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Alexithymia and Cutaneous Disease Morbidity: A Systematic Review

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Keywords
Psychodermatology · Psychocutaneous medicine · Alexithymia · Emotional deficit · Quality of life

Abstract
Background: Alexithymia is a psychological construct that describes one's difficulty in understanding and describing their own emotions as well as differentiating feelings from bodily signals of arousal. In the general population, alexithymia's prevalence is approximately 10%. Alexithymia may act as a triggering factor for many medical and psychiatric disorders. In patients with physical disease, alexithymia's prevalence reaches up to 63%. Additionally, alexithymia is associated with worse outcomes and heightened psychosocial comorbidities. ***Objective:*** This review continues where an earlier review (Willemsen, 2008) left off to (1) clarify alexithymia's prevalence in dermatology patients and (2) further investigate alexithymia's impact on disease burden, psychosocial comorbidities, and treatment. ***Methods:*** Systematic searches on alexithymia and dermatologic conditions were conducted using PubMed, Embase, PsycInfo, and Web of Science databases from March 8, 2021, to March 12, 2021. Data from eligible publications, which were full-text, clinical studies published after September 1, 2008, and available in English, were extracted by two medical students and summarized. ***Results:*** Despite a small number of publications (n = 37), data showed a markedly greater prevalence and severity of alexithymia in patients with alopecia, vitiligo, psoriasis, hidradenitis suppurativa, atopic dermatitis, chronic idiopathic urticaria, and primary focal hyperhidrosis compared to healthy controls. Further, data consistently demonstrate a complex interplay between alexithymia, disease burden, and psychosocial comorbidity. ***Conclusions:*** Identifying and addressing alexithymia in dermatology patients may improve treatment outcomes, associated comorbidities, and health-related quality of life.

Introduction

Alexithymia, meaning "no words for emotion" in Greek, is a psychological construct that describes one's difficulty in understanding and describing their own emotions as well as differentiating feelings from bodily signals of arousal [1]. Alexithymia is comprised of three main facets: (1) difficulty in identifying feelings (DIF)

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and, further, difficulty distinguishing between feelings and the bodily sensations of emotional arousal; (2) difficulty in describing feelings (DDF) to other people; and, (3) constricted imaginative processes and externally oriented cognitive style [2]. Commonly, these three facets are assessed with the twenty-question, self-report Toronto Alexithymia Scale (TAS-20) [2].

Each question on the TAS-20 is answered on a 1–5 scale and the summation of total and categorical scores correlate to the level of alexithymia and its subdimensions, respectively. Total TAS-20 scores ≥51 are considered clinically significant, with scores between 51 and 61 representing borderline alexithymia, and scores ≥61 representing alexithymia. Individuals exceeding the clinical cut-off are considered to be at increased risk of developing medical and mental health conditions. Though less precise than clinical interviews due to its self-report nature, TAS-20 is considered the "gold standard" in medical research given its high validity, internal and external consistency, and short administration time [3, 4]. In the context of dermatology, 89.2% of studies identified for this review used the TAS-20 to assess alexithymia and its subdimensions. Therefore, the current review focuses on alexithymia in dermatology patients as assessed with the TAS-20.

Historically, much of the attention regarding alexithymia was focused toward its common co-occurrence with autism spectrum disorder (ASD). Alexithymia's prevalence in ASD has been reported to be up to 63%, compared to approximately 10% in the general population. Further, alexithymia has been demonstrated to mediate the social-emotional deficits associated with ASD [5–8]. To understand the link between alexithymia – a psychological construct – with physical disease, it is helpful to be aware that (1) alexithymic patients are frequently observed to be hypersensitive to physical stimuli and this increased sensitivity may increase their likelihood of experiencing somatic symptoms for extended periods of time; (2) alexithymia, particularly DIF and DDF, is often accompanied by disconcordance between the mind and body and poor quality of social relationships, which in turn may result in psychological distress and the experience of negative emotions; (3) such negative emotions and the physical sensations by which they are accompanied (e.g., increased heart rate, sweating) tend to be mistaken for symptoms of disease; and (4) the extended arousal to stimuli, that is truly from disease symptoms, or misinterpreted as such, may precipitate an intensified response of the nervous system and neuroendocrine system, further contributing to somatic disease (for comprehensive reviews on the link between alexithymia and physical disease, see Lumley et al., 1996; 2007 and Kuty-Pachecka et al., 2015) [4, 9, 10].

Beyond somatic disease, a trend has emerged of alexithymia co-occurring with mental illness, both in the general population and across specialties. Not only does it appear that up to 58%, 51%, and 49% of alexithymic patients suffer from anxiety, depression, and addictive behaviors, respectively [8, 11] but also higher levels of alexithymia seem to be related to more severe manifestations of psychiatric illness [12]. Additionally, alexithymia has been linked to suicidal ideation [13], maladaptive coping strategies, poor sleep, and impaired relationships that contribute to a paucity of social support for patients [14].

Over the last 50 years, alexithymia has become an important consideration in diseases beyond ASD. Patients with coronary heart disease have been shown to have a greater prevalence of alexithymia and data suggest that complementary treatment addressing alexithymia may lead to significantly fewer cardiac events, including reinfarction and sudden cardiac death [15]. In patients with eating disorders, there is an increased incidence of alexithymia and a reported improvement in disease when alexithymia is addressed [16, 17]. In obstetrics and gynecology, data suggest that alexithymia may be important in infertility management, as it seemed to predict in vitro fertilization success [18].

Within dermatology, a complex interplay between alexithymia and skin disease has been reported. Most recently, a 2008 review concluded that alexithymia – being linked to changes in sympathetic activity, immunity, and brain activity – is associated with a number of dermatologic diseases (see Table 1 for a summary of findings) [19]. A review of findings reported up to 9/2008, concluded that patients with alopecia areata (AA) [20], vitiligo [21], and urticaria [22] have greater prevalence and severity of alexithymia compared to healthy controls. For patients with psoriasis and atopic dermatitis, there was conflicting evidence, with some studies suggesting a greater prevalence of alexithymia in patients with these diagnoses [23, 24], and others not [25, 26]. Here, we reviewed the evidence accumulated after September 1, 2008 (up to March 12, 2021) to better understand the relationship between alexithymia and dermatologic conditions. Given that one's inability to understand, describe, and process emotions may also create a significant barrier to self-management, essential in dermatology given the chronicity of many conditions, we also investigated the impact of alexithymia on disease burden, psychosocial comorbidities, quality of life, and treatment success.

Table 1. Summary of findings from the most recent review of alexithymia and dermatology [19]

Condition (Publications, *n*)	Patient, *n*	Control, *n*	Findings
General skin disease (1)	545	–	TAS-20 score for study population was within normal range Patients with concurrent alexithymia have significantly lower psychosocial functioning
Atopic dermatitis (1)	6	–	Alexithymia is associated with less REM sleep
Psoriasis (7)	538	Healthy, 255	Three of seven studies show statistically significant association between alexithymia and psoriasis Prevalence of alexithymia is 34.1% in psoriasis patients (*n* = 170/498) Attachment-related avoidance is associated with psoriasis exacerbation (statistically significant in 1 of 2 studies)
AA (3)	95	Healthy, 195	46.3% prevalence of alexithymia (*n* = 44/95) Higher TAS-20 scores in patients (statistically significant in 2 of 3 studies) Greater prevalence of depression and anxiety in alexithymic patients (statistically significant in 1 of 2 studies)
Vitiligo (1)	31	Healthy, 116	35.5% prevalence of alexithymia (*n* = 11/31) Vitiligo patients have higher rates of insecure attachment and lower perceived social support
CU (2)	71	Psychogenic excoriations, 31	50% of patients with CU are alexithymic (*n* = 20/40) Highest subscale score was DIF
Prurigo nodularis (1)	94	Psoriasis, 91	No significant difference in prevalence of alexithymia, anxiety, or depression between patients with prurigo nodularis and psoriasis
Psychogenic excoriations (1)	31	CU, 31	Higher rates of both alexithymia and anger in patients with psychogenic excoriations compared to CU

CU, chronic urtiracia; AA, alopecia areata; DIF, difficulty in identifying feelings; TAS-20, Toronto Alexithymia Scale.

Materials and Methods

This systematic review was registered with PROSPERO (#CRD42021239140), performed in accordance with PRISMA guidelines, and guided by the following questions: (1) what is the prevalence of alexithymia in patients with cutaneous disease? (2) what is the impact of alexithymia on psychosocial comorbidity? and (3) how does alexithymia impact treatment outcomes? Research librarian, C.R., and corresponding author, A.H., generated the following search string with the intention of being inclusive of all cutaneous conditions and capturing any publication for which alexithymia was a focus: (Alexithymia OR "affective symptom*" OR "emotional disturbance*") and ("skin disease*" OR "skin disorder*" OR dermatosis* OR dermatoses* OR "skin and subcutaneous tissue disorder*"). The search was conducted by C.R. from March 8, 2021 to March 12, 2021, on four electronic databases, selected to cover the range of fields related to emotional disturbances and cutaneous disease: PubMed, PsycINFO, Web of Science, Embase. The following exclusion criteria were used: (a) non-English language articles; (b) animal studies; (c) case reports; (d) review articles; (e) systematic reviews; and (f) scoping reviews. In PsycINFO and Web of Science databases, criteria c-f were not utilized due to small retrieval sets and/or the absence of subject headings. All search results were imported into a citation management program, and duplicate references were removed. Article titles and abstracts were screened for relevance and full-text publications were reviewed for eligibility. Eligible articles were full-text publications, published after September 1, 2008, available in English, and explicitly addressing both dermatologic conditions, without systemic involvement, and alexithymia. Additional articles were identified via reference lists within identified publications. Data were extracted independently by two authors (A.H. and P.M.) using predefined data fields which captured information including quality of evidence; study demographics; risk of bias (guided by the University of Pennsylvania's Modified Newcastle-Ottawa Risk of Bias tool); prevalence and severity of alexithymia; disease burden; psychosocial comorbidities and treatment success in patient and control groups, reported as proportions; mean difference; odds ratio; and risk ratio [27]. Concordance was assessed and discrepancies were resolved through consensus.

Results

Thirty-seven studies met inclusion criteria for this review (Fig. 1). Across the 37 studies, the following conditions were addressed: psoriasis (15), alopecia (8), atopic dermatitis (2), vitiligo (2), chronic urticaria (CU) (5), acne vulgaris (2), hidradenitis suppurativa (2), seborrheic dermatitis (SD) (1), skin-restricted lupus (SRL) (2), trichotil-

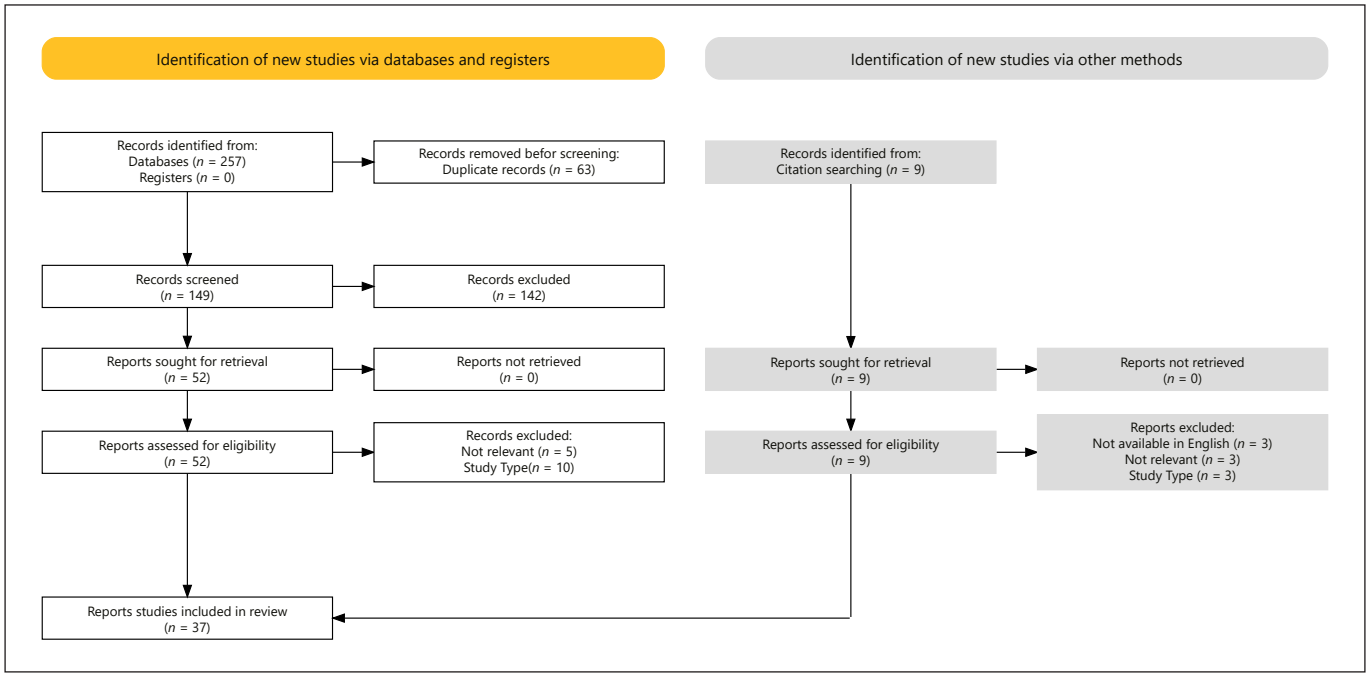

Fig. 1. PRISMA flow diagram of selection of publications included in this review [30].

lomania (TTM) (1), and primary focal hyperhidrosis (PFH) (1) (online suppl. Table 1; for all online suppl. material , see www.karger.com/doi/10.1159/000524736). Two studies explored alexithymia in cohorts with a variety of dermatologic conditions but did not report findings by condition [28, 29].

Psoriasis

Fifteen studies, involving a total of 3,434 people, consistently showed an increased prevalence of alexithymia in patients compared to controls. A minority of smaller studies, some using assessments other than the TAS-20 questionnaire, reported a 5–29.4% prevalence of clinically significant alexithymia in patients [31, 32]. Studies consistently using the TAS-20 questionnaire (86.7%) and accounting for 3,132 patients suggested the prevalence of clinically significant alexithymia in patients to be higher, between 36.2% and 67.7% [33–40].

Age, geographic location, disease duration, and severity did not appear to influence prevalence or severity of alexithymia; but, alexithymic patients were reported to experience a higher burden of psoriasis (PASI >10) compared to non-alexithymic patients [33, 36, 39–41]. Involvement of sensitive areas (hands, face, neck, and/or genitals), lower education level, unemployment, and higher body mass index (BMI) were positively associated with alexithymia [33, 35, 36, 38, 40]. While a majority of studies found the TAS-20 total score not to be significantly influenced by gender [33, 36, 39, 41], one study of 250 patients reported a positive association between logistical regression of alexithymia and female sex (male to female odds ratio: 0.21) [40].

Regarding psychosocial comorbidity, alexithymic psoriasis patients may have greater prevalence of depression, anxiety, and alcohol misuse compared to non-alexithymic patients [38, 39, 41–43]. A cyclic relationship between alexithymia and mental illness may exist. One study showed alexithymia accounting for a 7–12% and 7–14% variance in anxiety and depression among psoriasis patients, respectively [43], and others showed anxiety and depression accounting for a 9% and 4% variance in alexithymia, respectively [39, 42]. However, a different study's logistical regression model did not find prevalence and severity of alexithymia to explain variance in mental health [38]. Across studies, alexithymic psoriasis patients were found to have significantly decreased quality of life compared to non-alexithymic patients as well as increased worry and work productivity loss [32, 33, 41, 43]. Data also showed that alexithymic patients may demonstrate more interpersonal sensitivity, phobic anxiety, and register higher scores on measures of family dysfunction [34, 39, 43].

Moreover, alexithymic patients appeared to have poorer self-management of disease, inferior illness perception, increased somatization, and higher illness frequency compared to non-alexithymic patients [33, 35, 39]. Additionally, alexithymic patients were found to register lower scores on the Health Education Impact Questionnaire (heiQ), particularly, "self-monitoring and insight" and "skill and technique acquisition" [35].

Alopecia Areata

The prevalence of clinically significant alexithymia in AA patients reached up to 46.7% [44–46]. While most studies reported that AA patients have higher prevalence and severity of alexithymia in AA [34, 44, 47], one study did not [45]. Disease severity and gender were not associated with alexithymia [44, 45]. Education level may be associated with the severity of alexithymia as one study reported education and total TAS-20 scores as inversely related [44], and another did not [45]. While no significant difference in the prevalence of depression was observed between patients with and without alexithymia, a significant difference in prevalence and severity of anxiety does seem to exist [45, 48]. Further, anxiety accounted for a 14% variance in alexithymia [45]. Going beyond, alexithymic AA patients may have a more critical attitude towards their bodies [46]. No correlations were reported between TAS-20 total scores and a number of traumatic events nor childhood neglect; though, a positive correlation between TAS-20 total scores and family dysfunction was identified ($r = 0.63$) [34, 44].

Androgenic Alopecia

The reported prevalence of clinically significant alexithymia in androgenic alopecia (AGA) patients, 23.5%, was not significantly different from the prevalence in healthy controls [49]. AGA severity did not appear to influence total TAS-20 scores; however, female AGA patients scored significantly worse on TAS-20 subscales DIF and externally oriented cognitive style than male AGA patients [49]. While data suggested that alexithymia may be negatively associated with problem-focused coping strategies (alexithymia to control odds ratio: 0.48) and positively associated with avoidant coping strategies (alexithymia to control odds ratio: 4.12), alexithymia appeared to only modify coping strategies in female patients [49].

Primary Focal Hyperhidrosis

One study reported a 45.7% prevalence of clinically significant alexithymia in PFH patients [50]. Compared to healthy controls, PFH patients scored significantly higher on DIF, DDF, and total TAS-20 [50].

Atopic Dermatitis

Studies revealed a greater prevalence of clinically significant alexithymia in patients with AD compared to controls, up to 66.7% [34, 51]. Further, data suggest disease severity may predict alexithymia severity: for every one-point increase in Eczema Area and Severity Index (EASI), patients had a 9% enhanced likelihood of having a higher TAS-20 total score and an 11% increase in likelihood of having a clinically significant TAS-20 total score [51]. In terms of alexithymia's psychosocial implications in AD patients, a correlation between TAS-20 total score and greater family dysfunction was reported [34].

Chronic Urticaria

The prevalence of clinically significant alexithymia in CU patients was reported to be as high as 76.4% [52]. Across four studies involving 377 patients, CU patients had significantly higher TAS total scores than healthy controls [52–54]. Alexithymia did not appear to be influenced by disease severity or duration but was influenced by gender with greater TAS-20 scores in female CU patients, compared to male CU patients [52, 54, 55]. Regarding psychosocial comorbidity, alexithymia levels correlated with depression, anxiety, hostility, somatization, worse Global Severity Index (GSI) scores as well as anxious and avoidant attachment styles [52, 53]. Additionally, alexithymic patients were reported to display less extroversion and openness and more neuroticism, obsessive-compulsion, paranoid ideation as well as repression and defensiveness [52, 55].

With regard to anxiety, one study investigated 158 alexithymic CU patients with concurrent anxiety disorders: generalized anxiety disorder (GAD), social phobia, and panic disorders. Panic disorders did not appear to exacerbate alexithymia, but GAD and social phobia did [54]. Female alexithymic CU patients with GAD had the highest total TAS-20 scores [54]. Additionally, a significant association between PTSD symptoms and alexithymia was reported [55]. An inverse relationship of alexithymia with quality of life, physical functioning, mental health, vitality, and general health perception was reported [52].

Vitiligo

A prevalence of clinically significant alexithymia of up to 65.4% in patients was reported [56]. A case-control study involving 52 patients did not find a significant dif-

ference in prevalence between patients and controls, but a cross-sectional study involving 30 patients did [47, 56]. In both studies, patients had significantly higher total TAS-20 scores than controls [47, 56].

Hidradenitis Suppurativa

Two studies, involving 176 patients in total, revealed a greater prevalence of clinically significant alexithymia in patients, up to 61.6% [57, 58]. While no association between TAS-20 total score and disease severity was observed, women were more likely than men to be alexithymic [57, 58]. Of hidradenitis suppurativa patients suffering from psychological distress, 78% had clinically significant alexithymia [58]. Further, alexithymic patients scored worse on measures of quality of life [58].

Acne Vulgaris

Two studies, involving 141 total patients, showed a prevalence of alexithymia as high as 54.9%; however, no significant differences in severity or prevalence between patients and controls were found, suggesting that an association between alexithymia and acne vulgaris may not exist [47, 59]. Further, no association was shown between alexithymia, age, gender, education level, income, disease severity, or duration [59].

Seborrheic Dermatitis

One study observed a 44.4% prevalence of clinically significant alexithymia in SD patients, which was not significantly different from healthy controls. Patients with SD were more likely to suffer from anxiety, and patients with higher levels of anxiety had higher levels of alexithymia [60]. Disease severity, duration, and gender did not appear to influence alexithymia severity [60].

Skin-Restricted Lupus

While prevalence data for clinically significant alexithymia in SRL patients do not exist, data showed that, compared to healthy controls, patients with SRL had greater TAS-20 total scores [61]. While disease severity did not seem to influence the TAS-20 total score, disease duration did [62]. Patient's TAS-20 total scores appeared to be positively associated with concurrent personality disorders (defined by the Personality Diagnostic Questionnaire 4+) and psychiatric disorders (anxiety, depression, alcoholism, and suicide risk) and negatively associated with emotional awareness [61, 62]. Concurrent personality disorder affected TAS-20 total score most significantly at 2.5 years of follow-up ($r = 4.40$) [61].

Trichotillomania

A single study involving 105 TTM patients showed a 39% prevalence of clinically significant alexithymia. DIF appeared to significantly predict TTM severity [63].

Alexithymia and Treatment of Skin Disease

Despite the reported hindrance in self-management in alexithymic psoriasis patients, studies suggested alexithymic psoriasis patients may be receptive to treatment, showing improvement in disease and psychosocial comorbidities [64]. In fact, a multi-center study following 543 patients throughout a 1-year treatment period revealed: (1) alexithymia may be reversible with disease control and (2) reversion of alexithymia was associated with improvement in measures of disease severity, psychological comorbidities, work productivity, and quality of life [64]. For patients with AA, cognitive behavioral therapy (but not hypnosis) was associated with a paradoxical increase in total TAS-20 score [49, 65]. Another study of 21 AA patients suggested that completion of ten individual hypnosis sessions led to significant improvement in alexithymia, anxiety, depression, and mental well-being with effects persisting 6 months after completion [65]. No studies included in this review reported data on alexithymia and treatment for diseases beyond psoriasis and AA.

Discussion

Data from September 1, 2008, onward corroborate significant associations between alexithymia and dermatologic disease. Consistent with prior data, the prevalence of alexithymia in patients with cutaneous disease (5–76.4%) is notably greater than alexithymia's prevalence in the general population (10%) (Fig. 2). In fact, many studies excluded patients with known psychiatric illness, and given the propensity for alexithymia to coexist with mental illness, likely underestimated the actual prevalence of alexithymia in dermatology patients.

Regarding the physiological mechanisms linking alexithymia to dermatologic disease, the "stress-alexithymia hypothesis" proposes that specific cognitive, behavioral, and physiological components of alexithymia may contribute to the pathogenesis of stress-related disorders, including dermatologic diseases [66]. According to this hypothesis, the combined effects of lacking emotional awareness as well as affective expression and verbalization (cognitive component) may result in ineffective and/or maladaptive coping attempts (behavioral component).

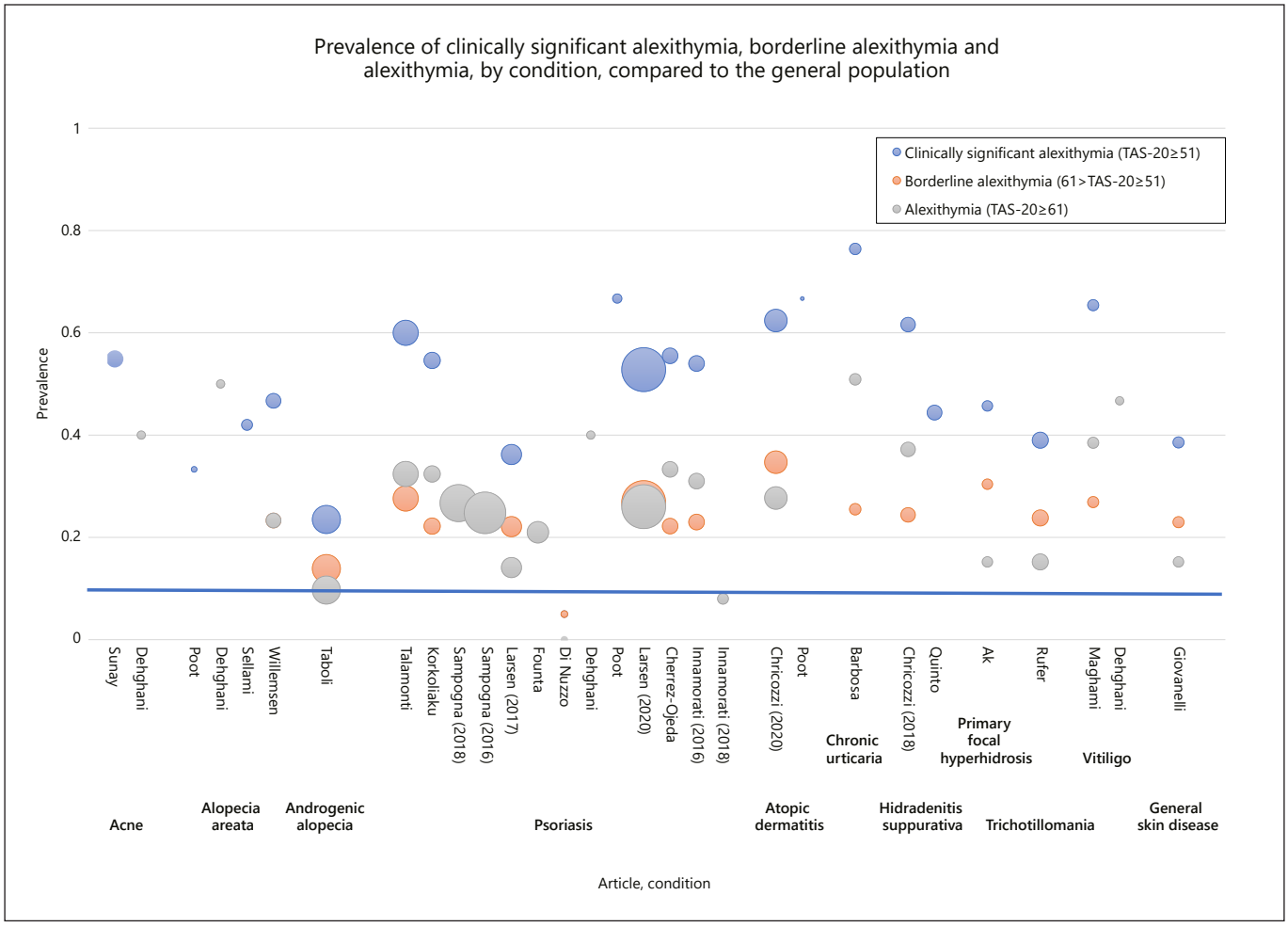

Fig. 2. Prevalence of clinically significant alexithymia and its subtypes, reported by condition with study size depicted by the size of the data point, as measured by TAS-20 questionnaire. The thick blue line serves as a reference for the prevalence of clinically significant alexithymia in the general population.

This, in turn, may lead to prolonged stress exposure, which exacerbates somato-visceral response (physiological component), thereby increasing disease susceptibility. A recent review of physiological markers of alexithymia concluded that most studies support the presence of decoupling between subjective and physiological reactivity in alexithymia as well as a tendency of alexithymic individuals to present with hyper-vigilance to threat and hyperarousal [67]. Moreover, the immune response in alexithymic individuals has been observed to be similar to individuals exposed to chronic stress, with increased production of glucocorticoids [68], predominance of depressed cell-mediated immunity, and a skewed Th1/Th2 ratio towards Th2 response [69] – factors associated with cutaneous disease.

In addition, perceived deficits in physical appearance associated with dermatologic disease can have significant emotional and social consequences – notably, the experience of shame, stigmatization, social exclusion, and loneliness [70]. Deficiency in discerning psychologic manifestations from physical symptoms may lead to additional inappropriate somato-visceral responses which further precipitate disease. Further, this impaired emotional self-awareness and regulation may also be linked to impaired self-management, possibly worsening disease duration and severity.

Beyond the prevalence of alexithymia in dermatologic patients, data continues to suggest that alexithymia bears influence on psychosocial comorbidities and treatment effects. This data considered begs the question of whether rec-

ognizing and addressing alexithymia may improve dermatologic care, specifically mitigating psychological comorbidities, improving quality of life, enhancing self-management, facilitating stronger patient-physician relationships, and curtailing inappropriate use of healthcare resources, as has been suggested in other specialities [4, 10, 71, 72].

Psychodermatology is an emerging subspecialty within dermatology dedicated to elucidating the bidirectional mind-skin connection. The data reported in this review suggest that alexithymia may be an important entity linking the mind and skin and, further, an entity to be identified and addressed in the management of dermatologic diseases. While research for addressing alexithymia in dermatology patients is limited, interventions used in other specialties (including neurology, surgery, psychiatry, and oncology) indicate treatment success by means of group therapy [15]; journaling [73]; emotion labeling [74]; structured exercises [75]; psychoeducational and skills training [76]. Other themes in these specialties include: treatment outcomes that are not impeded by patients' level of alexithymia or degree of suffering [78], sustained decreases in TAS-20 scores, and improvement in medical conditions [77].

Limitations and Future Directions

A significant limitation of this review is the paucity of published data on the interplay of alexithymia and dermatologic disease. The sparsity of published literature precluded the completion of a meta-analysis as the small number of studies generates statistically underpowered results. This scarcity of published data is particularly worse in certain countries, notably the USA (online suppl. Table 1). To ensure its generalizability, studies of alexithymia and dermatology should be conducted in countries where it is currently understudied. Another limitation of this review is that a majority of the included studies are case-control and cross-sectional studies, which register low scores on the quality rating scale. This, paired with relatively small cohort sizes, require caution to be taken when drawing conclusions from these studies.

Future work in alexithymia and dermatology is necessary and should focus on the following: prevalence and severity of alexithymia across diseases; sociodemographic and clinical characteristics' influence on alexithymia; correlations between alexithymia and psychosocial comorbidities, such as depression, anxiety, and alcohol misuse. Further, randomized clinical trials should be pursued to investigate the utility of therapeutic approaches targeting alexithymia to improve disease outcomes and patients' quality of life.

Key Message

Identifying and addressing alexithymia in dermatology patients may improve treatment outcomes, associated comorbidities, and health-related quality of life.

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Conflict of Interest Statement

The authors report no conflicts of interest relevant to this study, including but not limited to, having affiliation(s) with any organizations with a direct or indirect financial interest in the subject matters discussed in this article.

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Author Contributions

Alexis Holmes, MD, contributed to the conception and design of the work, acquisition, analysis, and interpretation of data for the work, and drafting and revising of the submitted work. Pooja Marella, BA, contributed to the analysis and interpretation of data for this work as well as drafting and critically revising this work. Carlos Rodriguez, MS, contributed to the acquisition of data for this work as well as critically revising this work. Donald Glass II, MD, PhD, contributed to the conception and design of the work and critically revised it. Katharina S. Goerlich, PhD, contributed to the conception and design of the work, interpretation of data for the work, and drafting and revising of the submitted work. All authors gave final approval for this work.

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