Hand eczema: from pathogenesis to novel treatments

Voorberg, Angelique Nadine

DOI:
10.33612/diss.626427608

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2023

Link to publication in University of Groningen/UMCG research database

Citation for published version (APA):

Copyright
Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

The publication may also be distributed here under the terms of Article 25fa of the Dutch Copyright Act, indicated by the “Taverne” license. More information can be found on the University of Groningen website: https://www.rug.nl/library/open-access/self-archiving-pure/taverne-amendment.

Take-down policy
If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Downloaded from the University of Groningen/UMCG research database (Pure): http://www.rug.nl/research/portal. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.
General introduction
INTRODUCTION

Every day people use their hands for daily tasks, from delicate actions such as writing to heavy tasks such as cleaning, but the hands are also one of the most important assets when it comes to communicating with the world around us. Talking with your hands helps you to express and give your words visual aid. When we look at manners of greeting around the globe, the handshake is the most commonly used type. Depictions and descriptions of this gesture date back to Ancient Greece, where shaking one’s right hand (dexiosis, δεξίωσις) was used to show respect and equality among the involved parties.

During the COVID-19 pandemic, shaking hands had to be avoided to minimize the risk of spreading the virus. The pandemic also showcased the importance of an intact skin barrier of our hands. Due to frequent hand washing with detergents such as soap and the use of disinfectants needed to minimize the risk of spreading virus particles, many people experienced an interruption of the integrity of their skin barrier. This led to an increase in the number of people with hand eczema, a painful and pruritic common skin disease, which can have a tremendous impact on everyday life and socio-economic consequences such as work incapacity.

The main topic of this thesis is hand eczema, and this general introduction gives a concise overview of the epidemiology, pathogenesis and treatment of hand eczema. All of the studies in this thesis are performed within the ‘Expert Center for Eczematous and Occupational Dermatoses’ at the department of Dermatology, University Medical Center Groningen, in Groningen, the Netherlands.

EPIDEMIOLOGY

Hand eczema is the most common skin disease of the hands, with a pooled lifetime prevalence of 15% (ranging from 3% to 31%)4, and is one of the most prevalent occupational diseases.5.6 Remarkably, most hand eczema prevalence studies have been conducted in Scandinavian countries.4,7-10 In persons with atopic dermatitis, the chance of developing hand eczema is higher. In the Dutch general population, a hand eczema prevalence up to 28.4% was found among subjects with atopic dermatitis.11 Although the prevalence of hand eczema in the general population has been investigated extensively, data on the proportion of individuals with chronic hand eczema in the general population has not been reported previously. Furthermore, data on the severity of hand eczema in the general population is scarce.
Chronic hand eczema, especially when it is severe, can have a high impact on a patient’s life, including a substantial decrease in quality of life. In a systematic review, it was found that more severe and occupational hand eczema in particular results in a high socio-economic burden. In another paper, it was reported that hand eczema related healthcare costs might be underestimated due to a high prevalence of presenteeism among patients with hand eczema; presenteeism refers to the phenomenon of individuals continuing to work even though even though a disease heavily influences their productivity. Furthermore, in a cross-sectional study among patients with vesicular hand eczema, it was found that more severe hand eczema is associated with higher impairment in health-related quality of life, based on the Quality Of Life in Hand Eczema Questionnaire (QOLHEQ).

PATHOGENESIS

Several risk factors have been identified for developing the skin disorder, such as wet work, having a contact allergy and being female. However, the relationship between the female gender and a higher prevalence of hand eczema has been discussed multiple times, since inclusion of the covariate ‘wet work’ eliminates the difference between the sexes and the prevalence of hand eczema. This suggests that the sex difference is most likely caused by environmental and other exogenous factors, such as caring for young children. Most studies that try to elucidate the pathogenesis of hand eczema are mainly epidemiological association studies and genetic studies linked to atopic dermatitis. This is obvious, since atopic dermatitis is an important risk factor for developing hand eczema. In a systematic review with meta-analysis by Ruff et al., studying the association between atopic dermatitis and hand eczema, the combined results from 26 studies revealed that patients with current atopic dermatitis or a history of atopic dermatitis had three to four times increased risk of developing hand eczema in the past year and in lifetime.

Especially loss-of-function mutations in the filaggrin gene (FLG) show a strong association with the development of hand eczema in patients with atopic dermatitis, and may be associated with a certain phenotype of hand eczema, characterized by erythematousquamous lesions on the dorsal aspects and hands (including the fingers) and both the dorsal and volar sides of the wrists. In a Swedish and a Danish population-based cohort study no associations between FLG mutations and hand eczema without atopic dermatitis were found. However, in a prospective case-control study in India FLG mutations were found to be associated with hand eczema in patients without allergic contact dermatitis, irritant contact dermatitis or atopic dermatitis. Moreover, FLG mutations were found to be associated with more severe hand eczema. The conflicting evidence on the role of FLG mutations in hand eczema might be explained by genetic...
differences between ethnicities. In atopic dermatitis, most carriers of FLG mutations are of European ancestry, followed by people of Asian descent. These FLG mutations have not been found in atopic dermatitis patients of African descent.\textsuperscript{21} Contrastingly FLG2 mutations are associated with atopic dermatitis in patients of African descent, but are not associated in patients of European descent.\textsuperscript{22} So far, genetic differences in hand eczema between ethnicities, including differences in FLG mutations, have not been investigated yet.

Other studies point towards an unrecognized genetic risk factor of importance for the development of hand eczema.\textsuperscript{23,24} In a Danish dizygotic twin study, it was found that aggregation of hand eczema within these dizygotic twins can only be explained to a small extent by atopic dermatitis or contact allergies.\textsuperscript{21} Moreover, in the additional questionnaire study within the same Danish Twin Registry, it was found that genetic factors, independent of atopic dermatitis, are responsible for 41\% of the variability in developing hand eczema.\textsuperscript{24} Therefore, genetic factors might exist that are associated with the development of hand eczema, but not with the development of atopic dermatitis.

Within the etiological subtypes of hand eczema, we distinguish four different subtypes, namely allergic contact dermatitis, irritant contact dermatitis, atopic hand dermatitis and protein contact dermatitis/contact urticaria.\textsuperscript{25} Sometimes it is hard to establish a distinct etiological subtype and often, more than one etiological factor is present in a patient. \textbf{Figure 1} provides a graphical overview of the immune mechanisms in the pathogenesis of irritant contact dermatitis, allergic contact dermatitis and atopic hand dermatitis.

In allergic contact dermatitis, a type IV delayed hypersensitivity reaction after skin contact with a hapten occurs, consisting of two phases: the sensitization phase and the elicitation phase.\textsuperscript{26} In the sensitization phase, the keratinocytes release inflammatory cytokines including interleukin (IL)-1\(\alpha\), IL-1\(\beta\), IL-8, tumor necrosis factor (TNF)-\(\alpha\) and (granulocyte-macrophage colony-stimulating factor) GM-CSF (\textbf{Figure 1}).\textsuperscript{27,28} These cytokines activate the innate immune system, mainly Langerhans cells and leukocytes in the epidermis, upon repeated exposure to a contact allergen. The Langerhans cells capture the allergens and migrate to nearby lymph nodes, to present the antigen of the specific contact allergen to the still naïve and antigen specific T-cells. These antigen-specific T-cells bind to the antigen and start to recognize the hapten, leading to the proliferation and differentiation of these T-cells into memory T-cells. In the elicitation phase of allergic contact dermatitis, the sensitized T-cells initiate an inflammatory response including inflammatory cytokines and cellular infiltrate at the site of exposure. Specific immune polarization depends on the allergen. Some allergens, e.g. fragrance, initiate more of a T-helper cell (Th) 2/Th22 polarization instead of a mainly Th1/Th17 polarization, e.g. nickel sulphate.\textsuperscript{29}
Due to chronic skin barrier dysfunction and dysfunction of the skin microbiome, eosinophils. Th2 cells release IL-4, IL-5, and IL-13, which, through the JAK-STAT pathway, stimulate infiltration of neutrophils, macrophages, and histamines and inflammatory mediators by mast cells.

Th2 cells release IL-4 and IL-5, which, through the JAK-STAT pathway, stimulate IgE synthesis by B-cells, which potentiate release of Treg cells, allowing for more T-cells to be activated.

Th2 cells release IL-4 and IL-5, which, through the JAK-STAT pathway, stimulate IgE synthesis by B-cells, which potentiate release of Treg cells, allowing for more T-cells to be activated.

Th0 cells differentiate into Th2 cells via the JAK-STAT pathway under the influence of IL-4. JAK-STAT also suppresses Foxp3, which regulates Treg cells, allowing for more T-cells to be activated.

Th17 and Th22 release IL-17 and IL-22, which contribute to further barrier dysfunction.

Allergens/irritants/toxins are taken up by Langerhans cells, which present them to TH0, Th17, and Th22, among others. 3. Th17 and Th22 release IL-17 and IL-22, which contribute to further barrier dysfunction. 4. Th0 cells differentiate into Th2 cells via the JAK-STAT pathway under the influence of IL-4. JAK-STAT also suppresses Foxp3, which regulates Treg cells, allowing for more T-cells to be activated. 5. Th2 cells release IL-4 and IL-5, which, through the JAK-STAT pathway, stimulate IgE synthesis by B-cells, which potentiate release of histamines and inflammatory mediators by mast cells. 6. Th2 cells release IL-4, IL-5, and IL-13, which, through the JAK-STAT pathway, stimulate infiltration of neutrophils, macrophages, and eosinophils. 7. Th2 cells also release IL-4, which causes keratinocyte proliferation, and IL-31, which, with TLSP released from keratinocytes, results in pruritus. 8. Due to chronic skin barrier dysfunction and dysfunction of the skin microbiome, S. aureus colonization occurs.

**Figure 1.** Immune mechanisms in the pathogenesis of irritant contact dermatitis, allergic contact dermatitis and atopic hand dermatitis. Reprinted from Lee et al. (2019), with permission from Wiley.
In irritant contact dermatitis, the keratinocytes become damaged due to exposure to irritant factors. This results in the keratinocytes causing the release of IL-1α, IL-1β, IL-8, TNF-α and GM-CSF, which activate the innate immune system and keratinocyte proliferation (Figure 1). The activated leukocytes, including lymphocytes, neutrophils and macrophages, together with dendritic cells and mast cells, infiltrate the exposed skin site and release further inflammatory cytokines, resulting in further inflammation. Particularly conditions that cause a decreased state of the epidermal skin barrier can elevate the risk of irritant contact dermatitis, such as genetic factors (e.g. FLG mutations) or working in a high risk occupation for hand eczema.

The pathogenesis of atopic dermatitis is complex and not yet completely understood. An impaired skin barrier plays a key role in the pathogenesis, characterized by decreased lipids, increased trans-epidermal water loss and loss-of-function filaggrin gene (FLG) mutations. These loss-of-function FLG mutations cause the C-terminal part of profilaggrin to be absent, which is responsible for the initiation of the proteolytic process of profilaggrin to filaggrin units. Degradation of profilaggrin leads to a high level in free amino acids in the stratum corneum, which, combined with derived amino acids, minerals and sugars, form the natural moisturizing factor (NMF). Due to the presence of NMF, the stratum corneum is able to maintain hydration. Moreover, NMF might play a role in several biochemical events, such as barrier permeability and cutaneous antimicrobial defence. Furthermore, filaggrin has an important role in the aggregation of keratin filaments and it flattens the shape of keratinocytes. Therefore, deficiency of filaggrin causes a deteriorated epidermal skin barrier. The impairment of the epidermal barrier in atopic dermatitis enables irritant factors, toxins and allergens to easily penetrate the epidermis, which are captured by the Langerhans cells and presented to T-cells, including naïve T-cells, T-helper cells (Th) 17 and Th22 cells. Through the Janus Kinase-Signalling Transducer and Activator of Transcription proteins (JAK-STAT) pathway, the naïve T-cells differentiate into Th2 cells, releasing IL-4, IL-5 and IL-13. Release of IL-4/IL-5 results in elevated immunoglobulin E (IgE) levels by B-cell stimulation through the JAK-STAT pathway, and IL-4/IL-5/IL-13 release stimulates an influx of neutrophils, macrophages and eosinophils through the JAK-STAT pathway. Additionally, the release of IL-4 by Th2 cells results in keratinocyte hyperproliferation and release of IL-31. IL-31 is known as the 'itchy cytokine', as it stimulates eosinophil and mast cell production, activates sensory nerves, and increases the secretion of itch-mediating chemokines by keratinocytes, which leads to pruritus. IL-17, released by Th17 cells, is known to further reduce the expression of filaggrin and involucrin of the skin, resulting in further impairment of the skin barrier. The release of Th22 also contributes to the skin barrier disruption by inhibiting the terminal differentiation of keratinocytes. Besides the Th2, Th17 and Th22 pathways, chronic atopic dermatitis lesions are characterized by a mostly Th1-driven response, which, like Th2 cytokines, promotes IgE-mediated hypersensitivity.
More insight in the pathogenesis of hand eczema might result in new treatment strategies for hand eczema based on the involved pathways. Only a few studies have looked into the proteome and transcriptome of hand eczema. Molin et al. published cross-sectional data on the epidermal barrier proteome in six patients with chronic hand eczema, compared to six healthy controls. While this yields much information, this method incorporates all possible processes involved in chronic skin inflammation at the same time, making it difficult to draw conclusions on time sequence. A study by Kumari et al. reported on the expression level of several prespecified genes and proteins (Ki-67, various skin barrier genes and thymic stromal lymphopoietin (TSLP)) in chronic hand eczema. In this study, hyperproliferation of keratinocytes was found, as demonstrated by an increase of Ki-67 positive cells. Additionally, a downregulation of FLG, LOR and KRT10 was reported. The expression of barrier genes and proteins was normalized following treatment with alitretinoin. In this paper, RNA microarray was used to identify expression levels of the target genes. This technique has significant limitations, as it is based on previously ascertained knowledge of the genome. A method providing more direct insight into cell- and tissue-specific gene expression features is transcriptomics analysis, where gene expression is assessed by measuring the ribonucleic acid (RNA) transcripts in a cell. RNA-sequencing, gives a comprehensive view of the tissue-specific expression profile with a higher coverage than RNA microarray, without requiring a priori knowledge of the genome. This means that this technique grants the opportunity for broad discovery studies.

TREATMENT

An overview of treatment recommendations according to the most recent guidelines of the European Society of Contact Dermatitis (ESCD) can be found in Table 1. While mild hand eczema can be treated with topical corticosteroids or topical calcineurin inhibitors, the treatment for moderate to severe hand eczema remains challenging since systemic treatment options are scarce. In a study regarding the quality of life of patients with hand eczema, it was found that patients were the least satisfied with the ‘effectiveness’ of treatment, especially if patients had severe or very severe hand eczema, highlighting the need for new treatment options.

At the moment, alitretinoin is the only approved systemic treatment option for all clinical subtypes of severe chronic hand eczema. The ESCD guidelines recommend alitretinoin as treatment option for severe chronic hand eczema in patients with inadequate response to topical corticosteroids, although alitretinoin shows variable efficacy. Alitretinoin is studied in pharmaceutical sponsored randomized controlled trials of more than 1,600
participants. Treatment with alitretinoin 30 mg daily, during 12-24 weeks, resulted in clear or almost clear hand eczema in 48% of the participants, compared to 17% in placebo. Alitretinoin was primarily effective in the clinical subtype of hyperkeratotic hand eczema; 54% reached clearance or almost clearance on a Physician Global Assessment compared to 12% in the placebo group. However, in other clinical subtypes of hand eczema, alitretinoin was found to be less effective. For vesicular hand eczema, the least effectiveness was achieved; 33% compared to 16% in the placebo group.

Table 1. Treatment recommendations for hand eczema. Reprinted from Thyssen et al. (2022), with permission from Wiley.

<table>
<thead>
<tr>
<th>Severity</th>
<th>Standard therapy</th>
<th>Almost clear HE</th>
<th>Moderate HE</th>
<th>Severe or very severe HE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Recommend</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Emollients</td>
<td>Moderate topical corticosteroids</td>
<td>Moderate and potent topical corticosteroids</td>
<td>Moderate and potent topical corticosteroids</td>
<td>Alitretinoin</td>
</tr>
<tr>
<td>• Protective gloves</td>
<td>• Educational programs and instructions</td>
<td>• Avoidance of clinically relevant allergens</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| **Suggest** | | | |
| • Tacrolimus ointment | • Photo-therapy | • Cyclosporine A*1 |

| **May be considered** | | |
| • Methotrexate*2 | • Azathioprine*2 | • Acitretin*2, in hyperkeratotic hand eczema |

Severity is based on the photographic guide by Coenraads et al.
*1 Off-label systemic treatment, except for atopic hand eczema in some countries.
*2 Off-label systemic treatment for hand eczema.

Thus, patients with severe chronic hand eczema, who are refractory or intolerant to alitretinoin, have limited treatment options. Other off-label, treatment options, such as cyclosporine, may be effective, but long-term treatment can lead to serious adverse events including hypertension, nephrotoxicity, and risk of malignancy. Given the chronicity of hand eczema and the need for long term therapy, new treatment options are needed.

Currently, several novel treatment options are being investigated for the treatment of hand eczema. The most studied, potential novel treatment option for hand eczema, is the biological dupilumab. Dupilumab is a human monoclonal antibody, binding to the IL-4 receptor α chain, inhibiting IL-4 and IL-13, both type 2 inflammatory cytokines that mediate the pathogenesis of atopic dermatitis. It is, however, not licensed for the treatment of hand eczema. Several retrospective studies and case series have been published on the efficacy of dupilumab in patients with hand eczema, showing good response of hand eczema in patients with atopic hand eczema, but also in patients with non-atopic vesicular hand eczema and hyperkeratotic hand eczema.
Janus kinase (JAK) inhibitors are also a potential new treatment option for hand eczema. JAK-inhibitors target the JAK and Signal Transducer and Activator of Transcription (STAT) signalling pathway that modulates multiple cytokine pathways such as the interleukin (IL) 4, IL-13, IL-22 and IL-31 pathways. Hitherto, the effectiveness of the systemic JAK-inhibitors upadacitinib, gusacitinib and baricitinib on atopic and non-atopic hand eczema have been presented in small (case) studies, presentations at conferences and in press releases. The effect of the topical pan-JAK-inhibitor delgocitinib on mild-to-severe hand eczema has been recently published.

AIMS AND OUTLINE OF THIS THESIS

This thesis focuses on the pathogenesis and treatment of hand eczema. In Chapter 2, we investigate the prevalence and severity of (chronic) hand eczema in the Dutch general population with data from the Lifelines Cohort Study. Since studies on the pathogenesis of hand eczema are scarce, we analyse the transcriptome and proteome of lesional vesicular hand eczema in Chapter 3. Vesicular hand eczema, which can be present without any known etiological factors, is morphologically well characterized. It presents as a pruritic, frequent eruption of vesicles on the palms, palmar or lateral aspects of the digits. In this study, we take biopsies of lesional vesicular hand eczema skin and compare it to non-lesional vesicular hand eczema skin and healthy control skin.

We also focus on systemic treatments for moderate to very severe hand eczema. Alitretinoin is the only registered systemic treatment option, but it is less effective in hand eczema subtypes other than hyperkeratotic hand eczema. Therefore, in Chapter 4, we compare the treatments alitretinoin and azathioprine in an open-label, head-to-head study for the treatment of severe hand eczema. Chapter 5, Chapter 6, Chapter 7 and Chapter 8 focus on the biological dupilumab. In Chapter 5, we describe a retrospective cohort study in which we observe the effect of the biological dupilumab on hand eczema in a daily-practice cohort of 47 patients with atopic dermatitis over a period of 16 weeks. Chapter 6 is the long-term follow-up study, in which we investigate the 52-week effect of dupilumab on hand eczema in a cohort of 72 patients with atopic dermatitis, including its effect on hand eczema related quality of life. Additionally, in Chapter 7, we report the results of the 16-week randomized, placebo-controlled, double blind phase II trial in which we study the efficacy of dupilumab in severe to very severe hand eczema, in patients who do not respond to or do not tolerate treatment with alitretinoin. Then, in Chapter 8, we explore a case of dupilumab-related conjunctivitis, which is the most common adverse event in patients with atopic dermatitis receiving treatment with dupilumab. In dupilumab-related conjunctivitis, a reduction or complete depletion of conjunctival goblet cells is observed. Here, we investigate if there will be a recurrence of
these conjunctival goblet cells after discontinuation of dupilumab.

The main findings of this thesis, together with future perspectives on the pathogenesis and treatment of hand eczema, will be reviewed and discussed in Chapter 9.
REFERENCES


27. Leonard A, Cuttman-Yassky E. The unique


