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# Comparing skin characteristics and molecular markers of xerotic foot skin between diabetic and non-diabetic subjects: An exploratory study

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ABSTRACT

*Background:* Xerosis cutis of the feet is one of the most common skin conditions among type 2 diabetics. Whether skin dryness among diabetic patients is different from 'general' skin dryness is unclear. The overall aim was to compare the structure, function and molecular markers of dry and cracked foot skin between diabetics and non-diabetics.

*Methods:* The foot skin of 40 diabetics and 20 non-diabetics was evaluated. A clinical assessment of skin dryness was performed and transepidermal water loss, stratum corneum hydration, skin surface pH, epidermal thickness, skin roughness, elasticity and structural stiffness were measured. Ceramides, natural moisturizing factors, histamines, proteins and molecular markers of oxidative stress were analyzed based on a non-invasive sampling method for collection of surface biomarkers.

*Results:* The mean number of superficial fissures in the diabetic group was nearly three times higher than in the non-diabetic group (11.0 (SD 6.2) vs. 3.9 (SD 4.2)). The skin stiffness was higher in the diabetic group and the values of almost all molecular markers showed considerably higher values compared to non-diabetics. Malondialdehyde and glutathione were lower in the diabetic sample.

*Conclusions:* The high number of superficial fissures may be based on an increased stiffness of dry diabetic foot skin combined with different concentrations of molecular markers in the stratum corneum compared to dry foot skin of non-diabetics.

## 1. Introduction

Xerosis cutis is one of the most common skin conditions among patients with type 2 diabetes mellitus [1–4]. About 25% of diabetic patients are affected by xerosis and associated pruritus [5]. Scaling, roughness, redness and fissures are the main clinical signs of skin dryness [6]. There are many factors, which may cause dry skin. An imbalance of natural moisturizing factors (NMFs) and intercellular lipids are common reasons [7,8]. Intercellular lipids like ceramides play an important physicochemical role in maintaining the barrier function and determining the water permeability of the stratum corneum (SC) [9], whereas NMFs, which are produced by proteolysis of filaggrin, are important for maintaining the hydration of the SC [10]. Low hydration of the SC triggers the de novo synthesis of NMF. Especially at the foot, where the stratum corneum (SC) is thickest, dry skin is prone to develop fissures. This facilitates the entry of germs and foreign substances into the skin, leading to increased risks of infections and ulceration [4,11–14]. Foot ulcers are one of the most serious complications in the course of diabetes mellitus [3,15–17]. Diabetes mellitus induces microvascular changes which result in impaired blood circulation of the foot and delayed wound healing. Up to 15% of patients with diabetes mellitus are affected by non-healing ulcers [3,15], often leading to some form of lower extremity amputation [15,18–21].

Type 2 diabetes mellitus is characterized by increased insulin resistance and beta cell failure, finally resulting in hyperglycemia [22], which in the long-term leads to glycation of proteins, lipids and nucleic

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acids [1,5,23]. These so called 'Advanced Glycation Endproducts' (AGEs) are associated with many dysfunctions and damages of organs, including the retina, the kidney, the nervous system and also the skin [1,22]. The accumulation of AGEs is considered to cause skin alterations, which promotes xerosis cutis, delays wound healing and increases the susceptibility for infections [1,5,18]. As AGEs alter collagen properties the skin also becomes stiffer [1,24]. Furthermore, high glucose levels impair the proliferation and migration of keratinocytes [1,5,23].

However, there are only few studies investigating the properties of diabetic skin [5,25–28] and results are partially inconsistent [5]. For example, while dry skin in the context of atopic dermatitis is well-differentiated from other forms of dry skin (e.g. 'senile xerosis'), it is unclear whether xerotic foot skin in diabetic patients also show different signs and patterns compared to dry foot skin of non-diabetics. Therefore, the aim of this study was to compare the structure, function and biomarkers of dry to very dry foot skin between diabetic and non-diabetic subjects.

## 2. Methods

### 2.1. Study design

A descriptive, exploratory study was conducted to compare diabetic and non-diabetic dry foot skin.

### 2.2. Participants and setting

The study took place at the Department of Dermatology and Allergy, Charité-Universitätsmedizin Berlin between September 2016 and April 2017. Eligible for inclusion were patients affected by diabetes mellitus type 2 for at least 2 years and non-diabetics. The participants had to be between 40 and 75 years and affected by moderate or severe skin dryness at their feet (see Appendix A) with comparable degree of dryness at both feet (maximum of 1 category difference according to Rogers at al., see Appendix B). The presence of neuropathy assessed with a Semmes-Weinstein monofilament test [29] and the absence of pedal pulses (posterior tibial artery and dorsalis pedis artery) were an exclusion criteria for diabetics.

### 2.3. Sample size

Due to the exploratory nature of this study, a formal sample size estimation was not conducted. Samples of 20 non-diabetics and 40 diabetics were considered as sufficient to describe possible differences between both groups.

### 2.4. Data collection and variables

The skin of both feet was evaluated by an investigator and instrumental measurements were conducted. Prior to instrumental measurements, the skin of the subjects' feet was acclimatized in a room with controlled environmental conditions (room temperature of 22 °C ± 2 °C; relative humidity of 50% ± 10%) for 30 min. After the instrumental measurements were conducted, samples of molecular markers were collected from three-quarter of each group, i.e. from 15 non-diabetics and 30 diabetics.

#### 2.4.1. Clinical evaluation and allocation to skin dryness group

An investigator clinically evaluated both feet regarding signs of skin dryness. The clinical signs of scaling were assessed by using the classification system of Rogers et al. (1989, Appendix B) [30]. Fissures were assessed separately by recording the presence (yes/no) and the number (n) of fissures. Furthermore, the severity of fissures was categorized according to Oe et al. (2012) into 'superficial, extending to epidermis' and 'deep, extending to dermis' [31]. Based on the signs of scaling and the depth of fissures the subjects were then allocated to the groups "severe dryness" or "moderate dryness" according to Appendix A. In addition, the presence (yes/no), number (n) and severity of callus were assessed. Grade 1 represented 'no specific callus plaque, but diffuse or pinch callus tissue present or in narrow bands' and grade 2 'circumscribed, punctate oval or circular, well-defined thickening of keratinized tissue' [32].

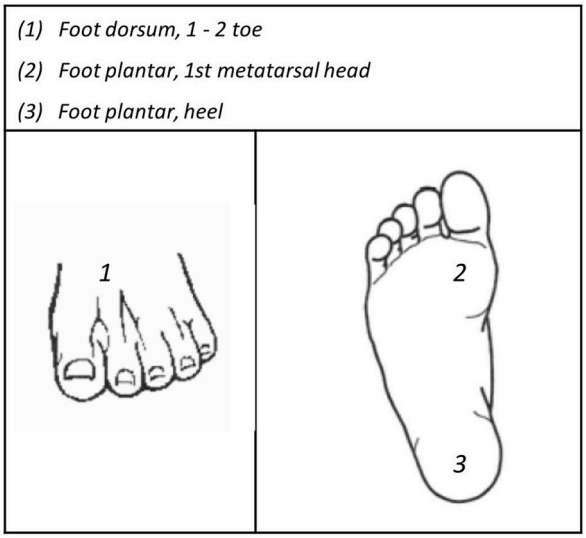


**Fig. 1.** Measurement areas.

#### 2.4.2. Instrumental measurements

Instrumental skin measurements were conducted at both feet at the dorsum between the first and second toe, at the plantar 1st metatarsal head as well as at plantar heel (see Fig. 1). In order to minimize the possible influence of one skin measurement on the subsequent skin measurements the following order was determined according to Kottner et al. (2014) [33]. The transepidermal water loss (TEWL) was measured first, as this parameter is very sensitive. The TEWL was captured with an open chamber device (Tewemeter TM 300, Courage & Khazaka electronic GmbH Cologne, Germany) and is expressed in g/m$^2$/h [34,35]. After this, the Corneometer CM 825 (Courage & Khazaka electronic GmbH Cologne, Germany) was used to measure the SC hydration, expressing the results with arbitrary units (AU) which range from 0 to 120 AU [34]. Next, the skin surface pH was captured by a glass electrode (Skin-pH-Meter PH 905, Courage & Khazaka electronic GmbH Cologne, Germany) [36]. The optical coherence tomography (OCT, Thorlabs Telesto, Spectral Domain OCT System) enables a non-invasive imaging of the epidermal-dermal junction zone (see Fig. 2). The calculation of the epidermal thickness (mm) was based on the mean of three epidermal thickness measurements. Skin surface images were taken with the Visioscan VC98 camera (Courage & Khazaka Electronic GmbH Cologne, Germany) (see Fig. 3). Based on the grey level distribution, the mean roughness (Rz, µm) was calculated with the corresponding software [37]. Finally, the stiffness and elasticity of the skin were measured using a Cutometer (MPA 5 80, Courage & Khazaka Electronic GmbH Cologne, Germany) with a probe opening diameter of 4 mm, 20 s suction phase and 30 s off-phase. The parameters skin total deformation (Uf, mm), which is an indicator for stiffness, and the elasticity (Ur/Uf, %) were calculated.

#### 2.4.3. Molecular markers

Ceramides (epidermal, intercellular lipids) [9,38], NMFs (intracellular hygroscopic and hydrosoluble substances) and its main single compounds pyrrolidone carboxylic acid (PCA), urocanic acid trans (UCA trans), urocanic acid cis (UCA cis), serine and amino acids in total were measured [10,39]. Also proteins in total, histamines

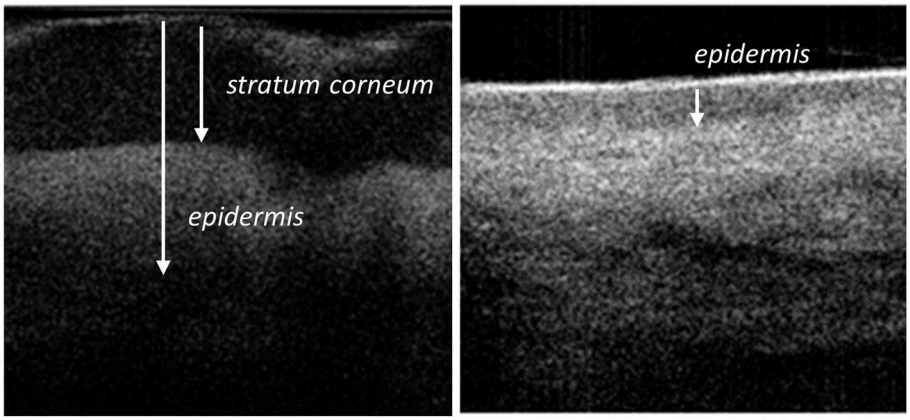


**Fig. 2.** Examples of OCT images (left: plantar heel; right: dorsum).

(neurotransmitters and tissue hormones with pro-inflammatory and itching effects) [40,41], glutathione (GSH) and malondialdehyde (MDA), both biomarkers for oxidative stress, were analyzed [42–45].

The biomarker samples were taken from two zones of the right foot: the dorsum (1–2 toe) and plantar heel (see Fig. 1). Two sterile cotton swabs were wetted in solution consisting of chelating agents and non-ionic surfactants, and then rolled onto the defined foot area for 45 s with a firm pressure. After this, the heads of the swabs were cut from the handle and placed into an eppendorff vessel, which contained a stabilizing storage solution, comprising antioxidant and chelating agents. The samples were immediately frozen, stored in a −20 °C freezer and shipped on dry ice to Synelvia laboratory in France [46]. The biochemical compounds were analyzed by a liquid chromatography-tandem mass spectrometry (LC/MS/MS) system, using an UltiMate™ 3000 liquid chromatography system (ThermoScientific, Sunnyvale, California), coupled to a Quattro Micro Atmosphere Pressure Ionization (API) system (Waters, Milford, Massachusetts).

### 2.5. Data analysis

Demographic characteristics and the number of persons with clinical signs at feet were described using proportions, medians, means, interquartile ranges (IQR) and standard deviations (SD). For clinical and instrumental variables and laboratory parameters medians, means, interquartile ranges (IQR) and standard deviations (SD) were calculated. In addition, mean differences (95% CI) and the Mann Whitney *U* Test were used to determine possible statistically significantly differences between non-diabetics and diabetics. Alpha-values below 5% (two-sided) were applied. Due to the exploratory design all p-values are considered descriptive.

## 3. Results

### 3.1. Participants

More than 200 subjects were contacted, of which 71 were screened. In total 60 participants took part, comprising 40 diabetics and 20 non-diabetics. Based on the clinical evaluation, 20 diabetics were allocated to the group with moderate skin dryness and 20 diabetics to the groups with severe skin dryness at feet. Regarding non-diabetics this applies to 7 (moderate) and 13 (severe). Demographic characteristics for non-diabetics and diabetics are shown in Table 1. Diabetics were older (63.5 (SD 7.8) years) than non-diabetics (56.2 (SD 9.3) years) and had a higher BMI (28.7 (SD 4.3) kg/m$^2$ vs. 24.2 (SD 2.5) kg/m$^2$).

### 3.2. Main results

#### 3.2.1. Clinical parameters

Table 1 shows the results of the clinical assessments. More diabetics were affected by superficial fissures and showed slightly more severe scaling compared to the non-diabetics. The proportions of subjects with at least one callus was higher in the non-diabetic group.

Table 2 presents comparative results of the number of fissures and instrumental measurements at the right foot. Statistically significantly group differences are highlighted in bold. The mean number of superficial fissures in the diabetic group was nearly three times higher than in the non-diabetic group (11.0 (SD 6.2) vs. 3.9 (SD 4.2)). The mean number of 2.2 deep fissures per foot was similar in diabetics and non-diabetics. Results of the left feet were similar and are presented in Appendix C.

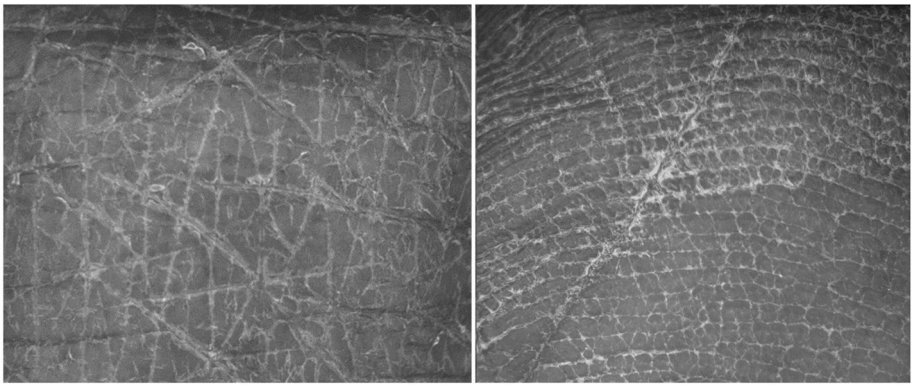

**Fig. 3.** Examples of Visioscan images, left: foot dorsum; right: plantar metatarsal head (with superficial fissure).

**Table 1**
Demographic characteristics and number of persons with clinical signs of dry skin at feet.

| Demographics | Total n = 60 (100%) | Non-diabetics n = 20 (100%) | Diabetics n = 40 (100%) |
|---|---|---|---|
| **Age (years)** | | | |
| Mean (SD) | 61.1 (9.0) | 56.2 (9.3) | 63.5 (7.8) |
| Median (IQR) | 62.0 (42.0–75.0) | 57.0 (47.5–65.5) | 63.0 (57.0–71.0) |
| **Sex female (n, %)** | 28 (47) | 15 (75) | 13 (33) |
| **Body mass index (kg/m$^2$)** | | | |
| Mean (SD) | 27.2 (4.3) | 24.2 (2.5) | 28.7 (4.3) |
| Median (IQR) | 26.6 (24.0–30.8) | 24.3 (23.2–25.4) | 29.3 (25.0–31.2) |
| **Skin dryness group** | | | |
| Moderate (n, %) | 27 (45) | 7 (35) | 20 (50) |
| Severe (n, %) | 33 (55) | 13 (65) | 20 (50) |
| **Scaling of skin** | | | |
| Right foot (n, %) | 60 (100) | 20 (100) | 40 (100) |
| Category 3 (n, %) | 25 (42) | 11 (55) | 14 (35) |
| Category 4 (n, %) | 17 (28) | 4 (20) | 13 (33) |
| Category 5 (n, %) | 18 (30) | 5 (25) | 13 (33) |
| Left foot (n, %) | 60 (100) | 20 (100) | 40 (100) |
| Category 2 (n, %) | 2 (3) | 0 (0) | 2 (5) |
| Category 3 (n, %) | 21 (35) | 10 (50) | 11 (28) |
| Category 4 (n, %) | 18 (30) | 4 (20) | 14 (35) |
| Category 5 (n, %) | 19 (32) | 6 (30) | 13 (33) |
| **Fissures** | | | |
| Right foot (n, %) | 55 (92) | 15 (75) | 40 (100) |
| Superficial fissures (n, %) | 54 (90) | 15 (75) | 39 (98) |
| Deep fissures (n, %) | 28 (47) | 9 (45) | 19 (48) |
| Left foot (n, %) | 57 (95) | 17 (85) | 40 (100) |
| Superficial fissures (n, %) | 57 (95) | 17 (85) | 40 (100) |
| Deep fissures (n, %) | 31 (52) | 11 (55) | 20 (50) |
| **Callus (at least one)** | | | |
| Right foot (n, %) | 32 (53) | 13 (65) | 19 (48) |
| Highest grade = 1 (n, %) | 21 (35) | 9 (45) | 12 (30) |
| Highest grade = 2 (n, %) | 11 (18) | 4 (20) | 7 (18) |
| Left foot (n, %) | 31 (52) | 13 (65) | 18 (45) |
| Highest grade = 1 (n, %) | 21 (35) | 8 (40) | 13 (33) |
| Highest grade = 2 (n, %) | 10 (17) | 5 (25) | 5 (13) |

#### *3.2.2. Biophysical skin properties*

The TEWL values of the investigated areas were similar between diabetics and non-diabetics and showed highest values at the metatarsal head (16.3 (SD 5.9) in total sample).

The stratum corneum hydration was highest at the dorsal skin (20.5 (SD 7.8) in total sample). In the diabetic sample, hydration of stratum corneum was lower at dorsum and at the heels, e.g. 19.6 (SD 6.2) versus 22.5 (SD 10.1) at dorsum.

The pH-values in diabetics as well as in non-diabetics were approximately 5.0 and comparable between diabetics and non-diabetics.

#### *3.2.3. Structural skin properties*

In the total sample, the dorsum had a mean epidermal thickness of 0.11 (SD 0.02) mm and showed therefore the thinnest epidermis of all investigated areas, followed by the metatarsal head and the plantar heel, both with a much thicker epidermis (e.g. plantar heel right 0.97 (SD 0.25) mm). Diabetics and non-diabetics showed similar epidermal thicknesses at plantar skin areas. At the dorsal skin of diabetics a significant thinner epidermis was detected at the right and left foot ($p < 0.001$).

The average roughness Rz at the metatarsal head and the plantar heel were comparable between the diabetics and non-diabetics. However, the roughness of the dorsum was higher in the diabetic group with Rz 47.70 (SD 18.16) versus Rz 40.70 (SD 13.21) at the right and Rz 62.83 (SD 25.89) versus Rz 49.05 (SD 24.20) at the left foot (Appendix C).

At the plantar heel, the total deformation (Uf) was lowest and therefore the skin stiffness highest, followed by the metatarsal head and the dorsum. Stiffness was generally higher in the diabetics at all skin areas. The elasticity (Ur/Uf) was highest at the dorsum of the feet and showed similar values in non-diabetics and diabetics.

#### *3.2.4. Molecular markers*

The concentrations of the molecular markers are shown in Table 3. Statistically significantly group differences are highlighted in bold. The values of almost all markers showed considerably higher values in the diabetic group. The concentration of the markers MDA and GSH were lower in the diabetic sample. GSH could only be detected in the non-diabetic group, but not in the diabetic sample.

## 4. Discussion

### *4.1. Clinical parameters*

Overall, the clinical signs of skin dryness between both groups as well as the mean numbers of deep fissures were comparable. However, there were much more superficial fissures in the diabetic group. The underlying reason is unclear. Oe et al. (2012) proposed different etiologies of superficial and deep fissures in diabetic subjects and described a correlation between autonomic neuropathy and the presence of superficial fissures, while deep fissures were additionally correlated with angiopathy [31]. However, as we excluded diabetic subjects with neuropathy in our study, this explanation is not suitable for our study participants. The higher number of superficial fissures is more likely a result of skin alterations in diabetics, resulting in more superficial cracks.

### *4.2. Biophysical and structural characteristics of the skin*

The mean SC hydration in diabetic subjects was slightly lower at the foot dorsum (19.6 vs. 22.5) and at heels (1.4 vs. 2.6). The clinical relevance of these differences is unclear, but nevertheless it corresponds to the higher number of superficial fissures and the more severe scaling.

**Table 2**
Number of fissures and results of instrumental measurements at right feet.

| | Total n = 60 (100%) | Non-diabetics n = 20 (100%) | Diabetics n = 40 (100%) | Mean difference (95% CI)/p-Value[a] |
|---|---|---|---|---|
| **Fissures per foot** | | | | |
| overall | | | | |
| Mean (SD) | 10.9 (7.4) | **6.0 (5.8)** | **13.3 (6.9)** | **−7.4 (11.0 to -3.8)** |
| Median (IQR) | 11.0 (4.3–16.0) | **5.0 (0.3 to 11.5)** | **14.0 (9.3 to 17.0)** | **< 0.001** |
| superficial | | | | |
| Mean (SD) | 8.7 (6.5) | **3.9 (4.2)** | **11.0 (6.2)** | **−7.1 (-9.8 to -4.4)** |
| Median (IQR) | 8.0 (4.0–14.0) | **3.5 (0.3 to 5.0)** | **11.0 (6.0 to 16.0)** | **< 0.001** |
| deep | | | | |
| Mean (SD) | 2.2 (3.1) | 2.1 (2.9) | 2.3 (3.2) | −0.3 (−2.0 to 1.4) |
| Median (IQR) | 0.0 (0.0–4.0) | 0.0 (0.0–4.5) | 0.0 (0.0–4.0) | 0.81 |
| **TEWL in g/m²/h** | | | | |
| dorsum | | | | |
| Mean (SD) | 8.3 (3.3) | 8.6 (3.0) | 8.1 (3.5) | 0.5 (−1.3 to 2.3) |
| Median (IQR) | 7.8 (6.3–9.1) | 8.2 (6.3–10.2) | 7.8 (6.1–8.9) | 0.42 |
| metatarsal head | | | | |
| Mean (SD) | 16.3 (5.9) | 16.6 (4.1) | 16.1 (6.7) | 0.5; (2.8–3.8) |
| Median (IQR) | 14.8 (12.3–19.1) | 16.1 (14.1–18.5) | 14.0 (11.5–19.2) | 0.21 |
| plantar heel | | | | |
| Mean (SD) | 15.2 (4.9) | 15.1 (4.1) | 15.2 (5.3) | −0.1; (−2.9 to 2.6) |
| Median (IQR) | 14.2 (12.3–18.0) | 14.2 (13.0–17.7) | 14.5 (11.4–18.3) | 0.93 |
| **Stratum corneum hydration** | | | | |
| dorsum | | | | |
| Mean (SD) | 20.5 (7.8) | 22.5 (10.1) | 19.6 (6.2) | 2.9 (−1.3 to 7.1) |
| Median (IQR) | 20.5 (14.5–25.8) | 22.2 (15.7–29.9) | 19.3 (13.5–23.5) | 0.17 |
| metatarsal head | | | | |
| Mean (SD) | 5.9 (4.6) | 5.6 (4.2) | 6.0 (4.9) | −0.4 (−3.0 to 2.1) |
| Median (IQR) | 5.1 (1.8–9.3) | 4.5 (1.7–9.3) | 5.6 (1.8–9.4) | 0.94 |
| plantar heel | | | | |
| Mean (SD) | 1.8 (2.6) | 2.6 (3.1) | 1.4 (2.2) | 1.2 (−0.2 to 2.5) |
| Median (IQR) | 0.45 (0.0–3.1) | 1.1 (0.1–4.4) | 0.3 (0.0–2.9) | 0.10 |
| **Skin surface pH** | | | | |
| dorsum | | | | |
| Mean (SD) | 4.9 (0.6) | 4.8 (0.7) | 5.0 (0.6) | −0.2 (−0.5 to 0.1) |
| Median (IQR) | 4.7 (4.4–5.3) | 4.6 (4.3–5.0) | 4.9 (4.4–5.4) | 0.16 |
| metatarsal head | | | | |
| Mean (SD) | 5.1 (0.4) | 5.0 (0.3) | 5.1 (0.4) | −0.1 (−0.3 to 0.1) |
| Median (IQR) | 5.0 (4.8–5.3) | 5.0 (4.7–5.4) | 5.0 (4.8–5.3) | 0.37 |
| plantar heel | | | | |
| Mean (SD) | 5.1 (0.4) | 5.0 (0.4) | 5.1 (0.4) | −0.1 (−0.3 to 0.1) |
| Median (IQR) | 5.0 (4.8–5.3) | 5.2 (4.8–5.2) | 5.0 (4.8–5.4) | 0.90 |
| **Epidermal thickness in mm** | | | | |
| dorsum | | | | |
| Mean (SD) | 0.11 (0.02) | **0.12 (0.02)** | **0.10 (0.02)** | **0.03 (0.02 to 0.04)** |
| Median (IQR) | 0.10 (0.09–0.12) | **0.12 (0.10 to 0.15)** | **0.10 (0.08 to 0.11)** | **< 0.001** |
| metatarsal head | | | | |
| Mean (SD) | 0.79 (0.22) | 0.77 (0.25) | 0.80 (0.22) | −0.03 (−0.16 to 0.10) |
| Median (IQR) | 0.80 (0.60–0.94) | 0.77 (0.56–0.91) | 0.82 (0.66–0.94) | 0.56 |
| plantar heel | | | | |
| Mean (SD) | 0.97 (0.25) | 1.02 (0.30) | 0.95 (0.23) | 0.07 (−0.07 to 0.21) |
| Median (IQR) | 1.00 (0.75–1.13) | 1.08 (0.80–1.31) | 1.00 (0.73–1.07) | 0.31 |
| **Skin Surface Topography Rz in µm** | | | | |
| dorsum | | | | |
| Mean (SD) | 45.37 (16.89) | 40.70 (13.21) | 47.70 (18.16) | −7.0 (−16.2 to 2.2) |
| Median (IQR) | 39.25 (32.63–53.88) | 36.5 (31.13–49.75) | 40.75 (33.50–60.13) | 0.17 |
| metatarsal head | | | | |
| Mean (SD) | 64.28 (21.14) | 64.88 (18.25) | 63.99 (22.66) | 0.9 (−10.8 to 12.6) |
| Median (IQR) | 59.75 (49.00–79.25) | 64.00 (50.50–80.25) | 58.75 (49.00–78.25) | 0.60 |
| plantar heel | | | | |
| Mean (SD) | 75.42 (23.90) | 75.10 (26.54) | 75.58 (22.83) | −0.5 (−13.7 to 12.7) |
| Median (IQR) | 76.00 (58.5–85.38) | 73.5 (52.63–92.63) | 76.00 (61.50–84.75) | 0.95 |
| **Total deformation Uf in mm** | | | | |
| dorsum | | | | |
| Mean (SD) | 0.55 (0.13) | **0.66 (0.13)** | **0.49 (0.09)** | **0.17 (0.11 to 0.23)** |
| Median (IQR) | 0.53 (0.45–0.63) | **0.68 (0.58 to 0.74)** | **0.51 (0.42 to 0.57)** | **< 0.001** |
| metatarsal head | | | | |
| Mean (SD) | 0.40 (0.14) | **0.48 (0.10)** | **0.36 (0.13)** | **0.12 (0.06 to 0.19)** |
| Median (IQR) | 0.39 (0.30–0.49) | **0.44 (0.41 to 0.55)** | **0.34 (0.24 to 0.45)** | **0.001** |
| plantar heel | | | | |
| Mean (SD) | 0.25 (0.11) | 0.28 (0.13) | 0.24 (0.10) | 0.04 (−0.02 to 0.11) |
| Median (IQR) | 0.26 (0.17–0.34) | 0.27 (0.17–0.40) | 0.24 (0.17–0.31) | 0.21 |
| **Elasticity Ur/Uf** | | | | |
| dorsum | | | | |
| Mean (SD) | 0.29 (0.12) | 0.33 (0.17) | 0.27 (0.08) | 0.06 (−0.02 to 0.14) |
| Median (IQR) | 0.27 (0.21–0.33) | 0.27 (0.20–0.43) | 0.27 (0.21–0.32) | 0.43 |
| metatarsal head | | | | |

(*continued on next page*)

**Table 2** (*continued*)

| | | | | |
|---|---|---|---|---|
| Mean (SD) | 0.15 (0.05) | **0.13 (0.04)** | **0.16 (0.06)** | **−0.03 (-0.06 to 0.001)** |
| Median (IQR) | 0.14 (0.11–0.18) | **0.12 (0.10 to 0.14)** | **0.16 (0.12 to 0.19)** | **0.04** |
| plantar heel | | | | |
| Mean (SD) | 0.20 (0.11) | 0.22 (0.13) | 0.19 (0.09) | 0.02 (−0.04 to 0.08) |
| Median (IQR) | 0.17 (0.13–0.24) | 0.18 (0.13–0.25) | 0.17 (0.12–0.23) | 0.64 |

[a] Mann-Whitney *U* test.

The skin functional parameter TEWL was generally comparable between the diabetic and non-diabetic group, which is consistent with previous studies [25,47,48]. Sakai et al. (2003) as well as Sekijima et al. (2018) investigated skin changes in mice, in which diabetes symptoms were previously induced. Both reported that in the diabetic mice, a decrease of SC hydration was observed without having any impairment of the SC barrier function, measured by means of TEWL values [47,48]. Sakai et al. could support their findings in a later study, including 49 patients with diabetes (78% of patients with type 2) [25]. Diabetic patients with high fasting plasma glucose (FPG) had a significant lower SC hydration status and similar TEWL values compared to diabetics with low FPG [25]. They concluded, that the state of SC hydration is rather influenced by the current hyperglycemic state at the time of the measurement than by the long-term glucose parameter HbA1c. Seirafi et al. investigated biophysical characteristics of diabetics (89% with type 2) and non-diabetics (2009) at forehead, forearm and lower legs. In this study, neither SC hydration values nor TEWL showed a significant difference [26].

The skin surface pH showed values in the normal range of about 5 in both groups. In a study of Yosipovitch et al. the skin pH of non-insulin dependent diabetics and healthy volunteers was compared. Only in the more moist and intertriginous skin areas of diabetics significantly higher pH values were measured. However, at the forearms no differences of the pH values were observed, which is in accordance to our results [28,49,50].

Our results showed that the differences of the parameters skin roughness, epidermal thickness and SC hydration were more pronounced at the dorsal skin areas. The dorsal skin of the diabetics showed higher roughness, was thinner and less hydrated, clinically possibly leading to higher fragility. Some studies suggest an epidermal thinning due to diabetes mellitus [51–53]. However, clear results were only shown in studies with rats [52,53]. Skin at dorsum (patterned skin) is morphological different to plantar (hairless) skin. This may be one reason why differences between diabetic and non-diabetic skin are more pronounced at dorsum.

Structural stiffness was substantially higher in the diabetic group sample at all investigated areas. This observation is supported by previous studies, which reported collagen alterations under chronic hyperglycemic conditions, like the increase of collagen fiber diameter and the cross linking of collagen fibrils due to non-enzymatic glycosylation, which are finally leading to an increased cutaneous rigidity [1,24,51,54]. It was shown that tissue stiffening considerably magnifies stress levels at plantar skin and cause significant stress concentrations especially at the plantar forefoot during standing [55]. These increased stress concentrations may cause micro-tears to the skin and may be a reason for the significant higher number of fissures in the diabetic group [14,55]. However the question rises why the number of fissures were increased in superficial fissures and not in deep fissures, which extend to the dermis, even though it is the dermis where collagen fibers are located [55]. Further studies are needed to investigate the possible association between skin stiffness and the occurrence of skin tears.

### 4.3. Molecular markers

The concentration of ceramides, the main component of SC lipids, was approximately two times higher in diabetics compared to non-diabetics. Our study results fit to previous findings of Sakai et al. in diabetic mice skin, who reported higher amounts of ceramides and other SC lipids in these animals compared to control mice [3,48]. In this study diabetic mice showed however lower triglyceride levels, which indicates that in diabetics only triglyceride metabolism may be impaired in patterned skin but not the metabolism of other lipids.

In the diabetics of our study the contents of NMFs in total as well as its primary compounds amino acids, serine, PCA and UCA trans were clearly higher [10,56,57]. Sakai et al. reported that in mice with induced diabetes, which showed a clear decrease of SC water content, the amount of profilaggrin and filaggrin were almost unchanged and the content of the NMF component amino acid in the SC was higher compared to the control mice [48]. In elderly people dry skin is a frequent condition, which is explained, inter alia, by a decrease of NMFs and lipid content [3,58]. Our results as well as the previous findings of Sakai et al. indicate, that the etiology of dry skin in diabetics might be different to senile xerosis sensu stricto. Dry skin in diabetics seems to be based on a more complex mechanism than only a decline of filaggrin/NMFs or intercellular lipids.

Interestingly we observed a doubled histamine level in diabetics compared to non-diabetics. This is quite relevant for diabetics as histamine is known for its pro-inflammatory and itching effect, which could explain an increased inflammation in diabetic foot skin. In addition, currently histamine is discussed to be involved in skin barrier defects and in thinning of the epidermis [40,41,59]. This observation raise the question, if specific topical treatment using antihistamines is advantageous in diabetics with severe skin dryness in order to improve skin barrier stabilisation. Further studies are necessary to investigate the role of histamines in plantar inflammation and normalization in skin barrier defects.

Regarding the biomarkers of oxidative stress, GSH and MDA, we observed lower concentrations in diabetics. An astonishing result was that glutathione could only be detected in non-diabetics, but not at all in the diabetic sample. GSH is a relevant antioxidant factor and protector from oxidative damage as it reacts with reactive oxygen species to the oxidized form glutathione disulfide (GSSG). Not detecting GSH in our diabetic sample thus indicates an increased consumption of GSH and therefore a clear increase of oxidative stress in diabetics [45,60]. MDA however showed contradictory results. MDA is generated by lipid peroxidation, a process during which reactive oxygen species react with cell lipids. It is used as a biomarker of oxidative stress due to lipid peroxidation [42,43]. Studies have shown that its concentration is increased in diabetes mellitus [43] and that MDA has stiffening effects on collagenous tissues [44,61]. Therefore, it was expected that MDA would be higher in the sample of diabetics. However, in comparison to the non-diabetics the concentration was lower both at dorsum and at heel. The reason for this could be that molecular markers were only resolved from the stratum corneum and not analyzed from deeper tissue layers, from urine or from blood samples like in other studies [43,45,61].

### 4.4. Limitations

Because of the exploratory nature of this study and the small sample size, confirmatory statements cannot be made. Although groups were similar in terms of clinical signs of skin dryness, the diabetic sample were slightly older and had a higher BMI. Whether this affected the measured skin barrier estimates or the molecular markers is unclear. The possibility should be taken into account that the increased amounts

**Table 3**
Biochemical markers right feet.

| | Total n = 45 (100%) | Non-diabetics n = 15 (100%) | Diabetics n = 30 (100%) | Mean difference (95% CI)/p-Value[a] |
|---|---|---|---|---|
| **Σ Ceramides (UA/cm²)** | | | | |
| dorsum | | | | |
| Mean (SD) | 220.8 (150.2) | **95.1 (35.4)** | **283.6 (146.2)** | **−188.4 (-245.7 to -131.2)** |
| Median (IQR) | 182.0 (111.8–313.8) | **99.1 (67.5 to 126.2)** | **232.7 (178.9 to 361.9)** | **< 0.001** |
| plantar heel | | | | |
| Mean (SD) | 693.1 (488.0) | **430.4 (97.1)** | **824.5 (550.7)** | **−394.2 (-605.1 to -183.2)** |
| Median (IQR) | 526.9 (408.8–793.7) | **422.1 (391.7 to 475.7)** | **616.5 (442.2 to 1157.6)** | **0.003** |
| **Σ NMFs (µg/cm²)** | | | | |
| dorsum | | | | |
| Mean (SD) | 89.5 (63.4) | 65.0 (37.1) | 101.7 (70.4) | −36.7; (−76.0 to 2.6) |
| Median (IQR) | 67.8 (47.3–110.8) | 57.5 (41.8–88.8) | 87.8 (52.1–113.6) | 0.05 |
| plantar heel | | | | |
| Mean (SD) | 182.1 (106.7) | 148.4 (86.0) | 199.0 (113.2) | −50.6 (−117.6 to 16.4) |
| Median (IQR) | 134.8 (102.7–280.6) | 126.4 (85.4–222.1) | 135.7 (112.5–296.8) | 0.11 |
| **Σ Amino Acids (UA/cm²)** | | | | |
| dorsum | | | | |
| Mean (SD) | 58.3 (35.8) | **39.8 (12.7)** | **67.5 (40.1)** | **−27.7 (-44.0 to -11.5)** |
| Median (IQR) | 45.2 (35.6–69.4) | **40.2 (35.3 to 52.1)** | **59.0 (38.0 to 87.0)** | **0.02** |
| plantar heel | | | | |
| Mean (SD) | 123.0 (63.9) | **90.9 (42.2)** | **139.0 (67.4)** | **−48.0 (-81.3 to -14.8)** |
| Median (IQR) | 113.0 (65.9–167.3) | **74.1 (54.8 to 125.0)** | **120.9 (78.8 to 193.8)** | **0.01** |
| **Serine (µg/cm²)** | | | | |
| dorsum | | | | |
| Mean (SD) | 59.0 (38.3) | **42.4 (25.5)** | **67.3 (41.2)** | **−24.9(–48.4 to -1.5)** |
| Median (IQR) | 50.9 (30.7–82.2) | **38.4 (24.1 to 59.0)** | **59.8 (37.3 to 86.2)** | **0.04** |
| plantar heel | | | | |
| Mean (SD) | 130.2 (71.6) | **99.1 (60.6)** | **145.8 (72.5)** | **−46.7 (-90.5 to -2.8)** |
| Median (IQR) | 105.0 (75.2–187.8) | **80.6 (52.8 to 167.6)** | **111.2 (91.1 to 196.3)** | **0.02** |
| **PCA (µg/cm²)** | | | | |
| dorsum | | | | |
| Mean (SD) | 75.4 (52.1) | 54.1 (31.2) | 86.1 (57.4) | −32.0 (−64.1 to 0.1) |
| Median (IQR) | 61.2 (40.7–96.5) | 50.5 (33.1–76.6) | 70.7 (44.3–97.9) | 0.05 |
| plantar heel | | | | |
| Mean (SD) | 156.7 (92.1) | 125.5 (75.4) | 172.3 (96.8) | −46.8 (−104.4 to 10.9) |
| Median (IQR) | 116.5 (88.3–237.9) | 102.2 (71.0–196.6) | 122.2 (96.1–248.9) | 0.07 |
| **UCATrans (µg/cm²)** | | | | |
| dorsum | | | | |
| Mean (SD) | 8.9 (8.8) | **6.0 (4.6)** | **10.3 (10.0)** | **−4.3 (-9.8 to 1.2)** |
| Median (IQR) | 5.6 (3.7–11.3) | **4.9 (3.4 to 6.2)** | **7.8 (4.6 to 13.4)** | **0.03** |
| plantar heel | | | | |
| Mean (SD) | 18.9 (12.1) | 16.4 (9.7) | 20.2 (13.2) | −3.8 (−11.5 to 4.0) |
| Median (IQR) | 14.2 (9.7–27.7) | 14.2 (8.0–22.9) | 14.6 (10.3–29.9) | 0.39 |
| **UCACis (µg/cm²)** | | | | |
| dorsum | | | | |
| Mean (SD) | 5.2 (4.1) | 4.9 (2.6) | 5.3 (4.7) | −0.4 (−2.6 to 1.8) |
| Median (IQR) | 3.8 (2.4–6.6) | 4.5 (3.5–6.4) | 3.7 (2.0–8.1) | 0.44 |
| plantar heel | | | | |
| Mean (SD) | 6.5 (5.6) | 6.5 (5.5) | 6.5 (5.8) | −0.03 (−3.7 to 3.6) |
| Median (IQR) | 3.9 (2.0–9.4) | 3.9 (2.0–8.8) | 3.8 (2.0–10.2) | 0.89 |
| **Histamine (ng/cm²)** | | | | |
| dorsum | | | | |
| Mean (SD) | 10.8 (10.2) | **5.3 (2.9)** | **13.5 (11.5)** | **−8.2 (-12.7 to -3.7)** |
| Median (IQR) | 8.8 (3.6–13.0) | **4.8 (2.8 to 7.6)** | **11.3 (5.6 to 21.0)** | **0.005** |
| plantar heel | | | | |
| Mean (SD) | 18.5 (14.3) | **9.0 (5.2)** | **23.3 (15.0)** | **−14.3 (-20.5 to -8.1)** |
| Median (IQR) | 16.2 (7.5–24.0) | **6.7 (5.4 to 12.6)** | **18.9 (14.2 to 30.0)** | **< 0.001** |
| **Total proteins (µg/ml)** | | | | |
| dorsum | | | | |
| Mean (SD) | 37.7 (18.0) | **28.7 (15.2)** | **42.2 (17.7)** | **−13.6 (-24.4 to -2.7)** |
| Median (IQR) | 35.4 (26.1–45.3) | **28.9 (15.9 to 35.9)** | **38.6 (29.3 to 50.6)** | **0.02** |
| plantar heel | | | | |
| Mean (SD) | 89.8 (50.5) | **66.5 (56.2)** | **101.5 (43.8)** | **−35.0 (-65.7 to -4.3)** |
| Median (IQR) | 80.2 (51.4–126.3) | **49.6 (32.2 to 73.7)** | **93.6 (71.7 to 128.4)** | **0.003** |
| **GSH (ng/cm²)** | | | | |
| dorsum | | | | |
| Mean (SD) | 31.5 (8.0) | 31.5 (8.0) | ND[b] | – |
| Median (IQR) | 31.60 (24.4–37.2) | 31.6 (24.4 tp 37.2) | ND | – |
| plantar heel | | | | |
| Mean (SD) | 35.9 (9.4) | 35.9 (9.4) | ND | – |
| Median (IQR) | 36.5 (31.4–41.6) | 36.5 (31.4–41.6) | ND | – |
| **MDA (ng/cm²)** | | | | |
| dorsum | | | | |
| Mean (SD) | 52.0 (10.2) | **60.8 (7.2)** | **47.7 (8.6)** | **13.1 (7.9 to 18.3)** |
| Median (IQR) | 52.3 (43.4–60.1) | **61.2 (55.8 to 64.4)** | **47.1 (41.4 to 53.6)** | **< 0.001** |

(*continued on next page*)

**Table 3** (*continued*)

| | | | | |
|---|---|---|---|---|
| plantar heel | | | | |
| Mean (SD) | 61.3 (14.5) | **66.7 (12.5)** | **58.7 (14.9)** | **8.0 (-0.6 to 16.6)** |
| Median (IQR) | 59.3 (51.9–69.2) | **67.8 (57.3 to 75.8)** | **57.8 (49.5 to 61.7)** | **0.03** |

[a] Mann-Whitney *U* test.

of ceramides, NMFs and other biomarkers in diabetics were because the diabetics had more superficial fissures at foot and a higher average roughness at dorsum. These factors could entail that more molecular markers were collected. However, not all biomarkers showed increased concentrations in diabetics.

## 5. Conclusion

Most clinical signs and skin barrier characteristics of xerotic foot skin in diabetics and non-diabetics are similar. However, dry diabetic foot skin is much stiffer and the number of superficial fissures is noticeable higher, indicating a higher risk for superficial wounding. The reason for the high number of superficial fissures may be because of the differences in molecular concentrations together with the increased stiffness.

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## Ethical approval

An ethical approval by the responsible Ethics Committee of the Charité - Universitätsmedizin Berlin has been obtained (EA1/207/16). The study was carried out in accordance with the principles of the Declaration of Helsinki and the guidelines of Good Clinical Practice (ICH GCP). Written informed consent was received before inclusion.

## Declaration of competing interest

The authors AL, MA, TT, TB, AM, UBP and JK declare that they have no competing interests. NL is employed by Galderma S.A.

## Appendix

*Appendix A. Allocation to skin dryness groups*

| Degree of skin dryness | Criteria for group allocation |
|---|---|
| severe dryness at feet | At least one foot of subject:<br>(1) Met the criteria of grade 5 in regard of scaling (see Rogers et al., 1989, Appendix B)<br>(2) And/Or showed deep heel fissures extending to dermis (see Oe et al., 2012) |
| moderate dryness at feet | At least one foot of subject:<br>(1) Met the criteria of grades 3 and 4 in regard of scaling (see Rogers et al., 1989, Appendix B)<br>(2) And/Or showed only superficial fissures limited to the epidermis (see Oe et al., 2012) |

*Appendix B. Categorization of dry skin according to Rogers et al., 1989*

| Degree of severity | Grade | Definition |
|---|---|---|
| Normal | 0 | Normal skin; no sign of dryness |
| Mild | 1 | Dusty appearance Or occasional minute skin flake |
| | 2 | Generalized dusty or ashy appearance or presence of many particles of minute skin flakes. May have small “lines” or “crevices” filled with nondescript material |
| Moderate | 3 | Defined (usually circular) scaling. Borders of scales are flat. May include characteristics of grade 1 or 2, as well as defined scaling |
| | 4 | Well-defined scaling with raised edges Size of scale plates may be larger than in grade 3 |
| Severe | 5 | Large-scale plates with increased lifting of edges. Small fissures may be seen between some scale plates. No erythema present |
| | 6 | Large-scale plates with high lifting of scale edges. Deep erythematous fissures between scale plates. Includes eczema craquele |

*Appendix C. Number of fissures and instrumental measurements at left feet*

| | Total n = 60 (100%) | Non-diabetics n = 20 (100%) | Diabetics n = 40 (100%) | Mean difference (95% CI)/p-Value[a] |
|---|---|---|---|---|
| **Fissures per foot** | | | | |
| overall | | | | |
| (Mean, SD) 4,25 | 10.9 (7.2) | 6.5 (5.8) | 13.1 (6.9) | −6.6; −10.2 to −2.9 |
| (Median, IQR) | 10.0 (4.3–16.0) | 5.5 (2.0–9.8) | 14.0 (7.0–19.0) | 0.001 |
| superficial | | | | |
| (Mean, SD) | 8.9 (6.4) | 4.5 (5.2) | 11.1 (5.8) | −6.7; −9.8 to −3.6 |
| (Median, IQR) | 7.0 (3.0–14.0) | 3.0 (1.3–4.0) | 12.0 (5.3–15.8) | < 0.001 |
| deep | | | | |
| (Mean, SD) | 2.0 (2.6) | 2.1 (2.6) | 1.9 (2.7) | 0.1; −1.3 to 1.6 |
| (Median, IQR) | 1.0 (0.0–3.8) | 1.0 (0.0–4.8) | 0.5 (0.0–3.0) | 0.83 |

| | | | | |
|---|---|---|---|---|
| **TEWL in g/m²/h** | | | | |
| dorsum | | | | |
| (Mean, SD) | 7.2 (2.9) | 7.4 (3.0) | 7.2 (2.9) | 0.3; −1.3 to 1.9 |
| (Median, IQR) | 6.6 (4.9–8.7) | 6.7 (5.3–8.7) | 6.6 (4.7–9.1) | 0.68 |
| metatarsal head | | | | |
| (Mean, SD) | 17.4 (7.3) | 16.0 (5.0) | 18.1 (8.2) | −2.0; −6.1 to 2.0 |
| (Median, IQR) | 15.5 (13.7–20.6) | 15.3 (14.3–18.0) | 15.9 (13.4–21.1) | 0.63 |
| plantar heel | | | | |
| (Mean, SD) | 15.4 (5.6) | 14.1 (5.8) | 16.0 (5.5) | −1.9; −5.0 to 1.1 |
| (Median, IQR) | 13.8 (11.1–18.0) | 13.1 (10.8–14.9) | 14.7 (11.7–19.5) | 0.11 |
| **Stratum corneum hydration** | | | | |
| dorsum | | | | |
| (Mean, SD) | 21.3 (8.9) | 22.8 (10.3) | 20.6 (8.1) | 2.2; −2.6 to 7.1 |
| (Median, IQR) | 20.6 (13.9–26.8) | 23.2 (13.9–32.1) | 18.6 (14.1–24.9) | 0.36 |
| metatarsal head | | | | |
| (Mean, SD) | 6.6 (5.9) | 6.8 (5.3) | 6.5 (6.3) | 0.3; −3.0 to 3.6 |
| (Median, IQR) | 5.7 (2.3–9.4) | 7.0 (2.3–11.6) | 5.5 (2.2–9.3) | 0.60 |
| plantar heel | | | | |
| (Mean, SD) | 2.1 (2.8) | 3.2 (3.4) | 1.6 (2.3) | 1.6; −0.1 to 3.3 |
| (Median, IQR) | 0.7 (0.0–4.1) | 1.8 (0.0–6.2) | 0.6 (0.0–2.8) | 0.16 |
| **Skin surface pH** | | | | |
| dorsum | | | | |
| (Mean, SD) | 4.9 (0.6) | 4.7 (0.5) | 5.0 (0.6) | −0.3; −0.6 to 0.0 |
| (Median, IQR) | 4.7 (4.5–5.3) | 4.7 (4.3–5.0) | 4.8 (4.6–5.3) | 0.10 |
| metatarsal head | | | | |
| (Mean, SD) | 5.1 (0.3) | 5.0 (0.3) | 5.1 (0.4) | −0.1; −0.3 to 0.1 |
| (Median, IQR) | 5.1 (4.9–5.3) | 5.1 (4.7–5.3) | 5.0 (4.9–5.4) | 0.53 |
| plantar heel | | | | |
| (Mean, SD) | 5.1 (0.4) | 5.1 (0.4) | 5.0 (0.4) | 0.0; −0.2 to 0.3 |
| (Median, IQR) | 5.0 (4.7–5.4) | 5.1 (4.7–5.5) | 5.0 (4.7–5.3) | 0.63 |
| **Epidermal Thickness in mm** | | | | |
| dorsum | | | | |
| (Mean, SD) | 0.10 (0.02) | 0.11 (0.03) | 0.09 (0.02) | 0.02; 0.01 to 0.03 |
| (Median, IQR) | 0.10 (0.08–0.11) | 0.11 (0.10–0.13) | 0.09 (0.08–0.10) | 0.001 |
| metatarsal head | | | | |
| (Mean, SD) | 0.81 (0.25) | 0.88 (0.26) | 0.78 (0.24) | 0.11; −0.03 to 0.25 |
| (Median, IQR) | 0.77 (0.63–0.97) | 0.83 (0.68–1.08) | 0.75 (0.63–0.90) | 0.17 |
| plantar heel | | | | |
| (Mean, SD) | 0.92 (0.25) | 0.93 (0.30) | 0.92 (0.23) | 0.01; −0.13 to 0.16 |
| (Median, IQR) | 0.90 (0.75–1.10) | 0.90 (0.75–1.14) | 0.89 (0.74–1.07) | 0.88 |
| **Skin Surface Topography Rz in µm** | | | | |
| dorsum | | | | |
| (Mean, SD) | 58.23 (25.97) | 49.05 (24.20) | 62.83 (25.89) | −13.8; −27.7 to 0.1 |
| (Median, IQR) | 49.00 (39.63–76.50) | 39.75 (34.88–58.75) | 55.50 (42.50–81.63) | 0.01 |
| metatarsal head | | | | |
| (Mean, SD) | 78.44 (22.30) | 78.73 (21.70) | 78.30 (22.87) | 0.4; −11.9 to 12.8 |
| (Median, IQR) | 77.25 (60.88–95.63) | 74.75 (64.50–94.25) | 78.75 (59.63–98.50) | 0.92 |
| plantar heel | | | | |
| (Mean, SD) | 89.77 (26.22) | 90.60 (27.77) | 89.35 (25.76) | 1.3; −13.2 to 15.7 |
| (Median, IQR) | 86.25 (68.5–111.75) | 88.75 (70.63–117.25) | 86.00 (67.25–108.13) | 0.83 |
| **Total deformation Uf in mm** | | | | |
| dorsum | | | | |
| (Mean, SD) | 0.57 (0.14) | 0.69 (0.14) | 0.51 (0.10) | 0.17; 0.11 to 0.24 |
| (Median, IQR) | 0.54 (0.48–0.67) | 0.69 (0.58–0.78) | 0.52 (0.45–0.57) | < 0.001 |
| metatarsal head | | | | |
| (Mean, SD) | 0.39 (0.12) | 0.47 (0.13) | 0.35 (0.10) | 0.12; 0.06 to 0.18 |
| (Median, IQR) | 0.37 (0.30–0.45) | 0.44 (0.38–0.56) | 0.35 (0.27–0.43) | 0.001 |
| plantar heel | | | | |
| (Mean, SD) | 0.26 (0.11) | 0.30 (0.11) | 0.24 (0.10) | 0.05; −0.01 to 0.11 |
| (Median, IQR) | 0.26 (0.19–0.34) | 0.32 (0.22–0.36) | 0.23 (0.18–0.31) | 0.06 |
| **Elasticity Ur/Uf** | | | | |
| dorsum | | | | |
| (Mean, SD) | 0.30 (0.11) | 0.34 (0.13) | 0.28 (0.10) | 0.06; −0.00 to 0.11 |
| (Median, IQR) | 0.28 (0.23–0.34) | 0.30 (0.25–0.38) | 0.27 (0.20–0.33) | 0.14 |
| metatarsal head | | | | |
| (Mean, SD) | 0.14 (0.05) | 0.12 (0.03) | 0.15 (0.06) | −0.03; −0.06 to −0.00 |
| (Median, IQR) | 0.13 (0.10–0.17) | 0.11 (0.09–0.14) | 0.13 (0.12–0.17) | 0.06 |
| plantar heel | | | | |
| (Mean, SD) | 0.19 (0.09) | 0.21 (0.13) | 0.18 (0.07) | 0.02; −0.04 to 0.08 |
| (Median, IQR) | 0.17 (0.13–0.22) | 0.16 (0.12–0.25) | 0.17 (0.14–0.22) | 0.84 |

[a] Mann-Whitney *U* test.

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