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PAPER

'Focus on feet' – the effects of systemic lupus erythematosus: a narrative review of the literature

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Background: The manifestations of systemic lupus erythematosus (SLE) vary between individuals, from the severe and life-threatening renal and central nervous system involvement, to the involvement of skin, musculoskeletal and vascular system, and the complications of infection influencing the quality of life. However, as specific manifestations affecting the lower limb are perceived as receiving little focus, the purpose of this narrative literature review is to identify the specific factors associated with SLE that may have implications for lower limb and foot morbidity. **Method:** A structured search of databases was conducted. The inclusion was restricted to publications in the English language, those that specifically investigate the feet as affected with SLE. No restriction on year of publication was imposed to reduce publication bias and to capture as many publication in relation to feet. **Results:** Eleven papers fulfilled the inclusion criteria. There were seven additional papers that made observations related to the articular or vascular complications of the feet. This narrative review provides some information on how SLE affects the lower limb and foot in relation to the musculoskeletal and vascular systems. However, there is a lack of literature that specifically focuses on all the manifestations of SLE and the complications associated with its management. **Discussion:** There are indications that SLE affects lower limb and foot morbidity but the scale of these problems is unclear and this is partly because of the absence of research and the lack of a 'gold standard' framework for the assessment of the lower limb and foot. In addition to clinical foot health assessment, ultrasonography may be a useful alternative to plain film radiography or magnetic resonance imaging (MRI) in capturing the extent of articular and extra-articular manifestations. Further, the Ankle Brachial Pressure Index (ABPI) may be useful in identifying those with atherosclerosis and ischaemia. **Conclusion:** There are indications that SLE affects lower limb and foot morbidity but the scale of these problems and effective management of them is unclear. Therefore, further research is warranted in order to better understand the impact of SLE on the foot and lower limb and its impact on quality of life. *Lupus* (2013) **0,** 1–7.

Key words: Musculoskeletal; systemic lupus erythematosus; atherosclerosis; ischaemia; feet

Introduction

Systemic lupus erythematosus (SLE) is a complex, chronic multi-system autoimmune disease which varies in prevalence and incidence depending on ethnicity.[1,2] In the United Kingdom (UK), it is more common in Afro-Caribbean, Chinese and Asian populations compared with Whites.[2] The disease varies in manifestations and severity between individuals, with potentially life-threatening effects on the renal or central nervous system. Disfigurement caused by the involvement of skin and joints[3] can affect the patient's perception of body image and sexuality,[4] and can have an impact on emotional health[5] and overall quality of life.[6]

The severity of SLE is assessed by measuring the activity of the disease, the amount of damage to the organs as a result of the disease or treatment, and the impact of the disease and/or treatment on the

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quality of life.[5] In relation to health-related quality of life, McElhone et al.[6] highlighted that the unpredictable nature of SLE impacted on life as much as the physical problems. Although several drugs can modify the disease sufficiently for the patient's symptoms to be tolerable or vital organs to be protected from permanent damage, none are curative. Treatment of severe disease involves the use of potent, and potentially toxic, immunosuppressive regimens with side effects being common and as problematic as the disease itself.[5] Further, the use of the immunosuppressive drugs increases an individual's susceptibility to systemic infections, which have the potential to be life threatening.[7]

Involvement of the musculoskeletal system is common during the clinical course of SLE in up to 95% of patients, with joint pain being the first presenting symptom in up to 50% of cases.[8] Richter Cohen et al.[9] suggested that the symptoms of joint stiffness and pain are similar to those reported by patients with rheumatoid arthritis (RA), but that the typical features associated with RA, such as bony erosions and fixed deformities, are not typical of SLE. However, Pipili et al.[10] identified that there are variations in the presenting features of SLE and described these as either an erosive symmetrical polyarthritis (called rhupus) with deformities similar to RA, or a mild deforming arthropathy, or a non-erosive arthropathy. The non-erosive arthropathy is the most frequent form and is characterized by ulnar deviation of the second to fifth fingers and subluxation of the metacarpo-phalangeal joints, which are voluntarily correctable by the patients (called Jaccoud's arthropathy).

The extra-articular manifestations of SLE include soft tissue pathology such as capsular swelling, synovial hypertrophy and tenosynovitis,[11] which can lead to tendon rupture[12] and tendon contractures.[13] Tendons are the force-transmitting units of the musculoskeletal system, but because of their low metabolic rate and slow healing, injury can result in considerable morbidity and prolonged disability. In relation to the symptoms associated with muscle involvement, it can range in severity from mild aches in up to 80% of cases to inflammatory myositis in up to 11% of cases.[8] Further, fibromyalgia can be associated with SLE, and whilst fatigue in SLE does not correlate with disease activity, fibromyalgia is a contributor to a lower quality of life.[14]

An additional factor that has the potential to contribute to a lower quality of life is vascular involvement, either as a direct complication of the disease or developing as an accompanying comorbidity, and represents the most frequent cause of death.[15] Mathieu et al.[16] identified that abnormal vascular reactivity and coagulopathy both contribute to an increased risk of atheroma and therefore careful monitoring of any vascular changes is recommended. Early vascular alterations are pronounced in SLE, which is in line with the higher cardiovascular risk of these patients when compared to those with RA.[17]

SLE affects both the musculoskeletal and vascular system and this may include direct effects on lower limb and foot morbidity. However, the specific manifestations of SLE affecting the lower limb were perceived by the authors as receiving little focus both in the research and clinical contexts. Therefore, the purpose of this narrative literature review is to identify the specific factors associated with SLE that may have implications for lower limb and foot morbidity.

Method

A structured search of PubMed, Embase, CINAHL, Science Direct and the Cochrane Collaboration Library was conducted 2 September 2013 using the search terms: 'systemic lupus erythematosus' and 'feet,' and/or 'lower limb', and/or 'joints', and/or 'musculoskeletal' and/or 'complications' and/or 'vascular' and/or infection. The inclusion was restricted to publications in the English language, those that specifically investigate the feet as affected with SLE. The reference lists of journal articles of interest were also searched. No restriction on year of publication was imposed to reduce publication bias and to capture as many publications as possible in relation to feet.

Results

From 20 papers which were found in the first search (Figure 1), there were 11 papers that fulfilled the inclusion criteria, including two single case studies and a review of the literature.[18–25] The papers selected described some of the various manifestations of SLE affecting the foot and lower leg, specifically, the musculoskeletal and vascular complications. There were seven additional papers[16,26–31] that made observations related to the articular or vascular complications of the feet.

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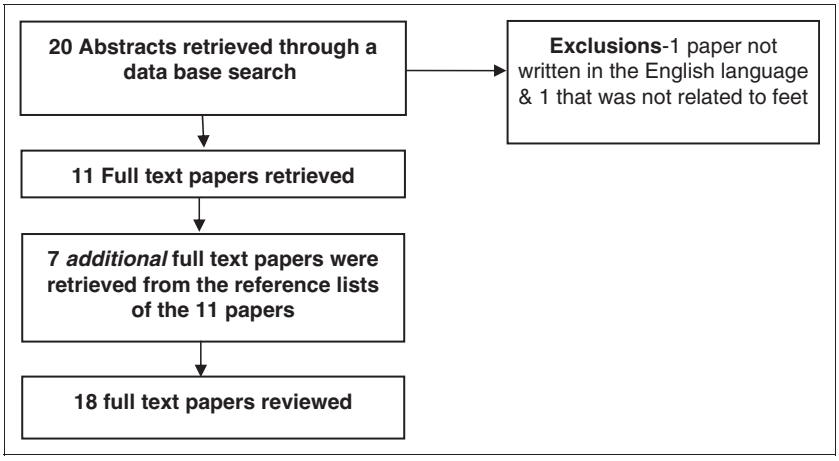

Figure 1 Literature search resulted in 20 papers.

Musculoskeletal complications

In relation to feet, there is some evidence that demonstrates the various manifestations of SLE in the feet. In a study by van Vugt et al.,[18] eight out of 176 patients presented with multiple non-erosive subluxations in the feet as assessed on plain film radiographs. They described the clinical presentation of joint involvement as varying, ranging from arthralgia without erosions or deformity to an erosive arthropathy and severe functional disability. 'Lupus arthritis' is described as having the potential to affect all joints.[19] Similarly, tendonitis, tenosynovitis and tendon rupture may occur and any could potentially be affected. Alves et al.[20] identified the patellar and Achilles tendons as being affected in the lower limb. In addition, if peroneous longus and tibialis posterior are affected, this could have a considerable effect on foot posture, function and gait as peroneus longus and brevis are likely to have a role in maintaining the transverse foot arch.[21] These problems, aligned with an adaptive compensation for joint pain and restriction, could affect function and mobility.

In a study investigating arthropathy of both the hands and feet,[22] feet were identified in 66.7% of the 51 patients as having at least one abnormality such as hallux valgus, and 8% had Jaccoud's-type arthropathy affecting the feet. The severity of these abnormalities was related to disease duration. An earlier study of 14 patients with SLE[23] and Jaccoud's deformity of the hands found that 13 (82.8%) had passively correctable hallux valgus, subluxation of the metatarso-phalangeal joints and widening of the forefoot. However, in those age-matched patients without Jaccoud's, only four of 16 (25%) showed similar deformities. This was a small study, but the authors observed that if there are visible structural changes in the hands, then the feet are likely to be affected. Jaccoud's arthropathy of the feet has been shown in a single case study to have implications for digital ulceration caused by pressure from the deviated toe on the next one.[24] The patient was on corticosteroid therapy which may have contributed to poor tissue viability that could not withstand the increased pressures. The problem was solved by amputating the fifth toes.

There is a link between arthropathy and tendon rupture although this is considered a rare and mostly spontaneous occurrence. Alves et al.,[20] in their review of the literature (mostly case studies), found that most frequently observed tendon rupture sites were in the lower limb, particularly the patellar and Achilles tendons. While almost all patients described were on various doses of corticosteroids, 29% concomitantly had Jaccoud's arthropathy. They concluded that the association between Jaccoud's arthropathy and tendon rupture has been underestimated and that this arthropathy may be recognized as a risk marker for tendon rupture. Further, trauma, overuse, tenosynovitis and corticosteroid therapy are considered as possible causes.[25,26]

In relation to the risk of infection, Piga et al.[27] found an association between systemic infection and bursitis of the retro-calcaneal bursitis and abscess which in turn caused Achilles tendon tearing. This highlights that infection, as a cause of 25% of all deaths in SLE, may manifest in the feet and need prompt attention.

Avascular necrosis (AVN) is associated with corticosteroid use, cytotoxic medication, vasculitis and peripheral neuropathy, causing joint pain and

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disability, typically in larger joints such as the hip and knee.[28] AVN has also been identified as affecting the bones of the foot.[19] The talus, tarsonavicular and metatarsal joints are suggested as being the most likely to be affected, with typical symptoms of pain on motion of the joint and effusion that is not warm, rest pain and limping during gait.[19] A recent case study identified the navicular and medical cuneiform as being affected[29] and treated with bilateral navicular and first cuneiform arthrodesis. In a study of osteonecrosis of the talus,[30] 13 patients out of the 24 in the study were identified as having SLE. The authors recommend the use of ankle foot orthoses as well as analgesics and that early detection may improve the non-surgical treatment outcomes and prognoses. However, early detection may be difficult as there is the possibility that patients may be asymptomatic as in one study,[31] 27% of patients on 40 mg a day or more of corticosteroids had AVN of the hip but no symptoms.

Vascular complications

Peripheral vascular occlusion, leading to amputation of the digits, is a severe complication in those patients with antiphospholipid syndrome.[32] Asherson et al.[32] also noted that digital ischaemia is preceded by Raynaud's phenomenon and/or livedo reticularis. In relation to lower limb vascular complications, Lui et al.[33] assessed the clinical characteristics, risk factors and outcome of patients with SLE complicated with digital gangrene in 2684 consecutive inpatients. Long disease duration, Raynaud's phenomenon and elevated serum C-reactive protein (CRP) were described in this study as independent predictive factors for people with SLE to develop digital gangrene. They also recommended early intervention with aggressive corticosteroid treatment to prevented gangrene from progressing. In a retrospective study of 485 patients[34] seven of the 485 patients (1.4%) had evidence of gangrene or critical peripheral ischaemia, with the onset being at any stage of the SLE disease, from it being an initial presenting feature to 27 years after SLE onset. Five out of the seven patients in this study suffered digit loss with autoamputation.

In relation to vasculitis, Gomes et al.[35] found that 27 out of 168 participants with SLE presented with digital vasculitis and associated mucocutaneous manifestations, haematological abnormalities and constitutional symptoms. Further, Olivieri et al.[36] describe a single case of digital gangrene associated with vasculitis and recommend early intervention with immunosuppressive drugs and hyperbaric oxygen for successful resolution of this problem.

Mathieu et al.[16] identified that abnormal vascular reactivity and coagulopathy contributes to an increased risk of atheroma, and Tso et al.[37] indicated a link between vascular stiffness, as measured by the brachial-ankle pulse wave velocity, and cardiovascular risk factors. As accelerated atheroma is a recognized complication, it is recommended[38] that early detection of accelerated atheroma using the Ankle Brachial Pressure Index (ABPI) is crucial.

Discussion

It is clear from this narrative review of the literature that there is little research into the effects of SLE on the foot and lower limb and none into the impact of these on function, mobility or quality of life. This may explain why there is a lack of focus on foot assessment in the clinical consultation and a lack of specialist foot care pervades. However, it may be that foot problems are uncommon and do not impact on an individual's ability to function. Despite this, it is clear from this narrative review that lower limb- and foot-related problems do exist in relation to the musculoskeletal system, the vascular system, the reduced resistance to infections and the effects of the medical management of SLE on tissue viability. Further, these can have severe consequences in relation to the symptoms associated with these problems and the consequences of negative outcomes.

The studies included in this narrative review provide some information that is useful to consider in clinical practice and certainly for future research. In relation to the effects of SLE on the musculoskeletal system, the foot can be affected with extensive tenosynovitis, synovial membrane hypertrophy and erosions.[19,22,23] In relation to vascular changes the prognosis can be poor in relation to lower limb morbidity, with the risk of gangrene and autoamputation of digits. Despite a recommendation in the Arthritis and Musculoskeletal Alliance (ARMA) guidelines[39] that a red flag for urgent referral for medical opinion is the presentation of painful, cold, blue or black fingers and/or toes, there is no focus on the early assessment, monitoring and prevention of vascular problems.

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In relation to *all* the potential problems that may impact on lower limb morbidity and quality of life in this group of patients, the literature is lacking. Focus is clearly needed on the impact of the known musculoskeletal problems on the lower limb and how these may affect gait and function. Further, it is not known how pre-existing abnormal gait and function, such as inherent biomechanical variations, may also cause and/or exacerbate the manifestations of SLE within the feet. Additionally, although the implications of vascular changes and infection are known, the lack of an assessment protocol in the context of assessing people with this complex multi-morbid pathology may mean that the opportunity for early identification and management is missed. There are no studies that investigate the potential impact of early diagnosis of both the vascular and musculoskeletal problems.

Whilst plain film radiography is a recognized standard technique to aid early diagnosis and identification of underlying pathology, it is not without its limitations. It may identify erosive symmetrical polyarthritis or subluxation of the joints, but it does not capture the extra-articular manifestations such as tenosynovitis. Further, it uses ionizing radiation and so repeated assessment is limited. Magnetic resonance imaging (MRI) is considered the gold standard imaging technique to quantify soft tissues in the foot,[40] and therefore has become more widely used in assessing both bony involvement and soft tissue changes.[8,11] However, with competing demands on MRI as a resource, access is often limited, and it is not readily available in the community setting where patients with foot and ankle conditions are more likely to be monitored. Musculoskeletal ultrasound on the other hand is more readily available, portable and has been shown to be highly reliable in assessment of intrinsic muscles in the foot.[41] Ultrasound has also been used successfully in assessments of isolated structures in the diabetic foot.[42–44] Whilst the role of ultrasound in the evaluation of the effects of RA on the foot has not been extensively reported, two recent studies[45,46] have used ultrasound to identify subtle changes in the articular and extra-articular structures of the foot. In SLE it has been used to evaluate hand arthritis,[47] with a small study[23] indicating that if there are visible structural changes in the hands then the feet are likely to be affected. Early detection of AVN[30] is important in both the prognosis and successful non-surgical treatment and hence ultrasonography could be a useful modality to enable earlier identification of pathological changes and enhance clinical diagnoses.

In relation to vascular problems, it has been identified by Sangle et al.[48] that in those with systemic vasculitides, there is an increased prevalence of an abnormal ABPI. Therefore, ABPI may be clinically useful in identifying those with SLE and the risk of accelerated atherosclerosis. In those with RA, ABPI measurement is considered useful to identify patients requiring close monitoring and/or prophylactic medications.[49]

Once a diagnosis has been made, it is clear, even from the small number of studies in this narrative review, that early detection of foot problems in those with SLE is crucial in order to monitor any deterioration and to instigate timely and targeted interventions. To achieve this, a framework for assessing the lower limb and foot needs to be developed. The focus of this assessment should be the musculoskeletal system (with musculoskeletal ultrasound as the imaging mode) and the vascular system (with ABPI).

Conclusion

From this narrative review there are indications that SLE affects lower limb and foot morbidity, and these have the potential to affect the quality of life in those individuals affected. However, the scale of these problems is unclear and this is partly because of the absence of research that focuses on lower limb and foot health. Indeed, there has been no study to define the 'gold standard' assessment of the lower limb and foot. This is considered by the authors to be a matter of priority in relation to being able to identify foot problems early so that appropriate interventions can be provided in a 'window of opportunity' which may be similar to those affected with RA.[50] There clearly needs to be more focus on feet, both in the clinical environment and in the context of the research world.

Key recommendations

- There is a need for the development of an assessment framework for evaluating the impact of SLE on the lower limb and foot. This could then be used in both clinical and research contexts.
- Research is needed in order to characterize lower limb and foot problems and their impact on the person with SLE.
- The impact of assessment of foot problems and resultant foot health interventions need to be evaluated both in the clinical and research contexts.

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Conflict of interest

The authors declare that there is no conflict of interest.

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