Systemic lupus erythematosus in Southern Africa: current status and challenges

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Abstract

Objective: To review the pathophysiology, clinical features and treatment of Systemic Lupus Erythematosus (SLE) and current status of lupus in Southern Africa.
Data source: A broad search was performed using PubMed/MEDLINE, Prime/PubMed, Wiley online library, African Journal Online (AJOL) and Google.
Study design: Evidence-based clinical review of the literature.
Data extraction: Both full text and abstract were reviewed and information was collected and compared with other studies from the region. Data extraction was aimed mostly to find demographic variation, population groups, clinical pattern, treatment and outcome of lupus.
Data synthesis: Our search result included studies and review articles published online on SLE pathophysiology, clinical feature and treatment. We also performed a detailed analysis of three retrospective studies, two prospective studies and three case reports from Southern Africa to identify the number of reported cases, clinical patterns and outcome.
Conclusions: Systemic lupus erythematous remains a rare disease in Southern Africa. There are diagnostic and therapeutic challenges in the treatment of SLE in a developing country. Due to improved health care, it is commonly believed that SLE is increasing in southern Africa but our review shows it is still infrequently reported disease in southern Africa.

Key words: Systemic lupus erythematosus, Southern Africa, Lupus nephritis, Challenges, Botswana

Introduction

Systemic Lupus Erythematosus (SLE) is a systemic autoimmune disease. Worldwide there is a wide variation of reported incidence and prevalence of the disease and there are also racial and geographical differences in the prevalence[1]. The incidence of SLE in North America is 23.2/100,000 whereas in Africa it is as low as 0.3/100,000 person-years[2]. SLE is predominantly observed in females of childbearing age[3].

The disease seems to be more frequent among African-Americans, and African ancestry is a predictor of lupus nephritis and of poor outcome[4]. Gender differences exist in all races and indeed African-American men are less commonly affected than females[5]. Unlike in African-Americans, SLE seems to be infrequently observed in Africans living in the continent. However, the low number of rheumatologists and the limited diagnostic facilities may contribute to the low number of cases reported. In an attempt to contribute to a clarification of the above issue, we have reviewed SLE cases reported from southern Africa.

Pathophysiology

The pathogenesis of systemic lupus erythematosus is incompletely understood. Genetic, infective, environmental factors and certain drugs are recognized as possible contributory factors. SLE is thought to be a multi-genic rather than monogenic disease[6]. Environmental factors such as smoking and exposure to ultraviolet light also favour the development of SLE in genetically susceptible individuals. Epstein-Barr virus infection may also play a role in the pathogenesis of the disease[7].

The preponderance of SLE among females has long been related to estrogen levels, and patients who have early menarche or are on estrogen-containing oral contraceptives seem to develop SLE more frequently[8].

Increased autoantibody production by B-lymphocytes is the main feature of SLE. Autoantibodies against nuclear antigens and immune complex deposition in tissues are important features of the

disease. The deposition of immune complexes in renal tissue, in particular, can lead to end-stage renal disease and lethal outcome

The SLE course is characterized by remissions and flares. Fatigue, malaise, and fever are common nonspecific constitutional symptoms to which specific cutaneous, musculoskeletal, lung, cardiac, or other target organ symptoms may be associated.

Skin manifestations in SLE can be variable. There are four cutaneous criteria used for SLE diagnosis- acute cutaneous (malar rash, photosensitivity), chronic cutaneous (discoid), non-scarring alopecia, oral ulcer or nasal ulcer[9]. Patients presents with the fixed erythematous rash in the malar area (check and nasal bridge), they usually spare the nasolabial fold. The second important cutaneous presentation is photosensitivity rash in the skin. These rashes are seen on exposure to ultraviolet light in face, hand, and arm.

Discoid rash is the characteristic of chronic lupus which can be present with or without systemic organ involvement. The discoid lesion is a disc-shaped plaque and mostly seen in head and neck area. All discoid lesions do not develop SLE. Only 5% of discoid lesion develop features of systemic lupus erythematosus[10]. SLE is associated with non- scarring alopecia, it causes patchy hair loss mostly in the temporal region. SLE associated Raynaud's phenomena is colour changes in skin, mostly at the digital tip. It is due to local vascular response on exposure to cold, emotional stress[10]. Other manifestations are cutaneous vasculitis, bullous lesion, pyoderma gangrenosum, nail fold infarct, and telangiectasia[11]. A photosensitive rash is treated by avoiding sun exposure, Ultraviolet (UV) protective sunscreen and topical steroids are beneficial for treating SLE associated rash[12]. Systemic treatment with chloroquine or hydroxychloroquine is useful in the chronic lupus-like discoid lesion[12]. However, long term use of antimalarial causes retinal toxicity. A patient should discontinue chloroquine if diagnosed with retinal toxicity. Although, hydroxychloroquine has less toxicity profile its doses should not exceed 6.5 mg/kg/day and patients should monitor visual acuity yearly[13].

Musculoskeletal system involvement is frequently seen in SLE and incidence ranges from 69-95%[14]. Systemic lupus erythematosus is associated with articular involvement mostly arthralgia and non-deforming arthritis. Jaccoud's is a type of arthritis in SLE with deformities that are mostly due to subluxation of joints. Joccaud's arthropathy patients are reversible with treatment of lupus and physiotherapy but in some chronic cases, they develop long-lasting deformity[15]. Less frequently SLE is also associated with erosive arthritis such as Rheumatoid arthritis (also called RHUPUS)[16].

Osteoporosis, osteonecrosis of the femoral head are other joint abnormality associated with SLE[17]. Glucocorticoid treatment also contributes to the joint abnormality in SLE. Muscle pain and muscle weakness occur in some patients in SLE. Lupus myositis is usually not severe and responds well to treatment. Corticosteroid treatment for a long time leads to iatrogenic muscle weakness[18].

Pulmonary manifestation is frequent in SLE. Most common pulmonary involvement is the involvement of pleura[19] and it causes pleuritic and pleural effusion. Around 15%-60% of individuals with SLE develops pleural effusion during the course of the disease[20]. SLE also leads to other pulmonary complications like pneumonitis, interstitial lung disease, and pulmonary hypertension.

The estimated prevalence of neurological manifestation in lupus among adults ranges from 14% to 80%[21]. SLE presents with a wide range of neuropsychiatric manifestation. It includes a headache, seizure, stroke, psychosis, movement disorder, cranial nerve abnormality and transverse myelitis[22]. Treatment of symptoms is indicated in every patient. To control SLE activity, corticosteroid treatment is used in a patient with neurological complication. Immunosuppressant like cyclophosphamide is used in unresponsive cases[21]. Medication used for treatment such as corticosteroid also causes altered mood and muscle weakness as its side effect. Neuro-imaging is beneficial in SLE patients particularly in a patient with focal neurological deficit and neuropsychiatric manifestation.

Most common gastrointestinal manifestation in SLE is oral mucosal ulceration seen in 7-52% of patients[23]. Other gastrointestinal manifestations are greatly overlooked in SLE. It is important to look for an oesophageal ulcer, peptic ulceration and intestinal vasculitis in a patient with abdominal pain. SLE is also associated with inflammatory bowel disease like ulcerative colitis. These patients usually presents with the symptom of persistent diarrhoea.

Most common cardiac manifestation in SLE occurs from pericardial involvement, mostly acute fibrinous pericarditis and pericardial effusion[24]. Endocardium and myocardium are also affected by SLE. Non-bacterial verrucous vegetation (Also known as Libmansack endocarditis) occurs in SLE. The prevalence of endocarditis is 13%-74% in autopsy studies[25]. Myocarditis is also commonly found in autopsied SLE patients. Occasionally SLE patients are associated with conduction abnormality and valvular dysfunction.

Lupus nephritis is seen in 40% of patients with systemic lupus erythematosus[26]. The clinical symptom in renal involvement varies from asymptomatic proteinuria, nephrotic syndrome and hypertension to severe end-stage renal impairment. Screening of patients for renal involvement is important in SLE.

Figure 1: SLE patient with an erythematous rash in the face

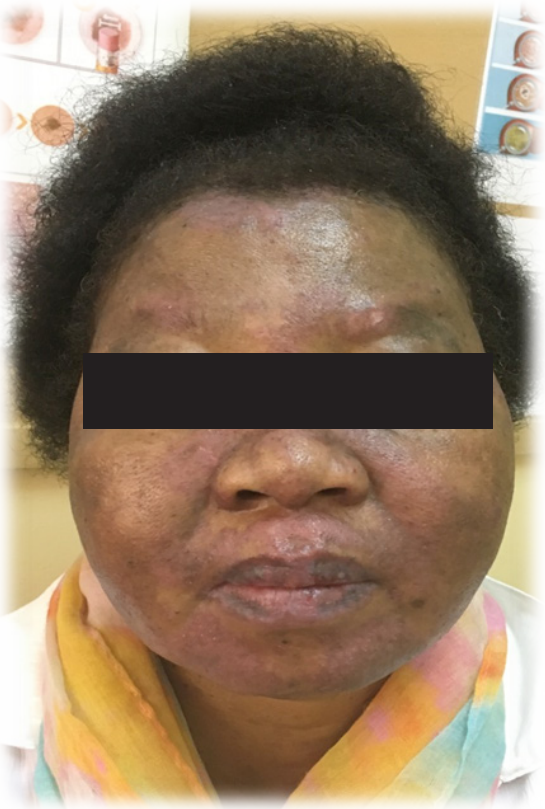
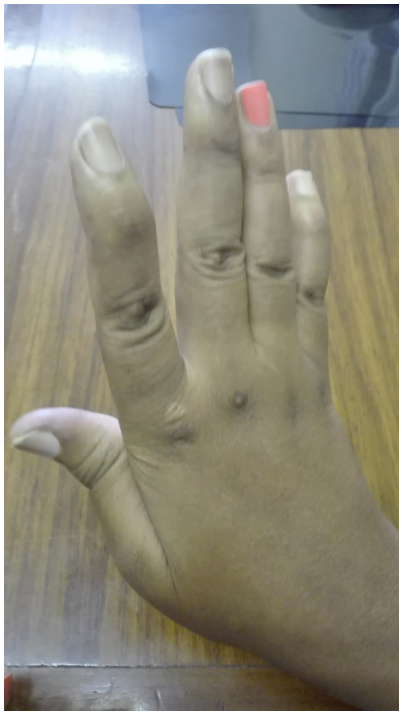


Figure 2: Jaccoud arthropathy in SLE



Investigations

These should be done after clinical assessment and guided by the clinical manifestations.

List of important investigations in SLE:

(i) *Complete Blood Count (CBC)*: To find leukopenia, lymphopenia, thrombocytopenia. Low haemoglobin due to haemolytic anaemia

(ii) *Renal Function Test (RFT):* Creatinine and urea will be elevated if patients renal function is impaired due to lupus nephritis.

(iii) Urinalysis is used to find protein, red blood cell cast, and white blood cell cast.

(iv) *Serum C3/C4 complements level:* C3 and C4 levels are low in a patient with lupus. They are indicative of active lupus.

(v) ANA (Antinuclear Antibody test), Anti-double-stranded DNA (Anti-dsDNA) are important autoantibody test in SLE. ANA is more sensitive but Anti-dsDNA is more specific.

(vi) *ENA panel (Extractable Nuclear Antigen):* ENA is a group of antibodies used to screen SLE and other connective tissue diseases. It includes anti-Sm (anti-Smith), anti -RNP, anti-La, anti –Jo and anti- Scl70.

(vii) Direct coombs test used to find autoimmune haemolytic anaemia.

(viii) Lupus anticoagulant, beta2 microglubulin, anti-cardiolipin antibody test to find the associated antiphospholipid syndrome.

(ix) Rheumatoid factor.

(x) 24-hour urinary protein/urine –protein creatinine ratio to identify renal involvement kidney biopsy to classify renal involvement.

(xi) Chest X-ray can reveal pleural effusion and pulmonary parenchymal involvement.

(xii) Imaging of the heart, brain, lungs, joints, muscles, and abdomen are used when indicated.

Initially a suspected individual is screened for high Erythrocyte Sedimentation Rate (ESR), antinuclear antibody (ANA) complete blood count with differential and urinalysis. The other investigations are advised to the patient for further confirmation and to find any suspected organ involvement.

An investigation is also done to find disease activity. ANA titer doesn't correlate with disease activity but anti-dsDNA titer is elevated and complement C3 and C4 level are decreased several months before a flare or increased disease activity. False positive ANA level is seen in HIV patients. Kopelman and Zolla-Pazner described the presence of ANA in 12% of HIV positive patients without underlying rheumatologic diseases[27]. In South African patients with SLE, the high frequency of anti-Sm and anti-RNP antibodies are similar to the observations in African-Americans and Afro-Caribbeans[28,29]. The prevalence of anti-cardiolipin antibodies in patients with lupus nephritis was 45% in South African patients with lupus nephritis[30].

Multiple factors are used for disease activity in the active renal disease called MCP-1 (monocyte chemo attractant protein-1), AAG (α1-acid glycoprotein)[31]. An investigation is also needed for regular treatment monitoring depending on the disease course but usually every 3-6 months[26].

Diagnosis of lupus clinically was difficult as it presents with symptoms of multiple system involvement. An American Rheumatology Association (ACR) criterion was used previously for SLE diagnosis. In 2012 SLICC (Systemic Lupus International Collaborative Clinic) was introduced as diagnostic criteria for SLE. The sensitivity and specificity of SLE SLICC criteria is 92% and 99% respectively compared to ACR criteria which are 97% and 99% but in SLICC criteria there are few more items that are helpful for a researcher[32].

Diagnostic criteria SLICC criteria: (Systemic Lupus International Collaborative Clinic)[9].

Requirement: >4 criteria (at least 1 clinical and 1 laboratory criteria) to diagnose as SLE

Clinical	Immunologic criteria
Acute cutaneous lupus	ANA (Antinuclear antibody)
Chronic cutaneous lupus	Anti Ds DNA
Oral or nasal ulcer	Anti-Sm (Anti Smith)
Non-scarring alopecia	Anti-phospholipid antibody
Arthritis	Low complement (C3,C4, CH50)
Serositis	Direct Coombs test (Don't count in the presence of haemolytic anaemia)
Renal	
Neurologic	
Haemolytic anaemia	
Leukopenia	
Thrombocytopenia (<100000/mm^3)	

SLICC criteria 2012[9]

Although systemic lupus erythematosus is the most predominant form of lupus, other forms of lupus are also important for differential diagnosis.

Neonatal lupus: This condition is not commonly seen in the neonate. The lupus-related cutaneous lesion is seen after birth or a few weeks after birth. It is characteristically associated with irreversible complete heart block. Anti-Ro and anti-La antibodies are commonly associated with neonatal lupus. However, only 1% of women with these antibodies develop neonatal lupus[33]. Prevention and early detection are important for avoiding more serious complications like complete heart block.

Drug-Induced Lupus (DIL): This entity of systemic lupus erythematosus is caused by ingestion of certain drugs in a susceptible individual. The most common drugs are hydralazine, procainamide, methyldopa, quinidine, diltiazem, isoniazid etc. The disease occurs months to years of continuous drug exposure. They mimic systemic lupus manifestation but milder than the classic SLE. Rarely, a severe form of DIL can be seen when they can involve systemic organs. It is associated with the positive anti-histone antibody (sensitivity 67% vs specificity 95%)[34]. Treatment is discontinuation of the offending drug.

Lupus Nephritis (LN)

Discussion of SLE separately is important as it leads to severe morbidity and mortality in the affected individual. There is a need for aggressive immune therapy in lupus nephritis. Pathogenesis of lupus nephritis is due to immune-complex deposition mainly in sub-endothelial and mesangial in early stages of SLE which eventually involve the membranous and sub-epithelial part. Also antibody binding to an intrarenal nuclear autoantigen and causing the local proinflammatory effect[35]. Lupus nephritis is classified histologically by the International Society of Nephrology and Renal Pathology Society (ISN/RPS) into six different classes[36]:

Class I: Minimal change disease
Class II: Masangiproliferative renal disease
Class III: Focal LN (<50% glomeruli)
Class IV: Membraneous LN
Class V: Advance sclerosing LN

Besides histology of kidney lupus nephritis is suspected if there is significant proteinuria- > 0.5g in 24-hour urinary protein, urine protein-creatinine ratio >0.5 and 3+ protein in urine in the absence of urinary tract infection[37].

Recently researchers have found an important biomarker that can predict lupus nephritis activity. Such biomarkers includes- urine protein creatinine ratio, MCP-1 (monocyte chemo attractant protein -1), AAG (α1-acid glycoprotein). While MCP-1, AAG, transferrin, creatinine clearance, and C4 proved to be a good diagnostic tool for membranous LN[31].

Most lupus nephritis treatment guidelines approve treatment of Grade III/IV lupus nephritis with cyclophosphamide (CYC) or mycophenolate mofetil (MMF) with the steroid. Treatment of lupus nephritis is divided into two phases; induction phase and maintenance phase using CYC or MMF. For induction, most review articles mentioned the benefit of low dose CYC six biweekly (500mg) vs 8 monthly intravenous pulses (0.5g/m^2 max 1.5g. However, they also reported the benefit of CYC pulse or MMF with steroid as an effective drug combination to induce remission. The dose of oral MMF is reported by most reviewers as 3g/d. For maintenance MMF or azathioprine is used along with low dose steroid[37,38].

In Africa, the CYC/glucocorticoid-based regimen remains the standard of treatment for adult patients with SLE[39]. In a study done in South Africa including LN patients, shows a high prevalence of membranous LN and good response to treatment[40].

SLE and pregnancy: Pregnancy in an SLE patient has a different challenge. The patient can have a variable percentage of flare during pregnancy. During pregnancy, 40%-50% of patients who have SLE develop flare[41]. Flare is mostly associated with lupus nephritis and among patients who discontinues chloroquine therapy[41].

Patients with active disease during pregnancy increases the risk of fetal loss or miscarriage. Lupus during pregnancy also causes many obstetric complications like preterm delivery, pregnancy-induced hypertension, caesarean section[42]. If such a pregnant female is associated with antibodies like lupus anticoagulant and anticardiolipin antibody, it increases fetal loss and miscarriage. Maternal antibody-like anti-Ro +/La is also associated with neonatal lupus[33]. Treatment of lupus can be challenging as many medications used in lupus have an adverse effect on the children. Pregnancy in lupus needs close monitoring by the multidisciplinary team. Corticosteroid is the mainstay of treatment of lupus but the dose should be limited to the lowest possible doses not exceeding 10mg/day[43,44]. Corticosteroid in mid and late pregnancy may cause IUGR (intrauterine growth retardation, postnatal hypertension, glucose intolerance[43].

Chloroquine, hydroxychloroquine, and azathioprine are considered safe in pregnancy. Methotrexate, cyclophosphamide and mycophenolate mofetil are unsafe in pregnancy as they can lead to fetal abnormality[44].

Treatment of SLE: Treatment of SLE has improved the outcome of SLE. The mainstay of therapy is corticosteroid and the initial dose is 1mg/kg /day. Methylprednisolone pulse therapy of 1g/d should be considered if a daily dose of prednisolone is >60mg/day[45]. For a patient who is on long term steroid, they need steroid-sparing therapy with azathioprine or MMF.

The following treatment regimen is used worldwide for SLE[46]:

(i) Patient with no, minor or moderate organ (serositis, skin, joint) involvement:
   - Hydroxychloroquine or chloroquine and/or glucocorticoid
   - Steroid-sparing medications include azathioprine, mycophenolate, and methotrexate.

(ii) Treatment for lupus nephritis and active organ involvement
   Induction therapy glucocorticoid with mycophenolate mofetil or low dose cyclophosphamide iv or azathioprine.

New treatment monoclonal antibody belimumab has been approved for renal relapse and flares in SLE. Belimumab acts against soluble B-lymphocyte stimulator[39]. Belimumab studies demonstrated that belimumab is most effective in the subset of patients with high disease activity (e.g. high titers of anti-dsDNA antibodies and low complement levels). Belimumab could be an effective and safe option to treat LN, refractory LN cases, allowing to spare glucocorticoids and immunosuppressants, such as MMF[47].

Other drugs used in SLE is methotrexate. Methotrexate is used predominantly to treat arthritis in SLE. Calcium, vitamin D, bisphosphonate are used for bone protection due to a side effect of chronic glucocorticoid use.

Estimates of SLE in Southern Africa

Southern Africa includes Angola, Botswana, Lesotho, Malawi, Mozambique, Namibia, South Africa, Swaziland, Zambia and Zimbabwe. Therefore the southern African region includes low and middle-income countries. Also, health care disparities exist due to racial, political and economic inequalities.

The studies done in the southern African countries are exclusively hospital-based and not reflective of the whole population. South Africa is the leading country in research in the region. There are few studies from Botswana, Zimbabwe and Zambia. There is an increasing trend of reported lupus patients from southern African countries. In South Africa, Wadee *et al*[48] found 226 patients with SLE in a retrospective study conducted at Chris Hani Baragwanath Hospital between January 1986 and July 2003. Arthritis and rash were the most common clinical manifestations[48]. Similarly, in a retrospective study conducted by Moody *et al*[49] in Durban from 1984 to 1990, cutaneous manifestations and arthritis were common. Both studies also found a significant number of patients with nephritis (43.3% in Wadee's *et al*[48] study). Death was mostly due to infections and renal disease, and nephritis was an independent factor of poor survival[48].

Two studies done many years ago in the region showed a completely different common clinical presentation among SLE patients. In a prospective study done by Jacyk *et al*[29], they compared the SLE features of 40 black South African patients with those observed in white South Africans. Rash, photosensitivity, and haematological involvement were less common in black South Africans[29]. In a study done in Zimbabwe in 31 black patients over a period of six years, arthritis (81%) and malar rash (61%) were the more frequently reported symptoms, and photosensitivity and serositis were the least common manifestations. Haematological abnormalities (61%) were also common. This limited study compared the findings in Zimbabweans with those of patients in the USA and renal involvement appeared more common in Zimbabwe[50].

There are very few published reports from Zambia, Botswana, and Malawi and most of them are case reports[51-53].

Experience in Botswana

In Botswana, rheumatology patients used to be managed in district hospitals by general physicians. In 2013, an adult rheumatology clinic was established in Princess Marina National Referral Hospital in Gaborone, and now receives patients referred from all over the country. The clinic has noticed an increase in systemic lupus erythematosus patients and many new patients are added every year. However, there is no epidemiological study of the incidence and prevalence of SLE in Botswana. A recent retrospective study done in dermatology at Princess Marina Hospital has reported 12 patients with systemic lupus with cutaneous[54].

Challenges

The southern African region has its own challenges. The low incidence rate in the whole of Africa may be the result of multiple factors. In the majority of cases, there is a delay in diagnosis, Tiffin *et al*[55] have reported in 93% of cases there is a complete delay or some delay in diagnosis. Lack of awareness about SLE, limited facilities in primary health care settings, limited diagnostic centre to carry out the serological and histological test for SLE and availability of specialist physicians are the major factors across Africa. Treatment of SLE in Africa is difficult due to the high cost of drugs. Tiffin *et al*[55] mentioned in their review of SLE patients in Africa that the cost of MMF is about US$100 and the cost of one session of dialysis ranges from US$100-150$[55]. This high cost of treatment is also seen in a developed country. But the poor socioeconomic condition of patients in a developing country is a major contributor to the overall outcome of SLE[56]. A review identified the paucity of prevalence data, decreased funding for rheumatology-related research and low numbers of rheumatologists are important contributing factors. There is a low ratio of rheumatologists per population, which varies from 1:35000 to 1:1600000[57].

Diagnostic delay is seen if the laboratory facility to do the serological test, urinalysis and facility for tissue biopsy are unavailable. Renal complication like lupus nephritis is a poor prognostic indicator of SLE and need early diagnosis. Renal biopsy is the gold standard investigation for lupus nephritis. These services are not available in many centres in southern Africa. Delay in diagnosis leads to a more adverse outcome[58]. The antinuclear antibody test (ANA) facility is available in most countries in southern Africa.

Follow-up of SLE treatment is a major concern to avoid complications. The lack of laboratory facility at primary, secondary and tertiary hospital level have a negative impact on the outcome of a patient treated as SLE. It is important to monitor the treatment-related toxicity. Tazi Mezalek *et al*[56] have mentioned in their review that MMF treated patient have less infections and treatment-related hospital admissions than CYC. Immunosuppressive, biologic needs screening for tuberculosis before treatment. HIV patients with low CD4 also needs treatment adjustment to avoid opportunistic infections. The limited number of rheumatologists can compromise the early initiation of appropriate medication. The standard clinical guidelines are modified in a developing country due to cost and availability of the drugs. There are some universal problems in the management of SLE. Such problems includes complications of medication; adherence and drug-drug interaction due to other illness are a challenge in lupus management. Patient's poor adherence also contributes to their poor outcome. Tazi Mazalek *et al*[56] in their review of a study in Brazil mentioned that 51% of non-adherence among SLE patients is due to financial reasons[56].

Future directions

The understanding of complex disease like SLE is changing over the years. The treatment and diagnosis methods will be more effective in future. In southern Africa, it is important to increase public awareness and highlight the problem of SLE. To improve outcomes of SLE in these developing countries, there is a need to increase resources allocated to non-communicable diseases. Medical schools need to introduce students about the diagnosis and treatment of autoimmune disorders early, general physicians and other specialists needs to have greater exposure to these conditions and primary care workers should be trained to manage these disorders early with disease modifying anti-rheumatic drug therapy[57].

Conclusions

This review shows that an autoimmune disease like SLE is still a very infrequently reported disease in southern Africa. There is need to do more research to find out actual incidence, prevalence, and characteristics of SLE patients in southern African countries. In the future, increased awareness and improved healthcare facility will help in early diagnosis and treatment of SLE patients in southern Africa.

Data sources: A broad search of PubMed/MEDLINE using the key term systemic lupus in Africa, then epidemiology of lupus worldwide. Then SLE in southern African countries like South Africa, Botswana, Zimbabwe in Prime/PubMed/ Wiley online library/African Journal Online (AJOL)/Google. The subsequent search was conducted using additional key terms, such as incidence, prevalence, pathogenesis, diagnosis, and treatment of SLE. Searches were repeated with each draft of the manuscript.

Ethical consideration

Informed consents have been taken for publication of images.

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