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MALAYSIAN JOURNAL OF DERMATOLOGY

ORIGINAL ARTICLE

CASE REPORT

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ORIGINAL ARTICLE

Relationship between *Staphylococcus aureus* Colonization and Face Mask-associated Adverse Cutaneous Reactions during the COVID-19 Pandemic

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Abstract

Background

Adverse reactions on the skin due to face masks are well documented following the COVID-19 pandemic. This study aims to investigate *Staphylococcus aureus* colonization in relation to face mask-associated adverse cutaneous reactions (FMACR).

Methods

This was a case-control study involving adult patients attending dermatology clinic, Hospital Tengku Ampuan Afzan, Pahang, Malaysia. FMACR was determined via a structured interview. Subjects and healthy controls were matched for age and gender. Skin swabs from the alar crease and glabella were obtained and cultured. The possible risk factors for FMACR including type of mask, frequency of change, average duration of use, and skin care practices were also attained.

Results

A total of 114 adult participants, which consisted of 57 case and 57 control were recruited. Itching was the most frequent (32; 32.4%) FMACR noted, followed by acne (31; 31.4%) and rashes (22; 22.2%). The presence of facial dermatoses and oily skin type increased the risk of FAMCR (adjusted OR=5.96, 95% CI (1.96,18.12), *p=0.002* and adjusted OR=1.94, 95% CI (0.28,13.28), *p=0.009*) respectively. Cosmetic use was associated with lower risk of FMACR, (adjusted OR=0.16, 95% CI (0.05, 0.56), *p=0.004*). No significant association was noted between *S. aureus* skin colonization and FMACR (*p=0.409*).

Conclusion

Staphylococcus aureus skin colonization was not associated with FMACR. Risk factors for FMACR were the presence of facial dermatoses and oily skin type while cosmetic use appears to have a protective effect.

Key words: *COVID-19, face mask, Staphylococcus aureus*

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Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-Cov-2) is the virus that causes COVID-19. The COVID-19 virus spreads primarily through droplets of saliva or discharge from the nose when an infected person coughs or sneezes. Face masks have been shown to provide protection from human-

to-human respiratory viral transmission.[1] In March 2020, during the initial stage of the COVID-19 outbreak in Malaysia, face masks were only required for frontliners and suspected cases with symptoms. Given the rapid rise in the incidence of COVID-19 infection, the Malaysian government has made the wearing of face masks mandatory in public spaces effective from 1st August 2020. Thus, the wearing of face masks during the COVID-19 pandemic became a new norm for the Malaysian population.

Due to the increased use of face masks and other personal protective equipment (PPE) during the COVID-19 pandemic, especially among health care workers, several studies have reported adverse skin reactions due to the wearing of face masks.[2-10] The types of face mask-associated adverse cutaneous reactions (FMACR) reported included itching, rashes on the face, pressure-related skin injury, and acne, among others. There are also reports of the worsening of underlying facial dermatoses related to face mask usage and some other studies have investigated possible contributing factors for FMACR.[2-13] Other studies have also looked into the influence of face mask use on skin characteristics, including trans-epidermal water loss, sebum secretion, skin temperature, and others, to look for possible relationships to FMACR.[14-16] Avoidance of all these risk factors could potentially help in decreasing FMACR. However, none had studied the role of *Staphylococcus aureus* (*S. aureus*) in the development of FMACR.

Studies have shown the role of *S. aureus* as a potential mechanism for both primary and secondary inflammation in skin diseases.[17] In atopic dermatitis (AD), patients with the disease are more likely to be colonized with *S. aureus* than healthy controls, and colonization increases with AD severity.[18] Studies have also shown an increased risk of *S. aureus* colonization in patients with psoriasis.[17,19] The same study also reported a statistically significant relationship between a higher psoriasis area and severity index (PASI) score and colonization by enterotoxin-positive *S. aureus*.[19]

Considering the potential role of *S. aureus* in amplifying symptoms in other chronic inflammatory skin diseases, we aim to determine the role of *S. aureus* skin colonization in FMACR. We also aim to identify various other factors which may contribute to FMACR, namely, demographics, mask use practice, and skin care practice.

Materials and Methods

Study Design and Subject Selection

This was a single-centre, hospital-based case-control study conducted at the Dermatology Clinic of Hospital Tengku Ampuan Afzan (HTAA), Kuantan, Pahang, Malaysia between 1 July 2021 and 31 December 2021. Written informed consent was obtained from the participants. Ethical approval was obtained from the Medical Research and Ethical Committee (MREC), Malaysia with research code NMRR-21-1208-59944.

The selection of case and control groups was based on convenience sampling. All participants age 18 and older were eligible. The subjects of the case group were patients who attended the clinic and subsequently diagnosed with FMACR via a structured interview. The control group consisted of participants who did not suffer from FMACR determined via the same structured interview and they matched the patients with respect to age and gender. Exclusion criteria included those who have been on any antibiotics within the past 6 weeks that may alter *S. aureus* colonization in both groups.

A face-to-face interview was performed to determine baseline variables including age, sex, comorbidities, and underlying skin diseases. Body mass index (BMI; weight (kg)/height (m^2)) and waist circumference (cm) were recorded. The possible risk factors for FAMCR, including mask practices such as type of mask, frequency of change, average duration of use, and skin care practices such as the use of facial cleanser, moisturizer, sunscreen, and cosmetic products, were also obtained in the interview.

Skin swab for *Staphylococcus aureus* colonization

The investigators obtained skin swabs from the right alar crease (left alar crease swabbed if there was a presence of skin disease at the right alar crease) and glabella with the use of two labelled sterile cotton wool swabs (Citoswab regular dry swab; Citotest labware manufacturing, Haimen, China). The specimens were placed in the transport medium (Citoswab Stuart gel; Citotest labware manufacturing, Haimen, China) and delivered to the laboratory where they were inoculated onto sterilized blood agar plates, subsequently incubated at 37^0C for 24 hours. All cultures were carried out at the microbiology department of HTAA.

Sample size

This is a pilot study to look for the role of *S. aureus* colonization in FMACR. Hence, the sample size of this study is calculated based on a similar case-control study carried out by Ali, Emad *et al*: Prevalence of *Staphylococcus aureus* in Atopic Dermatitis (Eczema) cases in Al- Najaf City/Iraq.[20]

Sample size estimation was calculated using two population proportions formulae. Prior data indicate that the proportion of Ali, Emad *et al*. of the (Group I) group was 0.54 and the proportion of (Group II) group was 0.2. Thus, a minimum sample size of 41 samples per group to be able to reject the null hypothesis with probability (power) 0.8. The Type I error probability associated with this test of this null hypothesis is 0.05. With an additional of 20% dropout rate, the sample size is 52 samples per group.

Statistical analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS Version 24.0, IBM Corp). Descriptive statistical methods, such as means, standard deviations (SD), medians, and frequencies, were used to describe the characteristics of the study population and data set. Both Simple Logistic Regression Analysis (univariable analysis) and Multiple Logistic Regression Analysis (multivariable analysis) were performed to test the associations between the proposed factors with FMACR and *S. aureus* colonization respectively. Simple Logistic Regression analysis identified potential significant associated factors ($p < .25$). These potential significant associated factors were then included in multiple logistic regression to confirm whether these are significant independent associated factors ($p < 0.05$).

Table 1. Demographic and clinical characteristics of the study population

Demographic data	Total (N=114)		*p–value*
	Case (n=57) Mean ± SD / n (%)	Control (n=57) Mean ± SD / n (%)	
Age, in years[a]	33.37±12.05	31.60±11.15	0.417
Gender			
Male	19 (33.3)	19 (33.3)	1.000
Female	38 (66.7)	38 (66.7)	
Race			
Malay	46 (80.7)	50 (87.7)	0.442
Chinese	10 (17.5)	7 (12.3)	
Indian	1 (1.8)	0 (0.0)	
Comorbid	22 (38.6)	18 (31.6)	0.432
Smoking	4(7.0)	5 (8.8)	1.00
Weight (kg)	67.86±16.45	68.04±9.83	0.956
BMI (kg/m2)	26.23±5.66	26.46±6.24	0.834
Abdominal Girth (cm)	86.68±14.54	87.47±15.79	0.779

Table 2. Types of face mask-associated adverse cutaneous reactions (FMACR)

FMACR	Cases (N = 57) n (%)
Itching	32 (32.4)
Acne	31 (31.4)
Dermatitis on face	22 (22.2)
Rashes behind ears	5 (5.0)
Hyperpigmentation	5 (5.0)
Pressure related skin injury	4 (4.0)

Results

A total number of 114 participants were enrolled, 76 (66.7%) were female and 38 (33.3%) were male. The mean age of FMACR and the control group was 33.37±12.05 and 31.60±11.15, respectively, with no statistically significant age difference (*p=0.417*). The case and control groups had similar mean BMIs of 26.23±5.66 and 26.46±6.24, respectively

Table 3. Factors associated with FMACR

Factors	Simple Logistic Regression		Multiple Logistic Regression	
	Crude OR (95% CI)	*p-value*	Adjusted OR (95%CI)	*p-value*
Comorbid				
No	1		-	-
Yes	1.36 (0.63, 2.95)	0.433		
Smoking				
No	1		-	-
Yes	0.79 (0.20, 3.09)	0.729		
BMI	0.99 (0.93, 1.06)	0.832	-	-
Abd circumference	0.99 (0,97, 1.02)	0.777	-	-
History of Skin Disease				
No	1		-	-
Yes	1.00 (0.33, 3.06)	1.000		
History of Facial dermatoses				
No	1		1	
Yes	6.81 (2.74, 16.92)	<0.001	5.96 (1.96, 18.12)	0.002
Skin Type				
Normal	1		1	
Oily	5.44 (2.11, 14.01)	<0.001	4.50 (1.45, 13.93)	0.009
Dry	0.75 (0.18, 3.17)	0.690	0.46 (0.07, 2.87)	0.407
Combination	5.22 (0.97, 28.01)	0.054	1.94 (0.28, 13.28)	0.498
Mask type				
Surgical mask	1			
Cloth mask	0.70 (0.15, 3.32)	0.655	-	-
Double mask	1.64 (0.45, 5.98)	0.455		
KN94	0 (0, 0)	0.999		
Frequency of change				
A few times a day	1		1	
Everyday	0.46 (0.20, 1.07)	0.071	0.44 (0.16, 1.25)	0.124
Every 2-3 days	0.14 (0.01, 1.43)	0.098	0.30 (0.02, 4.07)	0.368
Every week	0 (0, 0)	1.000	0 (0, 0)	1.000
Average time of use per day				
< 4 hours	1		1	
4-8 hours	1.28 (0.59, 2.78)	0.525	1.52 (0.55, 4.18)	0.421
>8 hours	2.93 (0.53, 16.26)	0.219	8.21 (0.80, 84.82)	0.077
Moisturizers				
No	1		1	
Yes	1.95 (0.91, 4.18)	0.086	2.69 (0.80, 9.11)	0.111
Sunscreen				
No	1		-	-
Yes	1.47 (0.68, 3.16)	0.330		
Facial Cleanser				
No	1		1	
Yes	1.69 (0.74, 3.87)	0.213	1.31 (0.38, 4.55)	0.668
Cosmetic products				
No	1		1	
Yes	0.44 (0.19, 0.99)	0.046	0.16 (0.05, 0.56)	0.004
***Staph Aureus* Colonisation**				
Negative	1			
Positive	1.59 (0.53, 4.82)	0.409	-	-

(*p=0.834*). There was no significant difference in the presence of comorbidities, which include type II diabetes mellitus, hypertension, chronic respiratory disease, and autoimmune diseases, among others, between the FMACR and control groups (*p=0.432*). The demographic and clinical characteristics of study population are shown in more detail in Table 1 below.

Among the types of adverse skin reactions found in the FMACR group, itching was the most frequent adverse skin reaction found (32; 32.4%), followed by acne (31; 31.4%), and dermatitis on the face (22; 22.2%) (Table 2). Among the patients who presented with FMACR acne, 16 (51.6%) also complained of itching.

Table 4: Factors associated with *S. aureus* colonization on the face

Variables	Simple Logistic Regression		Multiple Logistic Regression	
	Crude OR (95% CI)	*p-value*	Adjusted OR (95%CI)	*p-value*
Comorbid				
No	1		-	-
Yes	0.91 (0.29, 2.89)	0.879		
Smoking				
No	1		-	-
Yes	0.81 (0.09, 7.00)	0.850		
BMI	0.96 (0.86, 1.05)	0.298	-	-
Abd circumference	0.99 (0.95, 1.02)	0.456	-	-
History of skin Disease				
No	1		-	-
Yes	0	0.999		
History of facial dermatoses				
No	1		1	0.104
Yes	1.92 (0.64, 5.76)	0.245	3.22 (0.79, 13.15)	
Skin Type				
Normal	1		1	
Oily	1.60 (0.40, 6.41)	0.507	1.90 (0.35, 10.35)	0.459
Dry	7.73 (1.62, 36.82)	0.010	7.19 (1.14, 45.42)	0.036
Combination	3.87 (0.61, 24.41)	0.150	3.41 (0.36, 32.75)	0.287
Mask type				
Surgical mask	1		1	
Cloth mask	3.64 (0.62, 21.58)	0.154	4.73 (0.61, 36.48)	0.136
Double mask	2.03 (0.38, 10.86)	0.410	3.64 (0.51, 26.18)	0.199
KN94	6.07 (0.89, 41.31)	0.065	2.89 (0.20, 41.64)	0.437
Frequency of change				
A few times a day	1			
Everyday	1.00 (0.29, 3.53)	0.995	-	-
Every 2-3 days	1.81 (0.16, 20.55)	0.631		
Every week	0	1.000		
Average time of use per day				
< 4 hours	1			
4-8 hours	0.53 (0.16, 1.81)	0.312	-	-
>8 hours	0.88 (0.10, 8.15)	0.913		
Moisturizers				
No	1		-	-
Yes	0.51 (0.15, 1.73)	0.282		
Sunscreen				
No	1		1	
Yes	0.24 (0.05, 1.11)	0.067	0.25 (0.04, 1.52)	0.131
Facial Cleanser				
No	1		1	
Yes	0.28 (0.09, 0.85)	0.025	0.35 (0.08, 1.55)	0.165
Cosmetic products				
No	1		1	
Yes	0.29 (0.06, 1.38)	0.121	0.62 (0.10, 3.97)	0.609
Affected by FMACR				
No	1		-	-
Yes	1.59 (0.53, 4.82)	0.409		

Simple and multiple logistic regression among factors associated with FMACR are presented in Table 3. There was no statistically significant correlation between mask practices, including types of masks used, frequency of masks changed, and average duration of face masks used, with having an adverse skin reaction on the face *(p>0.05)*. In terms of skin care practices, cosmetic products used on the face were associated with a 56% lower risk of developing FMACR compared to patients who did not use cosmetic products, which was statistically significant [adjusted OR (95% CI)=0.16 (0.05, 0.56), *p=0.004*]. We found no relationship between other skin care practices, including facial cleansers, sunscreens, and moisturizers used, and the risks of developing FMACR (*p>0.05*). Our data also showed that patients with facial dermatoses including acne vulgaris, psoriasis and others, were associated with a 5.96 times higher risk of developing adverse skin reactions compared to patients without [adjusted OR (95% CI)=5.96 (1.96,18.12), *p=0.002*]. When other confounding variables were controlled for, patients with oily skin had 4.50 times the odds of developing an adverse skin reaction as patients with normal skin [adjusted OR (95% CI)=1.94 (0.28, 13.28), *p=0.009*].

Among 114 participants, 15 (13.1%) were colonized with *S. aureus*. Although there was a higher proportion of *S. aureus* colonisation in the FMACR group, the analysis using simple logistic regression did not reach statistical significance (15.8% in FMACR subjects versus 10.9% in controls, *p=0.409*) (Table 4). Using the same analysis, without respect to other factors, dry skin type and not using facial cleansers increased the risk of *S. aureus* colonization [crude OR (95% CI)=7.73 (1.62, 36.82), *P=0.01* and crude OR (95% CI)=0.28 (0.09,0.85), *p=0.025*]. However, multivariate analysis showed that only dry skin type was independently associated with a higher risk for *S. aureus* colonization [adjusted OR (95% CI)=7.19 (1.14, 45.42), *p=0.036*]. Patients with dry skin type had a 7.19 times higher risk of being exposed to *S. aureus* colonization compared to patients with normal skin when other confounding variables were adjusted (Table 4).

Discussion

S. aureus is a ubiquitous bacterium commonly found in both the hospital and community.[21] Asymptomatic colonization of *S. aureus* on the skin is widespread, affecting approximately 30% of the population.[21,22] The primary site of colonization of this species is the anterior nares.[23] The frequency of carriage of *S. aureus* on different skin areas of adults varies, such as the anterior nares (44%), axillae (8%), chest/back (12%) and perineum (22%).[24] This may explain the lower rate of colonization in our participants (15.8% in FMACR subjects versus 10.9% in control), as swab samples were taken from both the alar crease and glabella. The lower proportion of male participants may also explain the lower rate of *S. aureus* colonization in our study, as previous studies have documented that males are more likely to be *S. aureus* carriers.[25,26] Gender differences in occupation, participation in contact sports, and hygiene practices may potentially influence *S. aureus* colonization in males.[25]

S. aureus has a role in the mechanism of both primary and secondary inflammation in skin diseases.[17] *S. aureus* colonization is increased in patients with atopic dermatitis (AD), causing more severe disease as well as exacerbations.[27,28] There is an increased risk of *S. aureus* skin colonization in both non-lesional and lesional skin of psoriasis patients compared with controls.[29,30] Psoriasis severity was significantly associated with enterotoxin-positive *S. aureus* colonization.[19] To the best of our knowledge, our study is the first attempt to investigate the role of *S. aureus* colonization in FMACR. We found no significant association between *S. aureus* colonization and FMACR and we propose that S. aureus may not play an important role in FMACR pathogenesis. However, as the pathogenic roles of several microorganisms have been demonstrated in various skin diseases, more research is needed to investigate the role of other microorganisms

in causing FMACR.

Longer duration of mask use was associated with development of FMACR.[2,4,5,7-9,13] There is conflicting data on whether the type of mask is associated with FMACR.[2,8-10] However, underlying facial dermatoses increases the risk of FMACR.[3,10,31,32] The most common FMACR in our patients was itching. Itch and acne are the two most common reported FMACR in previous studies.[9,33,34] Itch may be due to stress-induced histamine release from mast cell degranulation secondary to prolonged mask use. Thermal stimuli, alloknesis, may also contribute to increased itch.[35,36] The occurrence of acne (mask-induced acne or "maskne") may be related to 3 factors: friction or local pressure from the masks, alteration in local temperature and high humidity in the mask area leading to follicular occlusion and lastly, disruption of the skin microbiome.[10,12,37] Itch is a relatively common symptom of acne.[38] A Polish study in 2020 demonstrated that subjects with pre-existing acne were at significantly higher risk of itching due to the use of face masks.[8] Presence of facial dermatoses was found to be associated with an increased risk of FMACR among our patients. Face mask aggravates underlying seborrheic dermatitis, acne vulgaris, and rosacea.[10,31,32,34] An epidemiological study reported that prior history of acne vulgaris was associated with higher risks of developing new acne lesions or worsening of existing acne due to face masks.[39] The risk of redness in acne rosacea and contact dermatitis was found to be significantly increased after mask use.[34] Skin barrier dysfunction and probable skin microbiome dysbiosis might contribute to FMACR in patients with facial dermatoses.[10]

We found significant association between oily skin type and the risks of FMACR. *Yaqoob S et al* demonstrated a strong relationship between maskne and oily skin type.[40] A systematic review in 2020 also found a strong relationship between maskne and oily skin type.[41] Sebum secretion was shown to be higher after mask-wearing, and the consequences of excess sebum may contribute to the development of FMACR.[42]

Interestingly, we observed a significant FMACR reduction with the use of cosmetics. Cosmetics improved the hydration and texture of the skin.[43,44] Daily cosmetic use increases skin microbial alpha diversity, resulting in improved skin microbial health.[43] These factors could explain how cosmetics help reduce FMACR.

Dry skin type among our patients had higher rates of *S. aureus* colonization. Correlation between skin dryness and *S. aureus* colonization has been shown on non-lesional skin in atopic dermatitis patients.[45] Reduction of lipids and fatty acids in the skin, resulting in increased dryness, is one of the main factors predisposing to *S. aureus* colonization. In atopic dermatitis patients, ceramides and sphingosine levels in the stratum corneum are reduced, which also contribute to *S. aureus* colonization.[46] Various authors have encouraged the use of moisturizers as a preventive measure for FMACR.[47,48] Lotion and cream-based vehicles, are preferred over ointments due to their non-occlusive effect.[48]

We found that the use of common facial cleansers was not significantly associated with *S. aureus* colonization. This was consistent with a report by Aimee et al where the use of common commercial skin cleansers did not cause significant change in the bacterial community.[49] Thus, we recommend the use of facial cleansers, as these have not been shown to alter the normal microbiome on the skin. Various authors have also recommended the use of a daily facial cleanser to protect against FMACR and help maintain a healthy skin microbiome.[48,50]

Limitations

There are several limitations to this study. The major limitation is the small sample size, as it is a single-centre study, which might explain the insignificant statistical results observed.

Furthermore, our study is limited by the possibility of lower detection of *S. aureus* as swabs were taken from the alar crease and glabella while the anterior nares is the primary site of colonization. There was also possible under-detection of *S. aureus* colonisation as more sensitive molecular tests for *S. aureus*

identification was not performed.

Conclusion

There was no significant difference in the prevalence of *Staphylococcus aureus* skin colonization on the face between patients affected by FMACR and controls. The two most frequent adverse skin reactions observed were itching and acne. The risk factors for FMACR were the presence of facial dermatoses, oily skin type, and cosmetic-free facial skin.

Conflict of Interest Declaration

All authors have no financial/conflict of interest to be disclosed.

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ORIGINAL ARTICLE

Vitamin D Level among Psoriasis Patients, Healthy Controls and its Relationship with Sun Exposure and Dietary Intake - A Case Control Study

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Abstract

Background

Vitamin D deficiency has been implicated in psoriasis pathogenesis. Studies on the association of 25-hydroxyvitamin D [25(OH)D] with psoriasis have inconsistent results. We aimed to determine the serum 25(OH)D level among psoriasis patients versus healthy controls; to correlate it with sun exposure, dietary intake and psoriasis severity.

Methods

A case-control study on adults with plaque psoriasis in a Malaysian tertiary hospital. Control subjects were age, gender and race-matched healthy volunteers.

Results

There were 50 cases and 50 controls recruited: majority being males (68%) and Malays (66%). The mean serum 25(OH)D level was comparable between psoriasis patients and healthy subjects (51.59 nmol/L vs 49.13 nmol/L, *p=0.46*). Overall, there was a high percentage of subjects with insufficient 25(OH)D levels (25-75 nmol/L) among both groups (82% vs 94%, *p=0.06*). There were more psoriasis patients with deficient levels (<25 nmol/L) than controls but the difference was not significant (8% vs 2%, *p=0.36*). Sun exposure index (SEI) was significantly associated with serum 25(OH)D: for every unit of SEI increment, 25(OH)D is expected to increase by 4.39 units (*p=0.03*). There was no association between dietary intake with 25(OH)D level. Psoriasis area and severity index (PASI) score had a negative correlation with serum 25(OH)D among psoriasis subjects albeit not statistically significant [Mean -0.353 ± SE (0.262), *p=0.17*].

Conclusion

Vitamin D insufficiency is common among our population. There was no significant difference in terms of mean serum 25(OH)D level, percentage of insufficiency or deficiency in between psoriasis subjects and healthy controls. This study showed that higher SEI is associated with higher vitamin D level.

Key words: *Psoriasis, sun exposure, vitamin D*

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Introduction

Psoriasis is a chronic inflammatory, immune mediated skin condition that is characterized by skin inflammation and keratinocytes hyperproliferation with increased risk of painful, destructive arthritis. It is often associated with cardio-metabolic morbidity and psychosocial challenges.[1]

Vitamin D derivative has been one of the important topical treatments for mild to moderate psoriasis as it acts through the vitamin D receptor (VDR) on keratinocytes, hence the effect on cellular function. It also possesses immuno-modulatory effects on T lymphocytes, macrophages, monocytes and dendritic cells, in which it alters the gene expression involved in epidermal proliferation, differentiation, apoptosis and neovessels formation.[2-4] Studies have shown that vitamin D has a role in regulating terminal differentiation of basal keratinocytes. Hence, vitamin D deficiency may be associated with inflammatory and proliferative activities that are related to pathogenesis of psoriasis, in which abnormal and exaggerated proliferation of keratinocytes is present.[5] 25(OH)D is known to be the major circulating metabolite of vitamin D in human body and it reflects the input from dietary intake and cutaneous synthesis from sunlight exposure; it also circulates at levels 1,000 times higher than 1,25-hydroxyvitamin D [1,25$(OH)_2$D], hence serum 25(OH)D is considered as the standard clinical measure of vitamin D status.[6]

Several studies have demonstrated the association of low serum vitamin D level in psoriasis and that it is inversely correlated with disease severity and body mass index (BMI).[7-9] Ricerri F *et al* (2013) had reported a significantly lower serum level of 25(OH)D among psoriasis patients compared to healthy subjects, and similar findings were also noted from the study by Orgaz-Molina J *et al* (2012).[7-8] However, studies which were published in the more recent years, comparing serum 25(OH)D level among psoriasis subjects and healthy controls have yielded inconsistent results.[10-13] Maleki *et al* (2015) and Zuchi MF *et al* (2015) have reported that there was no statistical significance in serum 25(OH)D level among psoriasis subjects and healthy controls in their studies.[11-12]

To date, no local data on correlation of vitamin D level with psoriasis is available. Besides, limited studies have looked into the effect of sun exposure and dietary intake on the serum vitamin D level among psoriasis patients and their disease severity.

Our primary objective was to determine and compare the serum 25(OH)D level among psoriasis patients and healthy controls. The secondary objective was to determine the effect of sun exposure and dietary intake of vitamin D on the serum 25(OH)D level among the two groups, as well as to determine the correlation between serum vitamin D level with disease severity in psoriasis patients.

Material & Methods

Study design and subject recruitment

This was a case control study aimed to determine the association of serum 25(OH)D level with psoriasis subjects in comparison to healthy controls. The study was conducted at the Dermatology outpatient clinic of Hospital Raja Permaisuri Bainun, Ipoh, Malaysia. It is a tertiary hospital and the state referral center for Dermatology cases.

Adult psoriasis patients above 18 years old with plaque psoriasis of any disease severity who attended to the clinic during the period between 18 August 2021 – 28 February 2022 were recruited. Convenience sampling method was used to recruit psoriasis patients who attended the clinic and fulfilled the eligible criteria for the study, primarily because of the limitations encountered during the busy outpatient clinic and the sampling frame was not readily available. Healthy subjects were made up of age (within a 5-year gap), gender and race-matched volunteers who were relatives or staff without psoriasis or any active skin lesions. The psoriasis subjects were matched to a 1:1 ratio with healthy controls.

We have excluded individuals who were pregnant or lactating, those with preceding history of phototherapy in the past 3 months, on current oral or topical vitamin D and calcium supplement, bisphosphonates and systemic corticosteroid therapy. Subjects who were obese (BMI>25) or those with chronic medical illnesses which may alter vitamin D status, e.g. chronic liver disease, chronic kidney disease (eGFR <60mL/min/1.73m^2), hyperparathyroidism, bowel

disease with malabsorption and malignancy were also excluded.

The data collected included patient's demographic data, presence of comorbidities, smoking and alcohol consumption habits, psoriasis disease information, along with the duration and body surface area (BSA) of sun exposure, as well as dietary intake of vitamin D based on a validated food frequency questionnaire (FFQ)[14].

Sun exposure was quantified as an index (SEI), which was calculated by exposed BSA (in fraction) multiplied with the duration of exposure per week (in hour).[15]

We used a validated FFQ developed by Zaleha *et al* in 2015 to ascertain the estimated vitamin D intake of both case and control subjects based on their dietary intake within 1 month prior to the blood sampling.[14] The questionnaire consisted of various types of local food enriched with vitamin D and the participants were required to mark the frequency of consumption of each type of food, e.g. once daily/ weekly/ monthly with the estimated amount of intake based on standard portioning. The quantification of the vitamin D value was performed using the NutritionistPro software.

The disease severity was assessed among the psoriasis subjects using PASI score.[16] Inter-observer bias was minimized as there was only a single interviewer involved in collection of data and assessment of PASI scores.

Serum vitamin D sampling and analysis

3mL of venous blood was sampled from antecubital veins of participating subjects and the blood samples were processed in the Biochemical Lab of Putrajaya Hospital, Malaysia for serum 25(OH)D assay (using Chemiluminescence Immunoassay method). According to the reference ranges stated by the laboratory, serum 25(OH)D level of <25 nmol/L was defined as deficient, 25 - 75 nmol/L as insufficient, 76 - 250 nmol/L as sufficient and > 250 nmol/L was categorized as possible intoxication.[17]

Study size calculations

The sample size of this study was calculated based on the case-control study carried out by Orgaz-Molina J *et al* in 2012 on serum concentration of 25(OH)D in psoriasis patients versus healthy subjects. The mean and standard deviation (SD) of serum 25(OH)D level of the study group were 24.41 ng/mL (SD 7.80) and the healthy controls were 29.53 ng/mL (SD 9.38). We required a sample size of 45 for the study group and a sample size of 45 for the control group in order to reject the null hypothesis with a probability (power) of 0.8 and Sampling Ratio=1. The Type 1 error probability associated with this test of this null hypothesis is 0.05. To allow a 10% dropout rate, the total sample size was calculated to be 50 subjects per group.

Data analysis

Statistical analysis was performed using IBM SPSS version 26. Chi-Square test and Fisher's exact test were used to compare the demographic characteristics in between the two groups. Generalized Linear Model was used to test the correlation in between the serum 25(OH)D level with its predictors (SEI, dietary vitamin D intake and PASI score) for both study groups; whereas Mann-Whitney U test was employed to compare the SEI and dietary vitamin D intake in between the two groups, as well as PASI score among the psoriasis subjects. A value of $p<0.05$ was considered statistically significant. There was no missing data or dropout during data collection and analysis.

Ethical approval

This study was registered with the National Medical Research Registry (NMRR-21-1277-60526). Ethical approval for the study was obtained from the Medical Research Ethics Committee, Ministry of Health, Malaysia.

Results

The first 50 psoriasis patients who attended the clinic and fulfilled the eligible criteria were recruited into the study. The 50 control subjects selected were age, gender and race-matched healthy volunteers who were relatives or hospital staff.

Table 1. Demographic characteristics among case and control groups

Demographic Characteristics	Case (n = 50)	Control (n = 50)	*p value*
Age, median (IQR)	32.0 (24-46.25)	31.0 (23-46)	*0.99*
Gender, n (%)			
Male	34 (68.0)	34 (68.0)	*0.99*
Female	16 (32.0)	16 (32.0)	
Ethnicity, n (%)			
Malay	33 (66.0)	33 (66.0)	*0.99*
Chinese	7 (14.0)	7 (14.0)	
Indian	10 (20.0)	10 (20.0)	
BMI, median (IQR)	23.2 (21.14-24.9)	23.1 (20.16-24.26)	*0.84*
Comorbidities			
Hypertension	8 (16.0)	6 (12.0)	*0.56*
Diabetes mellitus*	3 (6.0)	0 (0.0)	*0.24*
Dyslipidaemia*	7 (14.0)	4 (8.0)	*0.26*
Smoking	12 (24.0)	4 (8.0)	***0.02***
Alcohol*	1 (2.0)	1 (2.0)	*0.99*

BMI = Body mass index; IQR = Interquartile range

**Fisher's exact test was used*

The demographic characteristics among case and control subjects were comparable in terms of age, gender, ethnicity, body mass index (BMI) and co-morbidities, except that smoking history was significantly higher among psoriasis subjects (*p=0.02*) as shown in Table 1. Chi-Square test was used for the majority of the variables, except the ones with *, where Fisher's exact test was used**.**

The mean serum 25(OH)D level was comparable between psoriasis and control subjects (51.59 nmol/L vs 49.13 nmol/L, *p=0.46*).

Overall, we noticed that there was a significant difference in serum 25(OH)D level for male (55.81 ± 16.41) and female (38.77 ± 10.90), *p=<0.001*. The comparisons among both genders in the two study groups were further illustrated in Table 2. Female subjects in both psoriasis group and healthy controls were noted to have a significantly lower level of serum 25(OH)D.

There was a higher percentage of subjects with insufficient levels (25-75 nmol/L) of serum 25(OH)D in both psoriasis and control groups (82% vs 94%, *p=0.06*). There were more psoriasis subjects with deficient serum 25(OH) D level (<25 nmol/L) compared to healthy controls (8% vs 2%, *p=0.36*) even though the difference was not significant. Only 5 psoriasis subjects (10%) and 2 healthy controls (4%) were noted to have normal 25(OH)D level (*p=0.43*)

By using Generalised Linear Model to test on the association of SEI, dietary vitamin D intake, PASI score and BMI with serum 25(OH)D level, as shown in Table 3, we noted that the SEI was significantly associated with serum 25(OH) D (*p=0.03*). It was deduced that for every unit of increment in SEI, serum 25(OH)D level is expected to increase by 4.39 units.

There was no significant association between dietary vitamin D intake and BMI with serum 25(OH)D level. Disease severity of psoriasis in terms of PASI score seemed to have a negative correlation with serum 25(OH)D level (Mean -0.353 ± SE 0.262), although it was not statistically significant (*p=0.17*).

The median level of SEI among the subjects were illustrated in Table 4. There was no significant difference in terms of SEI among psoriasis and control subjects even though SEI is lower in psoriasis than the control group (0.6 vs 0.875, *p=0.34*). Female subjects in both the groups were noted to have a much lower SEI (0.27 vs 1.04 among psoriasis subjects, *p=0.002*; 0.178 vs 1.14 among control subjects, *p<0.001*).

Table 2. Comparison of serum 25(OH)D level among both genders in two study groups, n = 100

	Gender	**Mean serum 25(OH)D (SE)**	***p value***
Overall	Male (n=68)	55.81 (16.41)	***<0.001***
	Female (n=32)	38.77 (10.90)	
Case	Male (n=34)	56.87 (19.28)	***0.003***
	Female (n=16)	40.34 (12.42)	
Control	Male (n=34)	54.75 (13.15)	***<0.001***
	Female (n=16)	37.20 (9.26)	
	Group	**Mean serum 25(OH)D (SE)**	***p value***
Male	Case (n=34)	56.87 (19.28)	*0.59*
	Control (n=34)	54.75 (13.15)	
Female	Case (n=16)	40.34 (12.42)	*0.42*
	Control (n=16)	37.20 (9.26)	

25(OH)D=25-hydroxyvitamin D; SE=Standard error

Table 3. Correlation of serum 25(OH)D with the variables tested by Generalised Linear Model, n = 100

Variables	**Mean ± SE***	***p value***
SEI	4.39 (2.08)	***0.03***
Dietary vitamin D intake	0.007 (0.0159)	*0.64*
PASI score	-0.353 (0.262)	*0.17*
BMI	1.007 (0.974)	*0.30*

BMI = Body mass index; PASI = Psoriasis area & severity index; SEI = Sun exposure index; 25(OH)D = 25-hydroxyvitamin D
**Regression coefficient (SE, Standard error)*

Table 4. Median level of SEI among both groups and gender, n = 100

SEI		**Case (Median, IQR)**	**Control (Median. IQR)**	***p value***
Gender	Overall	0.6 (0.22-1.5)	0.875 (0.24-2.99)	*0.34*
	Male (n = 68)	1.04 (0.32-2.50)	1.14 (0.56-3.65)	*0.11*
	Female (n = 32)	0.27 (0.08-0.66)	0.18 (0.09-0.75)	*0.77*

SEI = Sun exposure index; IQR = Interquartile range

Table 5. Median level of dietary vitamin D intake among the two groups and gender, n = 100

Dietary vitamin D intake		**Case (Median, IQR)**	**Control (Median, IQR)**	***p value***
Gender	Overall	170.10 (98.45-272.28)	224.9 (143.56-302.26)	*0.12*
	Male (n = 68)	190.47 (108.19-282.43)	244.47 (179.36-340.07)	*0.07*
	Female (n = 32)	136.16 (83.08-262.09)	179.14 (105.81-230.23)	*0.67*

IQR = Interquartile range

In general, the dietary intake of vitamin D among control group was higher compared to psoriasis subjects but the difference was not significant (224.0 iU vs 170.10 iU, *p=0.12*). (Table 5)

The overall median PASI score was 7.0 (IQR 3.8 - 17.58). Median PASI score was 6.3 (IQR 3.8 - 20.85) among the male psoriasis subjects and 7.3 (IQR 3.63 - 15.4) among their female counterparts. PASI score had a negative correlation with serum 25(OH)D among psoriasis subjects but the difference was not statistically significant [Mean -0.353 ± SE (0.262), *p=0.17*].

Discussion

There is currently no consensus over the optimal values of serum 25(OH)D levels. Levels below 25 nmol/L are defined as severe deficiency based on the recommendations by International Osteoporosis Foundation.[18] In 2011, the Endocrine Society Task Force had established recommendations for serum 25(OH) vitamin

D levels as followed: < 50 nmol/L as deficient, 50 - 75 nmol/L as insufficient, 75 - 250 nmol/L as sufficient and > 250 nmol/L as upper safety limit.[19]

From our study, we noticed that there was no difference of the mean serum 25(OH)D level in between psoriasis subjects with healthy controls, although the psoriasis group had a slightly higher percentage of vitamin D deficiency (8% vs 2%, *p=0.36*).

By using Generalised Linear Model to test on the association of SEI, dietary vitamin D intake and PASI score with serum 25(OH)D level, it was noted that SEI was significantly correlated with vitamin D level, of which for every unit of SEI increment, serum 25(OH)D is expected to increase by 4.39 units (*p=0.03*). However, there was no significant association in between dietary vitamin D intake with serum 25(OH) D level. The severity of psoriasis appeared to be negatively correlated with serum 25(OH)D level [Mean -0.353 ± SE (0.262), *p=0.17*].

The findings of our study had showed that there was no significant difference in between serum 25(OH)D level among psoriasis subjects with healthy controls, and this finding was in contrast with the case control study published by Gisondi P *et al* (2011), in which they have found a significantly lower level of serum 25(OH)D in psoriasis patients compared to healthy controls, but no difference was noted in between psoriasis subjects with those with rheumatoid arthritis.[9]

However, Maleki M *et al* (2015) had reported that no statistical significance was observed in serum 25(OH)D level among psoriasis subjects with the control group, which showed similar findings with our current study.[11] Another case control study conducted by Zuchi MF *et al* (2015) had also pointed out that no significant correlation was observed in serum vitamin D level among psoriasis patients with healthy subjects.[12] The possible reason for inconsistent results reported in the literature might be because vitamin D level may vary according to factors such as geography, seasonal variations, age factor, ethnicity, health conditions of study subjects, the use of vitamin D supplement, dietary habit, as well as environmental factors among the studies across different countries.[19]

Local studies comparing vitamin D level among patients with atopic dermatitis (AD) which are available to date have shown differing results among the adult and children subjects. A case control study conducted by Mohan A *et al* (2020) had demonstrated positive correlation of vitamin D in adult patients with AD, in which lower levels of vitamin D were noted among these subjects in comparison with controls. AD was identified as an independent risk for vitamin D deficiency and insufficiency in this study, however the levels did not correlate with AD severity.[20] On the other hand, another case control study done locally by YW Lee *et al* (2019) which examined serum 25(OH)D levels in children with AD and controls did not show statistical differences among the two groups. Similar to the findings of our study, serum vitamin D levels were noted to be significantly lower among children with severe AD compared to the subjects with mild to moderate AD.[21]

A case control study done by Ramalingam R *et al* (2018) looking at 25(OH)D level among vitiligo patients versus matched controls in Malaysia had reported no significant difference in the mean vitamin D level among the two cohorts. The study had also found out that two-thirds of subjects in both the groups had deficient and insufficient levels. This had tallied with one of the findings of our study, i.e. a high percentage of our study subjects were noted to have abnormal serum vitamin D levels.[22]

Comparing our local data on serum 25(OH) D level in the Malaysian adult population, we noticed that our local population generally has a lower-than normal vitamin D level (< 75 nmol/L). Shafinaz & Moy have reported in a cross sectional study done in Kuala Lumpur in 2016 which consisted of 858 subjects ranging from 30 - 49 years old, in which they noticed that as high as 80.9% of Indian subjects had a deficient level of vitamin D (< 50 nmol/L), followed by Malays (75.6%) and Chinese (25.1%).[23]

Chin *et al* (2014) had reported in a cross sectional study done in Kuala Lumpur on 383 male subjects which showed that the mean serum 25(OH)D level was 58.7 nmol/L.[24] Moy & Bulgiba (2011) had also noticed a mean serum 25(OH)D level of 56.2 nmol/L among the male subjects and 36.2 nmol/L in their female counterparts.[25] Lieu *et al* had reported in a cross sectional study in 2020 which was conducted among postmenopausal women, of which the mean serum 25(OH)D level of 214 subjects was 37.4 ± 14.3, and up to 82.7% of the study population had an abnormal level of vitamin D.[26]

On the other hand, our current study had demonstrated that sun exposure index was significantly associated with serum 25(OH) D level. This finding of positive correlation was further supported by the results reported by Sambrook PN *et al* in their randomized controlled trial in 2011, in which the vitamin D level was noted to be increased more among the subjects exposed to ultraviolet source compared to the control group.[27] Besides, the randomized controlled trial conducted by Lee YM *et al* (2011) had also shown a significant increment of serum 25(OH)D among the sunlight exposure group in comparison to the control subjects.[28]

In our current study, we have noted that the SEI among psoriasis subjects was slightly lower than their healthy counterparts (0.6 vs 0.875, *p=0.34*) but the difference was not significant. It could possibly be due to the fact that psoriasis patients have the tendency to cover up their body parts with psoriatic lesions during their outdoor activities. Besides, another observation noted was that our female subjects in both the groups had a much lower SEI compared to male subjects in general. This could be because the majority of the female subjects were Malay Muslims (68.8%) and due to cultural and religious reasons, Muslim women are usually dressed in clothing that cover up most of their body parts. Serum 25(OH)D levels were generally lower among the female subjects in both the study groups and this is likely related to the significantly lower duration or BSA of sun exposure. Another reason for lower sun exposure among women subjects could be due to the sociocultural norms in this region of Asia, where fair complexion is commonly being preferred.[29]

Our current study had also noticed a negative correlation of PASI score with serum 25(OH)D level among psoriasis subjects albeit statistically insignificant. A significant correlation was demonstrable by the case control study reported by Recerri F *et al* (2013), which showed that serum 25(OH)D had a significant negative correlation with PASI score.[7] Maleki M *et al* (2015) had suggested in a case control study that psoriasis disease severity does have an impact on the level of vitamin D in the body, as lower level of serum 25(OH)D was correlated with a higher PASI score.[11]

Besides, we have also noted that the majority of our study subjects (92%) were consuming a lower-than-recommended amount of dietary vitamin D as suggested by the National Health Service in the United Kingdom, i.e. 400iU per day.[30] This finding was further supported by another local study conducted by Ramalingam R *et al* (2018), in which they have reported that one of the independent variables which affected vitamin D level was dietary vitamin D intake, and the dietary intake in both vitiligo patients and matched subjects was extremely low.[22]

Generalisability

The results of our current study are generalisable for our local population and likely among the Asian population, given our similar background and cultural differences. It may however, not be applicable for psoriasis patients who are obese or those with factors which may alter vitamin D metabolism, e.g. chronic liver or kidney disease, other concurrent autoimmune conditions or those with malignancies.

Limitations

The limitations of this study may include recall bias among the participants, in particular on the recall of food intake or frequency, and sun exposure duration or percentage of BSA exposed. Besides, convenience sampling of subjects may have limited the representation of

the general psoriasis population being studied.

Conclusion

Vitamin D insufficiency is common among our population. There was no significant difference in terms of mean serum 25(OH)D level, percentage of insufficient or deficient level of serum 25(OH)D between psoriasis subjects and controls. This study showed that higher SEI is associated with higher vitamin D level.

Conflict of Interest Declaration

All authors have disclosed no conflicts of interest.

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ORIGINAL ARTICLE

Evaluation of Topical Corticosteroid Phobia As An Indicator of Topical Steroid Non-adherence Among Atopic Dermatitis Patients

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Abstract

Background

Topical steroid phobia is associated with a higher rate of non-adherence to topical corticosteroid, thereby resulting in poor treatment outcome. Detection of topical corticosteroid (TCS) non-adherence is a prerequisite to better adherence among atopic dermatitis (AD) patients with topical corticosteroid phobia (TCP). The objective of this study was to evaluate whether the intensity of TCP correlates with TCS- non-adherence, and if the Visual Analogue Scale (VAS) for TCP and TOPICOP© scales can be an indirect indicator for topical steroid non-adherence.

Methods

A cross-sectional study was conducted at the dermatology clinic and paediatric dermatology clinic, Hospital Ampang and Hospital Kuala Lumpur. MyMAAT scale, TOPICOP©scale and VAS for TCP were used for the survey.

Results

146 subjects were recruited. The overall good TCs-adherence rate was only 20.55%. The mean global scores of TOPICOP© scale was 51.45±19.25 and VAS for TCP was 4.53±2.27. TOPICOP©scale and VAS for TCP were identified to have significant correlation with TCs related non-adherence with the *p<0.001, p=0.012* respectively.

Conclusion

This study supports the usage of TOPICOP© scale and VAS for TCP as clinical tools for measuring the intensity of TCP and potentially detect TCs-non-adherence in a non-judgemental way. Further studies on optimising and assessing the effect of interventions to reduce TCP and improving clinically relevant outcomes such as TCs related adherence and quality of life among AD patients in Malaysia are warranted.

Key words: *Topical corticosteroid phobia (TCP), topical corticosteroid (TCS)-non adherence, atopic dermatitis (AD), TOPICOP© scale, VAS for TCP*

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Introduction

Atopic dermatitis (AD) is a chronic inflammatory skin disease[1], characterised by ill-defined erythema with vesicles, and weeping in the acute stage and lichenification in the chronic stage. Majority of cases develop during early childhood[1], with a prevalence of 13.4% in Malaysian children.[2] Topical corticosteroid

remains the cornerstone therapy for AD due to its potent anti-inflammatory and anti-proliferative effects.[3]

Topical corticosteroid phobia (TCP) is described as irrational concerns, fears, worries, or scepticism regarding corticosteroid use in patients, their caregivers or health professionals.[4] TCP may lead to non-adherence and poor disease control, resulting in more hospitalisation and increased healthcare socioeconomic burden.[4] TCP is highly prevalent in dermatology patients, especially among patients with AD or their caregivers.[4] A systematic review by *Li Aw et.al* [5]revealed TCP prevalence across countries ranged from 21% to 83.7%. In Malaysia, TCP was reported to be 39% in 2015[6] and the rate increased to 59.6% in 2018.[7] This suggests an increasing trend in the prevalence of TCP in Malaysia, although the method of assessments was not standardized.

A study by *Mazlin et al*[8] in 2013 concluded that the adherence to topical treatment was poor among AD patients in Malaysia with an adherence rate of only 14.7%. There were studies performed in France, Japan and Korea that found TCP is associated with a higher rate of non-adherence to topical corticosteroid (TCs).[4,9,10] TCP related non-adherence has been reported in 36-58% of patients prescribed TCs, emphasising the importance of these issues.[3-4,9] Detection of TCs non-adherence is a prerequisite to better adherence among AD patients with TCP.[11] However, no practical clinical tool to evaluate TCP related non-adherence is currently available.[3]

In addition, direct confrontation could affect the relationship between physician and patients whereas self-reporting of TCs non-adherence by patients might not be reliable. Alternative strategies to detect TCs non-adherence may therefore be helpful.[4,12] Visual analogue scale (VAS) for TCP has been been used to quantify TCP in many clinical trials.[13] On the other hand, the TOPICOP© scale is a 12-item questionnaire that was developed by Moret and colleagues[13] in 2013 as a standardised assessment tool for TCP. Instead of using a binary yes or no answer choice to establish the presence of TCP, TOPICOP© scale will not only be able to better quantify TCP but also discern the relative effects that these worries and beliefs have on treatment adherence.[14] Based on this rationale, the aim of this study is to evaluate whether the available tools for measuring the intensity of TCP might help to detect TCs related non-adherence.

Materials and Methods

This was a prospective cross-sectional study conducted at the paediatric dermatology clinic and adult dermatology clinic in Hospital Ampang and Hospital Kuala Lumpur, from 1st August 2021 to 31st December 2021. Our target population was clinically confirmed AD patients or primary caregivers of children with diagnosis of AD. Accompanying adults must be the primary caregivers of the child with AD, who are 12 years of age and below. The patients must be on TCs for the past one month or more. Subjects who were unable to understand Malay or English and had other coexisting inflammatory skin diseases were excluded from the study.

This study involves the use of 3 questionnaires. The study questionnaires were administered either in Malay or English language, consisting of six sections (Sections A-F). Section A is about the child / patient personal particulars, section B is about parent / caregiver personal particulars, section C about details on atopic eczema and section D is the information about the questionnaire on intensity of topical corticosteroid phobia by VAS and exploring the source of information with regards to topical corticosteroid and Section E is the questions on TOPICOP© scale. Section F is the questionnaire about Malaysia Medication Adherence Assessment Tool (MyMAAT) which is to assign respondents to an adherence or non-adherence group. All sections were obtained from the patients or caregivers using a self-administered questionnaire. Information on Section C was obtained from the dermatologist assessment of AD severity and topical treatment.

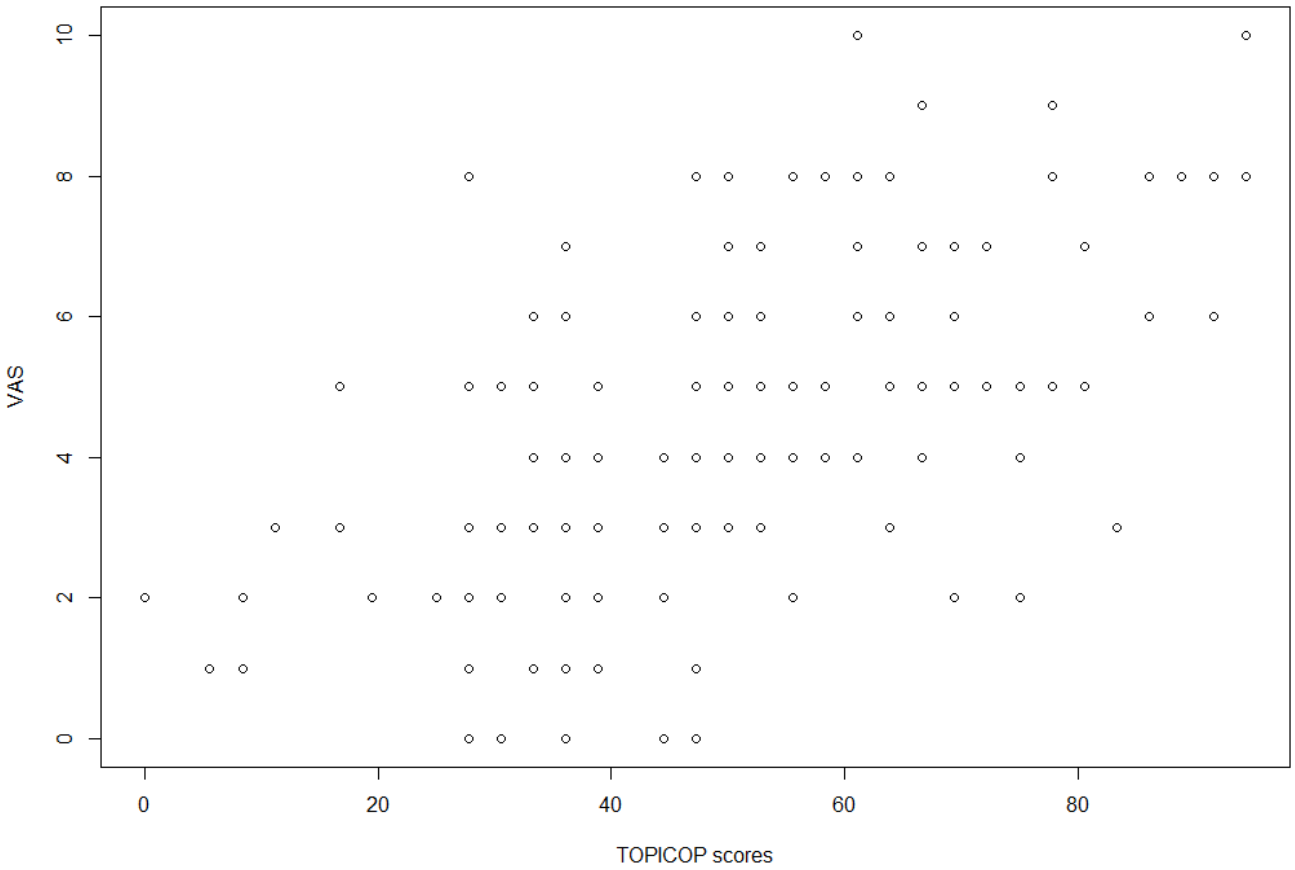
The TOPICOP© scale is a 12-item questionnaire, assessing two domains of TCP, namely worries and beliefs. Responses were graded on a four-point Likert scale (score range 0–3: 0=never, 1=sometimes, 2=often and 3=always; or 0=totally disagree, 1=do not really agree, 2=almost agree and 3=totally agree) to a maximum of 36 points. A higher TOPICOP© scale reflects a more pronounced TCP phenomenon.

VAS for TCP ranges from 0 to 10. The respondents were asked to identify, based on this scale, where would they place the intensity of their worries about TCs? 0 being calm at ease and 10 being extremely worried. Another additional question was to explore the source of information with regards to TCs among the respondents.

MyMAAT is a validated scale for assessing medication adherence in Malaysia.[14] It comprises 12 items, the scale ranging from 1-5, with the cut-off point of ≥54 deemed as good adherence.

Sample size estimation was calculated based on a pilot study done by *Simon M Muller et al*[2] Assessment of "corticophobia" as an indicator of non-adherence to topical corticosteroids. Burderer's formula was used for this estimated sample size calculation at the required absolute precision level for sensitivity and specificity. Based on *Simon et al*[2] study, the sensitivity and specificity of VAS for TCP with the cut-off point of 5 was 0.87 and 0.42 respectively, a minimum sample size of 146 was required. The data obtained from this study was analysed both descriptively and analytically. Data analysis was done by using the IBM® Statistical Package for Social Sciences (SPSS) Desktop version 23. Descriptive data was computed by using the same software. All the demographic data was presented as mean and standard deviation or frequency and percentages. For categorical data, differences between groups were analyzed using Chi-square test for independence or Fisher's exact test. On the other hand, continuous data was analyzed using independent t tests. Univariate and multivariate logistic regression

Figure 1. Correlation between TOPICOP© scale and VAS scores



Pearson correlation, r= 0.58, p=<0.001 (moderate correlation, positively correlated)

tests were used for the factors of TCP related to TCs non-adherence. All statistical analysis was performed on a two-sided confidence level of 5%.

The study was approved by the Medical Research and Ethics Committee (MREC) of the Ministry of Health, Malaysia with ethical approval number NMRR-21-1165-60133.

Results

All 146 subjects screened between 1st August 2021-31st December 2021 were recruited in this study. The patient's gender was distributed evenly, in which 49.3% were male and 50.7% were female. The mean age of the patients was 8.8±11.51 years. The mean age of AD onset was 2.31±3.67 years. Patient's duration of disease averaged at 6.48±10.14 years. The majority of the patients were Malay (85.6%), followed by Chinese (9.6%), and Indian (2.7%). Most of the respondents were the patients' mother (67.8%). Approximately half of the AD subjects with mild disease severity (47%) were recruited in this study. Only 24 respondents (16.4%) from our study used alternative therapy. Our study revealed that paediatricians (35.6%) were the most common source of information regarding TCs, followed by internet/social media (28.1%), dermatologists (24.7%), general practitioner (5.5%), pharmacists (4.8%) and the least common was friends & family (1.4%). The overall good adherence rate was only 20.6%. 79.5% of patients or caregivers had poor adherence to AD treatment. The total mean TOPICOP© scale was 51.45±19.25. Among the two domains, belief domain had higher mean scores, which was 63.93±22.28. On the other hand, the total mean VAS for TCP was 4.53±2.27. Other demographics and clinical characteristics are shown in Table 1.

An independent-samples t-test was conducted to compare TOPICOP© scale and VAS for TCP among TCs good adherence and poor adherence groups. Those in TCs-poor adherence group (M=54.62, SD=17.73) compared to those with good TCs-adherence (M=39.27, SD=20.23) demonstrate significantly higher mean of

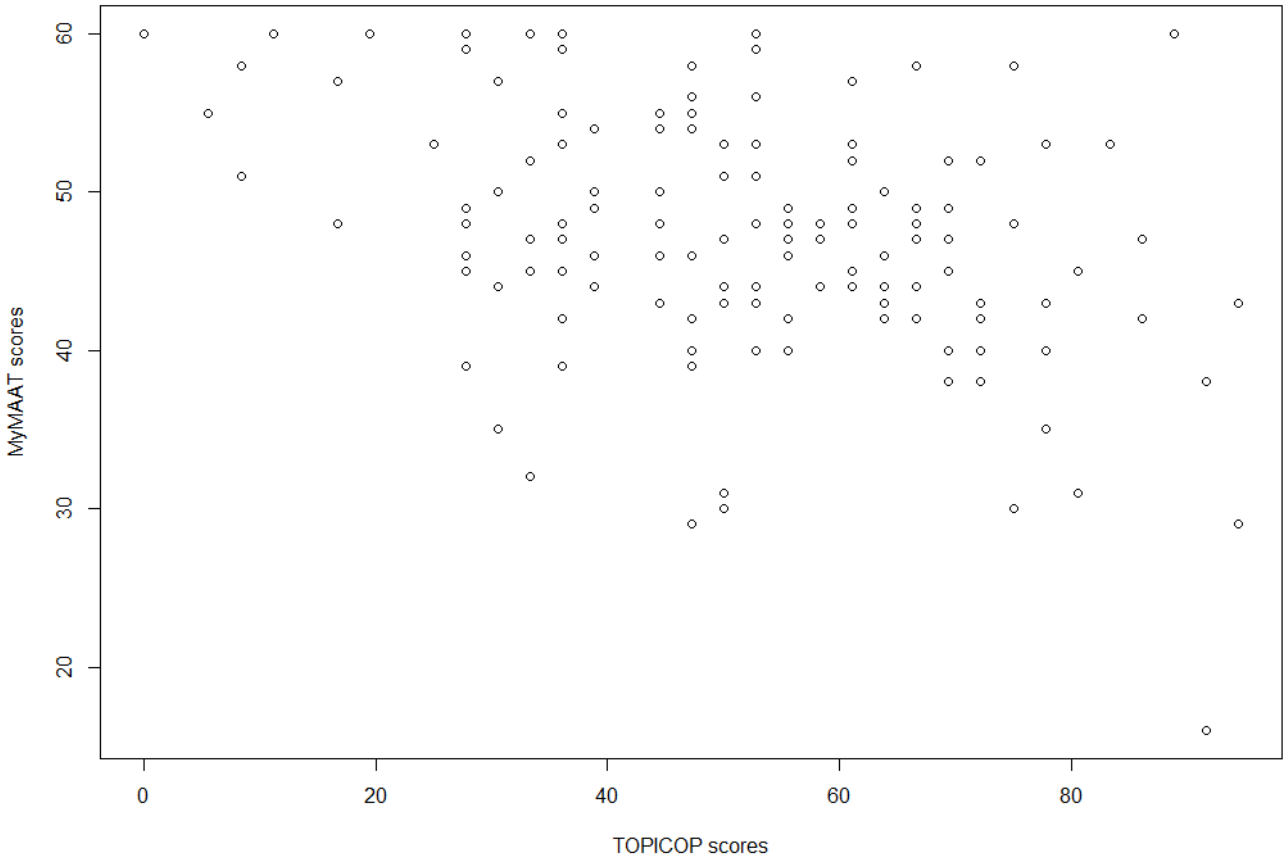
Table 1. Study population demographic and clinical characteristic, n=146

Characteristic	n (%) / mean (SD)
Age (years)	8.80 (11.51)
Age at onset (years)	2.31 (3.67)
Age of caregivers (years)	35.30 (6.04)
Age of subjects answered questionnaires (years)	34.25 (9.19)
Duration of disease (years)	6.48 (10.14)
Gender	
Female	74 (50.7)
Male	72 (49.3)
Ethnicity	
Chinese	14 (9.6)
Indian	4 (2.7)
Malay	125 (85.6)
Others	3 (2.1)
Site of Atopic Dermatitis	
Generalised	52 (35.6)
Localised	94 (64.4)
Severity of atopic dermatitis by IGA	
0-clear	1 (0.7)
1-almost clear	11 (7.5)
2-mild	70 (47.9)
3-moderate	37 (25.3)
4-severe	27 (18.5)
Previous history of hospitalisation	
Never	99 (67.8)
Yes	47 (32.2)
Topical therapy	
No	0 (0.0)
Yes	146 (100.0)
Systemic therapy	
No	113 (77.4)
Yes	33 (22.6)
Alternative treatment	
No	122 (83.6)
Yes	24 (16.4)
Caregiver occupation	
NA	24 (16.4)
Non-professional	55 (37.7)
Professional	36 (24.7)
Unemployed	31 (21.2)
Caregiver relationship with patient	
Father	23 (15.8)
Mother	99 (67.8)
NA	24 (16.4)
Information source regarding TCS	
Dermatologists	36 (24.7)
Paediatrician	52 (35.6)
General Practitioners	8 (5.5)
Pharmacists	7 (4.8)
Friends & family	2 (1.4)
Internet/ social media	41 (28.1)
MyMAAT adherence	
Good	30 (20.55)
Poor	116 (79.45)
TOPICOP© scale (total) - Worries domain - Belief domain	51.45 (19.25) 63.93 (22.28) 38.96 (20.72)
VAS scale for TCP	4.53 (2.27)

Table 2. Comparing TOPICOP© scale and VAS for TCP among good adherence and poor adherence (independent t-test)

Characteristic	n (%)/ mean (SD)		*p-value*
	Good adherence n=30	Poor adherence n=115	
TOPICOP© scale (mean (SD)	39.17 (20.23)	54.62 (17.73)	**<0.001**
TOPICOP© scale - Belief domain (mean (SD)	48.33 (24.42)	67.96 (19.89)	**<0.001**
TOPICOP© scale- Worries domain (mean (SD)	30.00 (22.20)	41.28 (19.76)	**0.007**
VAS for TCP (mean(SD)	3.60 (2.36)	4.77 (2.20)	**0.012**

Figure 2. Correlation between TOPICOP© scale and MyMAAT scale



Pearson correlation, r= -0.371, p<0.001 (low correlation, negatively correlated)

TOPICOP© scale (*p<0.01*). Similarly, there was a significant difference (*p=0.012*) in the mean VAS for TCP in the good adherence group (M=3.6, SD=2.36) which was lower than the poor-adherence group (M=4.77, SD=2.20).

Moderate correlation was found between TOPICOP©scale and VAS for TCP (r=0.58, *p <0.001*) as shown in Figure 1.

Significant weak negative correlation was observed between TOPICOP©scale and MyMAAT scale (r= -0.37, *p<0.001*) as shown in Figure 2.

As shown in Table 3, only severity of AD and low TOPICOP© scale were found to be statistically significantly associated with good TCs adherence. Patients with moderate to severe AD and patients who were in the first quartile of TOPCOP© scale were 4.01 and 7.12 times more likely to have good TCs adherence.

There were significant differences in TOPICOP© scale for those seeking alternative treatment were significantly higher (M=60.80, SD=18.83) than

those without history of alternative treatment (M=49.70, SD=18.92), *p-value=0.013*. Regarding sources of information, TOPICOP© scale for those seeking information from non-healthcare professionals (M=62.02, SD=15.75) were significantly higher than those seeking information from healthcare professional groups (M=47.03, SD=18.92) with the *p value of <0.001*.

Previous study showed that 30% to 40% of all medications taken for chronic conditions are not taken as prescribed.[12] Only 20.55% of good TCs- adherence rates were observed in our study, which is relatively low compared to *Alyson et al*[15] which reported the mean adherence rates ranging from 32% to 93%. This result highlights the fact that TCs- non-adherence is very prevalent among AD patients and their caregivers in Malaysia. This phenomenon could be explained by the fear

Table 3. Factors associated with good TCs-adherence

Variables	Crude OR (95% CI)	*p value*	Adjusted OR (95% CI)	*p value*
Gender				
- Female	1.0		-	-
- Male	1.45 (0.65, 3.31)	0.366		
Sources of information regarding TCS				
- Non health care professional	1.0			
- Health care professional	2.44 (0.93, 7.66)	0.072	-	-
Caregiver's occupation				
- Unemployed	1.0		-	-
- Non professional	1.16(0.37, 4.05)	0.810		
- Professional	1.73 (0.53, 6.29)	0.376		
Caregiver's education				
- Secondary	1.0		-	-
- Tertiary	1.41 (0.55, 3.94)	0.482		
Caregiver's relationship				
- Father	1.0		-	-
- Mother	1.20 (0.40, 4.49)	0.757		
Age (years)	1.02 (0.99, 1.06)	0.157	-	-
Age of onset (years)	1.09 (0.99, 1.21)	0.071	-	-
Family history of atopy				
- No	1.0		-	-
- Yes	2.86 (0.92, 12.62)	0.071		
Duration of disease (years)	1.02 (0.98, 1.05)	0.333	-	-
Ethnicity				
- Malay	0.83 (0.24, 3.87)	0.783		
- Chinese	1.0		-	-
- Indian	3.67 (0.33, 44.12)	0.276		
- Others	7.33 (0.53, 195.32)	0.151		
Site of atopic dermatitis				
- Localized	1.0		-	-
- Generalized	2.54 (1.12, 5.83)	0.025		
Severity of atopic dermatitis by IGA				
- 0,1,2 (clear, almost clear, mild)	1.0	-	-	-
- 3,4 (moderate, severe)	2.73 (1.20, 6.43)	0.016	4.01 (1.63, 10.51)	**0.002**
Alternative treatment				
- No	1.0	-	-	-
- Yes	0.31 (0.05, 1.13)	0.078	0.26 (0.04, 1.09)	0.068
TOPICOP© scale				
- First quartile (0-36.1)	7.12(1.93,34.70)	0.006	7.12 (1.80, 36.84)	**0.009**
- Second quartile (36.2-51.4)	3.56 (1.00, 16.78)	0.068	3.38 (0.91, 16.51)	0.089
- Third quartile (51.5-63.9)	1.72 (0.39, 8.94)	0.482	1.36 (0.29, 7.33)	0.700
- Fourth quartile (64.0-94.4)	1.0	-	-	1.0

OR = Odd ratio, [a] Likelihood Ratio (LR) test, [b] Z statistics, Z test

of topical corticosteroid side effects.[16]

A significant correlation between disease severity with TCs- adherence were observed in our study. This finding was in line with the results of *Krejci-Manwaring J et al*[17] considering that patients with more severe disease may be more adherent to TCs in order to halt the disease progression rapidly; whereas subsequent clearing of the disease may lead to a decrease in compliance. Another study in Japan also supports the notion that disease severity as perceived by caregivers prove to be an important predictor of adherence to topical therapy.[18]

A multicentre study conducted in 17 countries found a mean global TOPICOP© scale of 44.7±20.5.[19] In our study, the mean global scores of TOPICOP© scale was 51.45±19.25, which was comparable with a previous study by *KC Yap et al*[6] (54.94±16.92%) in year 2018. Therefore, TCP appears to be more pronounced in Malaysia as compared to most countries. Along the same vein, the total mean score of VAS for TCP in our study was 4.53±2.27, which is consistent with a study by *Aubert-Wastiaux H et al*[4] Numerous studies have concluded that TCP is exceedingly prevalent across the countries and results in TCs related non-adherence.[20]

In keeping with previous studies[4,9,10,16], TCP which was assessed by both VAS for TCP and TOPICOP©scale was found to be significantly higher in the TCs poor adherence group. This finding contradicts a similar study by *Muller et al*[3] which found that TOPICOP scales were unreliable to detect TCP related TCS non-adherence. These differences in findings could probably be attributed to their relatively small sample size and response bias that may happen because they solely grouped their subjects into adherence vs non-adherence based on binary answers. By doing so it could result in too low or too high non-adherence rates.[3] Additionally,

Table 4. Comparing between TOPICOP© scale and clinical characteristic

Characteristic	n (%)	TOPICOP scores, mean (SD)	T statistics (df) / F value (df)	*p-value*
Gender			0.49 (144)	0.626
- Female	74 (50.7)	52.21 (19.55)		
- Male	72 (49.3)	50.66 (19.04)		
Ethnicity			1.17 (3)	0.322[b]
- Malay	125 (85.6)	52.18 (19.49)		
- Chinese	14 (9.6)	42.66 (15.92)		
- Indian	4 (2.7)	56.94 (22.85)		
- Others	3 (2.1)	54.63 (15.30)		
Site of Atopic Dermatitis			-0.69 (144)	0.488
- Generalized	52 (35.6)	52.94 (18.58)		
- Localized	94 (64.4)	50.62 (19.66)		
Family history of Atopy			1.02 (144)	0.310
- No	31 (21.2)	54.57 (16.33)		
- Yes	115 (78.8)	50.60 (19.94)		
Severity of atopic dermatitis by IGA scores			0.81 (4)	0.519[b]
0-clear	1.0 (0.7)	69.44		
1-almost clear	11 (7.5)	56.82 (27.11)		
2-mild	70 (47.9)	49.01 (19.26)		
3-moderate	37 (25.3)	52.48 (17.23)		
4- severe	27 (18.5)	53.50(18.48)		
Previous history of hospitalisation			1.32 (144)	0.189
- Never	99 (67.8)	52.89 (19.07)		
- Yes	47 (32.2)	48.40 (19.47)		
Alternative treatment			-2.51 (144)	**0.013**
- No	122 (83.6)	49.70 (18.92)		
- Yes	24 (16.4)	60.30 (18.83)		
Information source regarding TCs			4.57 (144)	**<0.001**
- Non healthcare professional	43 (29.45)	62.02 (15.75)		
- Health care professional	103 (70.55)	47.03 (18.92)		

[a]*Independent t-test,* [b]*One-way ANOVA test*

we detected higher significant mean scores of both belief and worries domain of TOPICOP© scale among TCs poor adherence group, which emphasizes the need of targeted therapeutic education and patient-physician's relationship in order to address the false beliefs regarding TCs use. This is supported by a previous study, which observed an improvement in perception regarding TCs with therapeutic education on caregivers of AD patients with TCP.[9]

A significant, low and negative correlation between TOPICOP© scale and MyMAAT scale was detected in our study suggesting that TCP plays a pivotal role in contributing to TCs-non adherence among AD patients. This is further supported by a separate finding in our study which showed that subjects in the first quartile of TOPICOP© scale were associated with good TCs-adherence. However, these findings are in conflict with a previous local study by *Mazlin et al*[8] This could probably be due to different methodologies and the relatively small sample size in that study.

We were able to ascertain the factors associated with TCP including non-healthcare professionals being the primary source of information regarding TCs, as well as previous history of taking alternative treatment. The internet has been identified as the top information source leading to steroid phobia by *Lee et al*[9] Despite the questionable efficacy of complementary and alternative treatment (CAM)[21], the prevalence of CAM use among AD patients in Malaysia was remarkably high, at 46.8%.[22] CAM is preferred to TCs not only by Malaysians but is also rising in popularity globally.[23] This suggests that greater attention needs to be paid to clinical and social history to address misinformation in regard to TCP and CAM use. Interventions to direct patients to internet resources with accurate medical knowledge may help mitigate the sensationalization of steroid adverse effects while reassuring and counselling AD patients or their caregivers on appropriate TCs use. Similarly, discussions on TCs sparing agents such as tacrolimus and pimecrolimus earlier in the treatment course would empower patients or their caregivers to actively play their part in management. All these measures have been supported by a randomised controlled multi-centre study by *Heratizadeh et al*[24]. The study showed that AD patients who were educated in a multidisciplinary training programme had a significant improvement in their coping behaviour, quality of life and disease severity.

Limitation

Limitations in our study include inherent inability to avoid selection bias. As the questionnaire was administered only in English and Bahasa Malaysia, this may limit the generalisability of our findings to the overall Malaysian population. The Mandarin or Tamil only speaking populations were not adequately represented in our study population. This group, with perhaps different backgrounds and sources of knowledge, would be worth capturing in future studies.

Another major study limitation is the degree of complexity for TCP assessment. As of the time of writing, there are no established gold standard cut-off values for defining TCP and its intensity by using TOPICOP© scale. TCs-related adherence is exceedingly difficult to measure given multiple variables involved. Furthermore, as this was a self-administered questionnaire, limitations of potential misinterpretation of questions by participants were present and may be subjected to recall or response bias.

Conclusion

We conclude that there were significant positive correlations between TOPICOP© scale and VAS for TCP and TCs related non-adherence. This supports TOPICOP© scale and VAS for TCP as useful clinical tools for measuring the intensity of TCP and potentially detect TCs related non-adherence in a non-judgemental way. Further studies on optimising and assessing the effect of interventions to reduce TCP and improving clinically relevant outcomes such as TCs related adherence and quality of life among AD patients in Malaysia are warranted.

Conflict of Interest Declaration

The authors have no conflict of interest to declare.

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ORIGINAL ARTICLE

Attitudes, Health Seeking Behaviors, Expectations and Psychosocial Impact of Patients with Non- Scarring Alopecia: Results of Tertiary Outpatient Skin Specialist Clinics in Penang

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Abstract

Background

Hair loss can be a highly distressing condition due to the cosmetic value placed upon hair in many societies. This study is aimed to characterize the concerns, health care seeking behaviors, expectations and psychosocial impact of patients with alopecia plus the contributing factors.

Methods

A questionnaire-based cross-sectional study was conducted among patients who self-identified as having thinning hair, hair loss, and/or balding attending Dermatology Clinic in Hospital Pulau Pinang from July 2021 to June 2022.

Results

A total of 240 patients with hair loss problem were recruited. Approximately 75.4% of the patients had significant concern about their hair loss. Younger age, unmarried respondents and females showed higher degree of concern about hair loss ($p<0.0001$, $p=0.002$ and $p<0.0001$). The top reason for not consulting physicians were perceptions that hair loss is part of natural aging process (35.7%). Dissatisfaction among 46.5% of patients mainly stemmed from not receiving any specific treatment recommendation (48.1%) and not having all their questions answered (24.1%). About 43.8% of patients' quality of life (QoL) were at least moderately affected. Median Dermatology Life Quality Index (DLQI) was 4.0. Younger and employed respondents were more anxious, depressed and had worse QoL.

Conclusions

Individualized consideration of attitudes and concerns is crucial for effective management of patients with alopecia.

Key words: *Alopecia, attitudes, health seeking behaviors, psychosocial impact.*

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Introduction

Hair loss is a common presenting complaint in outpatient clinics, with nonscarring alopecia being the commonest cause.[1-5] Common causes of nonscarring alopecia include androgenic alopecia, alopecia areata, telogen effluvium and anagen effluvium.[6] In a community study of male androgenic alopecia in Bishan, Singapore, the prevalence of androgenic alopecia was

found to be 63%.[7] However, effective treatment modalities for alopecia are still limited and largely short-lived.[8-9]

Hair plays an important role in self-image, identity and social perception.[10-12] The psychological impact of hair loss is often overlooked due to the medically benign nature of the condition.[13] Yet, there are limited studies regarding psychological impact of patients with hair loss in Malaysia. Malaysia is a multiracial country with diverse cultures and the results from other countries might not be representative of Malaysia.

Many people with hair loss turn to non-prescription medicines, as evidenced by the fast-growing industry of non-prescription medicines for hair growth with unproven efficacy and safety.[5,14,15] Unmet expectations from hair loss consultation could have driven patients towards confusing panel of products and intervention claiming to be effective for hair loss. According to the National Center for Complementary and Integrative Health (NCCIH), a total of USD 30.2 billion dollars was spent annually on alternative medicine.[16]

To date, no study in Malaysia has attempted to evaluate the attitudes, behavior and expectations of people who do seek hair loss treatment from a physician. Studies like this are important to help physicians understand and meet patients' expectations in order to reduce the psychological barriers between patient and physician. Additionally, a better understanding on patients with alopecia will enable more effective management in the future. Hence, the objectives of this research were to study the attitudes, health seeking behaviors, expectations and psychosocial impact of patients with alopecia.

Materials and Methods

Study type and design

This is a questionnaire-based cross-sectional study conducted at the Dermatology Clinic in Hospital Pulau Pinang from July 2021 to June 2022. Hospital Pulau Pinang is the biggest tertiary public hospital in Penang receiving referrals from Northern Malaysia.

The inclusion criteria were as follows: (a) Adult patients ranging in age from 18 to 70 years old. (b) Patients who self-identified as having thinning of hair or hair loss regardless of whether they were referred for hair loss from other center or came for other skin diseases but incidentally also self-identified as having hair loss. (c) Patients who are able to give informed consent. Exclusion criteria: (a) Scarring alopecia (b) Foreigner (c) Pregnant ladies

Convenience sampling was used and direct interview by investigator was done for data collection. It was a face-to-face 30 minutes interview between investigator and patient using structured case report forms (CRF). The CRF was designed to include biodata, disease information, concerns and attitudes about hair loss, health seeking behaviors, expectations and experiences of hair loss management, and disease impact plus QoL (based on DLQI and Hospital Anxiety and Depression Scale, HADS).

Disease information gathered include onset of alopecia, anthropometric measurements and scalp examination by investigator to determine the type of alopecia. Patients convey their degree of concern on a scale from 1 = not at all concerned to 5 = extremely concerned. Attitudes and health seeking behaviors were assessed with multiple choice close-ended questions. Expectations and experiences of hair loss management was assessed with a total of 7 multiple choice close-ended questions using ratings on the level of satisfaction on a 5-point scale from 1 = completely disagree to 5 = completely agree. The questions were pilot tested on 50 patients and validated.

Both DLQI and HADS have been properly translated to native language for usage in Malaysia and validated. The DLQI questionnaire was used to assess the QoL of patients. DLQI scores 0-1=no effect at all, 2-5=small effect, 6-10=moderate effect, 11-20=very large effect and 21-30=extremely large effect on patient's

life. HADS is a 14-item scale with 7 items each for anxiety and depression subscales. HADS score 0-7=normal, 8-10=borderline abnormal and 11-21=abnormal. Approval to use HADS in English, Malay and Chinese version was obtained (ID 058041). License to use DLQI was obtained (license ID CUQoL3138).

Ethical approval was also obtained (NMRR-21-705-58779).

Statistical analysis

Sample size was calculated based on Openepi, version 3, open-source calculator. Using two-sided confidence level 95%, power 80% and odds ratio of 3.99 based on the objective of exploring the factors associated with poor quality of life.

Descriptive statistics were used to evaluate the characteristics of the sample. Mann-Whitney U test was used to compare two independent groups on an ordinal or continuous but not normally distributed dependent variable. Kruskal-Wallis test was used to determine if there was any differences between two or more groups of an independent variable on a continuous or ordinal dependent variable, followed by Dunn post hoc analysis for a significant Kruskal-Wallis test. Spearman rank correlation test (non-parametric) was used to establish the correlation between two variables measured on at least an ordinal scale. Chi-square test for independence was used to discover if there is a relationship between two categorical variables. Logistic regression was used to predict a dichotomous categorical outcome. Statistical significance was considered if $p<0.05$. Statistical analyses were performed using SPSS version 26.

Results

Sociodermographic and clinical features

Two hundred and forty patients were included in the study. The median (IQR) age was 38.5 (24) years, mostly female patients (55.4% female vs. 44.6% male). Majority was Malay (42.5%) followed by Chinese (38.3%), Indian (17.1%) and others (2.1%). Married patients accounted for 59.6% and unmarried patients 40.4%. Most patients were full time employed (54.2%) and white-collar worker (37.9%). Median age of alopecia onset (IQR) was 33.5 (21) years.

Table 1. Socio-demographic characteristics of surveyed patients (n=240)

Socio-demographic characteristics	n (%)
Age (years), median (range)	38.5 (18-70)
Age of onset (years), median (IQR)	33.5 (21)
Disease duration in months, median (IQR)	24 (75)
Sex, *n* (%)	
Male	107 (44.6%)
Female	133 (55.4%)
Race, *n* (%)	
Malay	102 (42.5%)
Chinese	92 (38.3%)
Indian	41 (17.1%)
Others	5 (2.1%)
Marital status (%)	
Married	59.6
Unmarried	40.4
Type of alopecia (%)	
Androgenic alopecia	45.0
Alopecia areata	18.8
Diffuse non scarring alopecia associated with SLE	12.9
Telogen effluvium	10.0
Others	13.3

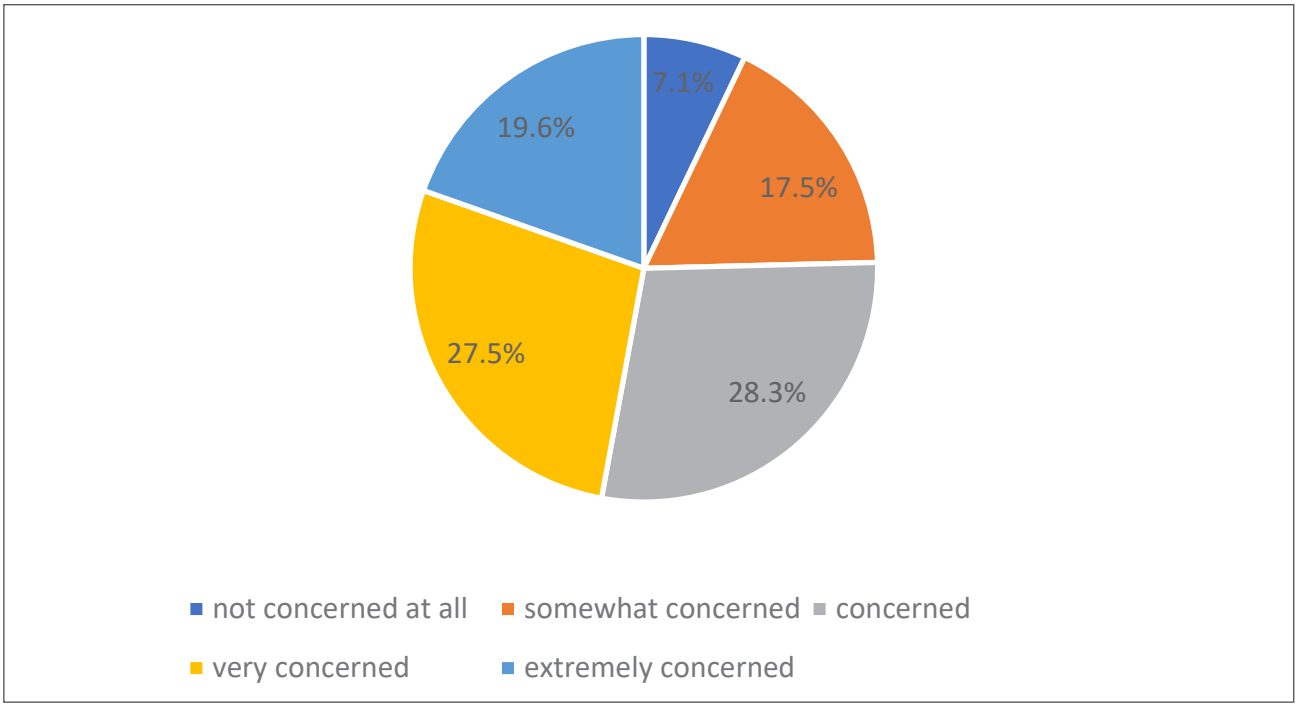
**Cell percentages may not sum to 100% due to rounding*

Table 2. Degree of concern, DLQI and HADS scores plus their correlation to a single variable

Variables	DLQI Median (IQR)[a]	HADS-A Median (IQR)[a]	HADS-D Median (IQR)[a]	Degree of concern, Median (IQR)[a]
Age in ranges (years)				
< 20	11.0 (12.5)	5.0 (7)	2.0 (4.5)	4 (2)
20 – 39	6.0 (9)	6.0 (6)	3.0 (6)	4 (2)
40 – 59	4.0 (9.8)	6.0 (6)	3.0 (4)	3 (2)
>59	1.0 (2.5)	3.0 (3)	1.0 (3)	3 (2.5)
Age 18 – 70 years	4 (8.75)	5 (6)	3.0 (5)	3 (1)
p value	*<0.0001*[b]	*<0.0001*[b]	*0.013*[b]	*<0.0001*[b]
Age of disease onset				
p value	*0.001*[b]	*0.001*[b]	*0.062*[b]	*0.003*[b]
Gender				
Male	4 (8)	5 (5)	2 (4)	3 (2)
Female	4 (10)	6 (5)	3 (5)	4 (1)
p value	*0.130*[c]	*0.201*[c]	*0.228*[c]	*<0.0001*[c]
Marital status				
Unmarried	5 (10)	6 (7)	3 (5)	4 (2)
Married	4 (8)	5 (5)	2 (4)	3 (2)
p value	*0.308*[c]	*<0.0001*[c]	*0.009*[c]	*0.002*[c]

HADS-A, Hospital Anxiety and Depression Scale-Anxiety subscale; HADS-D, Hospital Anxiety and Depression Scale-Depression subscale; DLQI, Dermatological life quality index; [a]Data presented are the median and interquartile range, [b]Spearman rank correlation test to measure association between age/age of disease onset and DLQI/HADS-A/HADS-D/Degree of concern, [c]Mann-Whitney U test to compare between gender/marital status and DLQI/HADS-A/HADS-D/Degree of concern.

Figure 1. Patients' degree of concern about hair loss, n = 240



Androgenic alopecia constitutes the main diagnosis (45.0%), followed by alopecia areata 18.8% (Table 1). A logistic regression analysis showed that patients with metabolic syndrome were more likely to exhibit androgenic alopecia (OR=3.33, 95% CI [1.60-6.96], *p=0.001*).

Concerns and attitudes about hair loss

Approximately 75.4% of the patients had significant concern (rating of 3 to 5) about their hair loss (Figure 1). Younger age and unmarried respondents showed higher degree of concern about hair loss (*p<0.0001* and *p=0.002*). Females were significantly more concerned than males (*p<0.0001*) (Table 2).

Two additional indicators of concern were the information seeking actions taken and the number of treatments tried. The most common action was discussing their hair loss with spouse or friends (62.3%), followed by researching treatments on the internet (61.3%) (Figure 2). Approximately 17.1% of the patients did not engage in any information seeking actions. In fact, 63.3% engaged in multiple information seeking actions.

Regarding treatments tried, patients were given a list of 13 types of treatments including prescription medicines, nonprescription medicines, alternative treatment, diet modification, hair filler, laser treatment, at home devices, tattoo, change hairstyle, wear headscarf, wigs or cap and stopping possible offending agent. Patients without prior treatments consist of 22.1%. Patients who had tried more than one treatment consist of 47.9%. Among those who tried treatment, 58.3% chose non-prescription medicines followed by prescription medicine 46.5% (Table 3). Further analysis showed that there was a significantly higher proportion of Malays that tried non-prescription and alternative medicine compared to other ethnicities ($p<0.0001$).

Table 3. Treatments tried or used before

Treatments tried or used before, *n* = 187	**Percentage**
Non-prescription medicines (mineral supplement/vitamin supplement/shampoo/hair tonic/others)	58.3
Prescription medicines (topical minoxidil/oral minoxidil/propecia/spironolactone/topical steroid/oral steroid/ injection steroid/methotrexate/azathioprine/cyclosporine/others)	46.5
Alternative treatments (herbal supplement/massage/others)	35.5
Change hairstyle	17.1
Wear cap	16.6
Wear headscarf	12.8
Diet modification	4.8
Wear wigs	1.1
Tattoo	0.5
Hair filler	0
Laser treatment	0
At home devices (laser comb/laser helmet/others)	0
Stop the offending agent	0

Figure 2. Information seeking actions

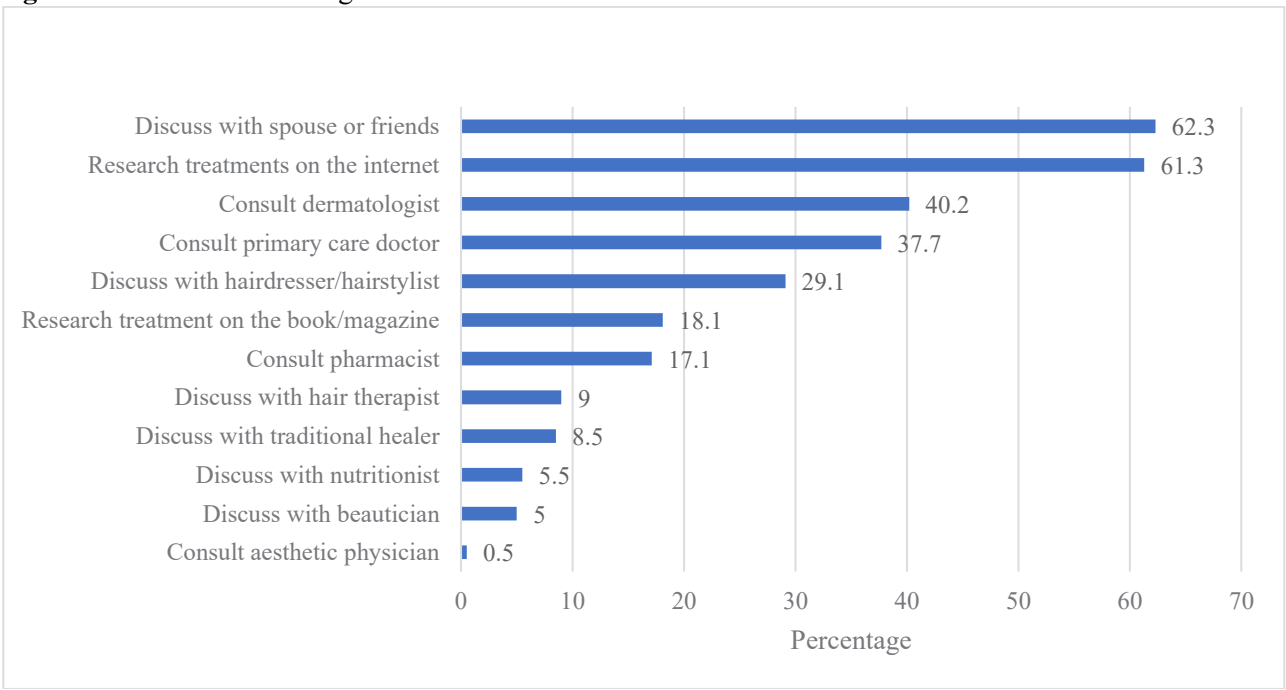


Figure 3. Reasons for not seeking physician consultation

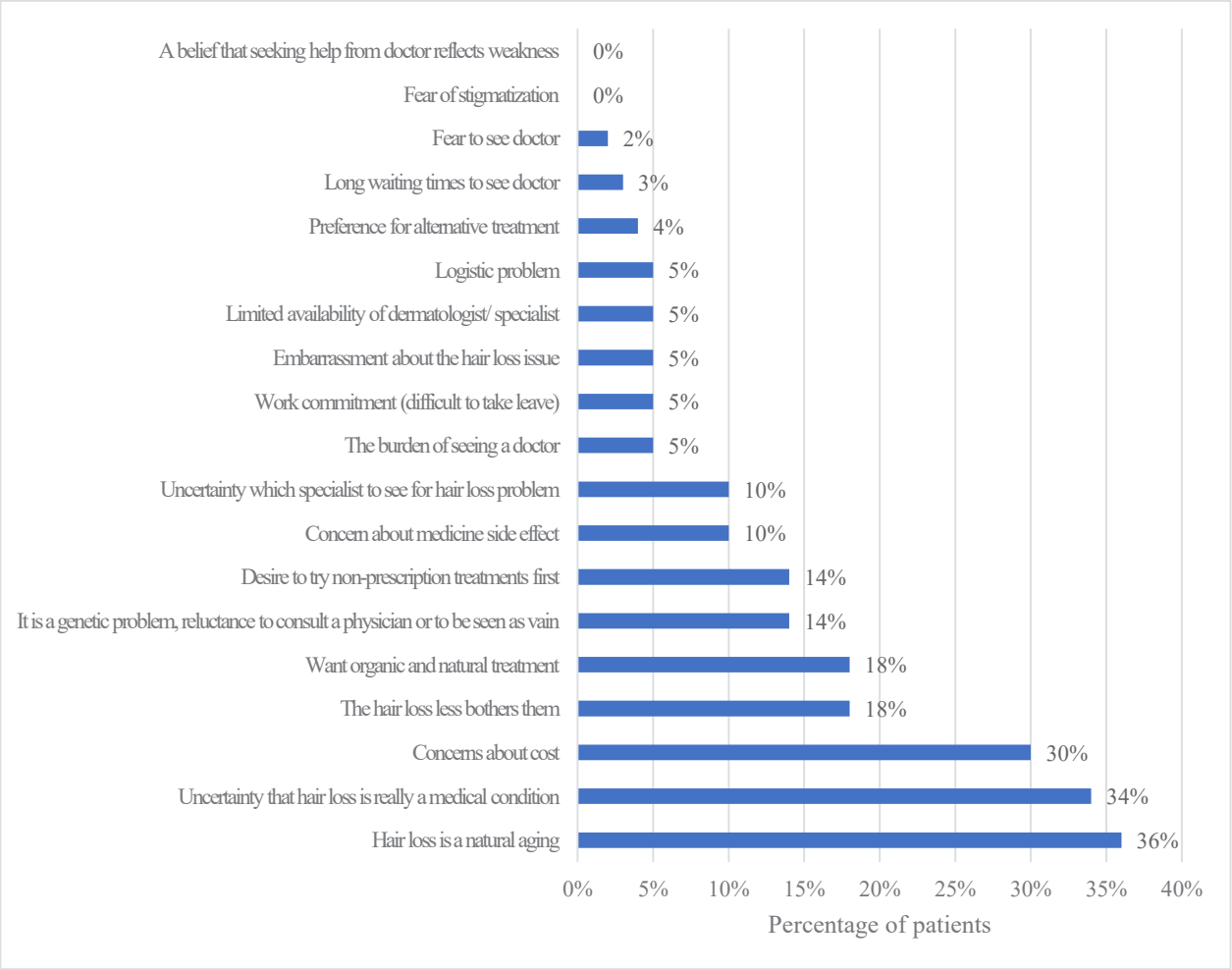


Figure 4. Reasons not satisfied with health care provider's service

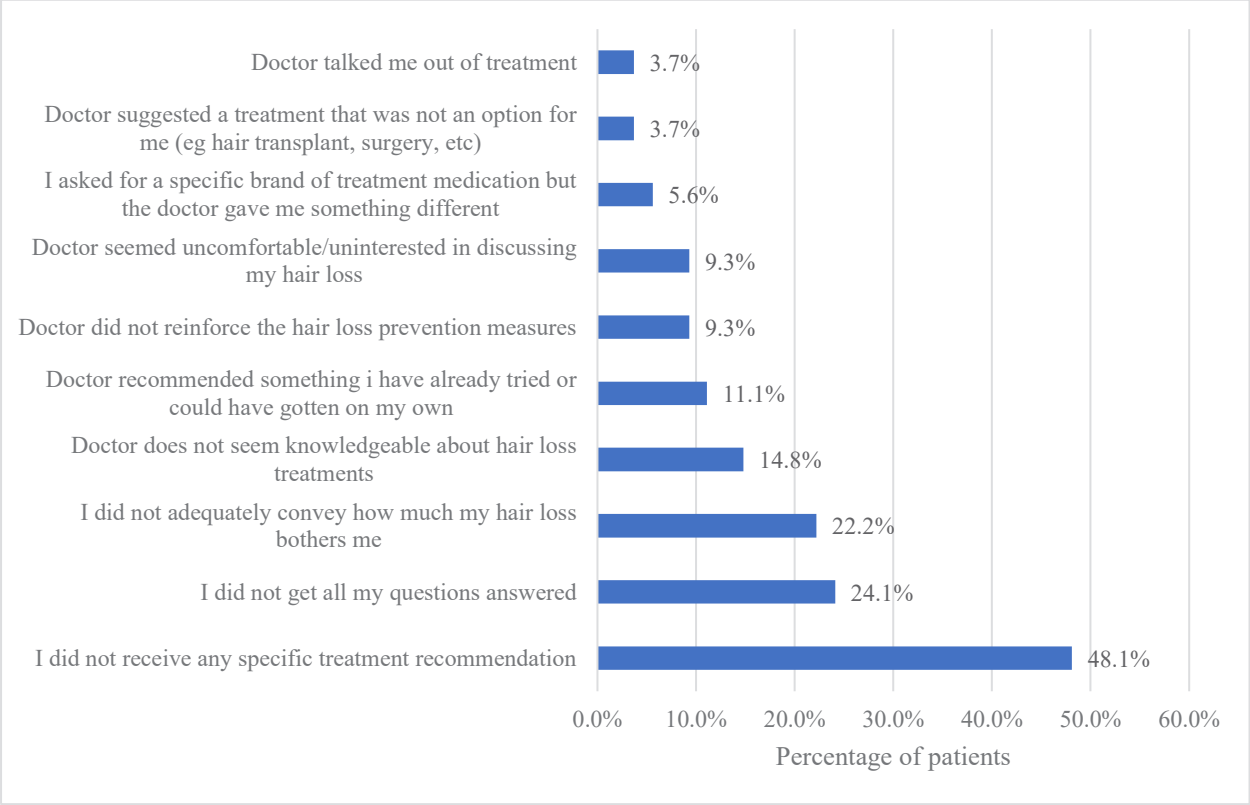


Table 4. Satisfaction with the medical and non-medical treatments that patient used to control hair loss

	Completely disagree or somewhat disagree (rating 1 or 2)	Neither agree or disagree (rating 3)	Somewhat agree or completely agree (rating 4 or 5)
Satisfaction with the medical treatments, *n* = 87			
I feel my current treatment are effective in relieving my hair loss	18.4%	34.5%	47.1%
I feel my current treatments are effective in preventing new flares of my hair loss problem	20.7%	35.6%	43.7%
The side effects are acceptable	24.1%	28.7%	47.1%
I think that my current treatments are convenient to use	9.2%	13.8%	77.0%
Satisfaction with the non-medical treatments, *n* = 146			
I feel my current treatment are effective in relieving my hair loss	34.9%	40.4%	24.7%
I feel my current treatments are effective in preventing new flares of my hair loss problem	39.7%	34.2%	26.0%
The side effects are acceptable	14.4%	22.6%	63.0%
I think that my current treatments are convenient to use	13.0%	19.2%	67.8%

Health seeking behavior

Patients seeking care at hospitals or clinics amounted to 52.9%. Among those who had consulted physicians, 68.5% had tried nonprescription medicines or alternative treatment. The top reasons for consulting a physician include concern about worsening hair loss (83.3%) and a desire to benefit from physicians' treatment expertise (58.7%). Similarly, patients who had yet to consult a physician were asked to specify the top two reasons from a list of 19 reasons. The result indicated that the top two reasons were perceptions that hair loss was part of natural aging process (35.7%) and uncertainty that hair loss is really a medical condition (33.9%) (Figure 3).

Expectations and experiences of hair loss management

Nearly half of the patients agreed (ratings 4 or 5) that medical treatments were effective in relieving hair loss problem compared to 24.7% of patients who sought non-medical treatments (Table 4). Regarding effectiveness of medical treatment in preventing new flares of hair loss, 43.7% agreed (ratings of 4 or 5) while only 26.0% for non-medical treatments. As for side effects, 47.1% (ratings of 4 or 5) thought the side effects of medical treatments were acceptable but 24.1% disagreed (ratings of 1 or 2) compared to 63.0% agreed and 14.4% disagreed for non-medical treatments. About 77.0% (ratings of 4 or 5) thought that the medical treatments were convenient to use while 9.2% disagreed (ratings of 1 or 2). As for convenience to use non-medical treatments, 67.8% agreed (ratings of 4 or 5) and 13.0% disagreed (ratings of 1 or 2). Despite these, average expenditure of non-medical treatment (RM156/month) was higher than medical treatment (RM64/month).

Evaluation of patients' experiences of their consultative visits showed that 64.6% (ratings 4 or 5) felt confident in managing their hair loss problem and able to select the right treatment by themselves after doctor's consultation compared to 27.9% after non-health care provider's visit (Table 5). There was higher percentage of patients agreed that doctors provide more relevant hair loss advice and treatment than non-health care provider (74.8% versus 35.6%). Furthermore, 75.6% (ratings of 4 or 5) of patients felt that their doctors understand how they felt about their hair loss problem versus 39.4% after non health care provider's visit. Additionally, when given a list of 10 reasons to choose from, the main reason of dissatisfaction after physician consultation was not receiving any specific treatment recommendation (48.1%) followed by not having all their questions answered (24.1%). Other common reasons were because they did not adequately convey how much their hair loss bothers them (22.2%) and their doctor did not seem knowledgeable about hair loss treatment (14.8%) (Figure 4).

Disease impact and quality of life (based on DLQI and HADS)

About 43.3% of patients' quality of life (QoL) were moderately affected (DLQI ≥6). Median (IQR) DLQI was 4.0 (9). The main domain affected in DLQI was the symptoms and feelings, followed by daily activities, leisure, interpersonal relationship, work/study and lastly treatment. Younger patients and younger age of alopecia onset were associated with worse DLQI ($p<0.0001$ and $p=0.001$). Being employed was also associated with worse DLQI compared to retired patients ($p=0.001$).

Median (IQR) Hospital Anxiety and Depression Scale-Anxiety subscale (HADS-A) was 5 (6). This is considered normal. However, further analysis comparing HADS-A score according to marital status and age showed that younger and unmarried patients were more anxious ($p<0.0001$) (Table 2). Similarly, employed patients as well as those who were unemployed due to disease were also found to have significantly worse anxiety score compared to retired patients ($p=0.002$).

Median (IQR) Hospital Anxiety and Depression Scale-Depression subscale (HADS-D) was 3.0 (5). This is considered normal. Nevertheless, further analysis revealed that younger patients were more depressed ($p=0.013$). Besides, unmarried patients with hair loss were also more depressed compared to married patients ($p=0.009$).

Table 5. Satisfaction with the health care provider or non-health care provider that patient consulted

	Completely disagree or somewhat disagree (rating 1 or 2)	Neither agree or disagree (rating 3)	Somewhat agree or completely agree (rating 4 or 5)
Satisfaction with the health care provider, *n* = 127			
I feel confident in managing my hair loss problem and I am able to select the right treatment by myself after my doctor's advice	13.6%	22.8%	64.6%
They provide relevant advice and treatment	10.2%	15.0%	74.8%
They understand how I feel about my hair loss problem	8.7%	15.7%	75.6%
Satisfaction with the non-health care provider, *n* = 104			
I feel confident in managing my hair loss problem and I am able to select the right treatment by myself with my therapist's advice	36.5%	35.6%	27.9%
They provide relevant advice and treatment	32.7%	31.7%	35.6%
They understand how I feel about my hair loss problem	23.1%	37.5%	39.4%

Table 6. DLQI and HADS scores within groups in status of occupation

Variables		DLQI Median (IQR)[a]	HADS-A Median (IQR)[a]	HADS-D Median (IQR)[a]
Status of occupation				
Employed	White collar	6 (10.75)	6 (6)	3 (5)
	Blue collar	4 (7)	6 (5)	2 (3)
	Pink collar	5 (11.5)	6 (6)	4 (6)
Unemployed	Due to disease	9 (16)	9 (8)	5 (6.5)
	Due to other reason	0 (7)	7 (12.5)	2 (8.5)
Retired		1 (3)	3 (4)	1.5 (2.25)
Student		8 (10.5)	6 (3)	2 (5.5)
Homemaker		4 (7)	4 (5)	2 (5)

HADS-A, Hospital Anxiety and Depression Scale-Anxiety subscale; HADS-D, Hospital Anxiety and Depression Scale-Depression subscale; DLQI, Dermatological life quality index; [a]Data presented are the median and interquartile range.

Discussion

In this study, androgenic alopecia constitutes the main diagnosis (45.0%), comparable to Western studies of 23% to 87%.[7] Interestingly, we found that patients with metabolic syndrome were more likely to exhibit androgenic alopecia, similar to a study by A. M. Hamed et al.[17] Further studies will be needed to assess the possible link between them.

Most patients with alopecia (75.4%) had profound concern about their hair loss, corroborated by previous studies.[18,19] Patients' concern was reflected in their behavior, with most engaging in multiple information seeking behaviors and trying multiple remedies. Sadly, most of them chose non-prescription or alternative treatments of unproven effectiveness and safety profile. Hence, public education with guidance on the appropriate help available would benefit people with hair loss problems.

Besides, our study showed that more Malays tried non-prescription and alternative medicine compared to other ethnicities. On the contrary, *Noraidatulakma et al* reported highest complementary medicine usage among Chinese with non-communicable diseases compared to other ethnicities in Malaysia.[20] Further studies are needed to look into this aspect among multi-ethnic population with hair loss in Malaysia.

Most patients did not seek care at hospitals or clinics mainly because of misconceptions about hair loss. Interventions to improve their knowledge might reduce the burden of hair loss. In this study, the main factors motivating patients to consult physicians were their concern about worsening hair loss and a desire to benefit from physicians' treatment expertise. Failure to meet these expectations resulted in dissatisfaction especially when they left without any specific treatment recommendation and with questions unanswered. These findings were similar to the study by *Cash et al* where the top two reasons for dissatisfaction with consultation among men who consulted a physician were the lack of specific treatment recommendation (66%) and having unanswered questions (54%).[18] Thus, time should be spent to discuss potential therapies and realistic treatment outcomes with patients seeking treatment for hair loss.

Expenditure on non-prescription medicines was high. In addition, *Dong et al* reported high safety risk for consumers of hair loss prevention cosmetics.[21] Hence, it is essential for physicians to be aware of the non-prescription medicines or alternative treatments available in the market boasting the ability to cure hair loss and also their safety profile to ensure effective patient counselling.

Younger patients showed higher degree of concern causing worse DLQI, anxiety and depression. This is consistent with other studies.[22-26] Younger patients were more psychologically disturbed by their hair condition because of the impact on their self-esteem, resulting in difficulty in looking for life partners.[27] Besides, peer pressure and the need for social acceptance makes them more vulnerable to depression and anxiety.[19]

Unmarried patients were also found to be more concerned and anxious compared to their married counterparts. This concurs with the study by *Ng KF et al* which showed that single patients with androgenic alopecia were more anxious and depressed compared to married patients.[22] Similarly, *Cash TF* reported considerable preoccupation, moderate stress and copious coping efforts among younger men, single men and those with earlier hair loss onset.[28] Both men and women believe that hair loss will erode their chances in romance.[29] Employed patients were similarly affected, having worse DLQI and anxiety compared to retirees. This could be because they fear that their appearances after hair loss will result in a change in their social status and job status as demonstrated by *Shi et al* in 2013.[25]

Our study shows that females were more concerned than males about their hair loss but there was no difference in DLQI or HADS. These findings are different from previous studies, whereby females felt more depressed and anxious compared to men.[22,30,31] Hence, the

possible explanation for our observation is that men's attitude towards their hair appearances nowadays are comparable to women. Men are probably as vulnerable as women to psychosocial impact of hair loss, yet less likely to admit their concern about hair loss.

The identification of these factors mentioned earlier as a risk to mental health will help physician to design specific consultations and interventions to improve patients' mental outcomes and quality of life. Psychological counselling and social support network can be used to address various psychological issues from hair loss.[13,22,32,33]

The median DLQI in our study was only 4, indicating small effect of hair loss on patients' life. This could be because DLQI is not designed specifically for alopecia. Therefore, some of the questions regarding itch, pain and physical activities are not suitable to assess the impact of hair loss. Arguably, DLQI is inappropriate to thoroughly assess quality of life related to hair loss because it mainly refers to cutaneous symptoms rather than alopecia.

Our study did not show any differences in degree of concern, DLQI or HADS among patients with different education levels, income levels or occupation. This finding is supported by the study by *Ng et al.*[22] Similarly, Zhang and Zhang found that QoL was not affected by education level.[34]

Conclusion

Alopecia leads to anxiety, depression and poor quality of life especially in younger patients. Being unmarried or employed are also added risks for psychological impact of hair loss. Appreciation of these risks and their pattern of health seeking behavior could help physicians and policy makers to improve the healthcare system and health promotion strategies. Recognition of patients' expectations and reasons for their dissatisfaction after physician consultations would help physicians to alter their communication style so as to improve treatment outcome mentally and physically.

Conflict of Interest Declaration

The authors declare no conflict of interest.

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ORIGINAL ARTICLE

Cutaneous Manifestations In Patients With Leukaemia: A 6 Months Cross-sectional Study in a Haematological Referral Centre

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Abstract

Background

Cutaneous disorders in haematological malignancies have become more common due to advancements in treatments which prolonged survival. Leukaemia is associated with a variety of cutaneous manifestations. We assessed the frequency and severity of cutaneous manifestations in patients with leukaemia in our population and identified patterns of cutaneous manifestations between myeloid and lymphocytic leukaemia.

Methods

All leukaemia patients in the Haematology ward and outpatient's clinic, Hospital Ampang were enrolled in a cross-sectional study.

Results

A total of 150 leukaemia patients were enrolled with 76 (50.7%) male and 74 (49.3%) female. Majority were Malay (58.7%) and acute myeloid leukaemia was the commonest leukaemia subtype (38.0%). 118 (78.7%) patients showed one or more cutaneous manifestations. Eczema was the commonest cutaneous manifestation (18.7%) followed by xerosis (14.7%). Cutaneous adverse drug reactions (11.3%) and infectious skin disorders (6.7%) primarily of fungal etiology (60.0%) were more frequent in myeloid leukaemia. Skin graft versus host disease (GvHD) was more common in lymphocytic leukaemia (10.3%). Interestingly, leukaemia cutis was only seen in myeloid leukaemia. Leukaemia patients with a disease duration of more than two years and previous history of eczema have significantly higher risk of developing eczema (OR=2.5, *p=0.048*; OR=3.09, *p=0.026)*.

Conclusion

Cutaneous manifestations were common in leukaemia patients and eczema was the most observed. Early identification and treatment will lead to more effective patient care and may reduce the prevalence of cutaneous manifestations in leukaemia patients.

Key words: *Leukaemia, cutaneous, manifestations*

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Introduction

Cutaneous manifestations in haematological malignancies have become more common over recent years due to advancements in treatment and transplants which prolonged survival.[1] Leukaemia is the 6th most common cancer in Malaysia with an incidence of 3.7 per 100,000 population.[2] Leukaemia is a neoplastic systemic proliferation of atypical hemopoietic cells primarily in the bone marrow with a tendency to involve peripheral blood and other

organs including the skin.[3] According to the WHO Classification of Hematopoietic and Lymphoid Tissues, leukaemia can be broadly divided into 2 types based on their origin: myeloid (myelogenous) or lymphoid (lymphocytic). Overall, there are four main subtypes of leukaemia: acute myeloid leukaemia (AML), acute lymphocytic leukaemia (ALL), chronic myeloid leukaemia (CML) and chronic lymphocytic leukaemia (CLL).[4]

Leukaemia is associated with a wide variety of cutaneous manifestations, either due to the underlying disease or secondary to their treatment. Diagnosis and management of these cutaneous diseases can be particularly challenging in patients with leukaemia who are immunosuppressed and often on multiple drugs and chemotherapeutic agents. The cutaneous manifestations are conventionally divided into specific malignant lesions and non-specific benign lesions. Approximately 25 – 50 % of patients with leukaemia or lymphoma have specific or non-specific cutaneous signs.[3] Cutaneous manifestations can be classified further into specific or primary skin disorders (leukaemia cutis) and non-specific which is either secondary to the disease (infectious dermatoses, infestations, inflammatory, neutrophilic dermatoses, paraneoplastic and other malignancies) or secondary to treatment (drug eruptions and graft vs host disease) and others such as pruritis, xerosis, acneiform eruptions and ichthyosis.

Literature on cutaneous manifestations in leukaemia is limited. There is paucity of data regarding the prevalence and types of cutaneous manifestations seen in patients with leukaemia in the Malaysian population. Therefore, the type, frequency and severity of cutaneous manifestations is unknown.

The findings of our study will allow us to fully explore the frequency and severity of cutaneous manifestations in patients with leukaemia in our population and identify the patterns of cutaneous manifestations between myeloid and lymphocytic leukaemia.

Materials and Methods

This is a cross-sectional study conducted on all leukaemia patients from September 2021 to February 2022 (6 months). Patients were recruited from the Haematology ward and outpatient's clinic, Hospital Ampang. Hospital Ampang is the main referral centre for Haematological diseases, which includes leukaemia in Malaysia. The ability to access a large cohort of leukaemia individuals allows us the opportunity to fully explore the prevalence of skin manifestations in patients with leukaemia in our local population. The inclusion criteria were patients with leukaemia confirmed from bone marrow aspiration aged 18 and above. Critically ill patients who were unable to give informed consent and where clinical assessment was difficult were excluded from the study.

All patients underwent a thorough interview and physical examination. Information was obtained on current and previous skin problems, type and status of leukaemia, full blood count and other relevant blood tests, previous history of transplant, drug history and demographic data. In cases of skin graft versus host disease (GvHD), information was also collected on the stage, severity and treatment given. Procedures such as skin scrapings, cultures and biopsy were performed according to clinical indications. The cutaneous manifestations were classified as either primary skin disorder (leukaemia cutis) or secondary to the leukaemia or treatment. Cutaneous manifestations secondary to the disease were further subclassified into infectious or inflammatory dermatoses and cutaneous manifestations secondary to treatment were subclassified into adverse drug reaction or GvHD.

The sample size of this study was calculated based on a cross-sectional study by *Aggarwal et al*[3] using a formula with finite population correction. Data from the study above indicated that the prevalence of cutaneous manifestations in leukaemia patients were 0.403. Assuming the similar prevalence in our population, we needed to recruit 142 patients to achieve 5% precision for 95% confidence interval, taking into account our population of 230 leukaemia patients from the hospital database. If the Type I error probability and precision are 0.05 and 0.05, we will need to study 142 samples. Considering the potential 5% loss of data or ineligible patients due to incomplete database, the final sample size for the study is estimated to be 150 patients.

Data analysis was performed using the IBM SPSS Statistics for Windows Version 22.0. Descriptive statistics were employed for selected variables and the findings presented based on the types and distribution of the data. Categorical data were described as frequencies and percentages, while numerical data were described as means and standard deviations, or as medians and interquartile ranges.

To study the association between two sets of categorical data, Pearson's chi-square test for independence was used, while Fisher's exact test was used if the assumptions for the Pearson's chi-square test for independence were violated. All probability values were two-sided and statistical significance was set at p less than 0.05 ($p<0.05$).

This study was conducted in compliance with ethical principles outlined in the Declaration of Helsinki and Malaysian Good Clinical Practice Guidelines. Ethical approval was obtained from the National Medical Research Registry, Malaysia (NMRR-21-1579-60940).

Results

Demographic Characteristics

A total of 150 leukaemia patients were enrolled in this study. The number of male patients were 76 (50.7%) and 74 (49.3%) were female. There was a higher proportion of patients diagnosed with myeloid leukaemia (61.3%) compared to lymphocytic leukaemia (38.7%). The mean age of patients with myeloid leukaemia was 49.5±16.55 years (ranging from 18 to 82 years) and 41.76±19.18 years (ranging from 18 to 81 years) in lymphocytic leukaemia. Majority of patients were Malay (58.7%), followed by Chinese (28.0%) and Indians (13.3%). AML was the commonest leukaemia subtype (38.0%),

Table 1. Baseline demographics and characteristics of study population

Characteristics		Myeloid leukaemia n=92 Mean±SD or n (%)	Lymphocytic leukaemia n=58 Mean±SD or n (%)
Age (years)	Mean ± SD Min, Max	49.50±16.55 18, 82	41.76±19.18 18, 81
Gender	Male	46 (50.0)	30 (51.7)
	Female	46 (50.0)	28 (48.3)
Ethnicity	Malay	55 (59.8)	33 (56.9)
	Chinese	25 (27.2)	17 (29.3)
	Indian	12 (13.0)	8 (13.8)
Duration of Leukaemia (months)	Mean ± SD Min, Max	40.78±67.90 1, 504	44.02±61.50 1, 252
Current Status:			
Acute Leukaemia	Newly diagnosed	27 (29.3)	15 (25.9)
	Remission	18 (19.6)	22 (37.9)
	Relapse	7 (7.6)	4 (6.9)
Chronic Leukaemia	Refractory	5 (5.4)	
	Chronic Phase	27 (29.3)	2 (3.4)
	Remission	1 (1.1)	12 (20.7)
	Relapse		3 (5.2)
	Blast	7 (7.6)	
Co-morbidities	Diabetes	2 (2.2)	4 (6.9)
	Chronic Kidney Disease	2 (2.2)	0 (0.0)
	Hypertension	5 (5.4)	0 (0.0)
	Ischaemic Heart disease	1 (1.1)	1 (1.7)
	Hepatitis B	2 (2.2)	1 (1.7)
Previous skin disorder	Eczema	6 (6.5)	2 (3.4)
	Psoriasis	2 (2.2)	0 (0.0)
Bone marrow Transplant		20 (21.7)	19 (32.8)
Type of transplant	Autologous	2 (2.2)	0 (0.0)
	Allogeneic	18 (19.6)	18 (31.0)
	Cord blood	0 (0.0)	1 (1.7)

followed by ALL (27.3%) and CML (23.3%). Patients diagnosed with lymphocytic leukaemia had a longer duration of disease (44.02 ± 61.50 months) compared to myeloid leukaemia (40.78 ± 67.90 months). In leukaemia patients with a previous history of skin disorder, eczema was the commonest in myeloid leukaemia (6.5%). In our cohort, 21.7% patients with myeloid leukaemia and 32.8% patients with lymphocytic leukaemia had bone marrow transplantation, with majority having allogeneic transplant (92.3%). The baseline demographics and clinical characteristics of the study population are shown in Table 1.

Cutaneous Manifestations of the Study Population

One hundred and eighteen (78.7%) of the patients showed one or more cutaneous manifestations. Table 2 summarises the characteristics of the cutaneous manifestations in the myeloid leukaemia and lymphocytic leukaemia group.

Primary Cutaneous Manifestations

Leukaemia cutis was the only specific cutaneous manifestation noted in 3(3.3%) patients with myeloid leukaemia. All 3 patients were diagnosed with AML, of which 2 patients were newly diagnosed. Leukaemic infiltrates presented as erythematous to brownish papules and nodules over the trunk and limbs. The diagnosis of leukaemia cutis was confirmed by skin biopsy in the 2 patients newly diagnosed with AML. Biopsy was refused by the third patient, as she had relapsed AML and was in the palliative stage of her disease.

Secondary Cutaneous Manifestations

One hundred and fifteen (76.7%) patients had non-specific cutaneous manifestations with 76.1% of patients in the myeloid leukaemia group and 77.6 % patients in the lymphocytic leukaemia group. The manifestations were inflammatory dermatoses (47.3%), infectious dermatoses (6.7%), other dermatoses (4.7%) and secondary to treatment (18.0%).

Inflammatory dermatoses (47.3%) were the most common cutaneous manifestation in both the myeloid leukaemia and lymphocytic leukaemia groups. Eczema was the most common (18.7%) followed by xerosis (14.7%). Of the eczema patients, majority had endogenous eczema in both the myeloid leukaemia (15.2%) and lymphocytic leukaemia groups (19.0%). The most common eczematous dermatoses were papular eczema (39.3%), followed by discoid eczema (28.6%) and seborrheic dermatitis (10.7%). Xerosis was seen in 12.0% of myeloid leukaemia patients and 19.0% of lymphocytic leukaemia patients. Psoriasis (2.0%), insect bite reaction (0.7%) and erythema nodosum (0.7%) were seen only in the myeloid leukaemia group. Acne vulgaris was more common in the myeloid leukaemia group whereas petechia/purpura and post inflammatory hyperpigmentation were more common in the lymphocytic leukaemia group. Infectious skin disorders were observed more frequently in the myeloid leukaemia group (8.7%) than the lymphocytic leukaemia group (3.4%). In the myeloid leukaemia group, fungal infections were the commonest (5.4%), followed by viral (2.2%) and bacterial (1.1%). However, in the lymphocytic leukaemia group, only two patients had an infectious dermatosis with one patient of bacterial and one patient of fungal aetiology respectively. The superficial fungal infections include, in order of frequency onychomycosis, tinea pedis, tinea corporis, tinea cruris and oral candidiasis.

Other dermatoses observed were seborrheic keratoses (two), keloid (one), dermatofibroma (one), idiopathic guttate hypomelanosis (one), trichoepithelioma (one) and angiokeratoma of Fordyce (one).

Cutaneous adverse drug reactions were more frequent in the myeloid leukaemia (14.1%) than the lymphocytic leukaemia group (6.9%). Anagen effluvium (5.3%) was the most common cutaneous adverse drug reaction, followed by maculopapular eruption (2.0%) and mucositis (2.0%). Most of the drug reaction in our study was due to chemotherapeutic agents (82.4%), followed by sulfamethoxazole/trimethoprim (11.8%) and allopurinol (5.9%).

Skin GvHD was more frequent in the lymphocytic leukaemia group (10.3%) than the myeloid leukaemia group (4.3%). All cases of GvHD occurred following allogeneic stem cell transplant. There were equal number of patients with acute (5.1%) and chronic GvHD (5.1%) in the lymphocytic leukaemia group. In our population of GvHD, majority of patients had chronic GvHD (60.0%). All chronic GvHD patients clinically had lichenoid manifestation. Sclerodermoid GvHD was not seen in our study. Of the patients with acute skin GvHD, all patients were in stage 1 and 2 of their disease.

Table 2. Characteristics of cutaneous manifestations

Cutaneous manifestations	All patients n=150 n (%)	Myeloid leukaemia n=92 n (%)	Lymphocytic leukaemia n=58 n (%)
All cutaneous manifestation	118 (78.7)	73 (79.3)	45 (77.6)
Leukaemia cutis*	3 (2.0)	3 (3.3)	0 (0.0)
Inflammatory dermatoses*	71 (47.3)	40 (43.5)	31 (53.4)
Eczema	28 (18.7)	16 (17.4)	12 (20.7)
Endogenous	25 (16.7)	14 (15.2)	11 (19.0)
Exogenous	3 (2.0)	2 (2.2)	1 (1.7)
Psoriasis	3 (2.0)	3 (3.3)	0 (0.0)
Insect bite reaction	1 (0.7)	1 (1.1)	0 (0.0)
Erythema nodosum	1 (0.7)	1 (1.1)	0 (0.0)
Acne vulgaris	6 (4.0)	4 (4.3)	2 (3.4)
Xerosis	22 (14.7)	11 (12.0)	11 (19.0)
Petechiae/purpura	7 (4.7)	3 (3.3)	4 (6.9)
Post inflammatory hyperpigmentation	3 (2.0)	1 (1.1)	2 (3.4)
Infection*	10 (6.7)	8 (8.7)	2 (3.4)
Bacterial Cellulitis	1 (0.7)	0 (0.0)	1 (1.7)
Paronychia	1 (0.7)	1 (1.1)	0 (0.0)
Viral Herpes Zoster	2 (1.3)	2 (2.2)	0 (0.0)
Fungal Candidiasis	1 (0.7)	1 (1.1)	0 (0.0)
Dermatophytes	5 (3.3)	4 (4.3)	1 (1.7)
Other Dermatoses*	7 (4.7)	5 (5.4)	2 (3.4)
Dermatoses Secondary to Treatment:	27 (18.0)	17 (18.5)	10 (17.2)
Cutaneous Adverse Drug Reaction (cADR)*	17 (11.3)	13 (14.1)	4 (6.9)
Anagen effluvium			
Maculopapular eruption	8 (5.3)	6 (6.5)	2 (3.4)
Mucositis	3 (2.0)	3 (3.3)	0 (0.0)
Erythema multiforme	3 (2.0)	2 (2.2)	1 (1.7)
Others	1 (0.7)	1 (1.1)	0 (0.0)
	2 (1.3)	1 (1.1)	1 (1.7)
Graft versus host disease (GvHD)*			
Acute Maculopapular	10 (6.7)	4 (4.3)	6 (10.3)
Vesicobullous	2 (1.3)	0 (0.0)	2 (3.4)
Chronic. Lichenoid	2 (1.3)	1 (1.1)	1 (1.7)
	6 (4.0)	3 (3.3)	3 (5.2)

**One patient may have more than one mucocutaneous manifestations; the percentage reported is based on the total patients in each group*

Table 3. Univariate analysis of risk factors for eczema

Risk factors for eczema		Crude Odds Ratio	95% Confidence Interval		*p value*
		Lower Limit	Upper Limit		
Age	40 and below	1.00	-	-	
	Above 40	1.73	0.73	4.14	0.22
Gender	Male	1.99	0.85	4.65	0.11
	Female	1.00	-	-	
Ethnicity	Malay	1.00	-	-	
	Chinese	1.73	0.71	4.18	0.23
	Indian	0.54	0.11	2.58	0.44
Diagnosis	Myeloid leukaemia	0.81	0.35	1.86	0.61
	Lymphoid leukaemia	1.00	-	-	
Duration	Less than 1 year	1.00	-	-	
	1 – 2 years	0.76	0.15	3.93	0.75
	More than 2 years	2.53	1.01	6.32	0.05
Previous history of eczema	No	1.00	-	-	0.03
	Yes	3.09	1.15	8.31	
Co-morbidity	No	1.00	-	-	
	Yes	1.01	0.34	3.60	0.87
Transplant	No	1.00	-	-	
	Yes	0.94	0.36	2.41	0.89

Sub analysis was performed to determine risk factors associated with development of eczema. In our cohort, patients with disease duration of more than 2 years have 2.53 odds of eczema compared to patients less than one year of disease (OR=2.53, 95% CI 1.01-6.32, *p=0.05*). Patients with previous history of eczema have 3.09 odds of eczema compared to patients without any previous history of eczema (OR=3.09, 95% CI 1.15-8.31, *p=0.03*). There was no significant association between age, gender, ethnicity, type of leukaemia, co-morbidities, and history of bone marrow transplant with the occurrence of eczema observed in our study. These findings are shown in Table 3.

Discussion

In 2020, leukaemia was estimated to be the 15th and 11th most frequent cause of cancer incidence and cancer-related mortality worldwide, accounting for 474,519 cases and 311,594 deaths respectively.[5] The Malaysian National Cancer Registry reported leukaemia as the sixth most common cancer in Malaysia, 7th in males and 9th in females. Malays had the highest incidence rates followed by Chinese and Indians in both sexes.[2] Majority of patients in this study were Malay with a male preponderance, consistent with national demographics. This similar finding of male preponderance was seen in previous studies.[6-8] The mean age of our patients with myeloid leukaemia was 49 years and lymphocytic leukaemia, 41 years. The National Cancer Registry showed a much higher age at 65-74 years for myeloid leukaemia and lower age in lymphocytic leukaemia at 0-14 years.[2] However, we recruited only patients aged 18 years and older, therefore we are unable to make a true comparison of the mean age.

Hospital Ampang is a tertiary referral centre for haematological cancer and serves as the main referral centre for patients with leukaemia in Malaysia. More than two thirds of our study population had acute leukaemia, and about a third had chronic leukaemia. CLL accounted for only 11.3% of our cases. CLL is the most common leukaemia among adults in western countries.[9] Asians and Asian descendants reported lower incidences of CLL and this is probably due to differences in genetic makeup.[3,7,10]

The prevalence of cutaneous manifestations in leukaemia patients range from 25-50%.[3,12] Up to 88% of patients admitted to a Hemato-Oncology unit had a mucocutaneous disorder.[11] The prevalence of cutaneous manifestations in our cohort was notably high (78.7%). Cutaneous manifestations occurred irrespective of gender, age, ethnicity, and leukaemia subtype. This high prevalence is likely attributed to the recruitment of patients in a tertiary haematology referral center similar to that observed by Pearson et al.[11]

Specific Cutaneous Manifestations

Leukaemia cutis also known as *myeloid or granulocytic sarcoma*, is the cutaneous infiltration by neoplastic leukocytes (myeloid or lymphoid) resulting in identifiable cutaneous lesions.[13,17] The incidence of leukaemia cutis varies based on the underlying type of leukaemia and is reported in 1-50% in patients with leukaemia.[14,15] Leukaemia cutis occurs most commonly in AML, where its prevalence has been reported to be approximately 3%–8%, up to 50% of cases of acute myelomonocytic (M4) and acute monocytic (M5) subtypes and in about 2% of patients with CML.[13,15-17] The prevalence of leukaemia cutis in our cohort was 2% and all patients were diagnosed with AML.

Leukaemia cutis does not have a characteristic clinical appearance. Depending on whether leukaemia cells infiltrate the epidermis, dermis, or subcutaneous fat, the clinical presentation is highly variable and may mimic other skin diseases.[3] Leukaemia cutis has varied clinical manifestations ranging from papules, macules, plaques, nodules, ecchymoses, palpable purpura, and ulcerative lesions. Therefore, a high index of clinical suspicion is required, and skin biopsy performed promptly. The most common lesions being multiple papules and nodules (60%) and infiltrated plaques (26%).[18] All our patients presented with multiple papules and nodules. The development of leukaemia cutis portends a poor prognosis. Presence of leukaemia cutis indicates that the disease will follow an aggressive course with shorter survival and predisposed to relapse.[17,19]

Inflammatory Dermatoses

Inflammatory dermatoses were the most common cutaneous manifestation seen in our study in both the myeloid leukaemia and lymphocytic leukaemia group. Of these, eczema was the most common followed by xerosis, petechiae/purpura and acne vulgaris. In contrast to our findings, *Aggarwal et al* showed that infectious dermatoses were the commonest manifestations seen in haematological and leukaemic patients.[3] A retrospective review conducted in the haematology unit in a tertiary level hospital in Singapore where more than half of the patients had myeloid or lymphoid malignancies,

showed that infectious dermatoses (15%) and eczematous dermatitis (13.33%) were the most common diagnoses.[20]

Our study showed that a longer duration of leukaemia and a previous history of eczema were risk factors associated with the development of eczema. Leukaemic patients are thought to have an increased risk for immune-mediated (eczematous) lesions compared to other onco-hematologic patients due to immunological mechanisms and production of cytokines or autoantibodies resulting from the neoplasm itself.[1]

Xerosis which is dryness of the skin was the second commonest cutaneous manifestation in our patients. Patients with advanced malignancy commonly exhibit non-specific cutaneous signs such as xerosis and pruritis which is attributable to many causes including malnutrition, dehydration, and cachexia.[21]

Pallor, spontaneous haemorrhage, petechiae and ulceration occur more frequently in acute than chronic leukaemia.[22] In our study population, 7 patients had petechia/purpura secondary to thrombocytopenia. All 7 patients had acute leukaemia and amongst them, 4 patients had ALL which is analogous to that reported by a study in Bangladesh.[22] However, a study by *Agnew et al* showed that from clinical experience ecchymoses and purpura were common in CLL patients.[12]

Infections

The immunosuppressed status in patients with leukaemia makes them prone to develop uncommon and opportunistic infections.[3] Infective dermatoses are the most common cutaneous disease in leukaemic patients.[3,20,22] However infective dermatoses was the second most common manifestation in our study. Superficial fungal infections were the predominant cause of infective dermatoses and was observed more frequently in patients with AML. Similar findings were also reported by Desch et al. and a higher prevalence of superficial fungal infections (14.69%) was reported in a Turkish study.[23,24] However, Aggarwal et al reported that fungal infections were more common in patients with CML.[3] There was no deep fungal infection in any of our cases. Although, superficial fungal infection was the most frequently observed finding, it's frequency probably reflects the high incidence in our local population independent of the patient's underlying leukaemia. Fungal infections are commonly seen in immunosuppressed conditions, but no relationship exists between superficial dermatophyte infections and internal malignant diseases.[24]

The risk of herpes zoster is generally increased in internal malignancies due to immune suppression. It is most often seen in haematological malignancies especially in leukaemia.[24] In our study, herpes zoster infection was seen in two patients with AML who were not on antiviral prophylaxis. Aggarwal et al reported that viral infections were more common in patients with ALL and oral acyclovir is recommended for prophylaxis against varicella infection in patients with haematological malignancies.[3] Interestingly, in our study there was a low prevalence of infective dermatoses, and this could possibly be because dermatology opinion was not sought as they were likely diagnosed and treated by the haematologist.

Cutaneous Adverse Drug Reactions

Dermatologic adverse events have become more prevalent and is a growing concern in patients with cancer with the introduction of novel anticancer agents.[25] The skin, mucous membranes and cutaneous appendages are tissues with rapid cellular proliferation and are thus susceptible to adverse reactions (toxic or hypersensitive) resulting from systemic chemotherapeutic treatment.[26] Haematology inpatients are often acutely sick and on multiple medications for treatment of the underlying disease and its complications and unsurprisingly this causes an increased number of cases of cutaneous adverse drug reactions (CADRs). Many of these drugs, such as beta-lactam, sulfa-based antibiotics, and allopurinol, are frequently associated with CADRs.[20]

In our study, anagen effluvium was the most common CADR, followed by mucositis and maculopapular

eruption. Similar CADRs were reported in an Egyptian study on leukaemia and lymphoma patients.[26] Most of our CADR were secondary to chemotherapy, followed by antibiotics such as sulfamethoxazole/trimethoprim and allopurinol, which was also portrayed in other studies.[20] Sulfamethoxazole/trimethoprim is often used in leukaemia patients for *Pneumocystis jirovecii* pneumonia prophylaxis as they are at increased risk of opportunistic infections. These CADRs can impede effective management of leukaemia patients. In our study, although patients were exposed to many medications, especially chemotherapeutic agents and antibiotics, there was a low prevalence of cutaneous adverse drug reactions and there was no incident of severe or life threatening CADR.

Graft versus Host Disease (GvHD)

GvHD is an immune-mediated reaction and a major complication following allogeneic hematopoietic stem cell transplantation (HSCT) and can affect between 40 and 60% of patients.[27] In our study, 6.7% of patients developed GvHD, an incidence which is much lower than that reported by previous studies.[27,28,29] This could be due to multiple factors such as patient characteristics, GvHD prophylaxis, different conditioning regimens, source of stem cells and short follow up duration. Cutaneous GvHD has been classified into acute (100 days post-transplant) and chronic (≥100 days after transplant). However, this classification may now be outdated. With novel therapies, clinical manifestations of acute GvHD can be seen after 100 days. Conversely, signs of chronic GvHD may be seen relatively early.[29] Chronic GvHD accounted for the majority of skin GvHD (60.0%) and all patients were clinically of the lichenoid type. Punatar et al. reported that ALL was significantly associated with an increased risk of chronic GvHD. However, the exact reason behind this remains unclear.[28] Interestingly, majority of our study patients had ALL. Acute mucocutaneous GvHD was seen in four patients and all patients were in clinical stage 1 and 2. Majority of our chronic GvHD patients (83.3%) had de novo chronic GvHD which is much higher than reported by Punatar et al.[28]

Limitations

This study involved only a single centre. Critically ill patients who were unable to give informed consent were not recruited, this may have an influence on the percentages of different types of cutaneous manifestations recorded in this study. Future prospective studies with a longer follow up period are needed to better describe the cutaneous manifestations in patients with leukaemia as cutaneous involvement in leukaemia patients has prognostic implications. These patients are more likely to have an advanced disease stage, poorer prognosis, and decreased overall survival.

Conclusion

Our study showed that leukaemia patients present with a wide variety of cutaneous manifestations which include leukaemia cutis, inflammatory and infective dermatoses, cutaneous adverse drug reactions and GvHD. Eczema was the most common dermatoses observed. Leukaemia cutis and GvHD may represent disease progression and warrant reassessment of the patients underlying disease state and treatment strategy. Prompt recognition and management of CADRs circumvents dose interruption or discontinuation of treatment. Hence, early identification and treatment of these patients will lead to more effective patient care.

Conflict of Interest Declaration

The authors have no conflict of interest to declare.

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ORIGINAL ARTICLE

Cutaneous Manifestations in Obese Patients and Their Risk Factors: A Cross-sectional Study in a Tertiary Center

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Abstract

Background

Obesity is increasing globally. Multiple obesity-related diseases and morbidities pose challenges in management with high health economic burden. This study investigated the type and prevalence of cutaneous diseases in obesity and its risk factors.

Methods

A cross-sectional study was conducted among patients with body mass index (BMI) >27.5kg/m^2 in Hospital Tuanku Jaafar, Negeri Sembilan, Malaysia. Data were collected via face-to-face interview. A physical examination was performed to obtain anthropometry and diagnose dermatoses.

Results

A total of 350 patients aged 54.0±11.73 years participated. There were 219 (62.6%) males and 131 (37.4%) females with 172 (49.1%) Malays, 55 (15.7%) Chinese and 119 (34.0%) Indians. Common dermatoses were acrochordon 284 (81.1%), plantar hyperkeratosis 246 (70.3%), and acanthosis nigricans 204 (58.3%). Females, grade 2&3 obesity, diabetes, and ischaemic heart disease (IHD) were significant independent risks for these dermatoses. Bacterial infection was observed in 49 (14.0%) patients, 137 (39.1%) had fungal infection. Folliculitis 41 (11.7%) and tinea pedis 55 (15.7%) were the prevalent infections. Males, grade 3 obesity, intertrigo, and hypertension were significant independent contributing factors for infections.

Conclusion

Cutaneous manifestations were common among obese patients. Recognizing risk factors and diagnosing these dermatoses will prevent further morbidities.

Key words: *Obesity, skin diseases, risk factors, body mass index, adiposity*

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Introduction

Obesity is a public health issue in Malaysia, affecting approximately 19.7% of the population.[1] In February 2020, the World Health Organization made a declaration that the prevalence of obesity had reached epidemic levels on a global scale.[2] According to the Global Burden of Disease 2019 Risk Factors Collaborators study, high body mass index (BMI) is a significant risk factor for several non-communicable diseases, ultimately

contributing to 4.7 million premature deaths in 2019. The primary cause of death was attributed to cardiovascular diseases.[3] The figures are grim in Malaysia too. According to the 2023 World Population Review, Malaysia leads Southeast Asia in obesity rates among adults, with a 15.6% prevalence. Brunei follows closely at 14.1%, while Thailand and Indonesia have rates of 10.0% and 6.9%, respectively.[4]

The National Health and Morbidity Survey (NHMS) 2019 found 50.1% of adults in Malaysia were either overweight (30.4%) or obese (19.7%).[1] Overweight and obesity levels were exceptionally high among women at 54.7%, ethnic Indians at 63.9%, and those in the 55-59 age group at 60.9%.[5]

The impact of obesity on the skin has received minimal attention. Recent studies have suggested strong associations between obesity and several skin conditions, including acanthosis nigricans, acrochordons, keratosis pilaris, and striae distensae, as well as the impact of obesity on skin homeostasis.

The dermatological ramifications of obesity stem from two main factors: firstly, the mechanical and physiological impacts resulting from the expansion of adipose tissue; and secondly, the secretion of endocrine, metabolic, and inflammatory peptides by enlarged fat cells, which essentially function as an auxiliary endocrine organ.[6]

This study aimed to describe the spectrum of cutaneous manifestation in the obese Malaysian population and to determine the association between various factors (demographic, grade of obesity, presence of other comorbidities) associated with dermatoses. This knowledge will prepare clinicians to be better at identifying and preventing these skin conditions before they become complex issues.

Materials and Methods

A cross-sectional study using a convenience sampling method was conducted among patients with obesity body mass index (BMI) >27.5 kg/m^2 between July 2021 and August 2022 at Hospital Tuanku Jaafar, Seremban, Negeri Sembilan. Patients were recruited from the Otolaryngology and General Medicine outpatient clinics. Pregnant women, lactating mothers, patients on steroid treatment, and patients less than 18 years old were excluded. Written consent was obtained. A thorough cutaneous examination from head to toe was performed. Demographic details, including age, height, weight, and the cutaneous finding were recorded.

Each participant's height was measured using a stadiometer (Health o Meter Professional), the subject stands straight with their back against the stadiometer and their feet together without shoes. The headpiece of the stadiometer is brought down to the top of the subject's head, and the height is recorded. An electronic scale (Health o Meter Professional) recorded their weight. Waist circumference was measured at the midpoint between the lower margin of the last rib and the top of the iliac crest using a standard measuring tape.

Body mass index (BMI) is a person's weight in kilograms divided by the square of height in meters. According to the Malaysian Obesity Clinical Practice Guidelines, obesity is categorized into three grades based on body mass index (BMI). Grade 1 obesity is defined as a BMI between 27.5 and 34.9, grade 2 obesity is defined as a BMI between 35.0 and 39.9, and grade 3 obesity is defined as a BMI of 40 or higher.[7]

The prevalence of obesity in Negeri Sembilan, Malaysia was estimated at 37%, with a BMI of more than 27.5kg/m2 from the National Health Morbidity Survey 2019.[1] Sample size of 399 was calculated based on these values with a 95% confidence level, 5% absolute precision and 10% dropout rate using a single proportion sample size formula.

This research was approved by the Research and Ethics Committee of Hospital Tuanku Jaafar and registered with the National Medical Research Registry. (NMRR-21-1442-60660).

Statistical analysis

The data were examined and evaluated using version 21.0 of the SPSS software. Numerical variables were displayed as mean and standard deviation, while categorical variables were presented as frequency and percentage. Pearson's chi-square tests or Fisher's exact tests were utilized to assess categorical variable distributions. A p-value below 0.05 was considered statistically significant. Simple Logistic Regression and Multiple Logistic Regression were used to determine the risk factors linked to skin manifestations in obese individuals, with or without adjusting for covariates. Odds ratios (ORs) are provided with 95% confidence intervals (CI).

Table 1. Baseline characteristics

Variables	n=350	
	Mean (SD)	n (%)
Age (yr.)	54.0 (11.73)	
Gender		
Male		219 (62.6)
Female		131 (37.4)
Race		
Malay		172 (49.1)
Chinese		55 (15.7)
Indian		119 (34.0)
Others		4 (1.1)
Education		
No schooling & Primary		54 (15.6)
Secondary		181 (52.2)
Tertiary		112 (32.3)
Marital status		
Single		36 (10.3)
Married		314 (89.7)
Smoking		
No		287 (82.0)
Yes		63 (18.0)
Alcohol consumption		
No		334 (95.4)
Yes		16 (4.6)
Blood pressure, mmHg		
Systolic	135.35 (17.97)	
Diastolic	76.12 (10.380	
Weight circumference	114.58 (15.40)	
Weight (kg)	93.72 (19.89)	
Height (cm)	162.93 (7.82)	
Body mass index (kg/m2)		
Mean BMI	35.28 (6.82)	
Grade 1 obesity	31.36 (2.06)	
Grade 2 obesity	36.93 (1.43)	
Grade 3 obesity	47.71 (6.30)	
Occupations		
Retired		88 (25.1)
Professionals		67 (19.1)
Technicians and associate professionals		10 (2.9)
Clerical support		10 (2.9)
Services and sales		46 (13.1)
Elementary		66 (18.9)
Unemployed		63 (18.0)
Co-morbidities		
Diabetes mellitus		189 (54)
Hypertension		272 (77.7)
Ischemic Heart disease		185 (52.9)
Dyslipidaemia		292 (83.4)
Metabolic syndrome		4 (1.1)

There are 3 missing data in the variable Education.

Results

A total of 350 patients participated in this study. The mean age of the patients was 54 ± 11.73 years old. Most of the patients were male, consisting of two-thirds of the total study population. Almost half of the patients belonged to the Malay ethnicity 172 (49.1%), followed by the Indians 119 (34%) and Chinese 55 (15.7%). Most at least received secondary education. Only a small number were illiterate or only received primary education. Up to 90% of patients were married, and about 80% did not smoke or consume alcohol.

The mean weight and height of the patients were 93.72±19.89kg and 162.93±7.92cm, with a waist circumference of 114±15.40cm. The mean BMI of this study patients was 35.28±6.82kg/m2. Patients from grade 1 obesity predominated, followed by grade 2 and grade 3. There were 220 (62.9%) grade 1 obese patients, 70 (20.0%) grade 2, and 60 (17.1%) grade 3. Patients also suffered from multiple comorbidities, dyslipidemia (83.4%) being the commonest, followed by hypertension (77.7%), diabetes (54.0%), and ischaemic heart disease (52.9%). The mean HbA1c was 6.85%. Table 1 summarized the characteristics of the study population.

Table 2. Cutaneous manifestation of the study population

Common Manifestation	Overall n=350 n (%) % of 300 subjects	Grade 1 obesity n=220 n (%) % of 220 subjects	Grade 2 & 3 obesity n=130 n (%) % of 130 subjects	*p-value*
Acanthosis nigricans	204 (58.3)	109 (49.5)	95 (73.1)	<0.001
Cellulite	197 (56.3)	90 (40.9)	107 (82.3)	<0.001
Androgenetic alopecia	74 (21.1)	56 (25.5)	18 (13.8)	0.010
Acrochordons	284 (81.1)	167 (75.9)	117 (90.0)	0.001
Striae distensae	167 (47.7)	78 (35.5)	89 (68.5)	<0.001
Plantar hyperkeratosis	246 (70.3)	150 (68.2)	96 (73.8)	0.263
Acne vulgaris	24 (4.9)	10 (4.5)	14 (10.8)	0.026
Keratosis pilaris	13 (3.7)	7 (3.2)	6 (4.6)	0.563[a]
Intertrigo	41 (11.7)	19 (8.6)	22 (16.9)	0.020
Hirsutism	8 (2.3)	7 (3.2)	1 (0.8)	0.267[a]
Hidradenitis suppurativa	2 (0.6)	1 (0.5)	1 (0.8)	>0.999[a]
Psoriasis	16 (4.6)	6 (2.7)	10 (7.7)	0.032
Infections				
Viral infection				
Warts	10 (2.9)	5 (2.3)	5 (3.8)	0.509[a]
Herpes labialis	1 (0.3)	1 (0.5)	0	>0.999[a]
Herpes Zoster	2 (0.6)	2 (0.9)	0	0.532[a]
Bacterial infection				
Any type of bacterial infection	49 (14.0)	27 (20.8)	22 (10.0)	0.005
Furunculosis	2 (0.6)	1 (0.5)	1 (0.8)	>0.999[a]
Folliculitis	41 (11.7)	19 (8.6)	22 (16.9)	0.020
Erysipelas	0	0	0	NE[b]
Erythrasma	1 (0.3)	0	1 (0.8)	0.371[a]
Cellulitis	9 (2.6)	3 (1.4)	6 (4.6)	0.083[a]
Fungal infection				
Any type of fungal infection	137 (39.1)	74 (33.6)	63 (48.5)	0.006
Tinea Cruris	54 (15.4)	34 (15.5)	20 (15.4)	0.986
Tinea Corporis	18 (5.1)	12 (5.5)	6 (4.6)	0.731
Tinea Unguium	9 (2.6)	3 (1.4)	6 (4.6)	0.083[a]
Tinea Pedis	55 (15.7)	26 (11.8)	29 (22.3)	0.009
Tinea Mannum	5 (1.4)	4 (1.8)	1 (0.8)	0.655[a]
Onychomycosis	39 (11.1)	25 (11.4)	14 910.8)	0.684
Candidiasis	0	0	0	NE[b]
Pityriasis Versicolor	9 (2.6)	4 (1.8)	5 (3.8)	0.301[a]
Eczema Reactions	176 (50.3)	110 (50.0)	66 (50.8)	0.889
Miscellaneous	12 (3.4)	9(4.1)	3 (2.3)	0.546 [a]

The results above were performed using Chi-Square unless specified otherwise.
a Fischer Exact Test
b non-estimable

Table 3. Factors associated with bacterial infections and fungal infections

	Bacterial Infections [a]			Fungal Infections [b]		
	Crude OR (95% CI)	**Adjusted OR (95% CI)**	***p***	**Crude OR (95% CI)**	**Adjusted OR (95% CI)**	***p***
Age, years	0.96 (0.93, 0.98)	0.95 (0.92, 0.98)	0.001	1.00 (0.99, 1.02)		
Gender				1	1	
Male	1			0.76 (049, 1.19)	0.53 (0.32, 0.88)	0.014
Female	0.97 (0.52, 1.81)					
Race						
Malay	1			1	1	
Chinese	0.69 (0.27, 1.77)			0.35 (0.17, 0.72)	0.36 (0.17, 0.76)	0.008
Indian	0.94 (0.48, 1.88)			0.88 (0.55, 1.42)	0.92 (0.55, 1.54)	0.760
Others	NE			NE	NE	NE
Level of education						
No schooling & Primary	1			1		
Secondary	3.24 (0.95, 11.10)			2.06 (1.06, 4.00)		
Tertiary	3.04 (0.85, 10.87)			1.56 (0.77, 3.17)		
Body mass index, kg/m2						
Grade 1 (27.5-35)	1	1		1	1	
Grade 2 (35-39.9)	0.69 (0.25, 1.90)	0.59 (0.21, 1.68)	0.323	1.48 (0.85, 2.56)	1.53 (0.85, 2.77)	0.156
Grade 3 (>40)	5.21 (2.63, 10.34)	3.96 (1.83, 8.55)	<0.001	2.41 (1.35, 4.31)	2.32 (1.21, 4.44)	0.011
Plantar hyperkeratosis						
No	1			1		
Yes	1.77 (0.85, 3.70)			1.32 (0.82, 2.12)		
Intertrigo						
No	1	1		1	1	
Yes	5.36 (2.44, 11.76)	6.69 (2.67, 16.76)	<0.001	4.57 (2.05, 10.22)	4.87 (2.02, 11.78)	<0.001
Presence of fungal infections						
No	1			Not applicable		
Yes	2.13 (1.16, 3.92)					
Presence of bacterial infections						
No	Not applicable			1		
Yes				2.13 (1.16, 3.92)		
Diabetes mellitus						
No	1			1		
Yes	1.05 (0.57, 1.93)			1.41 (0.91, 2.17)		
Hypertension						
No	1			1	1	
Yes	0.87 (0.43, 1.75)			1.73 (1.002, 2.97)	2.15 (1.19, 3.90)	0.011
Ischemic Heart Disease						
No	1	1		1		
Yes	0.84 (0.46, 1.53)	2.27 (1.03, 5.01)	0.042	1.08 (0.70, 1.60)		
Dyslipidemia						
No	1			1		
Yes	0.43 (0.21, 0.86)			1.16 (0.65, 2.08)		

a Multiple Logistic Regression with Forward LR was applied. Hosmer-Lemshow test (p=0.613), classification table (overall correctly classified percentage=86.7%), and Nagelkerke R^2 (0.233) were applied to check the model fitness

b Multiple Logistic Regression with Forward LR was applied. Hosmer-Lemshow test (p=0.976), classification table (overall correctly classified percentage=66.6%), and Nagelkerke R^2 (0.170) were applied to check the model fitness

Table 4. Factor associated with Acanthosis nigricans, Acrochordons and Plantar hyperkeratosis

	Acanthosis nigricans [a]			Acrochordons [b]			Plantar hyperkeratosis [c]		
	Crude OR (95% CI)	**Adjusted OR (95% CI)**	***p***	**Crude OR (95% CI)**	**Adjusted OR (95% CI)**	***p***	**Crude OR (95% CI)**	**Adjusted OR (95% CI)**	***p***
Age, years	0.99 (0.97, 1.005)			1.04 (1.02, 1.06)	1.06 (1.03, 1.09)	<0.001	1.01 (0.99, 1.03)		
Gender									
Male	1	1							
Female	0.63 (0.40, 0.97)	0.40 (0.23, 0.70)	0.001	0.66 (0.39, 1.14)	0.52 (0.28, 0.96)	0.037	0.71 (0.44, 1.13)		
Race									
Malay	1	1							
Chinese	0.20 (0.10, 0.42)	0.17 (0.07, 0.40)	<0.001	0.49 (0.25, 0.96)	0.42 (0.19, 0.92)	0.029	0.76 (0.40, 1.13)		
Indian	3.21 (1.87, 5.50)	4.59 (2.49, 8.40)	<0.001	1.78 (0.91, 3.50)	1.82 (0.87, 3.80)	0.111	1.29 (0.76, 2.18)		
Others	2.43 (0.25, 23.85)	2.33 (0.19, 27.93)	0.504	0.71 (0.07, 7.07)	0.28 (0.02, 3.25)	0.307	0.43 (0.06, 3.16)		
Level of education									
No schooling & Primary	1	1							
Secondary	1.14 (0.61, 2.13)	0.84 (0.38, 1.86)	0.659	0.78 (0.34, 1.81)			0.67 (0.33, 1.38)		
Tertiary	0.71 (0.37, 1.38)	0.41 (0.18, 0.97)	0.041	0.64 (0.27, 1.53)			0.58 (0.27, 1.23)		
Body mass index, kg/m2									
Grade 1 (27.5-35)	1	1							
Grade 2 (35-39.9)	1.95 (1.12, 3.42)	2.68 (1.36, 5.27)	0.004	1.90 (0.91, 3.98)	2.30 (1.02, 5.19)	0.046	0.89 (0.51, 1.58)	0.81 (0.44, 3.39)	0.482
Grade 3 (>40)	4.54 (2.24, 9.18)	6.40 (2.86, 14.33)	<0.001	6.03 (1.81, 20.05)	10.57 (2.93, 38.15)	<0.001	2.33 (1.12, 4.87)	3.14 (1.46, 6.74)	0.003
HbA1c	1.12 (1.01, 1.25)			1.08 (0.95, 1.24)			1.11 (0.99, 1.24)		
Presence of fungal infections									
No	1	1							
Yes	2.83 (,./1.78, 4.50)	2.32 (1.35, 4.01)	0.002	2.84 (1.50, 5.36)	2.07 (1.04, 4.11)	0.038	1.32 (0.82, 2.12)		
Presence of bacterial infections									
No	1								
Yes	1.95 (1.01, 3.78)			1.22 (0.54, 2.75)			1.77 (0.85, 3.70)		
Diabetes mellitus									
No	1								
Yes	1.67 (1.09, 2.57)			1.53 (0.89, 2.62)			1.48 (0.94, 2.35)	1.62 (1.001, 2.61)	0.050
Hypertension									
No	1								
Yes	0.78 (0.47, 1.32)			1.86 (1.03, 3.37)			1.56 (0.91, 2.64)		
Ischemic Heart Disease									
No	1								
Yes	1.11 (0.72, 1.70)			1.44 (0.84, 2.47)			1.73 (1.09, 2.75)	2.07 (1.26, 3.39)	0.004
Dyslipidemia									
No	1								
Yes	0.98 (0.56, 1.74)			1.47 (0.75, 2.88)			1.57 (0.87, 2.82)		

a Multiple Logistic Regression with Forward LR was applied. Hosmer-Lemshow test (p=0.0.610), classification table (overall correctly classified percentage=71.2%), and Nagelkerke R^2 (0.389) were applied to check the model fitness

b Multiple Logistic Regression with Forward LR was applied. Hosmer-Lemshow test (p=0.463), classification table (overall correctly classified percentage=82.4%), and Nagelkerke R^2 (0.242) were applied to check the model fitness

c Multiple Logistic Regression with Forward LR was applied. Hosmer-Lemshow test (p=0.797), classification table (overall correctly classified percentage=70.3%), and Nagelkerke R^2 (0.079) were applied to check the model fitness

The results showed that the most common type of cutaneous manifestations encountered in the obese population was acanthosis nigricans (58.3%), acrochordons (81.1%), and plantar hyperkeratosis (70.3%). Androgenetic alopecia (25.5%) was more commonly found in grade 1 obesity. On the other hand, the most common cutaneous manifestation found in Grade 2 and 3 Obesity were acanthosis nigricans (73.1%), acrochordons (90%), cellulite (82.3%), striae distensae (68.5%) and psoriasis (7.7%).

Fourteen percent of patients suffered from bacterial infection and 39.1% had fungal infection. Folliculitis was observed more with grade 2 and 3 obesity (*p=0.02*). Tinea pedis was significantly more common in grade 2 and 3 obesity (*p=0.009*). Other types of bacterial and fungal infections were not related to the grade of obesity.

There were 12 possible associated factors identified for each of these dermatoses. These factors were analysed using simple logistic regression with no adjustment for other covariates. Multiple logistic regression was then conducted to assess the independent relationship of these factors with each dermatosis.

The study found that patients with Grade 3 obesity and hypertension had significantly higher odds of developing fungal infections, with odds ratios (OR) of 2.32 (95% confidence interval [CI] 1.21-4.44) and 2.15 (95% CI 1.19-3.90), respectively. In addition to that, the study revealed significant associations between Grade 3 obesity and IHD with an increased risk of bacterial infections, with odds ratios of 3.96 (95% CI 1.83-8.55) and 2.27 (95% CI 1.03-5.01), respectively. These results are shown in Table 3.

BMI was a significant independent contributing factor in the occurrence of the three most common cutaneous manifestations. Grade 3 obesity was significantly associated with acanthosis nigricans (OR=6.4, 95% CI2.86-14.33), acrochordons (OR=10.57, 95% CI 2.93-38.15), and plantar hyperkeratosis (OR=3.14, 95% CI 1.46-6.74) compared to Grade 1. Age showed a positive relationship with the occurrence of acrochordons. Each additional increase of one year in age is associated with a 6% increase in the odds of having acrochordons (adjusted OR=1.06; 95% CI 1.03-1.09; *p<0.001*). Chinese patients have lesser odds of developing these manifestations than Malays and Indians. The odds for female patients having acanthosis nigricans, acrochordons, and plantar hyperkeratosis were less than 1. These findings are shown in Table 4.

Discussion

Without a doubt, obesity is a major health concern not only due to its widespread occurrence but also its considerable socioeconomic consequences. It leads to alterations in skin physiology, predisposing individuals with obesity to a variety of skin manifestations, the prevalence of which differs across the globe. These lesions typically have a subtle onset, are asymptomatic, and often occur in areas that are inconspicuous to the eye. This study identified acrochordons, plantar hyperkeratosis, and acanthosis nigricans as the three most common skin manifestations in individuals with obesity.

Acanthosis nigricans (AN) is an indicator of adult hyperinsulinemia or insulin resistance. Its global prevalence ranges from 49% to 73%.[8-11] Over half of the study patients had AN, with an equal number having diabetes mellitus or metabolic syndrome. AN is observed mainly in the axilla, groin, and neck, although it can also appear under the breasts, on the knuckles, elbows, and face.[12] The exact pathogenesis remains unclear, but insulin is known to have a strong proliferative effect on keratinocytes at high concentrations.[13] Obese individuals tend to have elevated levels of free Insulin-like growth factor 1 (IGF-1), which can cause epidermal hyperplasia and skin thickening by binding to IGF receptors with high affinity.[14] Recent research has shown that leptin may also play a paracrine role in the skin, affecting the proliferation, differentiation, growth, and apoptosis of epithelial cells. Leptin is a hormone produced by adipose tissue that regulates energy balance by suppressing appetite and increasing

energy expenditure.

For instance, *Yazici et al* speculated that high levels of leptin could be related to the development of acanthosis nigricans in their patient.[15] Numerous studies have shown a link between the occurrence of Acanthosis Nigricans (AN) and insulin resistance. For example, Yamazaki and colleagues found a positive correlation between these factors in obese Japanese children.[16] Copeland and co-authors examined the relationship between AN and insulin resistance in children and discovered that the severity of the skin condition was linked to the Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) value. They also found AN to be an independent risk factor for insulin resistance development.[17]

Sadeghian and team studied insulin resistance in obese women with and without AN and found that skin lesions served as an indicator for insulin resistance, with no notable differences in lipid profile, triglycerides, or hypertension prevalence between the two groups.[18] Both Stoddart et al. and Kong et al. identified AN as an independent risk factor linked to hyperinsulinemia and the onset of diabetes mellitus.[19, 20] Kong's study also revealed that children with a family history of type 2 diabetes had a higher prevalence of AN, and acanthosis was more common in patients with hypertension and elevated BMI.[20] However, Hirschler et al. disagreed with these findings in their study of 1,250 Hispanic children, suggesting that AN might be more reflective of obesity than an independent factor for insulin resistance. In their research, patients with AN had a higher BMI, but insulin resistance and HOMA values did not significantly differ compared to those without acanthosis.[21] The unsightly appearance of AN may cause significant psychological distress. Treatment focuses on addressing the underlying disease, with weight loss often helping to reduce insulin resistance and fade the lesion over time.

Acrochordons, also known as skin tags, are skin-coloured or brown soft pedunculated papules often found on the neck, axillae, and groin. They were present in 81% of patients in our study, a higher percentage than the 30% reported by *Al-Mutairi N et al* and 77% by *Gomez AP et al*[22-23] The higher prevalence in this study may be attributed to a larger number of older obese patients. Skin tags tend to increase in number and size with age and in areas prone to skin irritation.[24] Skin tags are commonly found in obese individuals and those with non-insulin-dependent diabetes, with insulin resistance being a common factor between the two conditions. Hyperinsulinemia is thought to cause fibroblast proliferation in skin tags by activating insulin-like growth factor (IGF-1) receptors on their surfaces.[25]

Recent studies have attempted to demonstrate a correlation between skin tags, insulin resistance, and serum IGF-1 levels. *Jowkar et al* reported that patients with skin tags had significantly higher insulin levels than control individuals, highlighting insulin's role in skin tag development. However, a connection with IGF-1 levels remains unestablished.[26] Similar to acanthosis nigricans, insulin may not be the sole factor in skin tag formation but is likely the most crucial.[27] *Tamega et al* discovered an independent association between the presence of more than five skin tags and a 1.4-unit increase in the HOMA-IR index in dermatological patients. The significant correlation with BMI and hypertriglyceridemia found in this study supports the idea that skin tags could be markers of insulin resistance.[28] Additionally, Singh et al. found that both skin tags and acanthosis nigricans were significantly linked to insulin resistance and HOMA-IR compared to controls.[29] Skin tags are strongly related to fasting insulin levels.[25] While patients often overlook these asymptomatic lesions, they hold great importance and should not be ignored during clinical examinations, as they can indicate the need for further testing to diagnose insulin resistance.

Although large skin tags may cause discomfort, they are not typically associated with increased cancer risk. Nonetheless, obese individuals are at higher risk of experiencing inflammation from twisted or irritated skin tags.[30] Removing these skin tags can enhance skin appearance and

minimize the risk of irritation and inflammation. In our study, we observed that over 50% of the participants with both acanthosis nigricans and acrochordons (skin tags) also had diabetes. However, this finding did not demonstrate statistical significance.

Plantar hyperkeratosis was highly prevalent in the study patients, with a higher rate than the 40% and 45% reported by *Usma et al* and DivyaShree, respectively.[31, 32] The increased prevalence could be attributed to a higher number of diabetic patients in this study whereby diabetes is a known risk factor for this condition. Additionally, 32% of the participants had jobs in sales and services or held elementary positions, which may have involved prolonged standing or walking, potentially contributing to the higher rate of plantar hyperkeratosis. Excess weight changes foot anatomy due to increased pressure on weight-bearing areas and bony prominences, causing skin thickening as a compensatory mechanism. A study by Menz et al. reported that obesity was associated with a higher prevalence of plantar hyperkeratosis, with individuals having a body mass index (BMI) of 30 or higher being at a significantly higher risk.[33] The thickened skin can limit mobility and cause discomfort, particularly in weight-bearing areas such as the heel and ball of the foot. This can make it difficult for individuals to engage in physical activity, exacerbating the effects of obesity and increasing the risk of other chronic health conditions.

Obesity heightens the risk of infectious diseases, including skin infections, and adversely affects outcomes.[34-35] The link between obesity and a pro-inflammatory state, as well as reduced cell-mediated immune responses, might contribute to this increased vulnerability.[35, 36] Additionally, limited mobility and challenges in maintaining proper hygiene compound the issue. Intertrigo is an inflammatory condition affecting skin folds where the opposing skin surfaces rub against each other.[37] Macerated erythematous patches or plaques form within skin folds of inframammary, genitocrural, axillary, or abdominal regions.

Enhanced subcutaneous fat raises skin friction and moisture, creating a humid environment that intensifies local inflammation and predisposes obese individuals to dermatoses like intertrigo, accompanied by secondary overgrowth of bacteria, Candida species, and dermatophytes.[12, 37-39] The skin is home to various bacterial, fungal, and viral communities, together forming the skin microbiome.[40] *Brandwein et al* found a correlation between BMI and the skin microbiome.[41] Overweight individuals display a less diverse microbiome and a relative increase in Corynebacterium, which promotes skin inflammation.[42] Interestingly, research has also shown that skin surface pH was higher in the inguinal folds of diabetic women with a BMI of more than 25 kg/m2, further elevating the risk of skin infections.[12] If left untreated, complications from these dermatoses can be severe, potentially leading to cellulitis and sepsis.

Over the past three decades, cellulite has garnered significant attention in the cosmetics industry. This study reports a prevalence of 56.3%, rising with increasing obesity grades (40% in Grade 1 and 82% in Grades 2 and 3). These figures are lower than those reported by Sakral et al., who found a prevalence of 68%.[43] In this study, a possible explanation for the observed discrepancy is the disproportionate gender distribution of the study sample. Specifically, the male-to-female ratio was 2:1. The composition of fibrous tissue differs between men and women, with women's fibrous tissue being more tightly woven, causing a more pronounced dimpling effect.[44] Cellulite formation commences in adolescence when estrogen triggers fat accumulation in the body, especially in the thighs and hips. Over time, subcutaneous fat cells expand, and lymph fluid accumulates in these tissues, compressing fat cells, which eventually harden into lumps, resulting in cellulite.[44] Although various therapeutic approaches have been attempted, such as topical agents, injectable treatments, and energy-based devices, successful long-term procedures have yet to be identified.[45]

This study has several limitations that should be considered. Firstly, the study had a cross-sectional design, which means that it could

only observe the relationship between obesity and skin manifestations at a single point in time. Additionally, the study was conducted at a single healthcare facility, which may limit the generalizability of the findings to other populations. Moreover, the absence of a control group consisting of non-obese individuals limits the ability to determine the specific effects of obesity on skin manifestations.

There is also a possibility of selection bias, as the study recruited subjects from patients who presented to a healthcare facility with a medical condition. Another limitation is that the sample size was too small to compare the prevalence of less common skin conditions such as hidradenitis suppurativa, psoriasis, cellulitis, and erythrasma. Therefore, further research is required to better comprehend the relationship between obesity and skin manifestations and to develop more effective treatments for these conditions.

Conclusion

Obesity is associated with various skin manifestations. The common manifestations are acrochordons, plantar hyperkeratosis, and acanthosis nigricans. Individuals with higher grades of obesity, specifically Grade 3 obesity, have higher odds of developing these cutaneous manifestations. Management of obesity-related dermatoses and their complications will increase the health economic burden. Understanding the skin changes that take place facilitates better treatment and prevents sequelae.

Conflict of Interest Declaration

The authors have no conflict of interest to declare.

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ORIGINAL ARTICLE

Association Between Acanthosis Nigricans and Metabolic Syndrome at Rural Tertiary Care Hospital in Central India: A Case Control Study

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Abstract

Background

Acanthosis nigricans (AN) characterized by papillomatosis and hyperkeratosis of skin symmetrically involves neck, axilla, face, groins, antecubital, popliteal fossae, face as well as dorsum of hands and fingers. Globally Metabolic Syndrome (MS) is found to be significantly associated with AN but there is a paucity of data from rural population in Indian literature. The aim of the study is to determine association of MS with AN and compare fasting blood sugar level, lipid profile, blood pressure, and waist circumference in patients with AN to healthy controls.

Methods

Descriptive case–control study with 80 cases of AN and 80 healthy controls without AN was conducted between November 2020 and November 2022 to assess association between AN and MS.

Results

Eighty cases and 80 controls were evaluated. MS was significantly more common in AN cases than controls (50% vs 27.5%, *p=0.003*). Cases had significantly increased waist circumference for females (72.34% vs 43.48%), hypertriglyceridemia (46.3% vs 16.3%), hypertension(31.25% vs 13.75%), elevated fasting blood sugar (45% vs 17.5%) and decreased high density lipoprotein cholesterol (63.64% males and 29.79% females vs 35.29% males and 13.04% females).The association of MS with AN in our cases was statistically significant in our study population.

Conclusion

Fifty percent of patients with AN suffering from MS showed statistically significant association with individual parameters of MS. We found positive correlation between neck severity, axilla severity and neck texture with MS. All patients of AN should be routinely screened for MS. Early screening and intervention for MS can prevent future complications.

Key words: *Acanthosis nigricans, case–control study, metabolic syndrome*

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Introduction

Acanthosis nigricans (AN) is a condition characterized by papillomatosis and hyperkeratosis of the skin[1] manifesting as asymptomatic and symmetrical darkening of intertriginous areas and associated with endocrine disturbances or malignancy. It is strongly associated with obesity.[2] It is in

turn accompanied by hyperinsulinemia with development of insulin resistant diabetes mellitus.[3-4] There is an increased incidence of obesity even in rural areas due to changes in life style and sedentary life pattern secondary to increased industrialization as well as urbanization of rural areas.[5] Hence more number of cases of AN are being seen even in rural setup. MS consists of a constellation of metabolic abnormalities that increases risk of cardiovascular disease and diabetes mellitus (DM). Its features include central obesity, hypertriglyceridemia, low levels of high-density lipoprotein (HDL) cholesterol, hyperglycemia and hypertension.[6]

We have conducted this study to assess the prevalence of the MS and its associated components among individuals with AN in a rural hospital in Central India. AN may be one of the complaints of MS presenting to the dermatologist for cosmetic purpose. Therefore, these patients should be investigated for MS to avoid serious consequences.

Materials and Methods

A descriptive case control study with 80 cases of AN and 80 healthy controls without AN was conducted between November 2020 to November 2022 in a rural tertiary care hospital located in Central India in outpatient department of Dermatology, Venereology and Leprosy. Ethical clearance for the study was taken from the Institutional Ethics Committee.

A. Inclusion criteria

Cases:

1. Patients with clinical diagnosis of AN comprising of both sexes
2. Patients of 13 to 65 years of age
3. Giving written informed consent for inclusion in the study

Controls:

1. All healthy individuals of age 13-65 years not having AN of same age and sex
2. Giving written informed consent for inclusion in the study

B. Exclusion criteria

Cases:

1. Patients less than 13 years and more than 65 years of age
2. Patients with a drug history of nicotinic acid, oral contraceptives, systemic steroids, diethylstilbesterols and anti-retroviral drugs which can cause AN.
3. Pregnancy and lactating female patients
4. AN due to malignancy associated conditions
5. Autoimmune causes of AN
6. Inherited causes of AN

Controls:

1. Pregnancy and lactating female
2. Refusal of consent

Table 1. Scale for acanthosis nigricans (Adapted from *Burke JP et al*)[1]

	Neck severity
0	Absent: not detectable on close inspection.
1	Present: clearly present on close visual inspection, not visible to the casual observer, extent not measurable
2	Mild: limited to the base of the skull, does not extend to the lateral margins of the neck (usually <3 inches in breadth).
3	Moderate: extending to the lateral margins of the neck (posterior border of the sternocleidomastoid) (usually 3–6 inches), should not be visible when the participant is viewed from the front
4	Severe: extending anteriorly (>6 inches), visible when the participant is viewed from the front.
	Axilla
0	Absent: not detectable on close inspection.
1	Present: clearly present on close visual inspection, not visible to the casual observer, extent not measurable
2	Mild: localized to the central portion of the axilla, may have gone unnoticed by the participant.
3	Moderate: involving the entire axillary fossa, but not visible when the arm is against the participant's side
4	Severe: visible from front or back in the unclothed participant when the arm is against the participant's side.
	Neck texture
0	Smooth to touch: no differentiation from normal skin to palpation.
1	Rough to touch: clearly differentiated from normal skin.
2	Coarseness can be observed visually, portions of the skin clearly raised above other Areas
3	Extremely coarse: "hills and valleys" observable on visual examination.
	Knuckles – Present/ Absent
	Elbows- Present/ Absent
	Knees- Present/ Absent

The Study Design

Semi-structured questionnaire was used to collect information regarding sociodemographic profile, clinical history and investigative work-up. The study participants were subjected to thorough history taking and clinical examination. Age, sex, occupation, age of onset of AN, duration of AN, progression of AN, history of weight gain, history of drug intake for medical illness, past history of AN, medical history and family history of DM, hypertension, obesity, ischemic heart disease, family history of AN, history of smoking, alcohol intake, physical activity and treatment history were noted.

Complete cutaneous and systemic examination was done for each of the study participants. A detailed cutaneous examination for site of AN, distribution of AN (Nape of neck / axilla / Face {zygomatic / temporal / forehead / periorbital / perioral} / Knuckle / elbow / knee / groin) was noted. The overall severity of AN, neck and axilla severity and neck texture severity was assessed using the Burke's quantitative scale for acanthosis nigricans [Table 1].

Measurement of height, weight, body mass index (BMI), waist circumference (WC) and blood pressure was done. BMI was calculated using weight (Kg) and height (meters) of the patient in kg/m^2. BMI grading was done as per the WHO criteria[7] as follows:

- Underweight - BMI under 18.5 kg/ m^2
- Normal weight - BMI greater than or equal to 18.5 to 24.9 kg/ m^2
- Overweight – BMI greater than or equal to 25 to 29.9 kg/ m^2
- Obesity – BMI greater than or equal to 30 kg/ m^2
  Obesity class I – BMI 30 to 34.9 kg/ m^2
  Obesity class II – BMI 35 to 39.9 kg/ m^2
  Obesity class III – BMI greater than or equal to 40 kg/ m^2

WC was measured using a non-stretchable flexible tape in the horizontal position. It was measured by placing the measuring tapes snugly around the abdomen at the level of the iliac crest and measured in cm.

Fasting blood sugar and lipid profile investigations were done among the study participants at Clinical Biochemistry Laboratory of Hospital after 8 hours of overnight fasting and values of the corresponding reports were recorded. Photographic evaluation of the lesions were done with patient's consent.

The diagnosis of MS was based on the National Cholesterol Education Program (NCEP) Adult Treatment Panel III criteria[8] by the presence of three or more of the following criteria.

1. Central obesity: WC of ≥102 cm in males and ≥88 cm in females are the cutoff points of abdominal girth.
2. Hypertriglyceridemia: Triglyceride level ≥150 mg/dl or specific medication.
3. Low HDL cholesterol: ≤40 mg/dl in males and ≤50 mg/dl in females or specific medication.
4. Hypertension: Blood pressure ≥130 mmHg systolic or ≥85 mmHg diastolic or specific medication.
5. Fasting plasma glucose level ≥100 mg/dl or specific medication or previously diagnosed type 2 diabetes mellitus.

Statistic Analysis

The collected data was encoded and entered electronically in the computer using Excel worksheet 2021 version. Statistical analysis was done by using descriptive and inferential statistics using chi-square test and Odd's Ratio. Software used in the analysis were SPSS 27.0 version and GraphPad Prism 7.0 version and $p<0.05$ is considered as level of significance.

Results

Majority number of cases and controls belonged to the age group of 26–35 years (40% and 38.75%, respectively). The mean age of AN cases studied was 33.95±10.90 years and in controls was 32.96±11.01. In our study, females outnumbered males, about 58.75% of the cases were females and 41.25% were males and, in control group 57.5% were females and 42.5% were males.

We found that most of cases (88.75%) and controls (98.75%) were from rural area.

Majority of the AN patients were students (35%). Mean age of onset of AN was found to be 24.13± 6.18 (12-40 years). Majority cases (60%) had onset of AN between 21-30 years of age. In our study, the mean duration of AN was 9.81 ± 7.91 years. More than 50% of patients had age of onset before 10 years. Progressive AN was seen in 80% cases. Medical illnesses like hypertension, obesity, ischemic heart disease (IHD) and hypothyroidism were more significantly found in cases than controls except for diabetes mellitus [Table 2]. Family history of AN, IHD and obesity were found significant in cases than controls. Almost 57% of cases and 40% of controls lacked physical activity implying that AN was associated with sedentary lifestyle.

In our study, among the cases, 26.3 % had normal BMI, 41.3% were pre-obese, and 32.5% were obese. Among the controls, 33.8 % had normal BMI, 43.8 % were pre-obese, and 20 % were obese. The difference of BMI among the cases and control groups was not statistically significant (*p = 0.15*).

The predominant sites affected were neck in 100% of the cases (Fig.1), axilla in 83.75 % (Fig.2), face in 43.75 %. Other sites of involvement were knuckles (17.50 %), elbow (10%) and knee (5%). Commonest site of facial acanthosis nigricans (FAN) was frontal area (20 %) followed by temporal region (16.25%), Periorbital area (10%) (Fig.3), zygomatic region (8.75%) and Perioral area (1.25%).

In our study, grade 3 and 4 neck severity were seen in 53.8% and 37.5% cases respectively. Almost 50% of patients suffering from MS had neck severity of grade 3 and 4. (Fig.4)

Grade 2, 3 and 4 axilla severity were seen in 27.5%, 51.2%, 7.5% cases respectively, out of these 30% had MS with grade 3 axilla severity followed 8.75% and 6.25% had MS with grade 2 and grade 4 axilla severity respectively. Out of 55% cases having MS, 35% patients had grade 3 neck texture changes whereas 11.25% out of 40% cases had grade 2 neck texture changes.

AN was significantly associated with MS. The prevalence of MS in cases (50%) was statistically significant when compared to the control group (27.5%) (*p=0.003*) [Table 3].

Table 2. Distribution according to medical illness in two groups

Medical illness	Cases	Controls	[α]χ^2-value	*p value*
Diabetes mellitus (DM)	13 (16.3%)	10 (12.5%)	0.36	*0.54*
Hypertension (HTN)	15 (18.8%)	7 (8.8%)	4.15	***0.04***
Obesity	20 (25.0%)	7 (8.8%)	9.07	***0.002***
Ischemic heart disease (IHD)	3 (3.8%)	0 (0.0%)	4.07	***0.04***
Hypothyroidism	3 (3.8%)	0 (0.0%)	4.07	***0.04***
Total	54 (67.5%)	24 (30.0%)		

[α] χ^2: Chi square test, p<0.05: Significant

Fig 1. Acanthosis nigricans over neck

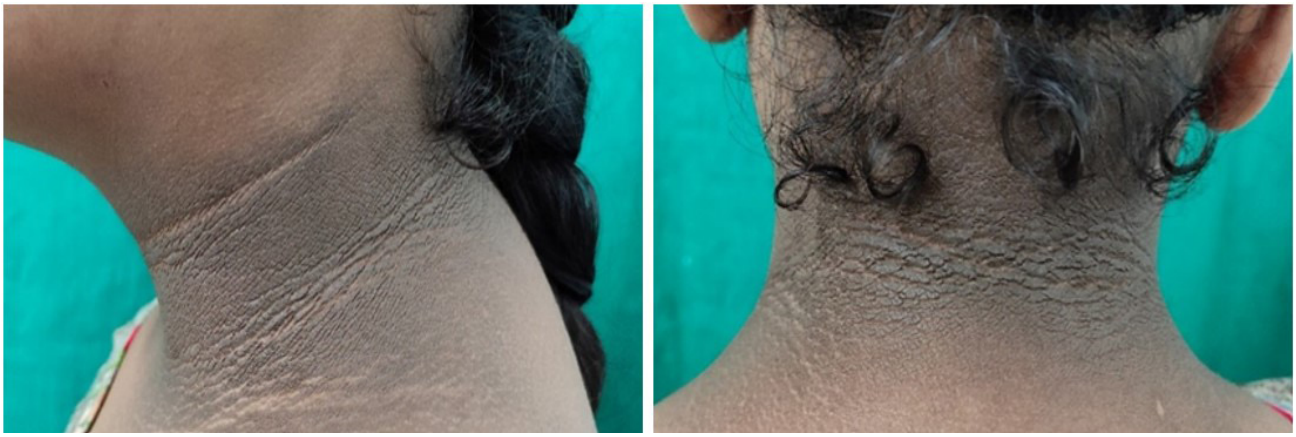


Fig 2. Acanthosis nigricans of the axilla

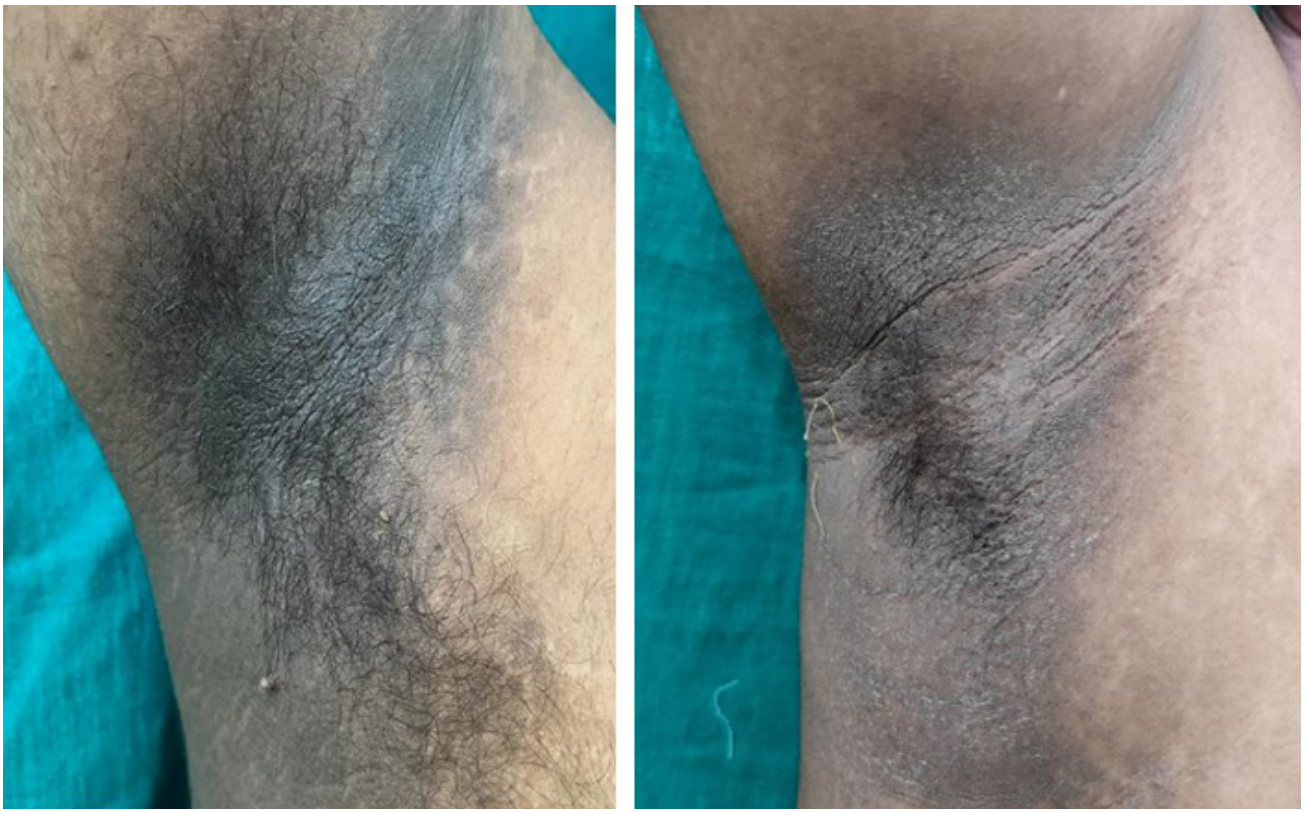
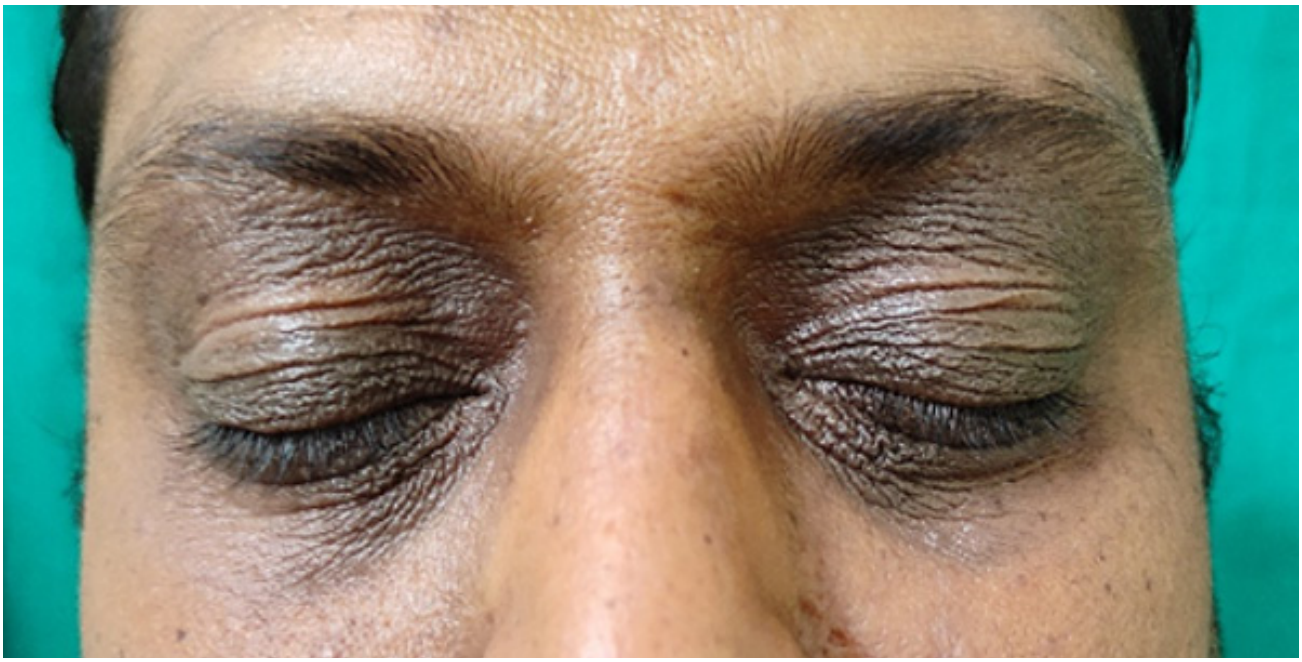


Fig 3. Periorbital facial acanthosis nigricans



We observed that parameters like HTN, FBS, HDL levels, serum TG level as well as WC for females had a positive correlation in cases as compared to the controls. However, WC for males was not statistically significant between cases of AN and controls, as summarized in [Table 4].

The above results signify that, patients of AN had higher chances of developing metabolic syndrome than normal population, so all of them should be screened meticulously and treated for the same simultaneously.

Fig 4. Patient of AN having grade 4 neck and axilla severity

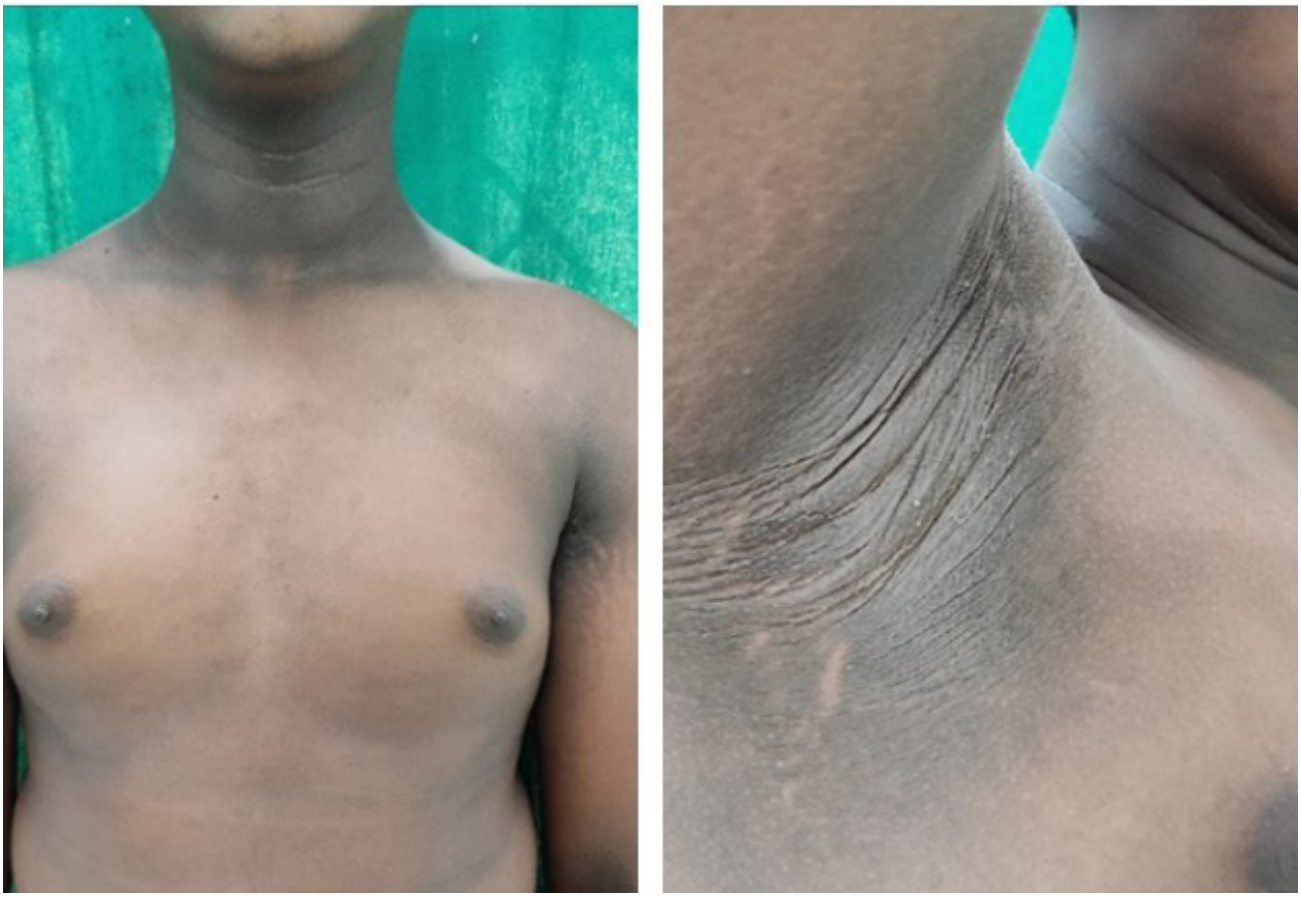


Table 3. Metabolic Syndrome (MS) in two groups

Metabolic Syndrome	Cases	Controls	χ^2-value
Present	40(50%)	22(27.5%)	**8.53** **P=0.003** ***OR=2.63** **95% CI# - 1.36-5.09**
Absent	40(50%)	58(72.5%)	
Total	80(100%)	80(100%)	

**OR: Odds ratio, # CI: Confidence interval*

Table 4. Components of metabolic syndrome in two groups

Metabolic Syndrome and it's components	Cases	Controls	χ^2-value	*p value*
MS	40(50%)	22(27.5%)	8.53	***0.003***
HTN (≥130/85mm Hg)	25(31.25%)	11(13.75%)	7.02	***0.008***
WC (>102cm for males)	18(54.55%)	11(32.35%)	3.36	*0.06*
WC (>88cm for females)	34(72.34%)	20(43.48%)	7.95	***0.004***
FBS (≥100mg/dl)	36(45%)	14(17.5%)	14.08	***0.0002***
HDL for male (<40mg/dl)	21(63.64%)	12(35.29%)	5.38	***0.020***
HDL for female (<50mg/dl)	14(29.79%)	6(13.04%)	3.86	***0.049***
TG (≥150mg/dl)	37(46.3%)	13(16.3%)	16.76	***0.0001***

Discussion

Mean age of AN cases in our study was of 33.95±10.90 years which was comparable to studies carried out by Shah et al[10] with 32.4 ± 9.8 years and Prakash et al[6] with 29.83±8.44years respectively.

In our study, females (58.75%) outnumbered males (41.25 %) comparable to studies carried out by *Prakash et al[6], Shah et al[10]* and *Puri N[12]* showing female preponderance. Grandhe et al[13] and Choudhary SV et al[14] found no significant difference in the prevalence of AN among males and females. The higher prevalence of AN in female population might be attributed to the fact that they are relatively more conscious cosmetically.

In our study the mean age of onset of AN was found to be 24.13±6.18 years(12-40 years) years. Study done by *Puri N[12]* reported the clustering of cases in the age group 11-40 years, which is comparable with our study which could be due to the cosmetic disfigurement. In our study, the mean duration of AN was 9.81 ± 7.91 years, whereas Shah et al[10] reported the mean duration to be 2.7 years which was less than found in our study.

In our study HTN (*p=0.04*), obesity (*p=0.002*), IHD (*p=0.04*) and hypothyroidism (*p=0.04*) was found significant in cases than controls except for the DM (*p=0.54*). In our study family history of AN, IHD, obesity were found significant in cases than controls which was in accordance with study conducted by *Kamel et al[9], Yadav et al[11], Nithun TM et al* thus almost confirming these associations.[16]

In our study, HTN was statistically significant in cases as compared to controls which was in accordance to study by *Shah et al[10]* and *Kamel et al[9]* again could be due to a more stressful lifestyle. In contrast to our study, *Prakash et al[6]* and *Panda et al[17]* found no association between AN and HTN. We found significant association between AN and WC in females but not in males which was in contrast to study by Dassanayake et al[18] where WC in both male and female were found statistically significant. In our study we found females had more central obesity than males because of hormonal changes, multiple gestations and sedentary lifestyle of the former.

In our study significant association was reported between AN and FBS analogous to study by *Shah et al[10], Kamel et al.[9]*

We found neck (100 %) was the commonest site of acanthosis nigricans followed by axilla (83.8%), face (43.8%), knuckles (17.5%), elbows (10.0%), knees (5.0%) which was comparable to several other studies carried out by various authors [Table 5]. Commonest site of facial AN was frontal area (forehead) followed by temporal region, periorbital area, zygomatic region, perioral area in our study similar to Panda et al[17] and *Verma et al[19]*. Acanthosis nigricans neck severity, axilla severity and neck texture showed positive correlation with MS.

With respect to dyslipidemia in our study, we found statistically significant association between AN and HDL, TG, TC but not with LDL and VLDL levels [Table 6]. AN was associated with low HDL in both males and females cases. Similar results were obtained by *Shah et al[10], Prakash et al[6]* and *Kamel et al.[9]* In this study, the value of triglycerides in cases was statistically significant (46.3%) when compared to that of controls (16.3%). Similar results were seen in studies conducted by *Shah et al[10]* and *Prakash et al.[6]*

Our study showed that AN was associated with raised total cholesterol, similar to study done by Kamel et al.[9] The prevalence of MS in cases (50%) was statistically highly significant (P< 0.01) when compared to the control group (27.5%). Similar results were seen in studies conducted by *Prakash et al[6], Shah et al[10], Balaji et al[20]* and *Dassanayake et al.[18]*

Limitations

AN cases were not investigated for serum insulin level and hence association of AN with insulin resistance was not studied.

Table 5. Comparing results of several other studies

Sites of AN	Studies with number of patients in percentage (%)				
	Present study	Kamel et al[9] 2013	Shah et al[10] 2019	Prakash et al[6] 2020	Yadav et al[11] 2022
Neck	100.0%	100.0%	100.0%	56.0%	88.0%
Axilla	83.8%	76.7%	31.0%	5.0%	46.0%
Face	43.8%	-	21.0%	2.0%	-
Knuckles	17.5%	30.0%	3.0%	-	14.0%
Elbows	10.0%	43.4%	5.0%	-	7.0%
Knees	5.0%	26.7%	-	-	-

Table 6. Dyslipidemia in cases and controls

Dyslipidemia	Cases	Controls	χ_3^2-value	*p value*
HDL<40mg/dl (male)	21 (63.6%)	12 (35.3%)	5.38	***0.02***
HDL<50mg/dl (female)	14 (29.8%)	6 (13.0%)	3.86	***0.049***
TG ≥150 mg/dl	37 (46.3%)	13 (16.3%)	16.76	***0.0001***
LDL ≥100mg/dl	18 (22.5%)	11 (13.8%)	2.06	*0.15*
VLDL≥30mg/dl	14 (17.5%)	7 (8.8%)	2.68	*0.10*
TC ≥200mg/dl	19 (23.8%)	7 (8.8%)	6.61	***0.010***

Conclusion

We conclude that Acanthosis nigricans (AN) is associated with metabolic syndrome (MS). AN is associated with individual parameters of MS (HTN, WC, FBS, HDL, TG) We found association between the neck severity, axilla severity and neck texture with MS. All the patients of AN should be routinely screened for parameters of metabolic syndrome. Early screening and intervention for metabolic syndrome and its components will be beneficial, as it prevents future complications.

Conflict of Interest Declaration

All authors have no financial/conflict of interest to be disclosed.

Acknowledgement

Nil

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CASE REPORT

Perplexing Pigmentation in a Young Child: A Case Report of Juvenile Systemic Sclerosis

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Summary
Juvenile systemic sclerosis (JSSc) is an uncommon childhood disorder involving multiple systems that leads to significant morbidity and potentially death. It differs from adult disease in its clinical presentation and the limited form is seen in only very few children. The pattern of organ involvement is also different from the adult form. In 95% of the JSS patients, prognosis appears to be better with a 5-yr survival. There is paucity of data in the literature regarding the standardised treatment of JSSc. So, here we report a rare case of 5-yr-old girl who presented with features of JSSc.

Key words: *Juvenile, systemic sclerosis, methotrexate*

Introduction
Scleroderma is a group of diseases varying in severity that can affect any stage of life, although the clinical patterns of scleroderma in children varies from those in adulthood.[1] Localized scleroderma is predominantly seen in childhood.[2] The juvenile systemic sclerosis (JSSc) form of scleroderma is an uncommon entity and has more serious, potentially life-threatening morbidity than the other sclerotic disorders. The estimated ratio of linear scleroderma to JSSc is at least 10:1 in paediatric age group.[3-4] A female predominance has been found in more than 75% patients of juvenile systemic sclerosis and disease appears to active before puberty. [5]

Case Report
A 5-year-old female child, born out of non-consanguineous marriage, delivered at term normally with an uneventful antenatal

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history came with complaints of discoloration of face, upper limbs, trunk and lower limb with tightness of skin [Figure 1] for 3 years. The symptoms first started with bilateral hands and face and gradually progressed to involve bilateral arms, neck, upper chest, bilateral feet, legs up to knee joint. [Figure 2] She had dyspnoea on exertion, early fatiguability and difficulty in swallowing of both solid and liquid food. She also had history of weight loss. There was no history of dyspepsia, or Raynaud's phenomenon. Past and family histories were non-contributory.

Clinical examination revealed a thin built child who was below 3rd percentile for weight, and below 3rd percentile for height, with a pulse rate of 88 bpm, respiratory rate 20/min and blood pressure of 90/60 mm Hg. She was pale. General and systemic examination revealed normal chest expansion. Musculoskeletal system revealed generalized wasting of muscles. Cutaneous examination showed hidebound skin in hands, forearms and legs. Salt- and-pepper dyspigmentation were noted over face, bilateral hands, legs, and feet. Facial folds were normal. Few telangiectasias were present over face. Partial flexion at proximal and distal interphalangeal joints of fingers with sclerodactyly was present.

Investigations revealed normochromic normocytic anaemia. Serum electrolytes, liver function test, renal function test, urine analysis, Chest X-ray and ECG were within normal limit. 2-D ECHO revealed no abnormality. ESR was raised. Serology revealed raised ANA levels, anti-dsDNA levels were within normal limit. Skin biopsy features were consistent with scleroderma. [Figure 3] Due to lack of facility anti-centromere and anti-topoisomerase antibodies, lung function test was not done.

Patient was started on oral Methotrexate at a dose of 10 mg/m^2 per week,[6] oral prednisolone 1mg/kg and topical tacrolimus 0.1 percent local application in rotation over tightened skin. Patient showed improvement of symptoms in one week and later was lost to follow up.

Figure 1. Skin pinch test: Inability to pinch skin due to tightness of skin

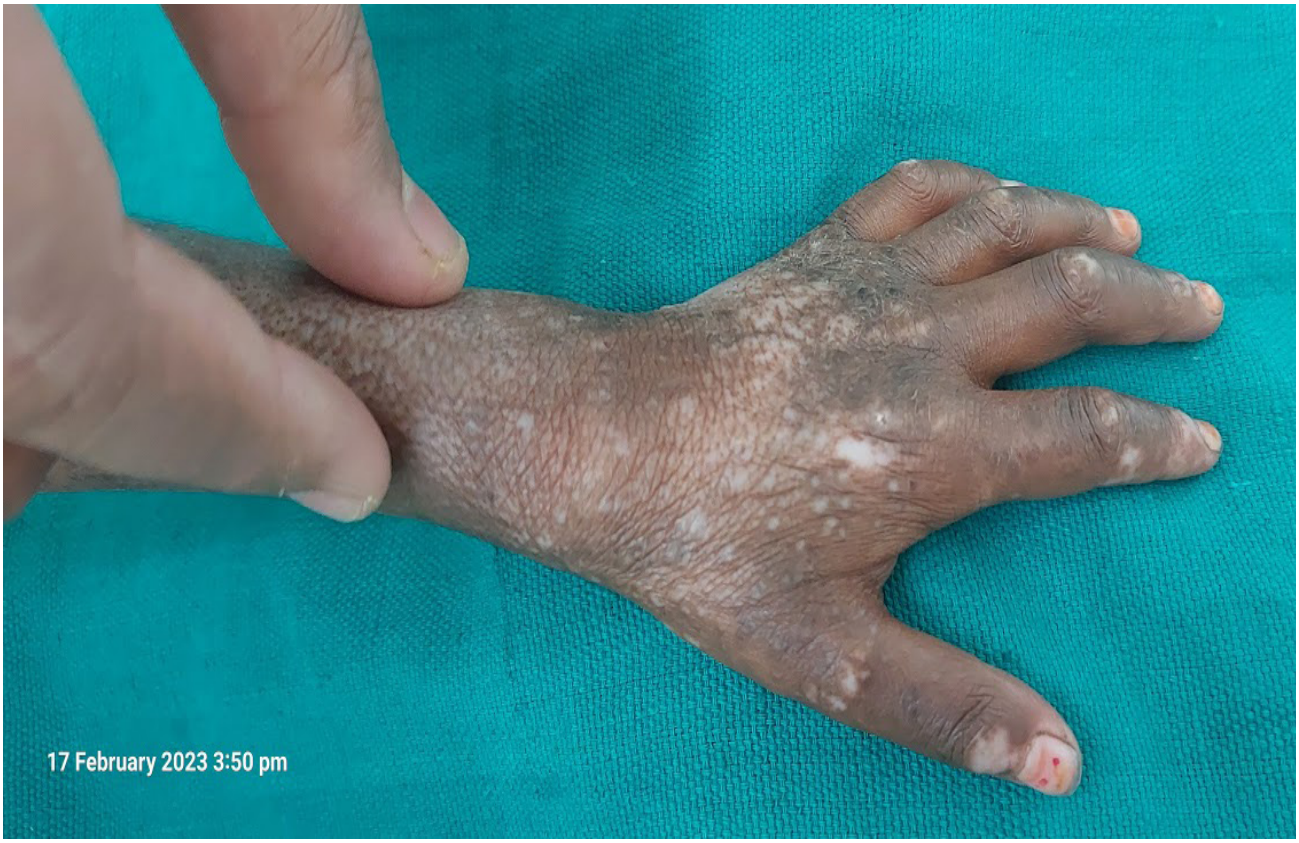
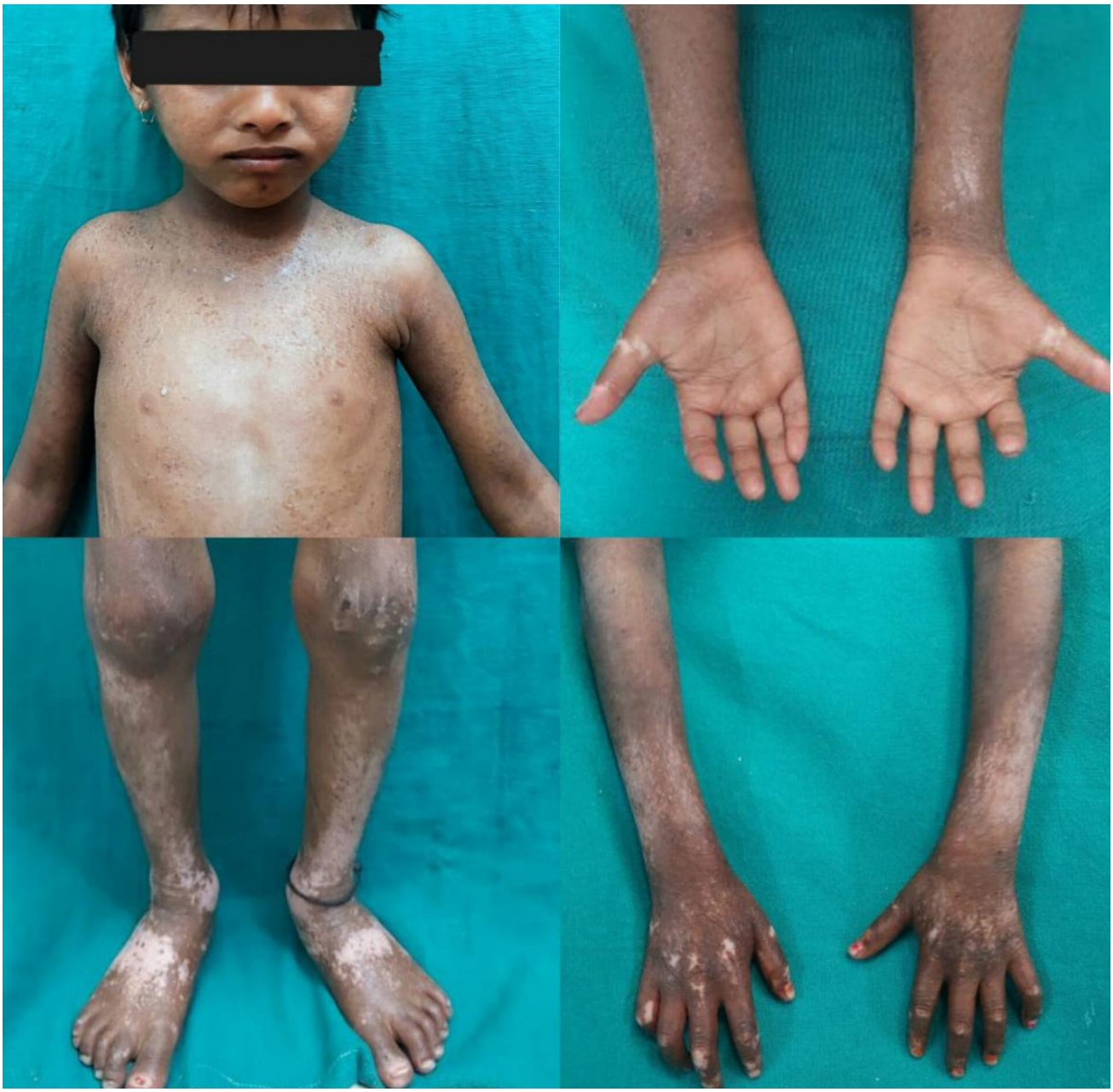


Figure 2. Salt and pepper dyspigmentation present over forehead, neck, upper chest and bilateral arms extending up to knee joint bilaterally, flexion deformity at inter-phalangeal joints of both hands showing clawing



Discussion

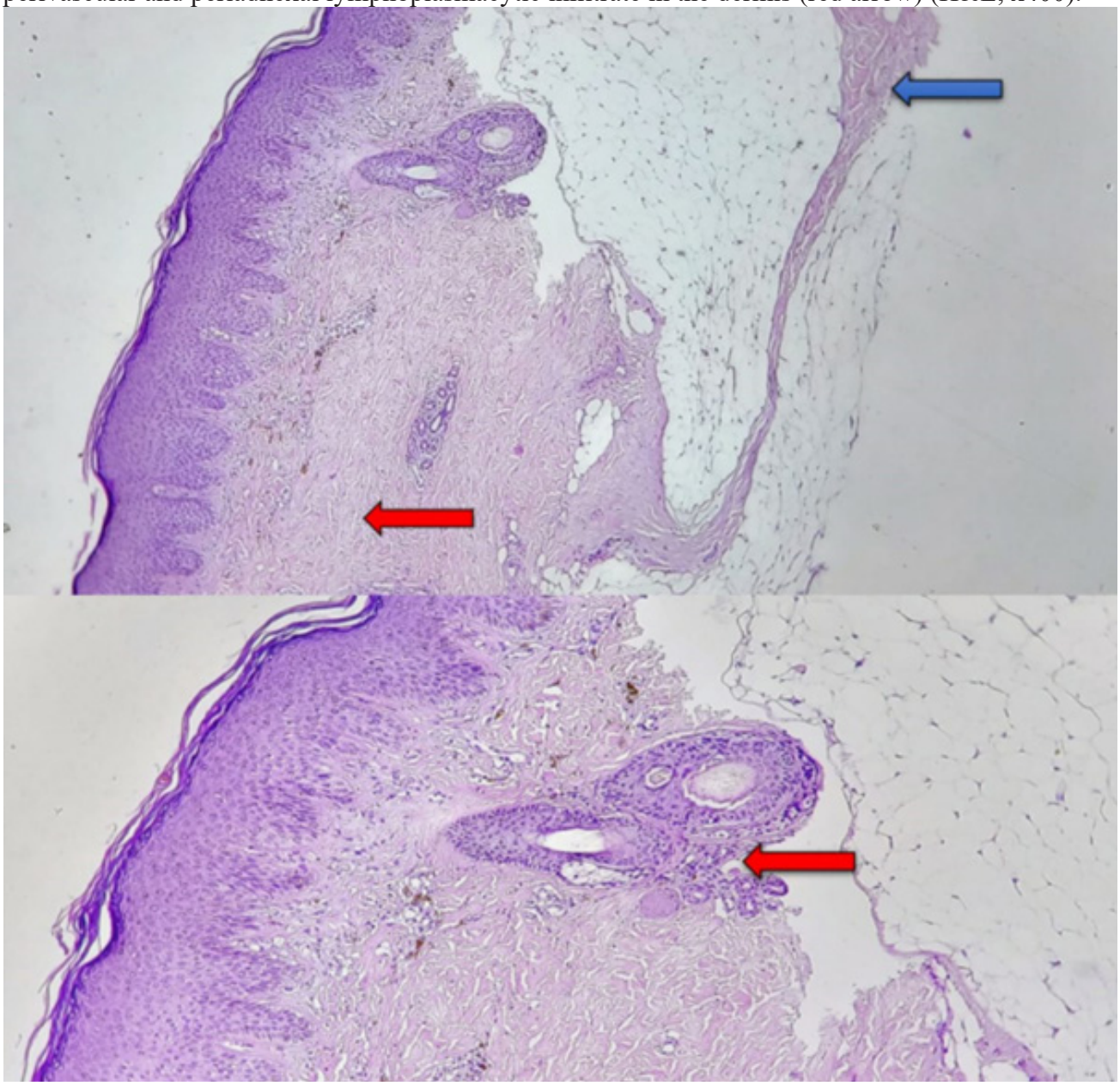
JSSc is a rare connective tissue disorder of unknown etiology. Though, it resembles adult progressive systemic sclerosis (PSS), it still has a number of distinguishing features.[7-8] Similar to the adult counterpart, there is Raynaud's phenomenon (90-95%), diffuse involvement of skin and micro vasculopathy which can lead to progressive dysfunction of the esophagus, heart, lungs and kidney.[5] Our patient presented with cutaneous features of PSS.

The criteria for diagnosing JSSc in a patient of less than sixteen years of age as given by Paediatric Rheumatology European Society (PRES), the American College of Rheumatology (ACR), and the European Alliance of Associations for Rheumatology depending on clinical manifestations and laboratory parameters includes one major criterion [induration of skin/ sclerosis] and two minor criteria indicating involvement of various organ systems e.g. cardiac (arrythmias, heart failures), pulmonary (pulmonary hypertension, pulmonary fibrosis), gastrointestinal (dysphagia, gastroesophageal reflux), vascular (Raynaud phenomenon, digital

tip ulcers, nail fold capillary abnormality), renal (renal crisis, new onset arterial hypertension), neurological (carpal tunnel syndrome, neuropathy), musculoskeletal (arthritis, myositis, tendon friction rubs) and serological (anti-nuclear antibodies, SSc selective auto antibodies).[9]

The pathogenesis of the disease involves an interplay of wide range of factors. Increased activity of Endothelin-1, intercellular adhesion molecule-1 (ICAM-1) along with increased production of profibrotic cytokine growth factors (IL-4, IL-6,IL-8, IL-8, IL-10, IL-13, IL-17, TGF-alpha) lead to increased myofibroblast activity and production of extracellular matrix leading to structurally normal collagen deposition.[10-15] Association has also been found with auto-antibodies, which includes topoisomerase I,[16] centromere antigens,[16] fibrillarin, ribonucleic acid (RNA) polymerase, PM-Scl, and fibrillin-1,[17] as well as RNA I, II, and III. A small cohort study found HLA DRB1*10, to be associated in 10.5 percent of patients with JSSc in contrast to 1.5 percent of controls.[18]

Figure 3. Section showing thickened collagen bundles in the dermis (red arrow) and extension of sclerosis into the underlying subcutaneous fat (blue arrow) (H&E, x100). Section showing mild perivascular and periadnexal lymphoplasmacytic infiltrate in the dermis (red arrow) (H&E, x400).



Skin biopsies taken from patients diagnosed with scleroderma portrays various histologic changes in dermal microvasculature which includes, thickened collagen bundles, swelling of endothelium, concentric thickening of vascular basement membrane.[19]

Pulmonary involvement, may present with dyspnoea and cough or patient may remain asymptomatic. *Rahman et al*[5] reported a restrictive pattern of lung disease. Our patient had complaints of dyspnoea on exertion.

The most important cause of gastrointestinal morbidity in children with JSSc is esophageal dysfunction.[20] Only half of the affected patients have complaints of dysphagia, our patient too had dysphagia. Bodemer et al.[4] have reported that in systemic sclerosis involving paediatric population cardiac abnormalities such as left or biventricular failure, pericarditis or arrhythmias are common, but no such complaints were there in our patient.

About 40-60% patients show renal involvement in the form of proteinuria, azotaemia and malignant hypertension. It usually affects within the first three years of PSS and indicates a guarded prognosis.[20] In a study of 135 children by Foeldvari et al.[21] mortality related to renal crisis was seen in only one patient.[21] Renal crisis prevalence is found to be less (4%) in JSSc than in adults.[22] Mortality related to renal crisis has markedly reduced with the usage of angiotensin converting enzyme inhibitors.[23] Our patients did not have so far developed any clinical or laboratory abnormalities suggestive of renal dysfunction. In 70% to 90% of patient, antinuclear antibodies have been reported.[5] Our patient showed a significantly raised titre for ANA.

There is dearth of literature involving standardized treatment for JSSc. Depending on organ involved, general measures such as use of antacids and prokinetic drugs for gastroesophageal reflux, vasodilators to impede Raynaud's phenomenon, for arthritis, non-steroidal anti-inflammatory drugs, and physical activity are recommended.[24] Immunosuppressants like methotrexate, mycophenolate mofetil have showed benefit in the treatment of skin manifestations. Myositis and arthritis have benefitted from use of corticosterioids.[25]

The patient's family were counseled about the disorder and its slow progression. Progressive visceral disease in childhood scleroderma is difficult to predict and prognosis is dependent on multi-system involvement.[26] Most patients suffering from juvenile systemic sclerosis have been found to have a successful outcome and a significant improvement in survival rate in contrast to their adult counterparts as reported by *Foeldvari et al*.[3]

Conclusion

The prevalence of JSSc is low. At times, incidence of cases is often sporadic, even at the level of tertiary care. The beginning of the disease may be indicated by Raynaud's phenomenon. The major adjuvant in the diagnosis is capillaroscopy, as determination of autoantibodies may not offer sensitive and specific markers. The most common clinical features are skin and vascular manifestations, while internal organ involvement is rare to be found. The most frequent visceral involvement is cardiopulmonary disease which can lead to significant morbidity, and potentially death. Due to the rare occurrence of systemic scleroderma in children, we are reporting our case with the possibility of achieving good results with early treatment initiation.

Conflict of Interest Declaration

All authors have no financial/conflict of interest to be disclosed.

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