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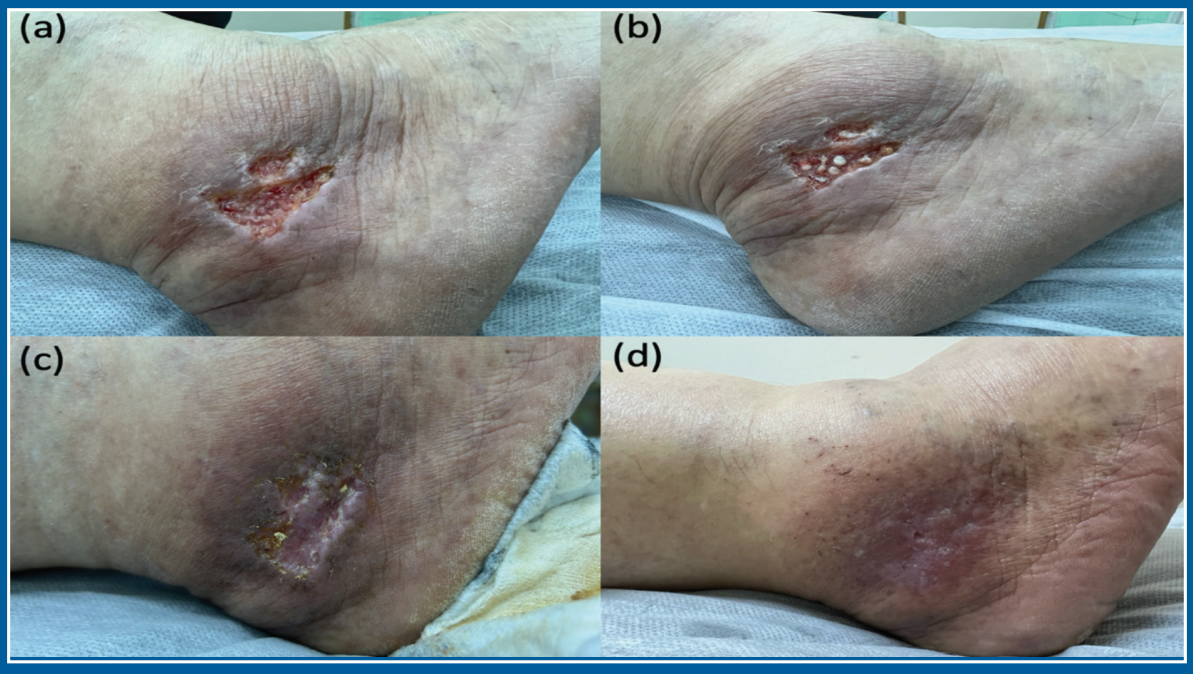

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CONTENTS

Orginal Article

Truncal Acne in Adolescents and Young Adults in Saudi Arabia: A Self-Reported Perception

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Department of Dermatology, Unaizah College of Medicine and Medical Sciences, Qassim University, Unaizah, Saudi Arabia

Abstract

Aim: Acne vulgaris is a prevalent chronic inflammatory disorder of the pilosebaceous unit, primarily affecting adolescents. The burden of acne goes beyond the skin, and several studies have confirmed the link between acne, psychiatric comorbidities, and impaired social interaction. Data on Truncal acne (TA), particularly its effects on everyday life and overall quality of life, are sparse in existing studies.

Materials and Methods: This cross-sectional, questionnaire-based study.

Results: A total of 755 participants completed the survey. Majority of them were 15-25 years old, and (55.1%) were female. Participants considered psychological stress, followed by a diet high in carbohydrates or lipids, and sleeplessness to be acne triggers. more participants aged > 20 years thought daily about TA than participants aged < 20 years, while no significant results were observed among participants age groups and the negative effect of TA on their daily life, embarrassment feeling during sport practicing or swimming, choosing their clothes, negative comments from friends, or poor self-confidence. A significant association was observed between truncal and facial acne.

Conclusion: Our findings advocate for a more nuanced understanding of TA, its psychological impact, and the necessity for tailored treatment approaches that consider the disease's repercussions.

Keywords: Acne vulgaris, Truncal acne, facial acne, adolescence

Introduction

Acne vulgaris is a prevalent chronic inflammatory disorder of the pilosebaceous unit, primarily affecting adolescents.[1] A recent population-based study conducted in 20 countries revealed that the overall prevalence of acne is 20.5%. The highest prevalence was 28.3% among the 16-24 years age group. Females have a higher prevalence of acne than males, 23.6% and 17.5%, respectively.[1] The pathophysiology of acne is multifactorial and involves four phases: sebum over-production, abnormal keratinization, hyperproliferation of *Cutibacteria acne*, and inflammatory immune response.[2]

Regarding Truncal acne (TA), notable differences in its pathophysiology have been observed. These include a reduced influence of sebum secretion and a decrease in the diversity of *C. acnes* phylotype, particularly phylotype IA1, which accounts for 95.6% of cases, compared with its prevalence of 72.7% on the face. Additionally, factors such as sweating and clothing that cause occlusion are significant in the development of TA.[3,4]

The burden of acne goes beyond the skin, and several studies have confirmed the link between acne, several psychiatric comorbidities, and impaired social interaction.[5] Acne manifests in two primary forms: inflammatory lesions, such as papules, pustules, nodules, and cysts, and non-inflammatory lesions, which include both open and closed comedones.[2] These lesions predominantly occur in areas rich in sebaceous glands, like the face, shoulders, and trunk (i.e., chest and back).[6] TA is more likely to develop inflammatory lesions.[3] The prevalence of acne varies between less than 1% to 14%, with about 30% to 60% of those experiencing facial acne also showing signs of TA, based on the demographics studied.[6]

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Research led by *Jerry Tan* and others has demonstrated that TA typically begins earlier than facial acne, can lead to more severe conditions, and shows no substantial difference between genders in its occurrence.[6] It has been noted that individuals suffering from TA often experience more severe symptoms, greater disruption to their quality of life (QoL), and increased stress compared to those with only facial acne.[6] Although acne is a prevalent condition among adolescents, the focus of most research has been on facial acne. Data on TA, particularly its effects on everyday life and overall QoL, are limited in existing studies.[3] This research aims to explore the self-reported rates and perceived effects of TA on the everyday lives of participants in Saudi Arabia, thereby addressing the knowledge gap concerning adolescent health.

Materials and Methods

This cross-sectional study was conducted in Saudi Arabia. An anonymous web-based questionnaire consisting of 18 items about demographic data, presence of TA, and TA repercussions on adolescent's life. The questionnaire used for data collection was adapted from a similar study.[3] Ethics Committee approval was obtained from the Qassim University College of Medicine (approval number: T010524, date: 01.05.2024). The inclusion criteria were male or female subjects aged ≥ 15 years who had self-reported acne, understood Arabic, and agreed to provide informed consent. Adolescents were invited to participate in the survey via social media.

Statistical analysis

In this primarily descriptive study, no specific minimum sample size was considered necessary. The analysis included subgroup evaluations based on sex, age categories (under 18, 18-25, and over 25 years), and varying degrees of TA severity-ranging from mild to very severe. The study also considered the impact on QoL by categorizing participants into groups from those not affected at all to those constantly affected. The percentages were computed after excluding any missing data. The chi-square test (χ^2) was used to determine the relationships among the conditions studied. All statistical analyses were performed using IBM SPSS Statistics software (25.0).

Results

Demographics and General Data

In terms of demographic and general information about TA, 755 participants completed the survey. Majority of them were 15-25 years old (67.5%), and (55.1%) were female. Among the global participants, only 650 (86.1%) have reported TA, with (48.2%) for females. When grouping TA severity for participants who have TA, (73.7%) reported mild to moderate, while (26.3%) reported severe to very severe TA, (87.2%) of TA patients had or already had facial acne (FA), (84.3%) of TA & FA patients reported mild to moderate FA, and (15.7%) reported severe to very severe FA. (73.23%) of TA patients reported at least, one member of the family also has TA. Detailed demographic truncal and facial acne data are shown in Table 1.

Truncal Acne Triggers

Participants considered psychological stress (51.8%), followed by a diet high in carbohydrates or lipids (42.6% and 42.4%), respectively, and sleeplessness (28.9%) were identified as acne triggers and (41.5%) were unaware of what could trigger TA. Notable statistical differences were noted in the identification of the following factors as triggers for TA: high carbohydrate diet (12-15 years: 1.9%, 15-20 years: 16.2%, 20-25 years: 14.7%, > 25 years: 10.5%; $P = 0.008$), smoking (12-15 years: 0.0%, 15-20 years: 0.5%, 20-25 years: 0.8%, > 25 years: 2.3%; $P = 0.001$), and psychological stress (12-15 years: 0.9%, 15-20 years: 18.4%, 20-25 years: 18.1%, > 25 years: 14.3%; $P = 0.018$).

More females than males (28.7% vs. 13.9%, $P = 0.0001$) considered that a high carbohydrate diet, high lipid diet (25.2% vs. 17.2%, $P = 0.043$), consumption of milk products (10.5 % vs. 2.4%, $P = 0.0001$), cosmetic products (9.0% vs. 2.4%, $P = 0.0001$), stress (36.0% vs. 15.8%, $P = 0.0001$), and sleeplessness (18.8% vs. 10.1%, $P = 0.0001$) triggered TA. Over three-quarters of the female participants (80.8%) indicated that menstruation was the primary trigger for their TA. Additionally, a significant difference was observed among age groups, with a higher percentage of females over 20 years old (49.5% compared to 31.2%; $P = 0.044$) identifying menstruation as a trigger for TA than those under 20 years old.

Treatment Information Sources

Worldwide, 56.4% of the respondents sought advice from at least one healthcare provider to learn about treatments for TA; of these, 38% approached a dermatologist, 11.8% consulted a pharmacist, and 6.6% visited a general practitioner. Additionally, 49.9% of the participants sourced their information from the internet. Family members were a source of information for 18.8% of respondents, while friends provided information for 14.4%. Notably, 28.2% of the participants did not seek any information regarding TA treatment.

The majority of participants aged > 20 years consulted a dermatologist than those aged < 20 years (27.7% vs. 10.3%; $P = 0.002$), family members (10% vs. 8.8%; $P = 0.001$), friends

(8.6% vs. 5.9%; $P = 0.017$), and gathering information form the internet (32.2% vs. 17.8%; $P = 0.001$).

More females consulted a dermatologist than males (23.8% vs. 14.2%; $P = 0.001$), family members (12.6% vs. 6.2%; $P = 0.002$), friends (10.2% vs. 4.2%; $P = 0.0001$), and the Internet (35.9% vs. 14%; $P = 0.0001$). No significant relationship was observed between the severity of TA and the availability of information by consulting a general practitioner or a dermatologist ($P = 0.573$, $P = 0.164$), respectively. The detailed results are shown in Figure 1-3.

Table 1. Demographic and general characteristics of truncal acne

	Global (n = 755)	Male (n = 339) (44.9%)	Female (n = 416) (55.1%)
Age, years			
12-15	24 (3.2%)	6 (0.8%)	18 (2.4%)
15-20	238 (31.5%)	94 (12.5%)	144 (19.1%)
20-25	272 (36%)	108 (14.3%)	164 (21.7%)
> 25	221 (29.3%)	131 (17.4%)	90 (11.9%)
Truncal acne, yes (%)	650 (86.1%)	286 (37.9%)	364 (48.2%)
Truncal acne severity (n = 650), n (%)			
Mild	137 (21.1%)	53 (8.15%)	84 (12.9%)
Moderate	342 (52.6%)	142 (21.85%)	200 (30.8%)
Severe	149 (22.9%)	78 (12.0%)	71 (10.9%)
Very severe	22 (3.4%)	13 (2.0%)	9 (1.4%)
Facial acne (n = 650), n (%)			
Never had acne	83 (12.8%)	39 (6.0%)	44 (6.8%)
I had acne in the past	144 (22.2%)	76 (11.7%)	68 (10.5%)
Currently having acne	423 (65.0%)	171 (26.3%)	252 (38.8%)
Facial acne severity (n = 650), n (%)			
Mild	300 (46.15%)	135 (20.8%)	165 (25.4%)
Moderate	248 (38.15%)	105 (16.2%)	143 (22.0%)
Severe	82 (12.6%)	38 (5.9%)	44 (6.8%)
Very severe	20 (3.1%)	8 (1.2%)	12 (1.9%)
Family history of acne: **yes** (n = 650), n (%)	476 (73.23 %)	197 (30.31 %)	279 (42.92 %)
Occupation (n = 650), n (%)			
High school student	128 (19.7%)	40 (6.15%)	88 (13.5%)
College student	227 (34.92%)	89 (13.7%)	138 (21.2%)
Employee	157 (24.15%)	113 (17.4%)	44 (6.8%)
Unemployed	138 (21.23%)	44 (6.8%)	94 (14.5%)

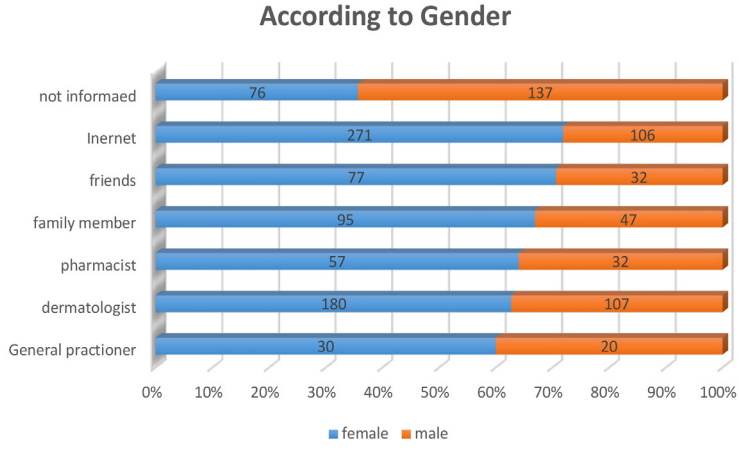

Figure 1. Information source according to gender

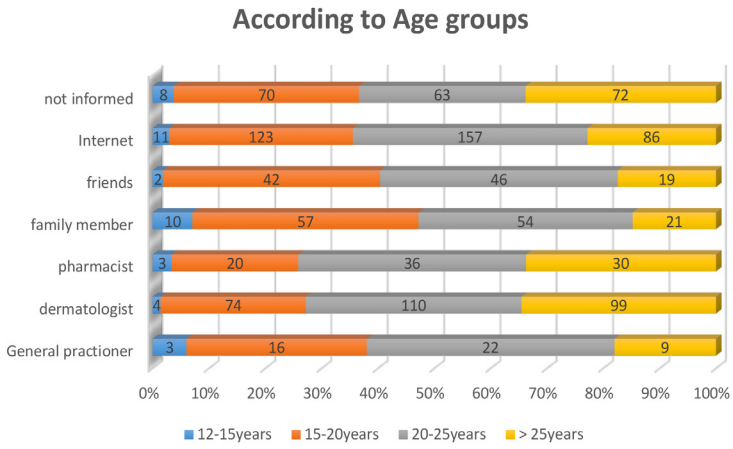

Figure 2. Information source according to age groups

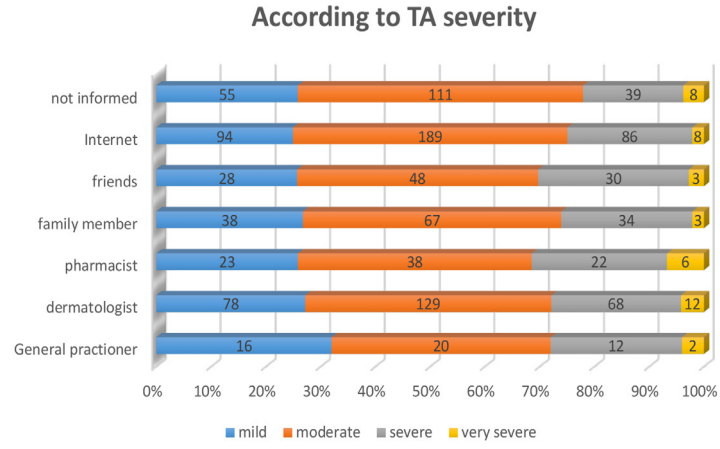

Figure 3. Information source according to TA severity
TA: Truncal acne

Daily Life and Quality of Life

More than three-quarters (85.7%) of participants thought about TA, among whom (23.4%) often (24.9%) daily. At the same time, (67%) of the participants reported negative effects on daily life (32.2% mild, 20.3% moderate, and 14.6% severe negative effects). On the other hand, 36.6% of the participants did not report any embarrassment in their social relationships because of TA and other factors (14.3% rarely, 30.3% sometimes, and 18.8% always).

62.1% of all participants felt embarrassment while practicing a sport or swimming (12.2 rarely, 26.9% sometimes, and 23.0% always). More than half of the participants reported that TA had an effect on choosing clothes (7.9% rarely, 22.5% sometimes, and 27.2% always).

About two-thirds of participants (68.9%) reported no negative comments from friends about their TA, while (5.4%) always faced such situations. Moreover, more than half of the participants felt poor self-confidence due to TA (14.4% rarely, 23.6% sometimes, and 15.2% always).

Significantly, participants who had mild to moderate TA thought in a daily manner about their acne more than participants who had severe or very severe (14.8% vs. 10.1%; $P = 0.0001$). Additionally, more participants with mild or moderate TA reported no negative effect on daily life. Compared with those with severe or very severe TA (29.1% vs. 3.9%; $P = 0.0001$). Participants with severe and very severe TA reported a stronger negative effect on daily life than participants with moderate or mild TA (7.3% severe and very severe TA, 6.4% moderate TA, and 0.9% mild TA; $P = 0.0001$).

More participants with mild or moderate TA reported no embarrassment in social relationships compared with participants with severe or very severe acne (30.9% vs. 5.7%: $P = 0.0001$). More participants with severe or very severe TA always reported feelings of embarrassment in social relationships than participants with moderate TA (8.8% vs. 8.3%: $P = 0.0001$). Similarly, more participants with mild or moderate TA reported no embarrassment feelings during sports practicing or swimming than participants with severe or very severe TA (32% vs. 5.8%; $P = 0.0001$).

According to the participants, more participants with mild or moderate TA reported that TA did not affect their clothes choices than participants with severe or very severe TA (34.5% vs. 7.8%; $P = 0.0001$). In addition, more participants with mild or moderate TA reported that they did not receive any negative comments from their friends due to their TA than participants with severe or very severe TA (56.8% vs. 12.1%; $P = 0.0001$). More participants with mild or moderate TA reported no poor self-confidence than those with severe or very severe TA (39.1% vs. 7.7%; $P = 0.0001$).

Significantly, more participants aged > 20 years were thinking daily about TA than participants aged < 20 years (11.9% vs. 11.0%; $P = 0.001$), while no significant results were observed among participants age groups and the negative effect of TA on their daily life, embarrassment feeling during sport practicing or swimming, choosing their clothes, negative comments from friends, or poor self-confidence.

More females think of TA daily regardless of the severity than males (17.5% vs. 7.4%; $P = 0.0001$). Additionally, more females reported a strong effect of TA on their daily life than males (10.5% vs. 4.1%; $P = 0.0001$). More females feel embarrassment in their social relationships than males ($P = 0.0001$), whereas more males reported no embarrassment in their social relationships (21.9% for males vs. 14.7% for females; $P = 0.0001$). Similarly, more males reported that TA does not affect their choosing of clothes than females (29.3% for males vs. 13.1% for females; $P = 0.0001$). On the other hand, more females reported that TA always affects their choice of clothes than males (21.1% vs. 6.1%; $P = 0.0001$). More females have poorer self-confidence due to TA than males (12.2% vs. 3.0%; $P = 0.0001$). Detailed results are shown in Figures 4-6.

Facial Acne

84.5% of the participants had facial acne at the time of the survey or had a history of facial acne. More females currently have facial acne than males (37.1% vs. 25.8%; $P = 0.016$), whereas more males had facial acne in the past than females (11.5% for males vs. 10.1% for females).

A total of 47.2% of the participants reported mild facial acne, 37.4% moderate, 12.5% severe, and 3.0% very severe facial acne. Participants aged > 20 years had facial acne more than participants aged < 20 years (36.6% vs. 26.2%; $P = 0.0001$), but participants aged > 20 years reported mild facial acne more than participants aged < 20 years (33.8% vs. 13.4%; $P = 0.002$).

A significant association between TA and facial acne was observed ($P = 0.0001$). 39.9% of patients with mild or moderate TA reported mild facial acne, and 7.7% of those with severe or very severe TA reported severe facial acne.

Discussion

The total number of participants who completed the online questionnaire regarding their TA was 650. The majority of respondents were 15-25 years old (67.5%), and (55.1%) were female. This age group is the most common for TA.[1,6] When grouping TA severity for participants who have TA, 73.7% have mild to moderate TA, and 26.3% reported severe to very severe TA. In contrast, Ballanger et al.[3] reported that 68.8% of the adolescents studied had a severe or very severe form. The observed difference in severity is attributed to differences in food and lifestyle among the populations. We found no significant difference between males and females regarding the TA severity.

The majority of the participants (65%) reported having concomitant facial acne, mostly of mild to moderate severity, 84.3%. TA alone is not common, whereas 30% to 60% of patients with FA present with TA, depending on the population.[6,7] Patients with TA reported having at least one member of their family with TA, 73.23%. The statistically significant factors that triggered TA were high carbohydrate diet, smoking, and psychological stress. These findings are similar to those of the TA triggers reported in a similar survey.[3] We found significant gender differences; females considered a high carbohydrate diet, high lipid diet, consumption of milk products, cosmetic products, stress, and sleeplessness to be triggers of their TA more than males.

Moreover, 80.8% of females believed that menstruation was the main trigger for their TA, and significantly more in those with more than 20 years old. This percentage is higher than that reported in another study, which was 51%.[3] Only 10.8% of females reported taking oral contraceptive pills as a trigger for TA.

A high percentage of respondents (83.1%) obtained their information from non-healthcare providers, mainly via internet searches. In a cross-European study, Szepietowski et al.[8] found that physicians were the source of acne information in 27.0% of the population, and the majority of them took their information from friends, family, and the Internet. These findings could explain the adolescents' misunderstanding and delay in treatment. For those who consulted a dermatologist, participants aged > 20 years were significantly higher than participants < 20 years. This could be explained by the cost of professional consultants and easy reach to internet sources. The TA severity dose does not influence the source of information; therefore, consult a general practitioner or dermatologist. In the analysis of the relationship between TA and QoL, 67% of the participants reported a negative effect on daily life, 34.9% rated this negative effect as moderate to severe, and 18.8% always reported embarrassment situations, mainly in activities

that involve exposure of the trunk like sport or swimming. More than half of the participants reported that TA affected their choice of clothes.

There was no significant relationship between age and acne's negative effects of QoL. Female adolescents were more vulnerable to the negative effects of acne than males. Tan et al.[9] reported similar findings regarding the psychological effects of TA in adolescents. Regarding the effects on social interaction, the Majority reported no negative comments from friends about their TA, which could be due to the clothing style in the kingdom that covers most of the body. Moreover, more than half of the participants felt poor self-confidence due to the TA. There is a significant relationship between TA severity and female sex and negative effects on daily life and (always) embarrassment feelings in social relationships, choosing clothes, negative comments from friends, and poor self-confidence.

Interestingly, those with mild to moderate TA tend to think about their condition more frequently than those with severe or very severe acne. A notable correlation was found between the presence of truncal and facial acne. A total of 84.5% of respondents reported either current or past facial acne, a

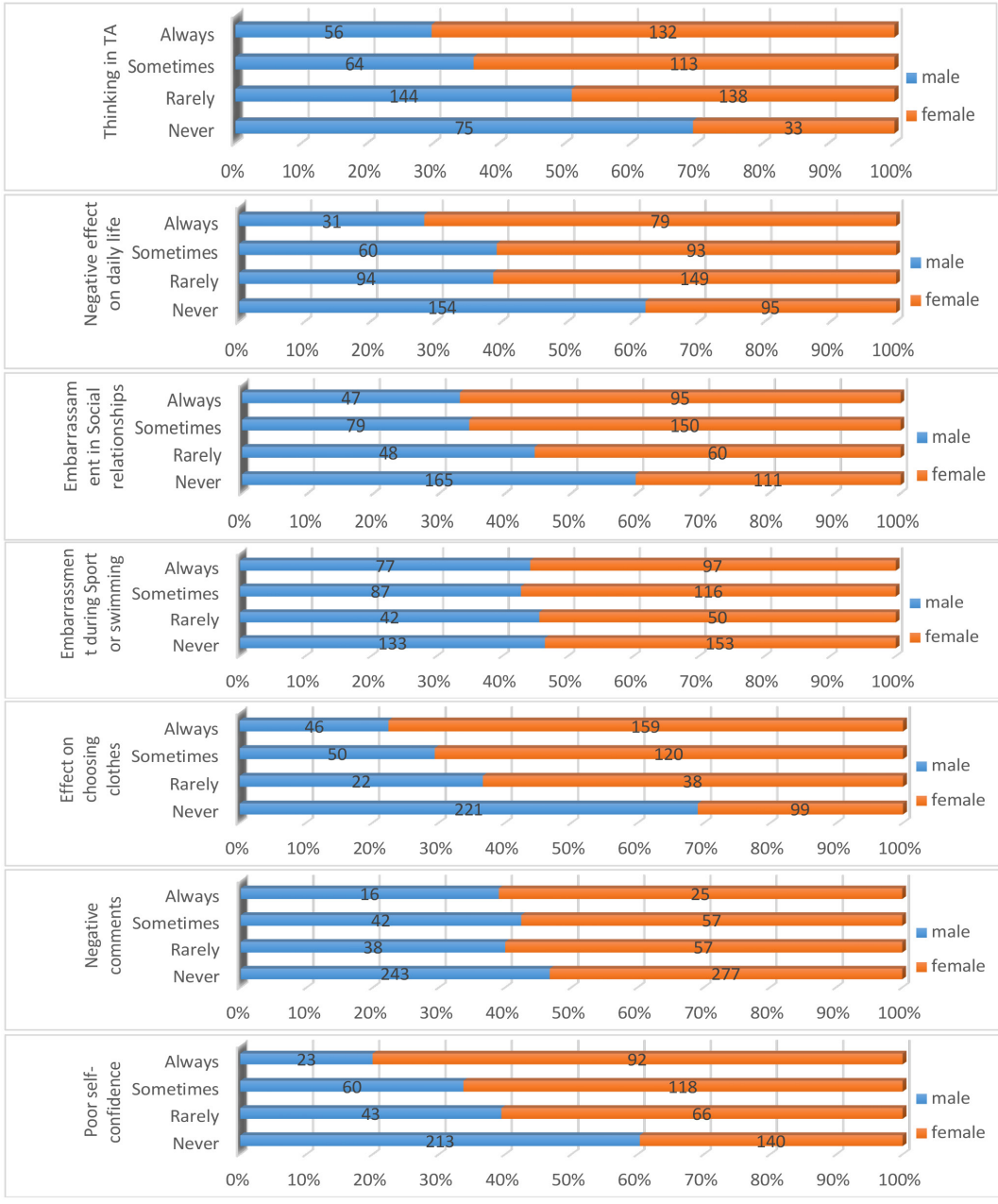

Figure 4. Quality of life according to gender
TA: Truncal acne

condition more prevalent among females. Tan et al.[9,10] reported similar detrimental effects of combined acne forms, affecting over half of the subjects in areas such as self-acceptance, emotional health, embarrassment, self-awareness, and confidence. It is crucial to note that the acne-QoL questionnaire predominantly targets facial acne, which might not provide an accurate assessment for TA.[11] The methodology should be revised to fully capture the personal impact of TA. The Personalizing Acne Consensus of Experts panel suggests that the severity and effects of TA should be evaluated separately from facial acne. They advocate for treatment plans that are tailored to the individual's specific condition and highlight the necessity for a new grading system.[12]

Conclusion

Our findings advocate for a more nuanced understanding of TA, its psychological impact, and the necessity for tailored treatment approaches. Developing a specific TA grading scale is imperative to assess its severity and guide effective management strategies. By assessing these needs, QoL for individuals affected by TA can be enhanced and treatment goals can be personalized and responsive to the unique challenges posed by this condition.

Figure 5. Quality of life according to age groups
TA: Truncal acne

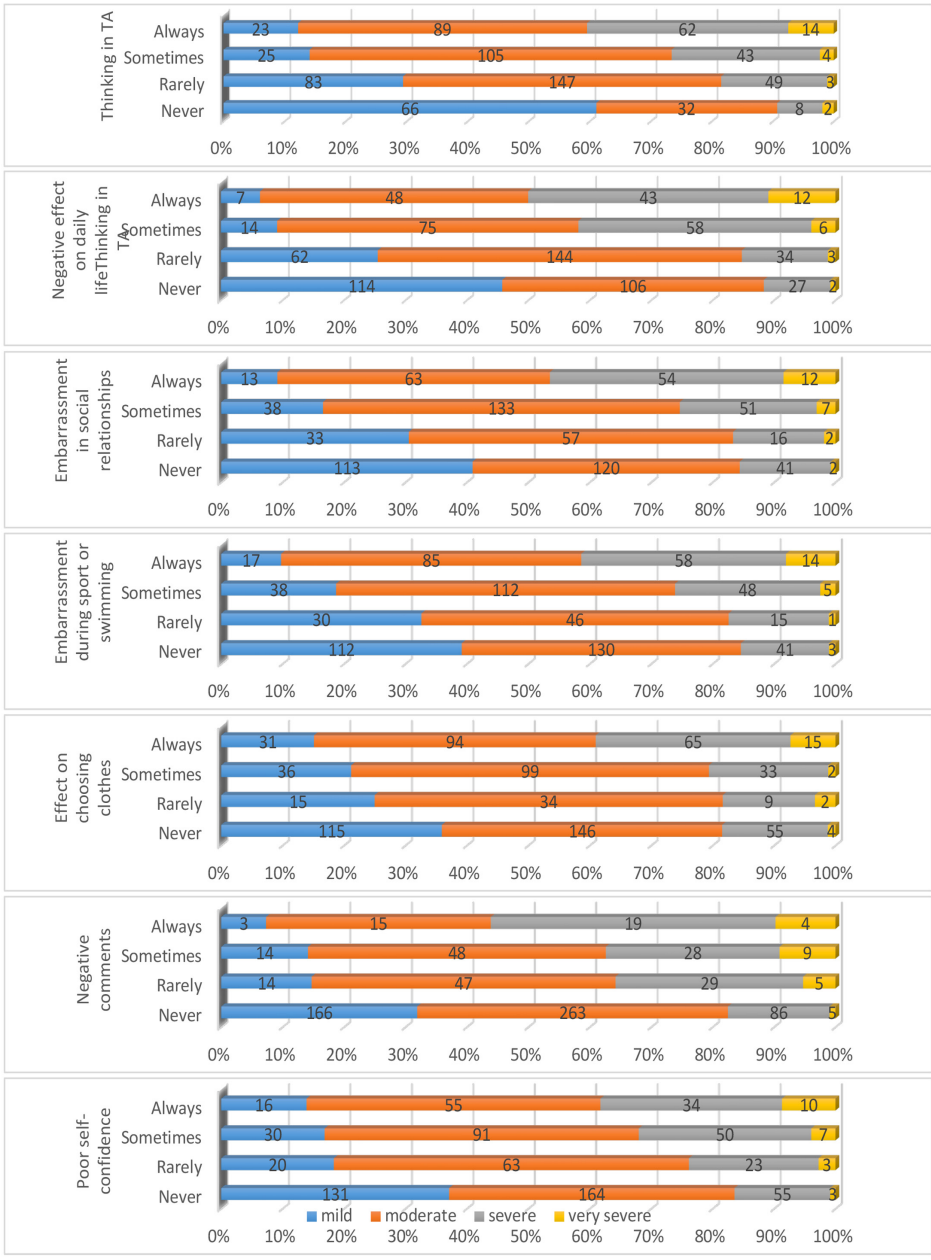

Figure 6. Quality of life according to TA severity
TA: Truncal acne

Ethics

Ethics Committee Approval: Ethics Committee approval was obtained from the Qassim University College of Medicine (approval number: T010524, date: 01.05.2024).

Informed Consent: It was obtained.

Footnotes

Financial Disclosure: The author declared that this study received no financial support.

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Orginal Article

Evaluation of Serum Tumor Necrosis Factor-alpha-Induced Adipose-Associated Protein (TIARP/STEAP4) Level and Its Association with Disease Activity in Patients with Psoriasis: A Single-Center Prospective Comparative Study

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Abstract

Aim: Tumor necrosis factor-alpha (TNF-α)-induced adipose-associated protein (TIARP/STEAP4) is a protective metalloreductase against oxidative stress that is induced by various proinflammatory cytokines, including TNF-α and interleukin-17. This study aimed to evaluate whether STEAP4 is elevated in patients with psoriasis and whether it is associated with disease activity.

Materials and Methods: In this prospective cross-sectional single-center study, serum STEAP4 levels measured by the ELISA method in serum samples collected from psoriasis patients and healthy individuals. The association between STEAP4 levels and demographic characteristics and clinical findings in patients with psoriasis was further evaluated.

Results: Forty-one psoriasis patients with a female: male ratio of 1:1 and a median age of 44 years and 40 controls were included in the study. The median STEAP4 level of the patients with psoriasis (9.25) was significantly higher than that of the control group (1.04) ($P < 0.001$). Although STEAP4 levels did not differ significantly in patients with psoriasis regarding sex, joint, and nail involvement, no significant correlation was found with age, age at disease onset, disease duration, and severity.

Conclusion: The high levels of STEAP4 detected in patients with psoriasis might reflect its anti-inflammatory effects on Th-1 and Th-17 responses and on neutrophil and macrophage infiltration. On the other hand, a possible genetic variation or defect at the receptor level for STEAP4 in patients with psoriasis might hamper an adequate anti-inflammatory effect and lead to increased STEAP4 expression as a compensation mechanism. The present study not only indicates that STEAP4 might play a role in the pathogenesis of psoriasis but also suggests potential implications for its role in treatment and follow-up, which offers a promising direction for further investigation.

Keywords: Psoriasis, inflammation, TIARP, STEAP4

Introduction

Psoriasis is a chronic inflammatory disease caused by defective innate and adaptive cutaneous immune responses. The complex interplay between dendritic cells, macrophages, mast cells, neutrophils, and keratinocytes, along with T-cells, plays a role in the basic pathogenesis of the disease. Through various cytokines, such as tumor necrosis factor-alpha

*The study was previously presented as an oral presentation at the "Psoriasis ve Kutanöz İnflamasyon Sempozyumu-2024" symposium held in Kemer/Antalya on 19.04.2024.

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(TNF-α), these cells induce a chronic inflammatory state and alter epidermal hyperproliferation, differentiation, apoptosis, and neoangiogenesis, producing the cutaneous manifestations observed in psoriasis.[1,2]

TNF-α-induced adipose-associated protein (TIARP), also known as TNF-α induced protein 9 (TNFAIP-9) or STAMP2, belongs to a family of six transmembrane proteins called STAMP or STEAP4, expressed on macrophages, neutrophils, and synoviocytes.[3,4] Previous studies showed that TIARP was a separate but similar cofactor with TNF-α, induced by TNF-α during adipose tissue differentiation.[3-5] Additionally, proinflammatory cytokines such as interleukin-17 (IL-17), IL-6, and IL-1β, which are essential in the pathogenesis of psoriasis, were shown to induce TIARP.[2,5-10]

TIARP/STEAP4 levels were reported to be increased in both mice models of arthritis and patients with rheumatoid arthritis (RA), and their levels were correlated with the severity of arthritis. Furthermore, a significant decline in TIARP/STEAP4 mRNA expression was detected in splenocytes following TNF-α antagonist treatment. Thus, it was proposed as a biomarker that might be used for evaluating the effectiveness of TNF-α antagonists, which are also frequently used in the treatment of psoriasis.[3,6] Additionally, genetic variations in STEAP4 have been associated with numerous metabolic disorders, such as obesity and type 2 diabetes, which are among the comorbid conditions of RA and psoriasis.[7]

Psoriasis is an inflammatory disease similar to RA in terms of pathogenesis and treatment modalities, such as TNF-α antagonists. Moreover, psoriasis is also known to be associated with metabolic disorders.[1] Based on these findings, we hypothesized that plasma STEAP4 levels might be higher in patients with psoriasis than in individuals without a history of psoriasis. We also aimed to evaluate the relationship between STEAP4 and disease activity.

Materials and Methods

This prospective, cross-sectional, single-center study included 50 patients diagnosed with psoriasis who were followed up in the dermatology outpatient clinic of our tertiary referral center as the patient group and 50 age and gender-matched healthy individuals without psoriasis as the control group. Individuals under 18 years of age and those with any other chronic inflammatory conditions [obesity (individuals with a body mass index ≥ 30) and diabetes mellitus], autoimmune disorder, known malignancy, or active acute/chronic infection were excluded from the study. Moreover, in the patient group, generalized or localized pustular psoriasis patients weren't included in this study due to different pathogenic mechanisms. In addition, patients who had problems with serum samples due to laboratory and kit-related problems were also excluded from the study. Written and verbal consent was obtained from participants who agreed to participate voluntarily before starting the study.

The sociodemographic characteristics and medical history of the participants were recorded. Disease severity was measured using the psoriasis area severity index (PASI), age at disease onset, duration of disease, presence of joint and nail involvement, and current treatment methods were also noted.

Serum samples were collected from the venous blood of patients and control subjects. The samples were subjected to ELISA using a STEAP4 kit (BT LAB, Bioassay Technology Laboratory, Shanghai, China). The test results were statistically compared between the two groups. The STEAP4 levels of the patient group were further evaluated in terms of demographic features, clinical findings, and current treatments used for psoriasis.

This study was approved by Çanakkale Onsekiz Mart University Clinical Research Ethical Committee (approval number: 2021-08, date: 03.11.2021). The Çanakkale Onsekiz Mart University Scientific Research Projects Unit provided the financial source of the study (project number THD-2022-3941).

Statistical analysis

SPSS for Windows version 26.0 (SPSS Inc., Chicago, IL, USA) was used for statistical evaluation. Descriptive statistics were calculated as mean ± standard deviation and median (minimum-maximum) values for continuous variables and as frequency and percentage for categorical variables. The chi-square test was used to evaluate the difference in the distribution of categorical variables between the two independent groups. Shapiro-Wilk test was used to assess the normality of the variable distribution. The Student's t-test and Mann-Whitney U test were used to compare two normally and non-normally distributed groups, respectively. Welch ANOVA test was used to compare whether two or more parameters were significantly different. P value < 0.05 was considered statistically significant.

Results

According to the exclusion criteria, 41 psoriasis patients with a female: male ratio of 1:1 and a median age of 44 years, and 40 healthy individuals were included as the patient and control groups, respectively. Table 1 summarizes the sociodemographic characteristics of the patients and controls, while the clinical characteristics of the psoriasis patients are shown in Table 2.

The median STEAP4 level of patients with psoriasis (9.25) was significantly higher than that of the control group (1.04) ($p<0.001$) (Figure 1).

STEAP4 levels did not differ significantly in psoriasis patients regarding sex or between those with and without joint or nail involvement (Table 3). There was also no significant difference in STEAP4 levels between the patients according to the currently used treatment method (Table 4). The STEAP4 level of patients with psoriasis was not significantly correlated with any parameters, including age, age at disease onset, disease duration, and disease severity (PASI).

Discussion

The present study demonstrated significantly high levels of STEAP4 in psoriasis patients regardless of demographic features, clinical findings, and treatment agents used. This result, which is consistent with the induction of TIARP/STEAP4 through cytokines involved in the pathogenesis of psoriasis, underscores the role of STEAP4 in the increased inflammatory environment.

Inoue et al.[11] reported that TIARP suppressed IL-6 production, STAT-3, and nuclear factor kappa B signaling and caused increased apoptosis in macrophages, thereby demonstrating a robust protective role against arthritis. This finding instills confidence in the potential of TIARP as a therapeutic target. The authors also observed increased autoreactive T-helper-1 (Th-1) and Th-17 responses in TIARP-deficient (TIARP-/-) mice, along with significant neutrophil-macrophage infiltration in the joints and spontaneous synovitis and enthesitis.[11] Inoue et al.[12], in another study, demonstrated that TIARP independently downregulated IL-6 production and the expression of chemokine receptors (CXCR1 and CXCR2) on neutrophils, ultimately reducing neutrophil migration to arthritic joints.

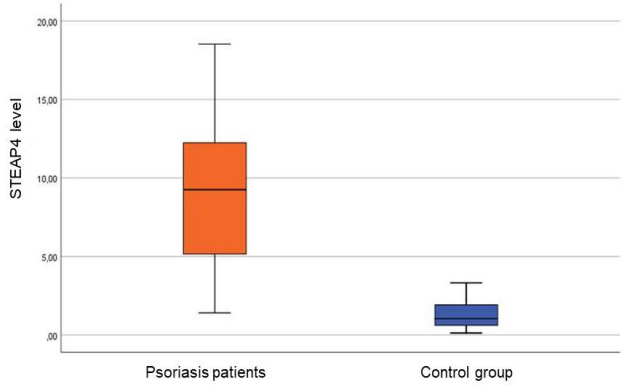

Figure 1. Comparison of STEAP4 levels among patient group (psoriasis patients) and control group

Several studies have shown that TIARP/STEAP4 protects cells against inflammation-induced oxidative stress. Thus, high levels of TIARP/STEAP4 might indicate increased inflammation and oxidative stress.[6-13] The present study revealed higher STEAP4 levels in patients with psoriasis, a disease characterized by inflammation, supporting the previous literature. This might be attributed to the increased inflammatory burden in the setting of psoriasis and suggests that STEAP4 levels might be elevated to suppress Th-1 and Th-17 responses, which play crucial roles in the pathogenesis of psoriasis, and to reduce neutrophil and macrophage infiltration. On the other hand, there might be a possible genetic variation or defect at the receptor level for STEAP4 in patients with psoriasis, preventing sufficient anti-inflammatory effects and causing increased STEAP4 expression due to a compensation mechanism.

Low-grade chronic inflammation is also present in obesity and type 2 diabetes, which are components of metabolic syndrome and might accompany both RA and psoriasis. However, interestingly, in patients with diabetes and obesity, unlike those with RA and psoriasis, TIARP levels were reported to decrease. Various inflammatory cytokines, hormones, and adipokine regulate TIARP expression. TIARP was reported to be a novel anti-obesity gene that was significantly downregulated in the adipose tissue of obese patients. Furthermore, overexpression of TIARP might improve glucose uptake and mitochondrial function by increasing insulin sensitivity.[10,11,14] In line with these findings, Wellen et al.[4] showed increased inflammation in the visceral adipose tissue of STAMP2 (TIARP) -/- mice and the development of spontaneous metabolic disease manifested by insulin resistance, glucose intolerance, mild

Table 1. Sociodemographic characteristics of patient group (psoriasis patients) and control group

	Psoriasis patients, (n=41)	Control group, (n=40)	p-value
Sex, n (%)			
Female	19 (46.3)	30 (75)	0.008[a]
Age, years, median (range)	44 (24-72)	24.5 (18-60)	0.001[b]
Smoking frequency, n (%)	20 (48.8)	18 (45.0)	0.733[a]
Alcohol intake, n (%)	7 (17.1)	14 (35.0)	0.066[a]

Alcohol intake: Individuals who consumed alcohol in the last 12 months. [a]Chi-square test, [b]Mann-Whitney U test

Table 2. Clinical characteristics of patients with psoriasis

Clinical characteristics of psoriasis patients (n=41)	
Psoriasis type, n (%)	
Plaque	35 (85.4)
Guttate	4 (9.8)
Palmoplantar	1 (2.4)
Inverse	1 (2.4)
Family history of psoriasis, n (%)	14 (34.1)
Age at disease onset, years, median (range)	25 (6-62)
Disease duration: years, median (range)	16 (1-53)
PASI, median (range)	3.4 (1-11.9)
Nail involvement, n (%)	24 (58.5)
Joint involvement, n (%)	8 (19.5)
Current treatment, n (%)	
Topical treatment only	12 (29.3)
Phototherapy (NB-UVB)	5 (12.2)
Acitretin	4 (9.8)
Methotrexate	4 (9.8)
Biological agent	16 (39.0)
Comorbidities, n (%)	
Hypertension	5 (12.2)
Psychiatric disorder	4 (9.8)

PASI: Psoriasis area severity index, NB-UVB: Narrow-band ultraviolet B

Table 3. Evaluation of STEAP4 levels in patients with psoriasis regarding sex, joint, and nail involvement

	STEAP4 levels, (mean ± SD)	p-value
Sex		
Female	8.6±5.2	0.392[a]
Male	9.9±4.5	
Joint involvement		
Yes	7.0±3.9	0.134[a]
No	9.8±4.9	
Nail involvement		
Yes	9.0±4.9	0.706[a]
No	9.6±4.8	

SD: Standard deviation, [a]Student's t-test

Table 4. Evaluation of STEAP4 levels in patients with psoriasis according to treatment method in the last 3 months

	STEAP4 levels Median (range)	p-value
Topical treatment*	11.01(1.46-17.85)	[a]0.157
Phototherapy (NB-UVB)	5.41 (1.40-7.37)	
Conventional agents**	9.92 (3.27-18.53)	
Biological treatment***	9.98 (3.66-18.23)	

*Corticosteroid, calcipotriol, **Methotrexate, acitretin, ***Adalimumab, ustekinumab, secukinumab, ixekizumab, guselkumab, risankizumab, NB-UVB: Narrow-band ultraviolet B, [a]Welch ANOVA test

hyperglycemia, dyslipidemia, and fatty liver. Gordon et al.[7] reported that TIARP expression was downregulated by chronic obesity and hyperglycemia. The authors speculated that obesity indirectly augments the destructive effect of inflammation by downregulating TIARP, which has a protective role against cellular stress.[7] These results might explain why obesity is a risk factor for the development of psoriasis.

It was reported that STAMP2 controlled macrophage inflammation through nicotinamide adenine dinucleotide phosphate homeostasis in atherosclerosis, another component of metabolic syndrome and comorbidity associated with psoriasis, and its deficiency accelerated atherosclerosis.[15] Moreover, STAMP2 was found to reduce cardiac dysfunction, insulin resistance, and atherosclerosis in diabetic cardiomyopathy.[16] The cardioprotective effect of metformin, an oxidative stress-reducing agent frequently used in patients with diabetes, was shown to be reduced in an environment in which STEAP4 was disabled.[17] In this context, TIARP/STEAP4 might play an important role in the relationship between psoriasis and metabolic syndrome. Therefore, STEAP4 levels should be measured during the follow-up of patients with psoriasis accompanied by metabolic syndrome.

TNF-α antagonists are the best-known and oldest biological agents for psoriasis patients. It is particularly preferred in patients with joint involvement and accompanying rheumatological disorders.[1,2] However, their contraindications and side effects might limit their use, and more reliable agents with similar effects are needed. Tanaka et al.[6] reported that STEAP4 was expressed on monocytes and neutrophils in the peripheral blood, regulated cell migration, and was downregulated by infliximab, a TNF-α antagonist, and thus may be a possible predictor of response to TNF-α antagonists. Priorly, Inoue et al.[3] also demonstrated a significant decrease in TIARP mRNA expression in splenocytes following TNF-α antagonist treatment. However, since only two patients were using TNF-α inhibitors, TNF-α inhibitors could not be evaluated separately in this study. Evaluation of STEAP4 levels before and after treatment in patients with psoriasis using TNF-α inhibitors may be the subject of a new study. If the demonstration of a decrease in STEAP4 levels following TNF-α antagonist treatment is supported, it may be considered that STEAP4 can be used as a predictor of TNF-α antagonist response in patients with psoriasis, similar to other studies.

TIARP/STEAP4 was investigated in only one study in the dermatological literature. Liang et al.[18] evaluated the levels of STEAP1 along with STEAP4 in generalized pustular psoriasis (GPP), palmoplantar pustulosis, and acute generalized exanthematous pustulosis, which are pustular diseases in which neutrophil chemotaxis is increased. The authors demonstrated increased expression of STEAP proteins (STEAP1 and

STEAP4) in lesion skin. They also reported that STEAP1 and STEAP4 were clustered and positively correlated with IL-1, IL-36, and CXCL1/8 around neutrophilic pustules.[18] Conversely, patients with localized or GPP were not included in our study.

Study Limitations

The main limitation of our study was the relatively small number of patients, which may have affected our results. More comprehensive studies could show that STEAP4 levels may vary depending on disease activity (PASI) and treatment methods. Another limitation was that the patient and control groups could not be matched in terms of age and gender because of the exclusion of individuals from the study due to laboratory-related problems. However, the fact that STEAP4 levels were not correlated with age and sex in our patient group might indicate that STEAP4 is a parameter that is not affected by age and sex. In addition, the currently used treatments for psoriasis might have affected the STEAP4 levels in this patient group. However, STEAP4 levels did not show a statistically significant difference between the patients using different treatment methods in our study. Despite the lowering effect of anti-inflammatory treatments on STEAP4 levels in previous studies, the high STEAP4 levels detected in our psoriasis patients who were actively undergoing these treatments show that our results are even more meaningful.

Conclusion

STEAP4 is a potential marker for the diagnosis, treatment, and follow-up of psoriasis in daily clinical practice. New treatment modalities for psoriasis are constantly being developed, and there is a trend toward targeted therapies. Our results should be supported by more comprehensive studies.

Ethics

Ethics Committee Approval: This study was approved by Çanakkale Onsekiz Mart University Clinical Research Ethical Committee (approval number: 2021-08, date: 03.11.2021).

Informed Consent: Written and verbal consent was obtained from participants who agreed to participate voluntarily before starting the study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: Ö.K., Z.K., M.H.Ş., S.I.M., S.O.K., Concept: Ö.K., Z.K., M.H.Ş., S.I.M., S.O.K., Design: Ö.K., Z.K., M.H.Ş., S.I.M., Data Collection or Processing: Ö.K., M.H.Ş., S.I.M., S.O.K., Analysis or Interpretation: Ö.K., Z.K., M.H.Ş., S.O.K., Literature Search: Ö.K., Z.K., Writing: Ö.K., Z.K., M.H.Ş., S.I.M., S.O.K.

Conflict of Interest: The authors declared that they have no conflict of interest.

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Orginal Article

Is Omalizumab Alone an Effective Treatment for Patients with Chronic Spontaneous Urticaria?

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Abstract

Aim: While 2nd generation antihistamines are the first-line treatment for chronic urticaria (CU), omalizumab is recommended for the treatment of patients with inadequate response to these drugs. This study investigated the need for additional treatment while using omalizumab and the factors affecting this need.

Materials and Methods: In this study, we retrospectively evaluated the patients who were admitted to our dermatology clinic who started and continued to receive omalizumab at the recommended standard dose between January 01, 2023 and May 01, 2023 for CU.

Results: Among 90 patients with chronic spontaneous urticaria receiving omalizumab, 51 (56.7%) needed additional treatment, whereas 39 (43.3%) did not need any additional treatment. However, of the 51 patients who developed complaints, 42 (82.4%) had their complaints controlled with antihistamines only, 7 (13.7%) with antihistamines and systemic steroids, 1 (2%) with systemic steroids only, and 1 (2%) with antihistamines, chloroquine, and cyclosporine. Among the patients who used antihistamines to control their complaints, the minimum antihistamine dose was once a day in 33 patients (66%), 2 times a day in 13 patients, 3 times a day in 3 patients and four times in 1 patient.

Conclusion: A considerable number of patients with CU using omalizumab did not need additional treatment, and the complaints of patients who needed additional treatment were managed with low-dose antihistamines in a short period.

Keywords: Chronic urticaria, omalizumab, antihistamine

Introduction

Omalizumab is a DNA-derived, recombinant humanized immunoglobulin G1κ (IgG1κ) monoclonal antibody that selectively binds to human IgE.[1] It downregulates the receptor and suppresses the secretion of inflammatory mediators by reducing the IgE response to allergic response by 95%.[2] This is the first pharmaceutical to be approved for use in patients with chronic idiopathic urticaria/chronic spontaneous urticaria (CSU) who have not responded to treatment with an H1 antihistamine.[3-5] The approval of omalizumab by health authorities in many countries and its use in clinical practice has provided significant progress in the treatment of patients with chronic urticaria (CU), but there are still groups of patients whose symptoms cannot be controlled with existing treatments and who need other options.[4,6]

Objectives

Omalizumab is recommended in the current guidelines to be used in addition to antihistamines in patients with refractory CSU.[7] Nevertheless, there is evidence that it is effective when used alone in some patient groups.[8,9] The objective of this study was to investigate the necessity for supplementary treatment

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and the factors influencing this requirement in patients with CU who are undergoing treatment with omalizumab at the recommended dosage.

Materials and Methods

In this study, patients who were admitted to Dicle University Faculty of Medicine, Department of Dermatology and started and continued to use omalizumab at the recommended dose between January 01, 2023 and May 01, 2023 due to CSU were retrospectively included. This study was approved by Dicle University Non-Interventional Clinical Research Ethics Committee (approval number: 219, date: 17.05.2023).

Patients were evaluated in terms of age, gender, occupation, educational status, height, weight, smoking history, duration of disease, duration of omalizumab use, history of systemic disease, need for additional treatment while using omalizumab until the next dose, if additional treatment was needed, with which group of drugs the symptoms were controlled, the dose and duration of use of the drug that controlled the symptoms, and the time it took for the symptoms to recur when the drug that controlled the symptoms was stopped. Patients with CSU lasting longer than 8 weeks who had used at least one approved antihistamine and who were followed up at our center were included in the study. The exclusion criteria were physical urticaria and weight 20 kg.

Statistical analysis

IBM SPSS 21.0 for windows statistical package was used for the statistical evaluation of the research data. Measurable variables were presented as mean ± standard deviation, and categorical variables were presented as number and percentage (%). We checked whether the data fit the normal distribution. The hypotheses were taken as two-way, and $P \leq 0.05$ was accepted as indicating statistical significance.

Results

A total of 90 patients were included in the study, of which 57 (63.3%) were female and 33 (36.7%) were male. The ages of the patients ranged from 10 to 73 years, with a mean age of 39.08±12.94 years. The average age of male patients was (40.18±14.32) and the average age of female patients was (38.45±12.15).

It was determined that 39 (43.3%) of the patients included in the study did not need any additional treatment during omalizumab therapy (Table 1).

Of the patients included in the study, 41 (45.6%) had chronic urticaria for more than 5 years, 39 (43.3%) for 1-5 years, and 10 (11.1%) for less than 1 year. Forty-seven (52.2%) patients had been on omalizumab for 6 months-1 year, 31 (34.4%) for less than 6 months, and 12 (13.3%) for more than 1 year.

When the duration of omalizumab use was compared according to patient sex, it was observed that the duration of omalizumab use in men and women was similar, and there was no significant difference between the groups ($P > 0.05$). There was a weak positive correlation ($r = 0.353$; $P < 0.05$) between the duration of chronic urticaria and the duration of omalizumab use.

The incidence of developing adverse effects before the administration of the subsequent dose of omalizumab was markedly higher in female patients enrolled in the study (64.9%) than in male patients (42.4%) ($P < 0.05$) (Table 2).

In the analysis performed to determine whether there was a relationshipbetween the duration of CU and the development of complaints until the time of administration of the other dose while using omalizumab, the rate of development of complaints until the time of administration of the other dose while using omalizumab was found to be 70% in patients with a CU duration of less than 1 year, 61.5% in patients with a duration of 1-5 years, and 48.8% in patients with a duration of more than 5 years, but there was no significant relationship ($P > 0.05$).

While using omalizumab, 51 of the patients included in the study developed complaints up to the time of administration of the next dose, of which 18 (35.3%) developed complaints at 4th week after the last dose, 14 (27.5%) at 3rd week, 10 (19.6%) at 2nd week, 6 (11.8%) at 1st week, and 3 (5.9%) at any time.

In the one-way analysis of variance performed to determine whether there was a difference in terms of mean age between patients who developed complaints and those who did not develop complaints until the time of administration of the other dose while using omalizumab, the mean age was found

Table 1. Distribution of patients according to the development of complaints during omalizumab therapy

Complaint	n, (%)
Yes	51 (56.7)
No	39 (43.3)
Total	90 (100)

Table 2. Comparison of the development of complaints while using omalizumab until the time of administration of the next dose according to patient gender

		Gender				
Complaint		Female	Male	Total	χ^2	p-value
Yes	n (%)	37 (64.9)	14 (42.4)	51 (56.7)		
No	n (%)	20 (35.1)	19 (57.6)	39 (43.3)	4.304	0.038
Total	n (%)	57 (100)	33 (100)	90 (100)		

Table 3. Distribution of patients according to the drug group they benefited from upon complaint

Drugs	n	(%)
Antihistamine	42	82.4
Systemic steroids	1	2.0
Antihistamine and systemic steroid use	7	13.4
Antihistamines, chloroquine, and cyclosporine	1	2.0
Total	51	100

to be higher in patients who developed complaints, but the difference between the groups in terms of mean age was not significant ($P > 0.05$).

In the calculation performed to determine whether there was a relationship between the duration of omalizumab use and the week of onset of complaints until the time of administration of the next dose while using omalizumab, a significant relationship was found between the duration of omalizumab use and the week of onset of complaints ($P < 0.05$). The results of the statistical analysis showed that complaints started in the 1st week in 35.3% of patients who had been using omalizumab for less than 6 months, in the 3rd week in 34.5% of those who had been using it for 6 months-1 year, and in the 3rd week in 40% of those who had been using it for more than 1 year.

Table 3 presents the drugs that patients benefited from when their complaint was initiated. Accordingly, 42 (82.4%) of the 51 patients with complaints benefited from antihistamine, 7 (13.7%) benefited from antihistamine and systemic steroid, 1 (2%) benefited from systemic steroid only, and 1 (2%) benefited from antihistamine, chloroquine, and cyclosporine.

When the drugs used by the patients who controlled their complaints with antihistamines were analyzed, 17 (34%) of the patients used bilastine, 13 (26%) levocetirizine, 7 (14%) cetirizine, 6 (12%) desloratadine, 3 (6%) ebastine, 2 (4%) loratadine, and one patient (2%) each used fexofenadine and bilastine + rupatadine.

The minimum antihistamine dose that controlled the complaints was once aday in 33 patients (66%), twice a day in 13, 3 times a day in 3, and four times a day in 1.

Twenty-three patients (46%) used antihistamines for 1 week, 19 (38%) for 2 weeks, 7 (14%) for 4 weeks, and 1 (2%) for 3 weeks until the next omalizumab dose.

It was observed that the use of methylprednisolone controlled the complaints in 8 of the patients included in the study, and the minimum dose of methylprednisolone that controlled the complaints was 36 mg in 4 (50%) of these patients, 16 mg in 3 (37.5%), and 48 mg in 1 (12.5%). Among the 8 patients who received methylprednisolone, 4 (50%) received it for 2 weeks, 3 (37.5%) for 1 week and 1 (12.5%) for 4 weeks. The body mass index (BMI) of the patients ranged from 17.10 to 29.30 kg/m^2, and the mean BMI was calculated as 23.31±2.64 kg/m^2. Although the mean BMI of women (23.51±2.63 kg/m^2) was found to be higher than that of men (22.95±2.67 kg/m^2), there was no significant difference between both genders in terms of BMI ($P > 0.05$). There was a significant correlation between the BMI of the patients included in the study and the duration of chronic urticaria disease ($P < 0.05$).

Discussion

According to the 2022 international EAACI/GA^{2}LEN/EuroGuiDerm/APAAACI guidelines in 2022, the use of standard doses of 2nd generation H1 antihistamines is recommended as the first-line symptomatic treatment for CSU. If needed, the dose can be increased up to four times. If symptoms do not improve, omalizumab (300 mg) should be added to the treatment within 2-4 weeks. If necessary, the dose can be increased and the intervals shortened. If symptoms do not resolve, cyclosporine up to 5 mg/kg can be added to treatment in addition to a second-generation antihistamine at 6 months or sooner. Short-term glucocorticoids may be considered in severe exacerbations.[7]

Although antihistamines remain the mainstay of urticaria treatment, some patients may not require antihistamines once the disease is controlled with omalizumab.[8]

Of the 90 patients included in this study, 39 (43.3%) did not require additional treatment. In contrast, 51 patients (56.7%) developed complaints during omalizumab therapy and required additional treatment. Melé-Ninot et al.[8] included 298 patients with CSU and reported that 23.5% of the patients stopped taking antihistamines during omalizumab treatment. However, Ensina et al.[9] reported that 17 out of 53 patients (32.1%) who used omalizumab and were treated for 24 months continued treatment without antihistamines.

In our study, the minimum dose of antihistamine that controlled the complaints was once a day in 33 (66%) of the patients who used antihistamines to control their complaints, 2 times a day in 13, 3 times a day in 3, and 4 times a day in 1. Among our patients who needed antihistamines, 23 (46%) used antihistamines for 1 week, 19 (38%) for 2 weeks, 7 (14%) for 4 weeks, and 1 (2%) for 3 weeks until the next omalizumab dose. Although no study has been conducted to support this finding, it was observed that most patients who needed additional treatment relieved their complaints with low doses, such as a single dose per day.

A weak, positive correlation (r=0.353; $P < 0.05$) was found between the duration of chronic urticaria and the duration

of omalizumab use. Ghazanfar et al.[10] reported a positive correlation between the duration of disease and the duration of omalizumab use in their study. Similarly, Vadasz et al.[11] reported a positive correlation between the duration of disease and the duration of omalizumab use. It can be seen that the results obtained from our study are compatible with the literature.

Female patients had a significantly higher rate of complaint (64.9%) than male patients (42.4%) when using omalizumab until the next dose. No study on this result was found in the literature.

The mean age was found to be higher in patients who developed complaints until the duration of treatment while using omalizumab, the difference between the groups in terms of mean age was not significant.

In a study by Maurer et al.[12], the average age of patients who developed complaints while using omalizumab was higher.

In the analysis performed to determine whether there was a relationship between the duration of CU and the development of complaints until the time of administration of the other dose while using omalizumab, the rate of development of complaints until the time of administration of the other dose while using omalizumab was found to be 70% in patients with a CU disease duration of less than 1 year, 61.5% in patients with a duration of 1-5 years, and 48.8% in patients with a duration of more than 5 years, but there was no significant relationship. No study on this result was found in the literature. The results demonstrated that as the duration of chronic urticaria increases, the rate of complaint development decreases until the next dose of omalizumab administered.

The mean ages of patients who developed complaints and those who did not develop complaints until the time of administration of the next dose while using omalizumab were similar. Maurer et al.[12] reported a relationship between age and complaint development and that the rate of complaint development increased with increasing age while using omalizumab.

As a result of the chi-square analysis performed to determine whether there was a relationship between the duration of omalizumab use and the week of onset of complaints until the time of administration of the next dose while using omalizumab, a significant relationship was found between the duration of omalizumab use and the week of onset of complaints ($P < 0.05$). As a result of the statistical analysis, 35.3% of patients who had been using omalizumab for less than 6 months started to complain in the 1st week, 34.5% of those who had been using it for 6 months-1 year started to complain in the 3rd week, and 40% of those who had been using it for more than 1 year started to complain in the 3rd week. Thus, as the duration of omalizumab use increases in patients with chronic urticaria, the week of onset of complaints until the administration of the next dose is postponed.

Of the 51 patients who developed complaints while using omalizumab, 42 (82.4%) benefited from antihistamines, 7 (13.7%) from antihistamines and systemic steroids, 1 (2%) from systemic steroids, and 1 (2%) from antihistamines, chloroquine, and cyclosporine. Forty-five (88.2%) patients who developed complaints stated that their complaints resumed when they stopped taking antihistamines for 1-5 days and 6 (11.8%) patients stated that their complaints resumed when they stopped taking antihistamines for 6-10 days.

There was a correlation between BMI and duration of chronic urticaria disease. The duration of chronic urticaria disease was longer in patients with higher BMI. Zbiciak-Nylec et al.[13] reported that obesity was an important risk factor for urticaria. The findings of our study are consistent with those reported in the existing literature on this topic.

Conclusion

Guidelines recommend the addition of omalizumab to the treatment of patients with inadequate response to antihistamines for the treatment of chronic urticaria. Nevertheless, the findings of this study indicate that a significant proportion of patients who received omalizumab did not require additional treatments, such as antihistamines. Furthermore, among those who required antihistamines, most demonstrated effective symptom control with short-term and low-dose antihistamines. Nevertheless, further research is required to inform the revision of the guidelines.

Ethics

Ethics Committee Approval: This study was approved by Dicle University Non-Interventional Clinical Research Ethics Committee (approval number: 219, date: 17.05.2023).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: H.İ.G., E.A., Concept: H.İ.G., E.A., Design: H.İ.G., E.A., Data Collection or Processing: H.İ.G., E.A., Analysis or Interpretation: H.İ.G., E.A., Literature Search: H.İ.G., Writing: H.İ.G., E.A.

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Orginal Article

Online Pemphigus Information Evaluation: Quality, Reliability, Readability, and Comprehensiveness

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Abstract

Aim: The internet is a key resource for information on medical conditions. Such information should be clear, high-quality, and comprehensive. We aimed to evaluate the quality, reliability, readability, recency, popularity, and comprehensiveness of online pemphigus information and examine how these factors are influenced by the producers of websites.

Materials and Methods: We searched for "pemphigus" on Google, Yahoo, and Bing, including the top 50 results from each. The websites were categorized as websites for professionals, government websites, dermatology societies, non-profit organizations, and miscellaneous websites. We evaluated reliability using Journal of American Medical Association (JAMA) Benchmark Criteria and assessed quality using the DISCERN instrument. Readability was measured using the Flesch Reading Ease Score (FRES), Flesch-Kincaid Grade Level (FKGL), Simple Measure of Gobbledygook Index, Gunning Fog Index (GFOG), Coleman-Liau Index, and Automated Readability Index. Popularity was based on SimilarWeb visit counts, and content was assessed using a 15-item checklist.

Results: Post-exclusion, the 35 websites had a mean JAMA score of 3.06 and a mean DISCERN score of 59.31, indicating good quality. The average reading-grade was 9.88, suggesting that approximately 10 years of education are required to understand the text. The mean FRES score was 46.03, indicating a college-level difficulty. The average comprehensiveness, based on a 15-item checklist, was 11.5. Follow-up visits were the least frequently mentioned topic (8.6%). Statistically significant differences were observed among the website groups in JAMA scores (p=0.009), FKGL (p=0.012), GFOG (p=0.008), popularity (p=0.002), and information on pemphigus epidemiology (p=0.021), types (p=0.014), differential diagnosis (p=0.008), and prognosis (p=0.023).

Conclusion: Although the reliability and quality of many websites were satisfactory, our study emphasizes the need for better readability in pemphigus resources. Dermatologists should help create clear and reliable online information to improve patient understanding and health outcomes.

Keywords: Online information, comprehensiveness, internet, pemphigus, quality, readability

Introduction

The Internet has become an increasingly vital resource for health information, with a growing number of individuals turning to it for advice on various medical conditions. In the United States, studies have indicated that approximately 70% of adult internet users have sought health-related information online.[1] This trend highlights the reliance on search engines as primary tools for accessing health information, often leading patients to a myriad of websites that compete for their attention. However, this competition raises significant concerns regarding the quality and reliability of the information presented.[2] Health-related websites provide a diverse array of content, ranging from highly reliable to potentially deceptive.

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However, many of these resources do not undergo peer-review and exhibit significant variations in quality.[3] Furthermore, the readability of online health information often exceeds the recommended sixth-grade reading level set by organizations such as the National Institutes of Health (NIH) and the American Medical Association (AMA). This higher level can hinder the comprehension of the average reader, making it essential to ensure that online health materials are evaluated appropriately before use.[4]

The literature includes studies that assess the quality, readability, and comprehensiveness of online health information for a range of dermatologic conditions, such as hidradenitis suppurativa, acral lentiginous melanoma, rosacea, psoriasis, generalized pustular psoriasis, vitiligo, Behçet's disease, laser tattoo removal, and oral leukoplakia.[5-13] Moreover, a study has examined how large language models can aid in creating patient education materials that are easier to read and understand.[14]

Pemphigus, a group of life-threatening autoimmune bullous diseases characterized by flaccid blisters and erosions of the mucous membranes and skin,[15] is one condition for which patients may seek information online. Previous studies only assessed the readability of online information sources related to pemphigus vulgaris.[16] In this study, we evaluated the readability, quality, reliability, recency, and popularity of internet-based information on pemphigus. Additionally, we investigated the comprehensiveness of the content. We also examined the effects of the category of website producers on these factors.

Materials and Methods

Internet Search Strategy

An internet search for the term "pemphigus" was conducted using three prominent search engines: Google, Yahoo, and Bing, on June 10, 2024. These search engines were selected based on their status as leading platforms in the UK as of March 2024, with the understanding that patients typically prefer general search tools over specialized medical databases, such as PubMed.[17,18] To ensure the integrity of the search results, geographical location settings were disabled, and browser data were cleared prior to conducting the search. This was performed using the private browsing mode to mitigate potential biases that could arise from the previous search history.

The search results were limited to the first 50 entries from each search engine, resulting in a total of 150 results. The following exclusion criteria were applied: repetitive websites, non-English content, websites lacking relevant information about pemphigus, sites requiring user registration or subscription, research articles, websites related to veterinary medicine, and websites that only provided video content. The process of website evaluation is illustrated in Figure 1.

During the evaluation of the websites, if relevant information could not be located on the homepage, the "three-click rule" was employed. This informal guideline suggests that users should be able to find the desired information in three mouse clicks. It is posited that if information is not accessible within this limit, users are likely to abandon the site.[4]

Website Typology

We categorized the websites into five distinct categories. Two independent authors classified the data, focusing on the ownership and type of the websites. The categories included: government websites (created and managed by official government agencies); dermatology societies' official websites (e.g., British Association of Dermatologists, American Academy of Dermatology Association); non-profit organizations' websites (charitable/supportive/educational websites created by non-profit organizations); miscellaneous websites (including sites that target the general population and do not fit into the other categories); and websites for professionals (containing detailed information primarily aimed at medical professionals). In instances where discrepancies arose between the authors' classifications, a collaborative re-evaluation was conducted to reach a consensus on the final categorization of each website.

Assessment of Reliability and Quality

To evaluate the reliability of the websites, we used the Journal of the American Medical Association (JAMA) benchmark criteria. The JAMA benchmark criteria encompass four key components: 1) identification of authorship, 2) identification of sources, 3) specification of the date of creation or update, and 4) disclosures regarding ownership, advertising policy, sponsorship, and conflicts of interest. Each criterion was recorded as present or absent, with a scoring system awarding one point for each criterion met. The final score ranged from 0 to 4.[2]

The DISCERN score was used to assess the quality of the selected websites. This tool assesses website quality by grading 16 items on a five-point scale, where 1 indicates "not at all" and 5 indicates "completely." The overall DISCERN score ranged from 16 to 80, with higher scores indicating higher quality information. Specifically, scores below 27 are categorized as "very poor", 27-38 as "poor", 39-50 as "fair", 51-62 as "good", and 63 and above as "excellent".[19] The final DISCERN score for each website was obtained by averaging the data from the two authors.

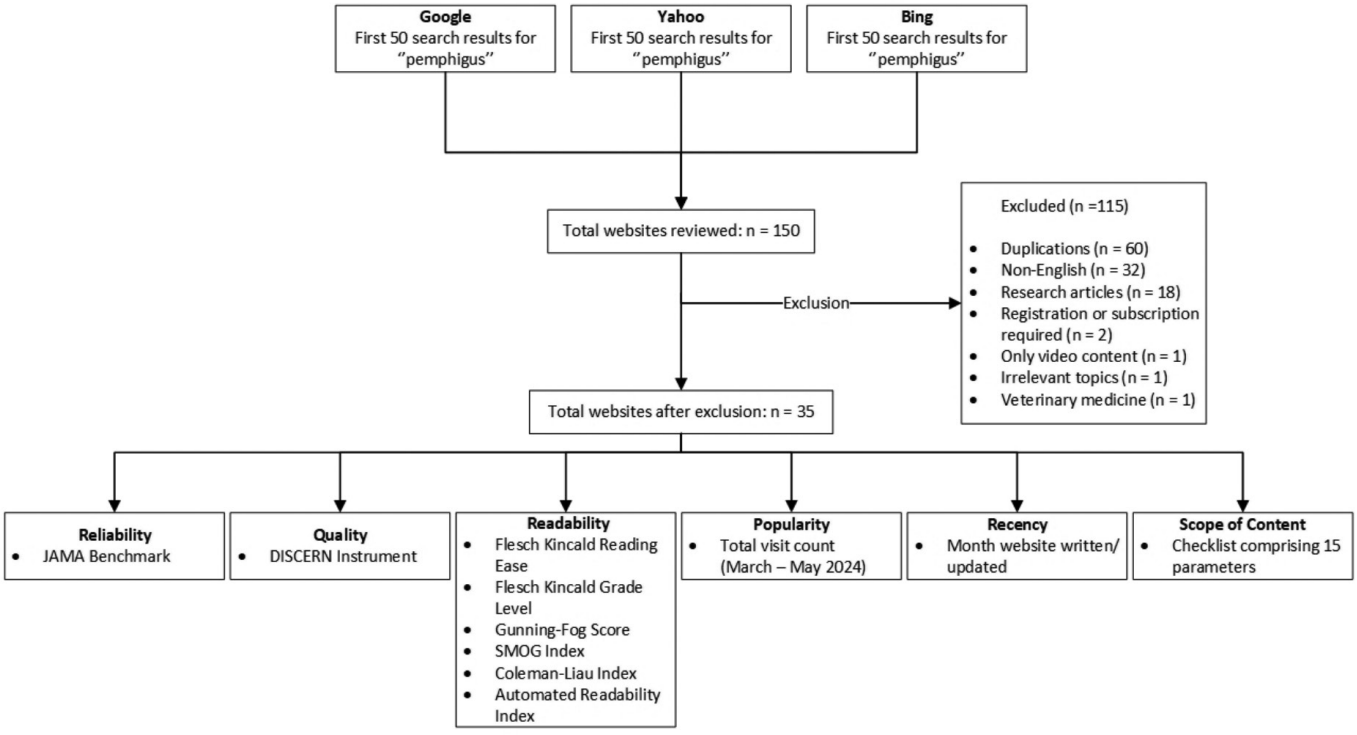

Figure 1. Schematic illustrating the process of selecting and evaluating the top websites for pemphigus

Assessment of Readability

Readability assessments of websites were conducted using automated tools available at "https://www.webfx.com/tools/read-able/". The evaluation employed six established readability scales: Flesch Reading Ease Score (FRES), Flesch-Kincaid Grade Level (FKGL), Simple Measure of Gobbledygook (SMOG), Gunning Fog Index (GFOG), Coleman-Liau Index (CLI), and the Automated Readability Index (ARI). The FRES was measured on a scale from 0 to 100, where a higher score indicates easier readability. Conversely, the FKGL, Gunning Fog Score, SMOG Index, CLI, and ARI provide educational grade levels that reflect the comprehension required for a given text. For optimal readability, the FRES should be ≥ 60, while the other five indices should yield scores of ≤ 6. Therefore, achieving higher FRES scores alongside lower scores in the other formulas indicates improved readability.[20,21]

Assessment of Popularity

To evaluate the popularity of the websites included in this study, we used total visit counts over a three-month period obtained from SimilarWeb, a widely recognized web analytics service.[22] The data were collected from March 2024 to May 2024. By incorporating these visit counts, we aimed not only to understand the quality of the information provided, but also to determine the extent of its dissemination and accessibility to the general public.

Assessment of Comprehensiveness

To evaluate the comprehensiveness of the websites, we established a checklist comprising 15 parameters. These parameters were in line with current clinical guidelines and relevant literature.[15,23,24] The checklist includes the following components: definition of pemphigus, epidemiology of the disease, types of pemphigus, pathophysiology, potential trigger factors and causes, symptoms associated with pemphigus, diagnostic evaluation methods, differential diagnoses, general management measures, treatment options, follow-up visit protocols, prognosis of the disease, complications related to pemphigus, references, and photographs as visual aids.

Statistical analysis

Statistical analyses were conducted using MATLAB R2024a (MathWorks Inc., Natick, MA, USA). Frequency data are presented as number (n) and percentage (%), whereas continuous data are expressed as the mean ± standard deviation. To assess statistical differences between groups, various statistical tests were employed. Chi-square tests were utilized for frequency variables, while the Kruskal-Wallis test was applied to analyze website readability indices, JAMA scores, DISCERN scores, popularity, and recency. For comparisons in which the Kruskal-Wallis test indicated significant differences, the post-hoc Dunn's test was performed to identify specific group differences. Additionally, Spearman's rank correlation analysis was performed to evaluate the correlations between

JAMA and DISCERN scores, readability indices, recency, and popularity. A *P* value of <0.05 was considered statistically significant.

Results

Website Typologies

A total of 150 websites were initially assessed, of which 115 were excluded based on predefined inclusion criteria, resulting in 35 websites that met the requirements for evaluation. Among these, 15 websites provided information under the title of "pemphigus", while 17 specifically focused on "pemphigus vulgaris", and 3 specifically focused on "pemphigus foliaceus".

When analyzing the typologies of the 35 evaluated websites, we found that websites targeting professionals comprised 8 websites (23%). In contrast, websites aimed at the general population constituted the majority, accounting for 27 websites (77%). This category of general population websites includes government (n = 5, 14%), dermatology societies' (n = 5, 14%), non-profit organizations' (n = 4, 12%), and miscellaneous (n = 13, 37%) websites, as shown in Figure 2.

Comparison of Reliability, Quality, Readability, Popularity, and Recency Among Website Groups

The mean JAMA score for all websites (n = 35) was 3.06±0.97. There was a statistically significant difference in JAMA scores among the different website groups (*P* = 0.009) (Table 1). The post-hoc Dunn test revealed a significant difference between websites targeting professionals and government websites (*P* = 0.002).

The mean quality score of all websites, as measured by DISCERN, was 59.31±11.59. The websites targeting professionals had the highest quality score of 66.75±9.97, while government websites had the lowest quality score of 52.80±4.21. However, the analysis revealed no statistically significant difference in quality scores among the different types of websites (*P* = 0.198) (Table 1).

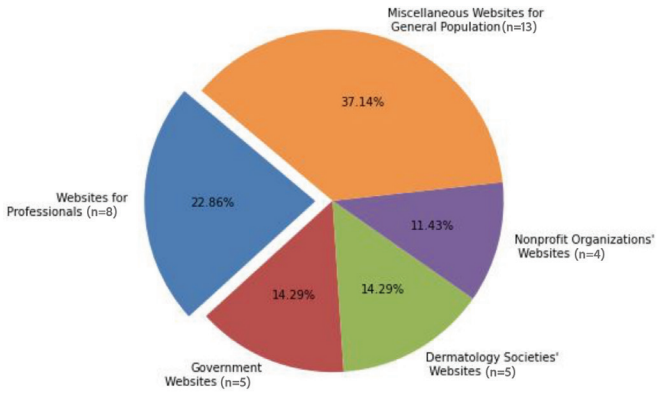

Figure 2. Distribution of websites by type

For readability, the mean FKGL for all websites (n = 35) was 8.64±1.94 years. There was a statistically significant difference in FKGL among the different website groups (*P* = 0.012). Websites targeting professionals had the highest mean FKGL, indicating more complex content than the other groups. The mean GFOG score for all websites was 10.22±2.45 years. There was a significant difference in GFOG among the website groups (*P* = 0.008). Post-hoc Dunn's test showed that websites for professionals scored significantly higher than both government websites (*P* = 0.001) and miscellaneous websites (*P* = 0.005). The mean FRES for all websites was 46.03±13.83, indicating college-level difficulty, with no significant differences among the website categories (*P* = 0.164). Similarly, the mean SMOG Index was 7.46±1.29 years of education, the mean CLI was 15.57±2.49 years of education, and the mean ARI was 7.49±1.51 years of education, with no significant differences among the groups (*P* = 0.349, *P* = 0.207, and *P* = 0.088, respectively) (Table 1).

According to each index, the number of websites at or below a sixth-grade reading level is as follows: 3 for FKGL, 1 for GFOG, 2 for SMOG, 0 for CLI, and 7 for ARI. The average readability-grade for all websites was 9.876±3.61, which was calculated by averaging the FKGL, SMOG, GFOG, CLI, and ARI scores.

In terms of popularity, measured by total visits from March to May 2024, all websites had a mean of 173.640.084. There was a statistically significant difference in popularity across different website categories (*P* = 0.002) (Table 1). Post-hoc Dunn's test indicated significant differences in website visits, showing that non-profit organizations' (*P* = 0.002) and dermatology societies' (*P* = 0.001) had fewer visits compared to miscellaneous websites, which had the highest mean visits.

The average recency (the time since the last update in months) for all websites is 24.42±21.99 months. However, when analyzed individually, 25 out of 35 websites were produced or updated within the last 2 years. There was no statistically significant difference in average recency among the groups (*P* = 0.959) (Table 1).

Correlation Analysis

Among the readability formulas tested, only the CLI showed a significant moderate positive correlation with the JAMA index (*r* = 0.352, *P* = 0.038). There were no significant correlations between the readability formulas and the DISCERN index. There was a significant strong positive correlation between JAMA and the DISCERN indices (*r* = 0.5069, *P* = 0.002).

Table 1. Comparative analysis of reliability, quality, readability, recency, and popularity according to website category

	All websites, (n=35)	Non-profit organization websites, (n=4)	Dermatology societies' websites (n=5)	Government websites, (n=5)	Miscellaneous websites, (n=13)	Websites for professionals, (n=8)	P+
Reliability (mean ± SD)							
JAMA	3.06±0.97	2.25±1.26	2.80±0.45	2.40±0.55	3.15±1.07	3.88±0.35	**0.009***
Quality (mean ± SD)							
DISCERN	59.31±11.59	57.25±14.97	58.00±10.46	52.80±4.21	58.38±12.91	66.75±9.97	0.198
Readability (mean ± SD)							
FRES	46.03±13.83	40.87±11.98	54.46±16.15	54.84±11.75	47.7±13.13	35.11±8.98	0.164
FKGL	8.64±1.94	9.75±1.16	7.18±2.51	7.38±1.38	8.39±1.62	10.17±1.54	**0.012***
GFOG	10.22±2.45	10.65±2.75	8.40±3.34	8.80±0.85	9.84±1.91	12.65±1.42	**0.008***
SMOG	7.46±1.29	8.27±1.34	6.48±1.74	6.92±0.59	7.26±0.95	8.34±1.27	0.349
CLI	15.57±2.49	16.27±2.90	13.74±4.28	14.48±2.24	15.74±2.07	16.75±0.89	0.207
ARI	7.49±1.51	8.67±1.43	6.62±1.14	6.36±1.61	7.44±1.45	8.25±1.20	0.088
Popularity (mean)							
Total visits (Mar-May 2024)	173.640.084	1.265.014	2.929.362	63.645.000	410.087.154	29.495.375	**0.002***
Recency (mean ± SD)							
Last updated (months ago)	24.42±21.99	21.00±21.70	29.00±31.35	33.80±32.75	21.85±19.22	21.75±17.53	0.959

FRES: Flesch Reading Ease Score, FKGL: Flesch-Kincaid Grade Level, SMOG: Simple Measure of Gobbledygook, GFOG: Gunning FOG, CLI: Coleman-Liau score, ARI: Automated Readability Index, JAMA: JAMA Benchmark Criteria, SD: Standard deviation, +P values were calculated using the Kruskal-Wallis test, *Statistically different at $p<0.05$

Additionally, there was a significant moderate positive correlation between JAMA and popularity (r = 0.384, P = 0.025). There were no significant correlations with recency for either index (Table 2).

Content Analysis

Based on the analysis of the websites using a 15-item checklist, certain statistically significant differences were observed in the presentation of information regarding pemphigus. The definition, pathophysiology, and symptoms of pemphigus were provided on all evaluated websites. Follow-up visits were the least mentioned topic, appearing in 8.6% of the websites. There were statistically significant differences in the inclusion of information on the epidemiology of pemphigus (P = 0.021), types of pemphigus (P = 0.014), differential diagnosis (P = 0.008), and prognosis (P = 0.023) among the groups. The detailed content analysis results are presented in Table 3.

In the analysis, the average total score for all 35 websites, based on a checklist where each item was assigned a score of 1 (with a minimum of 0 and a maximum of 15), was found to be 11.5 out of 15. The group-based average scores were as follows: miscellaneous websites scored 11.7; websites for professionals scored 13, government websites scored 9.2, dermatology societies' websites scored 11, and non-profit organizations' websites scored 11.2.

Discussion

Pemphigus, a rare chronic autoimmune blistering disease, severely affects patients' quality of life, especially in severe forms. Even in the early stages, the disease can significantly disrupt daily activities and overall well-being.[25] Consequently, many individuals turn to the internet to seek information about their condition, explore treatment options, and find support. However, patients often lack the ability to assess the quality of online information, making it essential for physicians to guide patients toward trustworthy websites.[26,27] To date, no comprehensive study has evaluated the most prominent websites offering information about pemphigus.

In our review of pemphigus websites, we observed that 77% were aimed at the general public, highlighting a significant effort to spread awareness about this condition. The presence of government websites, dermatology societies, and non-profit organizations underscores the importance of credible sources for educating the public. The largest proportion of websites (37.14%) falls under the category of miscellaneous websites, which raises concerns regarding the accuracy and comprehensiveness of the information presented. This distribution underscores the importance of critically evaluating online resources to ensure that they provide high-quality and reliable information for all users.

We note that websites targeting professionals received the highest scores for the JAMA criteria, which is not surprising given their adherence to stricter standards. These websites

Table 2. Correlation analysis of website metrics

	JAMA		DISCERN	
	r	p	r	p
FRES	-0.329	0.054	-0.316	0.064
FKGL	0.0835	0.633	0.176	0.311
GFOG	0.103	0.556	0.297	0.083
SMOG	-0.0101	0.954	0.155	0.374
CLI	**0.352**	**0.038***	0.204	0.240
ARI	-0.032	0.855	0.091	0.605
JAMA	-	-	**0.507**	**0.002***
DISCERN	**0.507**	**0.002***	-	-
Popularity	**0.384**	**0.025***	0.215	0.222
Recency	-0.024	0.892	0.128	0.479

FRES: Flesch Reading Ease Score, FKGL: Flesch-Kincaid Grade Level, SMOG: Simple Measure of Gobbledygook, GFOG: Gunning FOG, CLI, Coleman-Liau score, ARI: Automated Readability Index, JAMA: JAMA Benchmark Criteria. *Statistically different at $p<0.05$.

Table 3. Content analysis of websites based on a 15-item checklist

		All websites, (n=35)	Non-profit organization websites, (n=4)	Dermatology societies' websites, (n=5)	Government websites, (n=5)	Miscellaneous websites, (n=13)	Websites for professionals, (n=8)	P+
Definition	-	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	NA
	+	35 (100%)	4 (100%)	5 (100%)	5 (100%)	13 (100%)	8 (100%)	
Epidemiology	-	5 (14.3%)	1 (25%)	0 (0%)	3 (60%)	1 (7.7%)	0 (0%)	**0.021***
	+	30 (85.7%)	3 (75%)	5 (100%)	2 (40%)	12 (92.3%)	8 (100%)	
The types of pemphigus	-	9 (25.7%)	0 (0%)	2 (40%)	4 (80%)	3 (23.1%)	0 (0%)	**0.014***
	+	26 (74.3%)	4 (100%)	3 (60%)	1 (20%)	10 (76.9%)	8 (100%)	
Pathophysiology	-	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	NA
	+	35 (100%)	4 (100%)	5 (100%)	5 (100%)	13 (100%)	8 (100%)	
Potential trigger factors	-	8 (22.9%)	0 (0%)	2 (40%)	3 (60%)	2 (15.4%)	1 (12.5%)	0.145
	+	27 (77.1%)	4 (100%)	3 (60%)	2 (40%)	11 (84.6%)	7 (87.5%)	
Symptoms	-	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	NA
	+	35 (100%)	4 (100%)	5 (100%)	5 (100%)	13 (100%)	8 (100%)	
Diagnostic methods	-	3 (8.6%)	0 (0%)	0 (0%)	2 (40%)	1 (7.7%)	0 (0%)	0.095
	+	32 (91.4%)	4 (100%)	5 (100%)	3 (60%)	12 (92.3%)	8 (100%)	
Treatment methods	-	1 (2.9%)	1 (25%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0.09
	+	34 (97.1%)	3 (75%)	5 (100%)	5 (10%0)	13 (100%)	8 (100%)	
Follow-up visits	-	32 (91.4%)	4 (100%)	5 (100%)	5 (100%)	11 (84.6%)	7 (87.5%)	0.69
	+	3 (8.6%)	0 (0%)	0 (0%)	0 (0%)	2 (15.4%)	1 (12.5%)	
Prognosis	-	5 (14.3%)	0 (0%)	0 (0%)	3 (60%)	2 (15.4%)	0 (0%)	**0.023***
	+	30 (85.7%)	4 (100%)	5 (100%)	2 (40%)	11 (84.6%)	8 (100%)	
General measures	-	17 (48.6%)	3 (75%)	0 (0%)	2 (40%)	7 (53.8%)	5 (62.5%)	0.149
	+	18 (51.4%)	1 (25%)	5 (100%)	3 (60%)	6 (46.2%)	3 (37.5%)	
Differential diagnosis	-	12 (34.3%)	0 (0%)	5 (100%)	1 (20%)	5 (38.5%)	1 (12.5%)	**0.008***
	+	23 (65.7%)	4 (100%)	0 (0%)	4 (80%)	8 (61.5%)	7 (87.5%)	
Complications	-	5 (14.3%)	0 (0%)	2 (40%)	1 (20%)	2 (15.4%)	0 (0%)	0.303
	+	30 (85.7%)	4 (100%)	3 (60%)	4 (80%)	11 (84.6%)	8 (100%)	
References	-	13 (37.1%)	3 (75%)	3 (60%)	2 (40%)	4 (30.8%)	1 (12.5%)	0.207
	+	22 (62.9%)	1 (25%)	2 (40%)	3 (60%)	9(69.2%)	7 (87.5%)	
Photographs	-	13 (37.1%)	3 (75%)	1 (20%)	3 (60%)	5 (38.5%)	1 (12.5%)	0.178
	+	22 (62.9%)	1 (25%)	4 (80%)	2 (40%)	8 (61.5%)	7 (87.5%)	

+P-values were calculated using the chi-square test. NA: Not applicable, *Statistically different at $p<0.05$.

are often authored by experts in the field, ensuring high-quality, evidence-based information. Healthcare providers and those seeking professional-level information should prioritize these resources to ensure their reliability. In line with this, our analysis also revealed that these professional targeted websites had the highest average DISCERN score, which indicates excellent quality. For the other groups, even the lowest average score fell within the "good quality" range. This suggests that the overall quality of resources across all groups remains relatively consistent, reassuring users that reliable information can be found regardless of category. Similarly, in a study comparing online resources for another autoimmune blistering disease, bullous pemphigoid, categorized by whether they were written by dermatologists or non-dermatologists, there was no significant difference in average DISCERN scores between the two groups.[28]

In recent years, the readability of online health information has emerged as a critical concern. The AMA and the NIH advocate for health care materials to be composed at or below a sixth-grade reading level to ensure comprehension among a diverse patient population.[29,30] However, our analysis of online resources related to pemphigus revealed that the average reading levels exceed this recommendation, indicating a pervasive issue of accessibility in health communication. Ji-Xu et al.[16] reported that online patient education resources for pemphigus vulgaris and bullous pemphigoid are, on average, at least six reading grades above the recommended level, with materials authored by medical doctors, particularly dermatologists, being more complex than those written by non-medical professionals. This lack of readability is particularly detrimental to individuals with low health literacy who are already at an increased risk of misunderstanding their medical conditions and treatment options.[31] Such misunderstandings can lead to delayed medical care, poor health outcomes, and decreased adherence to prescribed therapies. In addition, misinterpretation of medical information can exacerbate patient anxiety and stress. Our findings also highlighted that FKGL and Gunning Fog Score indicate that professional websites are significantly more difficult to read than other websites. The increased readability challenge is justified for several reasons. Professional content is tailored to individuals with specialized knowledge, requiring the use of advanced terminology and detailed information to meet the sophisticated needs of audiences. Furthermore, professionals generally possess higher education and experience, enabling them to grasp more complex material.

Skrzypczak et al.'s[5] study on the readability of online documents about hidradenitis suppurativa evaluated 458 articles across 22 languages as non-profit, online shops, dermatology clinics, or pharmaceutical companies. The Lix score was used to assess readability, with most articles classified as very difficult to understand. Significant differences in readability were found across languages, but no notable differences were observed among the different origin categories.[5]

Jean-Pierre et al.[12] assessed the readability and comprehensiveness of 77 websites on laser tattoo removal. They found that most sites were above the eighth-grade reading level, and less than half addressed pigmentary risks for darker skin or the need for consulting a board-certified dermatologist or plastic surgeon. More than 90% of the participants mentioned the need for multiple sessions. This study highlighted a gap in accessible, high-quality information for informed decision-making regarding laser tattoo removal.[12]

Malik et al.[9] first evaluated the quality, comprehensiveness, and readability of online health information on generalized pustular psoriasis. An analysis of 500 websites with medical and layperson search terms revealed that only 16.8% were HONcode-accredited, and the mean DISCERN scores indicated notable gaps in reliability and treatment information. Additionally, only 4% of websites met the NIH-recommended sixth-grade reading level, with academic sites being harder to read than government sites, highlighting challenges for patients with low health literacy, who may already be at higher risk of not receiving timely medical care.[9]

Nayudu et al.[10] assessed the quality and readability of online health information on phototherapy for vitiligo. An analysis of 500 websites with medical search terms revealed that 35% were HONcode-accredited, indicating reliability. The DISCERN scores highlighted gaps in reliability (58.9%) and treatment information (51.7%). Notably, none of the 130 websites assessed met the NIH-recommended sixth-grade reading level, indicating potential health disparities among patients with lower health literacy.[10]

Given that dermatologic patient education materials are often written above the recommended reading level, Lambert et al.[14] evaluated the use of large language models (ChatGPT-3.5, GPT-4, DermGPT, and DocsGPT) to generate patient education materials at specific, accessible reading levels. The FKGL of existing American Academy of Dermatology materials for common and rare conditions was assessed. The models were prompted to create handouts at fifth- and seventh-grade FKGLs, with GPT-4 performing best at the fifth-grade level for both common and rare conditions, while ChatGPT-3.5 and DocsGPT outperformed GPT-4 at the seventh-grade level for rare conditions. They concluded that large language models could enhance health literacy by providing accessible and understandable patient education materials in dermatology.[14]

In our study, websites in the miscellaneous category were significantly more popular than those of both non-profit

organizations and dermatology societies. It is important to note that our analysis focused on general domains (e.g., https://patient.info) rather than specific pages (e.g., https://patient.info/doctor/pemphigus). This approach may not accurately reflect interest in specific topics but provides a broader perspective on overall website popularity.

Recent advancements in the treatment of pemphigus, particularly anti-CD20 therapy, have significantly improved treatment efficacy and reduced morbidity.[24] Given that pemphigus is a disease group that requires ongoing research, maintaining updated information is crucial for effective management.[32] Regarding content recency, a substantial proportion of the websites on pemphigus were updated within a reasonable timeframe, typically within the last two years. Furthermore, we observed no significant differences in the recency across the various website categories.

The CLI was positively correlated with JAMA, whereas other readability formulas did not show a significant relationship with JAMA. This may be due to these formulas evaluating different dimensions of text complexity. No significant correlations were observed between the readability formulas and the DISCERN index. Similarly, an analysis of online patient materials on dysplastic nevi found no correlation between DISCERN scores and readability metrics such as the Flesch Reading Ease and FKGL.[33] This lack of correlation can be attributed to the inherent complexity of medical terminology and the limitations associated with these readability formulas.

The strong positive correlation between the JAMA and DISCERN indices suggests that both measures evaluate overlapping quality and reliability criteria. This finding aligns with previous research, such as a study on the quality of information on septic arthritis, which found a strong positive correlation between DISCERN scores and JAMA scores ($r = 0.877$, $P < 0.05$).[34] Additionally, the positive correlation between JAMA and popularity implies a tendency for reliable information sources to attract more attention, which is beneficial for public health.

The analysis revealed that although fundamental information regarding the definition, pathophysiology, and symptoms of pemphigus was universally covered, crucial aspects such as follow-up visits were notably underrepresented, appearing in only 8.6% of the websites. Proper follow-up is essential for managing chronic conditions like pemphigus, as it allows for the monitoring of disease progression, assessment of treatment efficacy, and timely management of any complications.[15,23] Significant differences were noted in the availability of information on the epidemiology, types of pemphigus, differential diagnosis, and prognosis across the various website categories. These discrepancies indicate differences in the focus of the content, which are likely influenced by the intended audience and the expertise of the authors.

Study Limitations

This study has several limitations that should be acknowledged. First, there is no consensus on which readability index yields the most accurate results; therefore, we utilized various indices commonly referenced in the literature. Additionally, although the DISCERN instrument is well-established and evidence-based, it inherently involves a degree of subjectivity. Our search was restricted to English language materials, which limited our insight into the quality of patient education resources available in other languages. Furthermore, the content evaluation was based solely on whether specific topics were mentioned, without considering the depth or detail of the information provided. Lastly, given that the Internet is a rapidly changing medium, our current analysis represents a timely but limited snapshot of the available patient education materials, which may evolve significantly over time.

Conclusion

Our study highlights the critical need for improved readability of online resources related to pemphigus. Although the reliability and quality of the content on these websites were found to be satisfactory, the readability levels significantly exceeded the NIH's grade six recommendation, potentially hindering patient comprehension. It is important for dermatologists to actively engage in the evaluation and endorsement of online information, ensuring that patients are directed toward reliable and comprehensible resources. By prioritizing readability in the development of online content, dermatologists can enhance patient understanding and improve health outcomes.

Ethics

Ethics Committee Approval: Not applicable.

Informed Consent: Not applicable.

Footnotes

Authorship Contributions

Surgical and Medical Practices: C.A.G., H.A.K., Concept: C.A.G., Design: C.A.G., Data Collection or Processing: C.A.G., H.A.K., Analysis or Interpretation: C.A.G., H.A.K., Literature Search: C.A.G., H.A.K., Writing: C.A.G., H.A.K.

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Orginal Article

Genetic Expression of Transient Receptor Potential Channels in Plaque Psoriasis

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Abstract

Aim: Psoriasis is an immune-associated cutaneous condition characterized by inflammation. The transient receptor potential canonical (TRPC), transient receptor potential ankyrin (TRPA), transient receptor potential melastatin (TRPM), transient receptor potential vanilloid (TRPV), transient receptor potential polycystin (TRPP), and transient receptor potential mucolipin (TRPML) families are mammalian transient receptor potential (TRP) channels, and abnormal differentiation or barrier dysfunction may be attributed to their abnormal expression. This study aimed to investigate gene expression in TRP channels in psoriatic cases and to associate the expression level with disease severity.

Methods: This research was case-controlled and comprised 60 patients with psoriasis vulgaris and 60 years and sex-coordinated well-health volunteers as the control group. The patient's entire history was recorded, and a general and complete dermatological examination was performed. The disease severity was evaluated by applying the psoriasis area and severity index score. Venous blood samples were taken for the detection of *TRPC6*, *TRPM2*, and *TRPV1* gene expression by real-time polymerase chain reaction.

Results: Considering TRPC6; the mean expression level was lower in patients than in controls, with a statistically significant difference ($U = 661.5$ and $P < 0.001$). Nevertheless, TRPM2 and TRPV1 demonstrated higher expression levels in cases than controls ($U = 36$ and 78, resp., and $P < 0.001$ for both). Therefore, TRPM2 and TRPV1 can be used to distinguish cases from controls with significant accuracy ($P < 0.001$ for both).

Conclusion: Variations in TRP channel expression patterns may be involved in the etiopathogenesis of psoriasis and may be useful and promising agents for psoriasis treatment.

Keywords: Psoriasis, transient receptor potential channels, polymerase chain reaction

Introduction

Psoriasis is a persistent, inflammatory cutaneous illness affecting up to 3% of the global population. The prevalence of this condition varies by location and has a substantial impact on quality of life for affected individuals.[1] Psoriasis can be classified into five primary types: erythrodermic, pustular, inverted, guttate (eruptive), and plaque. Approximately 90% of cases are categorized as plaque psoriasis, which is characterized by symmetrically distributed, raised, and sharply defined scaly plaques on the scalp, knees, elbows, and lower back.[2]

Psoriasis is a complex illness caused by genetic, environmental, psychogenic, and metabolic factors. Excessive alcohol use and smoking can aggravate psoriasis, whereas the key mechanisms contributing to the development of psoriasis are related to the interactions between keratinocytes and immune system cells, such as dendritic cells, T-lymphocytes, neutrophils, and mast cells.[3]

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The transient receptor potential (TRP) channels assist receptor cells in controlling the sense of environmental alterations, such as temperature, pH variations, itching perception, and pain perception. Furthermore, they are crucial for molecular signal transduction cascades involved in several skin purposes, such as epidermal proliferation and differentiation of the epidermis and programed death.[4] Indeed, they are linked to the occurrence of various cutaneous disorders, such as psoriasis, atopic dermatitis, psoriasis, rosacea, and skin tumors.[5]

Six subfamilies, including transient receptor potential vanilloid (TRPV), transient receptor potential canonical (TRPC), transient receptor potential ankyrin (TRPA), transient receptor potential polycystin (TRPP), transient receptor potential melastatin (TRPM), and transient receptor potential mucolipin (TRPML) compromise the TRP channels based on amino acid sequence homology. In human keratinocytes, members of the TRPC, TRPV, TRPM, and TRPA subfamilies were discovered.[6] Cells in the epidermis, specifically keratinocytes, express various calcium channels, most of which are non-selective ion channels belonging to the TRP channel superfamily.[7]

The skin's protective epithelial barrier is constantly regulated, with a crucial balance between keratinocyte differentiation and proliferation. The diminished keratinocyte differentiation and proliferation can lead to significant skin conditions, such as atopic dermatitis and psoriasis. This process involves various TRP channels that are essential for the influx of Ca^{2+}.[8]

This study examined the genetic expression of TRPC6, TRPM2, and TRPV1 in plaque psoriasis using real-time polymerase chain reaction (RT-PCR) and associated their expression levels with available clinical information.

Materials and Methods

This case-control study involved 120 individuals categorized into two sets. The first set included 60 cases diagnosed and appraised clinically as chronic plaque psoriasis, and the second set included 60 sex- and age-matched controls. From July 2022 to July 2023, cases were selected from the outpatient dermatology, andrology, and STD clinics of Menoufia University Hospital, and the diagnosis was based on comprehensive history taking and the presence of representative dusky red erythematous scaly plaques.[3]

Ethical Authorization and Contribution Agreement

Before the study began and after a brief explanation of the study's aims, informed consent was obtained from each contributor. The consent form was developed in accordance with the Declaration of Helsinki and the Quality and Improvement System requirements of the Egyptian Ministry of Health and Population. The Local Ethical Scientific Committee of the Menoufia University Faculty of Medicine, approved this study (approval number and date: 3/2022 DERMA49).

The inclusion criteria were as follows: Individuals with psoriasis vulgaris, irrespective of sex and age, who did not receive any medication for their psoriasis, either systemic for six weeks or topical treatment, except emollients for 15 days prior to sample collection.

The exclusion criteria were as follows: Any patient with an inflammatory or autoimmune disorder; patients with other types of psoriasis except plaque psoriasis.

A comprehensive history was obtained, including patient name, age, sex, onset of psoriasis (either late onset after age 40 or early onset before age 40), and disease duration in years. Additionally, medical history was evaluated, focusing on disease course (either progressive or stationary) and family history of psoriasis. Then, a detailed dermatological examination was conducted to identify the site of affection, scalp affection, nail affection, and presence of koebnerization.

For each patient, disease severity was evaluated by applying the psoriasis area severity index (PASI) score, which was based on a complicated computation involving the percentage of the body surface affected by psoriasis, intensity of redness, flaking, and psoriatic patch thickness. The body was divided into four structural portions: cranium, trunk, and upper and lower limbs. Separate calculations were made for the lesion's severity and the extent of the covered body surface. On a scale of 0-4, erythema, infiltration, and desquamation were measured, and on a scale of 0-6, the involved body surface area was calculated.[3] Mild was defined when PASI is < 7, moderate when PASI is 7-12, and severe disease when the PASI score is > 12.[9]

Blood Sampling

Every subject underwent a sterile venipuncture performed in a completely sterile setting using disposable syringes, with minimum venous stasis and no foaming. Then, 3 mL of venous blood was withdrawn and placed into a vacutainer tube containing ethylenediaminetetraacetic acid (EDTA), which was used for total RNA extraction and further PCR.

TRPC6, *TRPM2*, and *TRPV1* Gene Expression by RT-PCR

QIAamp RNA Blood MiniKit (Qiagen, USA) was used for high-quality total RNA extraction, followed by RNA quality and purity measurement using a Nanophotometer N60 (IMPLEN GMBH, Germany). At 260 and 280 nm; the absorbance of the RNA sample was measured.

Two-step RT-PCR was performed as follows. First step: Complementary DNA (cDNA) was synthesized from RNA extract as 4 µL of 5x TransAmp buffer, 1 µL of reverse transcriptase enzyme, and 5 µL of RNase-free water were combined with RNA extract of 10 µL using highly reproducible first-strand cDNA synthesis MyTaq One-Step RT-PCR Kit (Bioline Meridian Bioscience, London, UK). The reverse transcriptase enzyme was stopped by a single cycle of 10 min at 25 °C, 15 min at 42 °C, and 5 min at 85 °C using an Applied Biosystems 2720 thermal cycler (Bioline, Singapore, USA). At -20 °C, the resultant cDNA was stored.

Second Step: Using the SensiFAST™ SYBR® Lo-ROX Kit (Bioline Meridian Bioscience, London, UK) and a premade QuantiTect Primer Assay (Qiagen, USA), SYBR green-based quantitative RT-PCR was performed using cDNA. To assess the amount of gene expression, the following primers (Midland, Texas) were used: primers for TRPC6 F (5′-ATTCTGAATGGGGATGTTGAA-3′) and R (5′-GCAAGTTTTAAACGGCTGAGA-3′); primers for TRPM2 F (5′-CAGCCTCTTCAAGAGCTGGA-3′) and R (5′-CCACACTGACACACCACCTT-3′); primers for TRPV1 F (5′-CATGCTCAACCTGCACGA-3′) and R (5′-GCTGTCTGGCCCTTGTAGTA-3′); primers for beta-actin_F (5′- ATTGGCAATGAGCGGTTC-3′) and R (5′-CGTGGATGCCACAGGAC-3′) as endogenous control.[10]

Moreover, 5 µL of the cDNA was added to 10 µL of 2x SYBR® Low-ROX MasterMix, 1 µL of each primer, and 4 µL of RNase-free water to create a mixture of 20 µL. In 45 cycles; the reaction was carried out, with 30 s spent for denaturation at 94 °C, 30 s spent for annealing at 55 °C, and 30 s spent for extension at 72 °C. Analysis of data was done by the Applied Biosystems 7500 software (version 2.0.1). Relative quantification was used to measure mRNA levels. Furthermore, the ΔΔCt method was employed to standardize the quantity of the target gene against β-actin; an endogenous reference gene, for comparison with the control. Melting analysis was conducted to verify the absence of primer dimers.[11]

Statistical analysis

Using Epi Info 2000 and SPSS version 20 on an IBM personal computer; statistical analysis was performed. (A) Validated quantitative data were specified as mean ($\bar{X}$), standard deviation (SD), and range. Descriptive statistics were expressed as numerical amounts (N) and percentages (%); also, (B) analytical statistics were used. An investigation into the relationship between two qualitative variables was conducted using the chi-square test (χ^2). Mann-Whitney U test, also known as the non-parametric test, is a significance test used to compare two groups with quantitative variables that are not regularly distributed. A non-parametric test of significance, the Kruskal-Wallis test, compares three or more groups with quantitative variables that are not regularly distributed. Spearman's correlation (r) test was used to quantify the association between quantitative and qualitative ordinal data. In receiver operating characteristic curves, the cut-off value with the highest accuracy was designated as the diagnostic cutoff point. $P < 0.05$ was the level of significance.[12]

Results

There were 29 (48.3%) women and 31 (51.7%) men. Their age extended from 26 to 68 years, with 45.0±11.72 years presented as $\bar{X}$ ± SD value. The control group included 29 (48.3%) females and 31 (51.7%) males. Their age extended from 26 to 68 years with 43.78±11.98 years old as $\bar{X}$ ± SD value, without noteworthy differences in gender and age ($P > 0.05$ for both). The clinical characteristics of the studied cases are presented in Table 1.

Evaluation of the Mean Expression Levels of TRPC6, TRPM2, and TRPV1 Between the Study and Control Groups

The mean expression level of TRPC6 was statistically significant, being lower in cases than in controls ($U = 661.5$ and $P < 0.001$). Furthermore, regarding TRPM2 and TRPV1; the mean expression levels were higher in cases than in controls, with statistically significant differences between cases and controls ($U = 36$ and 78, resp., and $P < 0.001$ for both), as depicted in Table 2.

Table 1. Clinical information of the studied patients (n = 60)

	n (%)
Onset	
Early	27 (45.0)
Late	33 (55.0)
Course	
Stationary	21 (35.0)
progressive	39 (65.0)
Duration of the disease (years)	
Min.-max.	1.0-8.0
Mean ± SD	3.75±2.07
Median (IQR)	3.0 (2.0-5.0)
Family history	
Positive	29 (48.3)
Negative	31 (51.7)
Risk factors	
Yes	18 (30.0)
DM	2 (13.3)
HTN	9 (15.0)
HTN, DM	1 (15.0)
Smoking	6 (10.0)
No	42 (70.0)

Table 1. Continued

	n (%)
Site of affection	
Extremities	16 (26.7)
Axial, extremities	33 (55.0)
Axial	11 (18.3)
Scalp involvement	
Yes	37 (61.7)
No	23 (38.3)
Nail involvement	
Yes	26 (43.3)
No	34 (56.7)
Joint involvement	
Yes	19 (31.7)
No	41 (68.3)
Palm & sole involvement	
Yes	22 (36.7)
No	38 (63.3)
Itching	
Yes	39 (65.0)
No	21 (35.0)
Koebnerization	
Yes	28 (46.7)
No	32 (53.3)
PASI score	
Min.-max.	1.20-30.40
Mean ± SD	11.53±7.60
Median (IQR)	9.45 (5.45-16.05)
Severity	
Mild	20 (33.3)
Moderate	20 (33.3)
Severe	20 (33.3)

Min.: Minimum, Max.: Maximum, SD: Standard deviation, IQR: Interquartile range, DM: Diabetes mellitus, HTN: Hypertension, PASI: Psoriasis area severity index

Association Between Mean TRPC6 Expression and Clinical Information of Patients

The mean expression TRPC6 level was significantly associated with the site of affection (H = 13,137, P = 0.001), scalp affection (U = 268.5, P = 0.017), joint affection (U = 172.5, P = 0.001), itching (U = 169.5, P < 0.001), koebnerization (U = 310.5, P = 0.042), and severity, which was higher in mild cases (U = 34,862, P < 0.001), as shown in Table 3. Furthermore, significant negative correlations between TRPC6 and disease duration in years (r = -0.410, P = 0.001) and PASI score (r = -0.736, P < 0.001) were documented (Figure 1a).

Association Between Mean TRPM2 Expression and Clinical Records of Patients

Higher mean TRPM2 expression was significantly associated with the course of psoriasis (U = 260,000, P = 0.021), scalp involvement (U = 195,000, P < 0.001), nail involvement (U = 244,000, P = 0.003), joint involvement (U = 266,000, P = 0.049), itching (U = 236,000, P = 0.007), koebnerization (U = 256.000, P = 0.004), and severity, which was higher in severe cases (U = 27,620, P < 0.001), as demonstrated in Table 4. Moreover, significant positive correlations were observed between the mean TRPM2 expression level and disease duration in years (r = 0.339, P = 0.008) and PASI score (r = 0.561, P < 0.001) were revealed (Figure 1b).

Association Between Mean TRPV1 Expression and Clinical Information of Patients

The higher mean expression level of TRPV1 was significantly associated with the course of disease (U = 272,000, P = 0.033), scalp involvement (U = 294,000, P < 0.046), nail involvement (U = 282,000, P = 0.017), joint involvement (U = 256,000, P = 0.034), palm and sole involvement (U = 289,000, P = 0.048),

Table 2. Comparison concerning mean expression level of TRPC6, TRPM2, TRPV1 between patients and control subjects

	Patients, (n = 60)	Control subjects, (n = 60)	Test of significance	P
TRPC6			**U**	
Min.-max.	0.19-2.95	1.0-3.78	661,500	<0.001*
Mean ± SD	1.10±0.66	1.92±0.67		
Median (IQR)	0.96 (0.59-1.57)	1.79 (1.48-2.25)		
TRPM2			**U**	
Min.-max.	1.48-9.87	0.54-1.95	36,000	<0.001*
Mean ± SD	4.87±2.41	1.23±0.34		
Median (IQR)	4.55 (2.77-6.32)	1.10 (1.0-1.47)		
TRPV1			**U**	
Min.-max.	1.06-9.87	0.10-1.87	78,000	<0.001*
Mean ± SD	4.75±2.67	0.97±0.36		
Median (IQR)	4.11 (2.64-6.90)	1.0 (0.79-1.09)		

Min.: Minimum, Max.: Maximum, SD: Standard deviation, IQR: Interquartile range, U: Mann-Whitney U test, TRPC6: Transient receptor potential canonical 6, TRPM2: Transient receptor potential melastatin 2, TRPV1: Transient receptor potential vanilloid 1, P: For comparing between the two studied groups, $P \leq 0.05$ is the level of significance, *: Significant

Table 3. Association concerning mean expression level of TRPC6 and clinical information of the studied patients

		TRPC6			
	n	Mean ± SD	Median (min.-max.)	Test of sig.	P
Sex					
Male	31	0.95±0.49	0.94 (0.19-2.09)	U=358,000	0.176
Female	29	1.26±0.79	0.99 (0.21-2.95)		
Onset					
Early	27	0.98±0.63	0.70 (0.19-2.32)	U=347,000	0.143
Late	33	1.20±0.68	0.99 (0.19-2.95)		
Course					
Stationary	21	1.27±0.85	0.95 (0.21-2.95)	U=358,000	0.425
Progressive	39	1.01±0.52	0.98 (0.19-2.42)		
Family history					
Positive	29	1.14±0.70	0.99 (0.19-2.95)	U=423,500	0.700
Negative	31	1.07±0.64	0.88 (0.19-2.42)		
Risk factors					
DM	1		1.35	H=3,295	0.348
HTN	9	1.51±0.95	1.10 (0.32-2.95)		
HTN, DM	2	1.32±0.47	1.32 (0.99-1.66)		
Smoking	6	1.04±0.59	1.11 (0.19-1.72)		
No	42	1.01±0.60	0.86 (0.19-2.32)		
Site of affection					
Extremities	16	1.63±0.69	1.65 (0.68-2.95)	H=13,137*	0.001*
Axial, extremities	33	0.88±0.48	0.71 (0.19-2.12)		
Axial	11	1.01±0.71	0.94 (0.21-2.32)		
Scalp involvement					
Yes	37	0.97±0.65	0.71 (0.19-2.95)	U=268,500*	0.017*
No	23	1.32±0.63	1.10 (0.32-2.42)		
Nail involvement					
Yes	26	0.95±0.64	0.80 (0.19-2.95)	U=321,500	0.072
No	34	1.22±0.66	1.26 (0.21-2.42)		
Joint involvement					
Yes	19	0.67±0.38	0.63 (0.19-1.56)	U=172,500*	0.001*
No	41	1.30±0.67	1.28 (0.19-2.95)		
Palm & sole involvement					
Yes	22	1.05±0.75	0.94 (0.19-2.95)	U=365,500	0.421
No	38	1.13±0.61	1.04 (0.21-2.42)		
Itching					
Yes	39	0.86±0.49	0.76 (0.19-2.12)	U=169,500*	<0.001*
No	21	1.56±0.71	1.57 (0.59-2.95)		
Koebnerization					
Yes	28	0.94±0.66	0.80 (0.19-2.95)	U=310,500*	0.042*
No	32	1.25±0.64	1.17 (0.28-2.42)		
Severity					
Mild	20	1.69±0.67	1.75 (0.59-2.95)	H=34,862*	<0.001*
Moderate	20	1.11±0.33	1.01 (0.32-1.57)		
Severe	20	0.50±0.22	0.54 (0.19-0.99)		

TRPC6: Transient receptor potential canonical 6, SD: Standard deviation, Min.: Minimum, Max.: Maximum, IQR: Interquartile range, $P \leq 0.05$ is the level of significance, DM: Diabetes mellitus, HTN: Hypertension, *: Significant, U: Mann-Whitney U test, H: H for Kruskal-Wallis test, *P*: For comparing between different categories

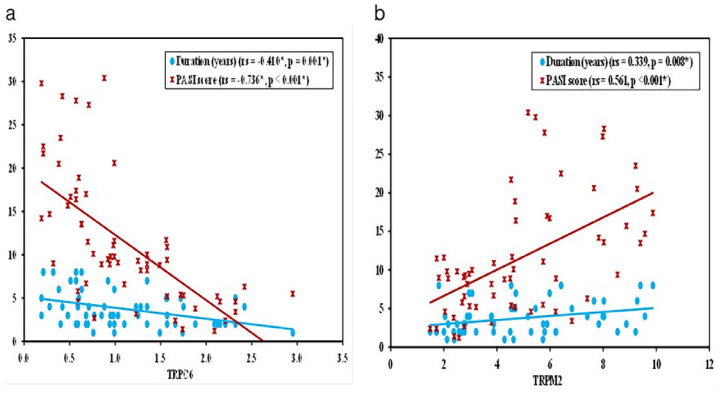

Figure 1. (a) Correlation between TRPC6 and disease duration in years and PASI score, (b) correlation between mean TRPM2 level and disease duration in years and PASI score
TRPC6: Transient receptor potential canonical 6, TRPM2: Transient receptor potential melastatin 2, PASI: Psoriasis area severity index

Table 4. Association concerning mean expression level of TRPM2 and clinical information of the studied patients (n = 60)

		TRPM2			
	n	Mean ± SD	Median (min.-max.)	Test of sig.	P
Sex					
Male	31	5.22±2.60	4.62 (1.48-9.87)	U=386,000	0.348
Female	29	4.51±2.18	4.53 (1.72-9.57)		
Onset					
Early	27	5.31±2.65	4.71 (1.72-9.87)	U=368,000	0.249
Late	33	4.52±2.17	4.28 (1.48-9.22)		
Course					
Stationary	21	4.02±2.46	2.77 (1.48-9.57)	U=260,000*	0.021*
Progressive	39	5.34±2.28	4.68 (1.73-9.87)		
Family history					
Positive	29	5.22±2.38	4.57 (2.12-9.87)	U=371,000	0.246
Negative	31	4.55±2.43	3.88 (1.48-9.57)		
Risk factors					
DM	1#		2.88	H=0.319	0.956
HTN	9	4.67±1.99	4.68 (1.81-7.40)		
HTN, DM	2	4.57±4.37	4.57 (1.48-7.65)		
Smoking	6	4.45±1.19	4.60 (2.50-5.79)		
No	42	5.04±2.61	4.55 (1.72-9.87)		
Site of affection					
Extremities	16	4.09±1.77	4.20 (1.72-7.40)	H=3,497	0.174
Axial, extremities	33	5.42±2.64	5.17 (1.48-9.87)		
Axial	11	4.37±2.25	3.79 (2.04-9.28)		
Scalp involvement					
Yes	37	5.68±2.39	5.45 (1.73-9.87)	U=195,000*	<0.001*
No	23	3.58±1.84	2.77 (1.48-7.65)		
Nail involvement					
Yes	26	5.91±2.36	5.77 (2.00-9.87)	U=244,000*	0.003*
No	34	4.08±2.16	3.50 (1.48-9.57)		
Joint involvement					
Yes	19	5.90±2.78	5.45 (2.00-9.87)	U=266,000*	0.049*
No	41	4.40±2.09	3.88 (1.48-8.87)		

Table 4. Continued

		TRPM2			
	n	Mean ± SD	Median (min.-max.)	Test of sig.	P
Palm & sole involvement					
Yes	22	5.71±2.66	5.59 (2.00-9.87)	U=306,000	0.086
No	38	4.39±2.14	3.88 (1.48-9.28)		
Itching					
Yes	39	5.47±2.54	5.17 (1.48-9.87)	U=236,000*	0.007*
No	21	3.77±1.72	2.77 (1.72-7.40)		
Koebnerization					
Yes	28	5.79±2.31	5.59 (2.00-9.87)	U=256,000*	0.004*
No	32	4.08±2.24	3.14 (1.48-9.57)		
Severity					
Mild	20	3.76±1.74	3.09 (1.48 -7.40)	H=27,620	<0.001*
Moderate	20	3.64±1.73	3.01 (1.73-8.54)		
Severe	20	7.22±1.84	7.74 (4.53-9.87)		

TRPM2: Transient receptor potential melastatin 2, Min.: Minimum, Max.: Maximum, SD: Standard deviation, DM: Diabetes mellitus, HTN: Hypertension, U: Mann-Whitney U test, $P \leq 0.05$ is the level of significance, *: Significant, H: H for Kruskal-Wallis test, *P*: For comparing between different categories

koebnerization ($U = 300{,}000$, $P = 0.028$), and severity, which was higher in severe cases ($U = 19{,}279$, $P < 0.001$) (Table 5). Furthermore, a significant positive correlation was detected between the mean TRPV1 level and the PASI score ($r = 0.469$, $P < 0.001$) (Figure 2a).

Receiver Operating Characteristic Curves for TRPC6, TRPM2, and TRPV1 in Healthy Subjects

With a sensitivity of 80.0, specificity of 63.33, and cutoff value of ≤ 1.66, TRPC6 can distinguish cases from controls with significant accuracy. With sensitivity and specificity of 95.0 and > 1,731 at the cutoff value, TRPM2 can be used to identify cases from controls with considerable accuracy. With a cutoff value of > 1.389, sensitivity of 93.33, and specificity of 88.33, TRPV1 can effectively differentiate cases from controls with significant accuracy ($P < 0.001$; for all) (Figure 2b).

Discussion

Psoriasis is a multifactorial inflammatory disease with a chronic course and multifaceted etiopathogenesis.[13] Recently, Kim et al.[14] revealed that keratinocytes, immune cells, dendritic cells, and the peripheral nervous system are affected by ion channels. The delicate balance between keratinocyte proliferation and differentiation governs the continuous control of the skin's protective epithelial barrier.[15]

The current study showed that the expression of TRPC6 was lower in cases than in controls, and their expression levels were negatively correlated with the PASI score. This was in agreement with Özcan et al.,[5] who detected that the mRNA expression level of TRPC6 was decreased in cases than in control subjects ($P = 0.009$) and stated that the keratinocyte maturation degree is dependent upon the calcium gradient within the cell. Also, they documented that the downregulation of TRPC6 channels is associated with a decrease in keratinocyte differentiation, signifying the potential utility of TRPC activators in psoriasis treatment.

In normal healthy skin, the levels of extracellular Ca^{2+} ($[Ca^{2+}]$) significantly increase as the epidermis moves from the basal to the spinous layer. Dysfunctions in the calcium gradient, which is believed to play a crucial role in controlling keratinocyte maturation, could account for changes in the growth and development of psoriatic keratinocytes. TRPC6 proteins play a significant role in regulating differentiation triggered by high $[Ca^{2+}]_{ex}$.[16]

Leuner et al.[17] reported that upon exposure of psoriatic keratinocytes to high extracellular Ca^{2+}, a slight influx of Ca^{2+} was detected because the surface membrane of these keratinocytes exhibited weakened functional expression of the TRPCs and downregulation of TRPC6 channels, which were associated with impaired keratinocyte differentiation. In contrast, in normal keratinocytes, the exact circumstances; at the start of the cell differentiation program and a corresponding increase in intracellular Ca^{2+}.

The current study revealed that TRPM2 level in cases of psoriasis was significantly higher than normal healthy controls. This was similar to the research by Özcan et al.,[5] who established that the mRNA expression level of TRPM2 was higher in cases than in control subjects ($P = 0.001$) and stated that TRPM2 is a sensor for reactive oxygen species (ROS) that aggravates psoriasis pathogenesis and that TRPM2 expression plays a key part in the proliferation of T-cells

Table 5. Association concerning mean expression level of TRPV1 and clinical information of the studied patients (n = 60)

		TRPV1			
	n	Mean ± SD	Median (min.-max.)	Test of sig.	P
Sex					
Male	31	5.16±2.74	5.12 (1.06-9.87)	U=373,000	0.258
Female	29	4.31±2.57	3.59 (1.37-9.39)		
Onset					
Early	27	4.60±2.49	4.55 (1.06-8.96)	U=423,000	0.738
Late	33	4.88±2.85	3.88 (1.35-9.87)		
Course					
Stationary	21	3.75±2.53	2.98 (1.35-9.21)	U=272,000*	0.033*
Progressive	39	5.29±2.62	4.77 (1.06-9.87)		
Family history					
Positive	29	5.01±2.61	4.55 (1.06-9.87)	U=398,000	0.446
Negative	31	4.51±2.75	3.82 (1.35-9.39)		
Risk factors					
DM	1		3.55	H=1,959	0.581
HTN	9	4.96±3.07	4.29 (1.37-9.21)		
HTN, DM	2	5.28±4.95	5.28 (1.78-8.78)		
Smoking	6	6.00±2.23	5.67 (3.46-9.87)		
No	42	4.53±2.62	3.85 (1.06-9.39)		
Site of affection					
Extremities	16	4.35±2.65	3.46 (1.57-9.21)	H=3,473	0.176
Axial, extremities	33	5.32±2.75	5.12 (1.35-9.87)		
Axial	11	3.63±2.17	3.48 (1.06-7.56)		
Scalp involvement					
Yes	37	5.30±2.64	4.78 (1.06-9.87)	U=294,000*	0.046*
No	23	3.86±2.53	3.26 (1.37-8.92)		
Nail involvement					
Yes	26	5.71±2.76	5.73 (1.35-9.87)	U=282,000*	0.017*
No	34	4.01±2.39	3.51 (1.06-8.96)		
Joint involvement					
Yes	19	5.90±2.80	6.73 (1.35-9.87)	U=256,000*	0.034*
No	41	4.22±2.47	3.82 (1.06-9.21)		
Palm & sole involvement					
Yes	22	5.64±2.70	5.25 (1.39-9.87)	U=289,000*	0.048*
No	38	4.24±2.55	3.57 (1.06-9.39)		
Itching					
Yes	39	5.20±2.68	4.78 (1.06-9.87)	U=296,000	0.079
No	21	3.92±2.52	3.46 (1.39-9.21)		
Koebnerization					
Yes	28	5.57±2.56	5.50 (1.35-9.87)	U=300,000*	0.028*
No	32	4.03±2.59	3.68 (1.06-8.96)		
Severity					
Mild	20	3.73±2.65	3.04 (1.06-9.21)	H=19,279*	<0.001*
Moderate	20	3.60±1.74	3.57 (1.35-7.56)		
Severe	20	6.92±2.16	7.03 (2.98-9.87)		

TRPV1: Transient receptor potential vanilloid 1, Min.: Minimum, Max.: Maximum, SD: Standard deviation, U: Mann-Whitney U test, H: H for Kruskal-Wallis test, *P*: For comparing between different categories, *: Statistically significant at $P \leq 0.05$

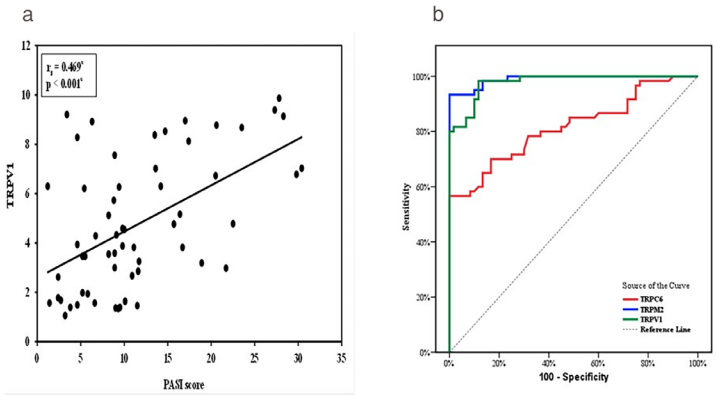

Figure 2. (a) Correlation between mean TRPV1 level and PASI score, (b) Receiver operating characteristic curve for TRPC6, TRPM2, and TRPV1 to discriminate cases from controls.
TRPV1: Transient receptor potential vanilloid 1, TRPC6: Transient receptor potential canonical 6, TRPM2: Transient receptor potential melastatin 2, PASI: Psoriasis area severity index

and proinflammatory cytokine production following T-cell receptor (TCR) stimulation.

TRPM2 is a non-selective, permeable Ca^{2+} cation channel that is conveyed in several types of innate immunity cells, such as dendritic cells, monocytes/macrophages, and adaptive immunity cells, such as T- and B-cells.[18]

Following TCR activation, TRPM2 channel expression is upregulated in T-cells. TRPM2 channels may be activated by TCR stimulation, which releases cyclic adenosine diphosphate ribose from the endoplasmic reticulum. This occurs notwithstanding the absence of direct evidence linking TRPM2 channels to Ca^{2+} influx in lymphocytes or T-cell activity. Additionally, NAD^{+} precursors control Ca^{2+} homeostasis through ADPR-mediated gating of TRPM2 channels, which, in response to mitogens; TRPM2 channels upregulate essential T-cell processes such as proliferation and interleukin-2 (IL-2) production.[19]

Melzer et al.[20] revealed that TRPM2 expression is present in primary CD^{4+} T-cells, and this expression aids in T-cell proliferation and proinflammatory cytokine generation upon TCR stimulation.

Significant positive correlations between the mean expression level of TRPM2 and PASI were found in the current study. Numerous studies have demonstrated that elevated reactive nitrogen species and ROS exacerbate psoriasis. TRPM2 acts as a sensor for ROS; thus, inflammatory cytokines are secreted as a result of the antioxidant defense system that is built up against this illness, and this is what causes skin inflammation.[21,22]

The current study displayed that the TRPV1 level in patients with psoriasis was higher than that of controls, with significant results. This was in the same line with Özcan et al.,[5] who established that the expression level of TRPV1 mRNA expression was elevated in the studied cases compared with controls (P = 0.028) and stated that primary human T-cells express TRPV1, resulting in Ca^{2+} influx and TCR-mediated T-cell activation. TRPV1 blockers also prevent T-cell activation and inflammatory cytokine release.

Yun et al.[23] found that the symptoms of a disease akin to atopic dermatitis, as indicated by a reduced transepidermal water loss score, can be inhibited by pharmacologic blocking of TRPV1 activation. Restoring the neutral lipid layer and reversing alterations in the production of loricrin and filaggrin-two essential epidermal barrier proteins that are decreased in psoriasis-are prerequisites for this inhibition.

Kashem et al.[24] reported that the synthesis of IL-23 by $CD301b^{+}$ dendritic cells is crucial for the production of IL-17 from T-17 cells. Skin innervation and IL-23 production are strategically connected, with calcitonin gene-related peptide (CGRP), produced by $TRPV1^{+}$ neurons, acting as the main stimulant for dendritic cells to synthesize IL-23.

On the other hand, the etiopathogenesis of psoriasis is referred to as IL-23.[25] In IL-23-dependent imiquimod (IMQ)-induced psoriasis-like skin inflammation, $TRPV1^{+}$ nociceptive sensory neurons are interrelated with dendritic cells to produce IL-23, thus controlling IL-17 and 22 production by $IL23R^{+}$ dermal γδ T-cells, which determine cutaneous inflammation skin.[26]

Additionally, Zhou et al.[27] documented a significant decrease in hyperplasia of the epidermis, dermal inflammatory cellular infiltrate, and production of cytokines such as IL-1, IL-6, and IL-23 in TRPV1-knockout mice treated with IMQ.

The current study showed that the relationship between mean TRPV1 expression and itching was non-significant. On the contrary, other studies reported a significant relationship between itching and TRPV1 level.[28,29] This difference may be attributed to different sample sizes, different ethnic

backgrounds of the studied population, and diverse clinical situations of the studied cases in each research.

Zhu et al.[30] reported a substantial association between innervation and psoriasis, suggesting that neurocutaneous pathways affect psoriasis development. Psoriatic plaques were cleared in the affected dermatomal regions with denervation due to either myelitis or traumatic damage. In contrast, the return of psoriasis lesions in the affected area was associated with the recovery of neural function following nerve loss. The discovery of significantly elevated TPRV1 signals in the psoriasis plaque epidermis further points to neurogenic component involvement in the psoriasis growth process. Moreover, psoriasis lesions express more of the neuropeptide CGRP, which is related to TRPV1.[31]

Future research should be more extensive, focusing on the investigation of TRP channels in various forms of psoriasis and encompassing diverse patient groups, including those with mild and severe cases.

Study limitations

The limitations of this study were the limited sample size, as cases were collected from one center, together with the limited availability of diagnostic instruments.

Conclusion

Diverse patterns of TRP channel expression in patients with chronic plaque psoriasis may play a role in psoriasis pathogenesis. These channels are therefore essential pharmacological targets for novel psoriasis treatments and serve as candidate targets for psoriatic skin disease treatment.

Ethics

Ethics Committee Approval: The Local Ethical Scientific Committee of the Menoufia University Faculty of Medicine, approved this study (approval number and date: 3/2022 DERMA49).

Informed Consent: Informed consent was obtained from each contributor.

Footnotes

Authorship Contributions

Concept: W.A.S., M.H., F.M.G., Design: W.A.S., M.H., F.M.G., Data Collection or Processing: W.A.S., R.A., Analysis or Interpretation: W.A.S., F.M.G., R.A., Literature Search: W.A.S., F.M.G., R.A., Writing: W.A.S., M.H., F.M.G., R.A.

Conflict of Interest: The authors declared that they have no conflict of interest.

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Orginal Article

Accuracy of Serological, Chemiluminescene Immunoassays, and Polymerase Chain Reaction Examination in Identification of *Treponema Pallidum*: Diagnostic Tests in High-Risk of Sexually Transmitted Infections Individuals

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Abstract

Aim: The diagnosis of syphilis can involve serological tests, such as venereal disease research laboratory (VDRL) and chemiluminescence immunoassay (CLIA), or molecular tests, such as polymerase chain reaction (PCR). However, research on the diagnostic accuracy of these three methods in detecting syphilis is still limited. This study aimed to analyze the association between VDRL, CLIA, and PCR serological examinations in patients with syphilis.

Materials and Methods: A cross-sectional diagnostic study was conducted on eligible individuals with high-risk sexually transmitted infection at Wahidin Sudirohusodo Hospital and its network hospitals from January to November 2023. Qualitative VDRL and CLIA were used to determine whether a sample is positive for syphilis. Nested PCR was used to identify *Treponema pallidum* bacteria.

Results: Among the 49 samples, according to the VDRL examination, the highest examination result was positive (87.8%). Based on the CLIA examination, the highest examination result was positive (89.8%). Based on the nested PCR examination, the highest examination result was negative (55.1%). There was no association between the syphilis stage and the results of VDRL ($P = 0.805$), CLIA ($P = 0.678$), and nested PCR ($P = 0.678$). There was no agreement between the VDRL results and nested PCR ($P = 0.678$) and between the CLIA results and nested PCR ($P = 0.646$).

Conclusion: The VDRL and CLIA examination results had different diagnostic accuracy than the nested PCR examination in patients with a diagnosis of syphilis. Although these three examinations have no relationship to the degree of syphilis, this study strengthens the recommendation for the need for nested PCR examination in clinical conditions and other examinations that suggest syphilis.

Keywords: Immunoassay, polymerase chain reaction, serodiagnosis, syphillis, *Treponema Pallidum*

Introduction

Syphilis is an infection caused by *Treponema subspecies* pallidum. The manifestations of the disease are diverse, with different stages occurring over time in untreated infections. The stages of syphilis are divided into primary, secondary, latent, and tertiary stages.[1,2]

Data from the Centers for Disease Control and Prevention (CDC) in 2019 revealed that 129,813 cases of all stages of syphilis were reported, including 38,992 cases of primary and secondary syphilis, which are the most infectious stages

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of syphilis.[3] World Health Organization (WHO) estimates that around 7 million new syphilis cases in 2020.[4] The Indonesian Ministry of Health estimated 76.923 new cases in 2020.[5]

The diagnosis of syphilis should be made in patients with signs or clinical symptoms of syphilis infection. In addition, asymptomatic patients should be screened for syphilis if they are at high risk of the disease or for transmission of the disease to others. Serologic testing is commonly used for the diagnosis of syphilis, and the test was first described by Wasserman in 1906.[2,6]

Patients suspected of having syphilis are usually screened with the venereal disease research laboratory (VDRL) non-treponemal test and rapid plasma reagin (RPR) test, which will be confirmed with a treponemal serology test if positive.[7] Treponemal tests such as the immunofluorescence test (FTA-Abs) or *Treponema pallidum* (*T. pallidum*) hemagglutination agglutination or *T. pallidum* agglutination (TP-PA) are among the tests to confirm *T. pallidum* infection.[8,9] Non-treponemal tests become positive within 3 weeks of *T. pallidum* infection, allowing these tests to be negative early in the infection. On the one hand, VDRL is better than RPR in terms of sensitivity. However, the specificity shows that RPR is superior to VDRL. VDRL has a sensitivity of 44.4-100% specificity of 74.0-100%.[10]

Another treponemal diagnostic test for syphilis infection is the chemiluminescence immunoassay (CLIA) examination to detect serum *T. pallidum*, which is specific to antibodies with high sensitivity and specificity for detecting syphilis. Another study in Türkiye showed that CLIA examination in patients who donated blood was positive in 10 out of 5000 people who donated blood, and none of them were positive for VDRL examination results in these individuals.[11]

The polymerase chain reaction (PCR) molecular diagnostic test can detect syphilis infection early before it is detected by serologic examination.[2,6] PCR provides high-sensitivity results for detecting treponema DNA in ulcer lesion samples from patients with primary syphilis. *T. pallidum* DNA can be detected in blood samples from patients with latent syphilis. This method is particularly useful in situations where DarkField examination is not available and serology tests are non-reactive. The FDA has approved PCR for the diagnosis of syphilis.[9,12] Research regarding the diagnostic accuracy of the three previously mentioned methods is limited. This study aimed to analyze the concordance between the VDRL, CLIA, and PCR serology tests in patients with syphilis.

Materials and Methods

Study Design

This study used a cross-sectional diagnostic test. The diagnostic suitability of VDRL against *T. pallidum*-positive and -negative PCR and between CLIA against *T. pallidum*-positive and -negative PCR were analyzed.

Study Setting and Sampling Methods

In this study, the diagnosis of clinically active primary, secondary, and latent syphilis at an early stage was made according to the CDC criteria. In this study, all patients with syphilis were confirmed to have syphilis infection. The diagnosis of primary syphilis was made if the patient showed one or more painless chancres. Patients are confirmed to have skin and mucosal lesions, both localized and spread throughout the body, with or without regional lymphadenopathy, and can be diagnosed with secondary syphilis. Positive results in both non-treponemal and treponemal serologic tests in patients with these clinical criteria may be the basis for the diagnosis of primary and secondary syphilis. Asymptomatic patients who contracted an initial infection within the last year were diagnosed with early latent syphilis if they met one of the following criteria: 1) Documented seroconversion or a fourfold increase in non-treponemal test titers in the past 12 months; 2) Symptoms consistent with primary or secondary syphilis in the last year; 3) Sexual contact with a partner diagnosed with confirmed or probable primary or secondary syphilis or likely early latent syphilis (independently documented for less than one year); or 4) positive results on both non-treponemal and treponemal tests following likely exposure in the past 12 months. Individuals at high-risk of sexually transmitted infections (STI) were admitted to Wahidin Sudirohusodo Hospital and its network hospitals in Makassar from January to November 2023. The entire reach population willing to participate in the study and meet the inclusion criteria, including individuals at risk of STIs, will be recruited as samples. Patients who do not agree to participate in this study will be excluded.

Blood sampling, 3 mL of blood was drawn from the patient's fossa cubiti vein and stored in EDTA tubes at 2-8 °C for VDRL, CLIA, and PCR testing.

The VDRL examination was performed using a qualitative method according to standard procedures. Carbon antigen is dripped into the patient's serum with 0.9% NaCl on the VDRL card. The card is then placed on a rotator at 100 rpm for 8 min and interpreted as positive if fine to coarse blackish clots are present.

The CLIA inspection procedure using the COBAS E 601 device followed the manufacturer's guidelines. Sample examination can be performed with or without a barcode. After that, the nested PCR examination was carried out by extracting DNA and mixing it with PCR primers for *T. pallidum*. PCR analysis was then performed until the results were obtained as gel photos.

The approximate sample size was calculated using the single proportion formula. The proportion of positive test results was 60%, whereas the proportion of no difference between positive and negative results was 40%. This study's alpha and beta values are 5% and 20%, respectively. The study should include a minimum sample size of 45.

Ethical Consideration

Each respondent who met the inclusion criteria had their identity recorded and received information, as well as a detailed explanation of what would be done during the study. Furthermore, the participants were asked for their willingness to be involved in the study by signing a 10-informed consent letter. The Health Research Ethics Committee of the Hasanuddin University Faculty of Medicine (approval number: 579/UN4.6.4.5.31/PP36/2022, date: 11.10.2022) has evaluated and approved the entire research protocol. No personal data were obtained, and confidentiality was ensured.

Statistical analysis

This study presented the proportion of each category as percentages. The primary analysis involved a chi-square diagnostic test using a 2x2 contingency table, in which a *P* value of 0.05 or less indicated statistical significance. All statistical analyses were performed using SPSS version 17.0 (IBM Software, USA). This rigorous approach ensured the reliability and validity of the findings and provided a robust framework for interpreting the diagnostic accuracy of the various tests examined in this study.

Results

Characteristics of the Research Sample

The total number of subjects included in this study was 49. Table 1 lists the characteristics of the study participants. The majority of the samples were male (93.8%), with an age range of 20-44 years. In addition, based on the syphilis stage, the majority of samples were in the latent stage, followed by the secondary and primary stages. Based on the VDRL examination, the highest examination result was positive for 43 respondents (87.8). Based on the CLIA examination, the highest examination result was positive for as many as 44 respondents (89.8%). Based on the nested PCR examination, the 13 highest examination results were negative for as many as 27 respondents (55.1%).

Concordance Between the Syphilis Stage and VDRL, CLIA, and Nested PCR Results

Table 2 presents the suitability of diagnosis of syphilis stage with VDRL. It is known that patients in the primary stage with a positive category were 2 respondents (100%). In the secondary stage, with as many as 5 respondents (83.3%) and a negative category as many as 1 respondent (16.7%). In the latent stage, with a positive category, as many as 36 respondents (87.8%) and a negative category, as many as 5 respondents (12.2%). There was no concordance between the diagnosis of the syphilis stage and the VDRL results ($P = 0.805$).

Table 3 presents the suitability of syphilis stage diagnosis results with CLIA. It is known that patients in the primary stage with a positive category were 2 respondents (100%). In the secondary stage, with a positive category, as many as 6 respondents (100%). In the latent stage, there is a positive category of as many as 36 respondents (87.8%) and a negative category of as many as 5 respondents (12.2%). There was no concordance between the diagnosis of the syphilis stage and the CLIA results ($P = 0.678$).

Table 4 presents the suitability of the results for the diagnosis of syphilis stage using nested PCR. It is known that patients in

Table 1. Characteristics of the participants

Variable	Frequencies	
	n	%
Gender		
Male	46	93.8
Female	3	6.2
Syphillis stadium		
Primary	2	4.1
Secondary	6	12.2
Latent	41	83.7
VDRL results		
Positive	43	87.8
Negative	6	12.2
CLIA resuts		
Positive	44	89.8
Negative	5	10.2
PCR nested		
Positive	22	44.9
Negative	27	55.1

CLIA: Chemiluminescence immunoassay, PCR: Polymerase chain reaction, VDRL: Venereal disease research laboratory

the primary stage with a positive category were 2 respondents (100%). In the secondary stage, there is a positive category with as many as 3 respondents (50%) and a negative category with as many as 3 respondents (50%). In the latent stage, there is a positive category of as many as 17 respondents (41.5%) and a negative category of 24 respondents (58.5%). There was no concordance between the diagnosis of syphilis stage and the results of nested PCR ($P = 0.678$).

Agreement Between the VDRL and CLIA Results for Nested PCR

Table 5 presents the concordance of VDRL and CLIA results against nested PCR. This study found no concordance between VDRL results and nested PCR ($P = 0.678$) and between CLIA results and nested PCR ($P = 0.646$).

Discussion

In this study, most (93.8%) participants were male, with a male to female ratio of 15.3:1. This shows that men's prevalence is higher than that of women. The research subjects had a homosexual/MSM orientation and sexual relations with men (heterosexual). These results are from research 3 conducted in America in 2016, and the rate of primary and secondary syphilis is higher in men (15.6 cases per 100,000 men) than in women (1.9 cases per 100,000 women). One of the reasons for the high rate of case incidence is the large number of same-sex relationships. In 2020, the WHO estimated that 7.1 million adults aged 15-49 years contracted syphilis worldwide. Several countries that systematically monitor syphilis have shown a significant increase in syphilis cases among men who have sex with men, including congenital syphilis.[13] Previous research conducted in Makassar by Kusumawaty et al.[14] reported similar results, in which the majority of samples were

Table 2. Concordance between syphilis stage diagnosis and VDRL

Diagnosis of syphillis stages	VDRL				Total		*P* value
	Positive		Negative				
	n	%	n	%	n	%	
Primary	2	100	0	0	2	100	0.805
Secondary	5	83.3	1	16.7	6	100	
Latent	36	87.8	5	12.2	41	100	
Total	43	87.8	6	12.2	49	100	

VDRL: Veneral disease research laboratory

Table 3. Concordance between syphilis stage diagnosis and CLIA

Diagnosis of syphillis stages	CLIA				Total		*P* value
	Positive		Negative				
	n	%	n	%	n	%	
Primary	2	100	0	0	2	100	0.678
Secondary	6	100	0	0	6	100	
Latent	36	87.8	5	12.2	41	100	
Total	44	89.8	5	10.2	49	100	

CLIA: Chemiluminescence immunoassay

Table 4. Concordance between syphilis stage diagnosis and nested PCR

Diagnosis of syphillis stages	PCR nested				Total		*P* value
	Positive		Negative				
	n	%	n	%	n	%	
Primary	2	100	0	0	2	100	0.526
Secondary	3	50	3	50	6	100	
Latent	17	41.5	24	58.5	41	100	
Total	22	44.9	27	55.1	49	100	

PCR: Polymerase chain reaction

Table 5. Conformity between VDRL and CLIA results in nested PCR

	PCR nested				Total		*P* value
	Positive		Negative				
	n	%	n	%	n	%	
VDRL							
Positive	20	46.5	23	53.5	43	100	0.678
Negative	2	33.3	4	66.7	6	100	
CLIA							
Positive	19	43.2	25	56.8	44	100	0.646
Negative	3	60.0	2	40.0	5	100	

CLIA: Chemiluminescence immunoassay, PCR: Polymerase chain reaction, VDRL: Venereal disease research laboratory

of MSM sexual orientation and had human immunodeficiency virus (HIV) infection. This indicates a lack of improvement in the prevention of STIs, especially syphilis, among MSM in Makassar.[14]

Most of the participants in this study probably had syphilis infection based on the VDRL method. Serological tests for syphilis are categorized into non-treponemal and treponemal tests, both of which are essential for diagnosis. Non-treponemal tests can monitor treatment progress but have low specificity.[15] The VDRL test, a non-treponemal test for syphilis, utilizes cardiolipin as an antigen and is favored for screening because of its simplicity, sensitivity, and cost-effectiveness. *T. pallidum* infection leads to the rapid production of two antibody types: specific antibodies targeting bacterial polypeptide antigens and non-specific antibodies (reagin antibodies) that react with non-treponemal antigens known as cardiolipins.[16]

The prozone phenomenon and biological false-positive reactions are notable limitations of this test. Serological tests provide indirect evidence of syphilis and may yield reactive results even in the absence of clinical, historical, or epidemiological evidence of the disease.[17]

In individuals treated for primary syphilis, non-treponemal tests become non-reactive in 60% of cases by four months and in almost all patients by 12 months. For patients treated for secondary syphilis, tests generally become non-reactive 12-24 months after treatment. If treatment is administered during the early latent stage, non-treponemal tests might remain reactive at low titers for up to 5 years or longer. Patients with late latent syphilis may have non-reactive non-treponemal test results even without a history of treatment. In some cases, non-treponemal antibodies can persist at low titers for extended periods, sometimes lifelong, a condition known as seroxat reactions, which may be more common in HIV-infected individuals.[16] A prospective study of early syphilis therapy found that 14% of patients had less than a fourfold decrease in serology titers within 12 months post-treatment; patients with HIV infection who had primary or secondary syphilis were more likely to have an insufficient response compared to those without HIV infection.[18]

The performance of the CLIA test in detecting syphilis was similar to that of the VDRL test in this study. CLIA is also a serological examination method for syphilis detection. Unlike VDRL, CLIA is a category of treponema antibody detection. The treponemal test is highly specific, but it can remain positive for life and is not useful for patient follow-up. In contrast to enzyme immunoassay (EIA), CLIA is a more advanced and automated method that uses paramagnetic particles coated with recombinant antigens to capture immunoglobulin M (IgM) and IgG, followed by the addition of a chemiluminescence substrate to generate a relative signal proportional to the amount of bound antigen-antibody complex. This method has recently become available for EIA and CLIA, making it the preferred screening tool for syphilis in large diagnostic laboratories. This test may be suitable for large-scale screening as a replacement treponemal test for TP-PA.[19] CLIA appears to have higher sensitivity than TP-PA in primary syphilis. Compared with ELISA, CLIA is more reliable, sensitive, and accurate for detecting *T. pallidum*-specific antibodies in serum. In the future, this method may be used as an alternative test with higher sensitivity than ELISA.[20]

Automated EIA, CLIA, and multiplex flow immunoassay tests allow for the detection of disease at an early stage but have limitations, with an increased risk of false-positive results in low prevalence populations.[6] This makes CLIA usable as an automated method to detect treponemal antibodies in human serum with high sensitivity and can be used to screen large-scale samples after non-treponemal screening tests.[19]

In contrast, the nested PCR test significantly differed from the previous two tests. The positivity rate of this test was relatively low. In the previous two serological examinations, more positive results were found than negative results.

PCR is an essential technique for molecular diagnosis and is considered a valuable resource for diagnosing early-

stage syphilis, particularly in individuals with conspicuous erythema. According to some researchers, PCR may enhance the detection rate of syphilis in patients with symptoms that are typically hidden by other infectious diseases. such as HIV/AIDS.[21]

Although serological tests have high specificity and sensitivity, they also have certain limitations. including reduced sensitivity in the early and late stages of syphilis, the risk of false-positive reactions due to other acute or chronic infections, and the tendency of non-treponemal tests to produce false-negative results because of the prozone effect. Since 1990, direct detection of treponemal DNA using PCR has become common; however, this method is still not a standard practice. Previous research has also shown that the most reliable samples for detecting treponemal DNA are swabs taken from syphilitic ulcers rather than whole blood samples.[22] Nested PCR is more specific and sensitive than routine PCR or single PCR using probes, which can improve the accuracy of amplification products. The specificity of nested PCR was 95%, whereas its sensitivity was 70%. Recently, Wang et al.[23] demonstrated that nested PCR is more sensitive, particularly in the early stages or infectious stages of syphilis. They also reported that the DNA load of *T. pallidum* was correlated with the RPR titer. These findings suggest that nested PCR may be a useful tool for the early diagnosis and prognosis of syphilis; however, further investigation is needed to determine the applicability of PCR screening, as the sample size in their study was limited.[21] As shown in European research, nested PCR can enhance the diagnosis of syphilis, especially in seronegative patients and those with varying serologies.[6]

The suitability for detecting syphilis between VDRL and CLIA against nested PCR in this study was not statistically significant. Previous research conducted by Vrbová et al.[22] in 2020 investigated the connection between serology and nested PCR in diagnosing syphilis. The study examined 126 samples, all of which tested negative for both treponemal and non-treponemal serological tests. Of these samples, nearly 9% (n = 11) were positive by PCR, indicating that PCR can detect *T. pallidum* in early-stage infections when patients may be seronegative. All samples, except for one whole blood sample, were collected from the genitoanal swabs. In conclusion, swab samples were found to be significantly higher than whole blood samples, and PCR detection in whole blood samples from patients with primary and secondary syphilis exceeded 40%.[22]

Study Limitations

In this study, the positivity rate of nested PCR was relatively low. This differs from the results of previous studies that have been discussed, which found that nested PCR detects false positives and false negatives because of its relatively high specificity and sensitivity. However, these results can be achieved if the nested PCR examination is performed in the early phase, particularly in individuals with conspicuous erythema. The majority of samples in this study were in the latent stage and were infected with HIV/AIDS, which is one of the main limitations of this study. Sampling using a similar research method is recommended for primary syphilis or ulcer lesions to provide more accurate results on comparative sensitivity and specificity comparative analysis between serological examinations, CLIA, and nested PCR for *T. pallidum* infection. Moreover, the differences between VDRL, CLIA, and nested PCR examinations in patients infected with *T. pallidum* may be due to the working principle of each examination and the stage of infection at the time of the examination.

Conclusion

The results of the VDRL and CLIA examinations did not correlate with the results of the nested PCR examination in patients with syphilis. In addition, these three tests were not associated with the degree of syphilis suffered by the patient. Nevertheless, this study strengthens the recommendation that a nested PCR examination is necessary in clinical conditions and other examinations that lead to suspected syphilis.

Ethics

Ethics Committee Approval: The Health Research Ethics Committee of the Hasanuddin University Faculty of Medicine (approval number: 579/UN4.6.4.5.31/PP36/2022, date: 11.10.2022) has evaluated and approved the entire research protocol.

Informed Consent: It was obtained.

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Footnotes

Authorship Contributions

Surgical and Medical Practices: F.S.K., Concept: F.S.K., Design: F.S.K., K.D., F.T., S.T., M., Data Collection or Processing: F.S.K., Analysis or Interpretation: F.S.K., K.D.,

F.T., S.T., M., F.I., M.N.M., M.I., Literature Search: F.S.K., F.I., M.N.M., M.I., Writing: F.S.K.

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Case Report

A Rare Case: Lipomembranous Panniculitis Associated with Peripheral Arterial Disease

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Abstract

Lipomembranous panniculitis (LP) is a rare type of fat necrosis characterized by membranocystic alterations. Rare cases of LP associated with peripheral arterial disease (PAD) have been reported. We report a case of 66-year-old female patient with a history of PAD who presented with multiple painful, tender, erythematous nodules and ulcers with irregular borders and violaceous edges on both thighs and legs. Histopathology confirmed the diagnosis of LP. Dermatologists should be aware of this entity when panniculitis is suspected, particularly in patients with vascular disorders.

Keywords: Panniculitis, fat necrosis, Nasu-Hakola disease, membranous fat necrosis

Introduction

Lipomembranous panniculitis (LP), also known as lipomembranous fat necrosis (LFN), lipomembranous changes, membranous fat necrosis, membranocystic changes or fat necrosis, membranous lipodystrophy-like changes, and pseudomembranous fat necrosis, is a rare and specific type of fat necrosis characterized by membranocystic alterations.[1,2] It may be primary or associated with different clinical conditions, such as venous insufficiency that is present most of the time, diabetes mellitus (DM), and rheumatoid arthritis (RA).[3-5] In addition, peripheral arterial disease (PAD) is one of the conditions associated with LP.[2,4-6] There are scarce reports of the entity in the literature.

Here, we present a 66-year-old female patient with a history of various systemic disorders and PAD who presented with painful erythematous papulonodular and ulcerated lesions, sclerotic plaques, and atrophic scars on both legs with acral necrosis of both feet.

Case Report

A 66-year-old female patient was admitted to our clinic with painful bilateral erythematous lesions and wounds for 2 years. She had a history of systemic disorders, including DM, PAD, RA, vertigo, hypertension, hypothyroidism, and arrhythmia. There was no history of smoking, trauma, or discharge. The patient was diagnosed with infection at an external center, and topical and oral antibiotics were initiated; however, there was no regression in the lesions. A history of balloon angioplasty performed on both legs by a cardiovascular surgeon was noted 1 month ago because of peripheral arterial insufficiency. However, balloon angioplasty was unsuccessful in the right leg, where acral necrosis was more severe. She did not report any joint or cardiac problems.

Dermatological examination revealed widespread painful, tender, erythematous papulonodule and ulcers with irregular borders with erythematous and violaceous surroundings and

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atrophic scars on both thighs and legs. Some ulcers had a punch-out appearance and crusts. The right leg has sclerotic plaques. There was necrosis in all right and second, third, and fifth toes of the left foot (Figure 1a-d). There were no signs of stasis dermatitis or varicose veins. During follow-up of the patient, the erythematous, tender papules, and nodules developed ulcers. An incisional biopsy was performed with the differential diagnosis of arterial ulcer, pyoderma gangrenosum, cutaneous embolism, erythema induratum of Bazin, panniculitis, and deep fungal infections for histopathological evaluation. In addition, tissue biopsy cultures of bacteria, mycobacterium, and fungi were also performed. Pseudomonas aeruginosa was identified in the tissue biopsy culture, and ceftazidime was started. Other tissue cultures resulted in negative.

Histopathological examination revealed mixed inflammation under the ulcer, which also inflamed the vascular structures. Lipomembranous structures and calcifications forming hairy appendages in the fatty lobules of subcutaneous fatty tissue were detected. A pale-colored eosinophilic material is present in the necrotic fat lobules (Figure 2a-c). The appearance of the membrane structures was consistent with the arabesque type and was stained with periodic acid-Schiff. The diagnosis of the LP was confirmed by the characteristic histopathological findings.

Deep vein thrombosis was excluded by venous Doppler ultrasound examination. In computed tomography angiography, dense calcific plaque formations were observed in both popliteal arteries along the superficial femoral artery traces and in the arterial segments distal to the popliteal arteries. The results were consistent with advanced peripheral vascular disease with arterial stenosis, and partial amputation was planned after mitigation of the infection.

The laboratory tests showed hemoglobin 104 gr/L [relative risk (RR): 115-155 gr/L], hematocrit: 28.5% (RR: 35.5-48%), erythrocytes: $3.46x10^{12}$/L (RR: $3.8-5.6x10^{12}$/L), neutrophils: $8.49x10^{9}$/L (RR: 1.56-6.13 $x10^{9}$/L), lymphocytes: $0.96x10^{9}$/L (RR: 1.18-3.74 $x10^{9}$/L), monocytes: $0.61x10^{9}$/L (RR: 0.24-0.36 $x10^{9}$/L), aspartate aminotransferase: 32 U/L (RR: 28-100 U/L), C-reactive protein: 333 mg/L (RR: < 5 mg/L),

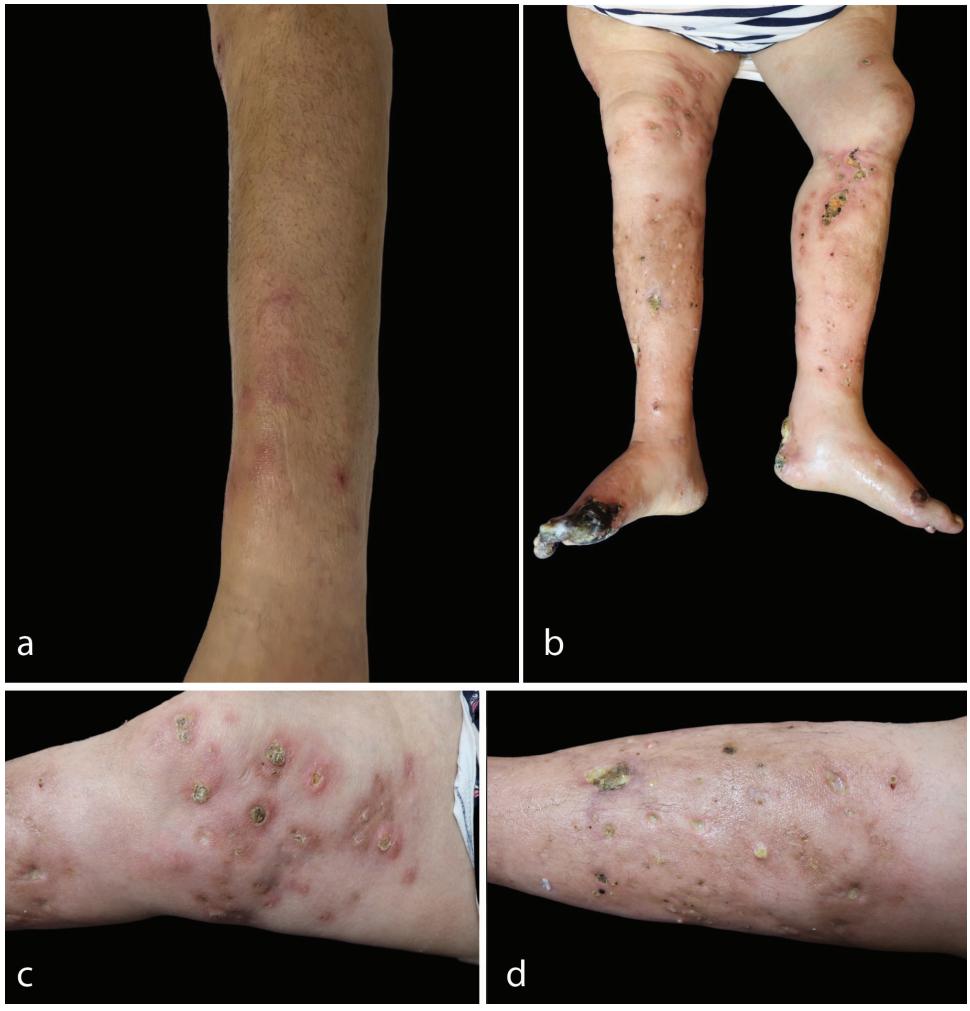

Figure 1. (a) Multiple erythematous nodules on the left leg. (b-d) Multiple ulcers with irregular borders and violaceous edges on both legs and thighs

erythrocyte sedimentation rate: 52 mm/h (RR: 2-20 mm/h), albumin: 30.5 g/L (RR: 35-52 g/L), sodium: 125 mmol/L (RR: 136-145 mmol/L), calcium: 8.4 mg/dL (RR: 8.5-10.3 mg/dL), chlorine: 90 mmol/L (RR: 98-107 mmol/L), creatinine: 3.42 mg/dL (RR: 0.5-0.9 mg/dL), lactate dehydrogenase: 361 U/L (RR: 135-214 U/L), creatine kinase: 389 U/L (RR: 26-192 U/L), blood glucose level: 138 mg/dL (RR: 74-109 mg/dL), total protein: 56.3 g/L (RR: 66-87 g/L), free T4: 20.2 ng/L (RR: 8.9-17.1 ng/L). Serum complement, alpha-1 antitrypsin, serum amylase, and lipase levels, and complete urinalysis were normal. Rheumatoid factor was positive, and antithrombin III activity was 73% (RR: 80-120%). Laboratory studies were negative for antinuclear antibodies, anti-dsDNA, anti-Ro, anti-La, anti-SM, anti-RNP, and anti-Scl 70.

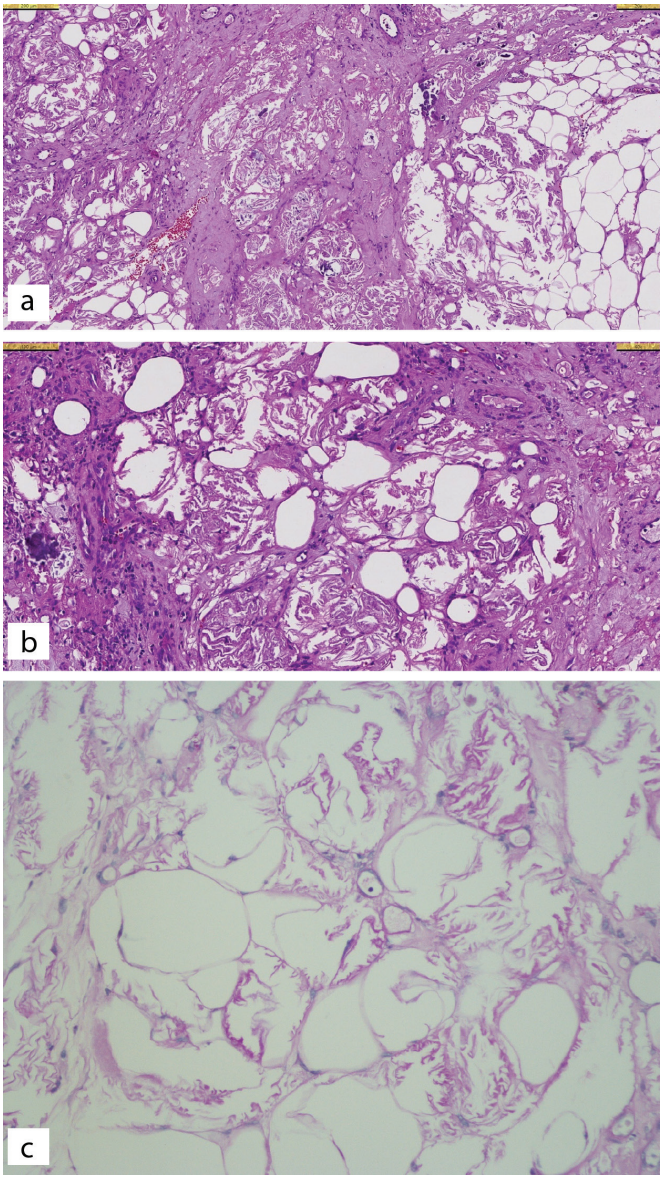

Figure 2. (a, b) Pseudocyst structures lined with thin eosinophilic biomembrane structures and hairy extensions in fat spaces. Hematoxylin and eosin: (x200, x400, respectively). (c) The membrane was stained with periodic acid-Schiff (x200)

Discussion

LP was first described in the Nasu-Hakola disease, which is characterized by the membranocystic degeneration of long bones and adipose tissues as well as the sudanophilic leukodystrophy of cerebral hemispheres first described by Nasu et al.[7] in 1973. However, subsequent reports demonstrated that the membranocystic changes could be associated with various conditions.[2-6,8] Considering data in the literature, factors such as diabetic microangiopathy, vasculitic involvement in RA, PAD, and susceptibility to thrombosis (low antithrombin III activity) are also included in the pathogenesis of this disease, which is thought to be a result of ischemia of the fatty tissue.[3-5,8,9] In our patient, there was a history of DM, PAD, RA, and low antithrombin III activity in laboratory findings. The coexistence of many conditions associated with the etiopathogenesis of the disease may explain why our patient's clinic was so acute and severe. In addition, following the emergence of symptoms such as pain and bruising related to PAD; painful, erythematous nodules subsequently turned into ulcers on the bilateral legs and thighs. Therefore, the onset of LP lesions in the legs occurred simultaneously with the symptoms of PAD, suggesting that PAD was the main factor in the pathogenesis of the disease in our patient. No treatment has been reported to be particularly effective in the literature.[10]

The typical clinical feature of this disease is the presence of subcutaneous nodules or sclerotic plaques, often found on the lower legs and symmetrically distributed. The clinical findings in our patient, clinical findings consistent with the literature. In addition, LFN may involve the joints and heart valves.[1] However, there was no evidence of joint or heart valve involvement in our case.

The histological features of the LP are characterized by cystic areas of fat necrosis lined by hyaline acidophilic membranes on hematoxylin and eosin (H & E)-stained sections. The membranes are projected into the cystic spaces. LFN can also be demonstrated by periodic acid-Schiff staining with or without diastasis, Sudan black B, oil red O staining, Azan-Mallory or Masson trichrome staining, orcein staining, long Ziehl-Neelsen staining, silver impregnation, phosphotungstic acid-hematoxylin staining, and Luxol fast blue staining. In addition, LFN membranes with an "arabesque" or "frost on a windowpane" appearance have been described by some authors.[1] Other variable histological features of LP include dilated veins, hemorrhage, endarteritis obliterans, sclerosis, calcified vessels, and hemosiderin deposition.[2] Previous studies have suggested that lipomembranous changes occur as a result of the interaction between residual elements of necrotic fat cells and macrophages, probably as a consequence of inflammatory and ischemic disorders in fatty tissues.[8] Other than LP, panniculitis associated with vascular disease includes

arteriosclerosis, diabetic microangiopathy, necrotizing vasculitis, panarteritis nodosa, thromboangiitis obliterans, and venous insufficiency.[11]

On the other hand, loss-of-function variants in TYROBP/DAP12 or TREM2 have been reported in "Nasu-Hakola disease", but patients without this hereditary disease have also been reported.[1] Unfortunately, we did not perform genetic testing in our case.

In a study conducted by Snow and Su[8], which evaluated 38 cases, the mean age of the patients was 57 years (range 32-86 years), and 34 patients (89%) were women. The most common clinical context in which this condition was observed was in patients with chronic sclerotic plaques of the lower legs associated with venous insufficiency (37% of the total cases). All patients were women, and the majority were obese in these cases.[6] The demographic and clinic features, such as age, sex, and location of the lesions, were compatible with the literature in our case.

In conclusion, in cases of suspected panniculitis, particularly in patients with vascular disorders, it is important to consider the LP, which is a rare histopathological variant. New studies are needed on the treatment of LP, regardless of any associated diseases and the underlying cause.

Footnotes

Informed Consent: It was obtained.

Authorship Contributions

Concept: İ.K.A., D.T., A.A., B.Ö.K., S.Ö.H., E.K., Design: D.T., Data Collection or Processing: K.A., D.T., A.A., B.Ö.K., Analysis or Interpretation: İ.K.A., B.Ö.K., Literature Search: İ.K.A., D.T., A.A., B.Ö.K., S.Ö.H., E.K., Writing: İ.K.A., D.T., B.Ö.K., S.Ö.H., E.K.

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Case Report

Papillon-Lefèvre Syndrome: A Report of Four Cases and a Brief Review of the Literature

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Abstract

Papillon-Lefèvre syndrome (PLS) is a rare autosomal recessive genodermatosis characterized by palmoplantar hyperkeratosis and early loss of primary teeth and permanent teeth secondary to periodontitis, as well as disorders in neutrophil function and chemotaxis, recurrent infections, and internal organ abscesses. Topical moisturizers, keratolytic agents, and topical-systemic retinoids can be used for the treatment of palmoplantar keratoderma, and oral hygiene, antiseptic mouthwashes, systemic antibiotic treatments, and regular dentist follow-up are critical for periodontitis management. In this case report, we present the clinical features and treatments of four patients with PLS who were diagnosed based on physical examination and genetic analysis. We aim to increase the awareness of PLS among clinicians by describing the clinical and treatment characteristics of four patients with PLS.

Keywords: Genodermatoses, palmoplantar keratoderma, Papillon Lefèvre syndrome

Introduction

Papillon-Lefèvre syndrome (PLS) is a rare genodermatosis characterized by palmoplantar keratoderma and premature tooth loss. Patients with PLS often experience dysregulation in immune response and an increased frequency of bacterial infections because of the inactivation of neutrophil serine proteases. Treatment for palmoplantar keratoderma typically involves the use of topical moisturizers, keratolytic agents, and topical or systemic retinoids. Regular follow-up with a dentist is important for managing periodontitis in PLS patients.[1]

In this case report, we present the clinical features and treatments of four patients with PLS who were diagnosed based on physical examination and genetic analysis [CTSC (11q14.2) mutation]. With this case series, we aimed to add new patients to the current literature to increase the cumulative data of patients with PLS.

Case Report

Of the four patients analyzed, two were male, and the average age was 16 years. The patients were followed up for an average of 11 years (range: 5-20 years). All patients exhibited palmoplantar hyperkeratosis and history of tooth loss. One patient also presented with erythematous, scaly plaque lesions on the knee and elbow (Figure 1). All patients experienced symptoms such as itching and burning in the palmoplantar area. Additionally, 75% of the patients had a family history of PLS. Three of the patients were related, two were siblings, and one was their cousins. In terms of accompanying systemic comorbidities, one patient had cystic fibrosis, nephrolithiasis, and gynecomastia, while another patient had multiple liver abscesses and mental retardation. Biopsy of the patients' palmar regions revealed hyperkeratosis and spongiosis in the epidermis in all cases. All patients were treated with topical moisturizers and keratolytic. Three patients received

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acitretin treatment, and one patient could not be treated due to the presence of multiple liver abscesses and abnormal liver function tests. Instead, the patient received tazarotene cream. During follow-up, topical or systemic retinoid treatments effectively improved palmoplantar hyperkeratosis and enhanced the patients' quality of life.

The demographic, clinical, and histopathological characteristics of the patients are presented in Table 1.

The patients in this manuscript has given written informed consent to the publication of their case details.

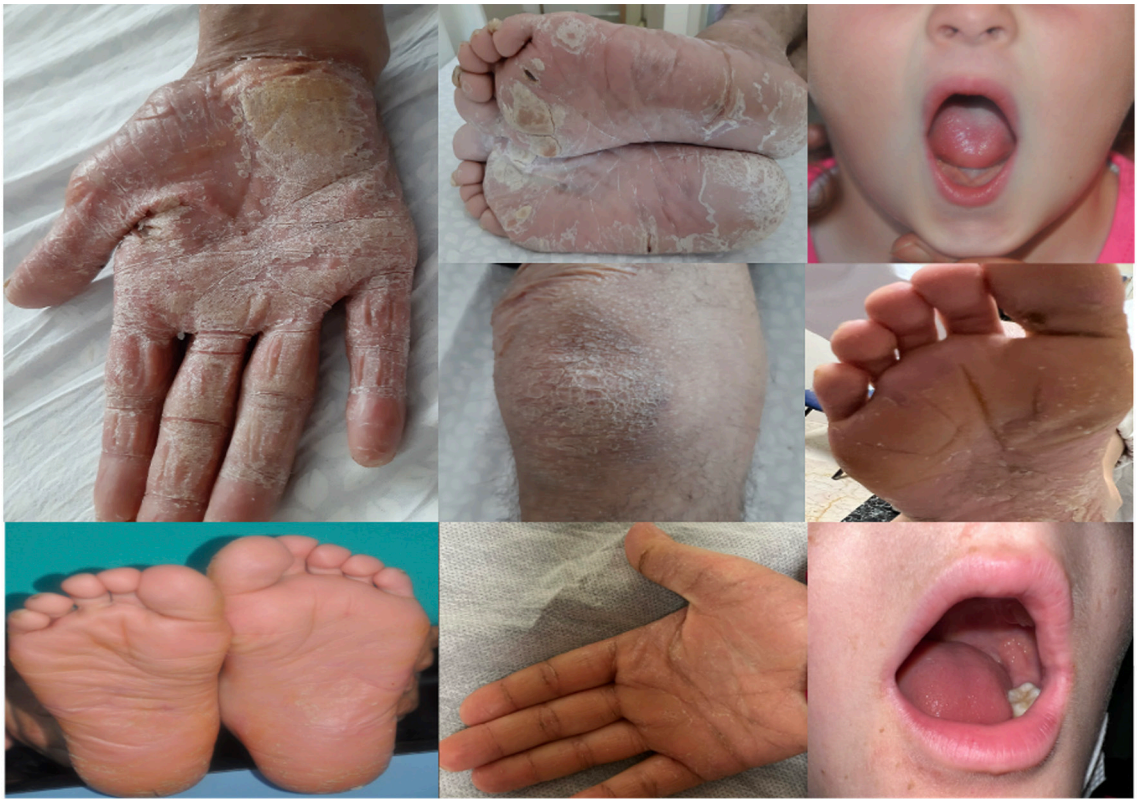

Figure 1. Clinical images of the lesions

Table 1. Demographic, clinical, and histopathological characteristics of the patients

Case	Age/sex	Age at diagnosis	Follow-up duration (year)	Family history	Dermatologic examination	Histopathologic analysis	Teeth loss	Comorbidity	Treatment
I	11/F	6	5	+	Erythema, hyperkeratosis in the palmoplantar area	Spongiotic dermatitis	+	-	Topical keratolytic, acitretin
II	15/M	4	11	+	Erythematous squamous plaque in the palmoplantar area	Spongiotic dermatitis	+	-	Topical keratolytic, acitretin
III	12/F	4	8	+	Erythema, hyperkeratosis in the palmoplantar area	Spongiotic dermatitis	+	Cystic fibrosis, nephrolithiasis, and gynecomastia	Topical keratolytic, acitretin
IV	26/M	6	20	-	Hyperkeratosis in the palmoplantar area, fissures, hyperkeratotic plaque in the knees and elbows	Spongiotic dermatitis	+	Multiple liver abcesses	Topical keratolytic, tazaroten

F: Female, M: Male

Discussion

PLS is a rare autosomal recessive genodermatosis caused by mutations in the *CTSC (11q14.2)* gene, which encodes the cathepsin C enzyme. Genetic, immunological, and microbiological factors contribute to the pathogenesis of PLS. Palmoplantar hyperkeratosis and early loss of primary and permanent teeth due to periodontitis are key features of the disease. Palmoplantar keratoderma and periodontitis typically develop simultaneously in patients aged between 1 and 4. However, there are cases of late-onset PLS without CTSC mutations.[1,2]

Palmoplantar keratoderma is characterized by widespread erythematous, hyperkeratotic plaques affecting the palms and soles, often leading to painful fissures that can interfere with daily activities. Patients with PLS may also exhibit hyperhidrosis, nail changes, and hyperkeratotic psoriasiform plaques on the knees and elbows.[1-4] Studies investigating the immunopathogenesis of PLS have identified activation of the T-helper 1 (Th-1)-Th-17 pathway and increased levels of interleukin-1 (IL-1) and IL-36 cytokines. It is thought that this cytokine profile may help explain how psoriasiform plaques located on the knees and elbows develop in patients and suggest that biological agents can be considered as potential treatment agents in resistant cases. Latour-Álvarez et al.[5] applied ustekinumab treatment (45 mg at weeks 0 and 4, then 45 mg every 8 weeks) to a 15-year-old girl with PLS who was resistant to topical steroid, phototherapy, isotretinoin, and acitretin treatments. The patients who received ustekinumab achieved regression of the erythematosquamous plaques and partial improvement of the palmoplantar keratoderma.[5,6]

Periodontitis presents as periodontal abscesses, halitosis, gum swelling, and difficulty in eating. Factors contributing to the development of periodontitis include impaired gingival sulcus epithelial permeability, decreased lymphocyte reactivation, impaired neutrophil chemotaxis, and an imbalance between pathogens and host immune response. Gram-negative anaerobic pathogens are considered the primary cause of periodontitis in PLS. Studies have shown elevated levels of IL-1β, IL-6, IL-8, and interferon-gamma in the gingival crevicular fluid of patients with PLS. Managing periodontal damage in PLS requires regular follow-up, oral hygiene maintenance, antiseptic mouthwash administration, and systemic antibiotic treatment. Intensive orthodontic treatment may be necessary during the growth period, and periodontal care can sometimes help preserve the patient's teeth.[7,8]

CTSC gene mutations can lead to neutrophil dysfunction, impaired chemotaxis, and recurrent infections, including internal organ abscesses in the liver and brain.[2] Patients with PLS should be monitored for the risk of pyogenic liver abscesses, especially when presenting with fever of unknown origin. *Staphylococcus aureus* is the most common causative agent of liver abscesses in PLS, usually occurring as a single abscess. Mental retardation, dura mater calcifications, growth retardation, hypothyroidism, atopic tendencies, and elevated immunoglobulin E levels are rare findings associated with this syndrome.[1-4] One of our cases had mental retardation and multiple liver abscesses.

Treatment options for palmoplantar keratoderma in PLS include topical moisturizers, keratolytic agents, and topical or systemic retinoids. Systemic retinoids have been shown to effectively reduce keratoderma, periodontal disease, and susceptibility to infection, making them a key therapeutic agent in PLS treatment.[1-4,6,9] A study by Leuenberger et al.[6] demonstrated that acitretin treatment decreased levels of IL-12B, IL-17C, IL-26, and IL-36 in a PLS patient. In cases where systemic retinoids cannot be used, such as in our case, topical retinoids can be a suitable alternative. Tazarotene, for example, regulates the proliferation and differentiation of keratinocytes and provides an additional anti-inflammatory effect, making it effective for treating keratoderma in PLS. Guldbakke et al.[10] used 40% urea cream and 0.1% tazarotene gel for palmoplantar keratoderma management after patient decline in oral retinoid treatment and achieved moderate improvement. Additionally, maintaining oral hygiene, using antiseptic mouthwashes, administering systemic antibiotics, and regular dental follow-up are crucial for managing periodontitis in the patients.[1,3] New studies on the *CTSC* gene indicate that there may be new possibilities for the treatment of the disease.[11]

Through this case report, we aimed to raise awareness about PLS among clinicians by presenting the clinical and treatment characteristics of four patients. Further studies and case series will contribute to our understanding of PLS pathogenesis and guide the development of new treatment options.

Ethics

Informed Consent: The patients in this manuscript has given written informed consent to the publication of their case details.

Footnotes

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Case Report

Platelet-Rich Fibrin and Punch Graft Combination in the Management of Venous Stasis Ulcer: A Great Duo

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Abstract

Venous leg ulcers are the most common cause of leg ulcers, and various factors, such as venous hypertension and venous reflux, play a role in the etiopathogenesis of these ulcers. Although various treatment modalities can be used for the treatment of venous leg ulcers, ulcer management can be challenging in some cases and has led to the search for new treatment modalities. In this case report, we present a male patient who underwent punch graft and platelet-rich fibrin treatment for venous stasis ulcer.

Keywords: Leg ulcer, platelet-rich fibrin, punch graft

Introduction

The most common type of leg ulcer is venous ulcer. The etiopathogenesis of venous ulcers may involve several components, including venous hypertension, venous reflux, venous thrombosis or non-thrombotic venous obstruction, and insufficient muscle pump function. The treatment options for venous ulcer include compression therapy, local wound care, wound dressings, and tissue grafts; however, venous ulcer care can be challenging occasionally and requires a combination of therapeutic approaches.[1] Here, we describe a male patient who underwent punch graft and platelet-rich fibrin (PRF) treatment for a venous stasis ulcer.

Case Report

A 55-year-old man presented to our dermatology outpatient clinic with a painful ulcer on his right leg. His past medical history included hypertension with perindopril + indapamide and chronic venous insufficiency with daflon. The patient described an ulcer on his right leg that had increased in size over the past month. Dermatologic examination revealed an ulcer on the right leg above the lateral malleolus measuring 2.5 cm^2 (calculated with imitoMeasure®) with irregular borders and fibrin tissue on the lesion (Figure 1). Based on clinical analysis and Doppler-ultrasound examination, the ulcer was considered a venous-stasis ulcer. Upon treatment resistance with ulcer debridement, wound dressing, and compression therapy, we decided to apply PRF treatment. Initially, 10 cc of the patient's venous blood was drawn into a PRF tube. The blood was centrifuged in a Nuve-NF 200 centrifuge device at 1300 rotations per minute for 8 minutes. PRF material was placed on the ulcer, covered with a sterile gauze piece, held in the area with a sterile bandage, and repeated weekly. Two weeks after PRF treatment, following wound bed preparation, we decided to apply the punch graft method, which stands out

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in the literature as an effective method for ulcer management, to ensure complete epithelialization. Graft material, including the epidermis and dermis, was taken from the anterolateral side of the thigh under sterile conditions using a 4 mm punch under local anesthesia. Topical antibiotic was applied to the donor area and allowed to heal with secondary intention. The collected grafts were placed in the holes opened with a 4 mm punch in the wound bed, wrapped with sterile gauze, and compression bandages were applied. During the patient's follow-up, after the placement of the grafts, rapid epithelialization of the ulcer was observed, and complete healing was observed in the fourth week after the procedure (Figure 2). Informed consent was obtained.

Discussion

The combined use of PRF and punch graft treatment modalities appears to be an effective combination treatment in ulcer management. PRF affects the wound healing process by having roles in cell proliferation, cell differentiation, chemotaxis, and angiogenesis through the platelets, growth factors, and cytokines it contains, as well as via its fibrin matrix.[2] Somani and Rai,[3] in their study to show the accelerating effect of PRF on ulcer treatment, divided 15 patients with venous ulcers into two groups, applied PRF closure to one group and saline closure to the other group, and at the end of four weeks, the reduction in ulcer area was 85.51% in the PRF group and 42.74% in the saline group. Dorjay and Sinha[4] used PRF in the treatment of various leg ulcers, venous ulcers, diabetic foot ulcers, and post-traumatic ulcers. In addition to its wound healing-accelerating effects in ulcer management, PRF is a safe and inexpensive treatment method, causing it to emerge as an increasingly used treatment method in dermatology practice.

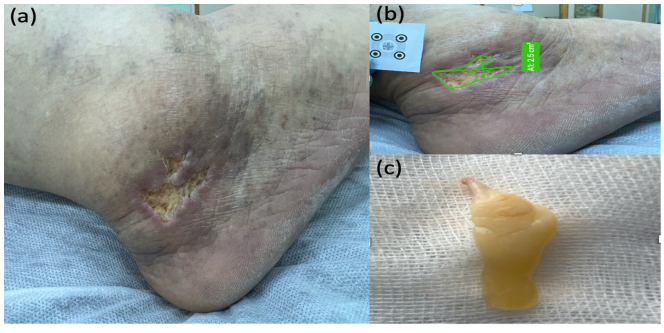

Figure 1. (a, b) Ulcer on the right leg above the lateral malleolus measuring 2.5 cm^2 (calculated with imitoMeasure®), with irregular borders and fibrin tissue on the lesion, (c) appearance of the PRF material
PRF: Platelet-rich fibrin

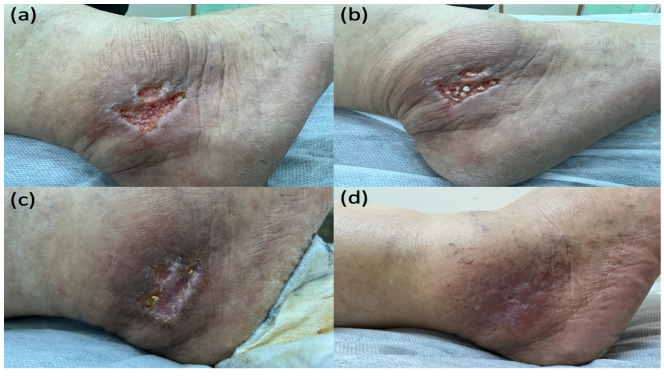

Figure 2. (a) Appearance of the ulcer 2 weeks after PRF treatment; (b) location of skin grafts on the ulcer; view of the ulcer 1 week (c) and 4 weeks (d) after the punch graft procedure
PRF: Platelet-rich fibrin

The punch graft method is a minimally invasive surgical method in which mini-graft materials containing the epidermis and papillary dermis are taken using a punch, scalpel, or curette and placed directly into the ulcerated area. One of the advantages of this method is its ability to be used as an outpatient procedure without the need for hospitalization. In addition to its impact on accelerating wound healing, it also plays a significant role in decreasing ulcer-related pain. Studies in the literature have reported the use of punch graft applications for treating venous, arterial, and diabetic ulcers.[5-7] Preparing the wound bed before applying the graft increases the success rate of the graft treatment. Negative-pressure wound therapy can be performed for this purpose, and PRF is also one of the methods that can be applied.[8,9] We used PRF before graft implantation to prepare the wound bed.

Although there is no case in the literature in which punch skin graft placement in combination with PRF application, in their study, Wang et al.[9] achieved lower postoperative infection and amputation rates via PRF treatment before full-thickness skin graft in diabetic foot management. Carducci et al.[10] achieved successful treatment results by combining the platelet-rich plasma (PRP) and punch graft method in mixed arterial and venous leg ulcer management.

In this case report, we describe the first case of a leg ulcer treated with a combination of PRF and punch graft in the literature. We want to emphasize that this combination can be an effective, practical, and inexpensive approach to ulcer management.

Ethics

Informed Consent: It was obtained.

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Teledermatology, Mpox, and Dermatological Emergencies

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Dear Editor,

The term "dermatologic emergency" encompasses skin disorders or conditions that necessitate urgent medical intervention because of their acute onset and potential for rapid progression to severe outcomes. These conditions pose significant risks to patient health, and early diagnosis and timely treatment are critical for preventing life-threatening complications.[1] Prompt and effective management of dermatologic emergencies is essential in mitigating morbidity and mortality.[1]

Mpox, caused by the monkeypox virus, is a viral infection characterized by symptoms such as pruritic skin eruptions, fever, and human-to-human transmission.[2] The typical clinical presentation of mpox includes high fever, chills, headache, lymphadenopathy, myalgia, and a painful cutaneous rash that often manifests as raised lesions, predominantly affecting the face, genital regions, and extremities.[2,3] The evolution of the rash typically follows a progression from macules to papules, vesicles, pustules, and eventually crusts. Not all lesions may be present simultaneously, and eruptions may appear in different stages across the body.[2,3]

In emergency settings, the accurate recognition of dermatologic emergencies, such as those caused by mpox, presents a substantial diagnostic challenge.[4] Although emergency departments and infectious disease units are proficient in identifying viral infections, the differential diagnosis of dermatologic conditions often proves difficult.[5] Moreover, other dermatologic emergencies frequently encountered in emergency departments, such as severe infections, acute allergic reactions, burns, Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN), can result in significant morbidity and even mortality.[6,7]

The expanding field of non-surgical esthetic procedures has drawn considerable attention from healthcare professionals, including dermatologists, with many shifting their focus toward esthetic medicine.[8] The non-surgical esthetics industry has experienced remarkable growth in recent years. By 2023, the global medical esthetics market was valued at approximately $60 billion, with an anticipated annual growth rate of 10-12% through 2028.[8,9] In Türkiye, the medical esthetics sector has also seen rapid expansion, with annual growth rates ranging from 15-20% between 2020 and 2022.[8,10] As of 2023, the market was valued at approximately $2 billion in Türkiye alone.[8,10] Dermatologists, due to their expertise in skin health and appearance, have become key players in the esthetic medicine landscape, offering a variety of procedures that address both esthetic and therapeutic needs.[10,11] However, this shift in focus has led to a reduction in the number of experienced dermatologists working in public hospitals, which may compromise the care of dermatologic emergencies.

A promising solution to this challenge lies in the advancement and implementation of teledermatology. Teledermatology, which integrates technology with dermatologic care, has gained significant traction in many developed countries and has demonstrated potential in addressing dermatologic emergencies in regions with limited access to specialists. The application of teledermatology could prove especially

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valuable in future pandemics, where rapid diagnosis and treatment are paramount. By facilitating timely consultation and diagnosis, teledermatology holds promise in reducing mortality rates associated with dermatologic emergencies. For example, in Türkiye, the National Poison Consultation Center operates 24/7, offering real-time access to toxicologists via telephone consultation at 114. Similarly, teleradiology services enable the evaluation of radiologic images from distant locations, providing expert opinions across different continents. The establishment of a teledermatology system could address the shortage of dermatologists and improve access to care in underserved areas, significantly enhancing the management of dermatologic emergencies.

Teledermatology is an effective method for remote diagnosis and treatment of dermatological issues, but it has certain limitations. First, a lack of physical examination is a significant constraint. Dermatologists often rely on palpating the skin and conducting a physical exam to diagnose skin lesions, but teledermatology does not offer this option. Second, image quality and lighting are critical for teledermatology. Low-resolution images or inadequate lighting can complicate diagnosis. Additionally, teledermatology may not be suitable for complex cases; some rare or complicated dermatological conditions require in-person evaluation. Another limitation is color discrepancies, as devices and screens may not accurately reflect skin tones, leading to potential misdiagnoses. Finally, some invasive diagnostic methods, like biopsies, cannot be performed remotely, making teledermatology insufficient for certain cases.

Teledermatology is a valuable tool for improving the diagnosis and management of dermatologic emergencies, such as SJS and TEN, as well as emerging infectious diseases like mpox. By providing more accurate and timely diagnosis, teledermatology has the potential to reduce mortality and improve patient outcomes in both acute and pandemic settings.

Footnotes

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Dhanalakshmi Kathirvel
Dilek Bayramgürler
Dilek Seçkin
Düriye Deniz Demirseren
Ece Erbağcı
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Ercan Çalışkan
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