DOES ALOPECIA HAVE DIAGNOSTIC WEIGHT IN SYSTEMIC LUPUS ERYTHEMATOSUS?

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2021

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DECLARATION:

I hereby declare the research reported here within is based on independent work performed myself, Lauren Kerry Knight, under the supervision of Dr Susan Jessop, Dr Mzudumile Ngwanya and Dr Ayanda Gcelu.

This work is submitted in fulfillment of the degree of Master of Medicine (MMed) in Dermatology, at the University of Cape Town. No part of the work has been, is being, or is to be submitted for another degree to any other university.

In addition, this work has not been published or reported prior to registration for the abovementioned degree.

Signed by candidate

Dr Lauren Kerry Knight

Date: 12th September 2021

ABSTRACT:

INTRODUCTION

Systemic lupus erythematosus (SLE) is a systemic autoimmune disorder characterised by autoantibody production and a broad spectrum of clinical manifestations. Non-scarring alopecia (hair loss) reportedly occurs in up to 80% of individuals with SLE, occurring primarily in the active phase. Alopecia is also reported in up to a third of the general population. So how much diagnostic weight does alopecia really have in SLE?

METHODS

We conducted a cross-sectional cohort study of patients with SLE, as defined by the 2012 Systemic Lupus International Collaborating Clinics (SLICC) classification criteria, managed at the Lupus clinic at Groote Schuur Hospital, a tertiary referral hospital in Cape Town, South Africa. Age, sex and race matched controls were recruited from the Dermatology clinic at the same hospital. Participants were questioned about alopecia ('self-reported') and examined for alopecia clinically and dermoscopically ('confirmed alopecia'). Alopecia was classified according to the likely cause and evaluated as to whether or not it was related to SLE and to disease activity.

RESULTS

The study included 90 participants with SLE and 90 controls. Females predominated in the study population, with a mean age of 37.13 (range 18-69) for cases and 37.62 (range 18-72) in controls. Demographics of the 2 groups were equally matched, with two thirds (64.4%) of cases and controls self-identified as being mixed race, 33.3% as black african and 2.3% as white. Alopecia (self-reported and confirmed) was found equally in cases and control groups.

In a third of the people with SLE (34, 38%) alopecia was recorded by the clinician as one of the classification criteria used by the clinician in recording the diagnosis of SLE. In 7/34 (21%) of these patients, the classification of SLE would not have been made by criteria in the absence of alopecia. Forty patients were found to have clinically apparent alopecia, 7 of these (17.5%) having diffuse alopecia. Of the remaining 33 patients with alopecia, androgenic alopecia (12/33) was the commonest form. Likewise, androgenic alopecia was the commonest type of confirmed alopecia in controls (11/33, 33.3%).

Patients with self-reported alopecia had significantly higher Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) scores than people without hair loss. However, no statistically significant difference in SLEDAI scores between those with clinically confirmed alopecia and those with self-reported alopecia was found ($n = 40$, $M = 2.88$, $SD = 3.35$ vs $n = 50$, $M = 2.56$, $SD = 3.37$: $t = 0.44$, $p = 0.660$, $d = 0.09$).

CONCLUSIONS

Within our population the incidence of alopecia was the same in people with SLE and in controls. Hair loss was identified as androgenic alopecia in the majority of affected cases and controls. This lack of difference in type of alopecia among participants highlights the low specificity of non-scarring alopecia as a criterion for SLE and further supports the weighting of classification criteria within the various domains in the EULAR/ACR criteria.

ACKNOWLEDGMENT

I would like to thank:

My supervisor, Dr Susan Jessop, for her continued enthusiasm, support, encouragement and advice throughout the project.

My co-supervisors, Dr Mzudumile Ngwanya and Dr Ayanda Gcelu, for their guidance and expertise with the project.

The staff from the Rheumatology and Dermatology divisions at Groote Schuur Hospital for their assistance with recruitment of participants.

The participants, both cases and controls for their patience and involvement in the project.

My husband for his understanding and support.

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ABBREVIATIONS:

ACR: American College of Rheumatology,

ANA: Antinuclear antibody,

CCCA: Central centrifugal cicatricial alopecia,

DLE: Discoid lupus erythematosus,

dsDNA: Double stranded DNA,

EULAR: European League Against Rheumatism,

HIV: Human immunodeficiency virus,

LPP: lichen planopilaris,

SLE: Systemic lupus erythematosus,

SLEDAI: Systemic Lupus Erythematosus Disease Activity Index

SLICC: Systemic Lupus International Collaborating Clinics Classification Criteria for SLE.

CHAPTER 1: Introduction and Literature review

Systemic lupus erythematosus

Systemic lupus erythematosus (SLE) is a systemic autoimmune disorder characterised by autoantibody production and a broad spectrum of clinical manifestations which can be both cutaneous and systemic (2, 3). Females are predominantly affected, with prevalence and incidence varying according to ethnicity (4-6). SLE runs a chronic unpredictable course, characterised by relapses and remissions. Individuals are affected to varying degrees, from non-specific manifestations of fever and loss of weight, to disfiguring manifestations of the hair and skin and most severely life-threatening involvement of the kidney or central nervous system (4, 7, 8).

Most patients with SLE (72-85%) have cutaneous manifestations of disease, in the form of skin, mucous membrane or hair involvement. These features are the first markers of disease in 25% of the affected patients (1). Koch et al. reported cutaneous lupus erythematosus in 76% of their 298 South African patients with SLE (9). Skin lesions may be lupus-specific or non-specific, commonly also occurring in other connective tissue disorders or non-rheumatological systemic disorders or in otherwise normal people. Figure 1 summarises the cutaneous manifestations typically seen in Lupus Erythematosus.

A. Acute cutaneous LE (ACLE)
   1. Localized ACLE
   2. Generalized ACLE
   3. Toxic epidermal necrolysis-like ACLE)
B. Subacute cutaneous LE (SCLE)
   1. Annular
   2. Papulosquamous
C. Chronic cutaneous LE (CCLE)
   1. Discoid LE (DLE)
      a) localized
      b) generalized
   2. Hypertrophic/verrucous LE
   3. Lupus panniculitis/profundus
   4. Chilblain LE
   5. DLE-lichen planus overlap
D. Intermittent cutaneous LE
   1. LE tumidus

Figure 1: Lupus erythematosus specific skin conditions (1).

Studies have reported discoid lupus erythematosus (DLE) to be the commonest specific cutaneous manifestation in black Africans (occurring in 55% of the study population), which is in contrast to the finding of acute cutaneous lupus being the more common manifestation in Caucasians (9). Non-specific cutaneous manifestations are common, occurring in up to 40% of participants, particularly oral or nasal ulcers and Raynaud's phenomenon. Non-scarring alopecia seems to be less common in black Africans than in other groups (14.5% as compared with 75%) (9).

Classification of systemic lupus erythematosus

Due to the complex clinical presentation of SLE coupled with the lack of a single diagnostic test, classification criteria have been developed to identify relatively homogenous groups of patients, largely for the purpose of comparative research studies and trials (10, 11). Classification by the development of criteria sets defines a condition based on a number of items that differentiate a given condition from another similar one. Specificity is key for classification, while bedside diagnosis is a more individualised approach applied to an individual patient and requires the exclusion of other possibilities (12). Classification and diagnosis will frequently concur (13). As understanding of SLE in terms of clinical manifestations and pathogenesis improves, classification criteria too advance (11, 14). Criteria have been shown to perform better

in patients with longstanding as compared to patients with new onset SLE, as further manifestations are accrued over time (15).

The American College of Rheumatology (ACR) initially proposed criteria for the classification of SLE in 1971 (later updated in 1982 and 1997) (16). These criteria focused on clinical manifestations, which differentiated individuals with SLE from those without (17). The ACR criteria included discoid lesions, which could be on the scalp, resulting in a scarring alopecia, but excluded non-scarring alopecia or the hair loss sometimes referred to as lupus hair (18). The criteria were then updated in the Systemic Lupus International Collaborating Clinics Classification Criteria for SLE (SLICC). This new criteria set is more sensitive than the 1997 ACR criteria, requiring individuals suspected of having SLE to have at least 1 clinical and one immunological criterion or biopsy proven renal involvement with antinuclear antibody (ANA) or anti-double-stranded DNA (dsDNA) antibodies (3, 15).

The SLICC criteria included non-scarring alopecia as a criterion for the classification of SLE. The non-scarring alopecia referred to a "diffuse thinning of the hair or hair fragility with visible broken hairs in the absence of other causes such as alopecia areata, drugs, iron deficiency or androgenic alopecia" (3). The latest 2019 EULAR/ACR classification criteria for SLE were developed with the aim of improving reliability and precision in classification. These new criteria require a positive antinuclear antibody (ANA) for entry into the classification of SLE, meaning that patients who are ANA negative cannot be classified as having SLE. Non-scarring alopecia remains a classification criterion, but criteria are weighted, with a nuanced contribution to classification (19). The EULAR/ACR classification criteria have reached a sensitivity of 96.1% and a specificity of 93.4%, compared to SLICC, which had a sensitivity of 89.3% (19).

Alopecia

Alopecia, or hair loss, is a common symptom, reported in up to a third of women, as a result of various factors (20). The scalp contains approximately 100, 000 hairs which are continuously cycling between the three stages of the hair cycle namely; anagen (the active growth stage), catagen (marked follicular regression and apoptosis) and

telogen (the resting phase). Anagen hairs are actively growing and anchored deeply in the subcutaneous fat. Telogen hairs on the other hand are located higher in the skin and can be pulled out relatively easily. About 100 telogen hairs are lost per day in the normal person. The hair is highly metabolically active and as a result alopecia may occur in metabolic derangements and may be a marker of systemic disease (20). Hair loss is usually characterised as being non-scarring or scarring (21).

Scarring Alopecia

Discoid lupus is the prototypic scalp lesion of lupus erythematosus of the scalp, occurring in up to 60% of people with discoid lupus erythematosus (DLE) (22). It is usually easily recognised but is not a classification criterion (22).

Non-Scarring Alopecia

Non-scarring alopecia is most commonly seen in androgenic alopecia, telogen effluvium or alopecia areata (20). Other causes of non-scarring alopecia include various hair care practices, trichotillomania and bacterial or fungal infections (20).

Androgenic alopecia, also known as female-pattern hair loss, is the commonest cause of diffuse alopecia in women (23). It is often familial, developing in many women after the age of 50, but can occur any time after puberty, with 38% of women being affected by age 70 (24, 25). Hair loss generally presents as widening of the midline parting on the crown, but thinning over the lateral scalp may also occur (26).

Alopecia as a criterion in Lupus

Alopecia is a commonly observed occurrence in SLE, occurring in up to 50% of patients during the course of their disease (27). Whether this hair loss is an inherent part of the condition or just coincidental in the patient with lupus erythematosus remains doubtful.

DLE is a typical lesion of lupus erythematosus and due to its specificity is included in the SLICC criteria for classification of SLE, whether on the skin or the scalp (22). When a DLE lesion occurs on the scalp it can result in a scarring alopecia (Figure 2).

Scalp DLE accounts for up to 40% of scarring alopecias in the general population (28). Onset is typically between the ages of 20 and 40 (29).

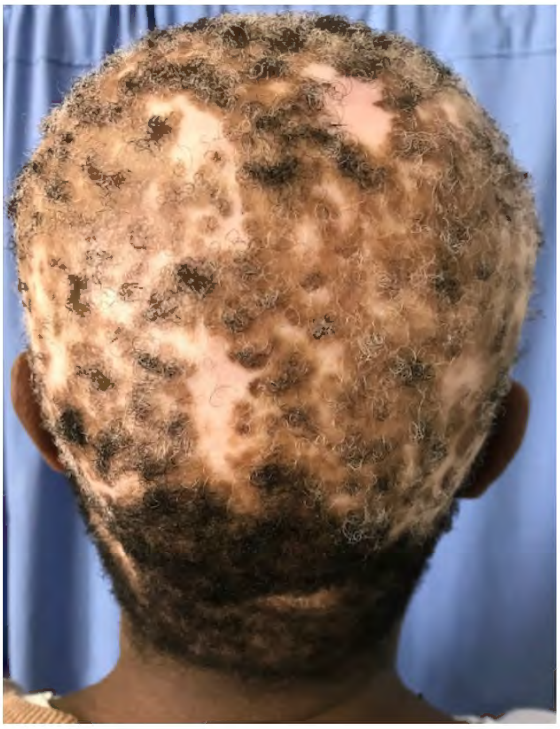

Figure 2: Discoid lupus erythematosus of the scalp.

Alopecia in SLE, apart from the scarring lesion of DLE, may be related to disease activity. Non-scarring alopecia, mentioned in the SLICC criteria as "'diffuse thinning or hair fragility with visible broken hairs, in the absence of other causes such as alopecia areata, drugs, iron deficiency, and androgenic alopecia" is an accepted sign of SLE (3). However, it is not specific to SLE.

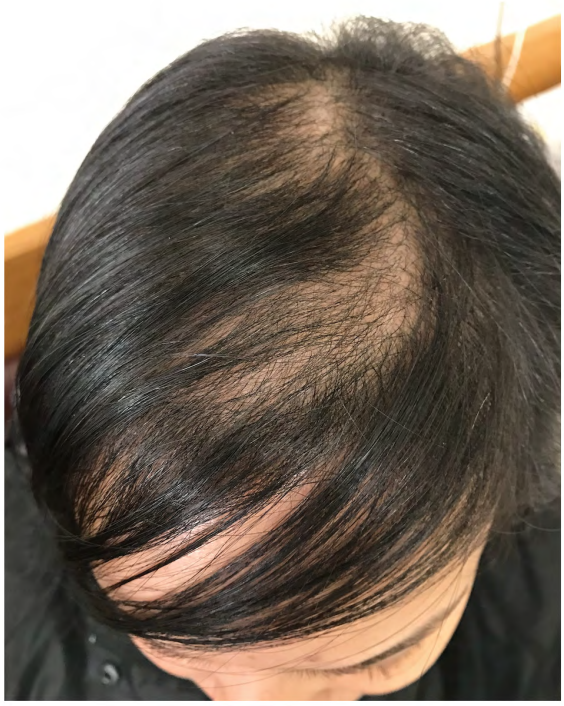

Figure 3: Widening of the midline parting on the crown in androgenic alopecia.

Telogen effluvium occurs as a result of an abrupt change of anagen to telogen hairs, with a change in the normal ratio of anagen to telogen hairs. This process is generally associated with major illness, stress or hormonal derangements. It is reported that patients can lose up to 300 hairs a day in telogen effluvium, resulting in a diffuse alopecia. Telogen effluvium will typically resolve within 6 months, should the precipitant be removed (30).

Alopecia areata is another cause of non-scarring alopecia, which typically manifests with round discrete patches of alopecia, occasionally coalescing to have a more generalised pattern.

When considering potential causes of non-scarring alopecia, one can consider if the alopecia is attributable to lupus. Non-scarring alopecia in lupus is described by some authors as being diffuse, patchy or lupus hair in terms of the possible patterns (31).

The diffuse pattern has been reported as the commonest presentation of non-scarring alopecia in both Thai and Korean cross-sectional studies, which assessed alopecia in patients with SLE (31, 32). This pattern was followed by patchy hair loss with 'Lupus hair' being less frequent and often more subtle (31).

Patchy non-scarring alopecia is another fairly commonly reported form of reversible alopecia encountered in patients with established SLE. Clinically patients have erythematous non-scarring patches of partial alopecia with the remaining hair being telogen or dystrophic anagen hairs (22). A non-scarring pattern of alopecia is present in the majority of patients with hair loss in lupus. This is often misdiagnosed as alopecia areata (33). Coincidentally alopecia areata has also been found in patients with SLE, likely on the basis of both conditions being autoimmune (22).

'Lupus hair' refers to hair loss with an associated uneven appearance of the frontal hairline due to increased hair fragility with weakened hairs that break at the scalp surface and are found especially at the scalp periphery (Figure 4) (34). The etiology may be similar to telogen effluvium and it is thought that severe inflammation promotes a catabolic state and negative nitrogen balance that affects hair growth (22, 35).

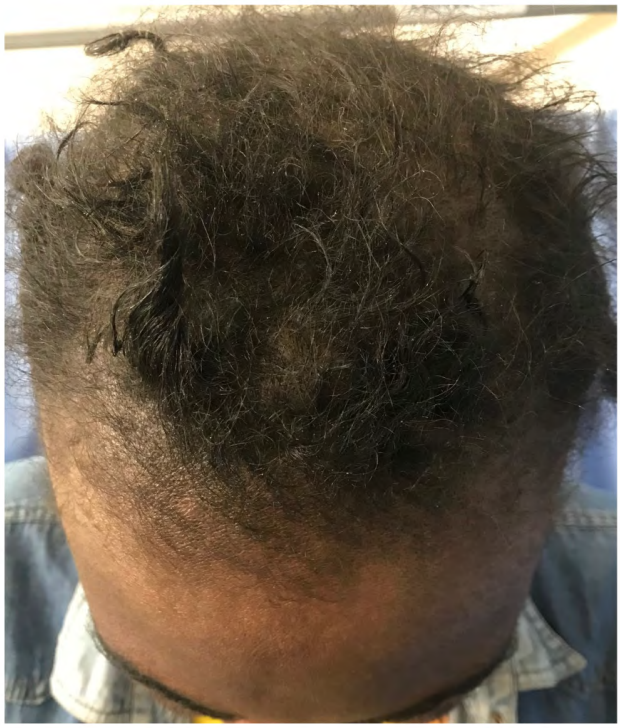

Figure 4: Diffuse alopecia with broken off hairs around the scalp periphery.

Alopecia is also a parameter included in the SLE Disease Activity Index (SLEDAI), which evaluates 24 weighted objective variables (16 clinical and 8 laboratory parameters) that have been present in the 10 days prior to the evaluation, dermoscopy

with the sum of the items used as a measure of disease activity (36).

Sensitivity of alopecia as a criterion for classifying SLE

The SLICC criteria for the classification of SLE have been validated by expert committees reviewing abstracted clinical scenarios as well as in real-life SLE populations (3). Most recently Ines et al. reviewed over 2000 patients diagnosed with SLE in Spain and Portugal in terms of the sensitivity of clinical features of SLE as per the SLICC and ACR criteria. The sensitivity for SLE classification was higher with the SLICC 2012 set than with the ACR 1997 (93.2% versus 85.6%; $P < 0.0001$) (15). Among this population, non-scarring alopecia was found to have a 28.8% sensitivity as a criterion for SLE. Petri et al. found non-scarring alopecia to have a sensitivity of 31.9 and a specificity of 95.7 (3). A positive ANA (98.9%) was the most sensitive criterion followed by anti-dsDNA with 74.3% (15). Although alopecia ranks fairly high in terms of sensitivity as a criterion, what is unclear is how this compares to alopecia that may be present in the general population in the absence of connective tissue disease.

How can alopecia be evaluated in patients with hair loss?

Hair loss is a common complaint and may be diffuse or localised. Evaluation of alopecia starts with thorough history taking, paying particular attention to possible triggers such as stress, medication in use (over the counter or prescription), illness or loss of weight. Further evaluation ranges from non-invasive clinical examination, which includes examination of scalp and hair, hair counts, pull tests and dermoscopy, to more invasive scalp biopsy. Family history and, in women, gynaecological history with reference to menstrual irregularities are important aspects to consider (37).

Examination requires identification of obvious areas of alopecia and how these areas are distributed. Density of hair is assessed as being normal or decreased and a pull test may be done to determine the severity of shedding. The pull test is performed by applying gentle traction to a group of 40-60 hairs in three different areas of the scalp. The test is deemed positive if six or more hairs are pulled from a single area. The

removed hairs are then examined microscopically to assess for dystrophy or damage and determine their stage in the hair growth cycle (38).

Dermoscopy for the evaluation of alopecia

Dermoscopy is a useful non-invasive tool, which has helped improve diagnostic accuracy and understanding of the pathogenesis of hair disorders (39, 40).
Normal healthy scalps have evenly spaced groups of few hair shafts emerging from the same follicle ostium (41). Single or double follicles are found in the temporal scalp and triple hair units in the occipital scalp. Normal scalp vessels are seen as interfollicular simple red loops (39). A perifollicular pigmented network comprising hyperchromic lines (melanocytes on rete ridges) and hypochromic areas (fewer melanocytes localized to suprapapillary epidermis), resembling a honeycomb pattern is often seen in darker skinned individuals (42). Specific variations of this pattern may be a useful adjunct to clinical examination, eliminating the need for scalp biopsy.

Alopecia areata is characterised by yellow dots on dermoscopy, representing follicular openings filled with a mixture of keratinous debris and sebum (43). Yellow dots and short vellus hairs are the most sensitive markers for diagnosis, while black dots (follicular ostia containing cadaverised hair), tapering hairs (exclamation mark hairs) and broken hairs correlate with disease activity (44).

Miniaturization of the hair follicles in androgenic alopecia results in hair diameter diversity. More than 20% variability in the diameter of hair shafts is diagnostic of androgenic alopecia (Figure 4) (45). Furthermore, follicular ostia have single hairs emerging as compared with the 2-4 hair shafts seen in normal scalp (46).

Figure 5: Dermoscopy image of androgenic alopecia characterised by more than 20% variability in hair shaft diameter.

Non-scarring alopecia in SLE may present with irregular patches of predominantly incomplete hair loss or may be diffuse (33). Non-scarring alopecia in SLE, is suggested on dermoscopy by features of hair shaft hypopigmentation, thinning and angiotelectasia (polymorphous vessels, arborizing vessels and simple red loops). Locations of angiotelectasia can be 1) interfollicular (between follicular units), 2) perifollicular (around follicles) and 3) panfollicular (between and around follicular units). In a study by Ye et al. that compared non-scarring alopecia in SLE with alopecia areata, interfollicular polymorphous vessels were the commonest pattern in the hair loss of SLE (33).

Scalp affected by DLE typically shows erythema, scaling, follicular plugging, atrophy and telangiectasia. Atrophy is simply seen as a diffuse white colour on dermoscopy, as a result of the loss of the normal pigment network typically seen within the lesion. Vascular patterns within DLE plaques include arborizing and tortuous vessels as well as red to pink-red, round and polycyclic uniformly sized dots that are regularly distributed around follicles (Figure 6). Peripheral follicles show hyperkeratotic follicular plugging. Blue-grey dots, representing pigmentary incontinence within the papillary dermis, can be seen scattered within the area of alopecia (43).

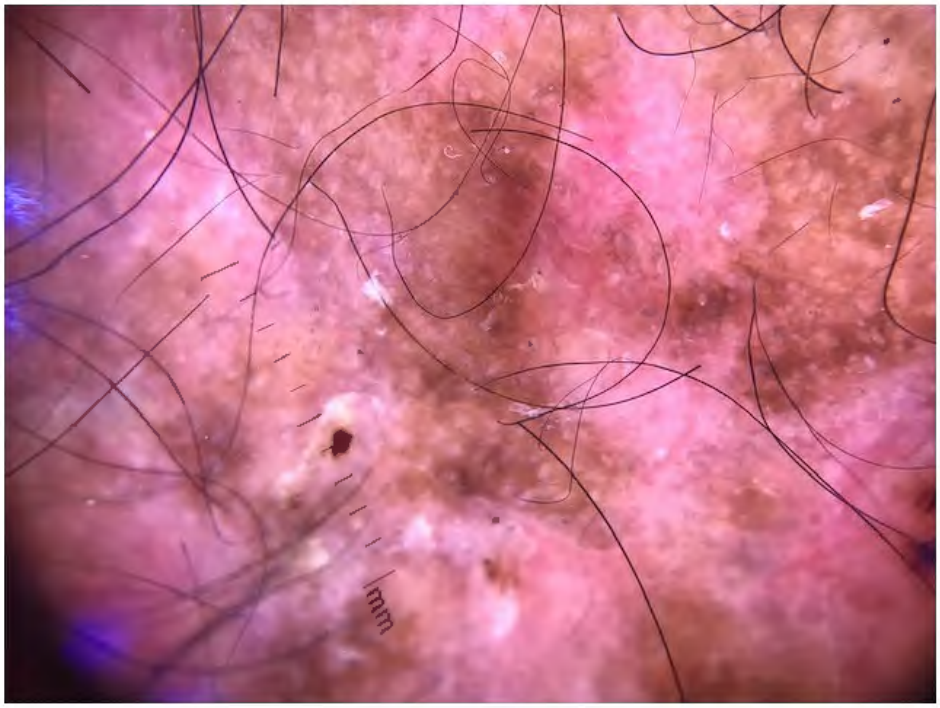

Figure 6: Branching capillaries and scale crust in discoid lupus erythematosus.

Summary: Question arising from the literature

According to the literature search, alopecia is a common complaint raised by patients, with and without SLE. Non-scarring alopecia, be it diffuse, patchy or lupus hair, is a recognised clinical manifestation of SLE and has been accepted as a classification criterion. However, alopecia as a presenting complaint needs to be evaluated thoroughly with an appropriate history and careful clinical examination, to avoid the inclusion of people with alopecia due to other causes, in the classification of SLE. This is particularly important in patients recruited into research projects, should they not have the other typical criteria at time of presentation and in whom the presence of alopecia carries significant weight.

The wide range of clinical manifestations of SLE, may make classification and often diagnosis of disease difficult. This is highlighted by the range of prevalence of the presentation of alopecia reported in the literature. Furthermore, there is a paucity of data pertaining to the cutaneous manifestations, particularly non-scarring alopecia, of

SLE in South African populations. These difficulties give rise to our posing the following questions, which we will attempt to address with the research project:

- How common is alopecia in our population of people with SLE?
- How does the prevalence of alopecia in patients with SLE compare with the prevalence in normal people?
- Should a dermatologist be consulted in patients thought to have SLE, as non-invasive dermoscopic examination is an effective way to distinguish between the different causes of alopecia.

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CHAPTER 2: Publication ready manuscript for submission to Rheumatology (Oxford).

DOES ALOPECIA HAVE DIAGNOSTIC WEIGHT IN SYSTEMIC LUPUS ERYTHEMATOSUS?

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ABSTRACT

INTRODUCTION

Non-scarring alopecia (hair loss) reportedly occurs in up to 80% of individuals with systemic lupus erythematosus (SLE). How much diagnostic weight does alopecia have in SLE?

METHODS

We conducted a cross-sectional cohort study of patients with confirmed SLE at the Lupus clinic at Groote Schuur Hospital. Age, sex and race matched controls were recruited from the Dermatology clinic. Participants were questioned about alopecia ('self-reported') and examined for alopecia clinically and dermoscopically ('confirmed'). Alopecia was classified according to the likely cause and evaluated as to whether or not it was related to SLE and disease activity.

RESULTS

Ninety participants with SLE and 90 controls were included. Females predominated, with a mean age of 37 years. Two thirds (64.4%) of participants self-identified as being mixed race, 33.3% as black african and 2.3% as white. Alopecia was found equally in both groups.

In a third of cases (34, 38%) alopecia was recorded as a criterion used for classification of SLE. In 7/34 (21%) of these patients, the classification of SLE would not have been made in the absence of alopecia. Forty patients were found to have clinically apparent alopecia, most commonly due to androgenic alopecia (12/33). Similarly, androgenic alopecia was the commonest type of alopecia in controls (11/33, 33.3%).

CONCLUSION

The incidence of alopecia was the same in patients and controls. Androgenic alopecia was the cause of alopecia in the majority of affected cases and controls. This highlights the low specificity of non-scarring alopecia as a criterion for SLE.

KEY WORDS: Alopecia, hair loss, systemic lupus erythematosus, frequency analysis.

KEY MESSAGES:

- Alopecia has the same prevalence in patients with SLE as it has in people without SLE.
- Alopecia in most instances is attributable to causes other than SLE and disease activity.
- Incorrect attribution of alopecia to SLE may lead to inaccurate classification of patients and result in over estimation of diagnosis or level of activity.

INTRODUCTION

Systemic lupus erythematosus (SLE) is a systemic autoimmune disorder characterised by autoantibody production and a wide spectrum of clinical manifestations (2, 3). SLE runs a chronic unpredictable course characterised by relapses and remissions. The majority of patients with SLE (72-85%), have cutaneous or mucocutaneous manifestations, which are the first markers of disease in 25% of affected people (1, 4, 5). As a result of this wide spectrum of clinical manifestations, which may be non-specific, classification criteria such as those developed by the American College of Rheumatology (ACR)/ European League Against Rheumatism (EULAR) and Systemic Lupus International Collaborating Clinics Classification Criteria for SLE (SLICC) have been developed to assist in the classification of SLE (3, 15, 17). These criteria require a constellation of clinical as well as laboratory features for the classification of SLE in an attempt to improve reproducibility across studies from different groups.

Non-scarring alopecia (hair loss) is an example of one of the more non-specific criteria which may be used in the classification of SLE. However, alopecia is a common symptom in normal people, reported in up to a third of women as a result of various factors (20). Alopecia is most commonly non-scarring, seen in the form of androgenic alopecia, telogen effluvium or alopecia areata (20). Other causes of non-scarring alopecia include traction , trichorrhexis nodosa, trichotillomania and tinea capitis (20).

Alopecia is reported in up to 80% of people with SLE by some authors (18, 32). Typically thought to manifest primarily in the active phase of disease (33). While alopecia may be a manifestation of discoid lupus of the scalp this is usually scarring, thus not meeting the criterion of non-scarring alopecia. The term 'lupus hair' is sometimes used to describe a form of transient alopecia in patients with chronically active SLE. Possibly similar in etiology to telogen effluvium, the condition is characterized by hairs that are thin and weakened and tend to break at the scalp surface especially at the edge of the scalp (34).

The SLICC, ACR and EULAR criteria sets specifically state that the alopecia should be "non-scarring diffuse, excluding all other potential causes". The exclusion of other causes may be problematic for less experienced clinicians, resulting in an over allocation of weight to the criterion of alopecia. Identification of the cause of alopecia requires a thorough history, appropriate hair and scalp examination and sometimes the use of trichoscopy or even biopsy and laboratory investigations (37, 47).

Ines et al. reviewed over 2000 patients diagnosed with SLE in Spain and Portugal in terms of the sensitivity of clinical features of SLE as per the SLICC and ACR criteria. Among this population, non-scarring alopecia was found in 28.8%. A positive antinuclear antibody (ANA) (98.9%) was the most sensitive criterion, followed by anti-double stranded DNA (anti-dsDNA), with a prevalence of 74.3% (15). Although alopecia ranks fairly high in terms of sensitivity as a criterion, what is unclear is how specific this manifestation might be. This is particularly important in patients who may not have the other typical criteria at time of presentation and in whom the presence of alopecia could be given inappropriate weight.

OBJECTIVES

We undertook to determine

1. Whether alopecia is more common in people with suspected or confirmed SLE when compared to the general population.
2. Whether hair loss is accurately attributed to SLE in clinical practice.
3. What types of alopecia occur in people with SLE.

METHODS

Study setting

The study population consisted of patients with confirmed SLE by SLICC criteria managed at the Lupus clinic at Groote Schuur Hospital, a tertiary referral hospital in Cape Town, South Africa. Age, sex and race matched controls were recruited from the Dermatology clinic at the same hospital. The study was approved by the Faculty of Health Sciences Human Research Ethics Committee of the University of Cape Town (HREC Ref 579/2018) and conducted within the provisions of the World Medical Association Declaration of Helsinki (48). Signed informed consent was given by all study participants.

Data was stored in a password-protected computer and participant identifiers were removed.

Permission to conduct the study was granted by the Medical Superintendent and by the Heads of divisions of Rheumatology and Dermatology at Groote Schuur Hospital.

Participants and data extraction

All successive patients over the age of 18 with SLE, (based on SLICC criteria), attending the Lupus clinic at Groote Schuur hospital, were approached for inclusion in the study, during the period from December 2018 to December 2020. Information with regard to date of diagnosis, criteria for classification and the treatment used to

date was extracted from the patient records. The primary investigator interviewed and examined all participants to assess overall disease control in terms of SLEDAI, while focusing on alopecia. Participants were asked whether or not they had hair loss (self-reported alopecia), about hair grooming practices and about previous treatments used for alopecia. Examination of the hair, skin and nails was carried out. A hair pull test was done and the scalp and hair were examined clinically, as well as dermoscopically, to determine if there was alopecia (clinically confirmed alopecia) and what the potential cause of alopecia was. In cases where a specific pattern of alopecia was identified, further investigations were carried out to determine or confirm the cause and patients were referred to the hair clinic as needed.

Following recruitment of the cases, age, race and sex matched controls were selected from the Dermatology clinic. Those with inflammatory disorders, such as eczema or psoriasis, known scalp or hair disorders and those with underlying endocrine disorders, such as polycystic ovarian syndrome and other metabolic disorders which may affect the scalp, were not eligible for inclusion. Controls were asked about hair loss, grooming practices and if they had used any treatment for alopecia. Controls were examined clinically and dermoscopically and were referred for further investigation and treatment if indicated.

Clinical as well as dermoscopy photographs were taken of all participants and were reviewed by two of the researchers independently to determine if alopecia was present and the likely cause of alopecia.

Data management and statistical analysis

Data was entered into a password protected excel spreadsheet. Descriptive statistics were reported as means and standard deviations for continuous variables, and as proportions for categorical variables. Data was inspected for normality using Q-Q plots and box and whisker plots.

All analyses were performed using SPSS Version 27, and the threshold for statistical significance was set at $p < 0.05$.

First, independent sample *t*-tests compared continuous outcome variables between cases and controls. Chi-square test compared categorical outcome variables between cases and controls. Second, independent sample *t*-tests were used to determine if any demographic data (age, age at diagnosis, or duration of SLE) were related to alopecia (either self-reported or confirmed). Chi-square tests were used to determine if any comorbidities were associated with alopecia (self-reported and confirmed). Third, chi-square tests were used to determine if there was any association between self-reported and clinically confirmed alopecia within each group. Fourth, independent sample *t*-tests compared SLEDAI scores between those with and without (a) self-reported alopecia, and (b) clinically confirmed alopecia. Fifth, chi-square tests examined the association between alopecia (either self-reported or confirmed) and treatment of their underlying disease (for example patients on immunosuppression).

RESULTS

Ninety patients with confirmed SLE by 2012 SLICC criteria and ninety age, race and sex matched controls were included in the study (Table 1). Females predominated in the study population, with a mean age of 37.13 (range 18-69) for cases and 37.62 (range 18-72) for controls.

Table 1: Baseline characteristics of the study population.

	Cases		Controls	
Variable name	***N***	**%**	***n***	**%**
Female	85	94.4	85	94.4
Ethnicity				
Black	30	33.3	30	33.3
Mixed	58	64.4	58	64.4
White	2	2.2	2	2.2
Co-morbidities	38	42.2	35	38.9
Hypertension	15	17	12	13
Antiphospholipid syndrome	8	9		
Human immunodeficiency virus	5	6	11	12
Diabetes mellitus	3	3	1	1.1
Valvular heart disease	2	2.2	1	1.1
Asthma	2	2.2	3	3.3
Extra-pulmonary tuberculosis	2	2.2		
Depression	2	2.2		
Fibromyalgia	2	2.	2	2.2
Atrial fibrillation	2	2		
Interstitial lung disease	2	2		
Epilepsy	2	2.2		
Hypothyroidism	1	1.1		
Optic neuritis	1	1.1		
Hypercholesterolaemia	1	1.1		
Abnormal uterine bleeding	1	1.1		
Pernicious anaemia	1	1.1		
Chronic obstructive pulmonary disease	1	1.1		
Inflammatory bowel disease	1	1.1	1	1.1
Vitiligo	1	1.1		
Pulmonary embolism	1	1.1		
Diverticular disease			1	1.1
Cervical carcinoma in situ			1	1.1
Uveitis			1	1.1
Raynaud's			1	1.1
Sarcoidosis			2	2.2
Myocardial infarction			1	1.1
Allergies			2	2.2
Medication used in last 6 months				
Chloroquine	88	97.78	3	3.33
Immunosuppression in last 6 months	35	39		
Prednisone (≥20mg/day)	8			
Methotrexate	17			
Azathioprine	10			
Mycophenolate mofetil	3			
Leflunomide	2			

Almost all patients with confirmed SLE were on chloroquine (88/90, 98%, p<0.001), while 55 had been on immunosuppressive medication (Table 1). Thirty-five (38.8%) were currently on immunosuppression, with methotrexate being the commonest agent used, followed by azathioprine, prednisone, mycophenolate mofetil and leflunomide.

The incidence of alopecia (self-reported and confirmed) was the same in the 2 groups, cases and controls (Table 2).

Table 2: Alopecia prevalence and causes in the study population.

	Cases		**Controls**		**Test statistics**		
	N	**%**	***n***	**%**	X^2	***P***	***V***
Self-reported alopecia	39	43.3	35	388	0.3	0.545	0.05
Clinically apparent alopecia	40	44.4	33	366	1.1	0.288	0.08
Alopecia used as criterion for classification	34	37.8					
Alopecia necessary for SLE classification	7	7.8					
Types of alopecia	***n(40)***	**%**	***n(33)***	**%**			
Diffuse alopecia	7	17.5	2	6.1			
Androgenic alopecia	12	30	11	333			
Traction alopecia	11	27.5	7	212			
Discoid lupus	7	17.5					
Trichorrhexis nodosa	2	5	8	242			
Tinea capitis	1	2.5					
CCCA			2	6.1			
Alopecia areata			3	9.1			

Key: CCCA=central centrifugal cicatricial alopecia, SLE= systemic lupus erythematosus.

In a third of the people with SLE (34, 38%), alopecia had been used as one of the classification criteria. In 7 (21%) of these cases, the diagnosis of SLE would not have been made in the absence of alopecia. In these 7 patients additional criteria included: positive ANA (7), positive dsDNA (6), synovitis (4), acute cutaneous lupus (2), oral ulcers (1) and thrombocytopenia (1). During the study period, 40 patients had clinically apparent alopecia, with 7/40 of these (17.5%) deemed to have diffuse alopecia, possibly related to lupus. Of the remaining 33 cases with clinically apparent alopecia, androgenic alopecia (12/40) was the commonest cause of the hair loss, followed by traction (11), discoid lupus (7), trichorrhexis nodosa (2) and tinea capitis (1). Androgenic alopecia was also the commonest cause of confirmed alopecia in controls (11/33, 33.3%).

In both cases and controls, people with confirmed alopecia were more likely to be HIV infected as compared to patients without alopecia ($p = 0.015$ cases, $p= 0.048$ controls).

In people with SLE, confirmed alopecia was more common in older individuals (age 41.03; SD 1.37; $p< 0.001$) and in those who were older at the time of diagnosis (age 36.35; SD 1.48; $p = 0.048$).

There was a statistically significant difference in SLEDAI scores between those with and without self-reported alopecia ($n = 39$, $M = 3.64$, $SD = 3.44$ vs $n = 51$, $M = 1.98$, $SD = 3.12$; $t = 2.39$, $p = 0.019$, $d = 0.51$). Patients with self-reported alopecia had significantly higher SLEDAI scores. However, no statistically significant difference in SLEDAI scores between those with clinically confirmed alopecia and those without alopecia was found ($n = 40$, $M = 2.88$, $SD = 3.35$ vs $n = 50$, $M = 2.56$, $SD = 3.37$; $t = 0.44$, $p = 0.660$, $d = 0.09$).

DISCUSSION

In this study, performed in a dedicated lupus clinic, a third of women overall had alopecia. This prevalence did not differ from the control group without SLE. Importantly, in 38% of SLE patients with alopecia, the SLE 2012 SLICC classification criteria would still have been met in the absence of alopecia. However, in 7% of cases the presence of alopecia was required to fulfil the SLICC classification criteria, suggesting that identification of the cause of hair loss may be important in these cases. Androgenic alopecia was the commonest type of hair loss seen in the patients (12/40, 30%), with diffuse alopecia possibly due to lupus in 7/40 (17.5%). Self-reported alopecia was associated with a higher disease activity of SLE as measured by SLEDAI, with this difference losing statistical significance in cases of confirmed alopecia.

SLE is a complex multisystem autoimmune disorder which varies in terms of manifestations and also in severity among affected individuals. A range of antibodies are found in affected individuals, but none are 100% diagnostic (49). This wide spectrum of clinical manifestations and lack of single unifying diagnostic test makes for diagnostic difficulty, but early diagnosis and screening for associated life-

threatening systemic involvement is paramount. Several groups have defined classification criteria, in order to allow reproducible trial results and comparisons between studies (3, 15, 17, 19). Classification criteria may aid in the diagnosis of SLE but are not themselves diagnostic in individual patients.

Hair loss is a non-specific symptom, with a number of underlying causes and is common in the general population. In people with SLE, it might have some diagnostic weight. Alopecia has been included in several sets of classification criteria (15, 17, 19). Alopecia in SLE is reported in 17.3-82.5% of patients during the active phase of their disease (18, 31). However, while hair loss is a common symptom in people with SLE, a third of otherwise healthy women are reported to have alopecia in the absence of SLE (20). These figures are in line with our findings.

Non-scarring alopecia as a criterion for the classification of SLE refers to a diffuse pattern of hair loss, described by some as a telogen effluvium. The term 'lupus hair', is used to describe a pattern characterised by short broken hairs around the hairline as a result of growth arrest (32, 50). Within our population, 40 of the 90 patients with SLE had confirmed alopecia. In 7 of these, lupus was the possible cause (17.5%), yet the prevalence was the same in our control group. The clinicians assessed these patients as having alopecia related to lupus on the basis that they presented with diffuse non-scarring, non-patterned alopecia in the absence of another likely cause. Using this definition Chanprapaph et al. found 32 (60%) of their cross-sectional study participants to have alopecia due to SLE (31). However, it is possible that there were other causes, such as iron deficiency, medication or other underlying illnesses.

Androgenic alopecia was the commonest type of hair loss in both patients and controls in this study (30% of cases and 33% controls). Confirmed alopecia in SLE patients was seen in older people (age 41.03; SD 1.37; $p< 0.001$) and alopecia was more common in those diagnosed with SLE at an older age (age 36.35; SD 1.48; $p = 0.048$), which is in keeping with the expected pattern of androgenic alopecia. Androgenic alopecia is reported as the commonest form of non-scarring alopecia in women. Onset is any time after puberty, with 38% of women being affected by age 70 (20, 51). In contrast, studies comparing two UK cohorts (those with juvenile-onset SLE vs adult onset SLE) reported alopecia to be more prevalent in younger age groups (47% vs. 23%, $p<0.001$)(52). In our study, fifteen people with confirmed

alopecia were under the age of 34, with 2 being between the age of 18 and 24 years old. One of the patients with possible lupus hair was 18 years old, while the hair loss in the other patient under 24 was attributed to traction alopecia. Distinguishing between androgenic alopecia and telogen effluvium attributed to SLE should be possible, based on clinical features of androgenic alopecia having a patterned appearance (widening of the central path in females and temporal or vertex hair loss in males) and dermoscopy, showing miniaturisation of >20% of shafts within a given field. Telogen effluvium is characterised by a widespread alopecia, with a positive hair pull test with telogen hairs removed, as shown by the bulb attached to the hair.

Not only is alopecia a criterion for the classification of SLE, but it is also a component of the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) (36). Assessing disease activity is important in clinical trials, in prognostication and in optimising management of patients (4). Among our cases, SLEDAI was increased in patients with self-reported alopecia as compared to those without alopecia ($n = 39$, $M = 3.64$, $SD = 3.44$ vs $n = 51$, $M = 1.98$, $SD = 3.12$; $t = 2.39$, $p = 0.019$, $d = 0.51$). However in those with confirmed alopecia there was no difference in SLEDAI ($n = 40$, $M = 2.88$, $SD = 3.35$ vs $n = 50$, $M = 2.56$, $SD = 3.37$; $t = 0.44$, $p = 0.660$, $d = 0.09$). This difference highlights the importance of how the assessment of alopecia is made. History alone is insufficient and the diagnosis of alopecia needs to be made in association with appropriate clinical and dermoscopic examination. Perhaps this criterion of alopecia for classification and assessing of disease activity should only be used when the diagnosis of the alopecia is confirmed by a dermatologist?

Ines et al. conducted a cross-sectional observational study of patients with a clinical diagnosis of SLE which compared the sensitivity for SLE classification between the ACR 1997 and the SLICC 2012 criteria sets. The SLICC 2012 criteria had a higher sensitivity for SLE classification as compared with the ACR 1997 criteria (93.2% versus 85.6%; $P < 0.0001$) (15). Within this comparison, non-scarring alopecia in the SLICC criteria was found to have a sensitivity of 28.8% (15). Various criteria ranged from a sensitivity of 98.9% (ANA) to 8.6% (neurologic). Petri et al. found non-scarring alopecia to have a sensitivity of 31.9 and a specificity of 95.7 (3).

Unsurprisingly in our population, all cases had a positive ANA as part of their classification criteria. The wide range of sensitivities is likely the basis for the new

EULAR/ACR classification criteria, which uses ANA as an entry criterion. To account for the different sensitivities among the criteria, items are structured in domains and have individual weights (2-10 points), with the highest item being counted. Ten points are required for classification. The new criteria have reached a sensitivity of 96.1% and a specificity of 93.4%, compared to SLICC which had a sensitivity of 89.3% (19). This ensures that classification is not made by counting up a multitude of less sensitive criteria as could be done in the SLICC criteria.

Almost all our patients with SLE were on chloroquine and it is well documented that chloroquine improves cutaneous manifestations in lupus (53).

While alopecia was recorded in the notes as a criterion, clinical details as to whether other causes were considered or excluded were not evident.

CONCLUSIONS

We conducted a cross-sectional cohort study comparing the presence of alopecia between those with SLE and those without. Within our population of 180 people (90 cases and 90 age, sex and race-matched controls) alopecia was found with equal frequency. While 7 patients had alopecia possibly as a result of SLE, the majority of cases and controls with alopecia had androgenic alopecia, which was unrelated to SLE. This similar incidence of alopecia in patients with SLE and in controls highlights the low sensitivity of non-scarring alopecia as a criterion for SLE and further supports the weighting of classification criteria within the various domains in the EULAR/ACR criteria. In view of the challenge of attribution of causes of hair loss, the use of alopecia as a criterion should perhaps be under the guidance of dermatologists.

LIMITATIONS OF STUDY

- The causes of alopecia were determined in the study population by one investigator clinically at the time of seeing the patients, while another investigator based his diagnosis on clinical and dermoscopic photographs.
- Current hair loss was used to assess the possible relationship to SLE and inferences made with regard to alopecia at diagnosis made by the rheumatologist, but without a description of the clinical features at the time of diagnosis. This assumption is open to error.
- Controls were obtained from a dermatology clinic and it is possible that alopecia may be more common in this population as a whole, as it is a reason for referral to dermatology services. Controls were included based on age, sex and race, rather than diagnosis. However, those with known scalp disorders and those with inflammatory or metabolic disorders were excluded from recruitment.
- The cause of alopecia, determined clinically and dermoscopically, was not confirmed by scalp biopsy. Histological examination could have added further information and thus strengthened the study.

SUGGESTIONS FOR FURTHER RESEARCH

Through this study the following areas for further research have been highlighted;

- *Further studies to assess the individual criteria making up the classification criteria of SLE.*

  Although criteria for SLE have been developed largely for the purpose of comparative research studies and trials, classification and diagnosis will frequently concur. This is more likely in the case where criteria used are more specific. Evaluation of the individual criteria as we have done in this study allows for the exclusion or appropriate lower weighting of non-specific criteria as has been implemented in the 2019 EULAR/ACR classification criteria for SLE.

A need to compare classification criteria used in experimental groups with the general population.

While our study had strength in that it was conducted in a multidisciplinary clinic, it would be of value to assess if rate of alopecia was as prevalent in a more general community based population as compared with a dermatology clinic which may have a higher proportion of patients presenting with hair concerns.

Evaluation of classification criteria across all population groups.

Certain patterns of alopecia are more common in specific races e.g. traction alopecia and central centrifugal cicatricial alopecia are more prevalent in black african populations. Having an experimental group with a high proportion of one population group may therefore skew data of alopecia prevalence. It would be interesting to conduct the same research across population groups to assess whether or not findings remain consistent.

Author contributions:

Conception and study design: SJ MN LK. Captured data: LK MN. Data analysis: LK. Development of materials/analysis tools: SJ MN AG LK. Write up: LK SJ MN AG.

Conflict of interest:

Nothing to declare.

Funding:

Not applicable.

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APPENDICES:

Clinical record form- Cases

PATTERN OF ALOPECIA IN SYSTEMIC LUPUS ERYTHEMATOSIS- CLINICAL RECORD FORM

Patient demographics:

A1: Name:_____ A2: Surname: _____

A3: DOB: _____ A4: Age: _____ A4: Sex: Female/Male

A5: Race: African/Mixed/White

Medical history:

B1: Comorbidities (circle):

HPT DM Hypothroidism Asthma COPD Arthritis Other: _____

B2: Allergies: Yes/No Specify: _____

B3: Chronic medications:

_____

_____

B4: Menopause: Y/N

B4.1 Date of last menses: _____

B4.2: Contraception: Y/N

B4.3 HRT: Y/N

Systemic Lupus Erythematosus:

C1: Date diagnosed: _____

C2: Basis for classification: (circle)

Clinical Criteria		Immunologic Criteria	
C2.1	Acute cutaneous lupus	C2.12	ANA
C2.2	Chronic cutaneous lupus	C2.13	Anti-dsDNA
C2.3	Oral or nasal ulcers	C2.14	Anti-Sm
C2.4	Non-scarring alopecia	C2.15	Antiphospholipid Ab
C2.5	Arthritis	C2.16	Low complement (C3, C4, CH50)

C2.6	Serositis	C2.17	Direct Coombs (in absence of haemolytic anaemia)
C2.7	Proteinuria		
C2.8	Neurologic		
C2.9	Haemolytic anaemia		
C2.10	Leukopaenia		
C2.11	Thrombocytopaenia (<100,000/mm^3)		

C3: Was alopecia in criteria for diagnosis of SLE?: Yes/No

C3.1: Would diagnosis have been made in absence of alopecia?: Yes/No

C4. Treatment of SLE

C4.1 Chloroquine: Yes/No date started: _____

C4.2 Immunomodulating therapy: Yes/No

Drug	Dose	Date started
Prednisone		
Cyclosporin		
MMF		
Other		

C5: Lupus disease activity-SLEDAI-2K: (tick and total at end):

Appendix 1. SLEDAI-2K data collection sheet. (Check weight in SLEDAI-2K score column if descriptor is present at the time of the visit or in the preceding 10 days.)

Weight (check)	Descriptor	Definition
8 ❑	Seizure	Recent onset, exclude metabolic, infectious, or drug causes.
8 ❑	Psychosis	Altered ability to function in normal activity due to severe disturbance in the perception of reality. Include hallucinations, incoherence, marked loose associations, impoverished thought content, marked illogical thinking, bizarre, disorganized, or catatonic behavior. Exclude uremia and drug causes.
8 ❑	Organic brain syndrome	Altered mental function with impaired orientation, memory, or other intellectual function, with rapid onset and fluctuating clinical features, inability to sustain attention to environment, plus at least two of the following: perceptual disturbance, incoherent speech, insomnia or daytime drowsiness, or increased or decreased psychomotor activity. Exclude metabolic, infectious, or drug causes.
8 ❑	Visual disturbance	Retinal changes of SLE. Include cytoid bodies, retinal hemorrhages, serous exudates or hemorrhages in the choroids, or optic neuritis. Exclude hypertension, infection, or drug causes.
8 ❑	Cranial nerve disorder	New onset of sensory or motor neuropathy involving cranial nerves.
8 ❑	Lupus headache	Severe, persistent headache; may be migrainous but must be nonresponsive to narcotic analgesia.
8 ❑	Cerebrovascular accident	New onset of cerebrovascular accident(s); exclude arteriosclerosis.
8 ❑	Vasculitis	Ulceration, gangrene, tender finger nodules, periungual infarction, splinter hemorrhages, or biopsy or angiogram proof of vasculitis.
4 ❑	Arthritis	Two or more joints with pain and signs of inflammation (i.e., tenderness, swelling, or effusion).
4 ❑	Myositis	Proximal muscle aching/weakness, associated with elevated creatine phosphokinase/aldolase or electromyogram changes or a biopsy showing myositis.
4 ❑	Urinary casts	Heme granular or red blood cell casts.
4 ❑	Hematuria	More than five red blood cells/high power field; exclude stone, infection, or other cause.
4 ❑	Proteinuria	> 0.5 g/24 hr.
4 ❑	Pyuria	More than five white blood cells/high power field; exclude infection.
2 ❑	Rash	Inflammatory type rash.
2 ❑	Alopecia	Abnormal, patchy, or diffuse loss of hair.
2 ❑	Mucosal ulcers	Oral or nasal ulcerations.
2 ❑	Pleurisy	Pleuritic chest pain with pleural rub or effusion or pleural thickening.
2 ❑	Pericarditis	Pericardial pain with at least one of the following: rub, effusion, or electrocardiogram or echocardiogram confirmation.
2 ❑	Low complement	Decrease in the complement proteins C3 and C4 or in total complement activity (CH50), below the lower limit of normal for testing laboratory.
2 ❑	Increased DNA binding	Increased DNA binding by Farr assay above normal range for testing laboratory.
1 ❑	Fever	> 38°C; exclude infectious cause.
1 ❑	Thrombocytopenia	< 100,000 platelets/$\times 10^9$/L; exclude drug causes.
1 ❑	Leukopenia	< 3,000 white blood cells/$\times 10^9$/L; exclude drug causes.
	Total score	

Reproduced with permission from Gladman et al. (2002).

Alopecia:

D1: Self-reported alopecia: Yes/No

D2: Clinically confirmed alopecia: Yes/No

D2.1 If yes,

D2.1.1. Total % _____ Frontal _____/40 Occipital _____/24 Right Temporal_____/18 Left Temporal _____/18

D2.1.2. Eyebrows Y/N Eyelash Y/N Axilla Y/N Genitalia Y/N
Other:_____

D2.1.3. Scarring: Yes/No

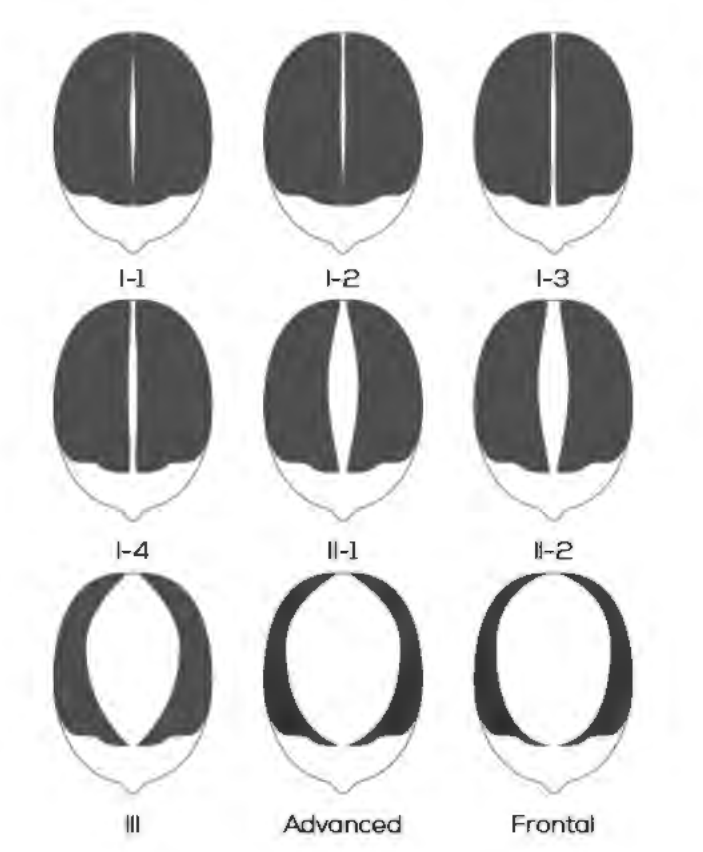
D2.1.4. Epidermal change. Yes/No

D2.1.5. Nails: _____

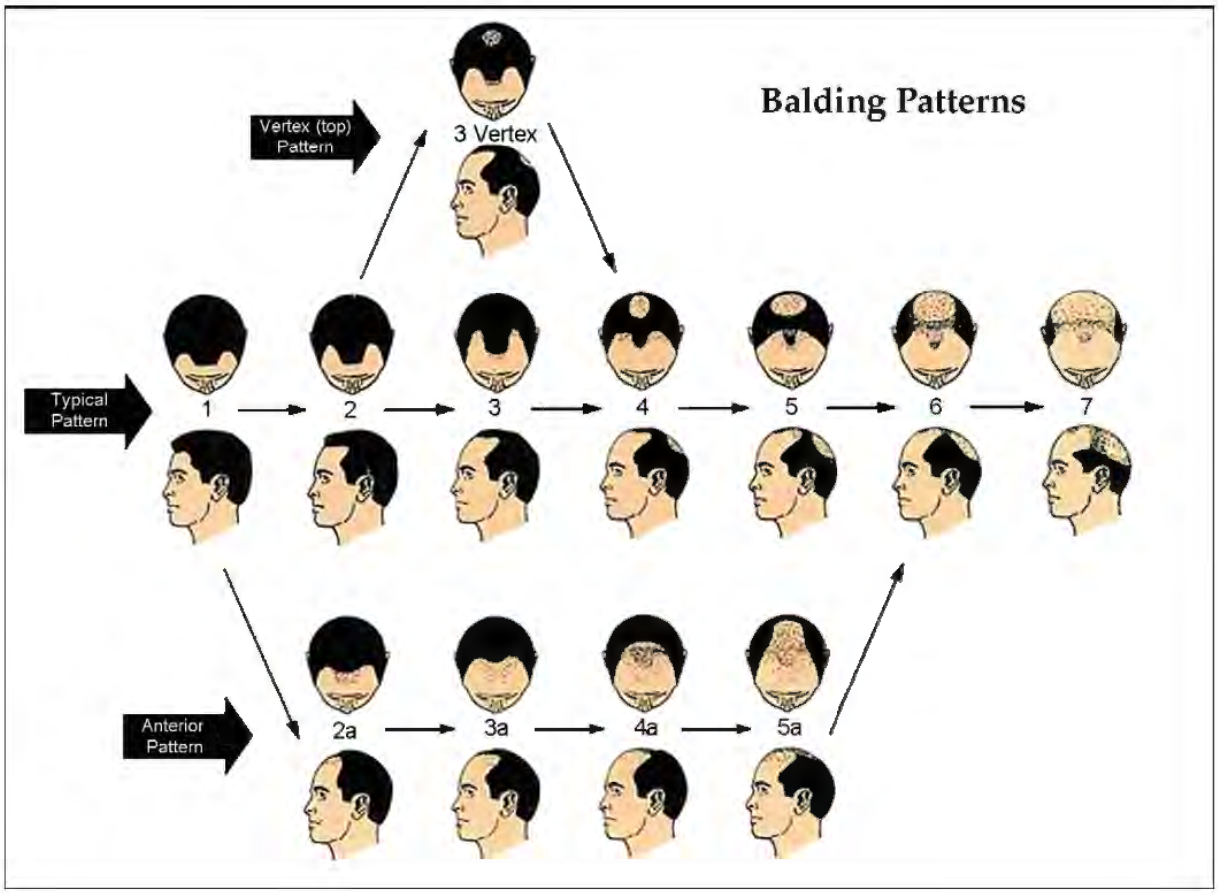
D2.1.6. Hair pull test: _____

D2.1.2 Pattern: Male pattern/ Female pattern/ Traction/ Alopecia Areata

D2.1.2.1: Female androgenic alopecia (circle):



D2.1.2.2: Male androgenic alopecia (circle):



D2.1.3 Dermoscopy:

Consistent with normal scalp		Miniaturization		Loss of perifollicular openings	
Yellow dots		Single hairs emerging from follicle ostia		White dots	
Erythema		Scaling		Follicular plugging	
Atrophy		Telangiectasia		Arborizing and tortuous vessels	
Blue-grey dots		Hair shaft hypopigmentation		Dilated vessels	
Short vellus hairs		Black dots		Tapering (exclamation) hairs	
Broken hairs		Other			

D2.1.4: Pictures number: _____

D3: Specific treatment used for alopecia: Yes /No if Yes specify:

_____

D4: Hair grooming techniques in past year:

Relaxers/chemical straighteners	Y/N	No:
Colouring	Y/N	
Flat ironing	Y/N	
Blow-drying	Y/N	
Swirling	Y/N	
Other:	Y/N	

D5: Current grooming practice:

Relaxers/chemical straighteners	Y/N	Frequency/wk:
Colouring	Y/N	
Flat ironing	Y/N	
Blow-drying	Y/N	
Swirling	Y/N	
Other:	Y/N	

D6: Tests to assess alternate cause of alopecia:

Test	**Value**	**Normal (Y/N)**
Thyroid		
Iron studies		
Syphilis serology		
Fungal brush		

Clinical record form- Controls

PATTERN OF ALOPECIA IN SYSTEMIC LUPUS ERYTHEMATOSIS- CLINICAL RECORD FORM

Patient demographics:

A1: Name:_____ A2: Surname: _____

A3: DOB: _____ A4: Age: _____ A4: Sex: Female/Male

A5: Race: African/Mixed/White

Medical history:

B1: Comorbidities (circle):

HPT DM Hypothroidism Asthma COPD Arthritis Other: _____

B2: Allergies: Yes/No Specify: _____

B3: Chronic medications: _____

_____

B4: Menopause: Y/N

B4.1 Date of last menses: _____

B4.2: Contraception: Y/Nx

B4.3 HRT: Y/N

Alopecia:

D1: Self-reported alopecia: Yes/No

D2: Clinically confirmed alopecia: Yes/No

D2.1 If yes,

D2.1.1. Total % _____ Frontal _____/40 Occipital _____/24 Right Temporal_____/18 Left Temporal _____/18

D2.1.2. Eyebrows Y/N Eyelash Y/N Axilla Y/N Genitalia Y/N
Other:_____

D2.1.3. Scarring: Yes/No

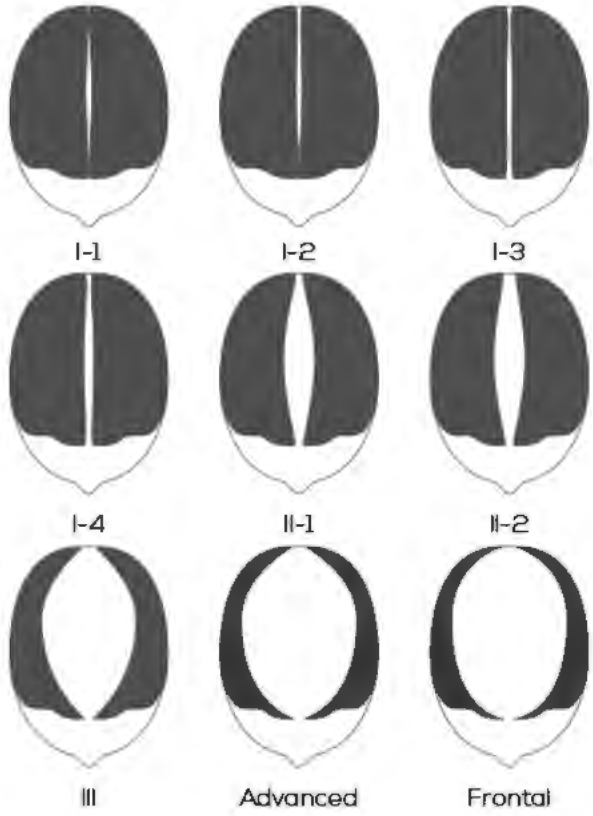
D2.1.4. Epidermal change. Yes/No

D2.1.5. Nails: _____

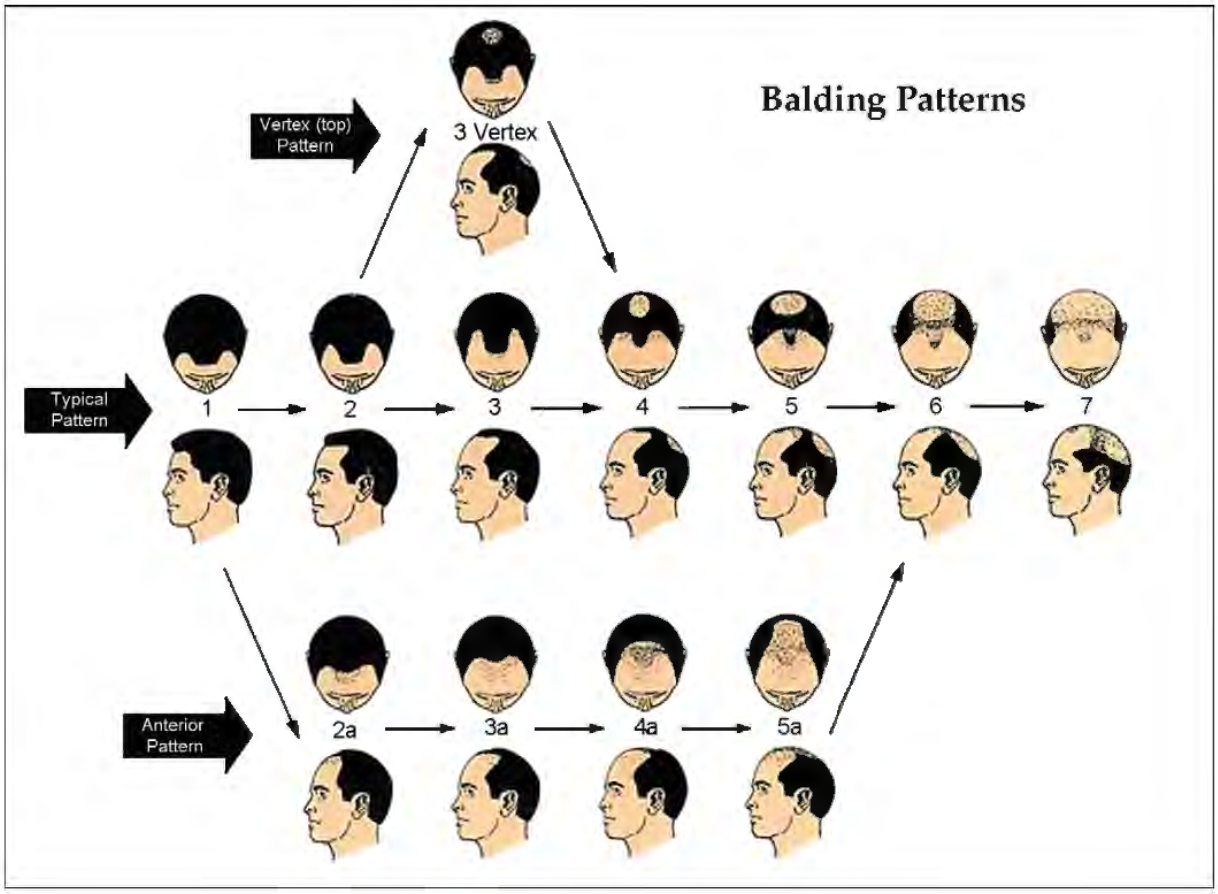
D2.1.6. Hair pull test: _____

D2.1.2 Pattern: Male pattern/ Female pattern/ Traction/ Alopecia Areata

D2.1.2.1: Female androgenic alopecia (circle):



D2.1.2.2: Male androgenic alopecia (circle):



D2.1.3 Dermoscopy:

Consistent with normal scalp		Miniaturization		Loss of perifollicular openings	
Yellow dots		Single hairs emerging from follicle ostia		White dots	
Erythema		Scaling		Follicular plugging	
Atrophy		Telangiectasia		Arborizing and tortuous vessels	
Blue-grey dots		Hair shaft hypopigmentation		Dilated vessels	
Short vellus hairs		Black dots		Tapering (exclamation) hairs	
Broken hairs		Other			

D2.1.4: Pictures number: _____

D3: Specific treatment used for alopecia: Yes /No if Yes specify:

_____

D4: Hair grooming techniques in past year:

Relaxers/chemical straighteners	Y/N	No:
Colouring	Y/N	
Flat ironing	Y/N	
Blow-drying	Y/N	
Swirling	Y/N	
Other:	Y/N	

D5: Current grooming practice:

Relaxers/chemical straighteners	Y/N	Frequency/wk:
Colouring	Y/N	
Flat ironing	Y/N	
Blow-drying	Y/N	
Swirling	Y/N	
Other:	Y/N	

D6: Tests to assess alternate cause of alopecia:

Test	**Value**	**Normal (Y/N)**
Thyroid		
Iron studies		
Syphilis serology		
Fungal brush		

Informed consent form- Cases

DOES ALOPECIA HAVE DIAGNOSTIC WEIGHT IN SYSTEMIC LUPUS ERYTHEMATOSIS

INFORMED CONSENT FORM- Participants

Note: This form, in English or translated into Afrikaans or isiXhosa, was completed by all participants.

I_____ give consent to take part in this study.

It was explained to me that:

- The aim of the study is to identify the way in which hair falls out in patients with systemic lupus erythematosus.
- This will be done by asking me a few questions, examining my folder and making a record of various aspects of my history and blood results.
- My hair and scalp will be examined with a dermatoscope (magnifying instrument) and if alopecia is identified a picture will be taken. Blood tests to assess my thyroid, iron levels and lupus disease activity will also be done to try to find out the cause of my hairloss.
- The results of the study may not directly help me but will help others with similar diseases.
- All my medical details, results and photographs of my scalp will be stored in a secure database that only the doctors working on the study will be able to access.
- If my hair loss requires treatment I may be invited to attend the hair clinic at Groote Schuur Hospital.
- I will not receive any payment for participation in the study as I will be coming to hospital as part of my routine care.
- Although the results of the study may be published in a scientific journal or discussed in scientific meetings, my identity will remain confidential.
- I give permission for photos taken as part of the study to be used if the study is published.
- If I have any problems related to the study I can contact Dr Knight or her colleagues at (021) 404 5269 or (021) 404 5275.
- If I have any problems regarding the conduct of the study or behaviour of the doctors conducting the study I can contact Professor Marc Blockman at 021 406-6496.
- I agree to take part of my own free will and I can withdraw at any time without affecting my future medical care.

Signed____________________________at________________________on_________________

Investigator_____________________________
Witness_______________________________________

Informed consent form- controls

DOES ALOPECIA HAVE DIAGNOSTIC WEIGHT IN SYSTEMIC LUPUS ERYTHEMATOSIS

INFORMED CONSENT FORM- Controls

Note: This form, in English or translated into Afrikaans or isiXhosa, was completed by all participants.

I_____ give consent to take part in this study.

It was explained to me that:

- The aim of the study is to identify the way in which hair falls out in patients with systemic lupus erythematosus. However, hairloss is also common in the general population and therefore patients without Lupus need to be examined to see if the hairloss is due to Lupus or other causes. As I do not have Lupus I will be a control patient representing the general population without Lupus.
- I will be asked a few questions relating to my medical history, medications and hair grooming practices.
- My hair and scalp will be examined with a dermatoscope (magnifying instrument) and if alopecia is identified a picture will be taken. Also, if I am found to have alopecia, blood tests to assess my thyroid and iron levels can be done to try to find out the cause of my hairloss.
- My personal medical details, results and photographs will be stored securely and only seen by the doctors involved in the trial.
- The results of the study may not directly help me but may help patients with alopecia.
- If I am found to have alopecia and my hair loss requires treatment I may be invited to attend the hair clinic at Groote Schuur Hospital.
- I will not receive any payment for participation in the study as I will be coming to hospital as part of my routine care.
- Although the results of the study may be published in a scientific journal or discussed in scientific meetings, my identity will remain confidential.
- I give permission for photos taken as part of the study to be used if the study is published.
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- I agree to take part of my own free will and I can withdraw at any time without affecting my future medical care.

Signed_____at_____on_____

Investigator_____
Witness_____

Ethics

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

Room E53-46 Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6626
Email: shuretta.thomas@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

29 November 2018

HREC REF: 579/2018

Dr S Jessop
Dermatology
G23, NGSH

Dear Dr Jessop

PROJECT TITLE: DOES ALOPECIA HAVE DIAGNOSTIC WEIGHT IN SYSTEMIC LUPUS ERYTHEMATOSUS? (MMED Candidate - Dr L Knight)

Thank you for submitting your response to the Faculty of Health Sciences Human Research Ethics Committee.

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

Approval is granted for one year until the 30 November 2019.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

Please quote the HREC REF in all your correspondence.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please note that for all studies approved by the HREC, the principal investigator **must** obtain appropriate institutional approval, where necessary, before the research may occur.

The HREC acknowledge that the student, Dr Lauren Knight will also be involved in this study.

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE
Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938

HREC 579/2018

UNIVERSITY OF CAPE TOWN

FACULTY OF HEALTH SCIENCES
Human Research Ethics Committee

FHS016: Annual Progress Report / Renewal

HREC office use only (FWA00001637; IRB00001938)			
This serves as notification of annual approval, including any documentation described below.			
☑ Approved	Annual progress report	Approved until/next renewal date	30.05.2022
☐ Not approved	See attached comments		
Signature Chairperson of the HREC/ Designee		Date Signed	6/5/21

Note: Please note that incomplete submissions will not be reviewed.
Please email this form and supporting documents (if applicable) in a combined pdf-file to hrec-enquiries@uct.ac.za.
Please clarify your plan for research-related activities during COVID-19 lockdown

Comments to PI from the HREC
Thank you for the deviation document

Principal Investigator to complete the following:

1. Protocol information

Date (when submitting this form)	04/05/2021		
HREC REF Number	579/2018	Current Ethics Approval was granted until	November 2020
Protocol title	Does alopecia have diagnostic weight in Systemic Lupus Erythematosus?		
Protocol number (if applicable)			
Are there any sub-studies linked to this study?	☐ Yes X No		
If yes, could you please provide the HREC Ref's for all sub-studies? **Note:** A separate FHS016 must be submitted for each sub-study.			
Principal Investigator	Dr Susan Jessop		

(Note: Please complete the Closure form (FHS010) if the study is completed within the approval period)

Institutional approval

Western Cape Government
Health

GROOTE SCHUUR HOSPITAL
Enquiries: Dr Bernadette Eick
e-mail: GSHReserach.Request@westerncape.gov.za

Dr Susan Jessop
MEDICINE - DERMATOLOGY

E-mail: drlaurenknight@gmail.com

Dear Dr Jessop,

RESEARCH PROJECT: Does Alopecia Have Diagnostic Weight In Systemic Lupus Erythematosus

Your recent letter to the hospital refers.

You are granted permission to proceed with your research, which is valid until **30 May 2022.**

Please note the following:

a) Your research may not interfere with normal patient care.
b) Hospital staff may not be asked to assist with the research.
c) **Confidentiality must always be maintained.**
d) No additional costs to the hospital should be incurred as indicated in your Annexure 2 i.e. Lab, consumables or stationery. **If access to TRACK Care/NHLS is required, kindly attach our letter of approval to the application form and approach Information Management to assist with data.**
e) **No patient folders may be removed from the premises or be inaccessible.**
f) Please provide the research assistant/field worker with a copy of this letter as verification of approval.
g) **Should you at any time require photographs of your subjects, please obtain the necessary indemnity forms from our Public Relations Office (E45 OMB or ext. 2187/2188).**
h) Should you require additional research time beyond the stipulated expiry date, please apply for an extension.
i) Please discuss the study with the HOD before commencing.
j) Please introduce yourself to the person in charge of an area before commencing.
k) On completion of your research, please forward any recommendations/findings that can be beneficial to use to take further action that may inform redevelopment of future policy / review guidelines.
l) Please contact Michelle Riley (Patient Fees) at ext. 2276 to ascertain if there will be charges for conducting the Research and to obtain a quote or to discuss charges
m) **Kindly submit a copy of the publication or report to this office on completion of the research.**
n) **At no time should any posters encouraging patients to partake in research, be displayed within a clinical area.**
o) **Please adhere to ALL COVID-19 regulations and Groote Schuur Hospital policies.**

I would like to wish you every success with the project.

Yours sincerely

***p.p.* DR BERNADETTE EICK**
CHIEF OPERATIONAL OFFICER
Date: 25 August 2021

C.C. Mr. L. Naidoo / Professor N. Ntusi / Professor N. Khumalo

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Head of division approvals (Dermatology & Rheumatology)

UNIVERSITY OF CAPE TOWN

RHEUMATOLOGY
IN GOOD HANDS UNIVERSITY OF CAPE TOWN

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To the Superintendent, Groote Schuur Hospital

Re: MMed research project "Does alopecia have diagnostic weight in systemic lupus erythematosus?"

I would like to confirm that Dr Lauren Knight has been granted permission to recruit participants from the rheumatology outpatients clinic in accordance with her protocol requirements as approved by ethics HREF 579/2018.

The study is being supervised by:

Dr Susan Jessop

Dr Reginald Ngwanya

Dr Ayanda Gcelu.

This recruitment should only take place after informed consent has been obtained from the participants.

Please contact me as necessary.

Bridget Hodkinson
Professor and Head
Rheumatology, Department of Medicine
Groote Schuur Hospital
Faculty of Health Sciences, University of Cape Town

UNIVERSITY OF CAPE TOWN

Department of Medicine
Division of Dermatology

Head: Associate Professor NP Khumalo (email: n.khumalo@uct.ac.za)
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05/12/2018

To Whom it may concern

Re: MMed research project "Does alopecia have diagnostic weight in systemic lupus erythematosus?"

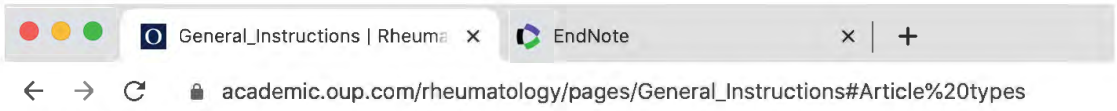
This letter serves to confirm that Dr Lauren Knight has been granted permission to recruit participants from the dermatology outpatient's clinic in accordance with her protocol requirements as approved by Faculty of Health Sciences Human Research Ethics Committee.

This recruitment should only take place after informed consent has been obtained from the participants.

Yours Sincerely

Nonhlanhla P Khumalo
Head of the Division of Dermatology.

Instruction for authors (Journal of Rheumatology- Oxford)



2A. Article Types

Original Article

Original articles are based on clinical, laboratory, therapeutic and translational research.

- Title page
- Abstract (250 words, divided into Objectives, Methods, Results and Conclusion)
- Clinical trial registration number (for all RCTs)
- Keywords (up to 10 – please note that the word count refers to individual words, not phrases)
- Key messages (up to 3, maximum 15 words each)
- References (up to 50)
- Tables/figures (up to 6, not including supplementary material)
- Word count: 3,500