9

SUMMARY, GENERAL DISCUSSION, AND FUTURE PERSPECTIVES

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SUMMARY, GENERAL DISCUSSION, AND FUTURE PERSPECTIVES

Hidradenitis suppurativa (HS) is a common, debilitating auto-inflammatory skin disease, characterized by inflamed nodules, abscesses and/or sinus tracts in the body folds. The exact aetiology and pathophysiologic sequence of events is unknown and a cure does not exist yet. Although there is a rapid rise in the number of publications about the multiple facets of HS there is still a lot to be learned about this unpleasant skin disease that was considered an orphan disease until recently. This thesis contributes to the epidemiological and clinical knowledge of HS.

Four main topics are covered in this thesis. First, the prevalence of HS in axial spondyloarthritis (SpA) and the prevalence of SpA features in HS patients were investigated and associated patient characteristics were determined. Interestingly, these two auto-inflammatory diseases share common denominators in pathogenesis and treatment. In the second part, the validation process of the refined Hurley classification for staging HS patients is described. In the third part, the identification of clinical patient categories within the HS disease spectrum is presented. Finally, the possible influence of mechanical stress as a risk factor for the development and maintenance of HS is discussed.

1. Hidradenitis suppurativa, beyond the surface of the skin

Chapter 2 and 3 contribute to the epidemiologic data on the concurrence of HS and SpA. SpA is an umbrella term for a group of inter-related chronic auto-inflammatory rheumatic conditions. Overall, SpA can be classified into predominantly axial or peripheral SpA according to the SpA classification criteria, defined by the ‘Assessment of SpondyloArthritis international Society (ASAS) in 2009. The most well-known phenotype for axial SpA is ankylosing spondylitis (AS) and for peripheral SpA, psoriatic arthritis. These ASAS criteria comprise a combination of clinical, laboratory and imaging SpA features (Chapter 1, Figure 2).1–3

A link between HS and SpA has been described previously since both auto-inflammatory disease share the same inflammatory pathways and therefore also treatment options. Few case reports and studies have described that SpA and HS occur at the same time in a patient. Epidemiological studies suggest that SpA is more prevalent in HS than in the general population. Variable prevalence rates between 2.3% to 28.2% vs. ±1% are reported.4–15 Vice versa, the prevalence of HS in SpA is unknown.

Therefore, in Chapter 2 we investigated the prevalence of HS in axial SpA patients from a large northern Dutch cohort “the Groningen-Leeuwarden axial SpA (GLAS) cohort”. A patient questionnaire based study containing validated diagnostic HS questions with a high sensitivity and specificity for HS (92-97% and 82–86%, respectively), including prototypical pictures of HS, was used.16 The self-reported HS symptoms were verified by
checking medical records for a previously reported HS diagnosis and the remaining cases were verified through a detailed standardized telephone call including a diagnostic question with high specificity (97%) for the diagnosis of HS. There was a very high patient questionnaire response rate of 76%. The estimated prevalence of HS was 9.1%, 6.9% when corrected for non-responders, which is much higher than in the general population (±1%). Female sex, a higher axial SpA patient reported disease activity and a combined axial SpA disease activity score, and worse quality of life (QoL) were significantly more prevalent among axial SpA patients with HS than without HS. Interestingly, the combined axial SpA disease activity score was independently associated with prevalence of HS.

Conversely, in Chapter 3 we investigated the prevalence of axial and peripheral SpA features in HS. In this two centre study, performed at the outpatient clinic of two Dutch tertiary HS referral centres (University Medical Center Groningen located in Groningen and Erasmus Medical Center in Rotterdam), a self-reported questionnaire concerning SpA features that are part of the ASAS classification criteria supported with prototypical pictures of the features was developed and presented to HS patients. Results show that approximately two-third of the respondents reported to fulfil one or more of the four ASAS entry criteria for axial or peripheral SpA, approximately 73% and 27%, respectively. Interestingly, the vast majority (87%) of these patients also reported one or more additional clinical SpA features. The clinical SpA features were mostly found in the ‘classic’ HS patient: female, overweight and smoker, with a longer HS disease duration and symptoms of active HS. These results are concordant with the results of Chapter 2, in which female patients with high SpA disease activity were also identified.

A body of evidence suggests that HS is an ‘immune mediated inflammatory disease’ (IMID). IMID is a term to describe a concept of multiple inflammatory diseases that share common dysregulated immune mediated inflammatory pathways, concerning mostly overproduction of (pro-)inflammatory cytokines. Clinically, these diseases seem unrelated because different organs are affected. Diseases that can be included into this concept, are among others: Crohn’s disease, pyoderma gangrenosum, and axial and peripheral SpA. Importantly, all these diseases are linked to HS. However, the IMID spectrum is broader, encompassing also rheumatoid arthritis, multiple sclerosis, diabetes mellitus type I, and systemic lupus erythematosus. In these diseases other inflammatory pathways may play a role.

The exact aetiology of IMIDs is uncertain and is thought to be multifactorial: a prerequisite is a genetically susceptible individual that is further exposed to certain endogenous and exogenous risk factors. Frequently, IMIDs run in families. IMIDs are known to negatively affect morbidity, QoL, and may lead to premature death.
Commonalities between HS and SpA are found on multiple levels. Regarding the involved immune mediated pathways, elevated pro-inflammatory cytokine levels of both the innate (e.g. interleukin (IL)-1β and tumor necrosis factor (TNF)-α) and the adaptive immune system (e.g. IL-17A and IL-23) are found in both diseases. The TNF-α pathway and the IL-23/IL-17 axis seem to be important in the pathogenesis of both axial SpA and HS.27–31 There is evidence for an unbalanced T-helper 17/T-regulator ratio.32 Moreover, both HS and SpA are epidemiologically associated with IBD, in HS particularly Crohn’s disease. In IBD, the above described cytokine pathways are also perturbed.33–35 Therefore, it is not surprising that these IMIDs respond to anti-cytokine therapy, i.e. biologics.25 Strong evidence is available showing effectiveness of anti-TNF-α therapy in HS, AS, and IBD.31,36,37 Furthermore, a body of evidence indicates that the environmental factors smoking and obesity are (highly) significant exogenous risk factor in HS and (axial) SpA: a higher incidence and disease activity are reported for both conditions.38–44 Interestingly, obesity is also reported as an important risk factor for IBD and smoking is an important risk factor in Crohn’s disease.45,46 Smoking and obesity can both lead to pro-inflammatory effects. Adipose tissue represents a metabolically and hormonally active organ, producing adipokines that causes a pro-inflammatory effect that drives disease activity in patients with IMIDs.47 Cigarette smoking can augment the production of pro- and anti-inflammatory cytokins as well.48 Interestingly, in Chapter 2 we found a trend for axial SpA patients with HS for both a higher (body mass index) BMI and a positive smoking history. The results of our studies presented in Chapter 2 and 3 strengthen the soundness of HS as an IMID and the IMID concept as a whole, and contribute to knowledge about the immunopathological basis of HS and SpA. Although we did not confirm a diagnosis of SpA in Chapter 3, we did find a high prevalence of more than one self-reported clinical SpA feature in HS patients, contributing to the existing literature that SpA is likely to be more prevalent in HS than in the general population. Moreover, with a prevalence of ±9% of HS in SpA, HS could perhaps be considered as a novel extra-articular manifestation of SpA, similar to psoriasis (9.3%) and IBD (6.8%).49 Clinically, it is also important to identify comorbidities, since they influence health outcomes such as QoL and treatment decisions.49 Additionally, also Blandizzi et al. reported the occurrence of two or more IMIDs in one patient.50 Combination of certain diseases that are more likely than others to present in the same patient are commonly named ‘disease associations’. In the context of IMIDs, combinations are also designated as ‘immune-mediated inflammatory syndromes’.26 Currently, it is only hypothesized why some IMIDs are likely to co-occur and others not. Suggested is a genetic susceptibility, based on genome wide association studies and a family history of IMIDs that is frequently present.26 Similar inflammatory pathways and shared external risk factors might also play a role. Another hypothesis could be that the
pro-inflammatory state of an individual caused by one auto-inflammatory disease is likely to lower the bar for another auto-inflammatory condition. This is supported by results from both Chapter 2 and 3, in which we have found that in both axial SpA patients with a high disease activity and HS patients with active HS symptoms the occurrence of HS symptoms or SpA symptoms was more prevalent. Furthermore, a positive smoking history and higher BMI were also more prevalent in both studies in patients with both HS and SpA symptoms. These two risk factors are both epidemiologically linked to HS and (axial) SpA, and associated with a higher disease activity.\textsuperscript{38,39,42–44,50,51} The inflammatory pathophysiologic commonalities between HS and SpA include dysregulation of inflammatory cytokines TNF-\(\alpha\), IL-1, IL-12, IL-23 and IL-17A.\textsuperscript{15,27,30,32,52} The IL-12/IL 23 pathway including IL-17A and TNF-\(\alpha\) are known to play an important role in the pathogenesis of HS and SpA. This is supported by the fact that both diseases respond well to anti-TNF\(\alpha\) therapy.\textsuperscript{15,36}

Therefore, we state that HS is not solely an auto-inflammatory skin disease, but an IMID. We suggest not to restricting the diagnostic and treatment approach to HS alone; the treating physician must keep in mind the possibility of another IMID in a patient diagnosed with HS as well as in the past, present or future. If beside HS one or more other IMIDs are present in a patient, a multidisciplinary approach towards diagnosis and a comprehensive treatment of HS and accompanying IMID(s) is warranted.

Future perspectives

Many challenges continue to exist and the prevalence of HS in SpA and vice versa remains to be investigated more profoundly to determine associations more accurately. The developed questionnaire concerning axial and peripheral clinical SpA features (Chapter 3) needs to be validated in a prospective cohort, by referring those patients with positive answers to a rheumatologist for further analysis and diagnosis. Patient self-reported symptoms about HS and SpA should be prospectively verified. Furthermore, it would be interesting to further investigate genetic, local and systemic dysregulations in patients who present with both diseases in an active state at the same time. This will provide more insight into the pathogenesis of both SpA and HS.

2. Refined classification for hidradenitis suppurativa

To date, no globally accepted and properly validated disease staging system, severity measurement, and phenotype classification exists for HS.\textsuperscript{53} HS is considered to be a dynamic disease with a diverse clinical picture. The clinical course of HS is highly variable, ranging from mild self-limiting disease to rapidly progressive inflammation with destruction of normal skin architecture and severe physical and psychological disability. Hitherto, it is still an enigma what causes HS disease manifestation and what drives
inflammation in HS. In order to gain more insight in the pathophysiology of HS and ultimately its cure, it is important to accurately stage and subtype patients within the HS disease spectrum. This provides a basis for disease definition and activity and to standardize enrolment and outcome criteria for clinical trials and the ability to compare the results of these (randomized controlled) trials.

Until now, the most frequently used staging system for HS is the Hurley classification (Chapter 1, Table 1).\textsuperscript{53-54} Hurley stage I represents single or multiple abscesses without sinus tract formation or scarring, stage II recurrent abscesses with one or more sinus tracts and scarring widely separated by normal skin, and stage III concerns diffuse involvement with multiple sinus tracts and no intervening normal skin. The Hurley classification was proposed 30 years ago (1989) to determine symptoms of HS in one particular affected body region in order to make treatment plans for this specific region.\textsuperscript{54} However, to date, the Hurley classification is also used to stage patients globally, both in clinical practise and in research. However, although straightforward in use, data regarding its validation to stage patients globally is very limited.\textsuperscript{53} Although knowledge about the pathophysiology of HS and treatment options have expanded, especially the last two decades, the Hurley classification was never adapted and validated to use in the whole patient. Therefore, recently, the Hurley classification was revisited by the Dutch Hidradenitis Suppurativa Expert Group (members of the European Hidradenitis Suppurativa Foundation e.V.).\textsuperscript{55} The refined Hurley classification is a modification, i.e. refinement, of the three staged Hurley classification, and is designed to describe current HS symptoms in the whole patient that is diagnosed with HS and to guide comprehensive treatment modalities per stage. It includes seven stages: refined Hurley stage I A, IB, IC, IIA, IIB, IIC, and III (Chapter 1, Figure 3). Refined Hurley stages I (A, B, and C) are characterized by the presence of inflammatory nodules and abscesses and no sinus tracts. Refined Hurley stages II (A, B, and C) are characterized by the presence of sinus tracts and scarring is not assessed anymore (in contrary to the original Hurley classification). The letters A, B, and C are said to represent mild, moderate, and severe HS disease. Refined Hurley stage III is redefined as the involvement of ≥ 1% body surface area of a body site with interconnected inflammatory sinus tracts, and is regarded as severe per definition.\textsuperscript{55}

In Chapter 4, we first analysed whether the refined Hurley classification accurately distinguishes mild, moderate and severe HS disease by determining its correlation to the validated patient’s reported QoL questionnaire (Dermatology Life Quality Index, DLQI) and a (largely) validated physician-assessed disease severity score (International Hidradenitis Suppurativa Severity Score System, IHS\textsubscript{4}).\textsuperscript{56,57} In this multicentre observational study in 433 patients, we found a significant positive correlation of DLQI and IHS\textsubscript{4} within refined Hurley stage I and II, from A through C (for DLQI $r_s =$
Subsequently, in Chapter 5 we determined the interrater and intrarater reliability of the refined Hurley classification in two sub studies. Two groups of each two trained raters (dermatology residents) classified 13 and 12 HS patients respectively at the regular HS outpatient clinic and we found a moderate to high interrater reliability (Krippendorff’s $\alpha = 0.68$, 95% confidence interval (CI) 0.32-0.95 to $\alpha = 0.92$, 95% CI 0.78-1.00). Through a photographic survey, ten trained raters (dermatology residents and dermatologists) assessed at two time points with approximately one month in between, 15 de-identified HS cases with standardized pictures showing HS symptoms. A moderate to high interrater reliability was found as well, and the intrarater reliability demonstrated a high reliability (intrarater reliability $\alpha = 0.74$, 95% CI 0.71-0.78 at first time and $\alpha = 0.80$, 95% CI 0.77-0.82) at second time point, and a mean intrarater reliability of $\alpha = 0.83$, 95% CI 0.78-0.89). Furthermore, the face validity assessment in Chapter 5 which indicates how well the raters found that the refined Hurley classification was covering the concept it aims to measure, showed good results ($78.7 \pm 10.3$ prior the first assessment and $76.5 \pm 9.7$ after the second assessment, on a scale of 0-100).

In the past few years important efforts have been made to develop and define core outcome sets for HS. One review from 2016 pointed out that 30 outcome measurement instruments, including the Hurley classification, were used in 12 randomized controlled trials for HS. Surprisingly, 27 (90%) of these outcome measurements were never validated, and the methodological quality of the ones with any validation data were mostly graded fair or poor. This indicates the urgency for validation of classification and outcome measurements in HS. For outcome measurements, specific guidelines are developed, such as the COSMIN study (CONsensus-based Standards for the selection of health Measurement INstruments), for classification systems specific guidelines are less defined, but the COSMIN study guidelines can be applied. According to these standards, the validation process includes the domains validity, reliability, interpretability, and responsiveness. Feasibility is also an important aspect to assess. In 2015, one study of fair methodological quality, found a statistically significant Pearson’s correlation coefficient of $\beta = 0.59$ between the Hurley classification and DLQI. This shows a higher correlation compared to our study, although the sample size in this study was very small ($n = 55$). In 2018 and 2019, the interrater and intrarater reliability of the original Hurley and/or refined Hurley classification were assessed. The first study included fifteen raters (five dermatologists, five plastic surgeons, and five general surgeons, all with at least two years of HS experience). The original Hurley classification was assessed in 30 photographic cases and demonstrated a moderate interrater and substantial intrarater reliability (Cohen’s $K = 0.59$, 95% CI 0.48-0.70 and $K = 0.65$, 95% CI
Authors concluded that photographic assessment, especially of Hurley stage III, is reliable and time efficient. The second study included 12 raters (all considered HS experts, with at least ten year of HS experience). In this study, nine instruments for HS, including the Hurley and refined Hurley classification, were each assessed consecutively in 24 HS patients. Outcomes showed good interrater results for Hurley classification when determined in axillae and gluteal regions, and fair for the groin (intra class correlation (ICC) of 0.72, 95% CI 0.63-0.81; 0.72, 95% CI 0.62-0.80; and 0.55, 95% CI 0.44-0.67, respectively), and for the refined Hurley classification fair interrater reliability (ICC = 0.51, 95% CI 0.35-0.68). In this study, intrarater reliability was not assessed. Of note, at the time this study was conducted, the refined Hurley classification had only just been developed, so raters were not acquainted with this classification prior to participation in this study. In the last study, 32 physicians (24 dermatology residents and eight specialists) assessed four scoring systems in five HS patients. Fair interrater reliability and good intrarater reliability results were reported for both the Hurley and refined Hurley classification (only the lower CI results were showed: Hurley interrater of $\kappa = 0.58$, intrarater of ICC 0.76; refined Hurley interrater of $\kappa = 0.47$, intrarater of ICC = 0.74). The second time patients were scored in this study revealed better results, indicating a positive learning curve. This was comparable to our results presented in Chapter 5. All these studies contribute to the validation data for classification systems in HS, and both the Hurley and the refined Hurley classification show similar reliability. Importantly, the refined Hurley classification adds a significant extra aspect since it reflects the extent and inflammatory activity of HS in the whole patient, and the original Hurley classification was not designed to do so.

In Chapter 6, we developed a patient symptom self-assessment questionnaire based on the refined Hurley classification algorithm. We investigated whether the derived refined Hurley stages from the patient questionnaire correspond to the physician’s dermatological examination and given refined Hurley stage. We found a substantial interrater agreement and reliability, indicating that in most cases the same refined Hurley stage could be extracted from the patients’ answers to our questionnaire, as assigned by the physician ($\alpha = 0.74$, 95% CI 0.62-0.85). This questionnaire could be valuable to use for research, but also for clinical purposes at the outpatient clinic or as part of “e-health” (healthcare services provided electronically via the Internet).

The refined Hurley classification allows recognizing severe HS throughout the entire original Hurley classification. We propose that using the refined Hurley classification will likely lead to more accurate stratification of HS patients for treatment in daily practice as well as for enrolment in epidemiologic and clinical studies. For example, within refined Hurley stage I, the IC patients who are characterized by numerous widespread inflammatory nodules/abscesses, are acknowledged similar to Hurley IIC and III patients,
as having severe HS. This opens possibilities for including these patients in certain clinical trials, e.g. trials testing biologics or other anti-inflammatory medicines.

**Future perspectives**

Although a few steps in the validation process still need to be taken which is depicted in Figure 1, current data indicates that the refined Hurley classification is a sound system for staging HS patients. However, after completing the whole validation process re-refinement of the refined Hurley classification could be in order (Figure 1). An additional suggestion could be to also include a refined Hurley stage ‘zero’ (0), since HS is a dynamic disease and lesions can resolve. For example, in refined Hurley stage I in calm periods or after successful surgery of refined Hurley stage II and III.

| Phase 1 | Development of the refined Hurley classification  
*by Horváth et al. 2017*

| Phase 2 | Construct validity of the refined Hurley classification: correlation to patient’s quality of life and objective severity assessment  
*this thesis, Chapter 4*

| Phase 3 | Reliability of the refined Hurley classification: interrater and intrarater reliability and face validity assessment  
*this thesis, Chapter 5*

| Phase 4 | Complete initial validation of the refined Hurley classification (interpretability, responsiveness, and feasibility)  
*future perspectives*

| Phase 5 | Propose modifications based on the results of Phase 2,3 and 4 to further enhance the accuracy of the refined Hurley classification  
*this thesis, Chapter 9 and future perspectives*

| Phase 6 | Final testing: validation assessments in a multicenter and multinational large patient cohort and multiple raters  
*future perspectives*

**Figure 1. Suggested validation process of the refined Hurley classification**
3. Towards phenotyping of the heterogenic disease hidradenitis suppurativa

In addition to staging patients by assessing current symptoms, other patient characteristics are important for the global clinical picture of an HS patient as well. Although HS is a clinical diagnosis, it is suggested that HS shows a marked heterogeneity in clinical manifestations and outcomes.67,68 Although about a third of the patients report a positive family history of HS, suggesting an autosomal dominant inheritance pattern, the genetic background of HS has not been uncovered yet.69 Determination of sound phenotypes of HS can contribute to our understanding of multiple aspects of this unpleasant skin disease, such as the aetiology, genetic profile, pathomechanism, and management of HS. Definitions for ‘clinical phenotype’ vary from a single to multiple or the sum of all observable (disease/patient) characteristics that describes differences between individuals with a certain disease as they relate to clinically meaningful outcomes. Ideally, phenotyping of a (heterogeneous) disease should be done based on the observational clinical characteristics, such as patient characteristics, morphology, and disease characteristics that are clinically meaningful.

In Chapter 7, we have explored in a multi-centre HS cohort through a cluster analysis technique whether distinct clinical patient categories within the HS disease spectrum exist. Four clinical variables were used: sex, smoking history, BMI and the presence of ≥1 follicular occlusion disease (acne conglobata, pilonidal sinus, and dissecting cellulitis of the scalp). We have critically chosen these four variables, partly based on the fact that a substantial body of evidence exists for a strong association with HS.52 Furthermore, these four variables can be evaluated in every HS patient.

Five categories were identified: 1. female stereotypical HS (40%), 2. females with single exogenous risk factor for HS (22.6%), 3. male HS (22.0%), 4. HS plus ≥1 other follicular occlusion disease (9.3%), and 5. limited HS (6.1%). Interestingly, the latter category (“limited HS”) that was revealed by the cluster analysis describes a group of HS patients that are not subjected to typical HS risk factors smoking and/or a high BMI, and they we are also not known with other follicular occlusion diseases. Two-third of the patients presented with mild HS disease (refined Hurley stage IA and IIA, 57% and 10% respectively). It would be very interesting to investigate what possibly triggered HS disease onset in these patients and how they respond to treatment. This could unravel certain aetiologies for instance.

Currently, no consensus exists on which variables are required for accurate phenotyping of HS patients. Previously, multiple publications have appeared regarding subtyping (subgroups/phenotypes/categories) of the HS disease spectrum, describing case-series with distinct clinical presentations, or as part of syndroms.70–79 Only one of these publications was a study based on a statistical method: latent class analysis without a priori hypothesis was performed with ten variables (three body locations, five lesion types,
association with acne, and family history of HS). However, none of these publications have reached international acceptance (yet), possibly due to lack of further investigating such as testing its validation. However, they all do contribute to knowledge of HS, and the viewpoint of HS being a heterogeneous disease.

Future perspectives
It should be considered that other characteristics such as morphological features and presences of one or multiple comorbidities that seem to be considerably prevalent amongst HS patients, could also significantly define the HS phenotype. Therefore, it is recommended to perform cluster analysis in other HS cohorts, to evaluate whether results from Chapter 7 can be duplicated. This will provide information about the robustness of our findings. It is also recommended to perform cluster analysis with other or more variables, in order to see whether other relevant categories can be found. Subsequently, (longitudinal) validation of the found categories is necessary to finally define robust phenotypes in HS. These outcomes might ultimately result in the comprehension of the HS disease spectrum.

4. Mechanical stress in hidradenitis suppurativa
The exact cause of HS is still unknown. As far as we know, the first histopathological event of HS takes place in the infundibulum of the terminal hair follicle. Hyperkeratosis of the infundibular epithelium leads to follicular plugging and subsequently to an infundibulitis. It is not clarified yet why HS has a strong preference for the body folds. In Chapter 8, we reported a case of a 28-year-old male patient known with HS and acne conglobata who developed an ectopic HS lesion on the dorsum of his foot. The lesion was removed surgically with the STEEP (skin-tissue-sparing excision with electrosurgical peeling) procedure for HS. Histologic findings showed follicular plugging, a chronic infiltrate and sinus tract development, which are in conformity with the histopathological findings for HS. Mechanical stress in combination with a similar local environment for typical (intertiginous) HS, seemed to be the triggering situation for the development of the HS lesion on his dorsal foot (Chapter 8, Figure 1).
Mechanical stress has been proposed by other authors and patients as a provoking or aggravating factor for HS. Mechanical stress can be caused by pressure, friction/rubbing, tension, pulling, and pinching. It is proposed that mechanical stress stimulates interfollicular hyperplasia, however evidence is still limited. There are some reported histological findings indicating aberrant or fragility of the structure of hair follicles in HS patients, which may suggest HS patients are at risk for ectopic HS. Contradictory evidence exists about the integrity of the basement membrane zone around the sebofollicular junction in perilesional HS skin. One group has found that it was
aberrant suggesting it could more easily rupture when exposed to e.g. friction, however, another group could not confirm these results.\textsuperscript{86,87} A recent publication found loss of key adherence junction proteins (E-cadherin and p\textsubscript{120} catenin) and reduced desmosome length in HS lesional skin compared to healthy controls (both samples taken from the axillae), and suggested that HS skin exhibits substantial inability to resist mechanical stress.\textsuperscript{83}

Several other case reports have proposed that in certain circumstances HS(-like) lesions can develop after the skin is exposed to mechanical stress, both in patients known with typical HS as patients without a history of HS.\textsuperscript{84-87} Commonalities in these cases are a favourable environment (warm, moist, and occlusive) and exposure to enhanced mechanical stress. For example, the reports about limb amputees without a pre-existing diagnosis of HS, who present with HS(-like) lesion development at the stump after wearing leg prosthesis.\textsuperscript{85}

One author (Boer) has proposed the hypothesis that development of HS after mechanical stress shows similarities to the Koebner phenomenon that is described in skin diseases such as vitiligo, psoriasis, and lichen planus.\textsuperscript{88} However, usually repetitive trauma, i.e. mechanical stress, is needed for the development of HS rather than acute trauma. Furthermore, the HS lesions usually do not develop as the typical described Koebnered lesions which exactly follow the traumatized location.

\textbf{Future perspectives}

We support the theory that mechanical stress, in combination with a favourable local environment and/or a predisposed patient, can induce HS(-like) lesions at for HS atypical body sites. However, basic experimental evidence to substantiate this hypothesis and clinical observations are warranted.
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