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ETHNIC SKIN AND HAIR DISORDERS IN KWAZULU-NATAL

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A STUDY OF THE SPECTRUM OF ETHNIC SKIN AND HAIR DISORDERS, AND THE COMPOSITION AND USE OF SKIN-LIGHTENING PREPARATIONS, TRADITIONAL COSMETICS AND SUNSCREEN

PhD THESIS

BY NCOZA CORDELIA NOXOLO DLOVA

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Submitted in fulfilment of the degree of Doctor of Philosophy

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DECLARATION

I, **Ncoza Cordelia Noxolo Dlova**, declare that:

1. The research reported in this dissertation, except where otherwise indicated, is my original work.

2. This dissertation has not been submitted for any degree or examination at any other university.

3. This dissertation does not contain other person's data, pictures, graphs or other information, unless specifically acknowledged as being sourced from other persons.

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Date:_____

As the candidate's supervisor, I agree to the submission of this dissertation

Supervisor: Prof Richard Hift: _____

DEDICATION

To my husband, Themba Mabaso for his scientific, emotional support and love, and my son, Wakithi Mabaso, for his encouragement, support, understanding and love. I am grateful to both, for being optimistic about my work even in the most challenging times for never standing in my way and allowing me the freedom to do as I please in order to achieve my academic aspirations.

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PERSONAL CONTRIBUTION TO THE WORK DESCRIBED IN THIS DISSERTATION

Since all or most of the work of this project is presented in the form of multi-authored papers, the candidate is required to state their personal contribution to the work described in each chapter. I declare my contribution as follows:

Chapter 2 - The spectrum of skin diseases in a black population in Durban, KwaZulu-Natal, South Africa.

Conceptualised the study, developed the methodology, collected the data, interpreted the data, contributed to the discussion and preparation of the manuscript as first author and submitted the papers. Statistical analysis was performed by a statistician, Ms Anneke Grobler. The other co-authors assisted with data collection and contributed to the editing of the draft manuscript.

Chapter 3 - Skin lightening practices an epidemiological study of South African women of African and Indian ancestries.

Designed the study, developed methodology, generated data, interpreted the data, contributed to the discussion and preparation of the manuscript as first author and submitted the paper. The statistician, Ms Anneke Grobler analysed the raw data. The other co-authors assisted with the design of the study and contributed to the editing of the draft manuscript.

Chapter 4 - Women's perceptions of the benefits and risks of skin-lightening creams in two South African communities.

Conceptualised the study, developed the methodology, collected the data, interpreted the data, contributed to the discussion and preparation of the manuscript as first author, and submitted the paper. The statistician, Ms Anneke Grobler analysed the raw data. My co-authors assisted with the design of the study and to the editing of the draft manuscript.

Chapter 5 - Skin-lightening creams used in Durban, South Africa.pdf

Conceptualised the clinical/laboratory study, purchased and collected study samples and provided the chemical standards, contributed to the interpretation of the data, contributed to the preparation of the manuscript as first author and submitted the paper to a clinical dermatology journal. Miss Nicole Hendricks conducted the laboratory experimental work and Prof Bice Martincigh supervised the experimental work which led to an Honours degree for Miss N Hendricks. Miss Hendricks did not contribute to the writing of the manuscript. Prof B Martincigh also contributed to the methodology section and part of the discussion on the submitted manuscript.

Chapter 6 - A survey of skin cancer awareness, sunscreen use and risk-appropriate behaviour among South Africans indicates a substantial knowledge deficit.

Conceptualised the study, developed the methodology, collected the data, interpreted the data, contributed to discussion and preparation of the manuscript as first author and submitted the paper. Dr Raechele Gathers contributed to the design of the study and to the discussion in the submitted manuscript. The other co-authors also participated in preparing and editing the draft manuscript. The statistician, Ms Anneke Grobler, and Prof R Hift analysed the raw data.

Chapter 7 - Chemical analysis and in vitro UV-protection characteristics of clays traditionally used for sun protection in South Africa.

Conceptualised the clinical/ laboratory collaborative study, identified and collected the clay samples, contributed to the interpretation of the data, contributed to the discussion and preparation of the manuscript as first author and submitted the paper to a clinical dermatology journal. Dr Elizabeth Mwangi performed the initial laboratory analysis supervised by Prof Dulcie Mulholland for her PhD degree. Prof Bice Martincigh subsequently improved the experimental methods used by Dr Elizabeth Mwangi and supervised Miss Funani Nevondo with a further analysis of the clays using the X-ray fluorescence, X-ray powder diffraction, Fourier transform infrared spectroscopy, transmission electron microscopy and thermogravimetric analysis. Prof Beverly Summers conducted the *in vitro* SPF analysis of the clays. Prof Bice Martincigh and Prof Beverly Summers participated in the writing of the paper especially the experimental aspect and part of the discussion. Dr Elizabeth Mwangi did not contribute to the writing of the manuscript.

Chapter 8 - Non-toxic melanin production inhibitors from Garcinia livingstonei (Clusiaceae).

I made the clinical observation on the use of plants by rural women for purposes of skin lightening and rejuvenation. I then conceptualised the study and approached Prof Dulcie Mulholland to collaborate with me. I collected and identified the samples, contributed to the writing and discussion of the paper. Dr Elizabeth Mwangi, a PhD student, supervised by Prof Dulcie Mulholland and co-supervised by myself conducted all the laboratory experimental studies and used this for a PhD dissertation. Dr Nick Plant supervised Dr Elizabeth Mwangi with the *in vitro* screening of compounds. Dr Neil Crouch assisted with the botanic identification of the plant species. I contributed to the discussion and preparation of the manuscript together Prof D Mulholland, Dr N Plant, and Dr Phillip Coombes. Prof D Mulholland submitted the paper in an Ethnopharmacology journal.

Chapter 9 - Autosomal dominant inheritance of central centrifugal cicatricial alopecia in black South Africans.

Conceptualised the study, developed methodology, performed the skin biopsies, interpreted the data, contributed to discussion and preparation of the manuscript as first author and submitted the paper.

Chapter 10 - Central centrifugal cicatricial alopecia: possible familial aetiology in two African families from South Africa.

Identified the cases, performed the skin biopsies, contributed to the discussion and preparation of the manuscript as first author and submitted the paper.

Chapter 11 - Frontal fibrosing alopecia - A clinical review of 20 black patients from South Africa.

Conceptualised the study, developed the methodology, performed the skin biopsies, interpreted the data, contributed to the discussion and preparation of the manuscript as first author and submitted the paper.

Chapter 12 - Frontal fibrosing alopecia and lichen planus pigmentosus: Is there a link?

Conceptualised the study, developed the methodology, performed the skin biopsies, interpreted the data, contributed to the discussion and preparation of the manuscript as first author and submitted the paper

Chapter 13 - Frontal fibrosing alopecia in an African man.pdf

Identified the case, performed the skin biopsy, contributed to the discussion and preparation of the manuscript as first author and submitted the paper.

Chapter 14 - Familial frontal fibrosing alopecia

Identified the cases, performed the skin biopsies, contributed to the discussion and preparation of the manuscript as first author and submitted the paper. Prof Antonella Tosti contributed her cases and edited the paper.

Chapter 15 - Quality of life in South African black women with alopecia: A pilot study

Conceptualised the study, developed the methodology, collected the data, contributed to the discussion and preparation of the manuscript as first author and will be submitting the paper. Prof Atonella Tosti contributed to the development of the patient survey questionnaire and editing of the manuscript. Drs G. Fabbrocini, C. Lauro, and M. Spano assisted with raw data analysis, interpretation of the results, tables and graphs as well as participating in writing of the paper. The other co-authors assisted with the editing of the manuscript.

REFERENCING

Published manuscripts reproduced in this dissertation use the referencing system required by the specific journal in which they were published. Since this is in most instances the Vancouver system, I have formatted the unpublished manuscripts (Chapters 6 and 15) in this format, with citations shown as a superscript. The bibliography for each chapter is found at the end of that chapter, as appropriate to a journal publication.

The Introduction and Conclusion (Chapters 1 and 16) use the Vancouver system: citations are enclosed in square brackets thus [23]; to distinguish them from references contained within the manuscripts. The bibliography is provided immediately after Chapter 16, before the appendices.

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INTRODUCTION, RESEARCH PAPERS AND DISCUSSION

CHAPTER 1
INTRODUCTION

THE IMPORTANCE OF SKIN DISORDERS

The skin is the largest organ of the body. It is the barrier that constitutes the body's first line of defense against external environmental hazards [1], thus maintaining a safe internal environment conducive to normal physiological function [2].

Skin disorders are common in all populations. The International Classification of Disease 10 index lists over 1,000 skin or skin-associated ailments, yet skin disease continues to receive relatively little attention in national and global health [3]. Between 30% and 70% of people are reported to experience significant skin disease [3, 4] during their lifetimes. As with all diseases, accurate data on the distribution and prevalence of individual skin disorders will provide key information for the rational allocation of health resources within communities and will provide an evidence base for policy in a number of domains, including health, education and regulatory [3, 5].

ETHNODERMATOLOGY

Ethnodermatology is a rapidly growing subspecialty within dermatology, and concerns itself with the study and treatment of 'ethnic' skin, given that African ethnic groups share closely related skin features, share similar reaction patterns to certain cutaneous stimuli and develop specific cutaneous disorders [6].

The terminology of race and ethnicity is contentious. For the purposes of this dissertation we have chosen to use the terms "white" to describe light-skin subject of European descent (a group frequently euphemistically termed "Caucasian" though the term is inexact and its use is currently questioned). We do not wish to characterise a large (indeed the predominant) proportion of the world's population who are not of European extraction and have darker skins in terms of negatives such as "non-white" or "non-Caucasian". Accordingly we refer to such populations as "ethnic", and further use the term *ethnic* to qualify nouns such as skin and disease. Where necessary, we will specify a specific population as African (implying sub-Saharan African) or Indian (which in our context, means South African citizens of Indian descent). The term *black* is however reserved for instances where attention is drawn to specific contrasts between the skins of white populations and those of other ethnic populations.

Ethnodermatoses are those skin conditions specific to people of different particular ethnicity, primarily black [7]. Recognition and diagnosis of ethnodermatoses necessitates a comprehensive understanding of the influence of ethnicity on the skin, of how it affects disease presentation and how therapy can be optimally adjusted for specific groups [7-9]. Yet, while the majority of the world's population is predominantly not of European descent, with approximately 80% possessing pigmented skin [10], there are limited data on the epidemiology of skin diseases in these subjects.

Conventional research and training in dermatology has rarely focused on 'skin of colour' or ethnic skin [11], leading to a lack of reliable data on the distribution of disease in ethnic populations, on aspects of pathophysiology peculiar to ethnic skin and its response to therapy.

However, recent years have seen a significant increase in research directed at the study of ethnic skin. This is in part, due to demographic changes in developed countries resulting from global migration as well as increasing affluence of people of colour, leading to an increased call on health-care resources [6, 12].

Whereas 32.8% of the United States population in 2006, it is projected that the sector will constitute the majority of the population by 2050 [13]. There is therefore an urgent imperative for substantial research in ethnodermatology, such that this large and overlooked population can receive the benefit of diagnosis, management and community interventions precisely targeted at the disease spectrum relevant to them [8, 10]. As part of this, it is essential that clinicians are familiar with the unique dermatoses most relevant to ethnic communities, as well as those differences in more widely spread disorders which are peculiar to ethnic skin.

THE SKIN

Fitzpatrick's classification of skin types

For the purposes of this thesis we define "ethnic skin" as the darker skin types found in ethnic populations, i.e. Fitzpatrick skin types IV, V, and VI [10]. Type IV is light brown in tone, burns minimally and tans well; type V is brown in skin tone, rarely burns and tans deeply; type V1 is dark brown in tone, never burns and tans deeply. Most Africans, African-Americans, Asians, Hispanics, Native Americans, Native Australians and natives of the far south eastern, Caribbean, and Hawaiian Islands and their diaspora fall into one of these categories. The majority of the South African population can be categorised as having skin colour corresponding to Fitzpatrick skin type IV-VI. This population includes sub-groups of African ancestry, Indian and 'coloured' people of variably mixed European, African and Khoi ancestry.

Physical characteristics of ethnic skin

Studies in the literature comparing racial differences in skin structure, function and biochemistry are often confusing, or inconclusive due to lack of standardized study design, absence of objective methodology, small sample size, age and differences in age, anatomic site and climatic conditions [8].

There are however marked differences between ethnic and white skins. The epidermis in ethnic skin has more layers to the stratum corneum and an increased ceramide content in comparison with the skin of white subjects [8, 12]; these differences may result in varying responses to skin irritants. Differences are also seen in the dermis of Africans, which is slightly thicker and more compact compared to that of white skin (51 ± 2 and 57 ± 2 μm) respectively [14].

Melanin is the major factor in the determination of skin colour. Ethnic skin has a higher eumelanin to pheomelanin ratio and melanin is effectively dispersed, providing increased

protection against ultraviolet radiation (UVR) [8, 15, 16]. The amount of epidermal melanin within melanosomes is significantly higher in darker compared to lighter skin types, [17] and is largely responsible for skin tone [18].

Although the number of melanocytes is similar in all races, there are differences in melanocyte activity and in the characteristics of the melanosomes [19]. In ethnic skin, melanosomes are distributed throughout the entire epidermis including the upper epidermal layers whereas in white skin, melanosomes are confined to the stratum basale and are absent in the upper epidermal layers. Fig 1.[20]. Ethnic skin patients have larger, more dispersed melanosomes compared to smaller and aggregated melanosomes in whites [8, 21]. The extent of these these differences correlates closely with skin colour.

It has been shown that on average the epidermis in individuals of African origin provides a sun protection factor (SPF) of 13.4 [22]. Although the increased melanin provides protection against the harmful effects of UV radiation including photodamage and skin cancers, it also makes darkly pigmented skin more vulnerable to dyschromia as a result of trauma and inflammation [23].

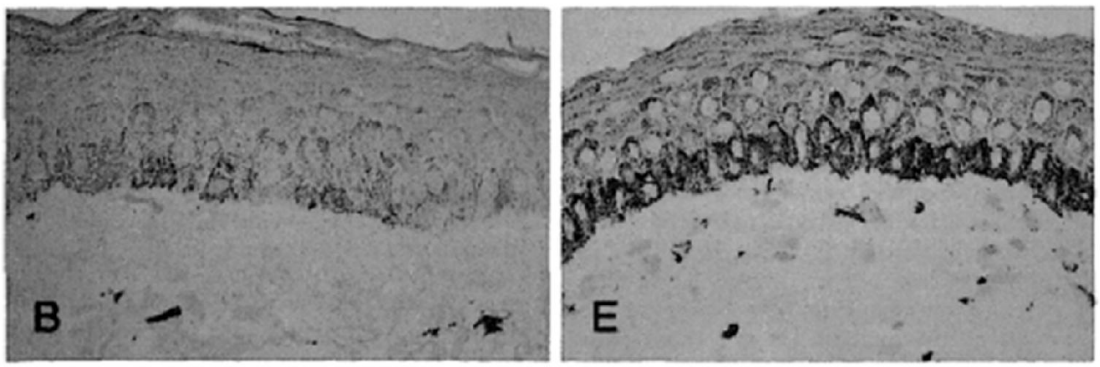

Fig. 1 A, Facial skin of a 40-year old, fair skinned white woman. Melanosomes have sparse and patchy distribution and minimal extension through upper epidermal layers. B, facial skin of a 41-year old ethnic woman. Larger, denser population of melanosomes with greater distribution within upper epidermal layers. (Adapted from Montagna and Carlisle [20].

Collagen fibre bundles are larger in ethnic skin whereas they are smaller and closely stacked in white skin. There are fewer fibroblasts in whites compared to the numerous, larger, binucleated and multinucleated fibroblasts in their ethnic counterparts. Ethnic skin has an increased number of macrophages in the papillary dermis and a decreased amount of collagenase. This partly explains the high tendency to keloid formation among ethnic populations [12, 21]. Elastic fibres within white skin are more numerous and show features of elastosis compared to Ethnic skin, which has less fibres and less elastosis. Racial differences in sebaceous gland size have been suggested, though the evidence is as yet inconclusive [12].

Hair texture varies greatly even within the black groups, from the short, tightly curled hair of sub-Saharan Africans to the long straight hair of Asians [24].

ETHNODERMATOSES

The biological differences between white and ethnic skin have major clinical implications. Some of these are biological. For example, the increased melanin content in the epidermis leads to low rates of skin cancer and increased melanosome dispersion protects against cutaneous photo-aging effects; on the other hand ethnic skin is markedly prone to pigmentation disorders and dyschromia, whereas differences in hair structure may predispose to certain types of alopecias in ethnic populations [8, 25].

Biologically influenced skin conditions with a strong genetic association [26, 27] such as keloids, dermatitis papulosa nigra, pseudofolliculitis barbae and central centrifugal cicatricial alopecia (CCCA) are prevalent in people of African ancestry, while dysplastic naevi are common in those of European ancestry [9, 27, 28]. Inherited differences may also act indirectly for example by affecting an individual's response to pharmacotherapy [8, 29].

Most ethnodermatoses are however, markedly influenced by cultural factors and cosmetic practices, which in turn are influenced by level of education, income and belief systems [8, 30]. A number of ethnodermatoses are related to cosmetic practices, such as exogenous ochronosis which may be caused by unsupervised and prolonged use of high concentrations of hydroquinone to lighten the skin [31-34] as well as pomade acne, secondary to use of commedogenic hair pomades [35-37]. Cupping, coining and moxibustion are traditional practices which may result in cutaneous manifestations [10]. Furthermore the widespread use of traditional medicinal plants and herbal remedies, particularly prevalent among lower socio-economic groups, may result in allergic or irritant contact dermatitis. Prolific use of chemical skin lightening preparations, which has been extensively reported in South Africa and other parts of Africa [38-40], commonly results in adverse effects such as dyschromia and steroid-induced acne. Mechanical pulling of the hairline as practised for certain hair grooming hairstyles often result in traction alopecia. Both traction alopecia and CCCA are commonly seen in black and Hispanic patients [30, 41, 42].

Ethnicity has been shown to have a significant impact on the clinical manifestations and severity of dermatoses [7, 8, 42, 43], and the presentation of dermatoses is often unique to ethnic populations.

The spectrum of skin diseases seen most commonly among ethnic populations include eczemas, acne, pigmentary disorders, skin bleaching, skin infections, hair disorders, keloids and urticarias [44-46]. The 2003 Jamaican study performed by Dunwell and Rose found that acne vulgaris and seborrhoeic eczema occurred in 29 and 22% of the study cohort respectively. With pigmentary disorders, these were the three most common dermatoses encountered [47]. A study on black people living in South London (UK) found that acne (13.7%), acne keloidalis (13.7%) and eczema (9.6%) were the three most common skin diseases [48]. Nnoruka found eczema to be the most common diagnosis in a Nigerian study, accounting for 24.9% of dermatoses, followed by infections and parasitic infestations (19.1%) [49]. Dyschromia and skin infections are also significant causes of dermatologic disease in ethnic patients [50].

Acne and eczema have been reported to be the most common conditions seen within the South African black population [46]. We have found that this is followed by pigmentary disorders, as described in this dissertation. There are however few data on skin conditions such as abuse of skin lighteners, pigmentation disorders, albinism and skin cancer among the African population. The first of our studies set out to identify the ethnodermatological issues relevant to ethnic skin in South Africa.

AIM OF THE STUDY

The work summarised within this dissertation arises from a number of related studies focussing on 5 key areas, and provides a broad narrative on ethnodermatology in South Africa, with a specific focus on the ethnic population of the province of KwaZulu-Natal. These studies are:

1. Delineation of the spectrum of skin diseases among the African population in a private dermatology clinics (Chapter 2).

2. Skin-lightening practices among South African women of African and Indian ancestry (Chapter 3).

3. Knowledge of and exposure to skin-lightening preparations among African and Indian women (Chapter 4).

4. The chemical constituents of commonly used, self-prescribed skin-lightening preparations (Chapter 5).

5. Knowledge regarding skin cancer risks and compliance with preventive measures among different ethnic groups (Chapter 6).

6. Chemical and efficiency analysis of clays traditionally used as sunscreens by African women (Chapter 7).

7. Analysis of indigenous plants used as traditional skin medicinals (Chapter 8).

8. Inheritance of central centrifugal cicatricial alopecia (Chapter 9).

9. A case series of central centrifugal cicatricial alopecia suggesting a familial aetiology (Chapter 10).

10. Frontal fibrosing alopecia (Chapter 11).

11. Frontal fibrosing alopecia; a possible link with lichen planus pigmentosus (Chapter 12).

12. Familial frontal fibrosing alopecia (Chapter 13).

13. Case report: frontal fibrosing alopecia in an African male (Chapter 14).

14. Impact of alopecia on quality of life in African women: a pilot study (Chapter 15).

15. Discussion and Conclusions (Chapter 16).

The introduction and background, details of subjects and methodology, results, discussion and conclusion are fully reported in the publications which constitute the major part of this dissertation. The purpose of Chapters 1 and 16 is to contextualise these studies.

CHAPTE R 2

The spectrum of skin diseases in a black population in Durban, KwaZulu-Natal, South Africa

Dlova NC, Mankahla A, Madala N, Grobler A, Tsoka-Gwegweni J, Hift RJ. The spectrum of skin diseases in a black population in Durban, KwaZulu-Natal, South Africa. Int J Dermatol 2014 [Cited 18 December 2014] DOI: 10.1111/ijd.12589. [Epub ahead of print]

International Journal of Dermatology

Report

The spectrum of skin diseases in a black population in Durban, KwaZulu-Natal, South Africa

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Abstract

Background Precise knowledge of the prevalence and spectrum of skin diseases in a population allows for effective planning for provision of dermatology services and distribution of resources. There are no published data on the epidemiology of skin disorders in Durban, KwaZulu-Natal.

Objective We investigated the prevalence of skin diseases in black African patients attending a predominantly black private healthcare facility and profiled the patients.

Methods Clinical charts of all black African patients seen between January 2003 and December 2010 in a private practice in Durban were reviewed. The diseases seen were described and the prevalence calculated.

Results A total of 6664 patient charts were reviewed. The five most common conditions were acne, eczemas, dyschromias, infections, and hair disorders. These data agree with reports from other parts of the world.

Limitations Selection bias was presented by a single private practice, thus data may not be fully representative of our population.

Conclusion Acne, eczemas, dyschromias, infections, and hair disorders are, in that order, the five most common disorders encountered.

Introduction

Knowledge of the incidence and spectrum of skin disease in a population allows for effective planning to provide appropriate dermatology services, distribute resources, institutionalize appropriate preventative measures, and target future research.[1] Skin disease patterns have been shown to be influenced by level of education, income, belief systems, as well as cultural habits and customs.[2] Skin diseases pose a significant public health problem in Africa and the developing world in general, and are mainly a result of common conditions that are due to preventable infections and infestations. Infectious dermatoses account for up to 85% of skin conditions in Tanzania, 78% in Malawi, 71% in Ethiopia, and 40% in Uganda.[3]

The objective of the study was to determine the prevalence of skin diseases in black patients attending a predominantly black private healthcare facility, and to investigate their distribution. For the purposes of this study, black refers to patients of African ancestry.

Of the 50.6 million inhabitants of the Republic of South Africa, KwaZulu-Natal (KZN) Province has the second largest population with 10.8 million (21.4%) people after Gauteng, with 11.3 million (22.4%) inhabitants.[4] Migration from rural to urban areas significantly contributes to the growth of the urban population with some living in informal settlements and the Durban Metropolitan Area (DMA) is experiencing a rapid population growth rate due to increasing urbanization, migration, and natural growth. Recent national surveys have

indicated a decline in the rates of increase in natural growth, attributable largely to a general decrease in family size and the impact of AIDS.[5] Urbanization levels for KZN are expected to increase from 59% in 2010 to 62% in 2020. This implies that in 10 years time, almost two-thirds of the total provincial population will be living in urban areas, of which the DMA is the largest[5] and may result in a changed profile of skin conditions in comparison with that reported by older studies.[6–8]

Previous epidemiological studies in South Africa have reported eczema, infections, and acne as the three of the most common dermatoses in black South Africans.[6–8] These studies have provided valuable insights into the epidemiology and prevalence of skin diseases in this group; however, they reported mainly on patients attending public healthcare facilities in other provinces (Table 1). There are no published data for KZN, nor indeed any recent data on the epidemiology of skin diseases in South Africa. The last study was undertaken 10 years ago by Hartshorne in Johannesburg.[7]

Materials and methods

This is a retrospective cross-sectional chart review targeted at all patients presenting with skin conditions at a private dermatology practice situated in central Durban. All records were eligible for inclusion; where no clear diagnosis was recorded, that patient was excluded from the analysis.

Ethical approval was obtained from the UKZN Biomedical Research Institutional Review Board (BE 180/11). Charts of all black patients seen between January 2003 and December 2010 (inclusive) were reviewed. All the patients were seen by three registered dermatologists who are familiar with African skin. The diagnosis was made on clinical grounds, supported by relevant laboratory investigations or histopathology where necessary. Only data relating to their first visits and main diagnosis were recorded for each patient.

Skin diseases were divided into the following broad disease categories using the International Classification of Diseases (ICD 10)[9]: acne, eczemas, dyschromias, infections, hair disorders, and skin neoplasms. Specific subtypes of these categories were also documented. Dermatosis that did not belong to the above broad disease categories were recorded under "other." The data were captured on a Microsoft Excel spreadsheet and analyzed using SAS (v 9.1.3, SAS institute Inc., Cary, NC, USA). Confidence intervals (CI 5%) were calculated for all prevalences.

Results

A total of 7064 patient charts were reviewed between January 2003 and December 2010, of which 6664 were black. Adults accounted for 86.9% and were aged between 19 and 86, with a mean age of 35.6 years, while the children were aged between 1 and 18 years, with a mean age of 11.3 years (74.1% of the patients were female and 25.9% male).

Acne was the most frequent diagnosis, with a prevalence of 44.3% (CI: 42.3–45.5%) (Table 2), with a prevalence of 48.0% (CI 46.6–49.4%) in males and 33.6% (CI 31.4–35.9%) in females. It was most prevalent in the age group 13–24 years (Table 4).

Eczemas were the second most common diagnosis, with a prevalence of 15.9% (CI: 15.1–16.8%). Table 3 provides the prevalence of skin diseases by disease category. The prevalence of eczema in females was 14.0% (CI 13.0–15.0%) and in males 21.5% (CI 19.6–23.6). The third most prevalent skin disease was dyschromia (see Table 3 where the diseases are listed by subtype). Infection was the fourth most frequent category: the common-

Table 1 Previous epidemiology of skin diseases studies conducted in South Africa

Year	Authors	Number of persons and population surveyed	Top 5 conditions seen	Reference
1957	Findlay	600 black: Pretoria	Infections, eczemas, acne, pellagra	Findlay[28]
1961	Schulz	2000 black: Pretoria 900 black: Pretoria 1000 black: Bloemfontein	Eczemas, infections, acne, pellagra	Schulz *et al.*[29]
1966	Ross	2100 black: Sibasa, Northern Transvaal	Infections, acne, eczemas, pellagra, papular urticaria	Ross[30]
1968	Park	4544 black: Pretoria	Infections, eczemas, acne, pellagra, porphyria (hepatic)	Park[31]
1969	Findlay	3935 black: Pretoria	Acne, eczema, infections, papular urticaria	Findlay[32]
1970	Dogliotti	2000 black: Johannesburg	Infections, eczemas, acne, pellagra, FDE	Dogliotti[33]
1975	Dogliotti	9474 black: Johannesburg	Infections, eczemas, acne, pellagra, psoriasis	Dogliotti[8]
1982	Schulz	5000 black: Pretoria	Eczemas, infections, acne, bleaching cream dermatitis, pityriasis rosea	Schulz[6]
2003	Hartshorne	5355 black: Johannesburg	Eczema, infections, acne, benign tumours, psoriasis	Hartshorne[7]
2013	Dlova (current study)	6664 black: Durban	Acne, eczema, dyschromia, infections, hair disorders	

Table 2 Prevalence of skin diseases by disease category

Skin disease category	Number *n* = 6664	Prevalence (%)	95% Confidence interval
Acne	2953	44.3	42.3–45.5
Eczemas	1061	15.9	15.1–16.8
Dyschromia	775	11.6	10.9–12.4
Infections	668	10.3	9.6–11.1
Hair disorders	318	4.8	4.26–5.28
Skin neoplasms	14	0.2	0.1–0.4
Other	875	31.1	

CI, confidence interval.

Table 3 Acne, eczema, and dyschromia prevalence by subtype

	Number *n* = 6664	Prevalence (%)	95% Confidence interval
Acne type			
Unspecified	1935	29.0	28.0–30.2
Acne vulgaris	687	10.3	9.6–11.1
Acne excoriee	177	2.7	2.3–3.1
Steroid-induced acne	169	2.5	2.2–3.0
Middle age acne	125	1.9	1.6–2.2
Nodulocystic acne	2	0.03	0.01–0.12
Eczema type			
Unspecified	519	7.8	7.1–8.5
Atopic dermatitis	482	7.2	6.6–7.9
Seborrheic dermatitis	159	2.4	2.0–2.8
HIV related	14	0.2	0.1–0.4
Allergic contact dermatitis	1	0.02	0–0.1
Stasis eczema	1	0.02	0–0.1
Dyschromia			
Unspecified	361	5.4	4.9–6.0
Melasma	266	4.0	3.5–4.5
Postinflammatory hyperpigmentation	145	2.2	1.9–2.6
Vitiligo	56	0.8	0.6–1.1
Lichen planus pigmentosus	3	0.05	0.01–0.14
Ochronosis	3	0.05	0.01–0.14

est infections were tinea versicolor (2.8%), tinea capitis (2.3%), molluscum contagiosum (1.6%), and human papillomavirus infections (1.4%) (Table 4) .

Hair disorders were the fifth most common diagnosis, and accounted for 4.7% of diagnoses, the most common being acne keloidalis (1.3%), followed by pseudofolliculitis barbae (1.2%), traction alopecia (0.7%), folliculitis decalvans (0.6%), lichenplanopilaris (0.5%), central centrifugal cicatricial alopecia (0.4%), hirsuitism (0.3%), and alopecia areata (0.2%). In sixth position were skin neoplasms: Kaposis sarcoma (0.1%), solar keratosis (0.1%), basal cell carcinoma (0.02%), and squamous cell carcinoma (0.02%), the latter three presenting in albino patients. Table 5 provides detail on those dermatoses listed as other, which included eosinophilic folliculitis (3.0%), pruritus (2.1%), papular urticaria (1.7%), xerosis (0.9%), keloids (0.9%), psoriasis (0.7%), and sarcoidosis (0.2%).

Table 4 Acne and eczema prevalence by age

	Number	Prevalence (%)	95% Confidence interval
Acne			
<12 years	20/465	4.3	2.7–6.7
13–24 years	884/1348	65.6	63.0–68.1
>25 years	2011/4766	42.2	40.8–43.6
Eczema			
<12 years	241/465	51.8	14.2–56.4
13–18 years	84/459	18.3	14.9–22.2
>25 years	605/4766	12.7	11.8–13.7

Table 5 Prevalence of other dermatoses

Skin condition	Number *n* = 6664	Proportion (%)	95% Confidence interval
Pruritus	141	2.12	1.79–2.5
Ochronosis	9	0.14	0.07–0.27
Eosinophilic folliculitis	197	2.96	2.57–3.4
Irritant contact dermatitis	56	0.84	0.64–1.1
Xerosis	60	0.9	0.69–1.17
Postinflammatory hyperpigmentation	104	1.56	1.28–1.9
Keratosis pilaris	28	0.42	0.28–0.62
Pityriasis alba	32	0.48	0.33–0.69
Psoriasis	43	0.65	0.47–0.88
Drug eruption	32	0.48	0.33–0.69
Keloid	58	0.87	0.67–1.13
Pityriasis rosea	33	0.5	0.35–0.7
Epidermodysplasia verruciformis	14	0.21	0.12–0.36
Granuloma annulare	1	0.02	0–0.1
Cellulitis	1	0.02	0–0.1
Sunburn	1	0.02	0–0.1
Steroid dermatitis	28	0.42	0.28–0.62
Papulonecrotic tuberculid	13	0.2	0.11–0.34
Hirsuitism	14	0.21	0.12–0.36
Prurigo	31	0.47	0.32–0.67
Idiopathic guttate hypomelanosis	15	0.23	0.13–0.38
Papular urticarial	112	1.68	1.39–2.03
Syringoma	13	0.2	0.11–0.34
Sarcoid	13	0.2	0.11–0.34
Albinism	3	0.05	0.01–0.14
Pityriasis rubra pilaris	1	0.02	0–0.1
Nickel allergy	3	0.05	0.01–0.14
Dissecting cellulitis	1	0.02	0–0.1
Hidradenitis suppurativa	1	0.02	0–0.1
Systemic lupus erythematosus	1	0.02	0–0.1

Discussion

Most consultations were in adults (86.9%) with a female preponderance (74.1%) suggesting that adults were more likely to consult a dermatologist. The relatively low presentation in children can be attributed to the fact that children tend to end up with specialist pediatricians and general practitioners before consulting dermatologists for their common skin conditions.

In a survey of 5000 black patients conducted in 1982 at Ga-Rankuwa Hospital in the Pretoria region of South Africa, the prevalence of eczema was 22%, followed by acne (11%) and skin damage resulting from the use of bleaching creams (6%)[6] (Table 1). The last study on the spectrum of skin conditions in South Africa was conducted in 2003 on 5355 black patients attending academic public hospitals in Johannesburg, in these patients, the commonest skin diseases were eczema (32.7%), acne (17.5%), and superficial fungal infections (5.7%).[7]

Our study has shown acne, eczemas, dyschromias, infections, and hair disorders as the five most common disorders. Our results demonstrate a changing trend on the prevalence of skin diseases in Africans. Infections that were previously ranked higher as common skin conditions in previous local studies (Table 1) now rank fourth, with acne, eczemas, and dyschromias as the leading disorders in the population studied. This suggests improved living conditions of the population studied. It is also possible that the change results in part from changes in health-seeking behavior, but this is not easy to determine in a retrospective chart review.

The changing pattern we report is in agreement with data from the USA, which indicate a changing trend in black patients, with acne increasingly reported as the commonest skin disorder.[10–13] Similarities can be drawn between our data and those encountered in North American black patients, although the order of conditions is different.[10,11] Improved socio-economic circumstances have allowed black patients in particular to seek skin care and dermatological care from private practitioners under conditions similar to those seen in the first world.[10,11]

Davis *et al.*,[14] in a study from 1993 to 2009, reported, acne, atopic dermatitis, unspecified dermatitis or eczema, seborrheic dermatitis, and dyschromia as the five most common diagnoses for African-American patients in dermatology clinics. In another US study, the five most common diagnoses in black patients were acne, dyschromia, contact dermatitis and other eczema, unspecified cause, alopecia, and seborrheic dermatitis.[10] A study by Halder *et al.*[11] between 1980 and 1982 among private black patients in Washington DC reported acne vulgaris (27.7%), followed by eczema (20.3%), pigmentary disorders other than vitiligo (9.0%), seborrheic dermatitis (6.5%), and alopecias (5.3%) as the most common dermatoses. In an Afro-Caribbean population, acne vulgaris (29.2%), seborrheic eczema (22.0%), pigmentary disorders (16.6%), and atopic eczema (6.1%) were the most common dermatoses.[15] A study done in south-east London reported acne (13.7%), acne keloidalis (13.7%), and eczema (9.6%) as the three most common skin diseases in black adults.[16]

In an African study, the five most common conditions seen in Ghana were infections, dermatitis, pruritus, autoimmune disease, and acne. This was compared with a UK enquiry, where malignant and premalignant dermatoses, benign tumors, dermatitis, infections, and psoriasis were listed as the five most prevalent conditions.[17] The high frequency of infections in Ghana, a developing country, was attributed to the hot, humid climate, as well as to adverse socio-economic conditions. The unregulated availability of depigmenting creams was implicated as the cause of the high prevalence of dermatitis in Ghana.[17]

In the present study, tinea versicolor was the most prevalent infection (2.8%). Tinea versicolor is a common superficial fungal infection of the skin with a higher prevalence in hot tropical zones with humid climates, and Durban is a coastal city with a humid climate.

The three most common conditions reported in our study, acne, eczema, and dyschromia are discussed in detail below.

Acne

The highest prevalence of acne (65.6%) was observed in patients who were between the ages of 13 and 24 years, with acne vulgaris being the most common diagnosis, accounting for 10.3% of cases, followed by acne excoriée. Notably, steroid-induced acne had a prevalence of 2.5%, resulting from inappropriate use of steroid creams to treat acne, post inflammatory hyper pigmentation, other dyschromias, and for skin bleaching. Unspecified acnes had a prevalence of 29.0%, which makes it difficult to draw conclusions on the various types of acne seen, as most could have been better classified had this been a prospective study.

The prevalence of acne was higher in females (48.0%) than in males (33.6%), suggesting that either acne is more common in females or that they tend to seek medical attention more frequently than males. A descriptive epidemiological study on acne in the USA reported that nearly two-thirds of visits (65.2%) were made by females.[18] In a study aimed at defining the prevalence of acne in women from different race groups, clinical acne prevalence was 37% in African-American women and 23%, 24%, and 30% for Continental Indians, Caucasians, and Asians (respectively women).[19] Our findings

are in line with the international literature with respect to gender and skin conditions.

A recent systematic review on the epidemiology of acne[20] suggested that it is unclear if acne is truly associated with ethnicity, although black individuals are more prone to post inflammatory hyper pigmentation and specific subtypes, such as pomade acne and steroid-induced acne.[20]

Eczema

Eczema prevalence was 15.9%, with atopic dermatitis being the most common type, with a prevalence of 7.2%. It was more common in males, with a prevalence of 21.5%. The highest prevalence (51.8%) of eczema was observed in children, suggesting that childhood eczemas are more common in this population. Atopic dermatitis has been shown in other studies to be the most common skin disease in children, with data reflecting 51% of referrals in black children and 39% in white children.[16]

Dyschromia

Dyschromias have been reported in several studies to be common in black patients. Pigmentary disorders have a significant psychological impact, as they tend to be more obvious in darker skins.[21,22] We have found dyschromias to be the third most common skin condition seen, with a prevalence of 11.6%. The commonest subtype was unspecified hyper pigmentation (5.4%) followed by melasma (4.0%) and post inflammatory hyper pigmentation (2.2%). Schulz reported in 1982 that dermatitis resulting from the use of bleaching creams was the third most common disorder in 324 black patients, nine (3%) had acute contact dermatitis and 49 (15%) had leukomelanoderma resulting from monobenzone containing creams, while 266 (82%) were found to have melanosis, ochronosis, or colloid millium as a result of using hydroquinone-containing creams.[6] A survey of 5355 black people in Johannesburg in 2003, where the first and largest number of ochronosis cases were reported by Findlay *et al.* in 1975,[23,24] found that only 27 (0.5%) had ochronosis.[7] However, in the current study, ochronosis only accounted for three (0.05%) of the patients seen, and they were all in their early and late sixties, implying that they are possibly survivors of the skin bleaching scourge of the 1970s and 1980s[23] (Figs 1 and 2). A comparison of the prevalence data in five national surveys shows a dramatic decline in ochronosis from 10% in 1978 to 0.05% in the present study, confirming the success of the stricter South African government regulations pertaining to the sale and use of hydroquinone containing skin-lighteners.[25] Thus, dyschromias are a common indication for black patients to consult a dermatologist; the psychological sequelae are enormous and treatment remains a challenge.

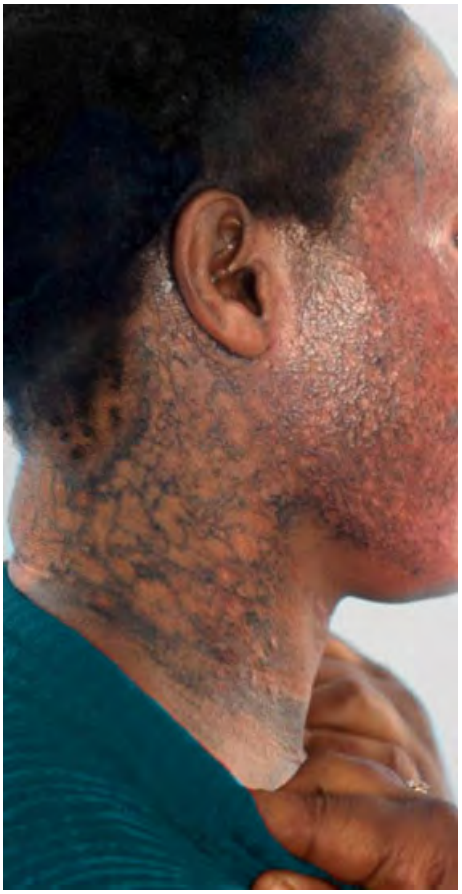

Figure 1 Ochronosis. Severe involvement of the face and neck in a black woman.

Hair

Acne keloidalis nuchae (1.3%), pseudofolliculitis barbae (1.2%), and traction alopecia (0.7%) were the most common hair disorders observed in our study. The low prevalence of traction alopecia could be explained by the fact that many patients do not seek treatment for it, as they regard it as a normal consequence of hair grooming.

Skin cancer

Very few patients presented with skin neoplasm, actinic keratosis, and basal and squamous cell carcinomas, as skin cancers are uncommonly seen in black patients. These were observed in albino patients who are prone to ultraviolet radiation-induced skin cancers.

HIV dermatoses

Eosinophilic folliculitis, an HIV-associated dermatosis, had a prevalence of 3.0%. HIV has changed the topography of skin diseases on the African continent, with Kaposis sarcoma, papular pruritic eruption, and drug reactions being the commonest dermatoses seen, followed by herpes zoster, dermatophyte infections, and molluscum contagiosum.[26]

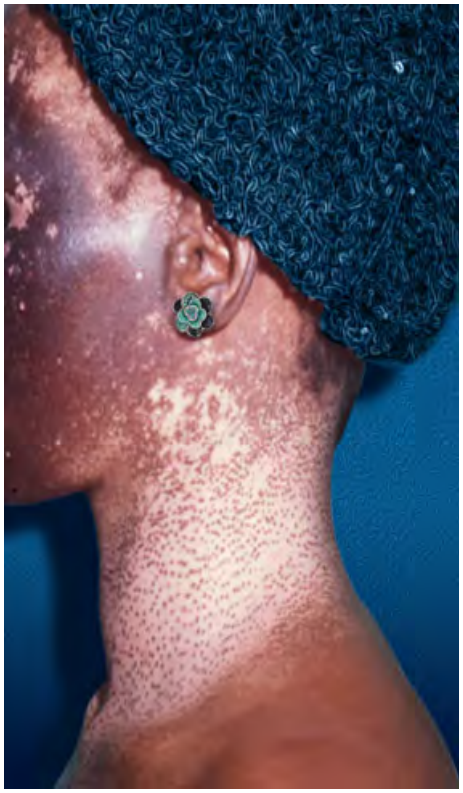

Figure 2 Ochronosis with leukoderma secondary to long-term abuse of hydroquinone.

Other

Keloids, which are known to be common in black patients,[11] were noted in 0.9% of the cases (Table 5).

We observed sarcoidosis in 0.2% of our cases; similar cases have previously been reported in Johannesburg.[27] Nutritional disorders, such as pellagra, which used to be among the common skin conditions seen previously (Table 1), did not feature at all in this study, suggesting an improvement in the socio-economic conditions of the population studied.

Conclusion

In this retrospective study, we documented the spectrum of skin diseases seen in a predominantly black private practice in Durban, South Africa. Acne, eczemas, dyschromias, infections, and hair disorders were found to be the five most common dermatoses presenting to dermatologists.

Our study limitations include the selection bias presented by a single practice, and the fact that only the presenting diagnosis was considered thus preventing the inclusion of secondary diagnoses. However, our study provides a reasonable premise to plan future larger population studies to map out accurately the epidemiology of skin disease for the DMA, and ultimately establishing the prevalence of skin diseases in KZN.

It is hoped that this new information on the spectrum of skin diseases in KZN will add to the body of knowledge, inform effective planning, and offer pertinent recommendations for the needs of the province as a whole. As our patients were recruited from a private healthcare facility, targeting a particular income group of the population that is able to afford medical insurance, and is therefore likely to be biased against those disorders associated with poverty. Further studies in the public sector, in rural communities and from other areas, as well as in other racial groups, are needed to provide a valid cross-sectional impression of the entire population. This will allow clinicians and policy makers to plan effectively for the provision of dermatology services, distribution of resources, and implementation of relevant preventative measures, including consumer and public education campaigns against the dangers of inappropriate and prolonged use of topical steroids.

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CHAPTE R 3

Skin lightening practi ces an e pidemiological study of South African women of African and I ndian ancestrie s.

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ORIGINAL ARTICLE

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Skin lightening practices: an epidemiological study of South African women of African and Indian ancestries

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Conflicts of interest
None declared.

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Summary

Background Cutaneous adverse sequelae of skin lightening creams present with myriad skin complications and affect dermatology practice, particularly in sub-Saharan Africa where such products are widely used, with a prevalence of 25–67%.

Objectives To examine the skin lightening practices of both African and Indian women living in South Africa.

Methods A cross-sectional survey was undertaken in the general outpatient departments of two regional university hospitals in Durban, South Africa. All consenting African and Indian women aged 18–70 years were recruited and asked to complete a questionnaire.

Results Six hundred women completed the questionnaire, of whom 32·7% reported using skin lightening products. The main reasons cited were treatment of skin problems (66·7%) and skin lightening (33·3%). Products were purchased from a variety of sources. Twenty-five per cent reported using sunscreen.

Conclusions The use of skin lightening cosmetics is common among darkly pigmented South African women, including those of both African and Indian ancestries. Despite more than 20 years of governmental regulations aimed at prohibiting both the sale of cosmetics containing mercury, hydroquinone and corticosteroids, and the advertising of any kind of skin lightener, they are far from having disappeared. The main motivations for using these products are the desire to treat skin disorders and to achieve a lighter skin colour. Television and magazine advertisements seem to influence womens' choice of these products and, thus, would be efficient channels for raising public awareness about the dangers of using uncontrolled skin lighteners.

The obsession with and wish for fair skin is a global phenomenon, particularly in dark-skinned cultures, not only restricted to African countries. A prevalence of skin lightening of 25–67% has been reported in African countries.[1–8] It is well known that South American, Asian and Middle Eastern cultures also have their own beliefs about skin lightening.[9]

Studies have shown that women engage in skin lightening practices more often than men, driven by a strong desire to lighten their skin colour.[6,7,10] Dadzie and Petit[7] summarized the studies conducted on the practice of skin bleaching, and showed that skin lightening is a widespread phenomenon, affecting diverse communities worldwide, including those in Africa, North America, Europe, Asia and the Middle East. Skin lightening agents have been used for decades, and the trend appears to be increasing.[9] However their use is associated with adverse effects, resulting in tremendous challenges for dermatologists.[2,8,11,12] Olumide *et al.*[8] reported a case of squamous cell carcinoma on an exogenous ochronotic area, raising concerns about the use of skin lightening agents without the concomitant use of a broad-spectrum sunscreen, as secondary longstanding sun damage may result in skin cancer on susceptible depigmented skin.

In South Africa, various ethnic languages specifically describe the practice of skin lightening: 'ukutsheyisa' in isiXhosa ('to chase beauty'), 'ukucreamer' in isiZulu ('applying creams on the skin') and 'hokgantsa sefatlhego' in Setswana ('to lighten the face'). Indians tend to refer to the practice as 'using fairness creams'. According to the literature, 75% of the population in Nigeria,[3] 52–67% of the Senegalese population and 35% of the population in Pretoria, South Africa,[3,4,13] use skin lightening products. One of the reasons cited for using skin lighteners is the belief that a lighter skin tone is more attractive. In certain Indian and Asian communities, it is believed that the prospects of marrying and belonging to a higher caste, with the attendant social economic benefits, are enhanced by fair skin.[9,14,15] Skin lightening creams account for 40% of all beauty products sold in India.[9,15] Cosmetic advertisements on television and in fashion magazines contribute to the magnification of light-coloured skin by featuring fair-skinned models as attractive and desirable symbols.[8,15,16] The desire for fair skin plays out among the Asian and black communities in the form of a colour bias, which privileges lighter over darker skin.[8,9,15]

South Africa possesses a unique history of skin lighteners. During the 1960s and 1970s – at the height of apartheid rule – the country's skin lightener market was robust and highly profitable. From the mid-1970s, the government began to regulate the active ingredients found in these products, first prohibiting ammoniated mercury and, later, limiting the level of hydroquinone permitted to 2%. In the 1980s, opposition to skin lighteners became a corollary of the antiapartheid movement as medical professionals and Black Consciousness activists called for their complete ban on both health and political grounds. In 1990, South African regulation prohibited the use of hydroquinone in cosmetics. Moreover, South Africa became the first – and is still the only – country in the world that prohibits advertisement of lighteners and adverts containing words such as 'bleach', 'lighten' or 'whiten'.[17,18]

In a study carried out in the U.S.A. in early 1980s, Findlay alluded to the notion that many black people dislike skin that has a dull, drab, dusty or scaly surface, and prefer brightness.[19] A recent paper investigating the contents of the top 10 bestselling skin lightening creams on the market in Durban, South Africa, showed that nearly half of the analysed products contained mercury as an active ingredient (banned for use in cosmetics), although this was neither declared on the ingredient listing nor the packaging label.[20,21] Four (40%) of the products analysed contained mercury as an active ingredient [Lemon Lite Vanishing Cream® (Tiger Brands, Byranston, South Africa); Shirley Cream (Shirley Woking, U.K.); Rico Complexion Cream (General Healthcare, Hayes, U.K.); and Cuticura (Godrej Consumer Products, Hounslow, U.K.)], two (20%) contained corticosteroids [Movate® cream (Movate, Milan, Italy); Persivate® cream (Pharmacare, Port Elizabeth, South Africa)], two (20%) resorcinol [Bee-co Cream (Pride of Africa, Durban, South Africa); Eskamel® (Mentholatum, Tokai, South Africa)], and one (10%) a hydroquinone derivative (Gentle Magic® skincare cream; Durmac, Durban, South Africa).[20]

The prevalence of and factors underlying the use and abuse of skin lightening creams among Indian women living in South Africa have never been investigated. Yet, in clinical practice, dermatologists witness the devastating effects of skin lighteners. Moreover, an in-depth and large-scale investigation of the reasons why African women use skin lighteners has never been undertaken. Clinical experience suggests that such women use skin lighteners for a variety of reasons, including, but not limited to, the pursuit of a lighter complexion. Many black South African women are frustrated by the challenges of postinflammatory hyperpigmentation, which is a characteristic feature of black skin,[22] and may use skin lightening creams as self-medication in an effort to get rid of this and other common dermatological conditions such as acne and melasma.[23–25]

Evaluating the extent of and motivations behind use of skin lighteners by African and Indian women should lead to the development of targeted interventions aimed at changing perceptions and educating consumers of the potential consequences of their use. Therefore, the objective of this study was to investigate the prevalence and misuse of skin lightening products, and the reasons and factors that encourage this practice among African and Indian women.

Materials and methods

A cross-sectional survey was conducted at the general outpatient departments (excluding skin clinics) of two regional teaching hospitals of the Nelson R. Mandela School of Medicine [R.K. Khan (RKK) and Prince Mshiyeni Memorial (PMM) hospitals]. RKK mainly treats an Indian urban population, while PMM hospital predominantly treats Africans. The study received ethical approval from the University of KwaZulu-Natal's biomedical research institutional review board (BE 180/11). South African Indian and African women aged between 18 and 70 years, with a Fitzpatrick's skin type ranging from 4 to 7, were enrolled in the study after providing written informed consent. Six hundred women (300 South African Indian and 300 African), were recruited to provide statistically significant results. Data were collected by a trained assistant who was proficient in both English and isiZulu. All women were invited to participate over a period of 4 months (1 September–31 December 2012). They were asked to complete a structured questionnaire, adapted from Hamed *et al.*[14] and listing well-known skin lightening creams. None of participants was examined during the survey. The questionnaire focused on the following items: sociodemographic characteristics (level of education, social class, marital status and employment status); cosmetic habits and skin lightening practices (therapeutic, cosmetic); and factors associated with the use of skin lighteners (therapeutic, cosmetic).

Data analysis

Data were entered into EXCEL® (Microsoft, Redmond, WA, U.S.A.) and analysed using SAS version 9.3 (SAS Institute Inc.,

Table 1 Sociodemographic characteristics of the study participants

Variable	African (n = 300)	Indian (n = 300)	Total (n = 600)
Race	292 (97·3)	286 (95·3)	578 (96·3)
Unknown	8 (2·7)	14 (4·7)	22 (3·7)
Residence			
Urban	31 (10·3)	155 (51·7)	186 (31·0)
Suburban	215 (71·7)	131 (43·7)	346 (57·7)
Rural	22 (7·3)	1 (0·3)	23 (3·8)
Semirural	26 (8·7)	2 (0·7)	28 (4·7)
Unknown	6 (2·0)	11 (3·6)	17 (2·8)
Age (years)			
< 20	27 (9·0)	6 (2·0)	33 (5·5)
20–30	102 (34·0)	41 (13·7)	143 (23·8)
31–40	80 (26·7)	48 (16·0)	128 (21·3)
41–50	43 (14·3)	77 (25·7)	120 (20·0)
> 50	45 (15·0)	118 (39·3)	163 (27·2)
Unknown	3 (1·0)	10 (3·3)	13 (2·2)
Marital status			
Married	85 (28·3)	197 (65·7)	282 (47·0)
Single	191 (63·7)	48 (16·0)	239 (39·9)
Divorced	7 (2·3)	22 (7·3)	29 (4·8)
Widowed	13 (4·3)	23 (7·7)	36 (6·0)
Unknown	4 (1·3)	10 (3·3)	14 (2·3)
Level of education (years)			
None	11 (3·7)	13 (4·3)	24 (4·0)
1–5	16 (5·3)	11 (3·7)	27 (4·5)
> 5–10	55 (18·3)	127 (42·3)	182 (30·3)
> 10–12	163 (54·3)	123 (41·0)	286 (47·7)
Postgraduate	50 (16·7)	15 (5·0)	65 (10·8)
Unknown	5 (1·7)	11 (3·7)	16 (2·7)
Skin tone (subjective)			
Light	94 (31·3)	97 (32·3)	191 (31·8)
Light brown	93 (31·0)	126 (42·0)	219 (36·5)
Dark brown	87 (29·0)	55 (18·3)	142 (23·7)
Black	21 (7·0)	11 (3·7)	32 (5·3)
Unknown	5 (1·7)	11 (3·7)	16 (2·7)
Monthly income			
Unemployed	182 (60·6)	211 (70·3)	393 (65·5)
< R200	2 (0·6)	0 (0)	2 (0·3)
R200–400	8 (2·7)	2 (0·7)	10 (1·7)
> R400–600	5 (1·7)	1 (0·3)	6 (1·0)
> R600	98 (32·7)	75 (25·0)	173 (28·8)
Unknown	5 (1·7)	11 (3·7)	16 (2·7)

Data are presented as n (%).

Cary, NC, U.S.A.). Data were summarized in contingency tables. Logistic regression models were fitted to calculate the odds ratios (ORs) with 95% confidence intervals (CIs).

Results

Sociodemographic characteristics of the study participants

Almost half of the women (47·0%) were married, 58·5% had received more than 10 years of education and 11·0% had a tertiary education qualification. Approximately 90·0% of the participants resided in either urban or suburban areas, with two-thirds reporting that they were unemployed. About 70·0% had a light or light brown skin tone, while the remainder reported a dark (black) or dark brown skin tone. Approximately 85·0% stated that they were satisfied with their skin tone (Table 1).

Cosmetic habits and skin lightening practices amongst black South African women

Five hundred and seventy-one women answered the question of whether they used skin lightening products. The overall prevalence of use was 187/571 (32·7%; 95% CI 28·9–36·8): 75/277 (27·1%) Indian women and 112/294 (38·1%) African women. The main reasons cited for use were treatment of facial pigmentation (35·3%), skin lightening (26·2%) and the

Table 2 Practice of skin lightening

Variable	African (n = 112)	Indian (n = 75)	Total (n = 187)
Prevalence of skin lightening	112/294 (38·1)	75/277 (27·1)	187/571 (32·7)
Reasons for use			
Pigmentation	33 (29·5)	33 (44·0)	66 (35·3)
Pimples	36 (32·1)	8 (10·7)	44 (23·5)
Dark skin	34 (30·4)	15 (20·0)	49 (26·2)
Unknown	9 (8·0)	19 (25·3)	28 (15·0)
Duration of use			
3 months	10 (8·9)	9 (12·0)	19 (10·2)
> 6 months	7 (6·2)	10 (13·3)	17 (9·1)
> 12 months	19 (17·0)	9 (12·0)	28 (15·0)
Many years	73 (65·2)	43 (57·3)	116 (62·0)
Unknown	3 (2·7)	4 (5·3)	7 (3·7)
Time of application			
Morning	50 (44·6)	25 (33·3)	75 (40·1)
Evening	7 (6·3)	2 (2·7)	9 (4·8)
Morning + evening	55 (49·1)	48 (64·0)	103 (55·1)
Site of application			
Face	101 (90·1)	72 (96·0)	173 (92·5)
Marks	3 (2·7)	0 (0)	3 (1·6)
Pimples	3 (2·7)	0 (0)	3 (1·6)
Body	5 (4·5)	0 (0)	5 (2·7)
Unknown	0 (0)	3 (4·0)	3 (1·6)
Where products are bought			
Pharmacy	46 (41·1)	10 (13·4)	56 (30·0)
Private doctor	4 (3·6)	1 (1·3)	5 (2·7)
Small stores	53 (47·3)	57 (76·0)	110 (58·8)
Street	8 (7·1)	0 (0)	8 (4·3)
Beautician	1 (0·9)	3 (4·0)	4 (2·1)
Unknown	0 (0)	4 (5·3)	4 (2·1)
Monthly cost of products (Rand)			
< 10	12 (10·7)	1 (1·3)	13 (7·0)
10–20	45 (40·2)	15 (20·0)	60 (32·1)
> 20–50	38 (33·9)	22 (29·3)	60 (32·1)
> 50–100	11 (9·8)	14 (18·7)	25 (13·4)
> 100–200	1 (0·9)	13 (17·3)	14 (7·5)
> 200–1000	1 (0·9)	9 (12·0)	10 (5·3)
> 1000–2000	3 (2·7)	1 (1·3)	4 (2·1)
Unknown	1 (0·9)	0 (0)	1 (0·5)
Who advised on product			
Doctor	4 (3·5)	2 (2·7)	6 (3·2)
Pharmacist	2 (1·8)	1 (1·3)	3 (1·6)
Friend	66 (58·9)	31 (41·3)	97 (51·9)
Television advert	4 (3·6)	0 (0)	4 (2·1)
Magazine or newspaper	18 (16·1)	12 (16·0)	30 (16·0)
In-store seller	3 (2·7)	3 (4·0)	6 (3·2)
On the street	3 (2·7)	2 (2·7)	5 (2·7)
Other	11 (9·8)	0 (0)	11 (5·9)
Unknown	1 (0·9)	24 (32·0)	25 (13·4)
Use of traditional plants	11 (9·8)	4 (5·3)	15 (8·0)
Use of ibomvu clay for sun protection	48 (42·9)	1 (1·3)	49 (26·2)
Use of sunscreen	13 (11·6)	27 (36·0)	40 (21·4)

Data are presented as n (%).

treatment of acne (23·5%) (Table 2). Twenty-five per cent of women reported using lightening cream for more than 6 or 12 months, and the majority (66·0%) had used skin lighteners for years. The products were purchased from a variety of sources, including small cosmetics stores (58·8%) pharmacies (29·9%), street vendors (4·3%) general practitioners (2·7%) and beauticians (0·9%). The data showed that most women used the products following advice from friends (60·0%) or

from seeing adverts in magazines (16·0%) (Table 2). For most women, monthly expenditure on skin lighteners ranged from R10 (US$1) to R200 (US$20). Three African women (2·7%) reported spending more than R1000 (US$100) a month on lightening creams. While a small proportion (8·0%) reported using traditional plants ('ummemezi' and 'umqonga') for skin lightening, more than a quarter reported using traditional sunscreen in the form of red clay ('ibomvu').[26] The latter was almost exclusively used by African women (only one Indian woman reported using clay as sunscreen). About a fifth of the women declared using commercial sunscreens (Table 2). More Indian women (36·0%) used sunscreens on their face than African women (11·6%; Table 3).

Factors associated with the use of skin lighteners

Ethnic background, education, age and residence were associated with the use of skin lightening products. African women were 1·71 times more likely to use skin lighteners than Indian women (95% CI 1·1–2·44; P < 0·01). Women aged 30 years or younger used less skin lightener than older women (OR 0·56, 95% CI 0·36–0·88; P < 0·01). Women who had received more than 10 years of education were also less likely to use skin lightening products, and urban women were more likely to engage in skin lightening practices than rural women (Table 4).

Factors associated with the use of sunscreen

Of the 187 women who said they engaged in skin lightening, only 21·4% declared using sunscreen. Ethnic background, age and employment were associated with the use of sunscreen. The frequency of sunscreen use by African women was three times less than that of Indian women (OR 0·26, 95% CI 0·16–0·44; P < 0·01). Women aged 30 years or younger used less sunscreen than older women (OR 0·50, 95% CI 0·27–0·93; P < 0·03). Employed women were 1·75 times more likely to use sunscreen than unemployed women (OR 1·75, 95% CI 1·11–2·76) (Table 3).

Discussion

Skin lightening was performed by 32·7% of the black African women included in this study, almost 50·0% lower than that reported in Senegal (67·2%), Nigeria (Lagos; 72·4%) and other African countries.[3,6,13]

The main reason for using skin lighteners by women included in this study was for the treatment of skin problems, including postinflammatory hyperpigmentation, melasma and acne (67·0%), followed by skin lightening (33·0%).

Twenty-five years ago, Hardwick *et al.*[10] conducted an epidemiological study of 195 patients with exogenous ochronosis attending the outpatient department of Kalafong and

Table 3 Factors associated with use of sunscreen

		Univariate			Multivariate		
Variable	n/N (%)	OR	95% CI	P-value	OR	95% CI	P-value
Ethnicity							
African	21/192 (10·9)	0·26	0·16–0·44	< 0·01	0·17	0·09–0·34	< 0·01
Indian	89/280 (31·8)						
Age (years)							
< 30	19/124 (15·3)	0·50	0·27–0·93	0·03	0·52	0·24–1·14	0·10
31–50	53/209 (25·4)	0·95	0·58–1·54	0·83	0·98	0·56–1·72	0·96
> 50	38/144 (26·4)						
Employment status							
Employed	40/131 (30·5)	1·75	(1·11–2·76)	0·02	1·57	0·94–2·61	0·08
Unemployed	69/344 (20·1)						
Marital status							
Married	62/240 (25·8)	1·37	0·89–2·11	0·15	0·84	0·50–1·41	0·51
Not married	48/237 (20·3)						
Education							
< Grade 10	47/217 (21·7)	0·53	0·25–1·12	0·10	0·27	0·11–0·67	< 0·01
Grades 10–12	50/222 (22·5)	0·56	0·27–1·17	0·12	0·37	0·16–0·85	0·02
Graduate	13/37 (35·1)						
Skin colour (subjective)							
Light	87/352 (24·7)	1·52	0·90–2·56	0·11	1·24	0·71–2·16	0·46
Dark	22/124 (17·7)						
Residence							
Urban	46/166 (27·7)	2·07	0·75–5·70	0·16	0·50	0·15–1·63	0·25
Suburban	59/279 (21·2)	1·45	0·53–3·92	0·47	0·66	0·21–2·02	0·47
Rural and semirural	3/28 (10·7)						

OR, odds ratio; CI, confidence interval.

Table 4 Factors associated with the use of skin lightening products

		Univariate			Multivariate		
	n/N (%)	OR	95% CI	P-value	OR	95% CI	P-value
Ethnicity							
African	111/289 (38·4)	1·71	1·19–2·44	< 0·01	2·11	1·29–3·46	< 0·01
Indian	73/273 (26·7)						
Age (years)							
< 30	51/174 (29·3)	0·56	0·36–0·88	< 0·01	0·49	0·27–0·90	0·02
31–50	68/237 (28·7)	0·54	0·36–0·83	< 0·01	0·53	0·32–0·86	0·01
> 50	68/160 (42·5)						
Employment status							
Employed	53/185 (28·6)	0·77	0·52–1·12	0·1725	0·91	0·59–1·39	0·66
Unemployed	132/384 (34·4)						
Marital status							
Married	83/275 (30·2)	0·79	0·56–1·13	0·20	0·86	0·56–1·33	0·51
Not married	104/295 (35·3)						
Education							
< Grade 10	91/231 (39·4)	4·12	1·94–8·72	< 0·01	3·84	1·67–8·86	< 0·01
Grade 10–12	87/274 (31·8)	2·95	1·40–6·22	< 0·01	3·05	1·40–6·63	< 0·01
Graduate	9/64 (14·1)						
Skin colour (subjective)							
Light	121/397 (30·5)	0·70	0·48–1·02	0·07	0·87	0·58–1·31	0·50
Dark	66/172 (38·4)						
Residence							
Urban	47/182 (25·8)	0·51	0·27–0·96	0·04	0·76	0·35–1·67	0·49
Suburban	118/335 (35·2)	0·79	0·44–1·42	0·43	0·97	0·50–1·86	0·92
Rural and semirural	18/50 (36·0)						

Mamelodi day hospital in Pretoria. The reasons that these patients cited for using skin lighteners included the pursuit of a fairer complexion (i.e. equating lightness with beauty; 32·0%), skin problems (31·9%), peer usage (19·3%), advertising influence (10·0%); family example (0·5%); and imitating a hero/heroine (0·8%). In contrast, the main reason put forward in the present study was for the treatment of skin problems (67·0%) followed by skin lightening (33%).

In a recent 7-year retrospective survey of 6664 African patients seen in a predominantly black urban dermatology practice in Durban, South Africa, we found a dramatic decline in ochronosis from 10·0% in 1978 to 0·05% in 2013,[27] suggesting the success of stricter South African government regulations introduced since 1990, especially pertaining to the sale and use of products containing hydroquinone. In their study, Hardwick *et al.* reported a 69·0% prevalence of ochronosis amongst users of skin lighteners. In addition, they found that the major demographic associations with ochronosis were a lower level of education and a high proportion of women,[10] which is consistent with our own findings (Table 3).

Contrary to popular belief among the Indian community that only African women use skin lighteners, the results show that women of both African (38·1%) and Indian ancestries (27·1%) follow this practice in South Africa. A study on the practices of women living in Jordan reported a higher prevalence (60·7%) of skin lightening amongst Arab women.[14]

Few women reported using sunscreen, with an especially low rate among African women (11·8%), which is of more concern considering the long-term effects of sunburn and skin cancers on skin lightened areas.[8] This finding indicates lack of knowledge and awareness about the dangers of ultraviolet rays, and highlights the unaffordability of sunscreens. Considering how common the practice of skin lightening is globally, there have been very few reported cases of skin cancers associated with this practice. Furthermore, to our knowledge, there are no scientific data that support the notion that use of sunscreens in the setting of chronic skin lightening prevents skin cancer. Most women who did not use sunscreens were unemployed.[26]

The use of skin lighteners in this study was associated with ethnic background, age, education and place of residence (Table 4). Generally, women aged 20–50 years were more likely to use skin lighteners, which could be explained by the high prevalence of acne and dyschromia encountered among this age group. Unlike other countries,[7,8,12,28] the population in this study tended to use the creams on their face only (92·5%) rather than on their whole body. Our study population declared that skin lighteners were easy to access and affordable ($1–5) from informal markets. The majority of women stated that they received advice about skin lighteners from friends and preferred to purchase products from small convenience stores rather than from health experts like pharmacists or doctors who would be more likely to educate them

about deleterious side-effects. It was of considerable concern to learn that many women could purchase moderate and potent steroid creams from street vendors and cosmetic shops despite the fact that, by law, these preparations require a medical prescription. This common circumvention of the law suggests the inadequacy of current government monitoring policies.[21]

Over the last two decades, the most common active ingredients found in skin lighteners have shifted from hydroquinone to corticosteroids and mercury,[20] indicating that this may be an opportune time to enforce stricter controls on the purchase and sale of unregulated skin lighteners as stipulated in the paper by Dlova and Ajose.[29] Their paper articulates the action plan of the African Dermatologist's interest group that convened at the 'Ethnic Skin and Hair' congress held in Kenya (November 2012). The comparatively lower use of skin lighteners in South Africa than in some other African countries suggests that governmental regulations on skin lighteners instituted in 1990 and afterwards have been partially successful.

The present study has some limitations. Firstly, for a variety of reasons, ranging from embarrassment over true motivations for using skin lighteners to possible knowledge of the illegality of some of the products used, some women may have provided inaccurate or false information in response to the survey questions. Secondly, the fact that the survey was not a population study but conducted among hospital attendees may have skewed our findings, perhaps resulting in an overestimation of the prevalence of skin lightener use in the general population. Nonetheless, we feel that our study provides a general picture of the extent of the problem and where the emphasis should be placed and directed on public health interventions and consumer education.

This study shows that skin lightening is common amongst African and Indian women in South Africa, with African women being 1·7 times more likely to engage in this practice.

These findings underscore the fact that any public health campaign related to skin lighteners would need to address the various reasons why women use them. The ease with which the women surveyed had purchased banned and scheduled substances suggests the need for the government to be more vigilant in its enforcement of existing regulations regarding skin lighteners.

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CHAPTE R 4

Women’s perceptions of the benefits and risks of skin-lightening c rea ms in two South African communities.

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Women's perceptions of the benefits and risks of skin-lightening creams in two South African communities

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Summary

Background Skin-lightening products are commonly used by black communities in South Africa and worldwide. This practice has deep historical and cultural roots and is associated with adverse cutaneous effects.
Methods A cross-sectional survey of 579 African and Indian women aged 18–70 years was conducted in two large public hospitals in Durban, South Africa.
Results There were 292 Africans and 287 Indians included in the survey sample. Of these 32.3% had used skin-lightening products (60% of Africans and 40% of Indians). Most of those who had used skin lighteners (85 of Africans and 76% of Indians) claimed awareness of the adverse effects of the products, although this did not appear to inform knowledge of the product, how it was used, nor the decision to use the product. Most users (90%) expressed satisfaction with results achieved but 32% reported adverse events.
Conclusion Skin-lightening products are used by a third of African and Indian women in South Africa Cultural and historical perceptions equating a fairer skin with social advantage are pervasive and strongly reinforced by the media. There is a poor understanding of the risks associated with the use of these products. Public education campaigns are required to teach consumers about these risks and the importance of concomitant use of sunscreens with these products.

Keywords: skin lightening, skin bleaching, cosmetic habits, ethnic, African, Indian

Introduction

Although skin-lightening products are medically indicated treatment for hyperpigmentation, they are widely abused as self-medication because of the cultural perception that lighter skin complexion is better than dark skin.[1]

Since ancient times, women in parts of Europe, the Mediterranean and Asia have used skin lighteners. In the past century and more recently, advertising of skin-lightening products is widespread albeit in subtle ways.[2–6]

In South Africa where the hue of one's skin determined social hierarchy and consequently economic opportunity, skin-lightening products became popular, not only among black African people, but also the Jew-

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ish and other racially marginalized groups.[7] From the 1930s certain products were marketed extensively to black people, developing into a lucrative market worth US$7 m by the late 1980′s.[7]

These products are now known to result in long-term adverse effects, such as telangiectasia, skin atrophy, hypertrichosis, steroid-induced acne, striae, dermatitis and opportunistic infections.[8–11] Hydroquinone-containing compounds are particularly associated with allergic and inflammatory reactions and paradoxical pigmentation, while topical steroids typically results in inflammatory acne,[5,8,9] dermatitis, photosensitivity and hyperpigmentation that may be slow to resolve.[12]

Hydroquinone-containing cosmetics were rescheduled to prescription only products in South Africa in 1991.[7] Policies regulating the sale of any active or potentially active depigmenting agents were reinforced. South African law requires the distributor to advise women to use a sunscreen when supplying a skin-lightening product.[13,14] Yet our experience has shown that though one in every three black South African women admits to using skin-lightening products, only 21% use sunscreen. The potential risks of this are emphasized by a recent case report of squamous cell carcinoma following prolonged use of hydroquinone without a sunscreen.[5]

Despite the restrictions on the sale and use of skin-lightening products, access to them is still widespread, mainly through illegal channels, and their usage continues to constitute a major public health issue, the extent of which still needs evaluation in South Africa.[6,15] Understanding the determinants of this illicit usage will inform the development of targeted interventions aimed at changing perceptions, educating the community and changing practice. We therefore set out to study perceptions of the benefits and risks associated with the use of skin-lightening products among black African and Indian women in Durban, South Africa.

Methods

A cross-sectional survey was conducted among patients attending the general outpatient departments of two regional hospitals in Durban, namely the R.K. Khan and Prince Mshiyeni Memorial Hospitals, which serve a large black African and Indian population. Patients attending dermatological clinics were excluded. The study was approved by the UKZN Biomedical Research Ethics Committee (BE 180/11). All respondents provided written informed consent.

African and Indian women aged 18 years and older were interviewed in either isiZulu (vernacular) or English, as preferred by the subject using a questionnaire modified from Hamed *et al.*[1] Participants were questioned on their knowledge and perceptions about skin-lightening products and the benefits and risks of using these products.

Data analysis

Microsoft Excel was used for data capturing, and analysis was performed using MEDCALC Statistical Software version 12.7.5 (MEDCALC Software bvba, Ostend, Belgium). Categorical data were summarized in contingency tables and analyzed for significance using a chi-squared test or Fisher's exact test as appropriate. Ordinal data were compared by Mann–Whitney *U*-test or Kruskal–Wallis test.

Results

Demographic profile

Data were obtained from 579 women, of whom 292 (50.4%) were African and 287 (49.6%) Indian (Fig. 1). The African respondents were younger, had achieved a higher educational standard and income and were mainly rural and peri-urban dwellers (all significant: $P < 0.0001$). The Indian respondents were older, less educated and were mainly urban residents. When asked whether they were satisfied with their skin color, 96% of the Indian respondents and 87% of Africans responded positively ($P = 0.0005$). Satisfaction correlated with income, with respondents in the primary-

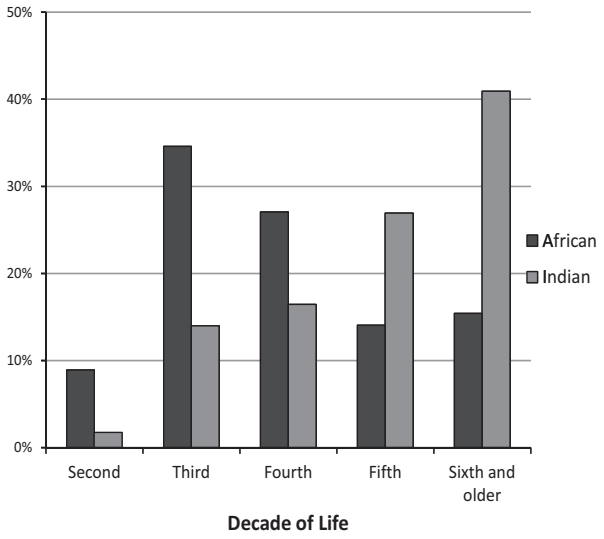

Figure 1 Age distribution of study participants. African respondents are significantly younger than Indian respondents ($P < 0.0001$).

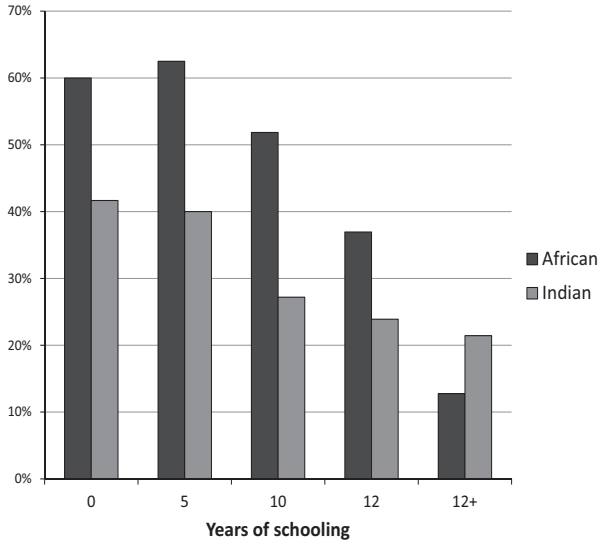

Figure 2 Proportion of women using skin lightening products categorized by educational achievement. Prevalence of use declines significantly with increasing level of education.

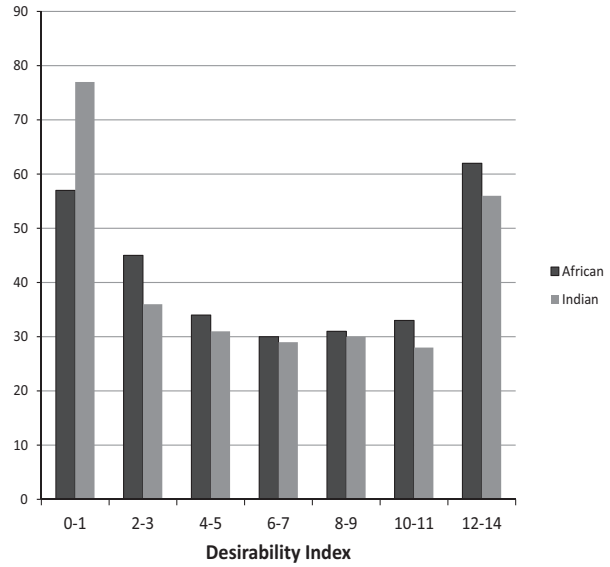

Figure 3 Desirability index. This is the sum of the responses, on a scale of 0 (disagree or neutral), 1 (agree) and 2 (Strongly agree), to 7 questions which test the proposition that a lighter skin is perceived as desirable. A high score represents strong identification with this proposition.

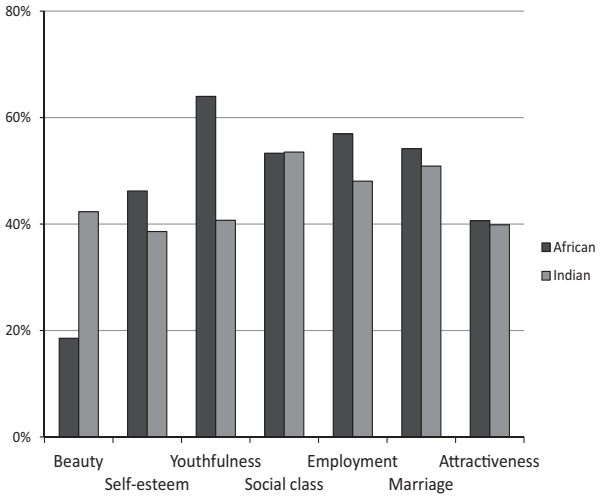

Figure 4 Positive responses to 7 questions (*Strongly agree or Agree*) (Table 1) which test the proposition that a lighter skin is perceived as desirable. Most propositions are held by a third or more of the respondents.

educated bands being significantly less satisfied at 74% and 86% than those who had received secondary and tertiary education at 93% and 95% ($P = 0.008$).There was no correlation with age or income.

Skin-lightening product experience

A total of 131 (32.3%) respondents had used skin-lightening products, *viz*. 38% of Africans and 27% of Indians ($P = 0.005$). Prevalence of use was negatively correlated with education with usage exceeding 50% for those with little formal education and 14% in those with tertiary qualifications ($P = 0.0005$) (Fig. 2). Although a significant increase with age was shown, this may represent cumulative experience as no distinction was made regarding recent use. There was no significant association with income, residence or skin tone. A third ((36%) of those who reported satisfaction with their skin tone used skin lighteners compared to 79% ($P < 0.0001$) of those who were dissatisfied. While this was low, it was a surprisingly high number which needs further investigation.

When probed about what influenced their selection of products, 71% responded that they were influenced by the brand name, 43% by price whereas 12% by the ingredients. There was no difference between African and Indian respondents.

Knowledge and perceptions about benefits and risks of using skin-lightening products

By assigning a score of 0, 1, and 2 to the categories *disagree or neutral, agree* and *strongly agree* to seven questions which probed the perceived social advantage of a lighter skin (Table 1); we derived an informal desirability index for the perceived benefits of lighter skin, with potential scores ranging from 0 (disagree that a lighter skin is advantageous on any count) to 14 (strongly believe that a lighter skin is advantageous on all counts). The scores did not correlate with any of the parameters except age ($P = 0.01$) (Fig. 3). More than a third of women believed that a lighter skin tone increased self-esteem, implied that a woman belongs to

Table 1 A panel of questions put to the respondents to assess their perceptions of the social advantages of a lighter skin. Responses were coded on a five-point scale: strongly *agree, agree, neutral, disagree*, and *strongly disagree*

1. A lighter skin tone is more beautiful
2. A lighter skin tone provides women with higher self-esteem
3. A lighter skin tone gives women a younger look
4. A lighter skin tone implies that a woman belongs to a higher social class
5. A lighter skin tone helps a woman get a better job
6. A lighter skin tone increases a woman's chance of getting married
7. Men consider women with lighter skin tone more beautiful

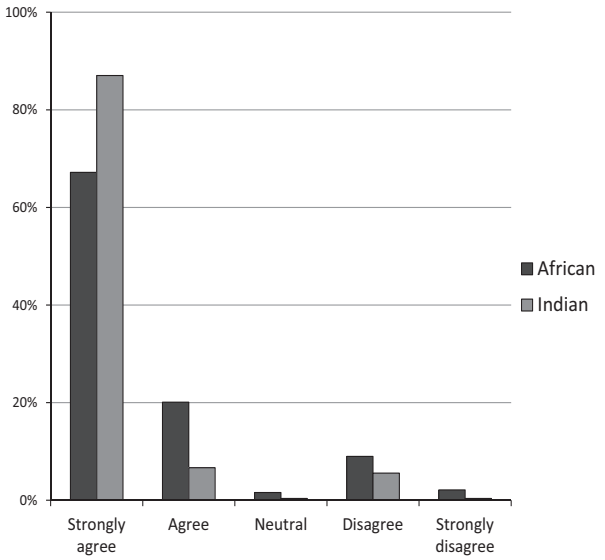

Figure 5 Satisfaction with the results obtained with use of a skin-lightening product. A high proportion of respondents viewed their experience positively, more so with Indian women than African ($P < 0.0001$).

a higher socio-economic class, helped women get better job opportunities, and increased a woman's chances of getting married as it is considered more beautiful by men (Fig. 4).

Respondents were ignorant of the active ingredients in their preparations of choice. Only 12 of 180 users of skin-lightening products knew the name(s) of the active ingredients: two mentioned hydroquinone, while the others named niacinamide, corticosteroids; vitamin C; and fruit extracts in various combinations. This would be expected because the respondents were lay people.

Of the studied respondents, 89% agreed that skin-lightening products can affect the skin adversely, with a slightly higher positive response among Africans than Indians (93% *vs.* 86%, $P = 0.03$). Awareness of risk was not affected by age, education, income or residence. We were unable to find a correlation between knowledge of adverse effects and avoidance of use.

Three quarters of those using skin-lightening products understood what a sunscreen is, with 69% agreeing that it was important to use a sunscreen when using skin-lightening products. In both cases, Africans were significantly less knowledgeable than Indians (51% *vs.* 92% and, 60% *vs.* 74%, $P < 0.0001$). Seventy-nine percentage were aware that sun exposure can reverse the effects of skin-lightening products, but only 11% of African and 32% of Indian respondents ($P < 0.0001$) applied sunscreen on the face when going outdoors. Only 40% of respondents had any idea whether their skin-lightening product contained a sunscreen or not: 22.9% thought it did, 18.1% that it did not.

The respondents' satisfaction with the results they had obtained with their skin-lightening product was overwhelmingly positive more so for Indian women than African ($P < 0.0001$) (Fig. 5). Women from a rural or semi-rural background were more likely to be satisfied than urban women ($P = 0.0004$). In addition those with lighter skin tone were more likely to be satisfied than those with darker color ($P < 0.0001$). A significant number reported that their skin had been damaged by the skin-lightening product that is, 23% of Africans and 11% of Indians ($P = 0.0001$). Yet, surprisingly, 90% of women who reported skin damage still expressed themselves as very satisfied with the result.

Discussion

Our results show that the use of skin lighteners is widespread among black communities in South Africa. Making the broad assumption that our results broadly represent prevalence of use nationally, this would translate into considerably more than 4 million users among the African and Indian adult female population.

Skin lightening and bleaching practices have a long provenance and attempt to achieve esthetic ideals rooted in precolonial conceptions of beauty[2,6,16] which were reinforced by colonial laws which classified people based on their complexion and race. This Johnson historical pre-occupation with fair skin is both racist and sexist and continues to be strongly expressed in popular media and reinforced by the contemporary beauty industry.[6,17] Advertising may contribute to the perception that fair skin is more desirable by showing fair-skinned models as a symbol of what is attractive and desirable.[2,3,6,15] For instance, Hamed *et al.* in a study conducted in Jordan showed that 77% of 318 women studied believed that advertisements influenced them

to prefer lighter skin tone regardless of their level of education.[1]

Our results indicate that similar cultural conceptions in black community are pervasive among the South African black communities. Indian women appear to hold these views more strongly than African women, findings consistent with those from other African and Asian countries.[1,2,6,15,18] Between 80% and 90% of our respondents agreed that this preference is reinforced by the way beauty products are advertised. These views are tenacious and are not affected by factors such as education or income, though there is a decline in the intensity of these views with advancing maturity.

It is concerning that such widespread use is accompanied by little understanding of the risks involved. Though most of the women interviewed agreed that skin lightening may have adverse consequences, almost none could name the active ingredient in their chosen product. In choosing a product they were guided by price and brand name, and not by the identity of the active ingredients in the formulation. Nor were they aware whether it contained a sunscreen. Few used a sunscreen in combination with the skin-lightening product, even though most understood that sun exposure can reverse the effects of skin lightening.

Self-prescribed use of skin-lightening products is widespread in many African countries,[19–21] and Ntambwe[15] has suggested that consumer ignorance regarding the potential harmful side effects of these creams indicates the need for public education as one way of reversing this.

Use of skin-lightening products was associated with very high levels of satisfaction. Our finding that satisfaction correlated inversely with darkness of the skin suggests that there may be an element of unrealistic expectations in the use of these products. Somewhat inexplicably, though some women reported that skin damage as a result of using skin lighteners, most of these women still reported that they were satisfied with the result they had obtained. It is possible, however, that some users have not yet used their products for a period longer enough for the long-term side effects to emerge,[8–11,22] as in the rebound phenomenon following topical steroid use reported by Plewig *et al.*[12] A conclusion to be drawn from our findings, however, is that adverse consequences to skin lightening are not a common experience among users; this may reflect referral bias among patients presenting to dermatologists, where large numbers may still reflect a small percentage of the very large product-using population from which they are drawn. It will certainly complicate attempts to reduce the prevalence of use among our population, given that both the perception and the experience of serious harm resulting from their use are low.

In conclusion, we have shown that use of skin-lightening products among black South African women is prevalent and is not associated with appropriate knowledge of risks or of safe practice. Culturally-linked perceptions of the social value of fair skin are pervasive and are perpetuated by the use of fair-skinned models to market cosmetics to black consumers. There are extraordinary difficulties to reduce the inappropriate use of skin lighteners given how deeply rooted cultural perceptions of the desirability of a light complexion are in black women. Extensive public education[23] coupled to effective policing of informal markets will be required.

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CHAPTE R 5

Skin-lightening c reams used in Durba n, South Africa.

Dlova NC, Hendricks NE, Martincgh BS. Skin-lightening creams used in Durban, South Africa. Int J Dermatol 2012; 51 Suppl 1: 51-3, 6-9.

International Journal of Dermatology

Report

Skin-lightening creams used in Durban, South Africa

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Introduction

Skin creams that have bleaching properties and that are reputed to improve the complexion are much sought after by black South African women. The legacy of apartheid in South Africa has left more than what is overtly obvious for black South Africans and indoctrinated misconceptions that will take many years to change. "Black" for the purposes of this paper refers to the African, coloured, and Indian women in South Africa.

Pigmentary conformists are viewed as unattractive. A lighter complexion is preferred by many. According to Findlay,[1] the skin that black people most wish to avoid is a dull, drab, dusty, or scaly surface. Brightness is what they are looking for. In addition, some of the patients use skin-lightening creams as self-medication in an effort to get rid of common dermatological conditions such as acne, melasma, and postinflammatory hyperpigmentation.

The use of creams to lighten the skin remains a widespread and common practice in many African countries[2]. The most common agents used include mercury-containing compounds,[3] hydroquinone (*p*-dihydroxybenzene) (HQ) and its derivatives, resorcinol, and topical steroids of various potency. Most frequently, more than one agent is used at a time.

Numerous studies on different populations of African men and women have demonstrated the occurrence of harmful long-term side effects from the use of skin-lightening cosmetics.[2,4,5] Mercury compounds have been banned in cosmetics in several countries owing to nephrotoxicity and neurotoxicity. Reactions to phenolic detergent germicides[6] and monobenzylether of HQ[3] have been reported.

In 1975, Findlay[7] reported ochronosis after prolonged use of skin-lightening creams containing HQ, which inhibits tyrosinase and prevents the conversion of tyrosine to dihydroxyphenylalanine, a precursor of melanin. The pigmentation, which is blue–black clinically, appears ochre-colored microscopically, hence the term ochronosis. In these patients, the facial skin overcomes this lightening effect and becomes darker with continued use of cream, particularly in sun-exposed areas. The darker areas, which have a reticulated and ripple-like sooty appearance, corresponds to those areas in which the cream is well rubbed in. The clinical findings can be graded into mild (coarsening and darkening of the skin), moderate (large black papules with normal skin in between), and severe (black, caviar-like papules) ochronosis[8]. Recommendations were made in 1983 by the South African Department of Health and Welfare to limit the concentration of HQ in over-the-counter (OTC) skin lighteners to no more than 2%, and this is now enforced.

We have noticed several African women presenting to us with steroid-induced acne and steroid addiction syndrome. An alarming number present with permanently damaged skin due to the use of OTC preparations and products sold by street vendors. We have also observed a change in the pattern in the last 10–15 years, as we are seeing more steroid-induced cutaneous side effects than exogenous ochronosis.

Topical steroids cause an array of cutaneous side effects such as telangiectasia, atrophy, hirsutism, steroid-

induced acne, striae, and opportunistic infections[2,4]. The initial clearing of the skin noticed after application of topical steroids might give a false sense of security and confidence, as it is later followed by a rebound worsening of acne. Of particular concern is the challenge in the treatment of steroid acne, which is a common sequelae of steroid abuse. The response to treatment is slow and patients may agonize for several months. During this period, they need proper advice and support during the withdrawal phase.

The last paper on skin-lightening products on the market in South Africa was published by Findlay and De Beer 31 years ago.[10] Here in we report the findings from an investigation of the contents of the top 10 best-selling skin-lightening creams available on the market in Durban, South Africa.

Methods

Ten commercial skin-lightening facial products, which are readily found in supermarkets, cosmetic shops, as well as sold by hawkers on city streets, in Durban, South Africa, were randomly selected for analysis. Selection criteria were based on:

1. Word of mouth recommendations for skin-lightening creams.

2. Facial cosmetic creams claiming skin-lightening properties (fades dark spots, marks or blemishes, complexion enhancer, exfoliative properties, etc.).

3. Prescribed products.

The 10 study products are listed in Table 1. The average cost is between R10 and R35 per unit, with content ranging from 20 g to 50 g per unit.

The creams were extracted with methanol and the resulting extracts were analyzed by means of high-performance liquid chromatography with both ultraviolet and fluorescence detection. An isocratic elution method was used to separate the components of the extracts.

Mercury in the creams was determined by cold vapour atomic absorption spectrometry. Before analysis for mercury the creams were digested in a (5:1 vol/vol) mixture of nitric and hydrochloric acids.

In all cases, the samples were analyzed in triplicate.

Results

Of the 10 top-selling skin-lightening creams nine (90%) were found to contain banned or illegal compounds. Six (60%) of them were manufactured in South Africa and the rest were illegally imported from Taiwan (1–10%), Italy (1–10%), and the UK (1–10%). Four products (40%) contained mercury as an active ingredient, two (20%) contained corticosteroids, two (20%) resorcinol, and one (10%) a derivative of HQ. The majority of products contained banned substances.

Only three (30%) products contained the active ingredients labeled on the packaging. Two (20%) were incorrectly labeled, as they were found to contain mercury instead of the natural albumen and placenta, or phenol and 8-hydroxyquinoline, that was declared on the packaging (Table 1). None of the products had a warning on the packaging alerting the consumer to stop using the cream if side effects were experienced or advice to use the product with a sunscreen, as is stipulated by law on the sale of cosmetics and toiletries in South Africa.[9]

Discussion

HQ was not found in the top 10 skin-bleaching products sold on the market in Durban. Only one product contained a HQ derivative. On the other hand, nearly half of the products contained mercury as an active ingredient, although there was no indication of this compound on the packaging label. The export of mercury-containing cosmetics was banned[11] in the EU in 2003, yet sample 6 (Rico complexion cream), which contains mercury, was manufactured in the UK and imported to South Africa.

Clobetasol propionate and betamethasone dipropionate are potent topical steroids. They are prescription drugs whose supply by unauthorized people is illegal in South Africa, and yet they are easily purchased from street vendors at a very low cost of R10 compared with the retail cost at pharmacies, which ranges between R100 and R150/unit.

Of major concern also is the fact that prescription drugs such as corticosteroid creams are easily dispensed by some unscrupulous pharmacies without an official prescription, and are sold at some general practitioner rooms by receptionists without the patient consulting the doctor. The risk of side-effects with such potent steroids is increased by their inappropriate and uncontrolled use, and moreover their application to thin skin areas such as the face and neck may result in skin atrophy and telangectasia. We have no knowledge of the original source of the preparations or whether they all originate from the same supplier.

Topical corticosteroids as well as mercury, resorcinol, and HQ-containing creams are widely available in South Africa, but there is no governing body that regulates or controls their sale and availability. Concern about the side-effects and easy availability of these products, has already been voiced by dermatologists.[1,2,7]

Although our sample number was small and represented only some central Durban city outlets, data analysis is ongoing and we are presently looking at the top 40 selling skin-lightening creams in the whole of South Africa for the presence of banned skin-lightening compounds and corticosteroids.

Conclusion

Since the last study by Findlay and De Beer, 31 years ago,[10] old brand names have come and gone and new appealing and provocative names continue to intrude and flood the South African market.

Stronger regulations and restrictions need to be imposed on cosmetic shops and supermarkets. In addition, continuous education of consumers about side-effects of these creams is mandatory. The South African Medicines Control Council and the South African National Consumer body need to be informed to investigate the unscrupulous distribution of these products.

Advertisements for skin-lightening creams should be controlled and the use of fair-skinned models for advertising skin products aimed at the black consumer should be banned.

On completion of the second larger battery of tests, we wish to commit to a massive, aggressive public education campaign based on the above findings and give better protection to consumers in an area fraught with consumer exploitation and selling of illegal skin lighteners.

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Table 1 List of 10 creams analysed together with the active skin-lightening agents declared on the packaging labels and those found to be present

Sample no.	Product label	Country of manufacture	Company	Declared active ingredients	Active ingredients found to be present
1	Lemon Lite – vanishing cream	South Africa	Adcock Ingram	–	Mercury
2	Movate Cream	Italy	Esapharma	Clobetasol propionate (0.05%)	Clobetasol propionate
3	Persivate	South Africa	Aspen	Betamethasone valerate	Betamethasone
4	Shirley	Taiwan	Shirley Chemical Corporation	Contains natural albumen and placenta base that have an effect on lightening facial skin	Mercury
5	Bee-Co cream	–	Unknown	–	Resorcinol
6	Rico complexion cream	UK	Rico Skin Care Ltd	–	Mercury
7	Eskamel – acne and pimple cream	South Africa	SmithKline Beecham	Resorcinol (2%)	Resorcinol
8	Ponds – vanishing cream	South Africa	The Elida Pond's Institute	–	–
9	Cuticura	South Africa	Novartis	Phenol, 8-hydroxyquinoline	Mercury
10	Gentle Magic skincare cream	South Africa	Du Marc CC	–	HQ derivative

CHAPTE R 6

A survey of skin cance r awarene ss, sunscreen use and risk - appropr iate behaviour among South Africans indic ates a substantial knowledge deficit

Manuscript in preparation for submission.

TITLE

A survey of skin cancer awareness, sunscreen use and risk-appropriate behaviour among South Africans indicates a substantial knowledge deficit.

RUNNING HEAD

Skin cancer awareness and sunscreen use

KEY WORDS

Sunscreen, melanoma, skin cancer, South Africa, screening, prevention, education

WORD, TABLE AND FIGURE COUNT

Abstract	178
Text	2656
Tables	3
Figures	3

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CONFLICT OF INTEREST

None

ABSTRACT

Background

Melanoma incidence among white South Africans is increasing. Among black South Africans, melanoma is associated with an advanced stage at presentation and significant mortality.

Objectives

To assess the perception of skin cancer risk, knowledge of skin cancer, and understanding of the importance and use of sunscreens among South Africans.

Methods

A cross-sectional survey conducted among general outpatients over 4 months at a large central hospital in Durban, South Africa.

Results

Only half of the white respondents reported regular use of sunscreen. The number was substantially lower among the African and Indian counterparts. Less than 20% of whites reported checking their skin for suspicious moles. Most Africans were not aware that they were at risk of skin cancer, and only 10% were aware of the risk of developing skin cancers on acral sites and nails.

Conclusions

There is a disturbing lack of knowledge about skin cancer and sun protection behaviours among all South Africans. Given the increase in melanoma incidence and racial disparities in survival rates, it is imperative to target each population with effective, culturally-sensitive educational programmes.

SUMMARY

Melanoma incidence is rising in South Africa. There is a marked racial disparity in melanoma survival. This study illustrates a serious knowledge and practice gap among South Africans regarding skin cancer risk, screening and sun-protective behaviours, with marked differences based on ethnicity, possibly resulting from a perception that these issues are not relevant in Africans. It emphasizes the need for effective, culturally sensitive education and screening efforts.

INTRODUCTION

Despite efforts to encourage preventative measures[1], melanoma incidence has increased over the last three decades. With its subtropical climate and long coastline promoting an outdoor lifestyle, South Africa has not escaped this trend. The ambient erythema ultraviolet radiation (EUV) in Durban is 25-35 minimal erythema dose (MED) units per day during summer[2], reflecting relatively high levels of UV exposure. The age-standardized melanoma incidence rate among the white population in Cape Town was reported as 24.4 per 100,000 in 1998[3], but was found to be 33.5 and 36.9 per 100,000 for women and men, respectively in 2008[4]. By comparison, incidence rates of between 0.9 and 1.2 per 100,000 among African South Africans have been reported[5,6]. Nearly three quarters of melanomas in the white South African population have been reported to have Breslow thickness <1.5mm[3]. By comparison, African patients present with significantly higher Breslow depths[7]. The South African melanoma data parallels US SEER (Surveillance, Epidemiology, and End Results Program) data in terms of the race-correlated differences in both incidence and in depth at presentation[1,8,9].

Early detection of melanoma through screening examination is associated with a lower probability of metastases[10,11]. In the absence of published data for SA, we endeavoured to determine the perception of skin cancer risk, skin cancer appearance, and general knowledge about sunscreen among South Africa's three dominant ethnic groups: indigenous African and Indian (Fitzpatrick skin types 4–6), and white (Fitzpatrick types 1-4).

MATERIALS AND METHODS

A cross-sectional survey was conducted in the general outpatient department of Inkosi Albert Luthuli Central Hospital, a major tertiary referral centre in Durban, KwaZulu-Natal Province. Durban is located on the eastern seaboard of South Africa and the hospital serves an ethnically diverse population. Ethical approval was received from the University of KwaZulu-Natal Biomedical Research Ethics Committee (BE 180/11). South African citizens aged between 18 and 90 years attending out-patient clinics between 1 September and 31 December 2012 were invited to participate, excluding those attending the dermatology clinic. A power analysis suggested that 300 subjects from each ethnic group were required. All subjects provided written informed consent. A structured questionnaire designed for this study was administered by a trained study assistant who was proficient in both English and isiZulu, the locally used African language. A pilot study, wherein the protocol-questionnaire was administered to 20 subjects for validation was conducted. Subjects were not subject to clinical examination.

The questionnaire sought information on the following:

- Socio-demographic characteristics, skin sensitivity, skin cancer risk and sun-protective behaviour.
- Knowledge regarding skin cancer appearance, use and effects of sunscreen.
- Self-initiated skin examination experience and that performed by practitioners.

Data analysis

Data were entered into a Microsoft Excel spreadsheet (Microsoft Corporation, Redmond WA, USA) and analysed with MedCalc Statistical Software version 12.7.5 (MedCalc Software BVBA, Ostend, Belgium). Data were summarised in contingency tables and analysed for significance using a chi-squared test or Fisher's exact test as appropriate. Ordinal data were compared between groups by Mann-Whitney or Kruskal-Wallis tests as appropriate. Correlations were performed using the Spearman rank-order test.

RESULTS

Demographics

During the four months 1000 people were approached and 963 participants were interviewed, of which 38.7% were African, 32.0% Indian and 29.3% white. The three groups differed in terms of sex ratio, age distribution, educational level and employment status. Women constituted 61%, 49% and 49% of the African, Indian and white samples respectively ($p=0.002$). The age distribution is shown in Fig. 1. The white group had higher levels of education and employment and a higher proportion of retired workers than the other two groups (data not shown). All differences are highly significant, and these effects should be borne in mind when correlating the responses to the questionnaire with race.

Data showed that 27%, 36% and 58% of respondents in the African, Indian and white groups respectively reported that their skin turns red (as opposed to darker) on prolonged sun-exposure ($p<0.0001$). This may represent a susceptibility to sunburn and therefore, by inference, to photodamage. The figure for the African population appears high, and may have been overstated by the respondents.

Understanding of sunscreen practice

The respondents' understanding of the rationale for sunscreen use was generally poor (Table 1). A majority of white respondents understood the link between sun-exposure and skin damage, the protective effects of sunscreens against photo aging, and the concept of the sun protection factor (SPF). Understanding was significantly poorer among the other two groups, and the African group in particular. Only 23% of Africans and 49% of Indians, were aware that regular use of sunscreen can prevent darkening of the skin. Similarly, only 20% and 33% of these groups, respectively, were aware of the role of sunscreen in photoaging. While 82% of whites were aware that sunscreen can prevent skin cancer, only 31% of Africans and 59% of the Indians were aware of this.

Cancer awareness

Although many of the respondents were aware of the risk of skin cancer, two trends emerged (Table 2). Firstly, there was a generally poor understanding of the risk of skin cancer irrespective of race, knowledge that sunscreen is protective, and a very poor knowledge of the practical steps to be taken to mitigate that risk. Only about 10% felt that they would recognise a potentially cancerous lesion or knew that the palms, soles and nails were potential sites for melanoma. Even among whites, who are at highest risk, 70% were unaware of the proper use of sunscreen to prevent skin cancer, and 82% were uncertain about the appearance of a potentially malignant lesion. Secondly, there was a clear differentiation between population groups, with Indian respondents demonstrating a lower level of knowledge than whites, and African respondents having the least knowledge. Regarding whether Africans require more information about the use of sunscreens and skin cancer, 97-98% of Africans agreed, whereas the figures were significantly lower for the other groups ($p<0.0001$), indicating a lack of awareness that African people are also subject to sun damage and skin cancer.

Knowledge index

Summing the answers to questions about photoprotection, cancer awareness and cancer prevention (but excluding those relating to actual practice), we derived an informal 'knowledge index' with a maximum score of 11 (Figure 2). Whites scored significantly higher than the other two groups ($p<0.000001$). There is a modal peak around a score of 6-7, with a second peak at the extreme left (indicating a near-complete lack of knowledge): 10% of whites, 20% of Indians and 50% of the African respondents fell at this end of the scale, suggesting a serious information-deficit within the community. Knowledge of those aged over 40 is significantly greater than those below, and was strongly correlated with completion of secondary school education and female gender (all $p<0.000001$).

Prevalence of sun-protective behaviour

One third of Indian respondents regularly practised sun-bathing (Table 3). The figure in whites is probably an underestimate given the significantly higher mean age of our sample. Approximately 50% reported sunscreen use, the frequency varying from 80% among whites to 24% in Africans. However, usage was found to be inconsistent, with only 30% applying it daily or frequently, however: this may represent an element of over-reporting. Regarding the application of sunscreen on most days, 15% of African, 24% of Indians and 53% of whites reported that they did this with a further 11%, 17% and 24% reporting occasional use (data not shown). This result is highly significant ($p<0.0001$).

Only 12% had ever inspected their skin for suspicious lesions and 6% had had their skin examined by a doctor, this figure being consistent across the groups. The examination was generally performed by a dermatologist, suggesting that family practitioners and other health care professionals are neglecting this important aspect of the physical examination. This may reflect deficiencies in medical training, which lacks emphasis on skin cancer screening.

Behaviour index

By summing the answers about probing sun-protective behaviour, we derived an informal 'behaviour index' with a maximum score of 6 (Figure 3). Although the white respondents scored significantly higher than the other groups ($p<0.000001$), approximately 10% across all groups scored above 3, largely due to the general failure noted to use sunscreens regularly, to inspect their own skins and to undergo regular medical skin examinations. As with the knowledge index, the behaviour score correlated significantly with age, education, employment and female gender (all $p<0.000001$).

DISCUSSION

Perceived skin cancer risk may correlate with risk-averse behaviours. Likewise, a lack of perceived risk may be a barrier to risk reduction[12,13]. The incidence of melanoma is strongly influenced by ethnicity. Most public education programs for melanoma are directed towards whites[14]. A consequence of this may be that ethnic groups with darker skin, including Africans and Indians, may not be reached by such programmes, despite being at risk of melanoma. One quarter of the Africans and a third of the Indians reported a susceptibility to sunburn, and therefore to photo damage. An understanding of the relationship between sun-exposure and risk of skin cancer is fundamental to prevention.

Our results indicate a lack of understanding of skin cancer and of sunscreen use in our population. This information deficit was particularly noticeable among African, and Indian populations Further, only half of whites, and considerably fewer from the other groups, reported frequent use of sunscreen, indicating that many of at-risk individuals are not in the habit of using sunscreen.

Sunscreen usage discrepancy may be explained in part by varying degrees of knowledge about its uses and benefit. While 86% of whites knew the definition of SPF, only half of the Indians (55%) and less than a third of African (30%) did. There was a general lack of understanding of the need for sunscreen in white people and of the differences in risk across ethnic groups, suggesting a lack of understanding of the link between light skin, propensity to sunburn, risk of melanoma and of the role of sun protection in ameliorating this risk.

Although Africans are at lower risk of melanoma than lighter-skinned groups, the risk is not negligible and may be reduced by limiting sun-exposure or using sunscreens. It is alarming that fewer than half of the African respondents were aware of their risk of skin cancer, or that they should use sunscreen. Aside from melanoma, basal cell carcinoma (BCC) has been reported to represent 12% to 35% of skin cancers in African Americans, and 2% to 8% of skin cancers in Africans. Further, the majority of BCC's in Africans and Indians occur in sun-exposed skin. Indicating that sun protection is paramount, regardless of pigment[9].

The benefits of sunscreen are not restricted to cancer prevention. Sunscreen may reduce wrinkling and photo damage, resulting in more even pigmentation. With age, darker skin types are more likely to demonstrate skin mottling and uneven skin pigmentation[15,16]. Only a quarter of Africans were aware that sunscreen could encourage a more even skin pigmentation (23%).

Prevalence rates of skin bleaching in sub-Saharan Africa have been reported between 26% and 67%, despite an array of potential adverse side effects from the practice[17]. Paradoxically, Africans are more likely to use bleaching products to lighten skin tone, often with adverse consequences, than to use sunscreen to reduce the darkening effects of the sun in the first place. Indeed, the increased sunscreen usage and education about sun avoidance among Africans and Indians might substantially reduce the perceived need for skin bleaching products.

Early detection of skin cancers, particularly melanoma, is vital. Public education programs are usually directed towards primary and secondary prevention measures. Seventy percent of melanomas in Africans have been reported to be on the lower limb, with 90% of those being below the ankle, and acral lentiginous melanoma being the most common subtype [18,19]. While melanoma incidence among Africans is low, with a reported incidence between 0.9 and 1.2 per 100, 000[5], Africans suffer a significant proportion of the morbidity and mortality associated with melanomas. Survival rates from plantar melanoma in Africans are very low with only 25% of 40 African patients with plantar melanoma surviving for, 5-years.[7]. In the USA African-Americans are more likely to present with advanced disease and to have a worse prognosis than whites [14]. Disturbingly, only 10% of Africans were aware that they could get skin cancer on the palms, soles and under the nails, fewer than 10% Africans felt that they could identify a suspicious mole or skin cancer, and fewer than 5% had ever done skin checks.

Melanoma incidence rates in white women and men have shown a 1.5 fold and 1.3 fold increases, respectively, over a ten year period[4]. Recent estimates indicate an extraordinarily high incidence in this population[6,20]. It is therefore disturbing that only 18% reported ever checking their skin for suspicious lesions, and 82% were not confident that they could recognize suspicious moles or skin cancer. Almost all our respondents, regardless of ethnicity, indicated a need for more information about skin cancer (97%, data not shown), and our findings confirm an information deficit on the related issues of sun protection, sun damage and melanoma prevention and detection. Given the significant morbidity, mortality and costs associated with advanced stage melanoma, early detection and prevention are critical.

Our study has revealed a lack of risk-averse behaviours, with our knowledge and behavioural indices being reasonably correlated ($r=0.49$, $p<0.0001$). Although we have shown significant correlations in both knowledge and behaviour with age, race, education, employment and gender; our three groups are not homogeneous and a significant degree of interaction is expected between all these factors.

There is a need to convey the message that hands, feet and nails are vulnerable in the African population, and should be inspected regularly. Physicians and health care providers should take a lead in instituting early detection and screening measures, and in educating the public on the need for these. Fewer than 10% of respondents reported that their doctor had ever talked to them about skin cancer or shown them how to check their skin, and fewer than 10% had ever had a medical examination of the skin. The high incidence of melanoma in whites and the disproportionate mortality burden of melanoma in Africans mandate public health and screening initiatives.

Our study indicates a pervasive lack of knowledge of the risks of sun-exposure, the benefits of sun protection and the measures necessary to prevent and detect melanoma. Africans and

Indians need to be educated about the benefits of using sunscreen not only to prevent skin cancer but to obviate skin mottling and uneven skin tone which is a characteristic feature in this population. This in turn may lessen some of the dependency of our African population on skin-lightening preparations. We believe that there is a need for major improvements in public education, and for an increased emphasis on these measures by health care providers. The results indicate the need for targeted and culturally inclusive programmes to increase the rate of early detection, decrease melanoma incidence and improve skin health more generally.

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TABLE 1

Knowledge of sun protection. The values represent all positive responses ("yes") to the questions put to the respondents.

	African (%)	Indian (%)	White (%)	All (%)	p
Do you know that suntanned skin means damaged skin? (n=949)	43 (12%)	89 (29%)	164 (59%)	296 (31%)	<0.0001
Do you know what SPF (sun protection factor) means? (n=948)	110 (30%)	165 (55%)	239 (86%)	514 (54%)	<0.0001
Did you know that sunscreen can make your skin colour/tone more even? (n=939)	89 (24%)	137 (46%)	157 (57%)	383 (41%)	<0.0001
Do you know that the use of a sunscreen can prevent further darkening of the skin? (n=947)	85 (23%)	147 (49%)	64 (23%)	296 (31%)	<0.0001
Did you know that sunscreen can help prevent your skin from wrinkling? (n=949)	73 (20%)	101 (33%)	162 (58%)	336 (35%)	<0.0001
Did you know that sunscreen can help prevent skin cancer? (n=947)	113 (31%)	178 (59%)	229 (82%)	520 (55%)	<0.0001

TABLE 2

Cancer awareness. The values represent all positive responses ("yes") to the questions put to the respondents.

	African (%)	Indian (%)	White (%)	All (%)	p
Can black skin get skin cancer? (n=928)	173 (49%)	225 (74%)	240 (88%)	638 (69%)	0.0001
Do Blacks need to wear sunscreen? (n=942)	166 (45%)	217 (73%)	213 (77%)	596 (63%)	<0.0001
Do you know what a suspicious mole or a skin cancer spot looks like? (n=940)	24 (7%)	37 (12%)	51 (18%)	112 (12%)	<0.0001
Did you know that black people can get skin cancer on the palms, soles, fingernails and toenails? (n=937)	37 (10%)	39 (13%)	21 (8%)	97 (10%)	0.13
Do you know that whites have to wear a sunscreen everyday for 365days from the age of 2 to prevent skin cancer? (n=953)	65 (18%)	142 (47%)	81 (29%)	288 (30%)	<0.0001

TABLE 1

Prevalence of risk-reducing behaviour among the respondents. The values represent all positive responses ("yes") to the questions put to the respondents.

	African (%)	**Indian (%)**	**white (%)**	**All (%)**	**p**
Do you like to lie out in the sun? (n=941)	29 (8%)	100 (33%)	30 (11%)	159 (17%)	<0.0001
Do you ever wear sunscreen? (n=951)	87 (24%)	128 (42%)	222 (80%)	437 (46%)	<0.0001
Do you ever check your skin for suspicious mole or skin cancer spots? (n=937)	17 (5%)	43 (15%)	51 (18%)	111 (12%)	<0.0001
Have you ever had a skin exam by a dermatologist to look for a skin cancer? (n= 952)	14 (4%)	21 (7%)	22 (8%)	57 (6%)	0.077
Have you ever had a skin exam by any doctor to look for skin cancer? (n=958)	15 (4%)	23 (7%)	24 (9%)	62 (6%)	0.08

FIGURE LEGENDS

Figure 1

Age distribution of respondents, categorised by race. The African population is significantly younger than the white population, with the Indian group demonstrating an intermediate profile.

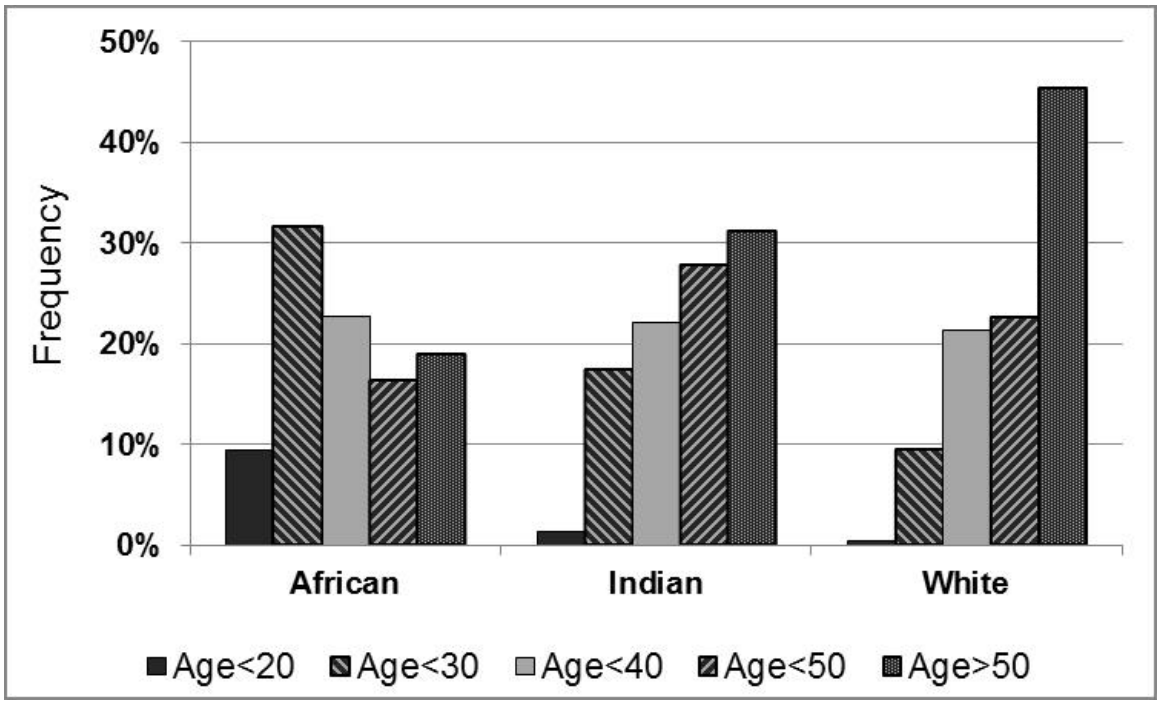
Figure 2

Knowledge index, based on responses to questions probing knowledge of sunscreen use, skin cancer and its detection and prevention. A scale of 0 (no appropriate response to any question) to 11 (appropriate response to all questions) is shown on the horizontal axis. The frequency of scores is shown on the vertical axis. There is a modal peak around a score of 6-7, with a second peak at the extreme left, indicating a near-complete lack of knowledge: 50% of the African respondents fell at this end.

Figure 3

Behaviour index, based on responses to questions probing sun-protective and cancer-detection behaviours. A scale of 0 (no appropriate behaviour reflected any response) to 6 (appropriate behaviour reflected in all responses) is shown on the horizontal axis. The frequency of responses is shown on the vertical axis. Though the white respondents scored significantly higher than the other groups ($p<0.001$), only about 10% across all groups scored above 3.

FIGURE 1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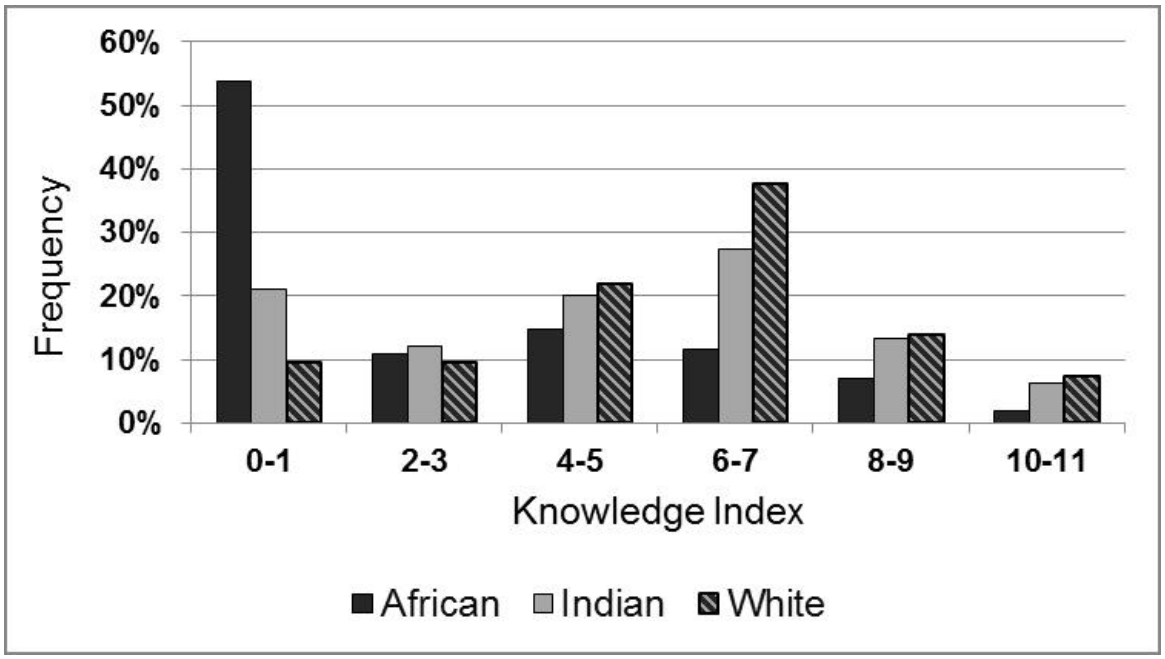
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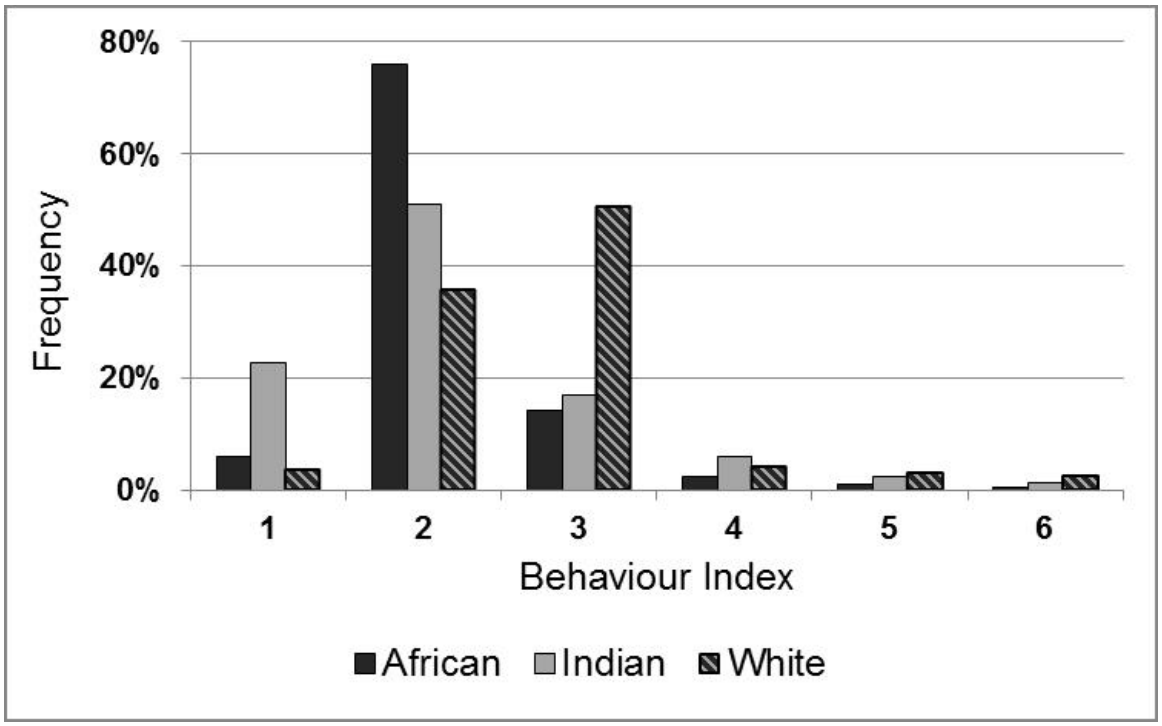
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CHAPTE R 7

Chemical analy sis and in vitro UV-protection char acteristics of clays traditio nally used for sun protection in South Africa

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Photodermatology, Photoimmunology & Photomedicine

BRIEF COMMUNICATION

Chemical analysis and *in vitro* UV-protection characteristics of clays traditionally used for sun protection in South Africa

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Key words:
African women; chemical analysis; clay; South Africa; sunscreen; UV protection

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None declared.

SUMMARY

Clays have been used in southern Africa as photoprotectants by the indigenous people. Typically, two types of clay are used: one white in colour and the other red. In this work, the two clays were identified and characterized, and their *in vitro* SPF values measured. The clays afford a low SPF but offer broad-spectrum protection. No cutaneous side effects from the use of these clays are known. Further consideration should be given to the potential use of clays in sunscreen preparations.

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In hot, sunny climates as experienced in Durban, South Africa, photoprotective measures are required all year round to prevent erythema, irrespective of photoskin type (1). Indigenous African women, particularly those from rural areas, use local clay material for photoprotection and decorative purposes. These women follow a subsistence lifestyle and are outdoors for many hours each day, gardening, fetching wood and water, cooking and performing other chores. They also lack the means to purchase commercial sunscreen products. Although these women typically present with Fitzpatrick skin types 5 and 6, for which skin cancer is less common, photoprotection is important to prevent hyperpigmentation disorders such as melasma.

Clay minerals are widely used in the pharmaceutical industry for a variety of purposes in oral and topical applications, as excipients and in aesthetic medicine (2). They have been used since ancient times (2), so it is not surprising that they form part of the heritage in southern Africa. Recently, the ultraviolet (UV)-protective capacity of clays was reported (3).

Two clays are typically used: one white in appearance and the other red. The white clay is known locally as *umcaku* (isiZulu/isiXhosa) and the red as *ibomvu* (isiZulu/isiXhosa). The women mix the clay (100 g) with water (125 cm^3) and glycerine (20 cm^3) to produce a paste that is applied to the face. The clays are used individually with some women preferring one over the other. The distinct appearance of patients wearing these clays is shown in Fig. 1. As very little is known of the composition and UV efficacy of these clays, it was of interest to undertake a study thereof.

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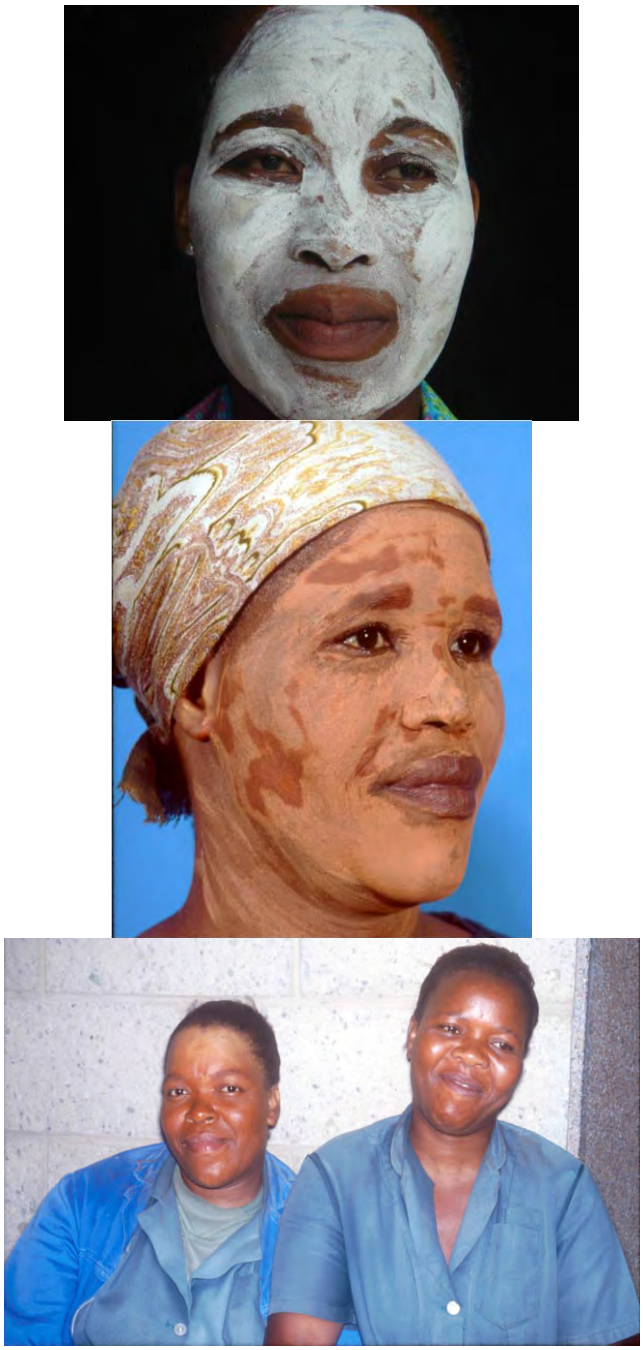


Fig. 1. Patients wearing the white and red clays.

METHODS

White and red clay samples were obtained from the local riverbank next to Inanda district in Durban. Informal traders, who are predominantly black women, buy 5-kg clay balls from the river traders and sell them at the local Durban market.

The clays were characterized by means of X-ray fluorescence, X-ray powder diffraction, Fourier transform infrared spectroscopy, transmission electron microscopy and thermogravimetric analysis. Particle-size analysis was performed on a Malvern Mastersizer 2000 instrument (Malvern Instruments Ltd., Malvern, Worcestershire, UK) that employs laser light scattering.

In order to estimate the UV-protective efficacy of the clays in their natural state, they were subjected to the *in vitro* SPF testing procedure, as developed by Diffey and Robson (4), on an Optometrics SPF 290 Analyser (Optometrics Corporation, Ayer, MA, USA). For this test, the clays were applied to Transpore tape at an application density of 2 mg/cm^2.

RESULTS

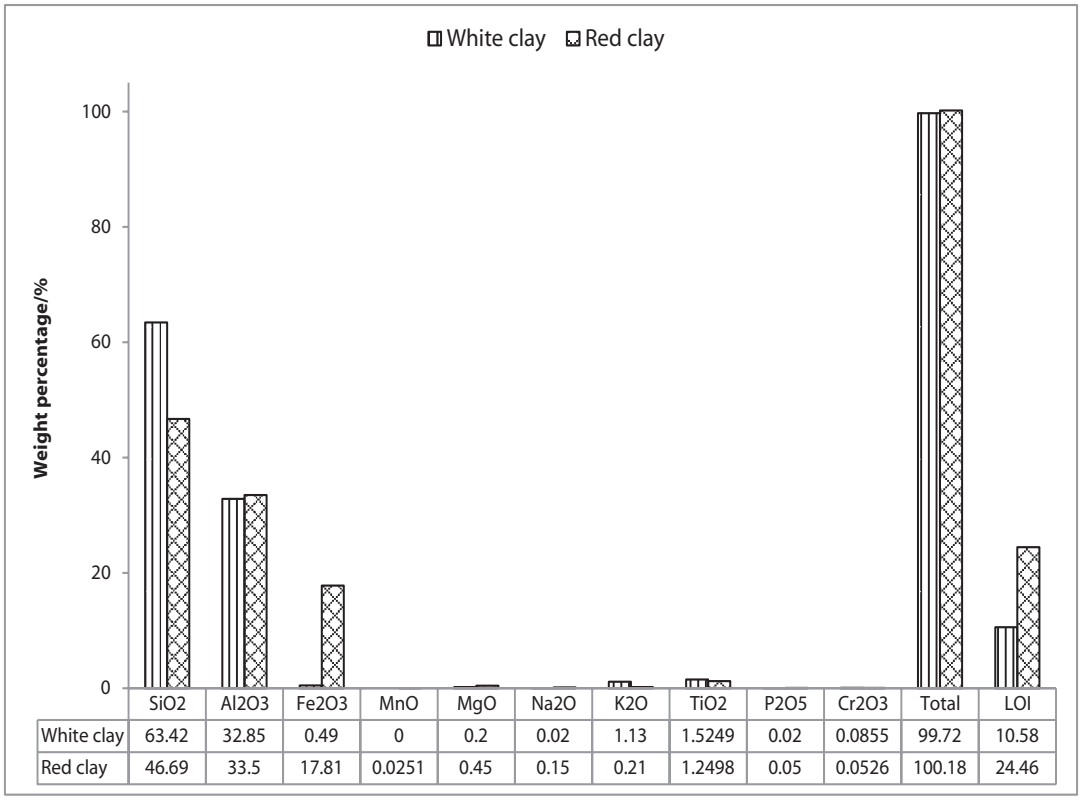
X-ray fluorescence was used to determine the chemical composition of the clays. The results are presented as weight percentages of the oxides in Fig. 2a. The major constituents of the clays were oxides of silicon and aluminium. In the case of the red clay, iron oxide was also present, which is consistent with the hue of the clay. A small percentage of titanium dioxide was also present in both clays. The main impurities were K_2O, MgO, Na_2O, P_2O_5, Cr_2O_3 and MnO. The loss on ignition was 10.58 and 24.46 wt% for the white and red clay, respectively. The mass loss is mainly due to the removal of structural water and organic substances.

The energy-dispersive X-ray spectrometry analysis spectra also confirm the presence of the major oxides (see Fig. 2b).

The phases of the oxides present were investigated by means of powder X-ray diffraction (Fig. 2c). The white clay consisted predominantly of kaolinite and quartz (as evidenced by the peaks at 3.52, 4.37 and 4.17 Å for kaolinite and 3.31 and 4.28 Å for quartz). The red clay instead contained kaolinite, quartz and haematite (peaks at 2.72, 2.55 and 1.81 Å). The presence of these phases was confirmed by Fourier transform infrared spectroscopy (Fig. 2d). Further confirmation that the major component of these clays was kaolinite was obtained from thermogravimetric analysis (Fig. 2e). The exotherm at 507°C in the case of the white clay and 481°C in that of the red clay correspond to loss of structural hydroxyl groups due to the transformation of kaolinite [$Al_2Si_2O_5(OH)_4$] to metakaolinite ($Al_2Si_2O_7$). The mass loss below 100°C is due to dehydration (removal of moisture). The mass losses between dehydration and dehydroxylation are due to the presence of the iron oxides, particularly for the red clay. Kaolin deposits have been reported in Inanda (the source of the clays) and the nearby Ndwedwe region (5).

The microstructure of the two clays, as observed by transmission electron microscopy and scanning electron

a



	SiO2	Al2O3	Fe2O3	MnO	MgO	Na2O	K2O	TiO2	P2O5	Cr2O3	Total	LOI
White clay	63.42	32.85	0.49	0	0.2	0.02	1.13	1.5249	0.02	0.0855	99.72	10.58
Red clay	46.69	33.5	17.81	0.0251	0.45	0.15	0.21	1.2498	0.05	0.0526	100.18	24.46

Fig. 2. Data recorded for the characterization of the ultraviolet-protective clays: (a) chemical composition of the clays obtained from X-ray fluorescence, (b) energy-dispersive X-ray spectra, (c) X-ray powder diffractograms, (d) attenuated total reflectance Fourier transform infrared spectra, (e) thermogravimetric analysis curves, (f) transmission electron micrographs, (g) scanning electron micrographs and (h) particle-size distribution curves.

microscopy, can be seen in Figs 2f and 2g, respectively. The white clay appears as platy particles that have the typical kaolinite pseudo-hexagonal shape. The red clay is less regular in morphology.

The white clay sample showed a broad, dispersed particle-size distribution, whereas the red clay showed a bimodal distribution (Fig. 2h). In the case of the white clay, 50% of the particles (by volume) had a diameter smaller than 12.463 μm. For the red clay, the value was 14.630 μm. Using the classification of clay ≤ 2 μm, silt = 2–63 μm and sand = 63–2000 μm, the fractions in the white clay were 9.9%, 58.9 % and 31.2%, respectively. For the red clay, the corresponding figures were 11.5%, 68.4% and 20.1%, respectively. That the white clay had a greater fraction of 'sand' is in keeping with a larger SiO_2/Al_2O_3 ratio (theoretical value for kaolinite is 1.16), indicative of a high-quartz content. The fact that the clay particles are mostly in the micron range accounts for the visible appearance of these clays when applied to the skin. Modern sunscreen formulations that contain metal oxides do so in a micronized form in which the particles have diameters in the nanometer range and appear almost invisible but have good UV blocking ability.

The white clay displayed an estimated SPF of 3.6, a UVA/UVB ratio of 0.9 and a critical wavelength of 388 nm. The red clay had an estimated SPF of 4, a UVA/UVB ratio of 1 and a critical wavelength of 389 nm. Both clays can therefore be classified as broad-spectrum protectants as their critical wavelengths are greater than 370 nm. The fact that the red clay has a higher proportion of smaller particle sizes improves its light scattering and absorbing ability. Particle dispersion is one aspect that sunscreen formulators keep foremost in mind in order to achieve good sun protection. Because the clays discussed here are formulated in the home by simple mixing with household reagents, namely, water and glycerine, particle aggregation is probably a limiting factor in achieving an improved SPF.

DISCUSSION

This work has shown that the clays typically used in rural parts of South Africa for UV protection consist chiefly of

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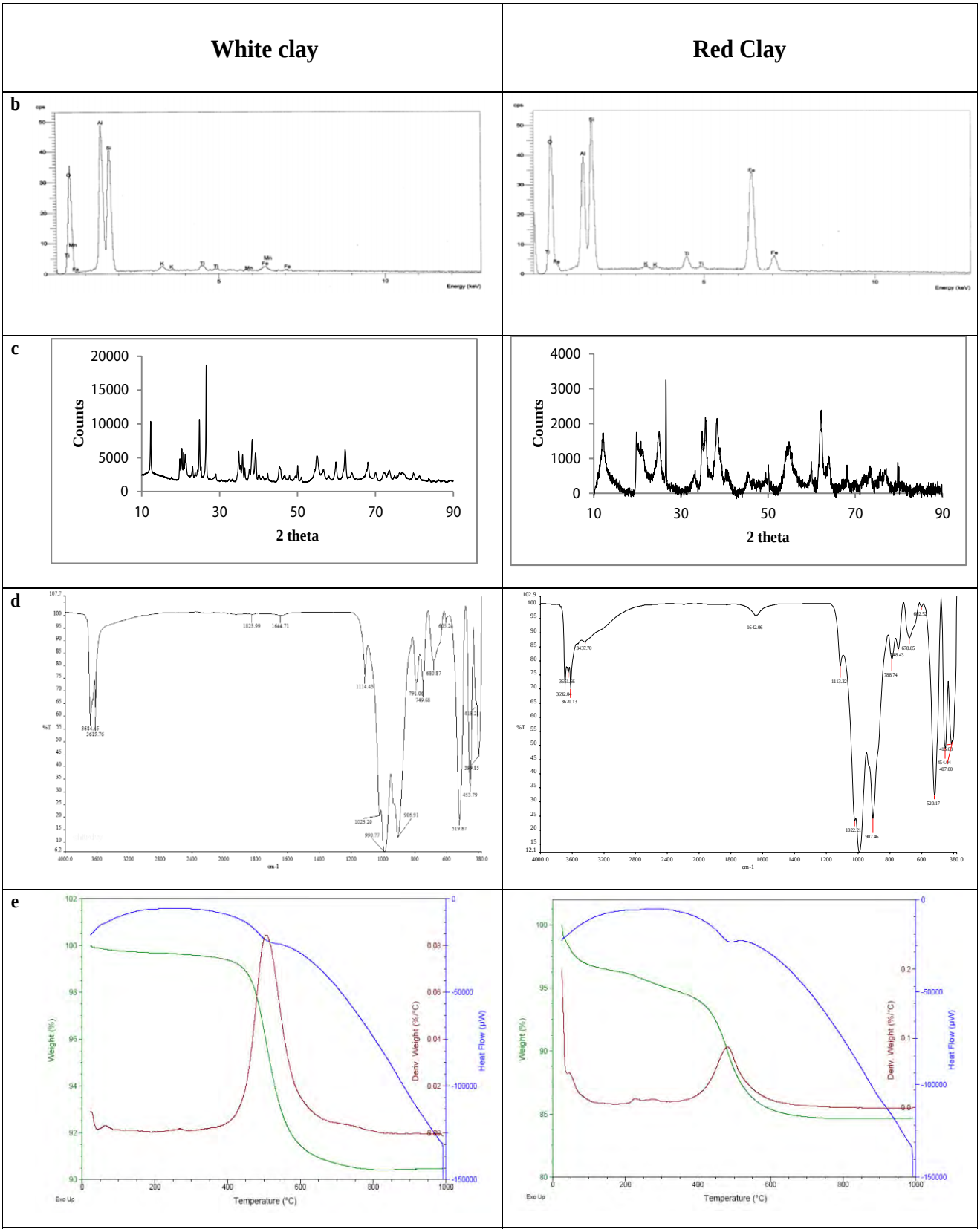

Fig. 2. Continued.

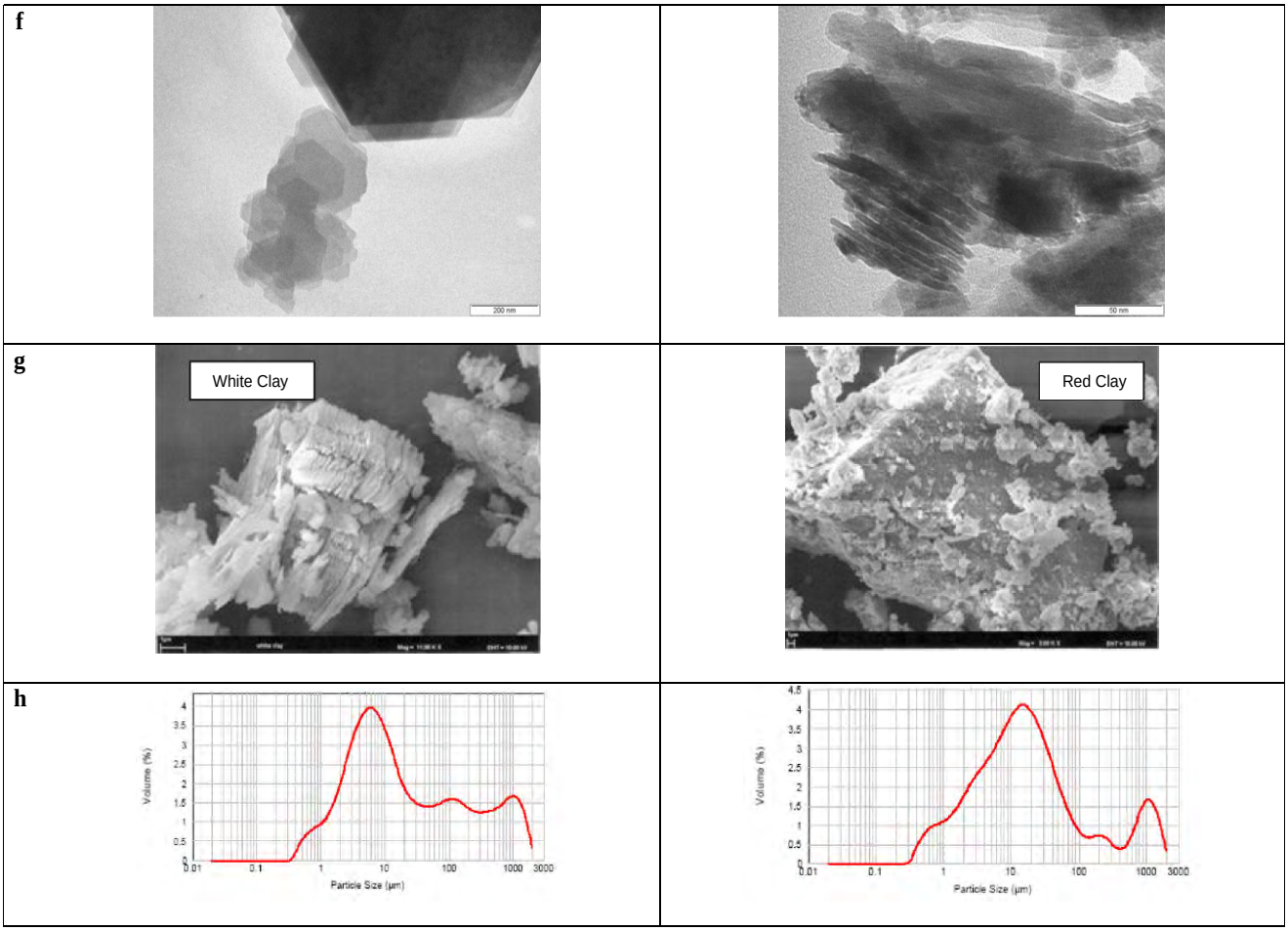

Fig. 2. Continued.

the mineral kaolinite. Traditionally, clay soils rich in this mineral are widely used in southern Africa for a variety of medicinal purposes because they exhibit low toxicity. However, it needs to be pointed out that in some regions clays are contaminated with arsenic; therefore, the toxicity of the clays needs to be assessed before widespread usage.

These traditional non-commercial sun protective measures bear some similarity to commercial physical sunblocks. They are both composed of metal/metalloid oxides. (In the case of commercial physical sunblocks, the typical active agents are either titanium dioxide or zinc oxide.) They are both messy to use and can cause staining. To improve their aesthetic appeal commercial sunblocks are available in designer colours and in South Africa these are widely used and popularized by surfers and cricketers. The traditional clays discussed here have their own inherent colouring.

Although the SPF of both clays is low, they do provide some degree of UVA protection. This is an important consideration as UVA constitutes the greater amount of incident solar UV radiation and has been implicated in skin cancer. Another aspect of sunscreen usage is application density. Typical commercial sunscreens are tested with an application density of 2 mg/cm^2, but it is well known that typical usage patterns are less than half this amount. Here, however, this is unlikely to be the case because of the 100 g of clay mixed they use 5 g to cover the face, which is greater than the amount advocated for sunscreens.

These clays provide a cost-effective, easily available and culturally appropriate product for rural South African women. Although our study did not consider the safety profile of these clays, the indigenous women who have used these clays for decades have not reported any cutaneous side effects apart from a residual orange hue on the skin. Given the difficulty in finding suitable photostable and non-toxic organic sunscreen absorbers, greater consideration should be given to the potential of clays as additives for sun-protection creams.

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CHAPTE R 8

Non-toxic melanin production inhibitors from Garcinia livingstonei (Clusiaceae).

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Non-toxic melanin production inhibitors from *Garcinia livingstonei* (Clusiaceae)

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ABSTRACT

Ethnopharmacological relevance: The stem bark of *Garcinia livingstonei* is used traditionally as a skin lightening agent.
Aim of the study: To isolate and identify compounds responsible for the observed skin lightening activity of *Garcinia livingstonei* and to evaluate their cytotoxicity.
Materials and methods: Constituents of the stem bark and fruits of *Garcinia livingstonei* were isolated using chromatographic techniques and structures were determined using 1D and 2D NMR and MS analysis. MeWo cells were used to evaluate the cytotoxicity and impact on melanin levels of extracts and compounds isolated, *in vitro*.
Results: Twelve known compounds, morelloflavone (**1**), morelloflavone-7″-sulphate (**2**), guttiferone A (**3**), sargaol (**4**), isojacareubin (**5**), 6-deoxyisojacareubin (**6**) and in addition to the common triterpenoids, betulin, betulin aldehyde, lupeol, lupenone, euphol and stigmasterol were isolated in this investigation. Morelloflavone, morelloflavone-7″-sulphate and sargaol, were found to be considerably less cytotoxic and more effective as skin lightening agents than hydroquinone.
Conclusions: A range of compounds was isolated from the stem bark and fruit of *Garcinia livingstonei*. Although the bark extract contained the cytotoxic guttiferone A, it was found to be less toxic than hydroquinone, and morelloflavone, the 7″-sulphate derivative and sargaol show potential for development as depigmentation/skin lightening agents.

1. Introduction

Garcinia livingstonei T. Anderson (syn. *Genetta angolensis* Vesque) (Clusiaceae) is found throughout tropical Africa, where it occurs as a distinctive small to medium sized (2–10 m) evergreen tree in low altitude riverine fringes and open woodlands (Palgrave and Palgrave, 2002). It is known variously in South Africa as the African or Lowveld Mangosteen, and *umPhimbi*, *isiHlumanye* or *uGobandlovu* (isiZulu) (Pooley, 1993; Hutchings et al., 1996). The wood is used as a general purpose timber, while the flesh of the pinkish orange fruit is edible, with a refreshing acid-sweet taste, and can also be fermented to prepare a pleasant alcoholic beverage (Palgrave and Palgrave, 2002).

The powdered root is used as an aphrodisiac in the treatment of impotence (Arnold and Gulumian, 1984), for abdominal pains during pregnancy (Samuelsson et al., 1992), and as an aid in childbirth (Yu, 1982), while steam from a decoction of the dried leaves is used to treat watering eyes (Arnold and Gulumian, 1984). Coughs, fevers and parasitic diseases are treated with infusions of the fruits and stems (Iwu, 1993).

Previous investigations of this species have resulted in the isolation of a variety of bioactive oxygenated aromatic compounds. A series of novel prenylated xanthones was isolated from *Garcinia livingstonei* which showed fungiostatic activity against *Cladosporium cucumerinum* comparable to that of miconazole, and inhibited SW 480 human colon carcinoma cell growth at levels similar to that of 5-fluorouracil (Sordat-Diserens et al., 1992a). Sordat-Diserens et al., (1992b) isolated the xanthone dimer garcilivin A,

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which has since been shown to display trypanosomal activity against *Trypanosoma brucei brucei* (Mbwambo et al., 2006). Bioassay-guided fractionation of the fruit has yielded the HIV-inhibitory tetraprenylated benzophenone guttiferone A (3) (Gustafson et al., 1992), and the biflavanoid *ent*-naringeninyl-(I-3α,II-8)-4′-*O*-methylnaringenin which is moderately active against a Ghanaian CQS strain of *Plasmodium falciparum* (Mbwambo et al., 2006).

Several tree species are used traditionally on the eastern seaboard of South Africa for the treatment of skin diseases and cosmetic purposes, such as for skin lightening, often under the Xhosa and Zulu name *umemezi* (Earle, 1976; Khan, 1996; Cocks and Dold, 2004; Momtaz et al., 2008). Although a highly valued ethnomedicinal species (Hutchings et al., 1996), dermatological uses for *Garcinia livingstonei* have not earlier been documented either locally, or elsewhere in its extensive tropical African range. Only recently has its application in skin treatment been reported through a personal communication to one of us (NCD) in her capacity as a dermatologist. Clinical observations (Dlova, unpublished results) have revealed that a water slurry of the powdered stem bark is an effective facial sunscreen and/or skin lightener. A literature search indicated that other *Garcinia* species such as *Garcinia indica* Choisy (Jain and DeFilipps, 1991) are used to treat skin diseases, with two taxa, the African *Garcinia kola* Heckel and the Asian *Garcinia subelliptica* Merr. reported to yield tyrosinase inhibitors, from leaves and fruit respectively (Masuda et al., 2005; Okunji et al., 2007).

As no previous studies have focused on this aspect of the use of *Garcinia livingstonei*, the current work was carried out with the aim of isolating compounds for screening for possible application in skin-lightening preparations.

Disorders of hyperpigmentation are seen in all skin types; however, they are encountered more frequently in skin of color (Kanthraj, 2010). While no single therapy has been shown to be superior or to be of benefit to all patients, sometimes combination therapy is recommended to maximize the management of complex cases (Sheth and Pandya, 2011). The main goal of treatment is to decrease the hyperpigmentation with minimal side effects. A range of topical agents are available to treat hyperpigmentation and act at different levels of the melanogenesis pathway (Kanthraj, 2010; Sheth and Pandya, 2011). The most common synthetic pharmacologic agents used are hydroquinone, corticosteroids, and mercurials (Olumide et al., 2008). The long-term use of these products may cause undesirable cutaneous or systemic side effects (Findlay et al., 1975; Findlay and de Beer, 1980; Olumide et al., 2008).

p-Hydroquinone (1,4-dihydroxybenzene) was one of the earliest products used for the treatment of hyperpigmentation and remains the standard against which other treatments for hyperpigmentation are measured. (Draelos, 2007; Sheth and Pandya, 2011). However, its use has been associated with various side effects, which include irritant contact dermatitis and exogenous ochronosis (Findlay and de Beer, 1980; Hardwick et al., 1989; Olumide et al., 2008). In 1975, Findlay and co-workers reported ochronosis amongst black South African women after prolonged use of skin lightening creams containing *p*-hydroquinone, which inhibits tyrosinase and prevents the conversion of tyrosine to dihydroxyphenylalanine, a precursor of melanin. Tyrosinase is, accordingly, a potential target in the search for a medically acceptable skin lightening agent from natural sources. This subject has been the focus of a recent review (Smit et al., 2009).

Given the problems related to hydroquinone use, there exists a need for the identification of novel agents that can be used as skin lightening products, either for cosmetic or clinical use. In this work we examine the properties of compounds isolated from *Garcinia livingstonei*, measuring both their ability to both alter melanin levels in human melanoma cells, and their relative cytotoxicity.

2. Experimental section

2.1. Plant material

Stembark of *Garcinia livingstonei* T. Anderson was collected in Zululand, KwaZulu-Natal Province, South Africa, in June 2002, and fruits were collected on the Howard College Campus of the University of KwaZulu-Natal in January 2004. Plant material was identified by Professor Neil Crouch and vouchers for bark (*N. Crouch 942*) and fruit (*N. Crouch 1137*) lodged at the KwaZulu-Natal Herbarium (NH) in Durban.

2.2. Isolation of compounds

The stem bark was air-dried at room temperature and milled, while the fresh fruits were first peeled and the nut-like kernels separated from the surrounding fruit flesh. The dry powdered stem bark (0.65 kg) was successively extracted with dichloromethane, ethyl acetate and methanol for 24 h each, using a Soxhlet apparatus, and the solvents concentrated *in vacuo* to yield 14.6, 18.7 and 62.2 g of extract, respectively. ^{1}H NMR and tlc analysis showed that the ethyl acetate and methanol extracts of the stem bark were very similar, and they were combined. Fresh seed kernels (1.2 kg), obtained as described above, were successively extracted in similar fashion with hexane, dichloromethane, ethyl acetate and methanol, yielding 38.9, 2.2, 6.4 and 50.0 g of extract, respectively. The fresh fruit peel (1 kg wet mass) was soaked in methanol overnight, filtered, and the filtrate concentrated *in vacuo* to give a suspension, which was extracted with ethyl acetate and concentrated *in vacuo*, yielding 18.8 g of extract.

Repeated separation by gravity column normal phase (Merck 9385 Si gel) and size exclusion (Sephadex LH-20) chromatography, and semi-preparative scale tlc (Merck 05554 aluminium-backed tlc plates) was undertaken using hexane:dichloromethane:ethyl acetate:acetone:methanol solvent mixtures. The dichloromethane extract of the stem bark yielded betulin, (2.5 g), betulin aldehyde (5 mg), lupeol (5 mg), lupenone (5 mg), euphol (50 mg) and stigmasterol (120 mg). The combined ethyl acetate/methanol extract of the stem bark yielded morelloflavone (**1**) (20 mg) and morelloflavone-7″-sulphate (**2**) (20 mg). Guttiferone A (**3**) (5 mg) was isolated from the fruit peel extract. The hexane extract of the fruit kernels yielded sargaol (**4**) (50 mg) and isojacareubin (**5**) (5 mg) and 6-deoxyisojacareubin (6) (5 mg) were isolated from the dichloromethane extract (Fig. 1).

2.3. Identification of compounds isolated

NMR anaylsis was performed on a Bruker 400 MHz NMR spectrophotometer and spectra were determined in $CDCl_3$ or CD_3OD. HRMS were recorded on a Finnigan MAT 95 XP high resolution Double Focussing MS at the University of Surrey. Structures of compounds isolated were confirmed by comparison of NMR and MS data against literature values as referenced in Section 3.

2.4. In-vitro screening of compounds isolated

A human granular fibroblast cell line derived from malignant melanoma was used in all *in vitro* assays (MeWo; ECACC No: 93082609) and was purchased from ECACC (Porton Down, UK). Cells were grown in EMEM supplemented with 2 mM glutamine, 1% non-essential amino acids, 10% foetal bovine serum and 100 U/ml penicillin, 100 μg/ml streptomycin. All cell culture medium and supplements were purchased from Invitrogen (Paisley, UK). MeWo cells were seeded into 96-well plates (Nunc International, Leicestershire, UK) at a concentration of 10,000 cells/well and incubated

at 37 °C for 48 h in a humidified container for attachment. Chemicals/crude extracts or vehicle (0.1% DMSO) was then added to the wells at the indicated concentrations and cells incubated for a further 48 h. Following exposure, medium was collected and cytotoxicity determined by LDH-leakage using the cytotoxicity detection kit (Roche, Lewes, Sussex, UK), as per the manufacturer's instructions. For evaluation of melanin content, cells were washed with PBS, lysed with 1 N NaOH and centrifuged to remove cellular debris. The melanin content of the supernatant was then determined by optical density at 405 nm (Takiwaki et al., 2004).

3. Results and discussion

Twelve known compounds, morelloflavone (**1**) (Li et al., 2002), morelloflavone-7″-sulphate (**2**) (Li et al., 2002), guttiferone A (**3**) (Gustafson et al., 1992), sargaol (2-geranyl-6-hydroxy-2,8-dimethylchromene) (**4**) (Numuta et al., 1992; Voutquenne et al., 1999), isojacareubin (**5**) (Helesbeux et al., 2004), 6-deoxyisojacareubin (**6**) (Ishiguro et al., 1993) and the common triterpenoids, betulin, betulin aldehyde, lupeol, lupenone, euphol and stigmasterol were isolated in this investigation The structures of the isolated compounds were established using NMR spectroscopy and mass spectrometry and by comparison against literature data as referenced above.

In addition to its HIV-inhibitory activity (Gustafson et al., 1992), guttiferone A (**3**) has also been shown to be a potent inhibitor of cholinesterase (Lenta et al., 2007) and glutathione transferase enzymes (Muleya et al., 2008), as well as exhibiting antioxidant (Ngouela et al., 2006), leishmanicidal (Lenta et al., 2007), antiplasmodial (Ngouela et al., 2006), trypanocidal (Abe et al., 2004), and cytotoxic (Williams et al., 2003) effects. The activity of morelloflavone (**1**) as an anti-inflammatory (Gil et al., 1997; Castardo et al., 2008) and antioxidant (Sanz et al., 1994; Deachathai et al., 2005; Hutadilok-Towatana et al., 2007) are well-documented; it has also been found to be a potent tyrosinase inhibitor (Masuda et al., 2005), anti-HIV-1 (Lin et al., 1997), and anti-bacterial (Verdi et al., 2004) agent, and to have antimalarial (Ngouamegne et al., 2008) and analgesic (Luzzi et al., 1997) properties. Isojacareubin (**5**) is known for its activity as an anticoagulant (Wu et al., 1998), and 6-deoxyisojacareubin (**6**) for its antifungal (Morel et al., 2002) and antibacterial (Kuete et al., 2007) properties, while sargaol (**4**) shows marked activity as an antioxidant (Nahas et al., 2007).

Morelloflavone (**1**), morelloflavone-7″-sulphate (**2**), guttiferone A (**3**), and sargaol (**4**) together with the ethyl acetate and methanol extracts of *Garcinia livingstonei* stem bark (crude extracts **39b** and **39c**, respectively), and the fruit peel extract, were selected for further *in vitro* analysis. MeWo cells, a human malignant melanoma cell line, were selected to investigate the action of these compounds and

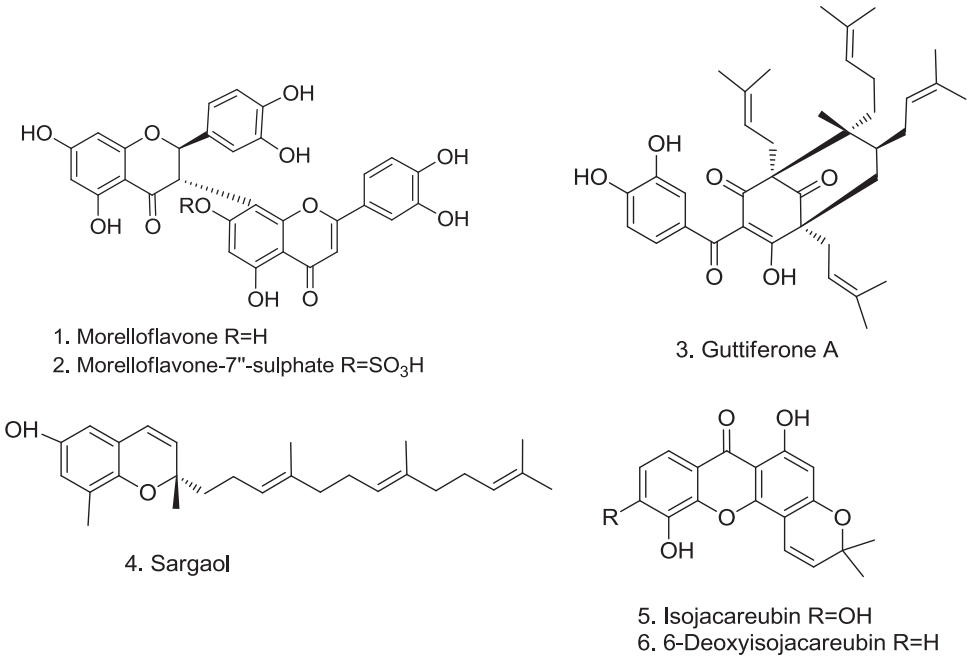

Fig. 1. Structures of compounds isolated from *Garcinia livingstonei*.

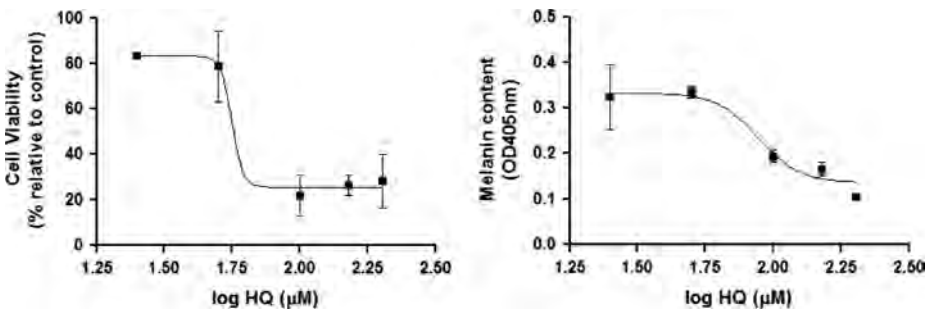

Fig. 2. The classical pro-oxidant hydroquinone decreases melanin content but is highly toxic to MeWo cells. MeWo melanoma cells were exposed to 25–200 μM hydroquinone or vehicle for 48 h. Following exposure, cell death was then measured by LDH assay, normalized to vehicle and TX100-treated cells, and melanin content by absorbance at 405 nM. Each data point represents $n=3\pm$SEM, and is representative of at least three independent experiments.

extracts *in vitro*, both in terms of impact on melanin levels and overall cytotoxicity. The melanin content of the melanocytes was determined after dosing these cells with known concentrations of the test extracts/compounds, whereas the cytotoxicity assay was based on the measurement of lactate dehydrogenase (LDH) released from the cytosol of damaged cells into the culture medium: Full details of the procedures used are given in Section 2.

Prior to examining the derived compounds and extracts, the response of MeWo cells to the classical pro-oxidant and skin-lightening agent hydroquinone was examined. As can be seen from Fig. 2, hydroquinone was able to elicit a dose-dependent decrease in melanin content of the cells, with an $EC_{50}=87\pm1.3$ μM. This effect on melanin content was accompanied by dose-dependent cytotoxicity, with an $IC_{50}=45\pm5.4$ μM.

Following characterization of the response of MeWo cells to hydroquinone, we next examined the effect of the 25 μM for pure chemicals and 100 mg/mL for crude extracts on both melanin content and cytotoxicity (Fig. 3). The fruit peel extract was extremely cytotoxic, leading to complete cell death within 48 h and compromising the LDH readings. In addition, the crude extracts **39b** and **39c** were both darkly coloured and their melanin readings were thus also compromised; these results will not be discussed further. As previously observed by Williams and colleagues, guttiferone A was shown to be cytotoxic, with 25 μM causing approximately 80% cell death, a value that is consistent with the reported IC_{50} value of approximately 1 μM (Williams et al. 2003). This was the most cytotoxic pure chemical examined, with 25 μM exposures of morrelloflavone, morelloflavone-7″-sulphate and sargaol only causing between 10 and 20% cell death (Fig. 3A).

In addition, all compounds were able to decrease the melanin content of the cells (Fig. 3B), although to differing extents. Again, guttiferone A produced the largest decrease, but this interesting activity was offset by the large cytotoxic effect observed at the same dose. Morelloflavone, morelloflavone-7″-sulphate and sargaol all caused significant decreases in melanin content (approximately 60% of control; Fig. 3), while causing less than 20% cell death at 25 μM. Accordingly, these compounds were selected for a more complete concentration–response examination. Fig. 4 shows concentration–response curves for each compound (1 to 100 μM), with both cytotoxicity (LDH) and melanin content measured. Morelloflavone, morelloflavone-7″-sulphate and sargaol all elicited a dose-dependent effect on cytotoxicity and melanin content (Fig. 4A–C, respectively). All three compounds elicited a concentration-dependent decrease in melanin content and cytotoxicity in MeWo cells, with morelloflavone-7″-sulphate having the most promising profile. Fig. 4b shows a clear separation of the curves for cytotoxicity ($IC_{50}=41.8\pm2.5$ μM) and melanin content ($EC_{50}=8.6\pm1.3$ μM), suggesting that this compound has the most

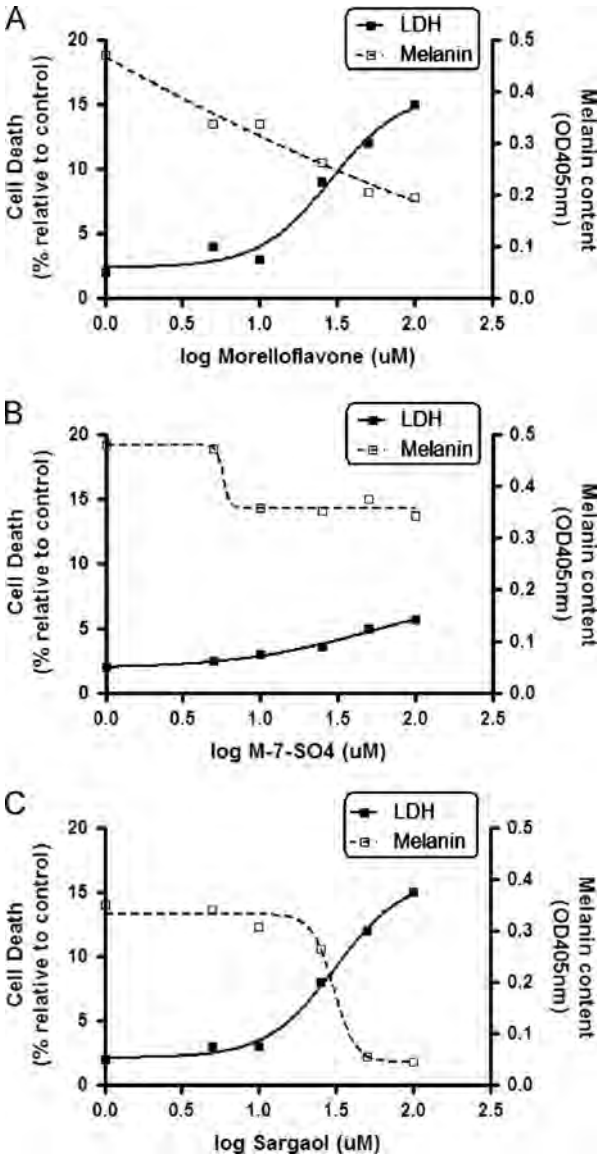

Fig. 4. Response of MeWo cells to morelloflavone, morelloflavone-7-sulphate and Sargaol from *Garcinia livingstonei.* MeWo melanoma cells were exposed to 1–100 μM of morelloflavone (A), morelloflavone-7-sulphate (B), sargaol (C) or vehicle for 48 h. Following exposure, cell death was then measured by LDH assay, normalized to vehicle and TX100-treated cells, and melanin content by absorbance at 405 nM. Each data point represents $n=3\pm$SEM, and is representative of at least three independent experiments.

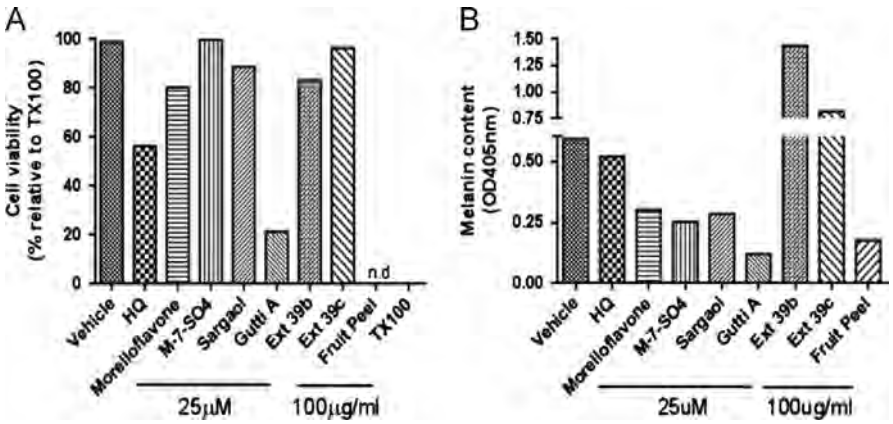

Fig. 3. Response of MeWo cells to 25 μM (pure compounds) and 100 mg/mL (extracts) from *Garcinia livingstonei.* MeWo melanoma cells were exposed to 25 μM pure compounds, 100 mg/mL mixed extracts or vehicle for 48 h. Following exposure, cell death was then measured by LDH assay, normalized to vehicle and TX100-treated cells, and melanin content by absorbance at 405 nM. HQ=hydroquinone, Mel=morelloflavone **6**, Mel-7-SO_4=morelloflavone-7″-sulphate **7,** Sargao=sargaol **10,** Gutti A=guttiferone A **4,** Ext 39b and Ext 39c=ethyl acetate and methanol extracts of *Garcinia livingstonei* stem bark, respectively, Fruit peel=fruit peel (methanolic) ethyl acetate extract. Data are representative of at three independent experiments.

favourable balance of maximal pharmacological effect with minimal toxicological liability. It should be noted, however, that of the three compounds tested morelloflavone-7″-sulphate also elicits the smallest absolute change in melanin content, being 74% of control, compared to 13% for sargaol; the current dose range was insufficient to determine a robust maximal effect for morelloflavone, but it is expected to be in excess of 60%.

4. Conclusion

Morelloflavone (**1**), morelloflavone-7″-sulphate (**2**), guttiferone A (**3**), and sargaol (**4**) are all more effective in reducing melanin content of MeWo human melanoma cells than hydroquinone. In addition, morelloflavone, morelloflavone-7″-sulphate, and sargaol are less cytotoxic. Although morelloflavone, isolated from Japanese material of *Garcinia subelliptica* has previously been shown to possess potent tyrosinase inhibitory activity (Masuda et al., 2005), the current investigation revealed that morelloflavone-7″-sulphate **7** possessed the best separation between reduction in melanin and induction of cell death.

In conclusion, preliminary results show that morelloflavone, morelloflavone-7″-sulphate and sargaol are highly effective melanin production inhibitors. When tested in the human melanoma cell line MeWo, they inhibit melanogenesis to a greater extent than hydroquinone, whilst causing less cytotoxicity. As such, these compounds represent good candidates for further development of novel skin lightening agents to be used in the cosmetic and clinical arenas.

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CHAPTE R 9

Autosomal dominant inheritance of central centrifugal cicatricial alopecia in black South Africans.

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Autosomal dominant inheritance of central centrifugal cicatricial alopecia in black South Africans

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Background: Central centrifugal cicatricial alopecia (CCCA) is the commonest type of primary scarring alopecia in women of African descent. Little is currently known about the disease genetics.

Objective: We sought to investigate patterns of inheritance in CCCA and ascertain the contribution of nongenetic factors such as hair-grooming habits to the pathogenesis of the disease.

Methods: Affected individuals with at least 1 available family member were recruited from 2005 through 2012 inclusive for pedigree analysis. CCCA was diagnosed on clinical and histopathological grounds.

Results: Fourteen index African families with 31 immediate family members participated in the initial screening. The female to male ratio was 29:2 with an average age of 50.4 years. All patients displayed histologic features typical for CCCA. Pedigree analysis suggested an autosomal dominant mode of inheritance. Hair-grooming habits were found to markedly influence disease expression.

Limitations: Small number of patients is a limitation.

Conclusion: CCCA can be inherited in an autosomal dominant fashion, with partial penetrance and a strong modifying effect of hairstyling and gender. (J Am Acad Dermatol 2014;70:679-82.)

Key words: African; black; familial; follicular degeneration syndrome; genetic; hair loss; lymphocytic primary scarring alopecia; scarring alopecia; South Africa.

Primary scarring alopecia is a form of hair loss in which hair follicles are destroyed and replaced by fibrous tissue.[1] Central centrifugal cicatricial alopecia (CCCA) is the most common type of primary scarring alopecia in African American women,[2-5] and characteristically manifests with irreversible hair loss involving either the vertex or mid scalp that tends to progress symmetrically in a centrifugal pattern.[6]

Abbreviations used:

CCCA: central centrifugal cicatricial alopecia
CHLG: central hair loss grading
DM: diabetes mellitus

Histologic features include perifollicular lymphocytic infiltrate and fibroplasia,[7] which may be

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associated with perivascular lymphocytic infiltrate and premature disintegration of the inner root sheath.[6,8]

The majority of CCCA studies have been conducted with African American participants. A survey by the North American Hair Research Society was carried out in Cleveland, OH, and showed that 28% of 326 African American females had clinical evidence of CCCA.[9]

Although the prevalence of CCCA in black South Africans is unknown, a cross-sectional study conducted among 874 African adults recruited from 2 church groups, 1 community organization, and 2 male hostels in Cape Town, South Africa, found that 1.9% of this population had CCCA, all of whom were women.[10] In a recent 7-year retrospective survey of 6664 African patients seen in a predominantly black urban dermatology practice in Durban, South Africa, hair disorders in general and CCCA more specifically accounted for 5.2% and 0.4% of all skin conditions seen, respectively.[11]

CAPSULE SUMMARY

- Central centrifugal cicatricial alopecia is a lymphocytic cicatricial alopecia occurring commonly in women of African descent.
- Central centrifugal cicatricial alopecia is familial, and is inherited in a dominant fashion. It is triggered by certain hairstyles. Although it also occurs in black males, gender-related hair-grooming habits may explain the preponderance of female patients.
- Early detection and counseling of family members regarding hair-grooming approaches may arrest progression of alopecia.

The cause of CCCA remains elusive, with interaction between a genetic predisposition and hair-grooming techniques in women of African descent having been suggested.[6,12] Although considerable effort has been invested in characterizing incriminated hairstyling techniques, much less is known regarding the genetics of the disease. Supporting a predominant role for inherited factors in the pathogenesis of CCCA, independent of hair-grooming habits, is a recent report on 2 families with natural hair and with clinical and histologic evidence of CCCA.[13]

The pathomechanisms underlying hair follicle scarring in primary scarring alopecia, and more specifically in CCCA, are not well understood. Everts et al[14] have shown altered retinoid metabolism in human and mouse models with primary cicatricial alopecia, particularly CCCA. Karnik et al,[15] in a recent study of lichen planopilaris, proposed that abnormal function of the peroxisome proliferator–activated receptor gamma could possibly trigger inflammation, with resultant abnormal lipid metabolism within the sebaceous gland, resulting in a toxic accumulation of lipids with ensuing inflammatory response. Whether this mechanism applies to CCCA as well remains to be determined.

In this article, we report 14 index families with 31 immediate family members in Durban, South Africa, all of whom had a clinical and histologic diagnosis of CCCA and provide evidence for autosomal dominant inheritance of this condition.

METHODS

Patients

Ethical approval for the study was obtained from the Nelson R. Mandela School of Medicine Institutional Review Board (BE 180/11). All patients who presented with CCCA from 2005 through 2012 inclusive were recruited from both the private- and public-sector hospitals in Durban, South Africa. To be included in the study, patients had to fulfill published clinical criteria for CCCA diagnosis.[2,7,16] A general skin and hair examination by an experienced dermatologist familiar with ethnic hair was undertaken to exclude skin and scalp infection, traction alopecia, or acne.

We used a central hair loss grading (CHLG) score as previously described.[17] A CHLG of 0 was taken as normal hair thickness without discernible alopecia; a CHLG of 1 was given in the presence of slight alopecia and early CCCA without obvious effect on hair density; a CHLG of 2 was indicative of subtle clinical alopecia; and a CHLG of 3 to 5 corresponded to clinically obvious mild, moderate, and severe CCCA. In addition, patients needed to have a minimum of 1 affected family member available for examination of the scalp and who agreed to be subjected to a confirmatory scalp biopsy, to be included in the study. Immediate family members included the index patient's parents, siblings, and offspring. Written informed consent was obtained from all participants or their legal guardians. A detailed history of personal and family history of diabetes mellitus (DM), along with hair grooming and drug consumption, was obtained.

Histopathology

Supportive evidence for CCCA was obtained through dermoscopic examination[18] and histopathological studies. Two dermoscope-guided 4-mm

punch scalp biopsies were performed for each individual with a clinical diagnosis of CCCA.

Scalp biopsy specimens were fixed in 10% buffered formalin and thereafter embedded in paraffin. Both horizontal and vertical sections were stained with hematoxylin-eosin for routine histopathological examination. All samples were reviewed by 1 dermatopathologist. The diagnosis of CCCA was established according to criteria previously published.[2,7,16] A numeric scoring system was devised to evaluate biopsy specimens for a diagnosis compatible with CCCA.

According to this system, 3 points were awarded for the presence of lichenoid lymphocytic folliculitis (lymphocytes surrounding follicles with exocytosis into follicular epithelium), 2 points for perifollicular lymphocytes (lymphocytes in the immediate vicinity of follicles but separated from the follicular epithelium), 1 point for perifollicular fibrosis (concentric fibrosis of variable thickness surrounding follicles), and 1 point for the presence of compound follicles (fused infundibula of follicles indicating disturbed follicular dynamics). A diagnosis of CCCA was considered likely with a score of 3 or more.

RESULTS

Clinical features

All patients were of African descent. There were 14 index African families with a total of 31 participating immediate family members, and the female to male ratio was 29:2. The average age was 50.4 years (range: 11-94) with 45% between age 30 and 50 years, whereas the average age of onset was 41 years (range: 11-75), with 48% being between age 30 and 50 years. All but 1 female had traction alopecia (28; 96.5%). This individual, aged 11 years, kept natural hairstyle only.

None of the participants had skin infections or a positive drug history; acne and DM were diagnosed in 1 participant each.

As defined by the inclusion criteria, all patients had 1 or 2 members of their family with a clinically and histologically confirmed diagnosis of CCCA. In 2 families, 2 generations were affected, whereas in another family, cousins were also affected. Only in 1 (2%) family were males given the diagnosis of CCCA, ie, father and son. All the affected families showed an autosomal dominant pattern of inheritance (Fig 1; available at http://www.jaad.org).

There appeared to be a strong correlation between the severity of CCCA as interpreted by the CHLG score, and the frequency and preference of hair-grooming methods. Fifteen (48%) participants who had CHLG greater than 2 practiced frequent braiding and weaving for hair grooming, of whom 9 (29%) gave a history of braiding or weaving chemically processed hair (relaxed or permed). Of those with CHLG 0 to 1, 11 (35%) had natural virgin hair, had never used any chemicals or traction on their hair, and maintained short hairstyles. These were either very young (<15 years) or very old (>75 years) female participants who had escaped the latest hair-grooming trends, or males who had kept natural short haircuts, as culturally accepted. With regards to symptomatology, 11 (35%) patients presented with thinning and breakage of the vertex hair as the main symptom, as observed by other authors,[4] 9 (29%) were asymptomatic and the remaining 11 (35, 5%) patients presented with either painful papules, tender scalp, dandruff, or pruritus.

Histopathology

A total of 31 scalp biopsy specimens were submitted. Twenty biopsy specimens of late lesions were submitted for vertical sectioning and 19 for horizontal sectioning. Eleven biopsy specimens of early lesions were submitted for vertical sectioning and 10 for horizontal sectioning. Combining vertical and horizontal sections increased the diagnostic yield and the diagnosis of CCCA was made on all 31 specimens. Hair shaft granulomas caused by disruption of follicular epithelium were evident in 2 biopsy specimens, as were atrophy of follicular epithelium, concentric perifollicular fibrosis, and lymphocytes.

DISCUSSION

We have described 14 index African families with a total of 31 immediate family members who displayed characteristic clinical and histologic features of CCCA.[2] To our knowledge, a similar cohort of patients has not been described in the literature. Each of the 14 index patients had at least 1 immediate family member who had CCCA. Family members were recruited and examined, and subjected to a confirmatory dermoscope-guided biopsy.[18] The pedigrees of the 14 families are highly suggestive of an autosomal dominant mode of inheritance (Fig 1; available at http://www.jaad.org), with partial penetrance and a strong modifying effect of hairstyling and gender. In the majority of patients, a strong family history of CCCA from the maternal side was observed. The case of paternal transmission rules out X-linked inheritance provided CCCA is genetically homogeneous. We believe that gender-related hair-grooming habits may explain the preponderance of female patients in our cohort. Indeed, most African males in South Africa keep their hair natural and very short, making it difficult to pick up the subtle areas of alopecia.

In fact, in the only family with male patients studied, the index patient had been using chemical hair relaxers and we have documented chemical hair grooming as an aggravating environmental factor. The absence of DM and skin infections in the majority of our patients casts doubt on any association of DM and skin infections in patients with CCCA, as was reported by Kyei et al.[19] Similarly, we could not find any association between CCCA and acne as previously reported.[19]

In contrast, we detected a positive correlation between use of traction-inducing hairstyles such as braids/weaving, and the severity of CCCA, more so in patients who applied traction on chemically processed hair.[6,15,19] Traction alopecia was found in most female patients (96.1%), as described by other authors suggesting that traction alopecia in CCCA may serve as an environmental trigger in patients with an inherited propensity to develop CCCA. However, the fact that 6 (19.4%) patients had natural hair, yet had clinical and histologic confirmation of CCCA, lends further support to the notion that endogenous factors play a pivotal role in the disease pathogenesis of some primary cicatricial alopecias.[20,21]

In conclusion, results of this study are strongly suggestive that CCCA can be inherited in a dominant fashion, and confirm the important contribution of hairstyling to the disease manifestations.[22] Certainly a population study to screen for early symptoms and signs of CCCA in younger African girls and women would be desirable, particularly those with affected family members.

Natural hairstyles should be encouraged in patients with CCCA and their relatives to obviate the rapid progression and severity of the hair loss, which may result in major psychological effects (unpublished data, October 2013). Public and hairstylist educational campaigns will hasten early recognition and diagnosis.

We thank Prof David Katerere (Tshwane University of Technology, Pretoria, South Africa), Prof Richard Hift (University of KwaZulu-Natal, Durban, South Africa), and Miss Alicia McDonald of Columbia University, New York, New York, for their invaluable intellectual input. We also thank colleagues in the Department of Dermatology, Nelson R. Mandela School of Medicine, for referring patients and performing some of the biopsies for the study patients and the secretarial services of Miss Phakama Jika Department of Dermatology, University of KwaZulu-Natal, Durban, South Africa, and Miss Lungie Shabalala, Durban, South Africa.

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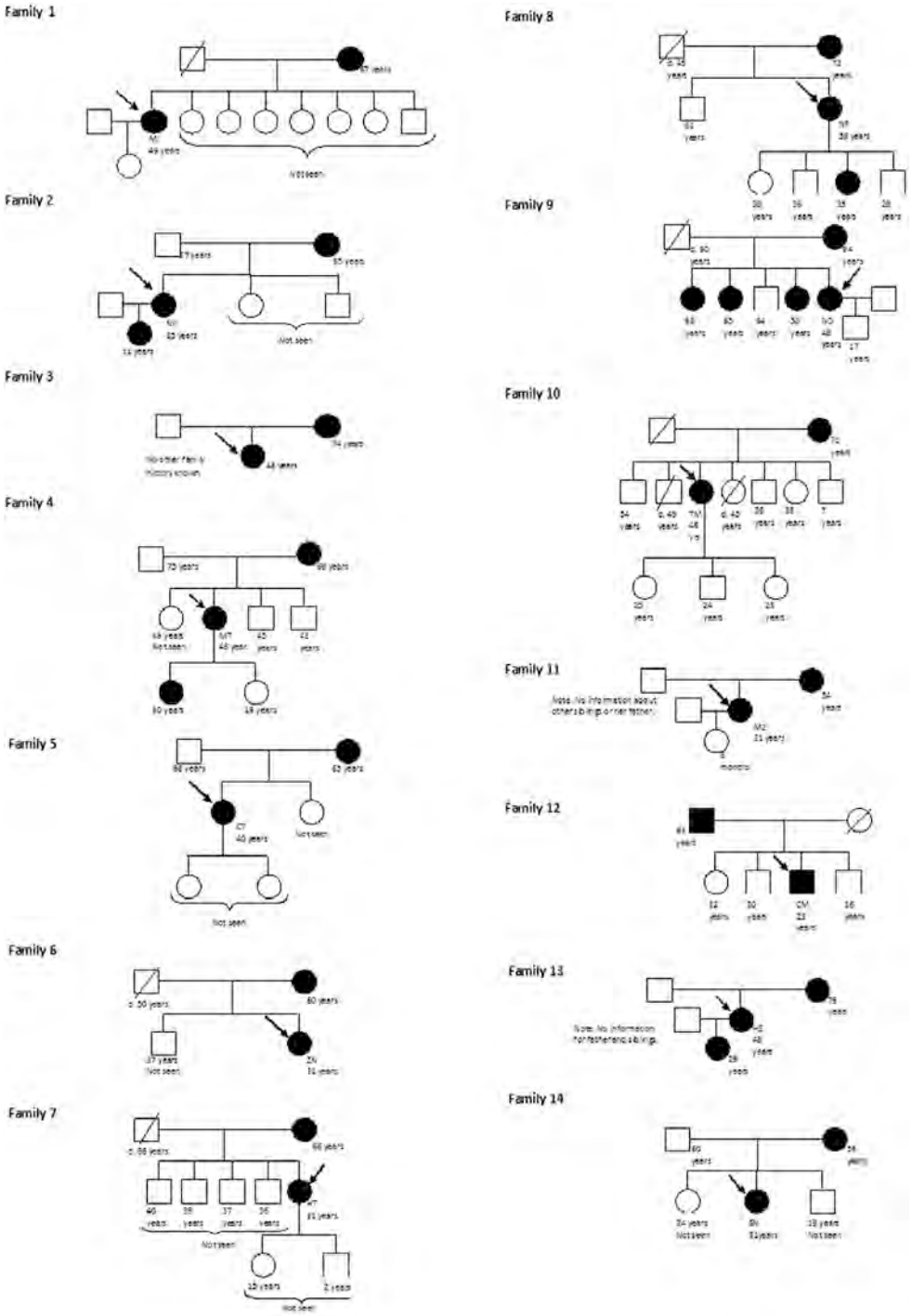

Fig 1. Pedigrees depicting autosomal dominant inheritance of central centrifugal cicatricial alopecia in all 14 affected families.

CHAPTER 10

Central centrifugal cicatricial alopecia - possible familial aetiology in two African families from South Africa .

Dlova NC, Forder M. Central centrifugal cicatricial alopecia: possible familial aetiology in two African families from South Africa. Int J Dermatol 2012; 51 Suppl 1: 17-20.

International Journal of Dermatology

Report

Central centrifugal cicatricial alopecia: possible familial aetiology in two African families from South Africa

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Background

Central centrifugal cicatricial alopecia (CCCA) is the most common type of primary scarring alopecia in African American women.[1] Cicatricial alopecia is characterised by both the destruction and replacement of the hair follicle by fibrous tissue However CCCA is a distinct form of scarring alopecia characterised by hair loss which starts at the vertex and gradually progresses in a centrifugal pattern. It was, first described in 1968 by Lopresti *et al.*[2] who originally coined it ''hot comb alopecia'' based on the hypothesis that heat from hot combing was responsible for the alopecia. The term follicular degeneration syndrome was later proposed by Sperling and Sau in 1992, as they found no etiological relationship between use of a hot comb and the scarring alopecia.[3] Then Headington[4] proposed scarring alopecia in African Americans, and Sperling denominated it central centrifugal scarring alopecia.[5] Finally, the term central centrifugal cicatricial alopecia was adopted by the North American Hair Research Society[6] in 2001.

Women of African ancestry have a higher predilection for CCCA, with a female/male ratio of 3:1.[7] Clinically, this condition usually presents in middle-aged women and is characterized by typical primary involvement of either the vertex or crown with symmetric spread in a centrifugal pattern. Symptoms may vary from asymptomatic to painful papules, pustules, tender scalp, or mild pruritus. The distribution of hair loss closely resembles that of androgenic alopecia or female pattern hair loss (FPHL) however a lack of follicular openings in CCCA signifies the presence of scarring. in females.[8]

The most frequent histological features of CCCA are lymphocytic folliculitis, premature degeneration of the inner root sheath, perifollicular granulomatous inflammation, destruction of folliculo sebaceous units with retention of arrector pili muscle, and associated scarring and fibrosis replacing some of the hair follicles are the most frequent histological features of CCCA.[8] Other primary scarring alopecia that can cause central cicatricial alopecia, such as lichen planopilaris, discoid lupus erythematosus, and folliculitis decalvans may pose difficulty in trying to distinguish from full blown end-stage CCCA.[1]

Various treatment modalitie for CCCAs have been used with varying success. They include moderate to potent topical steroids, intralesional steroids, oral antibiotics such as tetracyclines, hydroxychloroquine, and immunosuppressive agents such as mycophenolate mofetil, and ciclosporin.[8] In addition, avoidance of hair grooming has been recommended for affected patients.[8]

In this report we describe two African families with CCCA, each with a family member with a clinical and histological diagnosis of CCCA without any evidence of mechanical or chemical damage to the hair.

Family 1

A 45-year-old African woman presented with a 1-year history of hair loss involving the crown (Fig. 1e). She

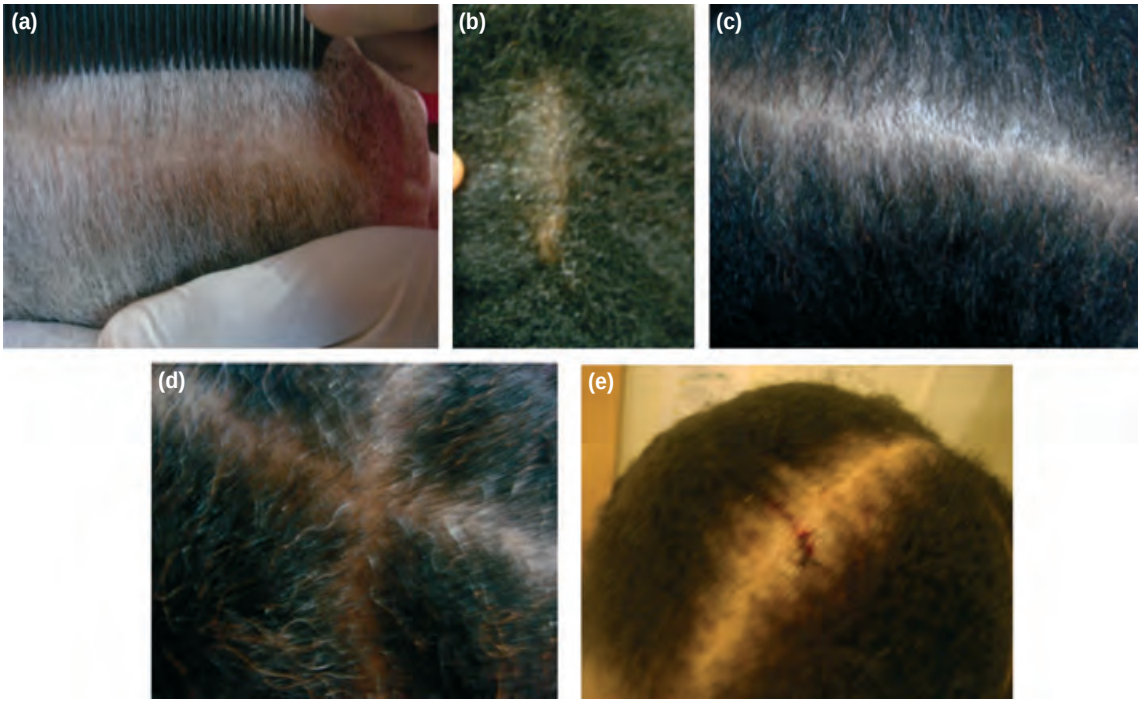

Figure 1 Family 1. (a) 92-year-old mother, with clinical and histological features of central centrifugal cicatricial alopecia (CCCA), no history of chemical or mechanical grooming of hair. (b) CCCA in a 65-year-old (first) daughter, very mild, kept natural hair most of the time, with occasional use of relaxers four times a year. (c) 63-year-old (second) daughter with CCCA, loose braids on natural hair most of the time. (d) 55-year-old (third) daughter with CCCA, grooming method is braids on natural hair most of the time. (e) 45-year-old (fourth) daughter with CCCA, grooming method is chemical relaxers every 2–3 months with occasional loose braiding of the hair.

admitted to having occasional pustules and painful papules or tender areas of the scalp concentrated mainly on the crown. Hair grooming involved occasional chemical relaxing of hair once every 4 months in the last 3 years and mainly natural twisting of the hair. The affected patient's family, which included her 92-year-old mother and three other female siblings aged 65 years, 63 years, and 55 years, respectively were called for scalp examination and a thorough hair grooming history was taken. A 4 mm scalp punch biopsy was taken for histological examination.

All four family members were found to have features of CCCA both clinically and histologically. (Fig. 1a–d) The 92 year-old mother who had natural virgin hair, which had never been subjected to any chemical or mechanical trauma had clinical and histological features of CCCA (Fig. 1a). Their grooming methods included mainly infrequent chemical relaxing once every 3–4 months and occasional braids. All the family members were not aware of the occurence of hair loss.

Family 2

A 35-year-old African woman presented with gross scarring alopecia involving the crown for 5 years (Fig. 2a). She noticed her hair was getting thinner and sparse over the crown but did not seek medical advice until later. She admitted to frequent use of chemical relaxers as well as sewn-in hair weaves and sometimes braids with extended hair for grooming her hair. She applied chemical relaxers on her hair every month and had hair braids with extended hair on relaxed hair. In between these hairstyles the patient would have sewn - in or glued-in hair weaves. Her family members, who included her 65-year-old mother and 11-year–old daughter, were called for examination and a thorough hair grooming history was taken. A 4 mm scalp punch biopsy was taken for histological examination. Unfortunately, her mother was not available for examination.

Her 11-year–old daughter had clinical and histological features of CCCA (Fig. 2b,c). She had natural virgin hair and had never used any form of chemical or mechanical trauma to the hair. Her daughter was not aware of hair loss, until examination by the dermatologist.

In all seven patients from families 1 and 2, skin histology showed perifollicular and perivascular lymphoid cell infiltrate with eccentric thinning of the follicular epithelium with concentric lamellar fibroplasia compatible with CCCA (Fig. 3).

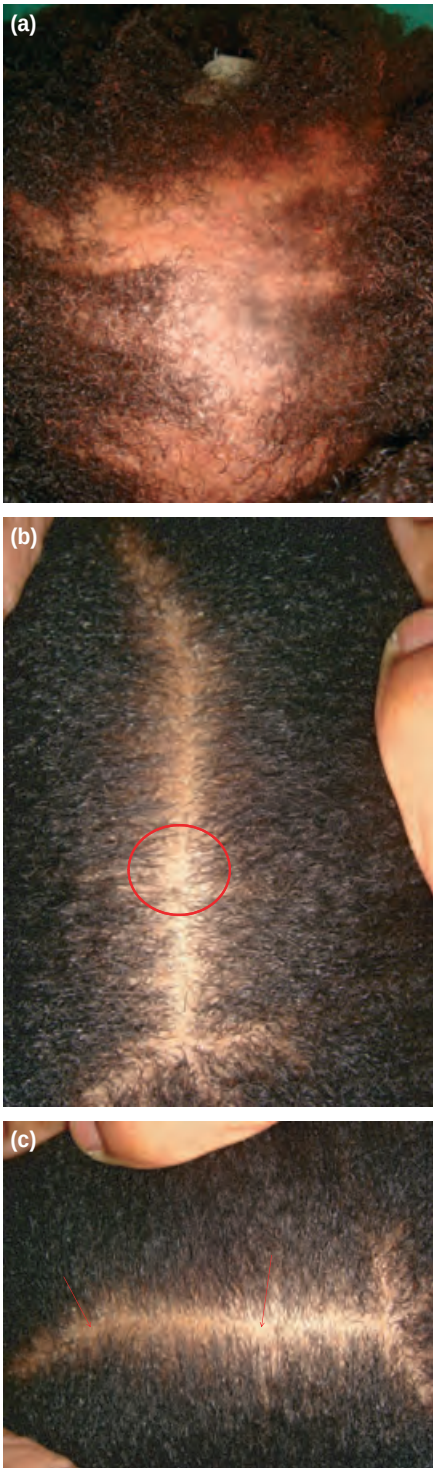

Figure 2 Family 2. (a) 35-year-old mother with central centrifugal cicatricial alopecia (CCCA), hair grooming involved a combination of chemical relaxers, tight braidswith extended hair, and sewn - in hair weaves. (b) 11-year-old daughter with clinical and histological features of CCCA, natural virgin hair with no history of any chemical or mechanical trauma. (c) Close up of the scalp showing small areas of scarring alopecia devoid of follicular pores confirmed on histology as CCCA in the 11-year-old girl with natural virgin hair

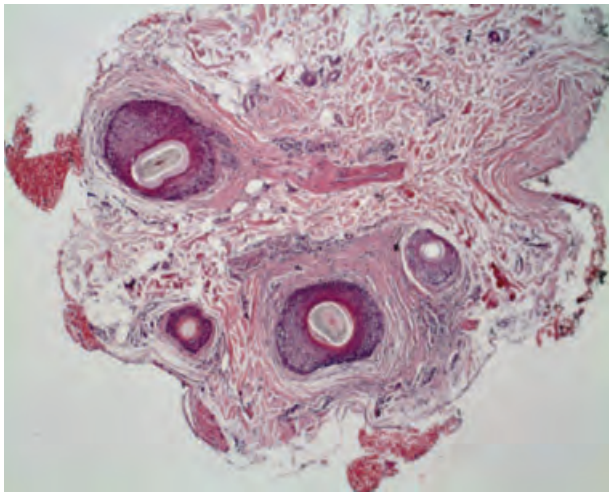

Figure 3 Histology: × 40 transverse section with features of central centrifugal cicatricial alopecia – eccentric thinning of the follicular epithelium with concentric lamellar fibroplasia

Discussion

The etiology of CCCA is the subject of much speculation but remains elusive. Gathers and Lim have found that sewn and glued hair weave, as well as cornrow or braided hairstyles seem to be positively associated with CCCA.[8]

Nnoruka, however, attribute CCCA to the duration of hair grooming practices such as chemical relaxers.[9] Kyei *et al*. in their survey of 326 African American women found an association between hairstyles causing traction alopecia and the occurence of CCCA. They also concluded that bacterial infection may play a role in the development of CCCA.[10] The treatment of CCCA remains challenging as well as loose braiding of the hair, guided only by case reports and expert opinion, in the absence of prospective or case-controlled studies.

Our documented cases seem to demonstrate that CCCA does occur in natural virgin hair which suggests a possible familial link. The affected family members who wore tight braids and had hair weaves on already chemically relaxed hair seemed to exhibit a more severe disease than those who only used chemical relaxers infrequently.

We therefore postulate that there might be a genetic defect of the internal root sheath in some Africans or African Americans as a primary pathologic event, which may be familial. This defect may manifest in adolescence, and predominantly among females, because of a higher frequency of hair grooming practices. Clinical disease manifests early; however, thick curly hair obscures the lesions, which become evident later with disease progression. The elderly members of affected families tend to demonstrate less severe disease than younger generations. This sparing is thought to be in line with less frequent use of potentially damaging combinations of hair grooming practices. The

combination of chemical relaxers and traction which I refer to as a the ''deadly duo'' appears to result in early severe, progressive hair loss. Early examination and diagnosis of affected family members may help halt the rapid progression of this devastating, progressive scarring disease. Furthermore, afflicted patients may benefit from early counselling and advice on proper gentle hair-grooming practices.

Conclusion

To our knowledge, this is the first case series documenting a familial association in CCCA.

Further family studies or case-controlled studies are needed to confirm this observation, which suggests CCCA may have a familial genetic predisposition, which can be aggravated or triggered by external factors such as cumulative effects of chemical and mechanical trauma. If confirmed in larger studies, the term ''familial central centrifugal cicatricial alopecia'' may be appropriate.

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CHAPTER 11

Frontal fibrosing alopecia - A clinical review of 20 black patients from South Africa.

Dlova NC, Jordaan HF, Skenjane A, Khoza N, Tosti A. Frontal fibrosing alopecia: a clinical review of 20 black patients from South Africa. Br J Dermatol 2013; 169: 939-41.

BJD
British Journal of Dermatology

Frontal fibrosing alopecia: a clinical review of 20 black patients from South Africa

DOI: 10.1111/bjd.12424

Dear Editor, Frontal fibrosing alopecia (FFA) is an uncommon clinical variant of lichen planopilaris (LPP), presenting with band-like scarring alopecia (SA) involving the hairline, first described by Kossard in 1994.[1] Lately, familial cases of FFA have been reported in both white and black patients,[2,3] suggesting among other factors the possibility of genetic inheritance. There is a paucity of information on the epidemiology of FFA in black patients, with only one report by Miteva *et al.*[4] in Miami, wherein they reported on 11 (7·8%) of 141 African American patients having FFA, 10 female and one male. No published reports were found regarding cases from Africa. The intention of this 5-year retrospective review is to provide insight on the demographic and clinical profile of black patients with FFA in South Africa.

We reviewed single-centre case notes and clinical pictures of patients presenting with a histopathologically confirmed diagnosis of FFA between 2006 and 2012, inclusive. In total 44 patients were seen; 20 had FFA only and 24 had associated lichen planus pigmentosus.[5] This study will focus on the 20 patients with FFA only, 19 (95%) female and one (5%) male, whose clinical data are summarized in Table 1. The age of onset ranged from 27 to 66 years, with a mean of 42 years. Most were African (19, 95%), with one (5%) female Indian patient. Fourteen of the 19 women (74%) were premenopausal.

Only one patient (5%) had a positive family history, citing her mother and first cousin as being affected.[2] FFA involved the frontotemporal region in all 20 cases, while two of the patients had associated patchy LPP. Traction alopecia (TA) presented in the majority of African female patients (n = 17), of whom 14 complained of hairline loss. Seven patients in total (35%) had pruritus, one of whom also had painful, tender pustules.

Histology confirmed LPP in all of the patients except one, who declined biopsy. Histology showed typical features of LPP, consisting of follicular loss with perifollicular fibrosis and lichenoid inflammation around hair follicles.[1,6] Only two patients (10%) had both eyebrow and limb hair loss, while eight (40%) had eyebrow loss and none had facial papules.

All 18 female African patients (90%) admitted to using chemicals or had traction-inducing hairstyles. The lonely hair sign (Figs 1, 2) described by Tosti *et al.*[7] was detected in 70% of the African patients with FFA. Loss of follicular ostia as a hallmark sign of scarring alopecia[8] may be misleading, as five patients (25%) had prominent follicular ostia despite histological confirmation of a scarring process (Figs 1, 2). Cutaneous or mucosal lesions of lichen planus were not observed. Treatment included hydroxychloroquine 200 mg twice daily for 6–-12 months, clobetasol dipropionate, tacrolimus 0·1% and minoxidil 2%.[9,10] Traction-inducing hairstyles and frequent use of chemical relaxers were discouraged. Wigs instead of weaving were recommended for those with extensive disease.

The cases of FFA reported in the literature have been mainly in postmenopausal white women.[1] While Miteva *et al.*[4] reported the occurrence of FFA in 11 postmenopausal black patients, our patients were predominantly premenopausal (74%). Both this series and that of Miteva *et al.* confirm that FFA is not exclusively a disease of postmenopausal white women, but affects the black population as well. Our report is similar to that of Miteva *et al.* in that almost all of our patients had used traction and/or chemicals for grooming and had evidence of TA, creating difficulties in diagnosis. The lonely hair sign[7] and loss of eyebrows are useful clinical signs in the early diagnosis of FFA. The age range of onset was much lower than in other studies,[1,11] explicable by the early use of traction-inducing hairstyles, which probably aggravate the progression of FFA.

Africans tend to be less hairy than their Indian and white counterparts, resulting in less noticeable body hair loss. This may explain why only one African patient showed limb hair loss, along with the Indian patient. At 2-year follow-up we were able to abort the progression of alopecia in five of the 20 patients with early disease who started on chloroquine and topical treatments. This is in line with the report of Chiang *et al.*[9], wherein they reported the efficacy of hydroxychloroquine in patients with low LPP activity score. One patient followed up for 5 years defaulted treatment and presented with generalized hair loss resembling alopecia universalis. This supports the observation made by Chew *et al.*[6] in which the process of scarring alopecia is somewhat generalized rather than confined to the hairline and eyebrows.

We have documented the largest series of FFA in black patients to date, and the first report in Africa. Despite the limitations of a retrospective review, we have shown that FFA can be easily confused with TA, as these two conditions often coexist in Africans, supporting the assertions of Miteva *et al.*[4] and Tosti *et al.*[7] While other studies have shown absence of follicular ostia as a hallmark of SA, we have shown that this is not necessarily so, and can be misleading. Therapeutic options are limited, and the goal of treatment is making early diagnosis, thus aborting active disease progression to minimize SA. Long-term prospective cohort studies are needed to elucidate

Table 1 Clinical and demographic data of frontal fibrosing alopecia in black patients

Patient no.	Sex	Ethnicity	Family history	Pre-/ postmenopause	Age of onset (years)	Loss of hair, eyebrows/ limbs	Area involved	Presenting symptoms	Associated skin diseases	Associated drug history	Associated medical disease	Features of FFA (scalp biopsy)	Grooming
1	F	African	Nil	Postmenopause	54	No/No	Frontotemporal	Hair loss	Traction alopecia	No	Nil	Yes	Traction, chemicals
2	F	African	Nil	Premenopause	32	Yes/No	Frontotemporal	Hair loss	Traction alopecia	No	Nil	Yes	Traction, chemicals
3	F	African	Nil	Premenopause	42	Yes/No	Frontotemporal	Pruritus	Traction alopecia	No	Nil	Yes	Traction, chemicals
4	F	African	Nil	Premenopause	41	No/No	Frontotemporal	Hair loss	Traction alopecia	No	Nil	Yes	Traction, chemicals
5	F	African	Nil	Premenopause	36	No/No	Frontotemporal	Hair loss	Traction alopecia	No	Nil	Yes	Traction, chemicals
6	F	African	Nil	Premenopause	37	No/No	Frontotemporal/patchy	Pruritus	Traction alopecia	No	Nil	Yes	Traction, chemicals
7	F	African	Nil	Premenopause	40	Yes/No	Frontotemporal	Pruritus	Traction alopecia	No	Nil	Yes	Traction, chemicals
8	F	African	Nil	Premenopause	47	No/No	Frontotemporal	Hair loss	Traction alopecia	HAART	HIV	Yes	Traction, chemicals
9	F	Indian	Nil	Premenopause	49	Yes/Yes	Frontotemporal	Hair loss	Nil	Eltroxin	HT	Yes	Nil
10	F	African	Nil	Premenopause	35	No/No	Frontotemporal	Hair loss	Traction alopecia	No	Nil	Yes	Traction, chemicals
11	F	African	Nil	Postmenopause	53	No/No	Frontotemporal/patchy	Hair loss	Traction alopecia	No	Nil	Yes	Traction, chemicals
12	M	African	Nil	–	35	Yes/No	Frontotemporal	Pruritus	Nil	No	Nil	Yes	Natural hair
13	F	African	Nil	Premenopause	37	No/No	Frontotemporal	Hair loss	Traction alopecia	No	Nil	Yes	Traction, chemicals
14	F	African	Nil	Postmenopause	49	Yes/Yes	Frontotemporal, occipital	Hair loss	Traction alopecia	No	Nil	Yes	Traction, chemicals
15	F	African	Nil	Postmenopause	66	Yes/No	Frontotemporal	Hair loss	Nil	Anti-HT, anti-DM	HT and DM	Declined biopsy	Traction
16	F	African	Nil	Premenopause	43	Yes/No	Frontotemporal	Hair loss	Traction alopecia	No	Nil	Yes	Traction, chemicals
17	F	African	Mother & cousin postmenopause	Postmenopause	50	No/No	Frontotemporal	Hair loss, pruritus and pustules	Traction alopecia	No	Nil	Yes	Traction, chemicals
18	F	African	Nil	Premenopause	27	No/No	Frontotemporal	Hair loss	Traction alopecia	No	Nil	Yes	Traction
19	F	African	Nil	Premenopause	37	No/No	Frontotemporal	Pruritus	Traction alopecia	No	Nil	Yes	Traction, chemicals
20	F	African	Nil	Premenopause	35	No/No	Frontotemporal	Pruritus	Traction alopecia	No	Nil	Yes	Traction, chemicals

F, female; M, male; HAART, highly active antiretroviral therapy; DM, diabetes mellitus; HT, hypothyroidism.

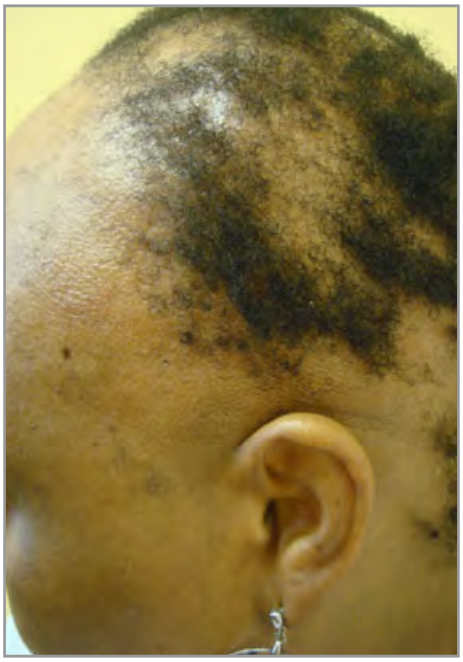

Fig 1. Frontal fibrosing alopecia, frontotemporal and with patchy distribution, prominent follicular ostia and lonely hair sign.

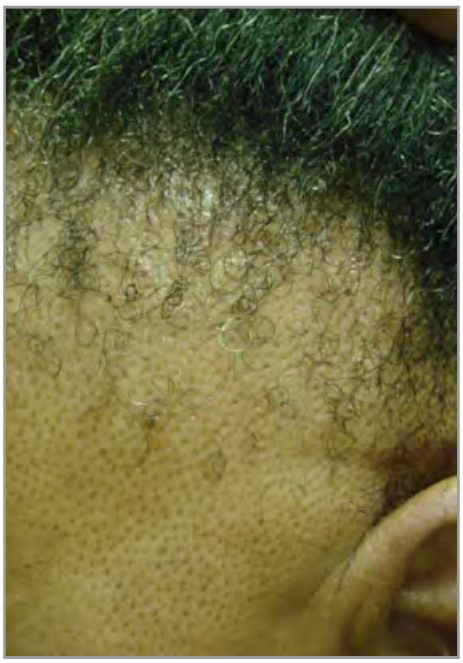

Fig 2. Frontal fibrosing alopecia showing prominent follicular ostia and lonely hair sign.

and predict treatment response, as well as to determine the aetiology and natural progression of FFA.

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Gene–gene interactions between *HLA-C*, *ERAP1*, *TNFAIP3* and *TRAF3IP2* and the risk of psoriasis in the Chinese Han population

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Dear Editor, Psoriasis is a common immune-mediated skin disorder characterized by epidermal hyperproliferation, vascular remodelling and inflammation.[1] It has a strong genetic component, and gene–gene and gene–environment interactions also contribute to the pathogenesis of psoriasis. Recently, almost 40 susceptibility genes have been identified for psoriasis through genome-wide association studies (GWASs) in diverse populations.[2–9] Several genes exhibited important roles in the development of psoriasis, including *HLA-C*, *ERAP1*, *TNFAIP3* and *TRAF3IP2*, through the nuclear factor-κB pathway or interleukin-17 signalling. Moreover, the interactions between *HLA-C* and *ERAP1*; *TNFAIP3* and *HLA-C*; and *HLA-C* and *TRAF3IP2* in a western ethnic population were revealed, greatly deepening the understanding of the genetic architecture in

CHAPTER 12

Frontal fibrosing alopecia and lichen planus pigmentosus - is there a link?

Dlova NC. Frontal fibrosing alopecia and lichen planus pigmentosus: is there a link? *Br J Dermatol* 2013; **168**: 439-42.

us to consider a causal link between the infiltration of the filler and the appearance of xanthelasma, much more likely than a casual association between the spontaneous start of xanthelasma and the filler injection. We suppose that the hyaluronic acid, injected to reduce the wrinkles of the lower eyelids, may have produced an inflammatory reaction with oedema resulting in an increase of vascular permeability. It is important to remember that, normally, LDL has a low percentage of capillary leakage but local trauma increases this rate.[10] The extravasated LDL may have formed complexes with the injected hyaluronic acid, which were internalized by histiocytes. Furthermore, hyaluronic acid favours the oxidation of LDL, increasing the formation of foam cells.

Our cases suggest that special attention should be paid while performing infiltration of hyaluronic acid in the periorbital region.

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Frontal fibrosing alopecia and lichen planus pigmentosus: is there a link?

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Madam, Frontal fibrosing alopecia (FFA) is a primary lymphocytic cicatricial alopecia with a distinctive pattern involving the hairline, eyebrows and other hair-bearing areas, first described by Kossard[1] as a progressive recession of the frontal hairline in postmenopausal white women. Miteva *et al.*[2] have reported for the first time the occurrence of FFA in African Americans.

Lichen planus pigmentosus (LPPigm), on the other hand, is an uncommon macular variant of lichen planus occurring as diffuse or reticulated macules on sun-exposed areas and in flexures. LPPigm resembles erythema dyschromicum perstans or ashy dermatosis on histology.[3] Ashy dermatosis is characterized by the progressive occurrence of ash-coloured macules with erythematous margins commonly distributed over the trunk and proximal extremities.[4]

The coexistence of FFA and idiopathic lichen planus has been reported,[5] but not LPPigm and FFA. We report here for the first time 24 cases of LPPigm preceding FFA in Durban, South Africa (Fig. 1a).

A retrospective review of 44 patients diagnosed with FFA (2006–2012) revealed that 24 patients had pigmentation on sun-exposed areas (LPPigm) while 20 had FFA only. This study will focus on the 24 patients with FFA and LPPigm.

The clinical diagnosis was corroborated by histology in all 24 patients (Table 1). Most patients were African (22; 91%), while two (9%) were Indian. There were 23 women (95%) and one African man (5%). The age at onset ranged from 25 to 56 years (mean 40). Most of the women were premenopausal (14/22; 64%), while 8/22 (36%) were postmenopausal. All patients had frontotemporal hair loss but only two exhibited facial papules on the forehead and cheeks, the histology of which confirmed sebaceous hyperplasia, with vellus hair involvement. The mean lag interval from LPPigm to FFA was 14 months (range 6–36). Eyebrow and limb hair loss affected 38% and 25% of the patients, respectively. Traction alopecia (TA) featured in most of the African women but in neither of the Indian women nor in the African man. None of the patients had a positive drug or family history. Human immunodeficiency virus (HIV) infection coexisted in one (4%); the rest had a noncontributory medical history.

LPPigm was first described in India by Bhutani *et al.*[3] as a rare variant of lichen planus characterized by hyperkeratosis, atrophy of epidermis as well as vacuolar degeneration of the basal layer (Fig. 1b). It has been reported in various ethnic groups, e.g. Latino, Korean, Japanese and Middle Eastern

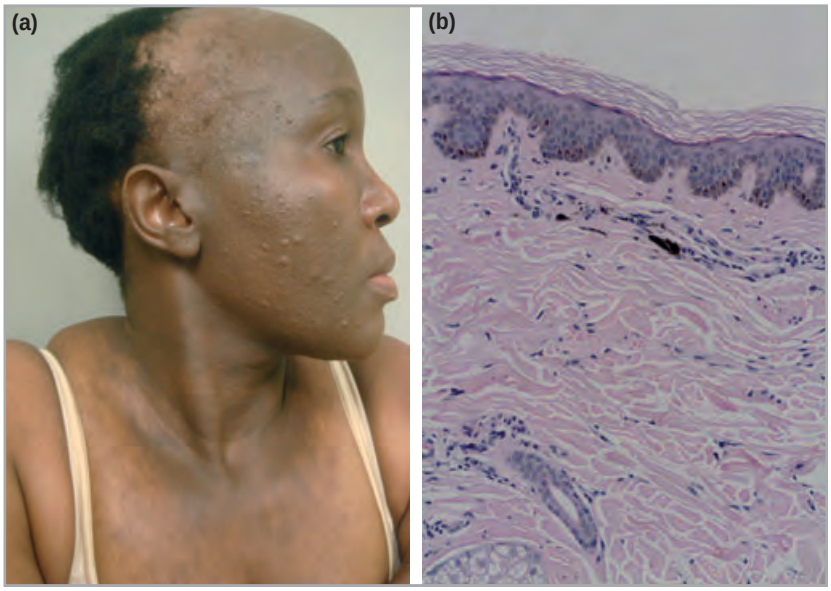

Fig 1. (a) Clinical appearance of lichen planus pigmentosus (LPPigm) on the face, ears and V of the neck, with evidence of frontal fibrosing alopecia to mid-scalp, and bilateral eyebrow loss. The patient was not on treatment, and predominantly wore tight braids. She noticed hair loss 1 year after onset of pigmentation. (b) Photomicrograph showing pigmentary incontinence with some mild basal vacuolar degeneration consistent with LPPigm (haematoxylin and eosin; original magnification × 100).

populations, but never in Africans. Although Faulkner *et al.*[5] reported FFA in association with idiopathic lichen planus in a premenopausal white woman in 2002, the coexistence of LPPigm and FFA has never been reported.

Interestingly, most patients were oblivious to the hair loss which was preceded by LPPigm by about 14 months, and dismissed it as TA, a not so uncommon finding in African women.[6] Two of the patients presented with skin-coloured facial papules. Donati *et al.*[7] and Tan and Messenger[8] have described vellus hair involvement in some of their cases. Most of our patients were African women and were premenopausal, with an age at presentation ranging from 25 to 56 years. This is lower than the age range of 53–72 years reported by Miteva *et al.*[2] It is possible that the mechanical trauma that is associated with hair grooming hairstyles could explain the early age at which manifestation of FFA in African patients occurs. The African man had a slower rate of frontal recession compared with his female counterparts, and this could be explained by absence of traction-inducing hairstyles.

It appears that LPPigm could be the herald sign for FFA. FFA can be easily dismissed as TA, particularly in black patients, missing the association described here. Therefore proper clinical examination using the diagnostic features distinguishing between FFA and TA described by Miteva *et al.*,[2] and a biopsy of the scalp margin, should be undertaken on all African patients presenting with LPPigm. On histological confirmation of FFA, patients should be commenced on appropriate treatment.[9]

Further advice and counselling, on gentle hair grooming hairstyles with avoidance of tight braids or frequent chemical treatment, should be provided. Topical retinoids, skin-lightening creams as well as strict sun protection were recommended for LPPigm as well as chloroquine 200 mg twice daily for 1 year for FFA. The psychological impact of the pigmentation on affected patients cannot be underestimated, particularly with the advent of HIV and its associated generalized pigmentation for which patients can be easily mislabelled.

The well-defined, sequential clinical progression from LPPigm to FFA, and its histological confirmation, suggest that LPPigm and FFA are but separate bands of the same spectrum of disease. The aetiology of FFA remains elusive; however, genetic and environmental factors have been implicated.[10]

There are insufficient data in the literature on the natural history of both diseases; however, it is known that FFA and LPPigm do stabilize after some time. As to when and how far they will stabilize remains unknown. Further to confirm the predictive status of LPPigm as the harbinger of FFA, further long-term prospective cohort studies need to be undertaken to elucidate this association.

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Table 1 Clinical and demographic data of patients with lichen planus pigmentosus (LPPigm) preceding frontal fibrosing alopecia (FFA)

Patient	Sex	Ethnicity	Family history	Pre-/ postmenopause	Age at onset of LPPigm (years)	Eyebrow involvement	Limb involvement	Frontotemporal recession	Presence of facial papules	Interval between LPPigm and FFA (months)	Associated medical diseases	Features of LPPigm, face biopsy	Features of FFA, scalp biopsy
1	F	African	Nil	Pre	30	Yes	Yes	Yes	Yes	12	Nil	Yes	Yes
2	F	African	Nil	Post	51	Yes	Yes	Yes	No	12	Nil	Yes	Yes
3	F	African	Nil	Unknown	Unknown	Yes	No	Yes	No	6	Nil	Yes	Yes
4	F	Indian	Nil	Pre	39	No	No	Yes	No	24	Nil	Yes	Yes
5	F	African	Nil	Pre	42	Yes	Yes	Yes	Yes	12	Nil	Yes	Yes
6	F	African	Nil	Pre	36	Yes	Yes	Yes	No	24	Nil	Yes	Yes
7	F	African	Nil	Pre	25	No	No	Yes	No	12	Nil	Yes	Yes
8	F	African	Nil	Post	53	No	No	Yes	No	12	Nil	Yes	Yes
9	F	African	Nil	Pre	31	No	No	Yes	No	12	HIV	Yes	Yes
10	F	African	Nil	Pre	48	No	No	Yes	No	14	Nil	Yes	Yes
11	F	African	Nil	Pre	45	No	No	Yes	No	18	Nil	Yes	Yes
12	M	African	Nil		33	Yes	No	Yes	No	13	Nil	Yes	Yes
13	F	African	Nil	Pre	39	No	No	Yes	No	12	Nil	Yes	Yes
14	F	African	Nil	Pre	43	No	Yes	Yes	No	18	Nil	Yes	Yes
15	F	African	Nil	Post	47	No	No	Yes	No	24	Nil	Yes	Yes
16	F	African	Nil	Post	56	No	No	Yes	No	36	Nil	Yes	Yes
17	F	African	Nil	Post	52	No	No	Yes	No	12	Nil	Yes	Yes
18	F	African	Nil	Post	54	No	No	Yes	No	12	Nil	Yes	Yes
19	F	Indian	Nil	Post	47	No	No	Yes	No	6	Nil	Yes	Yes
20	F	African	Nil	Pre	31	No	No	Yes	No	6	Nil	Yes	Yes
21	F	African	Nil	Post	53	No	No	Yes	No	18	Nil	Yes	Yes
22	F	African	Nil	Pre	43	Yes	No	Yes	No	12	Nil	Yes	Yes
23	F	African	Nil	Pre	37	Yes	No	Yes	No	12	Nil	Yes	Yes
24	F	African	Nil	Pre	31	Yes	Yes	Yes	No	12	Nil	Yes	Yes

HIV, human immunodeficiency virus.

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Conflicts of interest: none declared.

Lack of 'appropriately assessed' patient-reported outcomes in randomized controlled trials assessing the effectiveness of interventions for rosacea

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MADAM, Rosacea is a chronic skin disease, and psychological problems are fairly common in people affected by rosacea. The persistent red pimply rash on the face can be a source of embarrassment, anxiety and low self-esteem. It may instil a lack of confidence and even lead to depression or body dysmorphic disorder. Rosacea can also have a significant negative impact on health-related quality of life (HRQoL).We have documented the patient-reported outcomes (PROs) used in clinical trials identified in the Cochrane Review on the effectiveness of interventions for rosacea, published in the Cochrane Library March 2011, and we reported their measurement properties previously.[1] Here we discuss the results.

We independently evaluated the PROs in 58 included studies using the 'Checklist for describing and assessing patient-reported outcomes in Clinical Trials', as described in the *Cochrane Handbook for Systematic Reviews of Interventions*.[2] We extracted from the primary report details of the number of items or domains, the type of rating scales used, the timing of the assessments and whether symptoms were presented as scores at baseline or at follow-up or both, as well as any measurement property that we identified. We abstracted estimates of effect on PROs and applied GRADE (Grades of Recommendation Assessment, Development and Evaluation) methodology to create evidence profiles, summarizing results and confidence in effect estimates (all data available on request).[3]

Two of the 58 studies reported assessments of change in HRQoL as an outcome of the interventions. Other PROs were reported in 29 of 58 studies and included not only assessments of changes in severity but also, in 10 of them, the degree of patient satisfaction associated with these changes (Fig. 1). None of the PRO assessment tools met the recommended criteria based on the quality 'checklist'. In six of the studies the self-assessments were made by way of questionnaires of unsupported validity. Most of the instruments used in the remaining studies were based on Likert-type scales, and three of the studies utilized visual analogue scales (see Fig. 2). Moreover, the majority of the studies focused principally on the numbers of papules and pustules, which, although they may provide a quantifiable, objective and more readily understood outcome, are generally considered to be clinician-centred rather than patient-preferred. Two studies evaluating quality of life used validated tools that are internationally recognized: a disease-specific instrument, Ocular Surface Disease Index, was used in one study,[4] and the generic Dermatology Life Quality Index was applied in the other.[5]

The overall quality of the evidence based on the GRADE profile was generally considered low to moderate. However, based on patients' assessments there is evidence that topical metronidazole (four studies) and azelaic acid (three studies) improve papulopustular rosacea, and topical ciclosporin improves the quality of life of participants with ocular rosacea (one study). Most of the randomized controlled trials (RCTs) assessing the effects of tetracycline were old and less well designed, and of those studies that were eligible for inclusion most failed to show any effect on participant-assessed rosacea severity. Several recent, well-designed RCTs have investigated the effects of subantimicrobial anti-inflammatory dose doxycycline (40 mg) for the treatment of rosacea, but these did not address the patients' views.[1] Evidence provided by one RCT indicated that pulsed dye laser and intense pulsed light therapy can reduce erythema and telangiectasia on the face.[1] Clearance of the redness and telangiectasia is highly desirable, as these symptoms can be a source of personal embarrassment and may lead to low self-esteem. Therefore, further studies of laser- and light-based therapies should be considered a priority. Three treatments were rated as ineffective by the participants in the trials: (i) pimecrolimus, (ii) a cream containing

CHAPTER 13

Familial frontal fibrosing alopecia.

Dlova N, Goh CL, Tosti A. Familial frontal fibrosing alopecia. *Br J Dermatol* 2013; **168**: 220-2.

In human lymphoid malignancies, galectin-7 was reported to be expressed and to be a critical tumour-modulating gene. It may significantly affect lymphoma progression in the clinical setting.[6] Using an approach based on genomic analysis of an aggressive lymphoma variant and its nonaggressive parental cells, the most prominent change was the strong upregulation of galectin-7.[7] Galectin-7, a member of the galectin family, designated as the product of the p53-induced gene 1 (*PIG1*, now known as *LGALS7*), is a regulator of apoptosis and contributes to different events associated with the differentiation and development of pluristratified epithelia. Galectin-7 is thought to function in stratified epithelial tissue in response to environmental injuries, such as wound healing or UV radiation.[8] UV radiation exposure has been shown to induce skin keratinocytes to express rapidly galectin-7 mRNA and protein, and galectin-7 has been reported to take part in UV-induced apoptosis.[8,9] Microarray analysis revealed that galectin-7-transfected cells expressed approximately nine times more HMG-CoA synthase (HMGCS1) mRNA than untreated cells.[10] HMGCS1 is a key rate-limiting enzyme, preceding HMG-CoA reductase, in the pathway for endogenous cholesterol synthesis. Recently, we discovered that galectin-7 interacts with HMGCS1 while inducing its expression (Norihiro Fujimoto, Hideki Mieno, Ryoko Hosokawa, Eita Fujimoto, Shingo Tajima. unpublished data).

We present here two women with normolipaemic PX coinciding with tumour-stage MF treated with PUVA. MF, a cutaneous T-cell lymphoma, is considered to express galectin-7 even without PUVA treatment. Galectin-7 expression in MF lesions plays at least a partial role in generating PXs via inducing and holding HMGCS1. In our cases, UV irradiation (PUVA) might have accelerated galectin-7 expression and rendered the lesions ready to generate PXs. Overexpression of galectin-7 contributed to induction of epidermal apoptosis, cholesterol synthesis and subsequent lipid incontinence. This theory is supported by the result that lipid-laden macrophages in the upper dermis as well as epidermis were positively stained with antibodies against AE1/AE3 and galectin-7 (Fig. 2c, d). This explains well the possible aetiological process of DPXs in MF treated with PUVA.

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Familial frontal fibrosing alopecia

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Madam, Frontal fibrosing alopecia (FFA) is a cicatricial alopecia that was first described by Kossard in 1994.[1] It primarily affects caucasian postmenopausal women with progressive recession of the frontotemporal hairline. In recent years the disease has been increasingly reported in Europe,[2–4] the U.S.A.[5] and Japan.[6] Most authors consider FFA a variant of lichen planopilaris because of its similar pathological features. Three reports of familial cases of FFA have been published in the literature;[7–9] however, recent articles with large case series of FFA do not discuss the possibility that the disease may occur in families.[2–5] We report four new familial cases of FFA including two families with involvement of three members.

In all our 10 patients diagnosis was confirmed by pathological examination. Biopsies were taken from the frontal hairline in areas showing perifollicular erythema and/or scaling. Dermoscopy was utilized to select the biopsy site in seven patients. A biopsy from the forearms was also taken in the two hispanic sisters. Horizontal sections of 4-mm scalp biopsies showed reduced follicular density, a lichenoid lymphocytic infiltrate involving the outer root sheaths of the upper follicles, mild perifollicular fibrosis and follicular drop out.

Clinical data from our four families as well as from the previously published families with FFA are summarized in Table 1. In three of our four families FFA occurred in siblings as in the three other families reported in the literature.

Table 1 Clinical and demographic data of patients with familial frontal fibrosing alopecia, including literature review

Family or reference	Nationality/ethnicity	n	Relation	Sex	Age (years)	Eyebrows	Limbs	Duration (months)	Associated diseases
1	Italian/caucasian	3	Sisters	3F	55	Yes	Yes	12	
					61	Yes	Yes	24	
					73	Yes	Yes		
2	Italian/caucasian	2	Sister	1F	59	Yes	Yes	36	LPP
			Brother	1M	62	Yes	Yes	12	
3	American/hispanic	2	Sisters	2F	25	Yes	Yes	12	
					21	Yes	Yes	3	
4	South African/black	3	Mother	3F	74	No	No	24	TA
			Daughter		50	No	No	12	TA
			Cousin		44	Yes	No	12	TA
Roche *et al.*[8]	Unreported	2	Sister	1F	75	Yes	No	12	
			Brother	1M	71	Yes	No	8	
Junqueira Ribeiro Pereira *et al.*[7]	Italian/caucasian	2	Sisters	2F	57	Yes	No	12	
					59	Yes	No	12	
Miteva *et al.*[9]	American/caucasian	2	Twin sisters	2F	67	Yes	Yes	12	Vitiligo
						Yes	Yes	6	Vitiligo

LPP, lichen planopilaris; TA, traction alopecia.

Affected members of our families either lived together (family 1) or close by in the same town. In all our families the diagnosis of FFA was first made on one female patient who then diagnosed and referred her relatives. In two of our families FFA affected individuals who either because of their age or because of their sex differ from the typical demographics of FFA. In fact, family 3 consisted of two sisters who developed the disease in their twenties. Both gave a history of normal menses and blood tests showed a normal hormonal profile. To our knowledge these are the youngest patients with FFA reported in the literature. The youngest premenopausal women reported in the large case series of FFA were aged 31,[5] 34[2,4] and 40 years.[2] In family 2 FFA affected a brother and a sister, which is peculiar as the condition is extremely rare in men. The family reported by Roche *et al.*[8] also involved male and female siblings. The prevalence of men in familial cases of FFA (12·5%) is then significantly higher than in the series of FFA reported in the literature (3%[5] and 0%[2–4]).

We had two families with three affected members, including a black family from South Africa, from where the disease has never been reported. As most black women have traction alopecia due to their hairstyle practice, the diagnosis of FFA in the black population is more difficult. A concomitant FFA may be overlooked as both conditions affect the frontotemporal hairline.[10]

The epidemiology of FFA strongly suggests a role of environmental factors in its development. In fact, FFA is a relatively new condition that is becoming increasingly common worldwide. The occurrence of the disease in families can simply indicate exposure to common environmental triggers. However, genetic predisposition may also play a role as it is well documented that inherited genetic traits codetermine the susceptibility of an individual to toxic chemicals.[11] Dioxin-like chemicals are environmental pollutants that are ingested with fatty foods of animal origin. These toxins persist in the environment and are very slowly eliminated from the human body.[12] The possibility that dioxin-like substances can trigger the disease via the aryl hydrocarbon receptor is interesting but still unproven.[13]

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Expanding the therapeutic repertoire of infantile haemangiomas: cohort-blinded study of oral nadolol compared with propranolol

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MADAM, Infantile haemangiomas (IHs) are benign vascular endothelial neoplasms, with potential for significant complications and cosmetic disfigurement. Propranolol, a nonselective beta-blocker, was reported to be beneficial in the treatment of IHs either alone or in combination with corticosteroids.[1] Long-term safety data and appropriate dosage are currently being investigated. As the beta-adrenergic system is involved in novelty detection and memory modulation,[2] the potential long-term deleterious brain effects of prolonged propranolol use in infancy are not known. Nadolol is a synthetic, nonselective beta-blocker that is comparatively more beneficial due to a better safety profile,[3,4] its inability to cross the blood–brain barrier[5] and a longer half-life, requiring less frequent dosing and less rebound.[6,7] The objectives of our study were to explore the efficacy and safety of nadolol in patients with IH, and the feasibility of conducting a randomized controlled trial.

Patients and methods

This assessor-blinded, cohort study using oral nadolol was conducted at the Hospital for Sick Children, Toronto, ON, Canada from 2009 to 2011, and was approved by the institution's research ethics board, Health Canada, and registered (NCT01010308). The inclusion criteria for the intervention arm were infants 1 month to 1 year of age, with head and neck IH causing function loss, and/or potential disfigurement. The control group was randomly selected from patients treated with oral propranolol for at least 6 months between 2008 and 2010, and were matched for age and location. Patients with proven or suspected PHACES syndrome (posterior fossa abnormalities, haemangioma, arterial cerebral abnormalities, cardiac anomalies/coarctation of the aorta, eye anomalies, sternal anomalies) and medical contraindications to propranolol were excluded.

The intervention was nadolol suspension 10 mg mL^{-1}, administered orally, starting at 0·5 mg kg^{-1} per day divided twice daily with weekly increments of 0·5 mg kg^{-1} up to a maximum of 4 mg kg^{-1} per day according to the response. Propranolol oral suspension (1 mg mL^{-1}) was administered incrementally to a maximum of 2–3 mg kg^{-1} per day divided three times daily. The duration of the study was 24 weeks. Baseline procedures included history and physical examination, electrocardiogram, vital signs, growth parameters and standardized digital photography. Ten follow-up visits also included an adverse event review and parental assessment of improvement. An assessor who was blinded to the intervention and duration of treatment evaluated the improvement in the size or extent of IH by comparing photographs at each visit against baseline using a 100-mm visual analogue scale (VAS) with three anchors: (−), 100% worsening of the haemangioma; 0, no change and (+), 100% shrinkage of the haemangiomas, where 5 mm represented 10% change.[8,9] The primary outcome measure was the percentage improvement in the size or extent of the haemangioma at 24 weeks. Secondary analyses were correlation between assessor and parental assessments, and frequency and severity of adverse events.

Statistical methods

Descriptive statistics were used to summarize the data. Fisher exact tests (for categorical data) and Wilcoxon signed-rank tests (for continuous data) were used to compare the baseline characteristics. A mixed model analysis of variance was used for the primary outcome. A Pearson correlation [with 95% CI (confidence interval)] between investigator and parental VAS was calculated. Statistical tests were conducted at level 0·05. All analyses were performed using SAS v9.2 (2008, SAS Institute Inc., Cary, NC, U.S.A.).

Results

Ten patients, 30% girls, were recruited in the nadolol group and nine patients (67% girls) in the propranolol group. There were no baseline differences (Table 1) between the groups. Five patients in the nadolol group had an amblyogenic periorbital IH.

The mean dose was 2·19 ± 1·1 mg kg^{-1} in the nadolol group and 1·89 ± 0·29 mg kg^{-1} in the propranolol group. Patients receiving nadolol had a mean percentage IH shrinkage of 51 ± 18·45% at the 4-week visit, 83 ± 13·86% at the 12-week visit and 97 ± 3·05% at the end of the study (24 weeks). A good, but less favourable response was noted in the propranolol group, 28 ± 10·44%, 56 ± 16·55% and 86 ± 14·82% at 4, 12 and 24 weeks, respectively ($P < 0·001$,

CHAPTER 14

Frontal fibrosing alopecia in an African man.

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International Journal of Dermatology

Case report

Frontal fibrosing alopecia in an African man

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Case report

A 35-year-old African man developed an asymptomatic progressive recession of the frontal hairline over 1 year. Clinical examination revealed frontotemporal recession with loss of follicular orifices and partial loss of both eyebrows (Fig. 1a,b). Routine examination of the remaining scalp was normal. Further close inspection of the hair margin with a dermatoscope showed perifollicular plugging and very subtle erythema masked by pigmentation (Fig. 1c). The rest of the body, including the hair, nails and mucosa, was unaffected. The subjects general medical and drug history were insignificant. His family history showed no evidence of similar or any other scarring alopecia. The patient had always maintained natural virgin hair and had no history of using chemicals or mechanical manipulation for hair grooming purposes. Thyroid screen, antinuclear factor, complete blood count and hepatitis screen were normal.

Two 4-mm transverse and horizontal histopathological sections of the affected margin of the scalp revealed features typical of lichenplanopilaris,[1–3] including reduced follicular density, a lichenoid lymphocytic infiltrate involving the outer root sheaths of the upper follicles, mild perifollicular fibrosis and follicular dropout (Fig. 2).

A diagnosis of frontal fibrosing alopecia (FFA) was confirmed and the patient was commenced on hydroxychloroquine 200 mg twice per day for 6 months, topical steroid (clobetasol diproprionate), 0.1% tacrolimus and 2% minoxidil. The patient was followed up for 1 year and showed a good response to treatment evidenced by the slow progression of the disorder.

Discussion

Frontal fibrosing alopecia has been classified as a variant of lichenplanopilaris (LPP) based on some reports documenting an association with classical multifocal LPP over the vertex of the scalp and other sites, in addition to the typical histological findings.[1] Although LPP is uncommon, Ochoa *et al.* [4] have reported annual incidence rates of 1.15–7.59% in hair referral centers in the USA.

Typically, FFA presents with a frontoparietal pattern of hair loss and is usually associated with the loss of eyebrows.[2] It may also be associated with hair loss on other peripheral body hair sites, which was recently confirmed histopathologically.[3,5] The condition may be accompanied by pruritus, as well as evidence of perifollicular erythema, scaling and diminished follicular orifices.[1] Although our patient did not have evidence of hair loss from peripheral body sites at the time of examination, he did show clinical evidence of bilateral eyebrow hair loss; however, he declined eyebrow biopsy. Chew *et al.*[3] performed biopsies on eyebrows and the upper limbs of affected patients to show that LPP with scarring alopecia is a generalized process rather than one that is localized to the frontal scalp. 1

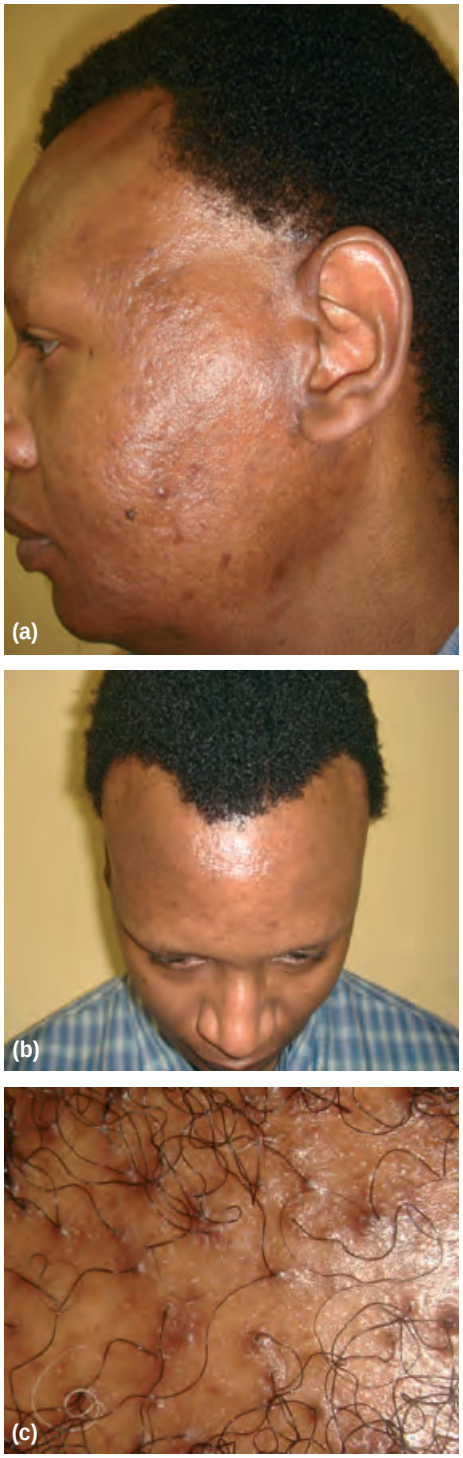

Figure 1 (a) Scarring alopecia presents with lighter skin and the loss of eyebrow hair. (b) Frontoparietal hairline recession is apparent. (c) Close examination shows perifollicular plugging and dusky erythema

Although our patient revealed intact peripheral body hair at the time of examination, it is possible that further evolution of the disease and ongoing follow-up will enable us to confirm Chew *et al*.s findings.[3]

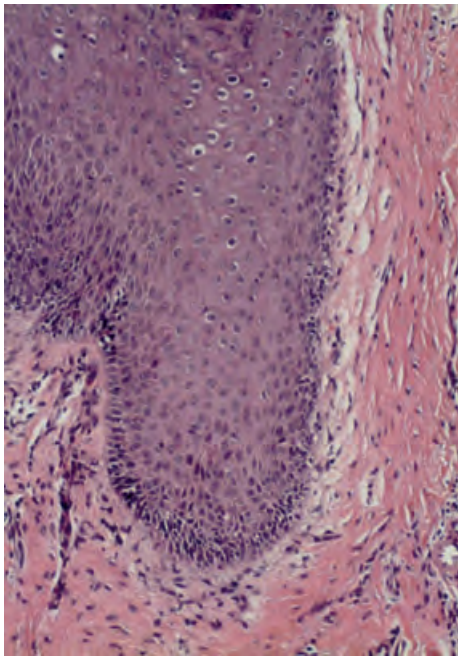

Figure 2 Histopathology shows vacuolar interface changes with scattered lymphocytes and perifollicular fibrosis in keeping with lichenplanopilaris. (Hematoxylin and eosin stain; original magnification ×100)

The etiology of this primary cicatricial alopecia remains uncertain and its treatment is therefore challenging. Suggested treatments comprise topical corticosteroids, tacrolimus, chloroquine, finasteride and dutasteride.[6–8] Frontal fibrosing alopecia predominantly occurs in post-menopausal women, but there are a few reports of its emergence in premenopausal women[6] and its sporadic occurrence in White men is well known.[1,9] In 2012, Miteva *et al.*[10] reported the first male of African-American descent with FFA amongst 10 Black female patients with FFA in a retrospective chart review study conducted in the USA and UK.

To our knowledge, the present patient is the second Black male and the first male of African descent from Africa with FFA to be reported in the English-language literature. The presentation, and clinical and histopathological findings in this case were similar to those in other male cases reported in the literature.[1,9,11] The present case, together with the series reported by Miteva *et al.*,[10] indicates that FFA occurs in patients of African, African-American and Afro-Caribbean descent and is not confined to White and Asian populations, and that practitioners should be alert to this condition in Black males, who, unlike Black females, may not be subject to traction alopecia. Frontal fibrosing alopecia has not been reported in the African continent previously. Hence, this case illustrates that the condition exists in Africa, where frontal hair recession is often attributed to traction alopecia.

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CHAPTER 15

Quality of life in South African black women with alopecia - a pilot study

Manuscript in preparation for submission.

TITLE

Quality of life in black South African women with alopecia: a pilot study.

RUNNING HEAD

Quality of life in black South African women with alopecia

KEY WORDS

Alopecia, quality of life, subjective symptoms, objective signs, relational impacts, composite indicators, partial least squares path modeling

WORD, TABLE AND FIGURE COUNT

Abstract	259
Text	1882
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Figures	6

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CONFLICT OF INTEREST

None

ABSTRACT

Background

Alopecia has been shown to have a significant impact on quality of life, particularly in women. There are however no data for African populations.

Objectives

To pilot an original questionnaire and a model-based methodology to measure the Quality of Life (QoL) and its determinants on a sample of black South African women of African ancestry affected by alopecia.

Methods

50 participants aged 21-79 were chosen at random from patients presenting to dermatologists with alopecia. We used an original questionnaire[1] consisting of 24 questions grouped into three categories assessing the impact of subjective symptoms, objective signs and relational impact, each measured on a 4-level Likert scale. These were then combined using component based structural equation model[2,3] to return a Quality of Life Index (QLI) and to rank the factors contributing to this.

Results

On a scale ranging from 0 (high QoL) to 100 (severely decreased QoL), we found a mean QLI score of 67.7. The negative impact of alopecia on QoL was higher in younger patients than older patients. The factors with the highest impact (as assessed by path coefficient, a measure of weighting) were those relating to the subjective experience of alopecia and self-image (56.3%), followed by those relevant to relationships and interaction with other people (34.8%). The presence of objective symptoms and signs such as pruritus were of minor importance (8.9%).

Conclusions

Although not a life-threatening condition, alopecia may seriously impair QoL of African black women, particularly by inducing anxiety and reducing self-esteem. Health care practitioners should be mindful of this and intervene appropriately to mitigate this.

INTRODUCTION

Primary alopecia of the scalp is usually classified into scarring and non-scarring, and requires a good history, reliable clinical records, adequate biopsy and histopathological interpretation to make a definitive diagnosis[4,5]. It has been established that the most common type of hair loss in both sexes is androgenetic alopecia, and racial differences in the prevalence or pattern have been observed[6].

Ascertaining the influence and impact of skin diseases on patients' quality of life (QoL), using quality of life indicators, is important, and is now well established in dermatology[1,7-11]. Hair plays such a vital role in aesthetics that few skin conditions carry as much emotional burden as alopecia, especially in women[6,12], some of whose emotions seem disproportionate to the degree of alopecia, indicating poor self-esteem and low QoL[6,13-16]. Such feelings can be easily aggravated by non-compassionate health care practitioners who may underestimate the impact of hair loss on such patients. However, there is little published information on the psychological effects of patients with hair loss in African countries, possibly in part because of a focus on the burden of infectious diseases, a priority in the developing countries[17], rather than aesthetics.

Schmidt *et al.* looked at the correlation between QoL and coping strategies in 50 female patients diagnosed with diffuse or androgenetic alopecia using Hairdex, an instrument developed to measure QoL in patients with hair loss[18]. Their findings indicated that patients with obvious hair loss reported a more negative impact on various Hairdex aspects (functioning, emotions, self-confidence and stigmatization) than those who had slightly visible hair loss. Their small group of studied patients showed striking signs of psychological disturbance despite having little obvious hair loss.

Van der Donk *et al.* studied 58 women with androgenetic alopecia[15] and found their daily behaviour to be influenced by alopecia in 88% of participants, with 75% indicating a loss of self-esteem. Other authors have emphasized the inherent intricacies and challenges of dealing with an unpredictable and yet visible and progressive disorder[19]. Although there are extensive reports on the psychosocial consequences of hair loss, most studies have used a medical instead of a holistic psychological approach[19]. Factors that determine the psychological impact of alopecia include those which are disease-related (visibility of hair loss), psychological (beliefs about illness), behavioural (coping) and demographic (gender)[12,15,19,20].

Although investigators have studied QoL in patients with acne[21], psoriasis[22] and general skin disorders the effect of alopecia on an African population has not been studied [6]. This is an omission, given the increasing prevalence of hair disorders among black women; such disorders are currently rated as the fifth commonest skin disorder amongst African Americans[23,24] and black South Africans[25].

The aim of this pilot study is to investigate the effectiveness of a newly developed questionnaire and algorithm for determining QoL in African women with alopecia, and secondarily to provide preliminary estimates of the impact of alopecia in this population.

MATERIALS AND METHODS

Patients

This cross-sectional study was conducted over a six month period, from 5th January to 31st July 2013 inclusive. Ethical approval was obtained from the Nelson R. Mandela School of Medicine Institutional Review Board (BE 180/11). African women patients who presented with alopecia were recruited randomly from the dermatology clinic at King Edward VIII Hospital and a private practice in Durban, South Africa. This hospital is a major public tertiary referral hospital for KwaZulu-Natal Province located on the eastern seaboard of South Africa, and sees predominantly patients of African and Indian extraction.

We administered to all patients the questionnaire for the Alopecia Quality of Life Indicators (A-QLI) developed by Fabbrocini *et al.*[1](Table 1). The first part of this questionnaire gathers demographic and general clinical data (age, race, duration of disease, clinical diagnosis, percentage of scalp affected). The second comprises multi-choice questions in a 4-point scale (*very much*, *a lot*, *a little*, *not at all*) about subjective symptoms, objective signs and relationship issues (patient's feeling, using bandanas or other devices to hide scalp area, the influence of alopecia on friendships, relationships, sexual activities, social relations etc.).

The questionnaire was administered by trained interviewers. We recruited 50 South African women of African ethnicity between 21 and 79 years of age, with a mean age of 45.18 years.

Statistical methods

The QoL assessment was determined using a component-based hierarchical Structural Equation Model, in which the calculated QLI is a function of three latent variables (the inner model), independent dimensions which would contribute collectively to the subject's sense of well-being. We identified three latent variables: *subjective symptoms*, *objective symptoms* and *relationships*. Each latent variable was inferred from a number of manifest variables, comprising the answers returned on the questions; 9 for subjective symptoms, 3 for objective symptoms and 7 for relationships. A further 5 questions were found to provide no relevant information and were excluded from the analysis (questions 10, 11, 22, 23, 24). The relationship between each latent variable and its manifest variables constitutes the outer model. We used a Partial Alternating Least Squares Optimal Scaling-Path Modelling (PALSOS-PM) algorithm[2,3,26] that calculates an overall score, and displays the weighted contribution of each latent variable to the overall score. Scores are expressed on a scale 0-100, where 0 represents the highest QoL and 100 the lowest.

RESULTS

All participants completed the questionnaire and were entered into the analysis. The unidimensionality of each latent variable in the model was confirmed by Cronbach's alpha and Dillon-Goldstain indexes which exceeded 0.7. The quality of the model was reflected by a Goodness of Fit index[27] of 0.89.

The model is summarised in Figure 1. The respective QoL score for the three latent variables *subjective symptoms, objective symptoms* and *relationships* were 72.4, 74.8 and 57.5 respectively. Their relative weighting was determined by their partial correlation coefficients (r^2) and returned values for the path coefficients of 0.485, 0.193 0.381 respectively. These relationships are summarised in Figure 1. The QLI is then calculated by the following equation:

$$QLI = 0.485\times \text{Score}_{\text{subjective symptoms}} + 0.193\times \text{Score}_{\text{objective symptoms}} + 0.381\times \text{Score}_{\text{relationship}}.$$

The calculated mean QLI for our subjects is 67.7. A QLI exceeding 50 is regarded as reflecting significant impairment of QoL and was shown in 74% of our patients.

Though both *subjective symptoms* and *objective symptoms* have high scores at 72 to 75, the major drivers of impaired quality of life are *subjective symptoms* and *relationships*, with partial coefficients (r2) values of 56.3 and 34.8; the the contribution of objective symptoms by contrast is low in comparison at 8.9.

The relative impact of the three latent variables is summarised in Figure 2. Here the y-axis represents the path coefficient, a measure of the relative weighting of the variable to the overall score, while the x-axis represents the QLI score for each variable. Variables falling in the right upper quadrant are highly significant in that they have both a high QLI and a high weighting. Variables falling in the left lower quadrant are of less significance in that they have a lower QLI and lower impact. The other two quadrants represent high QLI/low weighting and low QLI/high weighting respectively. *Subjective symptoms* is shown to be the most critical factor.

For each latent variable, the relative impact of the component manifest variables are shown in Figures 3-5. The most critical variables are again those in the upper right quadrant which represent a high QLI and high weighting. For the latent variable *subjective symptoms*, the highest-ranking concerns are: fear that children may develop alopecia, regret at personal appearance, inability to forget the presence of the problem, fear that it might spread and worries about cost implications. The highest-ranking concerns in terms of the latent variable *relationships* are embarrassment in social interaction, having to explain one's appearance to other people, fear of presenting an unpleasant appearance to other people, and fear of appearing unkempt. Concerns about contagiousness and deterioration in work or study performance are not significant factors. The manifest variables contributing to *objective symptoms*: scalp visibility; itch and physical hair loss on hair grooming are not major factors in their own right.

We identified age as an important factor influencing QoL. A radar plot summarising overall QLI, as well as the mean score for each of the latent variables, is shown in Figure 6. The mean values for the age groups 21-40, 41-16 and 60+ are plotted. Patients appear to become more accepting of their condition with increasing age.

DISCUSSION

Alopecia is highly prevalent. In a recent retrospective survey of 6,664 African patients seen in a predominantly black urban dermatology practice in Durban, hair disorders in general and CCCA in particular, accounted for 5.2% and 0.4% of all skin conditions seen respectively, and

constituted the fifth commonest skin disorder among black South Africans[25]. Studies have reported traction alopecia and central centrifugal cicatricial alopecia (CCCA) as the most common types seen in women of African ancestry[23]. In the present study lichen planus pigmentosus (LPP) and its variants constituted the most prevalent type of alopecia. The frontal fibrosing alopecia pattern was the most common. It is often recognised early as it affects the hairline unlike other hair disorders such as the patchy manifestations of LPP or CCCA, which are usually not noticed until they affect hair density. 64% of our patients reported a history of alopecia for more than one year, and only 12% of the participants had sought medical assistance within the first six months of onset. The delay in consultation could conceivably be due to a lack of understanding of alopecia by the patient, and particularly a failure to understand that there is a potential for irreversible scarring.

Given the major role that hair plays in the identity and self-image of women, it is not surprising that our study has shown a significant impairment in QoL in our patients. This is consistent with other reports[6,12,19]. Some of our patients were pre-occupied by the condition to the point of obsession. They worried about the cause, which they often do not know, their fear being compounded by societal misperceptions, such as an association between alopecia and HIV/AIDS. This was a cause of serious worry to 52% of the patients.

This is a preliminary study intended to pilot a model for determination of QLI, and is limited by sample size and selection bias. Our statistical model and the calculation of QLI in the identification of the determinants of QoL appears to hold promise and will be further refined and validated. Future prospective longitudinal studies and studies using a cross-sectional design will provide more definitive data on the impact of alopecia in African patients on QoL, and how the perceptions of those with the disease evolve over time. Finlay has recently stressed the importance of rigorous standards in reporting QoL studies in dermatology (and indeed in medicine generally), and has suggested that a set of minimum standards should be agreed[11]. It is therefore necessary that such follow-up studies conform to these standards.

Our study does however provide strong evidence that alopecia has a significant deleterious impact on QoL in this population, and has provided some indication of the principal factors affecting this as perceived by the patients. We therefore believe it essential that physicians address the psychosocial aspects of alopecia as part of the management of their patients. There may be significant psychological comorbidity in terms of anxiety and depression[12], and a multi-faceted approach involving psychologists, social workers and support groups is likely to be of benefit.

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TABLE 1

Summary of manifest variables, participant responses and calculated loading, with standard error of the mean (SEM) and interquartile range (IQR). Responses are classified as follows: A: *Distresses me very much*; B: *A lot*; C: *A little*; D: *Not at all.*

	Participant responses						
Manifest Variables	**A**	**B**	**C**	**D**	**Mean loading**	**Std. Error**	**IQR**
Latent variable: Subjective symptoms							
I am uncomfortable using a wig.	56%	16%	14%	14%	0.760	0.078	0.64-0.91
I need to hide my condition with hats and bandanas	44%	16%	06%	34%	0.838	0.049	0.74-0.93
It costs me a lot of money to look after my hair.	42%	24%	20%	%14	0.937	0.019	0.91-0.98
I am saddened by the appearance of my hair /eyebrows/eyelashes	5%	24%	08%	16%	0.971	0.009	0.95-0.99
I worry about having this hair problem for the rest of my life.	66%	16%	12%	06%	0.955	0.014	0.94-0.98
I cannot forget that i have this hair problem	52%	22	14%	10%	0.969	0.007	0.96-0.98
I worry that it might spread.	50%	26	08	16	0.969	0.011	0.945-0.986
I do not like to be seen without a wig in front of my partner/relative.	YES 60%	NO 40%			0.598	0.145	0.281-0.825
I am afraid my children may have alopecia	54%	14%	08%	24%	0.975	0.007	0.962-0.987
Latent variable: Objective symptoms							
My scalp is visible	38%	30%	24%	08%	0.970	0.012	0.941-0.988
I lose tufts of hair when I comb or shampoo	22%	22%	40%	16%	0.883	0.033	0.819-0.940
I feel itchy on my scalp.	26%	14%	30%	30%	0.952	0.018	0.914-0.980

	Participant responses						
Manifest Variables	**A**	**B**	**C**	**D**	**Mean loading**	**Std. Error**	**IQR**
Latent variable: Relationships							
I feel that people find it unpleasant to look at me?	32%	14%	30%	22%	0.967	0.009	0.95-0.98
I feel that other people notice my hair/eyebrows/eyelashes	26%	38%	22%	14%	0.938	0.0144	0.92-0.97
I am afraid that people think my hair is not well cared for.	24%	30%	26%	20%	0.964	0.010	0.94-0.98
I am embarassed when going out to a party or function	40%	16%	16%	28%	0.971	0.009	0.95-0.99
have to explain to others what is wrong with my hair	34%	32%	14%	20%	0.952	0.014	0.93-0.98
I feel that others are afraid of catching disease from me	12%	8%	22%	58	0.861	0.055	0.74-0.941
My work and studies have deteriorated because of my hair loss	14%	20%	12%	54%	0.893	0.0501	0.797-0.96

FIGURE LEGENDS

Figure 1

Summary of the structural equation model, indicating impact and relative weighting of the three latent variables *Subjective symptoms*, *Objective symptoms* and *Relationships*, and of 19 manifest variables on these. *l* represents loading, *p.c*. the path coefficiient, *R2* the R squared coefficient and *c.i*. the confidence interval.

Figure 2

The impact of the three latent variables on QoL, as measured by the QLI. Variables falling in the right upper quadrant have the highest impact in that they have both a high QL score and a high weighting.

Figure 3

Subjective symptoms: The impact of the relevant manifest variables on QOL, as measured by the QLI. Variables falling in the right upper quadrant have the highest impact in that they have both a high QL score and a high weighting.

Figure 4

Objective symptoms: The impact of the relevant manifest variables on QOL, as measured by the QLI. Variables falling in the right upper quadrant have the highest impact in that they have both a high QL score and a high weighting.

Figure 5

Relationships: The impact of the relevant manifest variables on QOL, as measured by the QLI. Variables falling in the right upper quadrant have the highest impact in that they have both a high QL score and a high weighting.

Figure 6

Radar plot indicating overall QLI and mean QLI for each latent variable for three age groups.

FIGURE 1

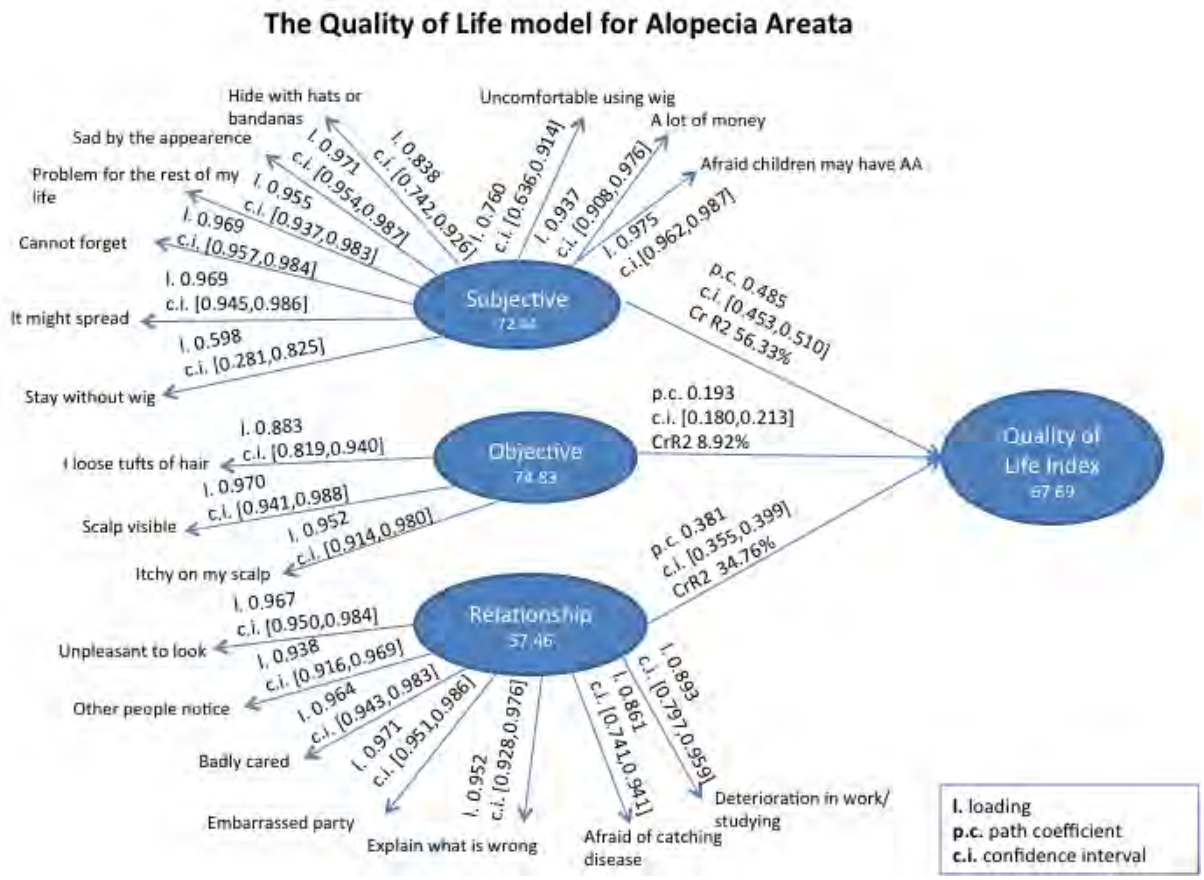

The Quality of Life model for Alopecia Areata
Hide with hats or bandanas
Sad by the appearence
Problem for the rest of my life
Cannot forget
It might spread
Stay without wig
Uncomfortable using wig
A lot of money
Afraid children may have AA
Subjective
72.44
l. 0.838 c.i. [0.742,0.926]
l. 0.971 c.i. [0.954,0.987]
l. 0.955 c.i. [0.937,0.983]
l. 0.969 c.i. [0.957,0.984]
l. 0.969 c.i. [0.945,0.986]
l. 0.598 c.i. [0.281,0.825]
l. 0.760 c.i. [0.636,0.914]
l. 0.937 c.i. [0.908,0.976]
l. 0.975 c.i. [0.962,0.987]
p.c. 0.485 c.i. [0.453,0.510] Cr R2 56.33%
p.c. 0.193 c.i. [0.180,0.213] CrR2 8.92%
Objective
74.83
l. 0.883 c.i. [0.819,0.940]
l. 0.970 c.i. [0.941,0.988]
l. 0.952 c.i. [0.914,0.980]
I loose tufts of hair
Scalp visible
Itchy on my scalp
Quality of Life Index
67.69
p.c. 0.381 c.i. [0.355,0.399] CrR2 34.76%
Relationship
57.46
l. 0.967 c.i. [0.950,0.984]
l. 0.938 c.i. [0.916,0.969]
l. 0.964 c.i. [0.943,0.983]
l. 0.971 c.i. [0.951,0.986]
l. 0.952 c.i. [0.928,0.976]
l. 0.861 c.i. [0.741,0.941]
l. 0.893 c.i. [0.797,0.959]
Unpleasant to look
Other people notice
Badly cared
Embarrassed party
Explain what is wrong
Afraid of catching disease
Deterioration in work/ studying
l. loading
p.c. path coefficient
c.i. confidence interval

FIGURE 2

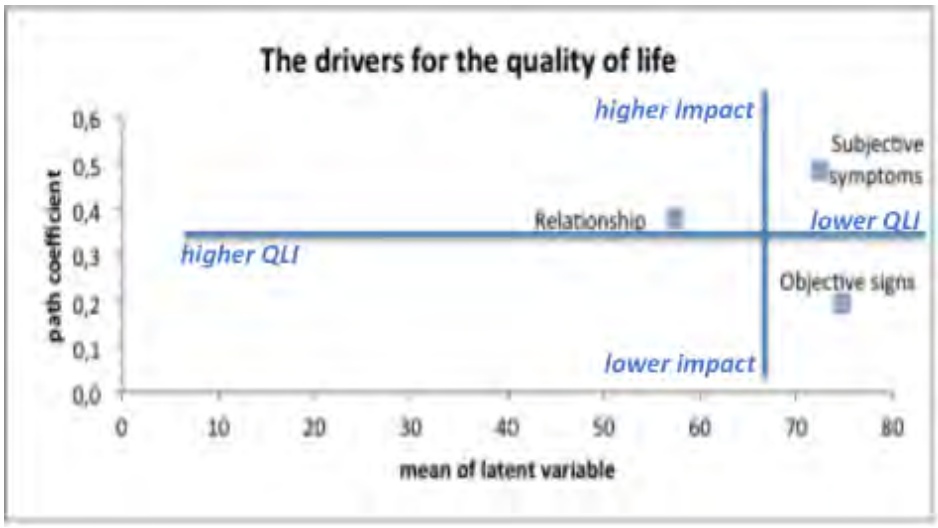

The drivers for the quality of life
higher impact
Subjective symptoms
Relationship
lower QLI
higher QLI
Objective signs
lower impact
path coefficient
0,6
0,5
0,4
0,3
0,2
0,1
0,0
0
10
20
30
40
50
60
70
80
mean of latent variable

FIGURE 3

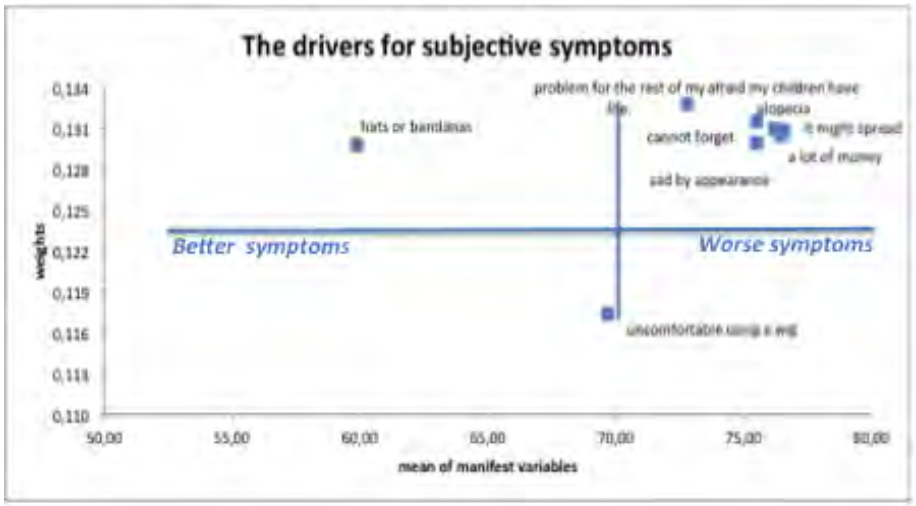

The drivers for subjective symptoms
problem for the rest of my
life
afraid my children have
alopecia
it might spread
hats or bandanas
cannot forget
a lot of money
sad by appearance
Better symptoms
Worse symptoms
uncomfortable using a wig
weights
0,134
0,131
0,128
0,125
0,122
0,119
0,116
0,113
0,110
50,00
55,00
60,00
65,00
70,00
75,00
80,00
mean of manifest variables

FIGURE 4

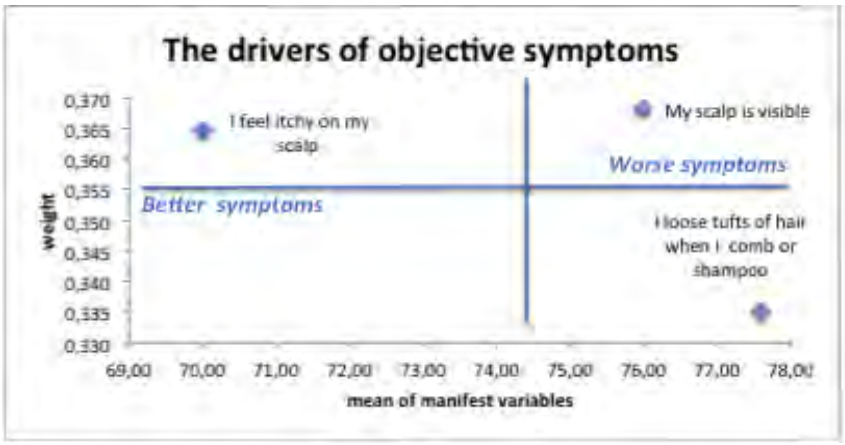

The drivers of objective symptoms
0,370
0,365
0,360
0,355
0,350
0,345
0,340
0,335
0,330
weight
I feel itchy on my scalp
My scalp is visible
Worse symptoms
Better symptoms
I loose tufts of hair when I comb or shampoo
69,00
70,00
71,00
72,00
73,00
74,00
75,00
76,00
77,00
78,00
mean of manifest variables

FIGURE 5

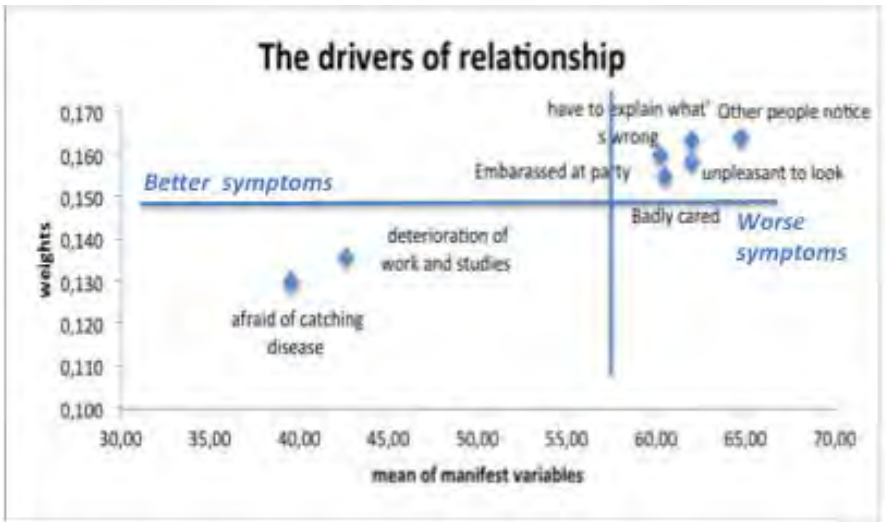
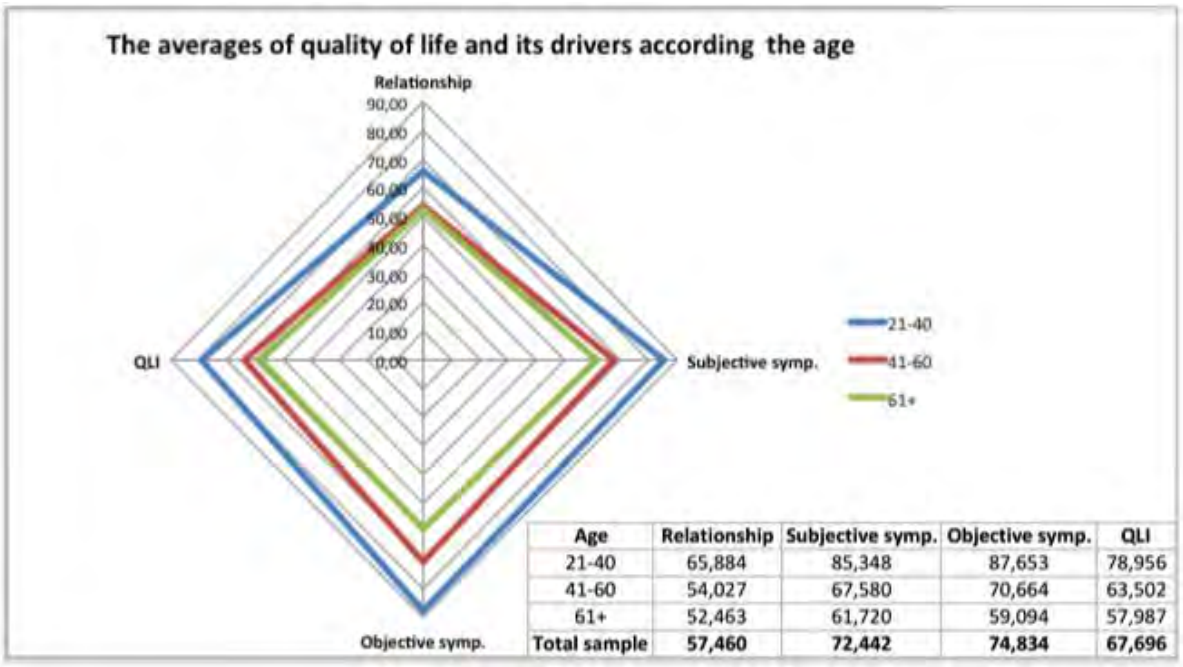

The drivers of relationship
0,170
0,160
0,150
0,140
0,130
0,120
0,110
0,100
weights
Better symptoms
have to explain what' s wrong
Other people notice
Embarassed at party
unpleasant to look
Badly cared
Worse symptoms
deterioration of work and studies
afraid of catching disease
30,00
35,00
40,00
45,00
50,00
55,00
60,00
65,00
70,00
mean of manifest variables

FIGURE 6



Age	Relationship	Subjective symp.	Objective symp.	QLI
21-40	65,884	85,348	87,653	78,956
41-60	54,027	67,580	70,664	63,502
61+	52,463	61,720	59,094	57,987
Total sample	**57,460**	**72,442**	**74,834**	**67,696**

CHAPTER 16
DISCUSSION AND CONCLUSIONS

SUMMARY OF THE STUDIES

This dissertation comprises 14 studies, which together, add significantly to the knowledge base of South African ethnodermatology. Globally people with ethnic skin types outnumber their white counterparts by at least 3 to 1 [50]; in South Africa the ratio is approximately 9:1. Historically dermatological research has focused predominantly on the skin disorders of white people, to the detriment of an understanding of ethnic skin. The studies summarised in this dissertation successfully sought to increase our understanding of skin disorders in South African ethnic population groups.

The initial study sought to describe the spectrum of skin conditions among Africans attending private healthcare facilities in KwaZulu–Natal (Chapter 2). The results provide a baseline for further studies, as well as establishing a rational basis for the selection of interventions, both medical and non-medical, which are required to improve skin health in our population.

Given the propensity of ethnic skin to dyschromia [23], and long-standing concerns about the widespread exposure of our population to potentially harmful skin-lightening preparations [51], we studied women's perceptions of the benefits and risks of skin lighteners (Chapter 3). The study found that despite implementation of legislation, prohibiting the sale of mercury, hydroquinone and corticosteroid-containing products, more than a third of South African women admitted to using skin lightening products purely for non-medical indications. Cultural and historical perceptions among both African and Indian women that fairer skin is preferable to darker skin tone and this is reinforced by media.

We then identified the active compounds in the skin lightening products commonly used by our patients (Chapter 5). According to the SA government's regulations on sale of skin lighteners, it is mandatory for manufacturers to include a sunscreen in the final skin lightening product, a policy driven by and strongly endorsed by the dermatology fraternity. Given its situation at latitude 29°S, mean UV exposure is sufficient to produce a high risk of both photodamage and skin cancer. Public awareness of this risk and of the measures necessary to mitigate it is therefore critical. We conducted a survey to determine the extent of knowledge of and compliance with these measures (Chapter 6). A majority of the African respondents lacked knowledge about skin cancer and appropriate preventative measures. Surprisingly only half of their white counterparts were found to adhere to sun-protective measures despite full knowledge of the dangers associated with sun exposure.

We further undertook two laboratory studies intended to explore the scientific basis for two aspects of indigenous knowledge. Firstly we analysed red and white clays, which are commonly used for sun protection (Chapter 7). We identified the mineral constituents and showed that these do indeed have sunscreen properties, amounting to a low SPF-equivalent, though with the advantage of an extended spectrum spanning both UVA and UVB wavelengths. Given the naturally sun-resistant characteristics of pigmented skin, this low-efficacy but effectively costless, freely-available sunscreen is likely to provide adequate sun protection during periods of sun exposure. Even though the mask like appearance of the clay may not be aesthetically pleasing to the average middle class women this did not deter its use amongst the rural low income group women, who needed it the most.

Secondly we analysed a local plant extract, derived from *Garcinia livingstonei,* which is traditionally used as a skin-lightening compound. The plant extracts were found to be less toxic than hydroquinone furthermore they show potential for further research and development into safer skin lightening agents (Chapter 8).

The final section of our study (Chapters 9-14) was directed at specific aspects of two scarring hair disorders to which African patients are particularly predisposed, namely central centrifugal cicatricial alopecia (CCCA) and frontal fibrosing alopecia (FFA) and how these impact on the quality of life (Chapter 15). We found that CCCA can be inherited as an autosomal dominant genetic disorder which can be aggravated by various hair grooming practices. In addition we found that FFA can be associated with lichen planus pigmentosus, the latter presenting as a herald sign for FFA.

DISCUSSION

The spectrum of skin diseases in a black population in KwaZulu-Natal, South Africa (Chapter 2)

The spectrum of disease in the KZN cohort is similar to that of previous studies conducted in Gauteng province; however the order of occurrence of dermatoses has changed to reflect changing socioeconomic conditions in SA. There is a difference in the ranking of dermatoses in ethnic skin between developed and developing countries. Acne and eczema are reported as the leading causes of dermatoses in countries such as USA and UK whilst countries such as Ghana and Nigeria, Tanzania, Malawi, Uganda and Ethiopia report infections as the leading cause [52]. In our study, not unexpectedly, South Africa occupies an intermediate position in that acne and eczema head the list but skin infections feature among the top five dermatoses. The order of disease occurrence is also reflective of socio-political changes over time, for example pellagra, which was a leading cause of dermatosis between the years 1957 and 1975, was virtually non-existent in 2013. This reflects an improvement in standard of living and nutrition, as well as the redistribution of health care priorities towards primary health care, accelerated by the demise of apartheid. Though a rise in incidence of pellagra has been reported in relation to HIV infection [53], the disease is not nearly as prevalent as it was 50 years ago.

This study is one of few to have documented the spectrum of dermatoses in the broader South African population, is relevant in that the relative prevalence of the various dermatoses is continually evolving, and is the first study to describe the spectrum and prevalence of skin conditions in KwaZulu-Natal, the second most populous province in South Africa. It will inform effective planning of healthcare service delivery, healthcare provider education and social and educational interventions and community for both this province and South Africa as a whole. The study is limited in that it assessed patients in a private practice who for socio-economic reasons may not be relevant of the African population as a whole. However, we have now performed a complementary study in the dermatology clinic of King Edward VIII hospital (currently in preparation for publication), a large public referral hospital in Durban.

The two studies together should provide an accurate appraisal of the importance of the various skin diseases in our population.

Skin lightening compounds in KwaZulu-Natal (Chapters 3-5)

Although skin lightening products are medically indicated in the treatment of hyperpigmentation, they are widely abused as self-medication because of a widespread cultural perception that a lighter skin complexion is preferable to a dark complexion [54]. We have identified both intentional use of skin lightening preparations and inadvertent exposure of the whole face in an effort to treat dyschromia as one of the commonest conditions seen in our patients. This prompted us to investigate skin lightening practices, women's perception of the benefits and risks of using skin lightening creams as well as an analysis of the active compounds of the commonly used skin lightening creams in Durban (Chapters 3-5).

The importance of dermatoses resulting from the abuse of skin lighteners was first reported by Findlay in 1975 [31], with further epidemiological data provided by Schultz in 1982 [44], when dyschromia was still reported as one of the commonest skin conditions, despite government legislation banning the use of hazardous products such as hydroquinone, mercury, resorcinol and phenol.

One of the factors contributing to dyschromia is the inappropriate use of topical steroids in an effort to treat acne. Our survey showed that 23.5% of women used these products to treat acne without full knowledge of the adverse effects on the skin. A similar number of women (26.2%) were found to use these creams in a deliberate effort to lighten the skin. This highlights a major concern: the strong culturally-driven perception that lighter skin is more attractive than darker skin. Furthermore, we found that this perception is not restricted to our African population, and that as many as 40% of women of Indian extraction in our province also deliberately engage in this practice for similar reasons.

We then investigated the active chemical compounds in the top-ten-selling over-the-counter skin lightening creams. The last study investigating skin lightening products was undertaken by Findlay *et al.* 33yrs ago [32]. We found that hydroquinone, formerly in common use, is no longer an ingredient of the most popular brands. Mercury however was detected in half the products. We also observed serious deficiencies in the labelling of products, which frequently failed to list the active compounds and their concentrations. Easy access to these products by the population, as well as a lack of package labelling by industry, will continue to give rise to dermatoses related to skin bleaching. We therefore recognise an imperative for more vigilant regulation of both industrial and retail practice as well as public health campaigns to educate consumers about the adverse effects of skin lightening products.

To obviate the adverse effects of skin lightening, it is recommended that they should be used together with a broad-spectrum sunscreen [55]. Since the last study by Findlay, further recommendations were made regarding complementary use of sunscreens when using skin lighteners and have been incorporated into the South African regulatory framework [56-58]. Yet our study showed that although one in every three African South African women admits to using skin lightening products, only 21% use sunscreen. The potential risks of this are

emphasised by a case report of squamous cell carcinoma following prolonged use of hydroquinone without a sunscreen [55], and an increased prevalence of skin cancer among African-Americans and Africans has indeed been documented [13].

Cancer awareness and sunscreen use (Chapter 6)

In anticipation of this, we set out to determine the level of awareness of skin cancer, of sunscreen use and the frequency of risk appropriate and risk-inappropriate behaviour among our population (Chapter 6). We found that a high proportion of African participants lacked knowledge about skin cancer and measures for its prevention. A widespread misconception that Blacks do not get skin cancer has contributed to the high levels of ignorance regarding skin cancer in this population [59]. This is compounded by a of skin cancer prevalence studies among Africans, resulting in a lack of scientific evidence to dispel this belief.

Whereas the white subgroup, who are known to be a higher risk for skin cancer, possessed a better knowledge of skin cancer, they were poor in their implementation of preventative measures. Only 12% claimed to practise self-examination for skin cancer and just 6% reported having consulted a doctor for skin examination.

Ethnopharmacology and indigenous knowledge systems: Use of traditional medicinals for sun-protection and skin-lightening (Chapters 7-8)

More than a quarter of African women reported using traditional sunscreen in the form of red clay (*ibomvu*) and white clay (*umcaku*) to prevent hyperpigmentation and sunburn. This was almost exclusively reported by African women, and only one Indian woman reported using clay as sunscreen. We studied these clays to determine whether there is a scientific rationale for their use. Clay minerals are widely used in the pharmaceutical industry for a variety of purposes in oral and topical applications, as excipients and in aesthetic medicine [60]. We studied two clays from riverside banks, red and white. These were found to contain oxides and silicates of aluminium (kaolinite) with additional iron oxide (haematite) confined to red clay. Although the clays afford only a modest SPF (3.6-4) against ultraviolet B, they also protected against longer UVA wavelengths, which are themselves not harmless, being implicated in skin cancer and hyperpigmentation disorders such as melasma, apparently without any adverse effect. Given the sun-protective effect afforded by the endogenous melanin of our African subjects, this modest additional protection would appear to be sufficient for its purpose, thus vindicating its use in traditional communities.

A number of our subjects reported using the plants *ummemezi* and *umqonga* as traditional medicinals for skin lightening. The use of plants in traditional medicine is a widespread phenomenon, with an estimated 75 000 tonnes of material consumed annually in South Africa and 72% of the black South African population making use of traditional health care systems, often in parallel with conventional allopathic medicine [61, 62]. We believe that this is the first time that traditional plants and minerals have been investigated solely for dermatological indications, and is the first study to validate the inhibitory effect of organic extracts and compounds isolated from the stem bark and fruit of *Garcinia Livingstonei* on melanin. The investigation showed that *Morelloflavone 7* sulphate and *Sargaol* extracts exact their

antimelanogenic effects by inhibiting tyrosinase. This suggests that these compounds are indeed biologically active; potentially product development opportunities should be explored: this, and indeed bioprospecting more generally, may yield compounds of both therapeutic and commercial value, with the further potential to empower indigenous communities through benefit sharing.

Ethnic hair disorders (Chapters 9-15)

Our study placed hair disorders among the five most prevalent dermatoses in KwaZulu-Natal, with alopecia being the most common of these. Though the field is both complex and extensive, we set out to describe the two common causes of scarring alopecia, CCCA and FFA and their impact on quality of life.

Central centrifugal cicatricial alopecia (CCCA) (Chapters 9-10)

CCCA is the most common type of primary scarring alopecia in women of African descent [63]. The exact prevalence of CCCA is still unclear, however figures varying from 2.7% to 5.7% have been documented, as well as its association with increasing age [64]. It is one of the five commonest conditions with which African Americans present to dermatologists [63]. While a genetic basis has been for the condition has been suggested, little is currently known about the disease genetics. We have shown evidence for a heritable component, initially in two families, followed by a series of 30 patients who showed a positive family history of this condition; pedigree analysis suggested an autosomal dominant mode of inheritance. However, we have shown that hair grooming habits markedly influence disease expression. To our knowledge this is the first study in the literature to show a genetic association with CCCA. The permanent, extensive hair loss that results in many patients makes CCCA, from the point of view of the patient, a very serious disorder and a full understanding of its aetiology, and therefore, potentially, of appropriate prevention and management, imperative. Our findings may serve as a useful foundation for further studies in this area.

Frontal fibrosing alopecia (FFA) (Chapters 11-14)

Previous studies on FFA are predominately based on studies in white and Asian patients; FFA is uncommon in patients of African descent [65]. Our study of FFA constitutes the first series of black patients in Africa. We have further reported the occurrence of FFA in an African male. Possibly the lack of recognition of FFA in African patients is due to the overlapping clinical presentations of FFA and traction alopecia, which is extraordinarily common in this population[65].

We have shown that, most African women with FFA are premenopausal, which is in contrast to the experience in white women [66]. We were also unable to confirm a loss of follicular ostia [66], as a sign of scarring; further study will be required to resolve this discrepancy. Furthermore we confirmed the observation by Khumalo *et al. (2007*) that traction-inducing hairstyles may aggravate the severity of FFA, particularly when traction alopecia is further aggravated by joining of weaves and braids to chemically treated hair.

Our data raises two interesting possibilities. Firstly, our report of three families with FFA may suggest a genetic aetiology for this challenging hair condition. Secondly, we have identified the co-occurrence of FFA with cutaneous lichen planus pigmentosus (LPPigm) as well as a possible familial association in patients of African ancestry. To our knowledge this is the first such report, though a combination of genetic and environmental factors have been postulated [67]. The well-defined, sequential, histologically confirmed clinical progression from LPPigm to FFA, raise the possibility that LPPigm and FFA share the same aetiology.

Quality of life in African patients with alopecia Chapter 15)

Finally we performed a pilot study to ascertain the influence and impact of skin diseases on patients' quality of life (QoL), using QoL indicators as described in previous publications [68-71]. Hair plays a vital role in aesthetics, and few skin conditions cause as much emotional distress as alopecia, especially in women, where several studies have shown an association with poor self-esteem and impaired quality of life [72-77]. Such distress can be easily aggravated by non-compassionate health care practitioners who may underestimate the impact of hair loss on such patients. Information on the psychological effects of hair loss on African patients is lacking. This may be in part a consequence of interest primarily focusing on diseases perceived as more common and of a higher priority, such as those of infectious origin [52]. The method employed in our pilot study appears valid, and has shown that alopecia in African women, as has been shown in other groups, has a significant, deleterious impact on quality of life, and suggests a need for focused interventions on the part of health care practitioners to mitigate this. Well-designed, larger cross-sectional and longitudinal studies are necessary to extend this work. In a recent editorial, Finlay summarises the evolution of QoL indices and their underlying methodology, and emphasizes the need for rigorous reporting of these using a set of criteria as yet to be agreed [78]. Such follow-up studies will conform to these standards.

STUDY LIMITATIONS

The studies contained in this thesis have a number of potential biases. The spectrum of disease was calculated from a sample of patients attending a single private clinic; with consequent potential selection bias. We have however now completed a complimentary study in a large public sector hospital; a study currently being prepared for publication. With the proviso that both studies were limited to single facilities, it is unlikely that they will be a major deviation from the actual experience within the province. Diagnoses reported in this study were in most instances those recorded in the patients' hospital records, and have not been independently reviewed and validated; there is the potential for some of these to be inaccurate, and some relevant clinical data may have been missing from the patient records.

All questionnaire-based surveys have their limitations, such as recall bias and the editing of replies for fear of judgement and feelings of embarrassment. The latter is a particular problem when questionnaires are administered face-to-face; on the other hand this format does allow the administrator to explain questions with the potential to be understood to the subject, allowing a more accurate response.

We were only able to obtain useful data on 10 skin-lightening products, and our findings may not be fully representative of the full spectrum of products in the market. This work continues, and we are currently analysing 40 more products in South Africa in order to establish a better understanding of the extent of the problem.

GENERAL CONCLUSIONS

Hay *et al*. have stated that skin conditions are the 4th leading contributor to the world's non-fatal disease burden and argued that their prevention and treatment deserves urgent attention [3]. In South Africa little is known about the spectrum and prevalence of skin diseases. The South African Medical Research Council has reported that skin diseases caused premature mortality in 790 cases of 12 million deaths in the year 2000 (Bradshaw *et al*. 2003). This is not a true reflection of the prevalence of skin diseases, since the above figures only reflect mortality. It is well known that skin disease affects quality of life and has economic and social impacts on patients [68, 69, 71, 79].

The work included in this dissertation represents the first study to assess the spectrum of skin disease seen in an ethnic population in KwaZulu-Natal. It is unlikely that results would differ significantly elsewhere in South Africa, and this work is therefore relevant and useful; it has already demonstrated clearly the changing profile of dermatoses in the African population over the past few decades. We have shown that acne, eczema, dyschromia, infections and hair disorders are, in order, the most prevalent dermatoses in KwaZulu-Natal. Steroid acne caused by inappropriate use of steroid creams to treat various skin conditions and for skin bleaching is a cause for concern. As anticipated, very few patients presented with skin cancers, confirming the very low prevalence of cancer in patients from dark-skinned ethnic populations, such as those of African ancestry.

There is a need to sensitize health care providers to ethnodermatology, to provide additional training and resources, and to include this important subject within undergraduate medical programme. This information should be used to inform effective planning and screening for skin diseases and offer pertinent recommendations for the needs of the country as a whole.

We have shown that the highly prevalent use of skin-lightening products among African and Indian South African women is not accompanied by appropriate knowledge of their risks and of the precautions which should be taken to reduce adverse effects. There are extraordinary difficulties in reducing the inappropriate use of skin lighteners as a result of deeply rooted, albeit misplaced, cultural perceptions about the desirability of a light complexion in black women. Culturally-linked perceptions of the social value of fair skin are pervasive, and are perpetuated by the use of fair-skinned models to market cosmetics to black consumers and the over-representation of light-complexioned black women on film and television. Extensive public education, coupled with effective policing of both the formal and informal markets where these products are bought is imperative. That these products are also used widely by Indian women in KwaZulu-Natal had not hitherto been suspected. Clearly this is a group which must be included in educational and social campaigns to reduce or at least promote safer use.

Through laboratory investigations of commonly used traditional plants, we have isolated a range of compounds from the stem bark and fruit of *Garcinia livingstonei* some of which proved less toxic and more potent than the standard universally used hydroquinone. This opens up potential for future research to develop safe innovative treatments for dyschromias, based on natural resources from indigenous plants. Similarly we have shown that clay products, long used for sun protection in African society, provide a useful degree of UVA protection. These clays play an important role for rural South African women in resource poor areas because they are cheap; easily accessible and culturally acceptable. Commercial sunscreens essentially unaffordable for many potential users in the developing world, and the potential for the development of a cheap, effective preparation utilising this abundant mineral resource deserves consideration.

We are particularly concerned by the serious gap in both knowledge and behaviour regarding skin cancer we identified among our population. This failure to understand the risk of skin cancer was most marked among our African population, and probably results from the perception that these issues are not relevant in blacks, thus emphasising the need for effective, culturally sensitive education and screening efforts. It is however worrying that the white population, though better informed, exhibits an essentially complacent attitude toward sun protection despite the very high lifetime risk of skin cancer to which they are subject.

Hair plays a vital role in aesthetics. We have shown that alopecia significantly impairs QoL by lowering self-esteem among black women in South Africa, and it is important that health care medical practitioners are aware of its psychological impact. CCCA is more common in women of African descent and has been linked to excessive use of hair-straightening relaxers. We have shown a possible genetic link to the etiology of CCCA, have provided the first published descriptions of FFA in Africans and have identified a probable association between FFA and LPPigm; this opens up the possibility that early detection may be possible, and allow the prevention of irreversible scarring alopecia. At the practical level, proper delineation of the contribution of a range of hair grooming styles to disease development and progression will assist us in establishing effective preventative and treatment strategies.

The genetic associations we have shown for CCCA and FFA require further study. We are presently looking at 20 families with CCCA and 15 families with FFA to analyze the gene expression patterns in CCCA and FFA through study of RNA samples obtained via 4mm scalp punch biopsies of affected subjects and age, race, and gender-matched controls. We are also in the process of identifying the genetic basis of CCCA as well as establishing a bank of DNA samples from patients with CCCA for the purpose of future research.

IMPLEMENTATION OF RESEARCH FINDINGS

Clinical practice

All dermatologists operating under the guidance of the Division of Dermatology are now with a list of products which contain banned skin lightening creams and are required to work through this list with any patient they see who has been using skin lighteners. We have also

hired a counsellor who will assist with proper counselling of patients and explain their conditions in their mother tongue.

Regulation

I have initiated a discussion with the Dermatology Society of South Africa (DSSA) and the analytical chemists with whom I have been collaborating to have all commonly-used skin lightening products analysed. Those which are legitimate will then be issued with a stamp of approval *endorsed by DSSA.* This will indicate to consumers which products are safe for use.

I am recommending measures to ensure that pharmacists are closely monitored so that they do not issue steroid and hydroquinone-containing creams without a valid prescription. (This was found to be a very common practice.) Similarly doctors in general practice need to be counselled against dispensing steroid creams from their rooms without seeing the patients, and issuing unlabelled creams, and then monitored for compliance.

Current and planned research projects

Skin cancer

Albinism

In co-operation with the Albinism Society, we are planning a database of all patients with albinism in the province of KZN. A priority is the study of the clinical types and evolution of skin cancers in these patients. We are also contemplating on conducting further research on albinism using the database which we are working on.

Ethnopharmacology

There is a need for further research on traditionally used medicines, and a thorough assessment of the potential for commercialisation of the extracted compounds.

Hair

CCCA

We are presently collaborating with Prof Amy McMichael at the University of North Carolina, and Prof Eli Sprecher in Tel Aviv, to analyze the gene expression patterns in CCCA through study of RNA samples obtained via 4mm scalp punch biopsies of 12 affected subjects and 12 matched controls. In addition, we will establish a bank of DNA samples from patients with CCCA for the purpose of future research.

FFA

We are working with Prof John McGrath, St Thomas Hospital. London, to analyse the gene expression patterns in families with FFA.

Spectrum of skin disease in the public sector

This is a follow up study on the study conducted in the private sector and is in preparation for publication. This will give a balanced overview of the spectrum of skin conditions seen in KwaZulu-Natal.

Education

We are modifying our undergraduate curriculum to reflect relevant findings. I am first author of a chapter *Common skin diseases and treatment in Africa* in Taylor and Kelly's *Dermatology for skin of color*, currently in press which covers skin conditions relevant to Africa and is directed towards the promotion of practice that is appropriate to the health of ethnic skin, to African culture and the African environment [80]. We are also producing a textbook comprising lecture notes for use in southern Africa and have received sponsorship for this. We have a programme of offering Dermatology workshops to provide continuing education to medical practitioners, emphasizing the importance of common ethnic skin conditions which were previously not adequately covered in the undergraduate curriculum.

Dermatological surgery has not previously formed part of our postgraduate curriculum for trainee dermatologists leading to deficiencies in the training of registrars for the management of the skin cancers seen in our albino African and white patients. We have therefore established a dermatological surgery training programme in collaboration with the dermatological surgery faculty at Harvard Medical School, which will initially run over a period of 5 years. This is the first programme in Africa, and we are hoping to export this expertise to dermatologists drawn from the rest of South Africa and indeed the rest of Africa.

Patient education and support

We have completed 25 patient-education pamphlets or posters and 10 video presentations dealing with common skin conditions to be made available to dermatology outpatient clinics, which the KwaZulu-Natal Department of Health has undertaken to make available at all its health care institutions , and will be recommending to the National Department of Health for national use.

Skin cancer

Albinism

The albino population is at greatest risk, presenting with advanced skin cancer, owing to poor access to health facilities, ignorance and poor socioeconomic factors. We are investigating ways of developing and teaching community workers who will in turn conduct educational workshops on skin care and skin cancer awareness for albinos in the rural areas. We will be working closely with social workers and psychologists. The *Albinism* folder which we have developed is aimed at assisting the community workers. We will be raising funds to assist with supply and or donation of sunscreens and protective sun hats to all rural patients who cannot afford to purchase these.

Skin cancer in the white population

We are implementing outreach programmes to educate the public about skin cancer and use of sunscreens. We already run a "beach spot examination programme" at holiday times which will be strengthened. We are planning a series of talks to schools targeting children with a view to educating them about the dangers of sun tanning and artificial tanning booths.

Care of the skin and use of skin lighteners

We have written a chapter on the care of the skin and hair for a children's textbook intended to raise interest in science, technology, engineering and mathematics among primary school children in South African schools. One aspect of this is a perceived need to empower girls to rise above inappropriate societal expectations, such as those surrounding the supposed desirability of a light complexion. Our contribution reinforces the important message that *the best skin is the one that you are born with*. We have also approached the producer of the popular TV soap opera *Generations*, widely viewed every weekday by a significant part of the African population, with the suggestion that material raising awareness of the dangers of skin lighteners be incorporated into the script. This suggestion was well-received. We have also written articles for popular magazines and participated in podcasts, TV and radio interviews to increase the awareness of the implications of our research findings among the public.

GENERAL CONCLUSIONS: ETHNODERMATOLOGY

The above studies show a growing need for the field of ethnodermatology, particularly in Africa. As previously mentioned general dermatology research has focused primarily on white skins neglecting a large proportion of a growing population. There has been a significant inclusion of black people within the middle class sector and this invariably calls for an increase in the knowledge and understanding of black skin. Indigenous knowledge systems and ethnobotany have the potential to enhance this untapped field.

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APPENDICES

APPENDIX 1

Selected international and national congress presentations emanating from this work

1. Dlova NC. *Use of clay as sunscreen by South African black rural women*. **Accra**, Ghana, (2010).

2. Dlova NC. Central centrifugal cicatricial alopecia: possible familial aetiology. Ethnic Skin and Hair meeting, **Nairobi**, Kenya (2012).

3. Dlova NC. *An enlightening tour of the skin lightening industry in SA*; *Lichen Planus Pigmentosus and Frontal Fibrosing Alopecia*; *Use of botanicals as skin lighteners in SA*. 3rd Continental Congress of the International Society of Dermatology (ISD) and the 65th National Congress of the Dermatology Society of South Africa (DSSA), **Durban**, South Africa (2012).

4. Dlova NC. *A chemical analysis of clays traditionally used for sun protection by rural African women in South Africa*; *A chemical analysis of commonly used skin lightening creams in South Africa: looking for the presence of banned skin lightening compounds*. Brazilian Dermatology congress, **Rio de Janeiro**, Brazil (2012).

5. Dlova NC. *Autosomal dominant inheritance of central centrifugal cicatricial alopecia*. American Academy of Dermatology Skin of Color Society, **Miami**, USA (2013).

6. Dlova NC. *Abuse of skin lighteners in South Africa.* European Academy of Dermatology and Venereology, **Istanbul**, Turkey (2013).

7. Dlova NC. *Autosomal dominant inheritance of central centrifugal cicatricial alopecia*. UKZN College Research Symposium, **Durban**, South Africa (2013).

8. Dlova NC. *Dermatoses in black skin*. International Society of Dermatology, **New Delhi**, India (2013).

9. Dlova NC. *Autosomal dominant inheritance of central centrifugal cicatricial alopecia in black South Africans*. Congress of the Dermatological Society of South Africa, **Cape Town,** South Africa (2013).

10. Dlova NC. *Evaluation of hair loss*. South African Dermatological surgeons, **Port Elizabeth**, South Africa (2013).

11. Dlova NC. *Using genetics to unravel scarring alopecia: focus on CCCA*. 4th International Ethnic Skin and Hair Conference**, London**, UK, (2014).

12. Dlova NC. *Cosmetic habits of black South African women*. 10th World Congress of the International Academy of Cosmetic Dermatology, **Rio de Janeiro**, Brazil (2014).

13. Dlova NC. *Hair loss in blacks*. 3rd Annual DASIL (Dermatologic & Aesthetic Surgical International League) Congress, **Sun City**, South Africa (2014).

14. Dlova NC. *Dermatoses in black skin*; *Frontal fibrosing alopecia and lichen planus pigmentosus.* 4th Continental Congress of the International Society of Dermatology (ISD), **Manila**, Philippines (2014).

15. Dlova NC. *Problems in Ethnic skin and Hair.* ISD, **Munich**, (Forthcoming, 2015; invited speaker).

16. Dlova NC. Symposium: *Alternative therapies;* Symposium: *What's new in Dermatology: New diseases in Ethnic skin and hair;* Symposium: *African Hair*. 23rd World Congress of Dermatology, **Vancouver**, Canada (Forthcoming, 2015; invited speaker).

17. Dlova NC. *Pigmentary Disorders in Africa.* International Tropical Dermatology, **Sri Lanka** (Forthcoming, 2016; invited speaker).

APPENDIX 2

Chapter contributions in textbooks

1) Dlova N, Mosam A, Ajose F. (in press). Common skin diseases and treatment in Africa. In: Taylor S, Kelly P (Eds.), Dermatology for skin of color. New York: McGraw-Hill.

APPENDIX 3

Patents emanating from this dissertation

1. South African Provisional Patent Application No. 2011/08423. “Skin Lightener” in the name of UNIVERSITY OF KWAZULU-NATAL.

2. South African Patent Application No. 2011/08263. Patent registered and approved for use of clay as a physical sunscreen. "CLAY SUNSCREEN" in the name of University of KwaZulu-Natal.