Joint Preservation. *Modern Research in Inflammation*, **13**, 43-57.
https://doi.org/10.4236/mri.2024.134004

Received: October 3, 2024
Accepted: November 26, 2024
Published: November 29, 2024

Abstract

The intersection of cutaneous lupus erythematosus (CLE) and osteonecrosis highlights a complex relationship between dermatologic and orthopedic pathology, underscoring the systemic nature of autoimmune disease. Osteonecrosis, characterized by ischemic bone death and subsequent joint degeneration, is a known complication in systemic lupus erythematosus (SLE), but emerging evidence suggests that CLE manifestations may serve as early indicators or contributory factors in its development. Chronic inflammation and microvascular injury, central to CLE pathophysiology, may predispose affected patients to compromised bone perfusion and ischemia, particularly in weight-bearing joints such as the hips and knees. Dermatologic signs, including persistent erythema, ulceration, or livedo reticularis, may reflect underlying vascular dysfunction that extends beyond the skin to subchondral bone, accelerating osteonecrotic processes. The role of autoantibodies, such as antiphospholipid antibodies, and their contribution to thrombotic microangiopathy in CLE further supports this potential mechanistic link. Early recognition of CLE-related vascular changes could guide orthopedic surveillance strategies, enabling timely imaging with MRI to detect early osteonecrosis before irreversible joint damage occurs. Therapeutic interventions for CLE, including corticosteroids and immunosuppressive agents, may inadvertently exacerbate osteonecrosis risk, necessitating careful balancing of treatment efficacy with preservation of joint health. Advances in vascular-targeted therapies and

bone-preserving interventions, such as bisphosphonates or regenerative techniques, offer potential avenues for mitigating joint degeneration in this patient population. Understanding the bidirectional relationship between CLE and osteonecrosis provides an opportunity for dermatologists and orthopedists to collaborate on predictive, preventive, and therapeutic strategies that preserve joint function and improve quality of life for affected individuals.

Keywords

Cutaneous Lupus Erythematosus, Osteonecrosis, Systemic Lupus Erythematosus, Autoimmune Disease, Chronic Inflammation, Microvascular Injury

1. Introduction

Systemic Lupus Erythematosus (SLE) is a complex autoimmune disease characterized by widespread tissue inflammation, immune system dysregulation, and environmental influences. Its clinical manifestations vary among patients, making diagnosis and treatment challenging. Oral corticosteroids are a primary treatment for SLE but can lead to severe side effects, including osteoporosis, fractures, and osteonecrosis [1]. Osteonecrosis is caused by disrupted blood circulation, leading to bone ischemia. Although often asymptomatic, it can progress during lupus flares and may present with severe pain from necrotic tissue, most commonly at the femoral head. Risk factors for avascular necrosis (AVN) include age, sex, steroid use, and coagulopathies. Severe cases may require surgical interventions, such as hip or knee arthroplasty, which carry additional risks like thromboembolism due to SLE pathophysiology.

Cutaneous Lupus Erythematosus (CLE) is a subset of SLE that presents with various skin lesions triggered by medications or sun exposure [2]. Emerging research highlights that CLE-associated vasculopathy and inflammation may uniquely predispose patients to osteonecrosis compared to the broader SLE population. Unlike systemic manifestations of SLE, CLE primarily affects the skin, yet emerging evidence suggests that its localized pathology, such as photosensitivity-induced inflammation and vasculopathy, may amplify the risk of osteonecrosis in this subset of patients [3]. For instance, CLE-associated vasculopathy could further compromise blood supply to bone tissue, exacerbating ischemic injury, particularly in patients already at risk due to steroid use or immune dysregulation.

Recent findings suggest specific CLE subtypes, such as chronic cutaneous lupus, may exhibit a stronger association with osteonecrosis development due to their persistent inflammatory profiles. Biomarkers, including elevated levels of tumor necrosis factor-alpha (TNF-α) and interferon-gamma (IFN-γ), may serve as predictive indicators for vascular complications in CLE patients [4] [5]. Additionally, skin lesions in CLE could serve as external indicators of disease progression and systemic involvement, potentially correlating with osteonecrosis development.

While CLE is linked to SLE, direct research on its relationship with osteonecrosis is limited. This gap emphasizes the importance of exploring molecular mechanisms that directly connect CLE-related inflammation and vascular damage to bone ischemia. Given that skin lesions may indicate SLE progression, it is plausible that CLE may serve as a risk factor for developing osteonecrosis [6]. This study explores the potential relationship between CLE and osteonecrosis, evaluates CLE staging in relation to AVN severity, and assesses the utility of CLE changes in informing treatment strategies for SLE patients at risk for osteonecrosis.

2. Pathophysiology of Cutaneous Lupus Erythematosus (CLE)

2.1. Environmental Triggers and Genetic Predispositions

CLE is an autoimmune disease primarily affecting the skin, but can involve systemic inflammatory processes, evolving into SLE. CLE is categorized into acute cutaneous lupus (ACLE), subacute cutaneous lupus (SCLE), and chronic cutaneous lupus (CCLE) based on clinical and histopathological findings. Its pathophysiology involves environmental factors, genetic predispositions, and chronic activation of the immune system. Environmental triggers, such as ultraviolet light, smoking, and certain medications can cause DNA alterations, reactive oxygen species (ROS) production, and apoptosis [7]. Genetic susceptibility includes variations in HLA genes (e.g., HLA-B8, DR3) and complement protein deficiencies, as well as mutations in the TREX1 gene, which degrades DNA [8]. A hallmark of CLE is the overactivation of the type I interferon (INF) pathway, driving persistent inflammation through immune pathway activation [9]. This cycle of immune activation and inflammation results in the clinical manifestations of CLE.

2.2. Immune System Activation

In CLE, chronic inflammation—amplified by type I interferons and pro-inflammatory cytokines—has systemic implications beyond the skin, including vascular damage. These inflammatory pathways may directly impair blood flow to subchondral bone, contributing to osteonecrosis [7]-[9]. The chronic inflammation in CLE has systemic implications, including atherosclerosis and thrombosis, contributing to cardiac, vascular, and skeletal complications like osteonecrosis. Inflammatory cytokines, such as tumor necrosis factor-alpha (TNF-α) and interferon-gamma (INF-γ), exacerbate microvascular injury by impairing endothelial function and promoting vascular inflammation [4] [5]. These processes, also observed in other inflammatory diseases like psoriasis, disrupt blood flow and increase ischemic conditions, elevating the risk of osteonecrosis. CLE's systemic effects underscore the interconnectedness of immune dysregulation and skeletal health, necessitating comprehensive care.

3. Systemic Implications of CLE

3.1. Osteonecrosis: Mechanisms and Risk Factors

Osteonecrosis, defined as ischemia-induced bone tissue death, results from an

imbalance between osteoclast-mediated resorption and osteoblast-mediated formation, leading to bone collapse and joint dysfunction. Clinically, it often presents as impaired mobility and reduced quality of life, particularly in weight-bearing joints, such as the femoral head [10]. The etiology of osteonecrosis is multifactorial, with traumatic injuries, prolonged corticosteroid use, and excessive alcohol consumption recognized as acute triggers. Chronic conditions, such as SLE, exacerbate vascular fragility and compromise the blood supply essential for bone health [11]. The underlying pathophysiology involves prolonged ischemia that deprives bone tissue of oxygen and nutrients, impairing cellular metabolism and leading to structural deterioration. This ischemic state disrupts bone marrow function, promotes adipocyte accumulation, and increases interosseous pressure, further obstructing vascular pathways. Thrombophilic conditions, such as Factor V Leiden and antiphospholipid syndrome, exacerbate disease progression by inducing thrombus formation and impairing circulation [12]. Additionally, direct vascular damage from fractures or fat embolisms can impede blood flow to affected regions. Corticosteroid use and chronic alcohol consumption compound these effects by inducing adipocyte hypertrophy, further restricting vascular integrity [13]. Together, these mechanisms highlight the intricate interplay between vascular health, metabolic function, and bone integrity.

3.2. Treatment Approaches and Future Directions

The treatment of osteonecrosis in CLE patients requires a multifaceted approach to manage the complex pathophysiology and prevent further bone damage. Future studies should examine the therapeutic potential of targeting these pathways in CLE-specific osteonecrosis. Investigating whether novel biomarkers, such as vascular endothelial growth factor (VEGF) or markers of oxidative stress, correlate with disease severity may enhance diagnostic precision and guide treatment. Pharmacological agents, such as bisphosphonates and denosumab, may help to reduce bone resorption and preserve bone integrity [1] [14] [15]. Additionally, anti-inflammatory therapies like corticosteroids, TNF-α inhibitors, and rituximab may be explored to address the underlying inflammation driving osteonecrosis in CLE. Treatment of osteonecrosis focuses on addressing underlying causes to mitigate ischemic conditions and preserve bone health. Acute interventions often aim to enhance blood circulation and reduce internal bone pressure to prevent further structural deterioration. However, prolonged exposure to risk factors without timely intervention can result in irreversible bone degradation and joint dysfunction, significantly impacting mobility and quality of life [16]. In advanced stages, surgical procedures, such as joint replacement, are frequently necessary to restore function and alleviate pain [17] [18].

3.3. Emerging Therapies

Beyond surgical approaches, emerging regenerative therapies, including mesenchymal stem cell implantation and gene therapy, offer promising avenues for

addressing osteonecrosis in CLE patients. These therapies aim to stimulate bone repair and regeneration, potentially improving outcomes for patients who are not candidates for traditional surgical interventions. Evaluating their safety and efficacy in this context may significantly advance care strategies.

3.4. Vulnerable Anatomical Sites and Implications

The femoral head is particularly vulnerable due to its vascular anatomy, relying heavily on the medial circumflex femoral artery [19]. Damage to the medial circumflex artery increases the risk of ischemia, while mechanical stress from weight-bearing activities exacerbates subchondral necrosis and joint collapse [19]. These factors emphasize the critical importance of maintaining adequate vascular integrity to support bone health and highlight the need for preventive strategies to mitigate the impact of osteonecrosis on weight-bearing joints [19]. Similarly, the knee, nourished by the inferior medial genicular arteries, is another common site of osteonecrosis, particularly involving the distal femur and proximal tibia [20]. Idiopathic causes and traumatic injuries often underlie knee osteonecrosis, with the epiphyseal arteries supplying the subchondral bone being especially vulnerable to localized ischemia. Activities, such as walking and running, further exacerbate mechanical stress, increasing the risk of joint damage. Severe cases may require surgical interventions like total knee arthroplasty to restore functionality and relieve pain.

In contrast, the shoulder, particularly the humeral head, is less commonly affected by osteonecrosis, but still poses significant clinical challenges due to its limited collateral circulation, primarily supplied by the posterior humeral circumflex artery [21]. Although the progression of disease in the humeral head is slower due to reduced mechanical stress compared to weight-bearing joints, untreated osteonecrosis in this region can severely impact upper-limb function, particularly during overhead movements like lifting and reaching [22].

Given the interdependence of CLE's inflammatory and vascular pathology, early detection of osteonecrosis via imaging or biomarker analysis may improve outcomes. Incorporating CLE staging into osteonecrosis management protocols could provide a more personalized and proactive approach to treatment.

4. The Role of Autoantibodies and Thrombotic Microangiopathy in CLE

Antiphospholipid antibodies (aPL) play a crucial role in the pathophysiology of CLE, contributing significantly to vascular dysfunction and increasing the risk of thrombotic events. These autoantibodies specifically target phospholipid-binding proteins, such as beta-2 glycoprotein, which leads to thrombosis and microvascular injury [23]. As a result, blood flow becomes impaired, jeopardizing perfusion to several tissues, including subchondral bone. The reduced blood flow significantly heightens the risk of osteonecrosis, particularly in weight-bearing joints like the hips and knees [24]. Over time, vascular damage deprives bone tissues of

oxygen and essential nutrients, exacerbating the degeneration of affected joints. Such progressive vascular injury underscores the need to monitor aPL levels in CLE patients closely. Additionally, incorporating markers such as endothelial dysfunction indicators, including E-selectin and soluble vascular cell adhesion molecule-1 (sVCAM-1), may provide further insight into the vascular pathways leading to osteonecrosis in CLE [5] [9]-[11]. While the literature on sVCAM-1 in CLE is limited, it could offer valuable future directions for research and targeted interventions to mitigate vascular complications.

The presence of other autoantibodies, such as anti-DNA and anti-Ro, in addition to aPL, further complicates CLE pathogenesis. These autoantibodies promote the deposition of immune complexes on endothelial cells, instigating vasculitis and additional vascular damage [25]. This endothelial injury often progresses to thrombotic microangiopathy, a condition characterized by capillary obstruction and diminished perfusion to oxygen- and nutrient-dependent bone tissues. Consequently, the restricted supply of essential elements leads to osteonecrosis and, in severe cases, collapse of the bone's structural components. Furthermore, the treatment of CLE frequently involves corticosteroids, which, while effective in managing inflammation, heighten the risk of osteonecrosis [3] [26].

These medications disrupt the bone's natural repair mechanisms, which exacerbates joint degeneration and adds complexity to patient management.

5. Therapeutic Challenges and Considerations

5.1. Balancing CLE Treatment with Bone Health Preservation

While CLE can be debilitating, the primary therapeutic challenge lies in balancing effective treatment of CLE symptoms with minimizing the adverse effects of long-term therapies, particularly on bone health. Key CLE treatments include topical corticosteroids, antimalarials like hydroxychloroquine, and immunosuppressive agents like methotrexate and azathioprine [27]. These therapies are essential for controlling skin inflammation and systemic involvement. However, they carry the potential for significant side effects. One of the most concerning complications of CLE is osteonecrosis, which is often exacerbated by medications like glucocorticoids. Minimizing corticosteroid use through alternative therapies is crucial in reducing this risk. Topical corticosteroids are typically considered first-line treatments for CLE [28] [29]. However, prolonged use of these treatments can lead to side effects such as atrophy, telangiectasias, osteoporosis, and dermatitis [29]-[31]. For example, a randomized controlled trial by Roenigk *et al.* (1980) found that 27% of patients using 0.05% fluocinonide experienced significant improvement, compared to only 10% of patients using 1% hydrocortisone [32]. Although highly potent steroids like fluocinonide may be more effective than low-potent steroids like hydrocortisone, careful consideration of their side effect profile is essential. This suggests that low-potent steroids can still serve as a viable treatment option for CLE when used appropriately.

5.2. Role of Antimalarials

Antimalarials, particularly hydroxychloroquine, are another common first-line therapy for CLE. A randomized controlled trial by Yokogawa *et al.* (2017) demonstrated significant improvements in the Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI) scores with hydroxychloroquine compared to placebo [33]. Beyond improving clinical outcomes, hydroxychloroquine has been shown to reduce flare rates significantly. Tsakonas *et al.* (1998) found that patients continuing hydroxychloroquine had fewer major disease flares compared to those on placebo, indicating its potential to provide long-term control of CLE [34]. However, in cases of refractory CLE, increasing hydroxychloroquine blood concentrations above 750 ng/mL has been associated with improved outcomes [35]. While this strategy can help manage challenging cases, it necessitates close monitoring to avoid long-term complications like retinal toxicity.

5.3. Immunosuppressants for Refractory CLE

When antimalarials or corticosteroids are insufficient or poorly tolerated, immunosuppressants like methotrexate, mycophenolate, and azathioprine are viable options. Methotrexate has shown effectiveness in improving both articular and cutaneous symptoms of SLE, making it a potential steroid-sparing alternative [36]. Similarly, mycophenolate has demonstrated efficacy in treating antimalarial-refractory CLE, with response rates comparable to methotrexate [37]. Azathioprine also offers an effective treatment option, especially for patients who cannot tolerate conventional therapies [38]. Its corticosteroid-sparing properties make it particularly valuable in pregnant patients, as it avoids the teratogenic risks associated with other medications [39]. These immunosuppressants provide critical alternatives for managing complex CLE cases while minimizing reliance on corticosteroids.

5.4. Osteonecrosis Risk Mitigation

CLE has been associated with an increased risk of osteonecrosis, a severe condition characterized by the death of bone tissue [40]. Corticosteroids are strongly linked to this complication, as they may compromise blood flow to affected bones [41]. Shigemura *et al.* (2011) reported that up to 37% of lupus patients on corticosteroids develop osteonecrosis, with the risk increasing at higher doses [42]. Minimizing corticosteroid use through alternative therapies is crucial in reducing this risk. Additionally, discontinuing corticosteroids as early as possible should be a primary therapeutic goal [43]. Although antimalarials do not increase osteonecrosis risk, they also do not provide protective effects against it, necessitating the consideration of other strategies to manage this complication effectively.

5.5. Steroid-Sparing Immunosuppressants

One effective approach to reducing osteonecrosis incidence in CLE patients involves the use of steroid-sparing immunosuppressants. Nawata *et al.* (2018) observed

that introducing calcineurin inhibitors led to decreased glucocorticoid use and a corresponding reduction in osteonecrosis cases in SLE patients [44]. While this highlights the potential of immunosuppressants to mitigate corticosteroid-related complications, these treatments may still carry risks of osteonecrosis through direct cytotoxic effects on bone cells [30]. Clinicians must remain vigilant in monitoring CLE patients for signs of osteonecrosis, regardless of the treatment regimen. This underscores the need for comprehensive management strategies that balance disease control with minimizing long-term complications.

6. Interdisciplinary Approaches: Dermatology and Orthopedics Collaboration

Central to the pathophysiology of CLE is chronic inflammation and microvascular injury, which may predispose patients to osteonecrosis. Dermatologists are crucial in preventing or diagnosing osteonecrosis early by identifying skin manifestations indicative of underlying vascular dysfunction. Persistent skin changes, such as erythema, ulceration, and vasculitic lesions in CLE may signal microvascular compromise that could extend beyond the skin to other organs like bones. Studies have suggested that microvascular damage contributes to the development of osteonecrosis in SLE, implying similar mechanisms may occur in CLE. Risk factors for osteonecrosis in CLE include vasculitis, Raynaud's phenomenon, leukopenia, fat emboli, youth, and the presence of aPL antibodies [45]. Of these, aPL antibodies are particularly significant because they promote blood coagulation and thrombosis, which are predisposing factors for osteonecrosis [46]. Defects in fibrinolysis, such as imbalances between tissue plasminogen activator (tPA) and its inhibitor PAI-1, further exacerbate the risk [3]. Skin patterns associated with thrombosis and defective fibrinolysis, including Raynaud's phenomenon, periungual telangiectasias, livedo reticularis, leukocytoclastic vasculitis, and urticarial vasculitis, are common in CLE [47] [48]. Dermatologists' ability to identify these vascular abnormalities underscores their essential role in initiating further investigations to diagnose or prevent osteonecrosis in CLE patients.

Orthopedic Surgeons in Early Osteonecrosis Detection and Management

Orthopedic surgeons are equally vital in identifying and managing early osteonecrosis in CLE patients, facilitating timely interventions that may prevent severe outcomes. By employing advanced imaging techniques, such as magnetic resonance imaging (MRI), orthopedists can screen high-risk CLE patients, particularly those receiving high-dose corticosteroid therapy. Corticosteroid treatment is believed to reduce bone blood flow, exacerbating ischemia and increasing the risk of osteonecrosis. A study by Oinuma *et al.* demonstrated that MRI can detect osteonecrosis lesions in SLE patients as early as one to five months after initiating high-dose corticosteroids, with the actual onset often occurring within the first month of treatment [49]. This highlights the importance of early and routine MRI

screening in CLE patients undergoing corticosteroid therapy, particularly during the early stages of treatment. Moreover, recurrence of SLE or CLE requiring increased corticosteroid doses further increases the risk of osteonecrosis. Nakamura *et al.* found that 45% of patients with recurrent SLE experienced delayed osteonecrosis, suggesting that disease recurrence is an additional risk factor [50]. These findings advocate for regular MRI screenings by orthopedic surgeons to detect osteonecrosis early, even in patients with fluctuating disease activity. Early detection through imaging can guide preventive orthopedic interventions, reducing irreversible joint damage and preserving the patients' quality of life.

7. Early Detection and Imaging for Osteonecrosis in CLE Patients

Osteonecrosis in SLE patients is a serious condition that requires early diagnosis to prevent joint destruction and bone collapse. This concern also applies to CLE patients, who, due to vascular complications and corticosteroid therapy, are similarly at risk for osteonecrosis [51]. Early detection is critical because untreated lesions can lead to debilitating disability and require surgical interventions, such as arthroplasty procedures [52]. MRI plays a key role in the early diagnosis of osteonecrosis, as it can detect subtle lesions that might not yet cause symptoms. This imaging modality is superior to traditional radiography, particularly for detecting low-intensity bands in T1-weighted images, which indicate the transition from healthy bone to necrotic tissue. For CLE patients, where vascular complications like vasculitis or thrombophilia are common, MRI can also reveal early joint inflammation or vascular involvement, providing valuable insights for timely intervention.

7.1. MRI Screening in Asymptomatic and High-Risk CLE Patients

Prior studies demonstrate that nearly half of SLE patients on high-dose corticosteroids develop osteonecrosis, often without clinical symptoms, which underscores the importance of early imaging in even asymptomatic patients [1]. In patients with vascular signs, such as altered lipid metabolism or thrombophilia, MRI screening becomes even more crucial, as these factors increase the risk of multifocal osteonecrosis. Clinical signs, such as Raynaud's phenomenon, digital ischemia, or persistent extremity pain should prompt early imaging to assess for vascular involvement and osteonecrosis [48]. Early MRI findings enable clinicians to adopt non-invasive treatment strategies, such as medications or regenerative therapies, to slow the progression of osteonecrosis, thus preserving joint function and avoiding the need for more invasive treatments. Additionally, MRI plays an ongoing role in monitoring disease progression and adjusting treatment plans to prevent further damage. MRI is crucial for assessing vascular involvement in CLE patients, as vascular complications can increase morbidity. Early MRI utilization can detect joint and soft tissue inflammation, such as in Jaccoud's arthropathy, identifying early periarticular changes that could lead to deformities [53] [54]. It

also helps differentiate disease-specific inflammatory pain from conditions like fibromyalgia, which require different treatments. For patients with vascular involvement, MRI can reveal subtle changes in blood vessels, like thickening or inflammation, which may not be visible on clinical exams, aiding in the management of systemic involvement and joint preservation.

7.2. Pharmacological Treatments for Osteonecrosis in CLE Patients

Pharmacological treatments are also important for managing osteonecrosis in SLE patients, especially when conservative measures, like pain management and activity modification, are insufficient. Bisphosphonates, such as alendronate, have proven effective in preventing the progression of osteonecrosis, particularly in cases induced by corticosteroid therapy [1]. Randomized controlled trials have shown that bisphosphonates can significantly reduce the incidence of femoral head collapse compared to placebo, making them a valuable tool for high-risk patients [1] [14] [15]. These drugs help prevent corticosteroid-induced bone loss, a common concern for SLE patients. Additionally, bisphosphonates may reduce the risk of vertebral fractures and treat bone loss at critical sites like the lumbar spine and femoral neck [14] [15]. However, it is important to note the potential risk of bisphosphonate-related osteonecrosis of the jaw, especially in patients undergoing invasive dental procedures [15]. Although this risk is relatively low, careful patient selection and monitoring are essential [55]. Other pharmacological options, such as anticoagulants and lipid-lowering agents, are being explored for their potential to reduce osteonecrosis risk, though further research is needed to establish their role. In the meantime, bisphosphonates remain a cornerstone in osteonecrosis management, with side effects generally being mild.

8. Conclusion

The findings of this study highlight the complex relationship between Cutaneous Lupus Erythematosus (CLE) and osteonecrosis in patients with Systemic Lupus Erythematosus (SLE). The chronic inflammation and vascular damage associated with CLE contribute to the development of osteonecrosis, particularly in weight-bearing joints like the hip and knee. The role of autoantibodies, such as antiphospholipid antibodies, further exacerbates vascular dysfunction, increasing the risk of bone ischemia and subsequent necrosis. Moreover, the long-term use of corticosteroids, commonly prescribed for CLE management, contributes to bone health deterioration, complicating the therapeutic approach. The potential for early detection of osteonecrosis through advanced imaging techniques, such as MRI, is crucial in preventing irreversible bone damage and preserving joint function. Regular screenings for osteonecrosis in high-risk CLE patients, especially those with a history of corticosteroid use or vascular complications, could improve outcomes by enabling timely interventions. There is a need for a more comprehensive understanding of the intersection between CLE, vascular health, and bone integrity, which can guide more effective treatment strategies and monitoring protocols.

These findings underline the necessity of individualized treatment regimens that balance the management of skin manifestations with the preservation of bone health in SLE patients. This research emphasizes the importance of a multidisciplinary approach to managing CLE and osteonecrosis, incorporating dermatological, rheumatologic, and orthopedic care to optimize patient outcomes and prevent long-term complications.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

References

[1] Caramaschi, P., Biasi, D., Dal Forno, I. and Adami, S. (2012) Osteonecrosis in Systemic Lupus Erythematosus: An Early, Frequent, and Not Always Symptomatic Complication. *Autoimmune Diseases*, **2012**, Article ID: 725249. https://doi.org/10.1155/2012/725249

[2] Dinkins, J., Slavinsky, V., Carney, B. and Frey, C. (2024) The Role of JAK Inhibitors in the Treatment of Cutaneous Lupus Erythematosus: A Review. *Journal of Drugs in Dermatology*, **23**, 1100-1107. https://doi.org/10.36849/jdd.8045

[3] Rascu, A., Manger, K., Kraetsch, H., Kalden, J. and Manger, B. (1996) Review: Osteonecrosis in Systemic Lupus Erythematosus, Steroid-Induced or a Lupus-Dependent Manifestation? *Lupus*, **5**, 323-327. https://doi.org/10.1177/096120339600500414

[4] Shah, K.N., Racine, J., Jones, L.C. and Aaron, R.K. (2015) Pathophysiology and Risk Factors for Osteonecrosis. *Current Reviews in Musculoskeletal Medicine*, **8**, 201-209. https://doi.org/10.1007/s12178-015-9277-8

[5] Guo, L.N. and Nambudiri, V.E. (2020) Cutaneous Lupus Erythematosus and Cardiovascular Disease: Current Knowledge and Insights into Pathogenesis. *Clinical Rheumatology*, **40**, 491-499. https://doi.org/10.1007/s10067-020-05257-3

[6] Sayarlioglu, M., Yuzbasioglu, N., Inanc, M., Kamali, S., Cefle, A., Karaman, O., *et al.* (2010) Risk Factors for Avascular Bone Necrosis in Patients with Systemic Lupus Erythematosus. *Rheumatology International*, **32**, 177-182. https://doi.org/10.1007/s00296-010-1597-9

[7] Tse, S.M. and Mok, C.C. (2016) Time Trend and Risk Factors of Avascular Bone Necrosis in Patients with Systemic Lupus Erythematosus. *Lupus*, **26**, 715-722. https://doi.org/10.1177/0961203316676384

[8] Lin, J.H., Dutz, J.P., Sontheimer, R.D. and Werth, V.P. (2007) Pathophysiology of Cutaneous Lupus Erythematosus. *Clinical Reviews in Allergy & Immunology*, **33**, 85-106. https://doi.org/10.1007/s12016-007-0031-x

[9] Merola, J.F., Nyberg, F., Franchimont, N., Barbey, C. and Werth, V.P. (2024) Editorial: Cutaneous Lupus Erythematosus Landscape: Pathophysiology, Unmet Needs, and Related Challenges in Clinical Practice. What Is on the Horizon? *Frontiers in Medicine*, **11**, Article 1373552. https://doi.org/10.3389/fmed.2024.1373552

[10] Miyagawa, F. (2023) Current Knowledge of the Molecular Pathogenesis of Cutaneous Lupus Erythematosus. *Journal of Clinical Medicine*, **12**, Article 987. https://doi.org/10.3390/jcm12030987

[11] Fetter, T., Braegelmann, C., de Vos, L. and Wenzel, J. (2022) Current Concepts on Pathogenic Mechanisms and Histopathology in Cutaneous Lupus Erythematosus. *Frontiers in Medicine*, **9**, Article 915828. https://doi.org/10.3389/fmed.2022.915828

[12] Jones Jr., J.P. (1994) Concepts of Etiology and Early Pathogenesis of Osteonecrosis. *Instructional Course Lectures*, **43**, 499-512. https://pubmed.ncbi.nlm.nih.gov/9097180/

[13] Mont, M.A., Salem, H.S., Piuzzi, N.S., Goodman, S.B. and Jones, L.C. (2020) Nontraumatic Osteonecrosis of the Femoral Head: Where Do We Stand Today? *Journal of Bone and Joint Surgery*, **102**, 1084-1099. https://doi.org/10.2106/jbjs.19.01271

[14] Allen, C.S., Yeung, J.H., Vandermeer, B. and Homik, J. (2016) Bisphosphonates for Steroid-Induced Osteoporosis. *Cochrane Database of Systematic Reviews*, No. 10, CD001347. https://doi.org/10.1002/14651858.cd001347.pub2

[15] Gupta, M. and Gupta, N. (2023) Bisphosphonate Related Jaw Osteonecrosis. StatPearls. https://www.ncbi.nlm.nih.gov/books/NBK534771/

[16] Eppenberger, D., Nilius, H., Anagnostelis, B., Huber, C.A. and Nagler, M. (2022) Current Knowledge on Factor V Leiden Mutation as a Risk Factor for Recurrent Venous Thromboembolism: A Systematic Review and Meta-analysis. *Frontiers in Cardiovascular Medicine*, **9**, Article 883986. https://doi.org/10.3389/fcvm.2022.883986

[17] McKay, L.I. and Cidlowski, J.A. (2003) Physiologic and Pharmacologic Effects of Corticosteroids. In: Kufe, D.W., Pollock, R.E., Weichselbaum, R.R., *et al.*, Eds., *Holland-Frei Cancer Medicine* (6*th Edition*), BC Decker. https://www.ncbi.nlm.nih.gov/books/NBK13780/

[18] Physiopedia (2022) Avascular Necrosis. https://www.physio-pedia.com/index.php?title=Avascular_Necrosis&oldid=323275

[19] Moya-Angeler, J. (2015) Current Concepts on Osteonecrosis of the Femoral Head. *World Journal of Orthopedics*, **6**, 590-601. https://doi.org/10.5312/wjo.v6.i8.590

[20] National Institute of Arthritis and Musculoskeletal and Skin Diseases (2023) Osteonecrosis (Avascular Necrosis) Symptoms & Causes. https://www.niams.nih.gov/health-topics/osteonecrosis

[21] Zalavras, C.G. and Lieberman, J.R. (2014) Osteonecrosis of the Femoral Head: Evaluation and Treatment. *Journal of the American Academy of Orthopaedic Surgeons*, **22**, 455-464. https://doi.org/10.5435/jaaos-22-07-455

[22] Karim, A.R., Cherian, J.J., Jauregui, J.J., Pierce, T. and Mont, M.A. (2015) Osteonecrosis of the Knee: Review. *Annals of Translational Medicine*, **3**, Article 6. https://doi.org/10.3978/j.issn.2305-5839.2014.11.13

[23] Hernigou, P., Hernigou, J. and Scarlat, M. (2020) Shoulder Osteonecrosis: Pathogenesis, Causes, Clinical Evaluation, Imaging, and Classification. *Orthopaedic Surgery*, **12**, 1340-1349. https://doi.org/10.1111/os.12788

[24] Rella, V., Rotondo, C., Altomare, A., Cantatore, F.P. and Corrado, A. (2022) Bone Involvement in Systemic Lupus Erythematosus. *International Journal of Molecular Sciences*, **23**, Article 5804. https://doi.org/10.3390/ijms23105804

[25] Salmon, J. and de Groot, P. (2008) Pathogenic Role of Antiphospholipid Antibodies. *Lupus*, **17**, 405-411. https://doi.org/10.1177/0961203308090025

[26] McCarthy, I. (2006) The Physiology of Bone Blood Flow: A Review. *Journal of Bone and Joint Surgery*, **88**, 4-9. https://doi.org/10.2106/jbjs.f.00890

[27] Leone, P., Prete, M., Malerba, E., Bray, A., Susca, N., Ingravallo, G., *et al.* (2021) Lupus Vasculitis: An Overview. *Biomedicines*, **9**, Article 1626. https://doi.org/10.3390/biomedicines9111626

[28] Téllez Arévalo, A.M., Quaye, A., Rojas-Rodríguez, L.C., Poole, B.D., Baracaldo-Santamaría, D. and Tellez Freitas, C.M. (2022) Synthetic Pharmacotherapy for Systemic Lupus Erythematosus: Potential Mechanisms of Action, Efficacy, and Safety. *Medicina*,

59, Article 56. https://doi.org/10.3390/medicina59010056

[29] Verdelli, A., Corrà, A., Mariotti, E.B., Aimo, C., Ruffo di Calabria, V., Volpi, W., *et al.* (2022) An Update on the Management of Refractory Cutaneous Lupus Erythematosus. *Frontiers in Medicine*, **9**, Article 941003. https://doi.org/10.3389/fmed.2022.941003

[30] Nevskaya, T., Gamble, M.P. and Pope, J.E. (2017) A Meta-Analysis of Avascular Necrosis in Systemic Lupus Erythematosus: Prevalence and Risk Factors. *Clinical and Experimental Rheumatology*, **35**, 700-710. https://pubmed.ncbi.nlm.nih.gov/28240590/

[31] Jessop, S., Whitelaw, D.A., Grainge, M.J. and Jayasekera, P. (2017) Drugs for Discoid Lupus Erythematosus. *Cochrane Database of Systematic Reviews*, No. 5, CD002954. https://doi.org/10.1002/14651858.cd002954.pub3

[32] Egeberg, A., Schwarz, P., Harsløf, T., Andersen, Y.M.F., Pottegård, A., Hallas, J., *et al.* (2021) Association of Potent and Very Potent Topical Corticosteroids and the Risk of Osteoporosis and Major Osteoporotic Fractures. *JAMA Dermatology*, **157**, 275-282. https://doi.org/10.1001/jamadermatol.2020.4968

[33] Okon, L.G. and Werth, V.P. (2013) Cutaneous Lupus Erythematosus: Diagnosis and Treatment. *Best Practice & Research Clinical Rheumatology*, **27**, 391-404. https://doi.org/10.1016/j.berh.2013.07.008

[34] Roenigk, H.H., Martin, J.S., Eichorn, P. and Gilliam, J.N. (1980) Discoid Lupus Erythematosus. Diagnostic Features and Evaluation of Topical Corticosteroid Therapy. *Cutis*, **25**, 281-285. https://pubmed.ncbi.nlm.nih.gov/6987043/

[35] Yokogawa, N., Eto, H., Tanikawa, A., Ikeda, T., Yamamoto, K., Takahashi, T., *et al.* (2017) Effects of Hydroxychloroquine in Patients with Cutaneous Lupus Erythematosus: A Multicenter, Double-Blind, Randomized, Parallel-Group Trial. *Arthritis & Rheumatology*, **69**, 791-799. https://doi.org/10.1002/art.40018

[36] Tsakonas, E., Joseph, L., Esdaile, J.M., Choquette, D., Senécal, J., Cividino, A., *et al.* (1998) A Long-Term Study of Hydroxychloroquine Withdrawal on Exacerbations in Systemic Lupus Erythematosus. *Lupus*, **7**, 80-85. https://doi.org/10.1191/096120398678919778

[37] Chasset, F., Arnaud, L., Costedoat-Chalumeau, N., Zahr, N., Bessis, D. and Francès, C. (2016) The Effect of Increasing the Dose of Hydroxychloroquine (HCQ) in Patients with Refractory Cutaneous Lupus Erythematosus (CLE): An Open-Label Prospective Pilot Study. *Journal of the American Academy of Dermatology*, **74**, 693-699.e3. https://doi.org/10.1016/j.jaad.2015.09.064

[38] Islam, M.N., Hossain, M., Haq, S.A., Alam, M.N., Ten Klooster, P.M. and Rasker, J.J. (2011) Efficacy and Safety of Methotrexate in Articular and Cutaneous Manifestations of Systemic Lupus Erythematosus. *International Journal of Rheumatic Diseases*, **15**, 62-68. https://doi.org/10.1111/j.1756-185x.2011.01665.x

[39] Keyes, E., Jobanputra, A., Feng, R., Grinnell, M., Vazquez, T., Diaz, D., *et al.* (2022) Comparative Responsiveness of Cutaneous Lupus Erythematosus Patients to Methotrexate and Mycophenolate Mofetil: A Cohort Study. *Journal of the American Academy of Dermatology*, **87**, 447-448. https://doi.org/10.1016/j.jaad.2021.09.017

[40] Callen, J.P. (1991) Azathioprine: An Effective, Corticosteroid-Sparing Therapy for Patients with Recalcitrant Cutaneous Lupus Erythematosus or With Recalcitrant Cutaneous Leukocytoclastic Vasculitis. *Archives of Dermatology*, **127**, 515-522. https://doi.org/10.1001/archderm.1991.04510010083008

[41] Saavedra, M.Á., Sánchez, A., Morales, S., Ángeles, U. and Jara, L.J. (2015) Azathioprine during Pregnancy in Systemic Lupus Erythematosus Patients Is Not Associated with

Poor Fetal Outcome. *Clinical Rheumatology*, **34**, 1211-1216. https://doi.org/10.1007/s10067-015-2987-x

[42] Gladman, D.D., Dhillon, N., Su, J. and Urowitz, M.B. (2017) Osteonecrosis in SLE: Prevalence, Patterns, Outcomes and Predictors. *Lupus*, **27**, 76-81. https://doi.org/10.1177/0961203317711012

[43] Cui, Q., Jo, W., Koo, K., Cheng, E.Y., Drescher, W., Goodman, S.B., *et al.* (2021) ARCO Consensus on the Pathogenesis of Non-Traumatic Osteonecrosis of the Femoral Head. *Journal of Korean Medical Science*, **36**, e65. https://doi.org/10.3346/jkms.2021.36.e65

[44] Shigemura, T., Nakamura, J., Kishida, S., Harada, Y., Ohtori, S., Kamikawa, K., *et al.* (2011) Incidence of Osteonecrosis Associated with Corticosteroid Therapy among Different Underlying Diseases: Prospective MRI Study. *Rheumatology*, **50**, 2023-2028. https://doi.org/10.1093/rheumatology/ker277

[45] Nawata, K., Nakamura, J., Ikeda, K., Furuta, S., Nakajima, H., Ohtori, S., *et al.* (2018) Transitional Changes in the Incidence of Osteonecrosis in Systemic Lupus Erythematosus Patients: Focus on Immunosuppressant Agents and Glucocorticoids. *Rheumatology*, **57**, 844-849. https://doi.org/10.1093/rheumatology/key009

[46] Hussein, S., Suitner, M., Béland-Bonenfant, S., Baril-Dionne, A., Vandermeer, B., Santesso, N., *et al.* (2018) Monitoring of Osteonecrosis in Systemic Lupus Erythematosus: A Systematic Review and Metaanalysis. *The Journal of Rheumatology*, **45**, 1462-1476. https://doi.org/10.3899/jrheum.170837

[47] Wei, Q., Zhou, M., Liu, J., Zhang, S., Gao, F., Lin, H., *et al.* (2021) Relationship between Osteonecrosis and Antiphospholipid Antibodies in Patients with Systemic Lupus Erythematosus: A Systematic Review Protocol. *BMJ Open*, **11**, e046163. https://doi.org/10.1136/bmjopen-2020-046163

[48] McMahan, Z.H. and Wigley, F.M. (2010) Raynaud's Phenomenon and Digital Ischemia: A Practical Approach to Risk Stratification, Diagnosis and Management. *International Journal of Clinical Rheumatology*, **5**, 355-370. https://doi.org/10.2217/ijr.10.17

[49] Sheikh, J.S., Retzinger, G.S. and Hess, E.V. (1998) Association of Osteonecrosis in Systemic Lupus Erythematosus with Abnormalities of Fibrinolysis. *Lupus*, **7**, 42-48. https://doi.org/10.1191/096120398678919732

[50] Fijałkowska, A., Kądziela, M. and Żebrowska, A. (2024) The Spectrum of Cutaneous Manifestations in Lupus Erythematosus: A Comprehensive Review. *Journal of Clinical Medicine*, **13**, Article 2419. https://doi.org/10.3390/jcm13082419

[51] Oinuma, K., Harada, Y., Nawata, Y., Takabayashi, K., Abe, I., Kamikawa, K., *et al.* (2001) Osteonecrosis in Patients with Systemic Lupus Erythematosus Develops Very Early after Starting High Dose Corticosteroid Treatment. *Annals of the Rheumatic Diseases*, **60**, 1145-1148. https://doi.org/10.1136/ard.60.12.1145

[52] Nakamura, J., Ohtori, S., Sakamoto, M., Chuma, A., Abe, I. and Shimizu, K. (2010) Development of New Osteonecrosis in Systemic Lupus Erythematosus Patients in Association with Long-Term Corticosteroid Therapy after Disease Recurrence. *Clinical and Experimental Rheumatology*, **28**, 13-18. https://pubmed.ncbi.nlm.nih.gov/20346232/

[53] Kaneko, K., Chen, H., Kaufman, M., Sverdlov, I., Stein, E.M. and Park-Min, K. (2021) Glucocorticoid-Induced Osteonecrosis in Systemic Lupus Erythematosus Patients. *Clinical and Translational Medicine*, **11**, e526. https://doi.org/10.1002/ctm2.526

[54] Li, D., Shamrock, A.G., Young, J.R., *et al.* (2024) Spontaneous Osteonecrosis of the Knee. StatPearls. https://www.ncbi.nlm.nih.gov/sites/books/NBK547722/

[55] Ostendorf, B., Scherer, A., Specker, C., Mödder, U. and Schneider, M. (2003) Jaccoud's Arthropathy in Systemic Lupus Erythematosus: Differentiation of Deforming and Erosive Patterns by Magnetic Resonance Imaging. *Arthritis & Rheumatism*, **48**, 157-165. https://doi.org/10.1002/art.10753