

# Prevalence and Severity of Dermatological Condition-Associated Skin Pain in the Chinese

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**Background/Aim:** Although the characteristics of cutaneous sensory symptoms in the general population have been documented, dermatological condition-associated skin pain has not been characterized yet. In the present study, we aimed to characterize dermatological condition-associated skin pain in the Chinese.

**Subjects and Methods:** A questionnaire was given to outpatients to identify self-proclaimed skin pain at our dermatology clinic. The severity of skin pain was assessed using pain scale 0–10. Prevalence and pain severity were compared between males and females.

**Results:** A total of 2144 patients, including 1254 females and 890 males aged 13–94 years, were included in this study. The overall prevalence of skin pain was 9.93% in this cohort. The prevalence of skin pain varied greatly with dermatological conditions ( $p < 0.0001$ ). Moreover, a higher prevalence of skin pain was observed in males than in females ( $p < 0.05$ ). Among the dermatological conditions reported, higher skin pain scales were found in subjects with either glucocorticoid-induced dermatitis ( $4.20 \pm 0.73$ ) or herpes zoster ( $4.00 \pm 0.29$ ). While the overall pain scales were comparable between males and females ( $2.38 \pm 0.13$  versus  $2.68 \pm 0.13$ ), pain scales in patients with eczematous dermatitis were higher in females than in males ( $p < 0.05$ ). Furthermore, pain scales correlated positively with age. However, pain scales did not differ between subjects with versus without a family history of cutaneous sensory symptoms. These results demonstrate that the prevalence and severity of dermatological condition-associated skin pain vary with dermatological conditions and gender in the Chinese.

**Conclusion:** Patients with some dermatological conditions may experience skin pain. Although the pain is moderate, it can negatively impact the quality of patients' lives. Alleviation of skin pain should be considered when treating patients with certain dermatological conditions.

**Keywords:** skin disorders, skin pain, gender, prevalence

## Introduction

Subjects with dermatological conditions can experience skin pain. Prior studies have shown that 20% of patients with skin sensory symptoms display characteristics of neuropathic pain<sup>1</sup> and that over 40% of psoriatic patients also suffer from skin pain.<sup>2–4</sup> Likewise, a substantial number of patients with atopic dermatitis experience skin pain with a pain intensity score as high as  $>7$ , evaluated using a pain scale 0 to 10.<sup>5,6</sup> Vakharia et al<sup>7</sup> reported that 14% of patients with atopic dermatitis had severe or very severe skin pain. Patients with rosacea displayed an overall reduction in heat pain sensitivity by 10% in comparison to those without rosacea or under normal healthy

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skin conditions.<sup>8</sup> Moreover, involved area of rosacea displayed an over 10% reduction in heat pain threshold in comparison to either uninvolved areas or normal healthy controls.<sup>8</sup> These patients can experience skin pain upon exposure to heat. Furthermore, over 30% of patients with hidradenitis suppurativa proclaimed skin pain.<sup>9</sup> Although evidence indicates that the prevalence of some dermatological condition-associated skin pain is high, reports are sporadic. In addition, characteristics of dermatological condition-associated skin pain in most dermatological conditions are still poorly understood. In the present study, we characterize skin pain in a large cohort of Chinese patients with a variety of dermatological conditions.

Materials and Methods

Study Subjects

All participants were diagnosed with skin disorder(s) at an outpatient clinic at the Dermatology Hospital, a tertiary hospital located in Guangzhou city, Guangdong province, China. A questionnaire (Supplemental Table 1) was given to participants who visited the clinic to self-report skin pain. Participants also scored the severity of skin pain scale 0 to 10. A designated nurse collected the questionnaire upon its completion onsite. This work was approved by the institutional review board of the Dermatology Hospital of Southern Medical University, and carried out in accordance with the Declaration of Helsinki. Written informed consent was obtained from either participants or participants’ parent if participants were under age of 18 years. This study was conducted between March and May.

Data Analysis

Common skin disorders were individually analyzed. Subjects with either multiple skin disorders or a skin disorder which was found in <10 patients were pooled together as “others”. GraphPad Prism 5 software was used for all statistical analyses. Chi-square test or unpaired *t*-test was used to determine significance. Data are expressed as either mean ± SEM or %.

Results

A total of 2144 subjects, including 890 males and 1254 females aged 13–94 years, were included in the analyses. The ages of males and females were comparable. Only 8% of subjects considered their skin to be dry skin, while a larger portion (69%) of subjects considered their skin to be normal. More males than females reported oily skin (28% vs 20%, *p*<0.0001), whereas more females than males exhibited normal skin type (71% vs 65%, *p*=0.0007). The majority of these subjects (93%) declared no family history of cutaneous sensory symptoms. The demographic characteristics of the participants are detailed in Table 1.

Prevalence of Skin Pain Varies with Skin Disorders and Gender

We first analyzed whether the prevalence of self-reported skin pain varies with dermatological disorders. As seen in Table 2, prevalence of skin pain varied greatly with skin disorders in both males and females (Chi-square=63.40 for males and Chi-square=94.06 for females, *p*<0.0001 for both males and females). The overall prevalence of skin pain in this cohort was 9.93%. A higher prevalence was observed in males than in females (11.69% versus 8.69%, *p*<0.05). Moreover, the prevalence of skin pain did not differ significantly among dry, oily, and normal skin (Chi-square=5.448, *p*=0.0656). Taken together, these results indicate that the prevalence of skin pain varies with dermatological condition and gender.

Association of the Severity of Skin Pain with Skin Disorders

We next analyzed the severity of skin pain in skin disorders. The overall pain scales in the entire cohort were 2.53 ± 0.09 (95% CI 2.349–2.712). Males and females displayed comparable overall pain scales (2.38 ± 0.13, 95% CI 2.119–2.631 versus 2.68 ± 0.13, 95% CI 2.421–2.937). However, pain scales in patients with eczematous dermatitis were higher in females than in males (*p*<0.05) (Table 3). A higher pain scale was found in subjects with either Glucocorticoid-induced

Table 1 Demographic Characteristics of Subjects

Gender	N	Age [Mean ± SEM (Range, 95% CI)]	Skin Type [N (%)]			Family History of Cutaneous Sensory Symptoms [N (%)]
			Normal	Dry	Oily	
Females	1254	33.46 ± 0.43 (13–92, 32.61–34.31)	898 (71)	104 (9)	252 (20)	96 (8)
Males	890	34.21 ± 0.63 (13–94, 32.97–35.44)	575 (65)	65 (7)	250 (28)	49 (6)
Total	2144	33.77 ± 0.36 (13–94, 33.06–34.48)	1473 (69)	169 (8)	502 (23)	145 (7)

**Table 2** Prevalence of Skin Pain in Males and Females (Mean  $\pm$  SEM)

Dermatoses	Males (N=890)	Females (N=1254)	Total
Acne	27/171 (15.78%)	23/201 (11.44%)	50/378 (13.23%)
Alopecia Areata	0/6 (0)	0/10 (0)	0/16 (0)
Atopic Dermatitis (AD)	0/8 (0)	0/14 (0)	0/22 (0)
Dermatitis Aestivale	0/9 (0)	0/11 (0)	0/20 (0)
Eczematous Dermatitis (excluding AD)	19/133 (14.29%)	26/207 (12.56%)	45/340 (13.24%)
Folliculitis	3/33 (9.09%)	3/42 (7.14%)	6/75 (8%)
Glucocorticoid-induced Dermatitis	0/2 (0)	5/77 (6.49%)	5/79 (6.33%)
Herpes Zoster	9/13 (69.23%)	9/13 (69.23%)	18/26 (69.23%)
Malassezia folliculitis	4/26 (15.38%)	1/19 (5.26%)	5/45 (11.11%)
Neurodermatitis	1/11 (9.09%)	1/4 (25%)	2/15 (13.33%)
Pityriasis Versicolor	0/4 (0)	0/6 (0)	0/10 (0)
Prurigo	2/16 (12.5%)	0/4 (0)	2/20 (10%)
Pruritus	0/3 (0)	0/8 (0)	0/11 (0)
Psoriasis	0/19 (0)	1/17 (5.88%)	1/36 (2.78%)
Rosacea	0/1 (0)	0/5 (0)	0/6 (0)
Scabies	2/23 (8.70%)	0/7 (0)	2/30 (6.67%)
Seborrheic Dermatitis	2/17 (85%)	2/49 (4.08%)	4/66 (6.06%)
Tinea	5/71 (7.04%)	6/72 (8.33%)	11/143 (7.69%)
Urticaria Papulosa	0/6 (0)	0/14 (0)	0/20 (0)
Urticaria	2/96 (2.08%)	1/195 (0.52%)	3/291 (1.03%)
Verruca Vulgaris	1/13 (7.69%)	2/19 (10.53%)	3/32 (9.38%)
Vitiligo	0/3 (0)	0/15 (0)	0/18 (0)
Others**	27/203 (13.30%)	29/244 (11.89%)	56/447 (12.53%)
Overall	104/890 (11.69%)*	109/1254 (8.69%)	213/2144 (9.93%)

**Notes:** \* $p=0.0271$  versus females, Two-sided Chi-square. \*\*Others included patients with  $\geq 2$  skin disorders, or syphilis, pityriasis rosea, palmoplantar keratoderma, keloid, genital herpes, lichen planus, axillary osmidrosis, basal cell carcinoma, etc.

Dermatitis (pain scale= $4.20 \pm 0.73$ , 95% CI 2.160–6.240) or herpes zoster (pain scale= $4.00 \pm 0.29$ , 95% CI 3.385–4.615). However, pain scales were no differences between subjects with and without a family history of cutaneous sensory symptoms ( $2.74 \pm 0.32$  versus  $2.51 \pm 0.10$ , 95% CI  $-0.4567$  to  $0.9244$ ). Interestingly, pain scales positively correlated with age (Pearson  $r=0.1714$ ,  $p=0.0122$ ). Collectively, these results demonstrate that severity of skin pain varies with dermatological condition and age.

## Discussion

Previous studies have shown that subjects with certain dermatological conditions, including psoriasis, atopic dermatitis and sensitive skin, experience skin pain.<sup>1–8</sup> The present study shows that a variety of other dermatological conditions are associated with skin pain, with an overall prevalence of 10%. Besides herpes zoster, which exhibits neuralgia because of damage to the nerve, a higher prevalence of skin pain was found in subjects with inflammatory dermatoses, such as acne and eczematous dermatitis. The underlying mechanism that causes skin pain in

dermatological conditions can be attributed to increased cytokines in the skin, primarily in the upper dermis.<sup>10</sup> Both eczematous dermatitis and acne display elevated levels of pro-inflammatory cytokines in the skin.<sup>11,12</sup> It is well known that the activation of the receptors in the primary afferent fibers is required for the sensation of pain. There are two types of afferent fibers in the skin, ie, unmyelinated C-fiber and myelinated A $\delta$ -fiber, which nociceptors can be activated by noxious stimuli.<sup>13</sup> Previous studies have demonstrated that TNF $\alpha$  can activate cAMP-dependent protein kinase and nociceptive neurons, resulting in a sensation of pain.<sup>14,15</sup> Moreover, TNF $\alpha$  can reduce the threshold of C fibers, resulting in an increased sensitivity to stimuli.<sup>16</sup> Other cytokines, such as IL-1 $\beta$ , IL-6 and IL-13, also play an important pathogenic role in the development of pain.<sup>16</sup> Furthermore, inflammatory skin disorders, such as acne, eczema, and psoriasis, are often accompanied by an increase in mast cells.<sup>17–19</sup> Mast cells can release algogenic substances, such as substance P and histamine, which can activate pruriceptors and nociceptors, leading to the transmission of nerve impulses by both

**Table 3** Pain Scales in Males and Females (Mean  $\pm$  SEM)

Dermatoses	Pain Scales in Males	Pain Scales in Females	Total (95% CI)
Acne	2.15 $\pm$ 0.25	2.35 $\pm$ 0.20	2.24 $\pm$ 0.16 (1.912–2.568)
Eczematous dermatitis	2.05 $\pm$ 0.21*	2.81 $\pm$ 0.30	2.49 $\pm$ 0.20 (2.081–2.897)
Folliculitis	2.67 $\pm$ 0.67	2.00 $\pm$ 0	2.33 $\pm$ 0.33 (1.476–3.190)
Glucocorticoid-induced dermatitis	0	4.20 $\pm$ 0.73	4.20 $\pm$ 0.73 (2.160–6.240)
Herpes zoster	4.33 $\pm$ 0.44	3.67 $\pm$ 0.37	4.00 $\pm$ 0.29 (3.385–4.615)
Malassezia folliculitis	1.75 $\pm$ 0.25	1.00 $\pm$ 0	1.60 $\pm$ 0.24 (0.9199–2.280)
Neurodermatitis	1.00 $\pm$ 0	1.00 $\pm$ 0	1.00 $\pm$ 0 (1.000–1.000)
Prurigo	1.50 $\pm$ 0.50	0	1.50 $\pm$ 0.50 (–4.853–7.853)
Psoriasis	0	2.00 $\pm$ 0	2.00 $\pm$ 0 (0–0)
Scabies	2.50 $\pm$ 1.50	0	2.50 $\pm$ 1.50 (–16.56–21.56)
Seborrheic dermatitis	1.00 $\pm$ 0	4.00 $\pm$ 1.00	2.50 $\pm$ 0.96 (–0.547–5.547)
Tinea	1.60 $\pm$ 0.24	2.83 $\pm$ 0.75	2.27 $\pm$ 0.45 (1.272–3.273)
Urticaria	2.00 $\pm$ 1.00	1.00 $\pm$ 0	1.67 $\pm$ 0.67 (–1.202–4.535)
Verruca vulgaris	1.00 $\pm$ 0	2.50 $\pm$ 0.50	2.00 $\pm$ 0.58 (–0.4841–4.484)
Others	2.59 $\pm$ 0.25	2.41 $\pm$ 0.22	2.50 $\pm$ 0.16 (2.173–2.827)
Overall	2.38 $\pm$ 0.13	2.68 $\pm$ 0.13	2.53 $\pm$ 0.09 (2.349–2.712)

Notes: \* $p < 0.05$  versus females. Unpaired t-test with Welch's correction.

unmyelinated C-fiber and myelinated A $\delta$ -fiber to the brain, where itch and pain sensation are generated.<sup>18</sup> Additionally, tryptase and SP released by mast cells can activate nociceptors on the nerve endings, resulting in the release of neuropeptides, and consequently leading to neurogenic inflammation and neurogenic pain.<sup>20</sup> Hence, subjects with inflammatory dermatoses display higher prevalence of skin pain.

In contrast to previous studies, it is worth noting that in the present study, a high prevalence of skin pain was not found in patients with either psoriasis or atopic dermatitis.<sup>2–6</sup> These discrepant results may be due to the differences in ethnicities and the environment, both of which can influence skin sensitivity.<sup>21–23</sup> Our study was carried out between March and May, during which the average atmospheric humidity and temperature were 83% and 21°C, respectively. Generally, psoriasis remits under environmental conditions of high humidity and/or exposure to high dose of UV irradiation.<sup>24,25</sup> Thus, the prevalence of skin pain associated with psoriasis and atopic dermatitis was lower in the present study. Moreover, the limited number of subjects (N=36 for psoriasis and N=22 for atopic dermatitis) in the present study can also render difficult to draw a solid conclusion of the prevalence of skin pain in these dermatological conditions. Further study in a larger cohort is required to determine the prevalence of skin pain in these dermatological conditions.

Interestingly, in contrast to inflammatory skin disorders, which exhibit both inflammatory pain and itch

primarily mediated by cytokines, some dermatological conditions with neural itch, such as cholestatic pruritus, display itch and analgesia via activation of G-protein-coupled bile acid receptor (TGR5). These proteins are expressed on the small diameter neurons of the dorsal root ganglia that transmit both itch and pain signals from the skin.<sup>26</sup> Activation of TGR5 with its ligand can induce itch and analgesia in mice.<sup>27</sup> In addition to the stimuli and mediators at the skin site, the neurons in the spinal cord also determine the sensation of itch and pain. In the laminae I and II of the spinal cord, there are excitatory interneurons expressing gastrin releasing peptide receptor (GRPR neurons), which can receive inputs from both A $\delta$  and C fibers.<sup>28</sup> These GRPR neurons only transmit itch signals, but not pain signals.<sup>29</sup> For example, mice with GRPR deficiency display less itching in comparison to the wild type mice.<sup>30</sup> By contrast, pain can inhibit GRPR neurons, resulting in a reduction in itch sensation.<sup>28</sup> Collectively, the pathogenesis of skin pain is complex, and varies with dermatological conditions.

In addition to well-known skin pain in herpes zoster, the present study also revealed various degrees of skin pain in other dermatoses, with an overall pain scale of 2.5. Although the pain is moderate, it can negatively impact the quality of patients' lives.<sup>31</sup> Because skin pain is associated with disease severity, alleviation of skin disorders could relieve pain,<sup>32</sup> leading to the improvement in the quality of patients' lives. Thus, appropriate treatments of these skin disorders can alleviate skin pain. Among the different types of medication,

glucocorticoids are the most commonly used in the treatments of inflammatory skin disorders, but it should be aware that glucocorticoids can cause skin pain, too. Studies have shown that either topical or systemic administrations of glucocorticoids can cause severe damage to epidermal function, including reductions in antimicrobial peptides and defective permeability barrier homeostasis, although glucocorticoids can also effectively inhibit cutaneous inflammation.<sup>33,34</sup> Compromised epidermal function predisposes to the development of infections and penetrations of substances into the skin. Hence, glucocorticoids should not be used for the long term. In contrast, safe emollients can benefit dermatological condition-associated skin pain because emollients can inhibit and prevent cutaneous inflammation, possibly via improvements in stratum corneum hydration and permeability barrier.<sup>35–37</sup> Moreover, some dermatological conditions, such as eczematous dermatitis and acne, display defective permeability barrier while compromised permeability barrier is linked to skin pain,<sup>38</sup> further suggesting the potential benefit of topical emollients for skin pain associated with, at least some, dermatological conditions. Finally, topical emollients can improve skin sensitivity. A considerable number of subjects with some dermatological conditions, including acne, psoriasis, and eczematous dermatitis, display sensitive skin,<sup>39,40</sup> which is possibly caused by small nerve fiber neuropathy.<sup>41</sup> Therefore, topical emollient could be a valuable regimen in the management of skin pain associated with some dermatological conditions. However, emollients can also induce adverse cutaneous reactions, including irritant and allergic reactions,<sup>42,43</sup> which is possibly attributable to some of the ingredients in emollients, especially at a high concentration. For example, Jojoba oil, which contains eicosadienoic acid, can increase the production of prostaglandin E2 and tumor necrotic factor- $\alpha$ , which both are pro-inflammatory mediators.<sup>44</sup> Similarly, stearic acid, cetear-eth 20, PEG-40 castor oil, and PEG-100 stearate can also induce inflammation.<sup>45,46</sup> Inflammation is linked to skin pain associated with some dermatological conditions. Thus, product safety should be considered when choosing emollients.

## Conclusions

Although the present study did not compare the skin pain between dermatosis-free normal subjects and subjects with skin disorders, it clearly demonstrates that both the prevalence and severity of skin pain vary with gender and dermatological conditions in the Chinese. Though dermatosis-associated skin pain is moderate, it can negatively impact the quality of

patients' lives. Management of skin pain should be considered in the treatments of subjects with skin disorders.

## Data Sharing Statement

Data are available upon request.

## Disclosure

The authors report no conflicts of interest in this work.

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