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Semi-quantitative assessment of the distribution of skin lesions in patients with psoriasis and psoriasis arthritis

Stefan Kazimierz Piechnik[1], Karin Øien Forseth[2] and Anne-Lene Krogstad[2,3]

[1]Department of Cardiovascular Medicine, Oxford Centre for Clinical Magnetic Resonance Research, Oxford University, Oxford, UK, [2]Section for Climate Therapy, Department of Rheumatology, Rikshospitalet, Oslo University Hospital, Oslo, Norway and [3]Department of Dermatology, Rikshospitalet, Oslo University Hospital, Oslo, Norway.

Background: We propose that the distribution of skin lesions in psoriasis may be assessed using parametric maps on a pixel-by-pixel basis.
Material and methods: We processed 428 patient-drawn self-descriptions of the psoriasis lesions on a supplied body template. We compared 195 patients with a confirmed diagnosis of psoriatic arthritis (PsA) with 89 who had this diagnosis rejected (Psor). Additionally, 28 Psor cases supplied drawings performed after 3 weeks of climate therapy (PsorCT) to test the treatment efficacy. The drawings were scanned, lesion areas were segmented, followed by construction of parametric maps of lesion distributions and calculation of statistical differences between groups.
Results and discussion: In PsorCT, the lesions occupied 11.2% (0–42%) [median (min.–max.)] of the body area. The area decreased to 2.4% (6–11%) after heliotherapy. The differences were statistically significant for all the areas studied and spread evenly over the body surface. PsA had a relatively low psoriasis lesion occupancy of 2.5% (0–42%) compared with Psor 9.8% (0–34%), which is attributed to the difference in recruitment. Correcting for this, we demonstrate a clear tendency for the head, palms, feet, groin and nails to be preferred lesion sites in PsA in contrast to psoriasis.
Conclusion: Pixel-based analysis of self-reported skin lesion distributions is a powerful tool to assess systematic differences due to treatment or disease variants.

Key words: psoriasis – psoriasis arthritis – image analysis – lesion distribution – climate/heliotherapy

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Psoriasis is a relatively common skin disease affecting about 2% of the population with varied extents of skin thickening, discolouration and scaling (1), and has a significant impact on life quality (2, 3). The disease is claimed to affect primarily the knees, elbows, scalp, hands, feet and lower back (4); however, this is based on qualitative compilations of clinical experience rather than quantitative analysis of any particular data. Ten per cent to 30% of patients with psoriasis also have joint inflammation (5, 6). Usually, cutaneous lesions appear first, but in about 20% of the cases arthritis precedes the skin lesions, and in 10–20% of the cases the lesions in the skin and joints emerge simultaneously (7). There are five subgroups of psoriatic arthritis (PsA), from rare mutilating serious arthritis to a commonly observed mild-type one characterised by affliction of less than four joints (8). There seems to be no connection between the outburst of skin lesions and inflammatic activity in the affected joints. To date, no specific marker, either clinical, immunohistochemical or genetic, has been identified, which can definitively predict the development of arthritis. Conversely, PsA is connected to changes in distribution in skin lesions (1). For example, approximately 80% of PsA patients have nail psoriasis, while the number of patients with nail psoriasis without joint inflammation is much lower – about 20% (9).

Several scales are used to measure the severity of psoriasis. All are based on various calculation methods for subjective assessment of the invasion area and other factors such as lesion redness, thickness or the amount of scaling (10). The subjectivity of such assessments has been known for long and has been criticised (11). Different tools for assessment have been compared (10, 12–14) in an attempt to obtain convenient clinically comparable results (15, 16). Several methods have been proposed for estimation of the relative involvement of body surface area (BSA) (4, 17,

18). While the proposed methods concentrated on the numeric value required for calculation of the psoriasis scores such as the Psoriasis Area and Severity Index (PASI), the potential wealth of information on the differences in the specific localisation of the lesions in response to therapy and between patient groups has never been explored. Therefore, in this work, we suggest a method to assess the spatial distribution of skin lesions across patient populations and test its potential to monitor the effects of treatment and the differences between patients with psoriasis and PsA.

Materials and Methods

Materials

All drawings utilised in this study were made by patients who had applied to participate in a treatment programme administrated by the Department of Rheumatology, Section for Climate Therapy (Behandlingsreiser, BHR), at National University Hospital in Oslo. All applications to the rheumatic programmes are evaluated by rheumatologists and the applications to the psoriasis programme by a dermatologist. We processed a total of 428 self-descriptions of the location of the psoriatic lesions provided on a predefined body template (Fig. 1a). Of these, 278 templates were from applicants with the initial diagnosis of psoriatic arthritis made by a rheumatologist. This study was performed before the introduction of the CASPAR criteria (19) and we based the confirmation of this diagnosis (KØF) on an accurate description of any inflamed joints by a rheumatologist or a radiologist (based on X-ray or MRI). This was available in 195 cases, which constitute the 'PsA' group (Table 1). Additional 150 drawings were supplied by patients treated primarily for psoriasis in a BHR Norwegian Health Centre (Argineguin, Gran Canaria, Spain). In this group, we aimed to exclude all the patients in whom the possibility of arthritis could not be clearly rejected (ALK). This yielded 89 clear 'Psor' patients (inclusive of seven confirmed negative cases from the rheumatology program) to demonstrate potential contrast due to arthritic involvement. In the 'Psor' group, 28 cases provided drawings both before and after 3 weeks of climate therapy (PsorCT: 'before' and 'after'), which is used for testing the impact of sun exposure. The selection of patients was performed before the image data analysis and blinded to the results.

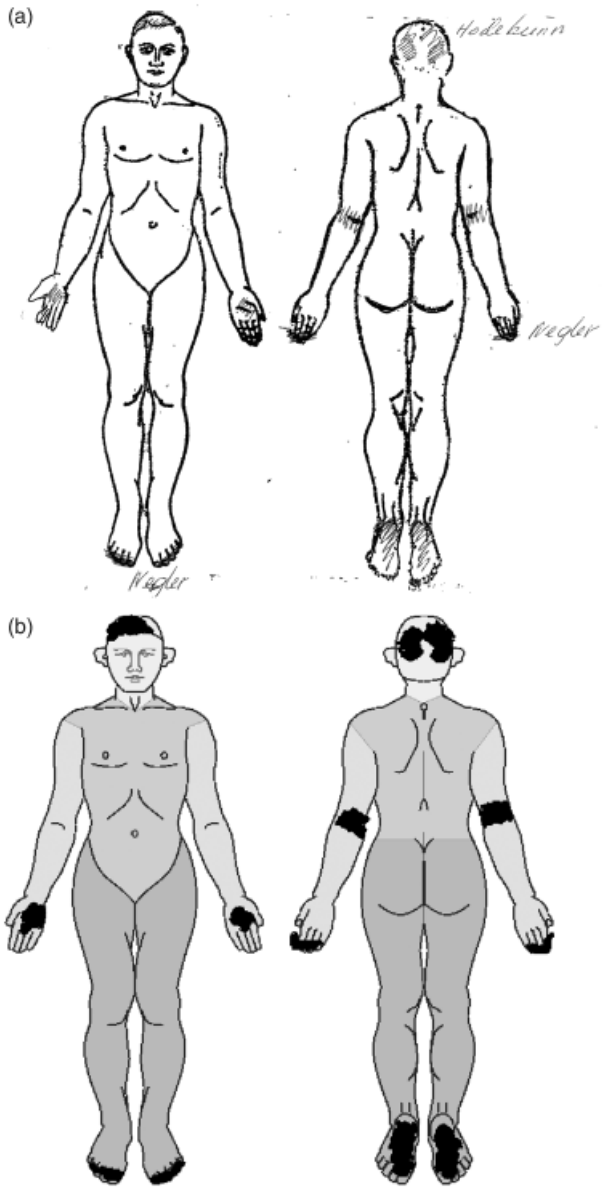

Fig. 1. (a) An example of original drawing with comments describing lesion distribution as supplied by the patient. (b) Lesions segmented out and overlaid on the final body layout. The trunk, legs, hands and head are indicated by varying grey shades and occupy 26%, 46%, 22% and 7% of the whole body area, respectively.

TABLE 1. Group size N, age and lesion area with respect to the whole body area in groups analysed in this study

Comparison	*N*	Age (years)	Lesion/body area (%)
Arthritis			
Psor	89	48 (8–84)	9.8 (0.0–34)
PsA	195	55 (27–82)	2.5 (0.0–43)
Climate therapy			
PsorCT before	28	54 (24–74)	11.2 (5–26)
PsorCT after	–	–	2.4 (0.1–11)
Excluded	116	54 (27–74)	–

The values represent median (range).
PsA, psoriatic arthritis; Psor, no psoriatic arthritis.

Methods

The patients marked the affected areas in a variety of ways, such as outlines, arrows and other marks, combined with textual clarification of their meaning (Fig. 1a). Based on this information we manually standardised the pictures to make a clear distinction between the body outline and the lesions that were painted over using a thick-tipped marker equivalent to ca. 1 cm in relation to the natural body size. Subsequently, the drawings were scanned at 300 DPI resolution using a standard document scanner equipped with an automatic paper feed. The segmentation of the lesions from the underlying outline was performed concurrently with the removal of thin lines and comments by erosion of thin features, followed by dilatation to close the gaps. The body outlines identified on scans were subsequently co-registered to the common body template (580 pixels in height and 260 pixels in width, pixel resolution equivalent to ca. 3 mm in real body-size scale, Fig. 1b). The co-registration was performed in two stages, first by rotation, translation and scaling in 2D of the whole template. When necessary, due to small differences in the shape of the body templates used in parts of this study, this was followed by the same transformation performed on a smaller area, such as the whole hand and leg to obtain a better local match. All final scans (Fig. 2b) were visually controlled for adequate similarity to the original drawing and, if necessary, the difficult to segment areas such as toes and fingers were manually retouched using Photoshop 6 (version 6.0, Adobe Systems, San Jose, CA, USA) and re-run through analysis.

Pixels contained within segmented lesion areas were coded as '1' and unaffected skin as '0'. The number of lesions (N_{lesion}) counted at any specific coordinate (x, y) divided by the total population in any selected group (N_{total}) represents the average frequency of finding a lesion at this coordinate, which can be interpreted as an empirical estimate of lesion probability (LP):

$$\text{LP}(x,y) = P_{\text{lesion}}(x,y) \approx \frac{N_{\text{lesion}}(x,y)}{N_{\text{total}}}$$

To improve the smoothness of calculated LP maps the individual body silhouettes were box-averaged with a kernel 5 pixel wide (ca. 1.5 cm in relation to the whole body size) and additionally folded over the midlines to reduce the image size for the display of multiple maps. The additional maps that were constructed included the differences between folded versions of lesion probability distributions (LPDs) and used statistical descriptors of their significance as might be obtained from the Student *t*-tests: probability of null hypothesis and the value of *t*-statistics.

Aiming to provide a reference between this study and previous analyses based on BSA estimates, we also calculated the coverage of selected body areas for each case. For this we divided the template into the major areas of the trunk, legs, hands and head (26%, 46%, 22% and 7% of the whole body area, respectively) as shown in Fig. 2c. The lesion occupancy was calculated as the ratio of the number of marked pixels to the total number of pixels in the respective area for each patient, followed by group comparisons. All data

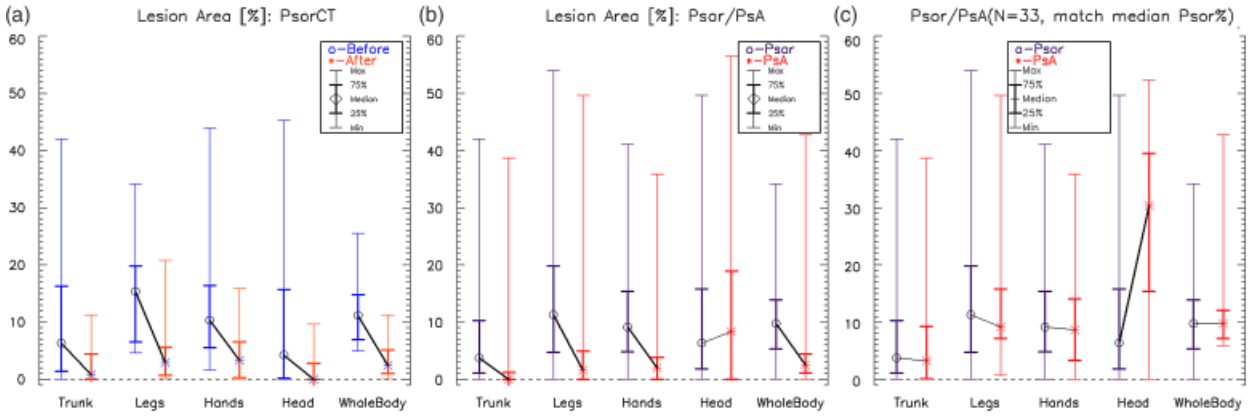

Fig. 2. The distributions of the areas of lesion relative to each body segment show (a) the expected improvement after climate therapy in patients with psoriasis and (b) a large confounding bias in the lesion area between groups with psoriasis and psoriasis–arthritis (see "Discussion"). (c) Differences in lesions in specific body areas after 162 PsA cases with the least lesion occupancy were removed ($N_{PsA} = 33$). *This reduction is required to match the much larger median occupancy of whole body in the Psor group.* Note*: Differences marked by thick black lines are statistically significant* ($P < 0.05$, t*-test, PsoCT: paired;, Psor/PsA: unpaired).*

processing and display was programmed in Interactive Data Language (version 6.1, Research Systems Inc., Boulder, CO, USA).

Results

Table 1 summarises the overall lesion statistics of the patient groups selected for analysis. There is an expected strong decrease in the total BSA from 11.2% (0–42%) [median, (min.–max.)] before therapy to 2.4% (6–11%) following heliotherapy ($P < 1e-7$, t-test paired). Figure 2a provides more information and details of the initial distributions of lesions across a typical selection of selected body segments and the significant extent of their reduction after sun therapy. While such a large difference was expected as a result of therapy, we also found unexpectedly significant smaller BSA in patients with PsA compared with those with isolated psoriasis ($P = 1e-19$, t-test, unpaired). The difference is as large as the effects of sun therapy, in all areas but the head, where its sign is opposite, albeit without statistical significance ($P = 0.35$). At this level of generalisation we thus only have a single marker indicating any discrepancy in the spatial distribution of lesions between these two groups of patients. These differences can be more subtle than division between just a few major body chunks that can be feasibly shown as a bar plot. Therefore, Fig. 3 introduces the concept of mapping of the LPD, which displays fine details of the focal prevalence of lesions. This is first demonstrated on the relatively straightforward effect of climate therapy. The LPD in these patients is uneven not only over the body surface but also across the range of its values. While the maximum expected point of occurrence lesions is located at the elbow (indicating that there is a 75% chance that it will be affected by a lesion in any given patient in our population), 99% of the LPD values lie below LPD = 0.35 and the median LPD is just 0.08. For this reason, the maps displayed in Fig. 3a and b that cover the whole range of values lack resolution to show differences at its lower end. In effect, the sun therapy seems to remove virtually all lesions in Fig. 3b. A common method to equalise such a distribution is to transform the values for the display using a non-linear function, such as logarithm. The appearance of the maps shown in Fig. 3c and d amplifies the differences in the low range of LPD values while preserving some resolution near the maximum.

In addition to comparing the maps side by side, their point-by-point spatial correspondence enables a whole range of calculations to be performed directly on a pixel basis. The simplest approach is subtraction of original LPD maps resulting in the focal estimates of improvement demonstrated in Fig. 4a. The improvement is

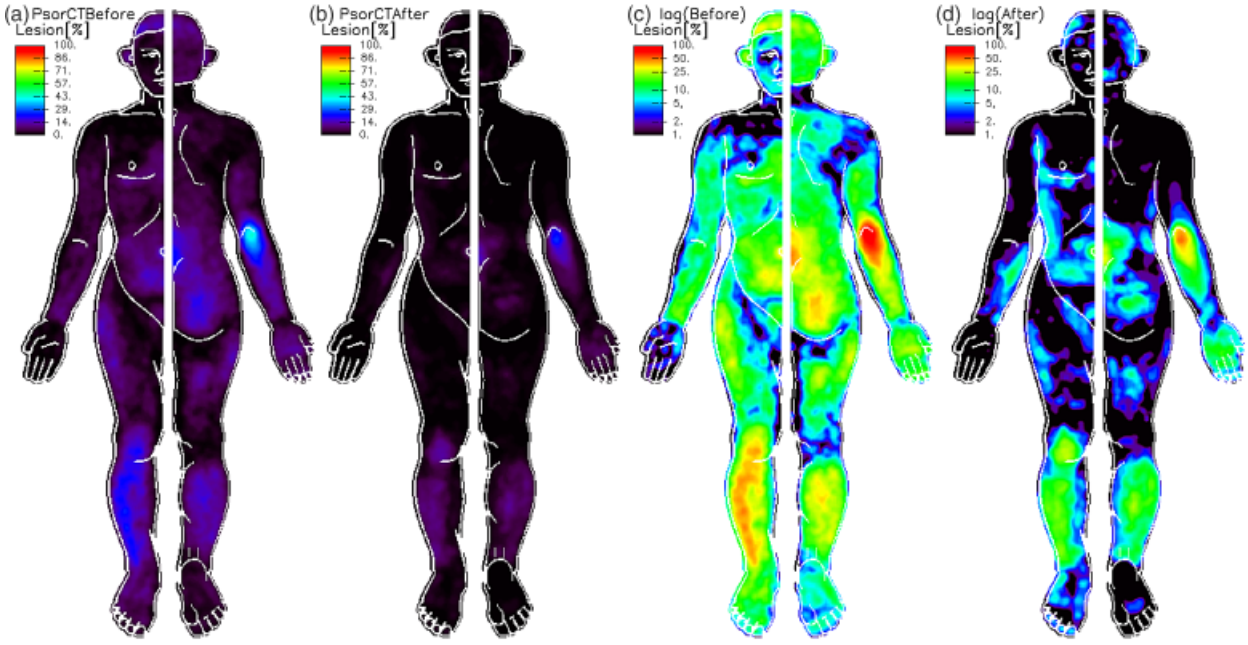

Fig. 3. Lesion probability distribution of psoriatic lesions in patients for whom data were available both before (a and c) and after (b and d) climate therapy treatment (N = 28). *The large improvement is seen clearly both on a linear colour scale (a and b) and the logarithmic scale (c and d), which serves to better delineate differences both in the low- and in the high-range values.*

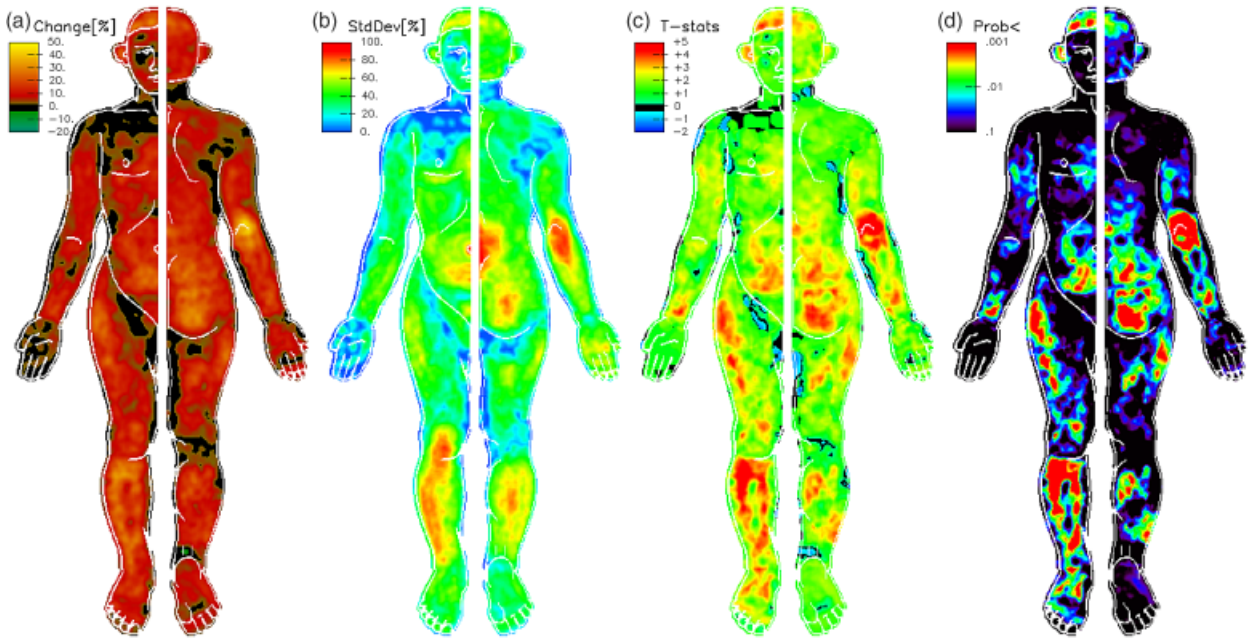

Fig. 4. Spatial distribution of the statistical descriptors of the improvement after climate therapy (N = 28 *cases). (a) Improvement measured by the amount of reduction in lesion probability density. (b) Standard deviation. (c) The ratio of the change to the regional variability measured by the* t*-statistic. (d) The probability of the null hypothesis that the observed change is a random observation.*

relatively evenly distributed over the whole body. The slightly larger improvement on the head and shins may be related either to easier sun tanning of these areas or their large initial LP. A contrary argument may be applied to the neck, inside of the hands or the thighs, which have shown no improvement or even a slight increase in the lesion density. The latter effects are likely chance related to the underlying random variability in the data. The latter can be estimated in a manner similar to the difference itself, and the map of standard deviation across combined data for each pixel is shown in Fig. 4b. This naturally leads to further statistical maps such as the ratio of the effect to the variability (Fig. 4c) and, finally, the estimate of the Student *t*-test probability (Fig. 4d). The latter, beyond the primary purpose of the method demonstrated, shows that the underlying data variability and the moderate group size ($N = 28$) mask the statistical significance of the changes in over two-thirds of the body area (i.e. $P > 0.05$).

The assessment of the focal differences due to arthritic complications is more interesting than the flat distribution of changes after sun therapy. A first glance of Fig. 6a and b reveals a remarkably large extent, size and statistical significance of differences. However, this mostly reflects overall differences in lesion area occupancy between the groups already shown in Table 1 and Fig. 2a and b. Therefore, comparison of the maps using the method shown earlier must be performed with care, as the largely significant negative differences shown relate mostly to the overall BSA difference, rather than preference to target specific body areas. For the latter, similar to the difference in the overall head region in Fig. 2b, we must concentrate on areas defying the inter-group bias and diminishing the statistical significance. These include involvement of the scalp, groin, toes and areas below the palms and feet. These areas are easier to identify when the ratio, rather than the difference, is displayed in Fig. 5c. It must be noted here that due to the fourfold difference in the overall occupancy between the groups, any area that has a ratio above 25% in Fig. 5c should be deemed preferred in psoriatic arthritis. Figure 5d demonstrates the same effect as the difference with LPDs for Psor and PsA normalised to match their overall group average. This results in maps where 'no difference' corresponds to a straightforward '0' rather than a somewhat arbitrary 0.25. An even more appropriate method is to match the Psor and PsA groups by selecting cases producing similar median values of whole-body involvement, as shown in Fig. 2c. This produces a more balanced map of the LPD differences (Fig. 6a). Such a method is most likely to represent the diagnosis rather than a large bias due to the initial selection of groups. The downside of this corrective reduction in the PsA group size to only 33 cases is a decrease in the area under the statistical significance limit (Fig. 6b).

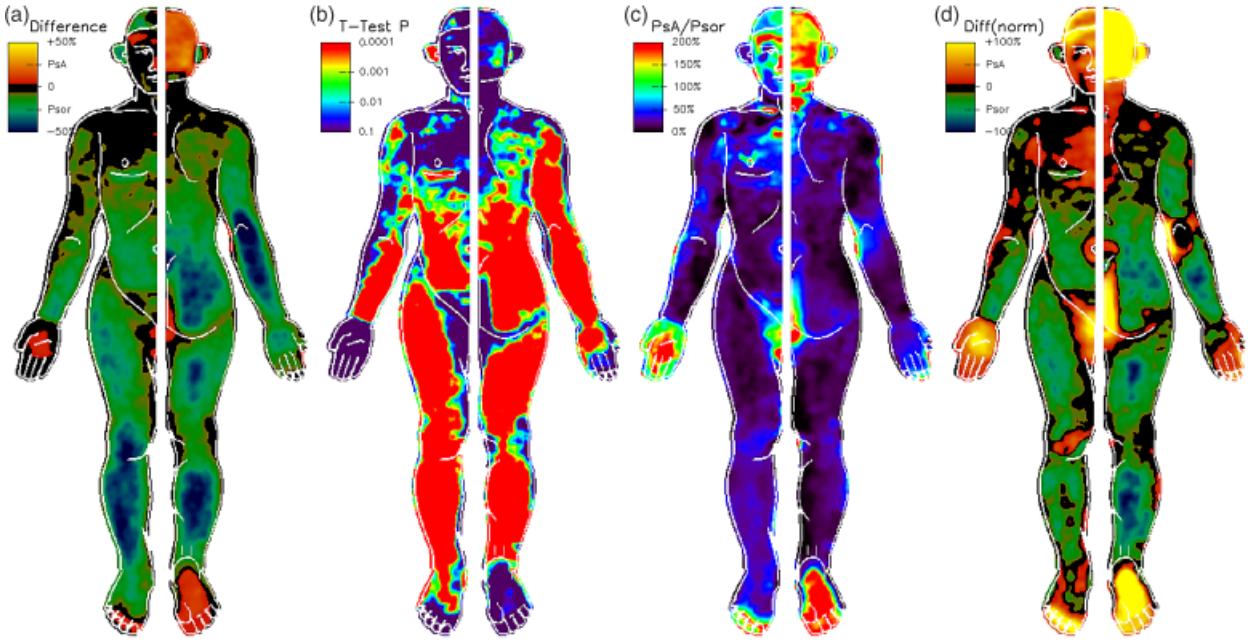

Fig. 5. Spatial distribution of the statistical descriptors of the difference between the groups of patients with psoriasis (N = 89) and psoriatic arthritis (N = 195). (a) Straightforward difference (PsA–Psor) in the distribution density, which indicates preference towards involvement of the scalp, groin, toes and areas below the palms and feet in patients with arthritis. (b) The ratio of the change to the regional variability measured by the t-statistic reveals additional involvement of fingers and fingernails. (c) The ratio between LPD in each group. (d) An attempt to unbias the difference map by re-scaling the PsA lesion probability density to match the larger value in the 'Psor' group.

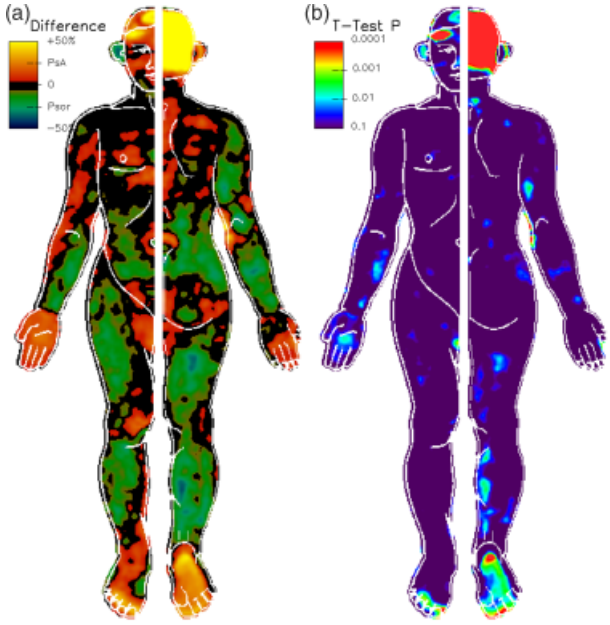

Fig. 6. Statistical maps calculated for 33 PsA cases with the highest lesion occupancy as required to match the median occupancy of the whole body in the Psor group (compare Fig. 2c). (a) Spatial distribution of the difference between the adjusted PsA group is visibly more balanced than in earlier comparisons. (b) The probability map shows the statistical significance expected in large areas of the head, toes and feet.

Discussion

In this paper, we propose a novel way of interpretation of binary maps describing the area affected by skin lesions. Rather than presentation of numeric values pooled over arbitrary large body areas we recommend calculation of the spatial distribution of lesion occurrence across patient populations. The LPD maps obtained in such a way constitute an intuitively easy descriptor of the extent of the lesion and its impact across a group of patients. The overall descriptors of the lesion occupancy, such as used in PASI, necessarily average over large arbitrary subdivisions of the body area. The resulting tables or bar graphs require training to comprehend them properly. Changes in the definition or even in the presentation order of selected regions can provide a misleading impression of the actual distribution or weight of the lesions on the patient's well-being. In contrast, the proposed method relates the value to the location of any particular data outlined in a body frame, which is universally intuitive to any human observer. Such maps give a clear impression of the overall extent of skin symptoms in groups of patients, but are particularly useful to identify potential symptom hot-spots without blending them together with the surrounding areas. In the results presented we demonstrated clearly the expected difference due to climate therapy (16, 20). The improvement is spread relatively evenly over the whole body area with some degree of correlation to initial

lesion probability rather than a potential for sun exposure demonstrated by a surprisingly good improvement in the area of the buttocks. On the other hand, the small number of lesions in the least likely to be exposed area near the genitals remained nearly unchanged.

The findings regarding the differences due to psoriatic arthritis have more impact. Surprisingly, we found a large overall difference in the lesion occupancy between the PsA and the general psoriasis groups. With the benefit of hindsight, it is possible to relate this difference to the method of patient recruitment, which was essentially a two-stage procedure. The PsA group was recruited based on the questionnaires already available in BHR obtained earlier in an internal study designed to probe the demographic base for establishing a new treatment centre specifically for the treatment of psoriatic arthritis. This study yielded the majority of PsA patients but only seven cases where arthritis could be clearly rejected. To increase the number of Psor cases, we distributed similar questionnaires among patients who were already admitted for climate therapy. However, the admission to such therapy was based on a PASI score beyond 7, which produces larger lesion occupancy in Psor patients than PsA patients who had no such requirement. Remarkably, despite this large inter-group bias, the PsA patients achieved a marginally larger BSA occupancy of the scalp. This fact might have been overlooked in overall comparisons as statistically insignificant but the appearance of maps in Fig. 5a, c and d indicates clear differences in the distribution of the lesions between Psor and PsA patients. These include areas with known preference in psoriasis–arthritis, such as the scalp and nails (1) but also additional areas on the feet, hands and genitalia. These regional differences co-exist with a large disparity in total BSA, which can be hot-fixed by a reduced value of the ratio threshold or by normalisation of the differences to reduce the effect of bias (Fig. 5c and d). A much more accurate method is to attempt to balance the total BSA between PsA and Psor groups (Figs 2c and 6), but this is at the cost of reduction in group sizes and, subsequently, the statistical significance of differences (Fig. 6b).

While the pixel-based calculations are relatively straightforward, the main drawback of this methodology is that the underlying data are semi-quantitative and based on a clearly subjective drawing of the lesions performed by patients themselves. We assume that patient impartiality is substantiated by the lack of any direct gains from manipulating the results. Another potential bias may be due to manual pre-processing that was required in a large number of drawings to fill in areas indicated by an outline only or mark lesions too small or too faint to be automatically segmented. This is likely to increase the impact of small lesions similar to the bias in lesion size assessed by the human eye (11). However, such a bias would impact all the groups under comparison in equal measure; thus, inter-group differences should remain unaffected. Potentially, it would be best to use camera capture, followed by automatic segmentation of skin lesions inclusive of the information on their severity. There are many promising publication titles regarding photometric measurements of lesion thickness (21), blood flow (22) and other markers of psoriasis. However, these methods require complicated and expensive equipment and methodology and their application is tested on selected skin areas ranging in size from microscopic (23), flat surfaces of limbs (22) to flattened large body chunks (4). It is clear that these methods are still under development and lack the ability to automatically resolve lesions on the whole skin surface. For a global approach the only available tool is an appropriately trained specialist's eye as recently demonstrated in a study utilising whole-body photographs taken with a standard camera (24). Even then it is not possible to address numerous potentially interesting areas such as the scalp and groins due to hair growth. This also applies to the hands, feet, armpits, breast and groin due to complicated skin folding, natural variation in skin colour and unavoidable conflicts with patient modesty. This list significantly overlaps with numerous novel differences discussed in our study. Hence, the subjective nature of estimates at least in these body parts seems to be unavoidable in the predictable future. On the other hand, the lack of involvement of any specialist equipment allows investigations to be performed anywhere and anytime, including periodic distribution and collection of questionnaires by mail. In this case, based on our experience, we strongly advise that future participants of similar studies receive a thorough instruction concerning the correct method of filling in the body outlines and are provided with uniform body outlines and adequate thick-tipped marker pens. This would serve to minimise the effort of manual correction and interpretation of drawings that was encountered in this study. Under such circumstances, the proposed method may

prove ideal to monitor a large number of cases for seasonal changes in lesion occupancy or response to drug administration. Numerous study designs can be conceived to study the differences on the whole body between groups of patients, or in selected areas under topical treatment with untreated areas serving as a control. There is an additional significant potential for expansion of this method with analysis of colour-coded drawings. For example, in case of psoriatic lesions, these may be obtained by instructing patients to mark any lesion in green, and then use a red pen to represent redness and then blue to indicate scaling. While technically feasible, the success of such improvements will depend strongly on the level of a patient's cooperation and its practicality remains to be tested in future. Pending verification, such multi-spectral analysis of the drawings could lead to a fully automated estimation of PASI scores.

Conclusion

A novel method has been proposed to study the differences in the distribution of skin lesions between patient populations. It has been illustrated by monitoring the significant effects of climate therapy and the fact that patients with psoriasis–arthritis have a clear tendency to show the head, palms, feet, groin and nails as the preferred psoriatic lesion sites.

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Address:
Anne-Lene Krogstad
Department of Dermatology
Rikshospitalet
0027 Oslo
Norway
Tel: +47 95 029 377
e-mail: anne-lene.krogstad@neuro.gu.se