DISSERTATION

Dry skin in older care dependent people

Trockene Haut bei älteren pflegebedürftigen Menschen

zur Erlangung des akademischen Grades
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List of abbreviations

ATC = Anatomical Therapeutic Chemical

AU = Arbitrary units

BMI = Body mass index

Cluster-RCT = Cluster-randomized controlled trial

ELISA = enzyme-linked immunosorbent assay

EPUAP = European Pressure Ulcer Advisory Panel

GDS = Global Deterioration Scale

GLOBIAD = The Ghent Global IAD Categorization Tool

IAD = Incontinence-associated dermatitis

ICD = International Classification of Diseases

IL = Interleukin

IQR = Interquartile range

NMFs = Natural moisturizing factors

NPIAP = National Pressure Injury Advisory Panel

OD = Odds ratio

ODS = Overall dry skin score

pH = pH hydrogen ion concentration

PPPIA = Pan Pacific Pressure Injury Alliance

PUs = Pressure ulcers

RCT = Randomized controlled trial

SC = Stratum corneum

SCH = Stratum corneum hydration

SD = Standard deviation

TEWL = Transepidermal water loss

TP = Total protein

Abstract

The prevalence of xerosis cutis (dry skin) in older people is high. Numerous molecular markers related to dry skin have been studied but there is still no agreement about the most relevant markers. Also, very little is known about the factors associated with different severities of dry skin. One aim of this thesis work was to identify the most useful markers for dry skin assessment, to find out the possible factors related with varying severities of skin dryness and to outline the relation between care dependency and leave-on product application. In addition, as dry skin poses a risk for skin tears, the effect of a leave-on product on the dermoepidermal adhesion of dry skin were investigated; the findings could be useful in reducing such a risk.

A systematic review was conducted to summarize the molecular markers of dry skin as well as to describe their association with dry skin severities and etiologies. The included 21 full-text articles reported 72 different molecules. Substantial heterogeneity was seen in terms of selection of markers and analytical methods. The evidence of the association between the amount of the markers and the condition of dry skin was heterogeneous, too.

To find out the factors related with varying severities of dry skin, baseline data of 314 nursing home residents, who participated in a cluster-randomized controlled trial, was compared between two groups with mild and severe dry skin. On distal body areas, more severe dryness was observed. Except for stratum corneum hydration (SCH) and skin surface pH, there were minor or no differences between the groups. Residents with severe dryness received leave-on products infrequently. Care dependent residents received the products more frequently and their legs and feet were less dry. Frequent skin care done by the nurses seems to be helpful in improving skin dryness in this population.

To investigate the effect of humectant enriched leave-on product on dermoepidermal adhesion, an exploratory, randomized controlled trial was conducted with 12 older adults having dry skin. Participants' forearms were assigned to treatment (product containing 5% urea) or control (no treatment) groups. At baseline, weeks 4 and 8, skin physiological and structural parameters were measured. Suction blisters were produced at week 8. In the blister roof and interstitial fluid, interleukin (IL)-1α, IL-6, and IL-8 were quantified. After 8 weeks of treatment, SCH was higher (median difference 11.6 AU) whereas transepidermal water loss (median difference -2.8 g/m^2/h), pH (median difference -0.14), mean roughness (Rz difference -12.2 µm), overall dry skin score (median

difference -1), and IL-1α (median difference -452 fg/µg total protein) were lower in the treatment arm in comparison to the control arm. On the treated forearm skin, time to blister formation was longer, indicating stronger dermoepidermal adhesion. This clarifies in part how topical application helps in preventing skin tears.

Zusammenfassung

Die Prävalenz von Xerosis cutis bei älteren Menschen ist hoch. Zahlreiche molekulare Marker sind auf ihren Zusammenhang mit Hauttrockenheit untersucht worden, bislang ohne Identifizierung der wichtigsten relevanten. Außerdem ist nur sehr wenig über die Assoziation von Faktoren und den verschiedenen Schweregraden der trockenen Haut bekannt. Ziel dieser Arbeit war es, die wichtigsten Marker für die Beurteilung trockener Haut zu identifizieren. Darüber hinaus sollten die möglichen Faktoren, die mit den verschiedenen Schweregraden der Hauttrockenheit assoziiert sind, bestimmt und mögliche Zusammenhänge zwischen (Haut-) Pflegeabhängigkeit und der Anwendung von Hautpflegeprodukte beschrieben werden. Da trockene Haut ein Risikofaktor für Hautrisse ist, wurden auch die Auswirkungen eines Hautpflegeprodukts auf die dermoepidermale Adhäsion der trockenen Haut untersucht, was zur Verringerung des Risikos von Hautrissen beitragen kann.

In einer systematischen Übersichtarbeit wurden die molekularen Biomarker zusammengefasst und ihr Zusammenhang mit trockener Haut beschrieben. In den 21 eingeschlossenen Volltextartikeln wurden 72 verschiedene Moleküle berichtet. Es zeigte sich eine erhebliche Heterogenität in Bezug auf die Marker und des Zusammenhangs zwischen der Menge der Marker und des Status der Hauttrockenheit.

Baselinedaten von 314 Pflegeheimbewohnern, die an einer Cluster-randomisierten kontrollierten Studie teilnahmen, wurden zwischen Gruppen mit leichter und schwerer trockener Haut verglichen. Mit Ausnahme der Hydratation und des Haut-pH-Werts gab es geringfügige oder keine Unterschiede zwischen den beiden Gruppen. Pflegebedürftige Bewohner hatten weniger stark trockene Haut. Hautpflege durch das Pflegepersonal könnte, wenn sie häufig genug durchgeführt wird, bei der Verbesserung von trockener Haut bei Pflegeheimbewohnern hilfreich sein.

Um die Wirkung eines Hautpflegeprodukts auf die dermoepidermale Adhäsion zu untersuchen, wurde eine randomisierte, kontrollierte Studie durchgeführt. Zwölf älteren Teilnehmern mit trockener Haut wurde je einen Unterarm einer Behandlungs- (Lipophile

Harnstoff-Creme 5%) oder Kontrollgruppe (keine Behandlung) zugewiesen. Die Hautparameter wurden zu Studienbeginn, an Wochen 4 und 8 gemessen. An Woche 8 wurden Saugblasen induziert. Im Blasendach und Flüssigkeit wurden Interleukin (IL)-1α, lL-6 und IL-8 quantifiziert. Im Behandlungsarm war die Hydratation höher (mediane Differenz 11,6 AU). Dagegen waren transepidermaler Wasserverlust (mediane Differenz -2,8 g/m^2/h), pH-Wert (mediane Differenz -0,14), mittlere Rauheit (Rz-Differenz -12,2 µm), Bewertung der Hauttrockenheit (mediane Differenz -1) und IL-1α (mediane Differenz -452 fg/µg Gesamtprotein) im Vergleich zum Kontrollarm niedriger. Am Behandlungsarm war die Zeit bis zur Blasenbildung länger, was auf eine stärkere dermoepidermale Adhäsion hinweist. Dies könnte teilweise erklären, weshalb die topische Anwendung von Hautpflegeprodukten dazu beiträgt, Hautrisse zu verhindern.

1 Introduction

1.1 Background

The skin acts as a barrier and provides mechanical protection to the human body from environmental influences. It also performs other tasks including sensory perception, thermal regulation and defense against microorganisms. Considering its essential roles, it is very important to maintain skin's integrity and optimal function over the entire span of life. Aging is a natural process of life which affects multiple organ systems including the skin. The skin undergoes many physiological and morphological changes. It loses resistance against outside environmental impacts and the regeneration capacity is reduced compared to the younger age (1-3), making the older adults vulnerable to cutaneous diseases and skin injuries (2). The changes might also be manifested by reduced stratum corneum hydration (SCH) (4), declined skin barrier function and impaired cutaneous integrity (5, 6). For example, xerosis cutis stands out as one of the most prevailing incidents in older adult population. The prevalence in different settings ranges from 41.2 to 99.1% (7-10). The prevalence of xerosis increases with age (11). Besides aging related skin changes, other endogenous causes, e.g., disease induced stress (12), hormonal alteration (13) may also cause xerosis cutis. Different causes might involve different molecular pathways, though the clinical symptoms appear similar. Xerosis manifests as skin surface having a rough, dry, and scaly appearance; with signs of inflammation in case of severe forms (14). There are various methods for classification of xerosis cutis; for example, scoring systems depending on grading of roughness, scaling, cracks, and redness or visual analogue scales (15, 16). The European Group on Efficacy Measurement of Cosmetics and other Topical Products described a five-point scale (0 to 4), named as overall dry skin score (ODS), used to assess dryness severity from ‘slight’ to ‘extreme’ xerosis (15). Table 1 presents an overview of the ODS scale describing the signs of skin dryness for corresponding scores. The ODS is commonly used in research (17) and the measurement properties also have been investigated (18).

Beyond the scope of visual assessment, there is also a growing interest in molecular markers which are correlated with the incidence and disease severity of xerosis cutis. The lipid matrix in the stratum corneum (SC) contains ceramides, glucosyl ceramides, cholesterol, cholesterol sulfate, fatty acids, phospholipids, enzymes, and proteins (19-21). Ceramides play crucial role as essential components in an optimal lipid structure and determine water permeability (19). Many other important components which contribute to

maintain SCH are collectively called natural moisturizing factors (NMFs) (22, 23). Alterations in the composition, arrangement, or amount of these components can result in reduced hydration of the SC, changes in barrier function, and may eventually impact the processes which regulate skin integrity (24).

Table 1: Categorization of dry skin according to overall dry skin score (ODS) scale.

Degree of severity of dry skin	Category	Description
Absent	0	No sign of skin dryness
Slight	1	Faint scaling, slight roughness, the skin appears dull
Moderate	2	Mostly small to a few larger scales besides roughness and whitish appearance
Severe	3	Uniformly distributed small to large scales with definite roughness, possibly with a few superficial cracks in addition to slight redness
Extreme	4	Large scales, pronounced roughness, eczematous changes, cracks as well as redness

Footnote: This table is based on Serup et al., 1995 (15)

Molecular markers play a vital role in dermatological research. Though recent advances in analytical methods facilitated analysis and discovery of molecular markers from skin samples (21, 25), the usefulness of measuring these markers in assessing xerosis remains uncertain. Despite the huge numbers of molecular markers used in research (24, 26-28), there is still no agreement on the most effective candidates for evaluating xerosis cutis. Therefore, one of the objectives was to describe and provide a summary of molecular markers of xerosis cutis, along with indicating possible associations of those markers with the disease severity and etiologies. (Project 1)

Besides reduced SC hydration, other physiological and structural changes are also manifested in xerosis cutis. Dry skin may produce less sebum and sweat (29). Transepidermal water loss (TEWL), skin pH and roughness may increase (30, 31). TEWL is an indicator of skin barrier function and impaired skin barrier function is identified as one of the contributing factors of dry skin (32). Because of barrier function impairment (33), the skin becomes more sensitive to external irritants and the risk of secondary infection is

increased (14). This can potentially promote the development of inflammatory dermatological diseases e.g., contact dermatitis (34). Elevated risk of pressure injuries is also observed in older adults with xerosis (35, 36). Xerosis cutis is considered as a modifiable risk factor contributing to the occurrence of skin tears (37). Despite the plentiful associations described between xerosis cutis and demographic and health characteristics in long-term care facilities (7-10), the severity of xerosis has never been taken into consideration. Controlled clinical studies have demonstrated that skin care interventions were beneficial in reducing the severity of xerosis in the treatment group (38, 39). However, until now there has been also no investigation into nursing practices related to skin care concerning the severity of xerosis cutis. Therefore, one of the objectives of this thesis work was to compare the participants' demographic, health-related and other characteristics depending on the severity of xerosis cutis. Furthermore, another aim was to describe the association between (skin) care dependency and the application of leave-on products. (Project 2)

Clinically relevant age-related structural changes are also evident at the skin's dermoepidermal junction (DEJ). DEJ serves as the interface between the epidermis and dermis, which form an anchoring system consisting of finger-like epidermal protrusions inserted into the dermis together with dermal papilla which are upwardly projected into the epidermis (40). This interdigitation facilitates skin's mechanical stability and structural integrity (41). However, in the process of aging, the epidermal protrusions and dermal papillae are reduced (42), so the interdigitation becomes gradually disorganized (43) and results into considerable thinning and flattening of DEJ (44). This indicates less strength of DEJ in terms of dermoepidermal adhesion, which is exhibited as reduced skin integrity and less resistant to shearing forces (41, 45). This might increase the risk of shear-type injuries (e.g., skin tears). Acute wounds like skin tears are also common in older adults in institutional long-term care, with a prevalence of up to 22% (46-48). Though a direct association between skin tears and a weakened DEJ has not been yet clinically established, in-vitro study indicated damage to the DEJ by inflammatory cytokines and subsequent formation of skin tears (49). To measure the strength of the adhesion of DEJ, the suction blistering technique is used, which is a controlled, artificial technique for dermoepidermal separation along the DEJ (50, 51). Suction blistering technique is being used in dermatology for epidermal grafting, studying wounds, etc. (52, 53). In this process, a negative pressure (suction) is employed on the skin surface. As the process proceeds, tiny subepidermal vesicles are formed and then, with the further continuation of the suction, the

vesicles coalesce to build a single blister filled with interstitial fluid resulting into complete separation of dermoepidermal junction within the area of suction applied skin (54). The time required for the formation of the vesicles and the cavity has been used as a parameter “time to blistering”, which reflects the resistance of DEJ against shearing force (43, 55, 56). Empirical evidences support the efficacy of leave-on products enhancing the skin barrier function (57) and dermoepidermal adhesion (55) in older adults. Regular application of suitable leave-on products is efficient in managing dry skin and reducing the susceptibility to skin tears (14, 57, 58). Urea, recognized as a potent humectant moisturizing agent, stands out as one of the most extensively researched ingredients in the treatment of dry skin (11). Specifically, in clinical trials involving dry skin, urea has been shown to enhance hydration and skin barrier function, reduce TEWL and skin surface pH (59, 60), and improve skin roughness (61). A concentration of 5% urea is generally regarded as well-tolerated and is recommended for use on moderately scaly skin, as it provides hydrating and smoothing effects (11). However, whether the application of leave-on products also improve the dermoepidermal adhesion in case of dry skin, is not yet known. The hypothesis was that, as dry skin is a recognized risk factor for skin tears, reducing skin dryness might enhance DEJ adhesion, consequently lowering the risk for skin tears. Thus, in project 3, the aim was to study the effect of a humectant containing leave-on product on the adhesion strength of DEJ in older adults having dry skin.

1.2 Research Questions

As part of this doctoral thesis, the following questions were addressed:

I. Which molecular markers are used in xerosis cutis research? Are the markers associated with the clinical signs, severity and underlying etiologies of xerosis cutis? (Project 1, Amin et al., 2021 (62))
II. In institutional long-term care, is there any association between the severity of xerosis cutis and demographic characteristics, health conditions, skin diseases, functional capacities, skin physiological parameters or application of leave-on products? Is there any association between (skin) care dependency and the application of leave-on products? (Project 2, Amin et al., 2023 (63))
III. Does topical application of a leave-on product have any effect on the strength of dermoepidermal adhesion in participants with xerosis cutis? (Project 3, Amin et al., 2024 (64))

2 Methods

2.1 Project 1

A systematic review was conducted to summarize the molecular markers which have been used in xerosis cutis research and to describe the possible relations of the markers with varying severities and etiologies of the disease (62). A review protocol was prospectively registered in the PROSPERO database (registration number: CRD42020214173).

2.1.1 Search strategy and selection process

The databases, 'EMBASE,' 'MEDLINE,' and 'Biological Abstracts' were searched concurrently via OvidSP using a search strategy. The search was conducted on September 29, 2020 with an additional search on January 1, 2021 for updates. Articles published specifically between 1990 and 2020 were sought. Article inclusion criteria comprised primary studies conducted in people of all ages, published in all languages and providing quantitative data regarding molecular markers associated with xerosis cutis. The focus was on xerosis caused by intrinsic factors such as aging and underlying internal conditions. The studies were required to provide information on the age of the participants, skin areas affected, and the severity or symptoms of xerosis cutis. Excluded from the review were articles discussing xerosis resulting from external factors, e.g., allergens, irritants, pathogens, inflammatory dermatological disorders, topical treatments, etc. The screening process and selection of full text articles involved two independent reviewers, who evaluated the retrieved articles and then confirmed through discussion with a third reviewer.

2.1.2 Data extraction and synthesis

Data from the included studies was extracted by two reviewers. The following data items were extracted using a standardized data extraction form: name of the author, year of publication, country/ethnicity, study design, signs of xerosis and the methodology used for scoring these signs, analyzed sample material, technique of sampling, analytical method, number of the participants, their age, sex, the specific skin areas assessed, the severity of xerosis cutis, analyzed molecular markers, study results, and the corresponding units of quantification. Study findings were summarized descriptively. Because the aim of this review was to narrate the characteristics and occurrence of the markers, a risk of bias assessment was not performed. We considered variations among the groups and evaluated the magnitude and strength of associations as effect measures. The extracted

study results were analyzed in a descriptive manner and a simplified evaluation scheme was applied to identify possible group differences. Differences exceeding 10% in quantities or proportions of the markers between normal and dry skin were interpreted as indicative of possible associations, denoted as 'Yes, higher/lower in dry skin'. Differences ranging between 5% and 10% were regarded as unclear and marked using a question mark (?). When the difference in the amount was less than 5%, it was attributed to biological variation and labeled as 'No'. When the markers were documented across three or more distinct severities of xerosis cutis, a consistent change in marker quantity alongside the severity category was seen as a potential association. Deviations from this trend pattern were interpreted as unclear associations. If there were no discernible differences in the marker quantity across different severities of xerosis, an association was deemed unlikely. A summary of potential associations was compiled for all of the markers investigated in the included articles. Additionally, a list presenting top markers was compiled with the markers reported in at least two articles, while a separate list included the molecular markers analyzed only in one publication.

2.2 Project 2

A cross-sectional study was done to identify the factors, which might be associated with different severities of xerosis cutis in older adult residents in institutional long-term care (63).

2.2.1 Study setting, size and selection criteria

A representative cluster-randomized controlled trial (cluster-RCT) was carried out between April 2019 and June 2021 in randomly selected nursing homes in the federal state of Berlin, Germany. The baseline data from this trial, which was gathered prior to the randomization process of the included participants, was analyzed. The study received approval from the Charité - Universitätsmedizin Berlin ethics committee (reference number EA1/243/18). Based on pragmatic considerations, the study aimed to include approximately 20 nursing homes. With an assumed rate of participation of up to 25% among approximately 100 residents per nursing home, an average of 25 residents per facility were expected to partake in the study, hence a sample size of roughly 500 participants were anticipated. Given the exploratory nature of the analysis, it was deemed adequate for the purpose of the outcomes. The primary inclusion criteria for nursing homes participating in this trial were: they had to be located in the federal state of Berlin, Germany,

and have a minimum bed capacity of 70. Eligible individuals for study participation were residents aged 65 and above, had a care level of at least II as per the German Code Book (Sozialgesetzbuch) XI. They were required to provide written informed consent, either directly from themselves or through a legal representative.

2.2.2 Variables, data source and management

Data on demographic characteristics, health and skin conditions, assessment of dry skin, functional capacities, skin measurements and topical application of products were collected. Data on sex (female, male), body mass index (BMI, expressed in kg/m^2), age (years) and the duration of stay in nursing homes (in months) were obtained from the nursing and medical records. The level of care, ranging from care level II to V, was used to denote the extent of care dependency, with higher care levels indicating greater care needs (65). If applicable, information regarding smoking status and quantity of smoking was collected (referred to as pack years; smoking 20 cigarettes per day for one year equals one pack year). To assess potential influences of sun exposure resulting from outdoor professional activities, information on the residents' outdoor occupations for at least one year at any point in their lives was recorded. Primary medical diagnoses were categorized in accordance with the International Classification of Diseases (ICD)-11 (66). The occurrence of incontinence (urinary, fecal or both) and diarrhea was documented. Regular medications were recorded and classified using the Anatomical Therapeutic Chemical (ATC) classification system (67). 'Polypharmacy' was defined as a participant's daily consumption of five or more separate pharmaceutical agents. Cortisone (or its derivative) taken orally on a regular basis was recorded as cortisone intake. For each skin area (face, trunk, arms, legs and feet), dermatologists assessed xerosis cutis using visual examinations following the ODS scale (15). If the residents exhibited an ODS of at least 1 in at least one of the assessed skin areas, they were classified as a prevalent case of xerosis cutis. When the assessment of the severity of xerosis resulted into different ODS values for different sides of the extremities, the higher value was selected for categorizing. The number of cases and corresponding proportions were calculated to present the severity of xerosis cutis for each specific skin area. Given that nearly every resident exhibited some degree of xerosis cutis, and recognizing that very mild forms of xerosis might be indistinguishable from no xerosis, individuals with an ODS of 0 (indicating no xerosis) were grouped together with those having an ODS of 1 (indicating slight xerosis). This particular group, named as ‘mild xerosis’, was compared with a group having ‘severe

forms' of xerosis. The latter group was formed with the residents with ODS values of 2, 3 and 4. Skin tears were evaluated based on the criteria established by the International Skin Tear Advisory Panel (68). The Ghent Global IAD Categorization Tool (GLOBIAD) was used to assess incontinence-associated dermatitis (IAD) (69). Intertrigo was evaluated based on the ICD-11 (66). Pressure ulcers (PUs) were evaluated following the guidelines of the National Pressure Injury Advisory Panel, European Pressure Ulcer Advisory Panel, and Pan Pacific Pressure Injury Alliance (NPIAP/EPUAP/PPPIA) (70). Functional abilities related to daily living activities were measured using the Barthel Index, which uses scores ranging from 0 (indicating high dependence) to 100 (indicating independence) (71). Skin self-care capacity was assessed across three categories: fully independent, needing some assistance, and dependent. Cognitive function was evaluated using the Global deterioration scale (GDS), categorizing residents into seven stages (GDS 1 to 7) (72), with Stage 1 represents individuals without memory deficits or cognitive impairments, while stage 7 indicates severe cognitive decline. Itch was evaluated using the 5-D itch scale in cases where participants were at GDS stage 1 (72, 73). Measurement of SCH, TEWL, skin surface temperature and pH were conducted using the Corneometer CM 825, Tewameter TM 300, Skin-Thermometer ST 500 and Skin-PH-meter pH 905, respectively. The instruments were from Courage + Khazaka, Cologne, Germany. SCH measurements are done on differences in the dielectric constant of water together with other substances available on the skin surface, denoted in arbitrary units (AU) within a range of 0 to 120, where higher values indicate greater SCH (74). The TEWL probe measures the continuous permeation of water through the SC using sensors placed at different heights from the skin surface. The humidity difference between these sensors are taken into account to calculate TEWL in grams per hour per square meter, where higher readings indicate greater TEWL (75). Skin surface temperature was recorded in degrees Celsius (°C). Skin surface pH was determined with hydrogen ion-sensitive glass electrode, with the values estimated by the extraction of water-soluble materials from the SC into the aqueous interface between the pH measuring electrode and the skin (76). The reliability of these skin physiological measurements had been previously demonstrated in this specific setting (77). All the measurements were conducted in duplicate on the upper area of the right ventral lower leg or, if necessary, on the contralateral extremity. On the day of skin physiological measurement, it was instructed not to apply products to the participants' skin and to avoid caffeinated beverages. Data regarding the application of leave-on products on various skin areas was collected through questionnaires and

chart reviews, with frequencies categorized as two to three times daily, once daily, two to three times per week, once per week or more rarely and never.

2.2.3 Bias

To ensure external validity, eligible nursing homes were selected randomly from a comprehensive list of nursing homes which are located in the federal state of Berlin, Germany. From the nursing homes, every resident meeting the inclusion criteria received an invitation to participate. For maintaining the internal validity, clear definitions and standardized case report forms were rigorously employed. The study personnel were trained and provided with necessary guidelines for skin evaluation. The skin was assessed by the dermatologists using standardized definition of the types and categories of the skin conditions. External monitoring was regularly conducted for ensuring data accuracy and adherence to the research protocol.

2.2.4 Statistical methods

Categorical variables were presented by calculating frequencies and proportions. Metric variables were described by presenting means and standard deviations. Group comparisons were conducted between two distinct groups: 'no xerosis to slight xerosis' and 'moderate to severe/extreme xerosis'. The comparison was done on the data obtained for the legs and feet because severe xerosis was most pronounced on these body parts and the participant count was adequate for conducting meaningful group comparisons. Residents who applied leave-on products 'two to three times daily' were grouped together with those who applied 'once daily', resulting in a new group termed 'one to three times daily'. For categorical variables, comparisons were done using odds ratios (OR). Corresponding 95% CIs were also reported. For metric variables, group comparisons were conducted through mean differences and independent samples t-tests. As this study was exploratory, all p-values were interpreted descriptively. The calculations were carried out using IBM SPSS Statistics for Windows, version 29 (IBM Corp., Armonk, N.Y., USA).

2.3 Project 3

A randomized, intraindividual, controlled trial was carried out to investigate the effect of a leave-on product on dermoepidermal adhesion in older adults with xerosis cutis (64).

2.3.1 Trial design, sample size and participants

From January to April 2023, a within-person randomized controlled trial (RCT) was carried out at the Clinical Research Center for Hair and Skin Science at Charité - Universitätsmedizin Berlin, Germany, including healthy older adults with xerosis cutis. The study protocol was registered in German Clinical Trials Register (registration number: DRKS00031151) (78). Approval for the study was granted from the ethics committee of Charité - Universitätsmedizin Berlin (reference number: EA1/228/22). The inclusion criteria were individuals aged 65 to 85, regardless of sex, with phototype I to III following the Fitzpatrick classification, a BMI ranging from 20 to 30 kg/m², non-smokers for minimum one year, and those who provided written informed consent. Due to the explorative nature of the study, sample size was not formally estimated. As per the recommendation regarding pilot studies as reported by Julious et al. (79), 12 participants were planned to include. Eligibility criteria for the skin areas were xerosis cutis of ODS category 1 or 2 on the volar surface of the forearms and absence of skin conditions such as psoriasis, atopic dermatitis or urticaria, as well as scars, acute or chronic wounds, or presence of tattoos in the investigational site. Major exclusion criteria were xerosis cutis of ODS category 3 or 4, unstable chronic conditions, diabetes mellitus, any current skin malignancies, known healing defects, hormone replacement therapy within the last three months, severe to extreme dryness in the skin area of interest, known allergies to any compounds present in the investigational product or band-aid, and any topical, systemic, or physical treatments applied to the investigational skin sites within the past four weeks that could potentially influence the assessment or intervention.

2.3.2 Intervention

For this study, participants were provided with lipophilic 5% Urea cream (Lipophile Harnstoff-Creme 5% NRF 11.129). They were given instructions to apply two-fingertip units (approximately 1 g) of the cream on the forearm randomly selected for intervention, twice a day (morning and evening), for a duration of 8 weeks. Participants were responsible for applying the cream at home and recorded each application in a diary. The use of any leave-on product for the control arm was not allowed throughout the study, which remained completely untreated. A placebo group was not used as urea was not investigated as an active ingredient in this study. The focus of this investigation was on the effect of a commonly used humectant enriched leave-on product on DEJ. Participants were discouraged to undergo strong sun exposure or UV-light sessions or physical therapies on the

forearms or to take systemic anti-inflammatory drugs, vitamin C, retinoids or any vitamin A derivatives during the participation in the study.

2.3.3 Outcomes

Because this was an exploratory study, there was no distinction between the primary and secondary outcomes. The following main outcomes were used.

Time to blistering: A clinically relevant measure of dermoepidermal adhesion strength, described as:

(a) Time to first vesicles: The duration in minutes, starting from the application of suction pressure to the emergence of the first macroscopically visible vesicles on the skin.

(b) Time to full blister: The duration in minutes, starting from the application of suction pressure to the formation of a complete blister. The suction blistering process was done at week 8 and involved the following steps described here:

Rooms were prepared with temperature ranging from 20 to 24 °C and relative humidity between 40 to 60%. Six skin areas were marked on identical locations on the left and right forearm, and the distances among the locations were measured. Following disinfection of the skin areas, participants' forearms were positioned on the arm support of the examination chair. A Styrofoam block was placed as a housing for syringe barrels placed upside-down, connected with tubes to a vacuum pump (MEDAP BORA UP 2080, FALK MedizinTechnik, Germany). Upon starting the vacuum pump, the syringe bases were placed simultaneously on the marked skin areas, with all syringe bases facing the same direction, while recording the initiation time of the blistering process. Vesicle formation was closely monitored and the duration of 'time to first vesicles' was recorded. Upon a full blister formation, the tubes were closed so that the negative pressure stops, and the duration of 'time to full blister' was recorded. When all the blisters were raised, the syringe barrels were detached, and the blister roofs as well as the blister fluids were collected and preserved at -80°C for laboratory analysis. White Vaseline was applied to the wounds and band-aids were placed. After two weeks, the wounds were examined to check if they had healed successfully.

2.3.4 Skin physiological parameters

SCH and TEWL were measured at the baseline visit and weeks 4 and 8. Skin pH was measured at baseline and week 8. All measurements were conducted in duplicate on the upper region of the anterior side of the forearms. The methods used here are similar to

the methods described in the section 2.2.2. Before the measurements, the participants were acclimatized for 30 minutes with the aforementioned temperature and relative humidity.

2.3.5 Skin structural parameters

To measure Mean roughness (Rz), Visioscan VC 98 USB device from Courage + Khazaka, Cologne, Germany was used. This tool provides an assessment of the grayscale picture from the surface of the epidermis. Rz is calculated as the mean of the maximum peak-to-valley height measured from five sections of the sampling line on the skin.

Epidermal thickness was estimated by optical coherence tomography (OCT) using the OCT imaging system manufactured by Thorlabs, Germany. Several adjacent depth scans are used to reconstitute transverse images, which provides a depth resolution of 1 to 10 micrometer (80). ImageJ software was used to analyze OCT images.

Structural skin stiffness was estimated according to the standard operating procedure with Cutometer MPA 580 from Courage + Khazaka, Cologne, Germany. A probe measuring 2 mm in diameter was positioned on the skin surface, 450 mbar intake pressure was used to pull the skin surface into the probe for 2 seconds (suction on) and released again for 2 seconds (suction off) with five repetitions, calculating the maximum extensibility, Uf (in mm) (81, 82). An increase in the Uf value indicates decreased skin stiffness.

2.3.6 Molecular inflammatory markers

IL-1α, IL-6 and IL-8 were analyzed in the samples from the blister fluid and blister roofs. Blister fluids were diluted in the assay buffer prior to analysis. To extract the analytes, blister roofs samples were shredded into tiny pieces, followed by incubation with an extraction buffer (1 % Triton-X-100, 100 mM Tris, 1 mM EDTA, 150 mM NaCL, pH 7.4) and sonication in ice-cold water. Total protein (TP) estimation was performed using Pierce™ 660 nm Protein assay reagent from Thermo Scientific™, Rockfeld, USA, following colorimetric method. The ILs were measured with commercial kits for specific enzyme-linked immunosorbent assay (ELISA) by following the manufacturers' protocols (Human IL-1 alpha/IL-1F1 DuoSet ELISA from R&D Systems, Minneapolis, USA; Human IL-6 and IL-8 CytoSet™ from Invitrogen by Thermo Fisher Scientific, Maryland, USA and Bender Medsystems GmbH, Vienna, Austria). EnSpireTM multilabel reader from Perkin Elmer Singapore Pte. Ltd., Singapore was used to measure the absorbance. TP values were

calculated as µg/ml. The IL concentrations were determined from the standard curve as pg/ml, normalized by dividing the values by the TP concentration of the sample, and then expressed as fg/µg TP.

2.3.7 Randomization and blinding

The treatment arms were allocated randomly through a concealed process. A statistician uninvolved in the trial created a computer-generated simple randomization table with a 1:1 allocation between left and right forearms. Sequentially numbered, sealed, opaque envelopes contained the allocation. The envelopes were opened only after eligibility confirmation and skin measurements at the baseline. Allocation of treatment, dispensation of product, and usage instructions were done independently by a study nurse, separate from the investigators. Due to the intervention's nature, participants couldn't be blinded. However, throughout the study, the outcome assessors and investigators remained blinded. Participants were instructed not to disclose their treatment allocation information during skin measurements or clinical assessments.

2.3.8 Statistical analysis

Mean and spread estimates were used to present participant characteristics. Group differences were calculated through comparisons between intervention and treatment arms using both parametric (mean, standard deviation) and non-parametric (median, interquartile range, IQR: 25% to 75%) statistics. Formal statistical testing of hypothesis was not done because the trial was exploratory in nature. Nevertheless, p-values derived from Wilcoxon signed-rank tests (related-samples, 2-sided test) from the group comparison were presented where all p-values are to be considered as descriptive. IBM SPSS Statistics version 29 for Windows (IBM Corp., Armonk, N.Y., USA) was used for the calculations.

3 Results

3.1 Project 1, publication 1 (62)

The searches in the 'Embase', 'Medline' and 'Biological Abstracts' databases yielded a total of 1,858 records. After screening titles and abstracts, 1,675 records were excluded. One hundred eighty-three publications underwent full-text evaluation and an additional 13 articles were discovered through reference list searches. Out of the total 196 references combined, 175 publications were excluded for not meeting the inclusion criteria. At the end, 21 articles which met the inclusion criteria were included for data extraction. The selected 21 articles included cross-sectional studies, controlled clinical trials, randomized control trials, case-control studies, and pre-post study. The sample sizes varied from 13 to 159 participants, and their age from 23 to 94 years. Various forms of xerosis were investigated e.g., senile xerosis (83-86), diabetic xerosis, drug-induced xerosis (87) or dry skin of patients undergoing hemodialysis (88, 89). In some articles research was conducted on apparently healthy participants without any mention of underlying disease, which was categorized as 'general skin dryness'.

Table 2 represents a list of top markers and their association with xerosis cutis. A total of 72 markers were reported from eight different skin areas. The predominant analytical method used for their assessment was liquid chromatography. The molecular markers were systematically categorized into four groups, namely: Lipids, NMFs, proteins, metabolites or metabolic products.

3.1.1 Lipids

Among 25 lipid or lipid-like markers, total ceramide levels were found to be higher in diabetic xerosis and senile xerosis (86, 90, 91). One study reported lower levels of total ceramide in general skin dryness (92) and another found no association (93). In general skin dryness, ceramide (NP) was lower (93-95), but was found higher in senile xerosis (86); the association was unclear in drug-induced xerosis (87). Ceramide (NS) levels were lower in senile xerosis compared to their age-matched controls (86) but in general skin dryness, it was reported as higher (93, 96); however, no association was also reported (97). Ceramide (NH), Ceramide (EOH), and Ceramide (EOS) were reported to be higher in senile xerosis (86) but lower in general skin dryness (93, 95, 96) as well as reports of no (97) and unclear (87) association. Hydroceramide I and Ceramide (AS) were associated with senile xerosis (86) but not with other dry skin conditions (93, 95, 96).

Table 2: Top markers determined by the total number of studies in which they were reported.

Total number of studies	Molecular markers	Association with xerosis cutis (number of studies)
7	Total free fatty acids (86, 87, 90, 92, 93, 97, 98)	Positive or negative association: 4, Unclear: 3
6	Total ceramide (86, 87, 90-93)	Positive or negative association: 4, No: 1, Unclear: 1
	Ceramide (NP) (86, 93-95, 97) (87)	Positive or negative association: 4, No: 1, Unclear: 1
5	Ceramide (NS) (86, 93, 96, 97) (87)	Positive or negative association: 3, No: 1, Unclear: 1
	Ceramide (EOS) (86, 87, 93, 96, 97)	Positive or negative association: 2, No: 1, Unclear: 2
4	Triglyceride (86, 90, 97, 98)	Positive or negative association: 3, Unclear: 1
	Serine (84, 91, 99, 100)	Positive or negative association: 3, No: 1
	Total free amino acids (83, 84, 91, 100)	Positive or negative association: 3, Unclear: 1
	Ceramide (NH) (86, 87, 95, 97)	Positive or negative association: 2, No: 1, Unclear: 1
	Urocanic acid (UCA) (84, 91, 100)	Positive or negative association: 2 (1 as UCA trans), No: 1, Unclear: 1 (as UCA cis)
	Ceramide (EOH) (86, 87, 93, 97)	Positive association: 1, No: 1, Unclear: 2
	Ceramide (AS) (86, 87, 93, 97)	No: 1, Unclear: 3
3	Pyrrolidone carboxylic acid (85, 91, 100)	Positive or negative association: 3
	Glycine (84, 99, 100)	Positive or negative association: 2, Unclear: 1
	Alanine (84, 99, 100)	Positive or negative association: 2, Unclear: 1
	Leucine (84, 99, 100)	Positive or negative association: 2, Unclear: 1
	Phenylalaine (84, 99, 100)	Positive or negative association: 2, No: 1
	Arginine (84, 99, 100)	Positive or negative association: 2, No: 1
	Threonine (84, 99, 100)	Positive or negative association: 2, Unclear: 1
	Cholesterol (86, 90, 92)	Positive or negative association: 2, No: 1
	Cholesterol sulfate (86, 87, 97)	Positive or negative association: 2, No: 1

Footnote: This table is based on Amin et al., 2021(62)

Ceramide (AP) and ceramide (NdS) were found in lower levels and no study reported any kind of association for ceramide (AdS), ceramide (AH), ceramide (EOP), and ceramide (EOdS). Total free fatty acids were lower in senile xerosis (86); were also found both higher (97) and lower (92) in general skin dryness with reports of unclear (87, 90, 93) association. In senile xerosis, triglycerides were found to be both higher and lower (90), while in general skin dryness, no (97) as well as negative association (98) were reported. Cholesterol and cholesterol sulfate were higher in drug-induced xerosis and senile xerosis (86, 87) and lower in general skin dryness (92). Sterol esters, free sterols, total lipid and wax showed variations in results (86, 90, 93, 97).

3.1.2 NMFs

Twenty-five NMF constituents were reported. In senile xerosis and diabetic xerosis, total free amino acids was higher (84, 91) with one study showing unclear association (83). Amounts of serine, alanine, leucine, phenylalanine, and threonine were mostly higher (84, 91) but lower in general skin dryness (27). Both In senile xerosis and general skin dryness, arginine and glycine were negatively associated (84, 100). Unclear or no association was also reported (99). For tyrosine, histidine, tryptophan, glutamic acid, and methionine, association were negative in general skin dryness (100) with unclear or no association in senile xerosis (84). Valine, isoleucine, proline, lysine, citrulline, and ornithine were higher in senile xerosis (84). No or unclear association was reported with general skin dryness (99, 100). In senile xerosis and general skin dryness, only unclear associations were found for gamma-aminobutyric acid and aspartic acid (84, 99, 100). In diabetic xerosis (91) and senile xerosis (84), trans urocanic acid was higher, but cis urocanic acid was not (91). Pyrrolidone carboxylic acid as well as carboxylic acids (total) was lower in senile xerosis (85, 100), however they were higher in diabetic xerosis (91).

3.1.3 Proteins / Enzymes / Cytokines

Corneodesmosin, plakoglobin, desmoglein 1, phosphatidylethanolamine-binding protein 1, and annexin A2 were higher in general skin dryness (101, 102). TP, chymotrypsin-like activities, trypsin-like activities, and caseinolytic activities were found in higher amounts in the skin of patients whose dry skin was related to underlying conditions (85, 91). Bleomycin hydrolase and N(6)-carboxymethyl-lysine activity were negatively associated with diabetic xerosis (100, 103). Glutathione was reported in dry skin in non-diabetics but not in diabetics (91). (Pro)filaggrin was not associated with general skin dryness (100). One

study reported unclear association of superoxide dismutase with diabetic xerosis (103). In general skin dryness, interleukin (IL)-8 and IL-1ra/IL-1β ratio was higher (98). IL-1α activity in diabetic xerosis was unclear (103).

3.1.4 Metabolites or Metabolic Products

Lactate was negatively associated with dry skin (85, 98). Patients with dry skin who were undergoing hemodialysis, exhibited higher urea (89) but it was lower in general skin dryness (98). Histamine was higher in diabetic xerosis, while melondialdehyde was lower (91). Amount of aluminium in the epidermis and dermis were higher in case of hemodialysis patients with dry skin (88).

3.2 Project 2, publication 2 (63)

Three hundred fourteen residents from 17 nursing homes took part in the study. Figure 1 presents the severity of xerosis on various skin areas. Most residents had mild dry skin. The most common sites of severe forms of xerosis were the feet (24.7%) and legs (19.1%). Only one resident had extreme xerosis on the foot. 63% of residents applied leave-on products once a week or less often, while 23% applied them once daily. Residents with severe forms of xerosis on the legs were older, had a slightly longer duration of stay in the nursing home, and smoked more than the residents with mild xerosis. Residents with incontinence were less likely to have severe xerosis on the legs. Residents exhibiting severe forms of xerosis on their legs also demonstrated lower dependency in terms of functional ability, as represented by a higher Barthel index. Residents who were dependent on nurses for skin care tended to have a reduced prevalence of severe forms of xerosis on the legs (OR: 0.60; 95% CI: 0.32 to 1.13). TEWL levels appeared indifferent between the two groups. The residents with severe forms of xerosis on their legs had 5.43 units less SCH value and 0.23 units higher skin pH value. The application of leave-on products on their legs also occurred less frequently in this group (OR 0.56; 95% CI 0.26 to 1.21). The comparison between ‘no xerosis to slight xerosis’ to ‘moderate to extreme xerosis’ on the feet shows that the number of females was smaller among the residents having severe forms of xerosis on their feet. Residents with incontinence were more likely to be in the group with mild dryness on the feet than others (for double incontinence, OR 0.41; 95% CI 0.23 to 0.73). Residents with severe forms of xerosis on their feet were less dependent, as represented by 12.48 units higher Barthel index. Residents dependent on nurses for their skin care had a lower prevalence of severe forms of xerosis

on their feet (OR 0.47; 95% CI 0.26 to 0.85). Infrequent leave-on product application on the feet appeared to be related with severe forms of xerosis (OR 1.88; 95% CI 0.92 to 3.85).

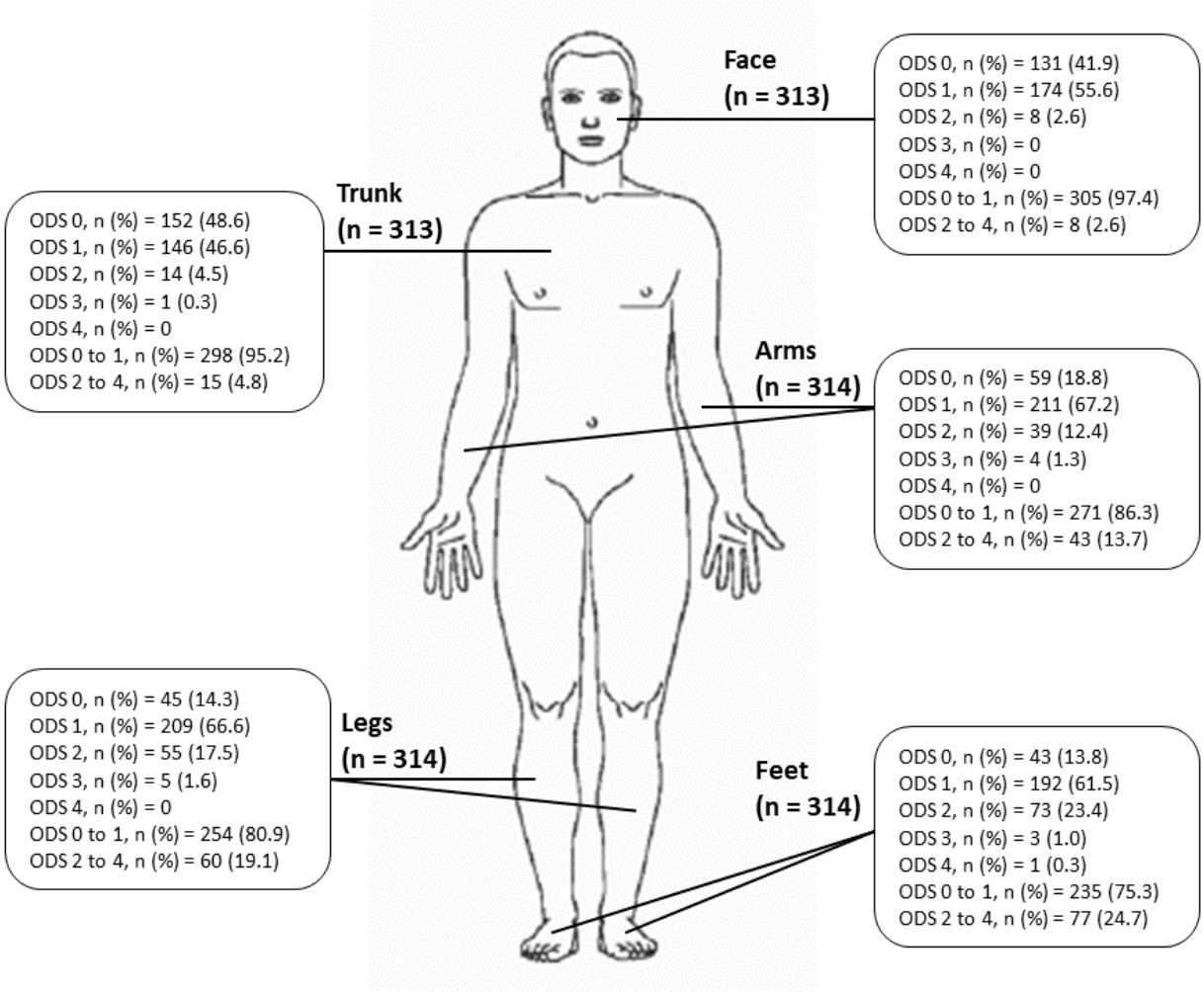


Figure 1: Severity of dry skin on various skin areas presented according to overall dry skin score (ODS), based on Amin et al., 2023 (63).

The analysis of the association between the dependency regarding skin care and application of leave-on products shows that, residents dependent on the nurses for skin self-care, received leave-on products daily and more often (OR 2.59; 95% CI 1.47 to 4.56).

3.3 Project 3, publication 3 (64)

Twelve participants enrolled in the study. All participants completed all scheduled study visits. Participants' mean age was 77.9 (SD 5.6) years and the mean BMI was 24.7 (SD 2.4) kg/m^2.

The results show that the "Time to first vesicles" for the treatment arms was longer than that of the control arms, with a median difference of 2.3 minutes. Similarly, the "Time to full blister" was also longer for the treatment arm, with a mean difference of 7.7 minutes (Figure 2). ODS score (median difference -1.0) as well as the mean roughness of the treatment arm was lower at week 8. Skin stiffness and epidermal thickness remained unchanged at week 8. The analyses of the amount of TP and ILs show that, IL-1α levels were lower in the treatment arms, both in the fluid and epidermis samples (median difference -2.2 fg/ µg TP - and 452.4 fg/ µg TP, respectively). IL-6 and IL-8 values were not different between the treatment and control arms. At week 8, SCH level in the intervention arm was higher but TEWL and pH were lower. Comparison of SCH, TEWL, and pH values are presented in Figure 3. During the trial, no adverse effects were reported by the participants.

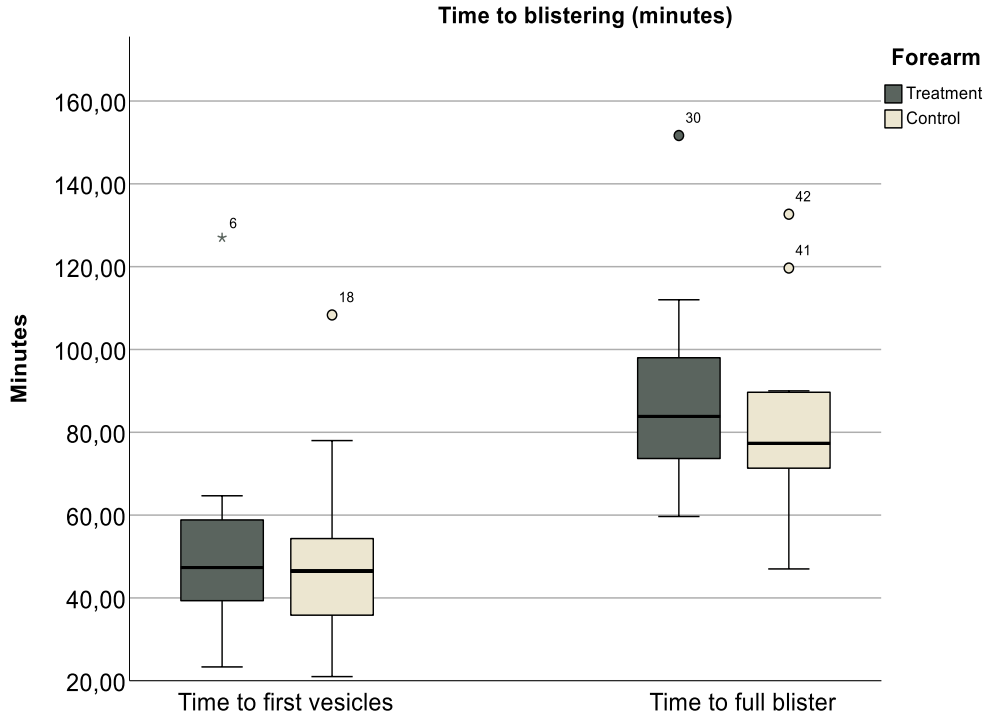
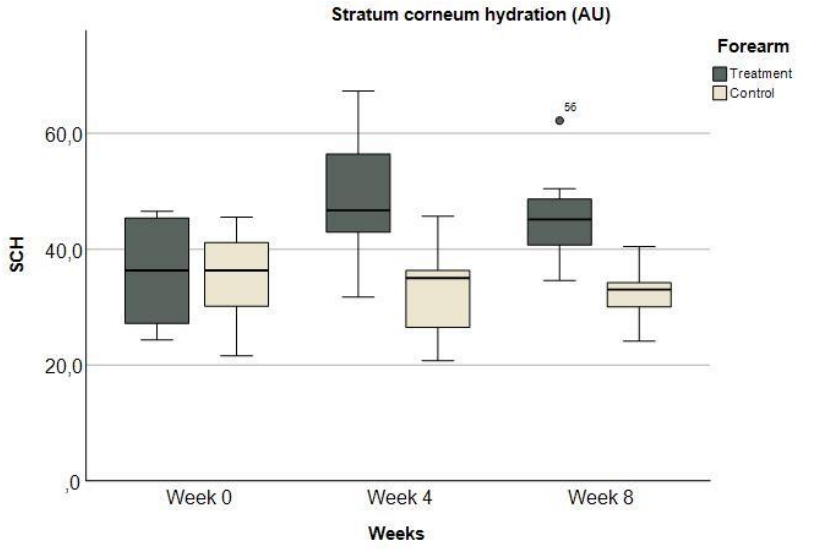


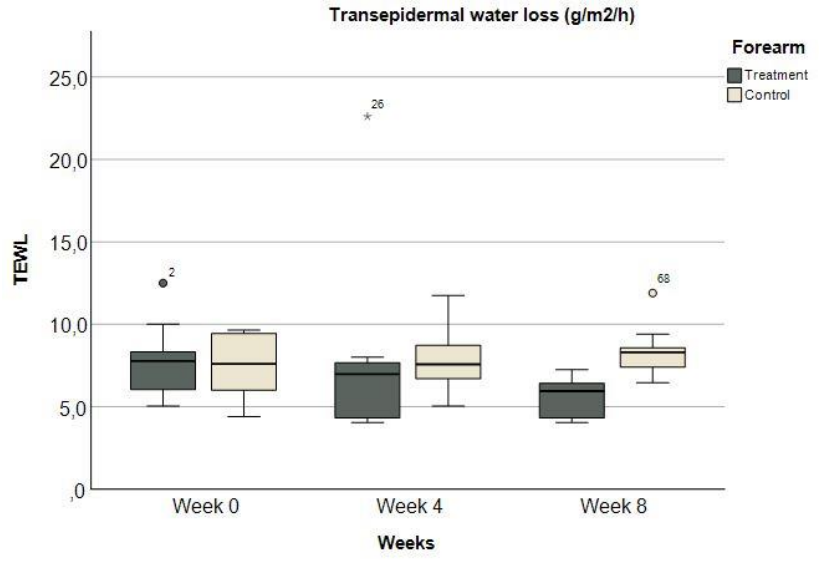
Figure 2: Boxplot representation of the comparison of time to blistering between the treatment and control forearms. Three suction blisters were produced on each forearm of all participants at week 8. The values of ‘time to first vesicles’ and ‘time to full blister’ are expressed in minutes.

Note: This figure is based on Amin et al., 2024 (64).

(A)



(B)



(C)

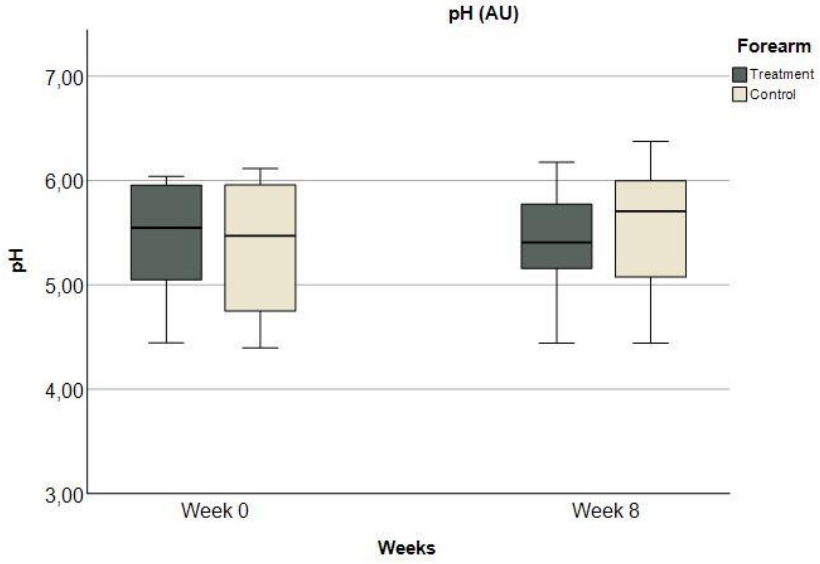


Figure 3: Boxplot representation of stratum corneum hydration (SCH), transepidermal water loss (TEWL) at week 0, 4 and 8 and skin pH values at week 0 and 8 between the treatment and control forearms. All measurements were performed in duplicates in all participants. SCH and pH values are expressed in arbitrary units (AU), A and C; TEWL in grams per hour per square meter, B.

Note: This figure is based on Amin et al., 2024 (64).

4 Discussion

4.1 Short summary of results

The systematic review identified 72 molecular markers reported in a total of 21 studies which include lipids, proteins, cytokines, NMFs, and metabolites. The most commonly investigated markers were total free fatty acids, total ceramides, triglycerides, and certain NMF components. Twelve molecular markers were investigated in at least four studies. For total free fatty acids, total free amino acids, total ceramide, triglyceride, ceramide (NS), ceramide (NP), and serine, a higher number of researches indicated associations with xerosis cutis compared to studies reporting unclear or no associations. Most markers were used only once or twice. Diverse sampling and analytical methods were followed. While associations between these molecular markers and xerosis cutis were observed, reports indicating unclear or lack of association were also common for almost every marker (62).

From the cluster-RCT including nursing home residents, group comparison between mild and severe forms of dryness indicated that there were only minor or no differences regarding demographic characteristics, other skin conditions or used medications between the groups. Residents with severe forms of dryness on the legs exhibited less SCH and higher pH levels, suggestive of dysfunction of the skin barrier. Severe forms of dryness on the legs and feet were related to less dependency on caregivers for daily activities. Residents who depended on the nurses for skin care showed a lower incidence of severe forms of dryness. Incontinence, often linked with dependency on nursing staff, was also associated with lower dryness, indicating that receiving care from the caregivers may had positive impact regarding xerosis severity (63).

The RCT evaluating the effect of humectant enriched leave-on product showed that, after regular application of the product, dermoepidermal adhesion as well as physiological, structural, clinical, and aspects of dry skin were improved. IL-1α was lower in the treatment arm. Longer time to blistering indicated stronger dermoepidermal adhesion in the intervention arm (64).

4.2 Interpretation of results

The systematic review summarized over 70 molecular markers, among those, seven demonstrated associations with xerosis cutis in two or more studies: ceramide (NP), ceramide (NH), ceramide (EOH), ceramide (EOS), total ceramide, serine, and total free

amino acids. These markers consistently exhibited lower levels in general skin dryness but higher levels in xerosis related to internal conditions. Additionally, cholesterol sulfate, cholesterol, leucine, threonine, alanine, phenylalanine, and urea displayed similar patterns; they were analyzed in fewer studies. In contrast, triglycerides, total free fatty acids and ceramide (NS) exhibited conflicting results and unclear associations with xerosis (92, 97, 98). Other four markers (corneodesmosin, lactate, pyrrolidone carboxylic acid, and urea) consistently showed associations with xerosis cutis (26-28, 59, 89, 98, 101). In some studies, ceramide (AP), ceramide (NP), ceramide (NH), triglycerides, lactate, and urea increased gradually with reported dryness severity, while cholesterol sulfate and total free fatty acids decreased. Remaining studies reported no or unclear associations, indicating overall expression heterogeneity. Among xerosis related to internal diseases, diabetic xerosis was extensively studied, with varying associations found for specific markers (28, 103). Variability in results may be attributed to diverse analytical methods, sampling techniques, sample materials and sensitivity differences among the methods used. This highlight significant heterogeneity in this field which makes direct comparisons difficult (62).

Results from the cluster-RCT with nursing home residents show that almost all older adult residents had some form of dry skin, which is consistent with previous research (9, 10, 104). However, other studies in similar settings found lower proportions of participants with dry skin (7, 8), possibly because nurses conducted the skin assessments and might have ignored the early signs of dry skin. Severe forms of xerosis was predominantly observed on the arms, legs, and feet, which is also consistent with previous reports (7, 8, 10). This is likely attributed to the lower density of sebaceous glands on these body sites (11). Several studies have shown associations between xerosis cutis and demographic characteristics (7-10, 105, 106), health conditions (8-10, 105, 106), medical treatments (106), numerous skin diseases (9, 105-107), nutrition (10), functional abilities (8, 10) and skin care practices (7) in hospitals (8, 10), primary care (106), nursing homes (7-10), and other settings (105, 107). However, the available information regarding factors linked to varying severities of xerosis in the older adult population is limited. In this study, minimal group differences were found concerning demographic characteristics, health and various skin conditions. Xerosis cutis was reported to be independent from other skin diseases e.g., incontinence-associated dermatitis, Intertrigo, Pus, and skin tears, which are also relevant for nursing practice (46). Residents with severe forms of xerosis on the legs showed lower SCH and a bit higher level of skin pH. Increased pH of dry skin surface

is likely to be associated with impaired barrier function (4) and lower amounts of lactate and pyrrolidone carboxylic acid (108, 109). TEWL was to a slight extent lower in the severe xerosis group. In diseased skin, due to defective barrier function, TEWL is increased (110). However, dry skin in older adults appears to differ from pathologically dry skin (111). This study also examined the frequency of leave-on product application and bathing. Less frequent application of leave-on products in the severe dry skin group indicates under-application, which was also reported previously (7). Low frequency of bathing was also linked to decreased dryness on the feet. The significance of healthcare professionals in the skin care of older adults is increasing continuously. (112). The results demonstrating mild dryness in the (skin) care dependent residents suggest that frequent topical application of leave-on products by the nurses seems to be helpful in reducing disease severity of xerosis cutis in the nursing home residents (63).

In the RCT, which evaluated the effect of a leave-on product on DEJ of dry skin, the time to blistering was longer in the treatment arm in comparison with the control arm. The median difference for the time to full blister was similar to that reported in a previous study which used petrolatum on intervention arm (55). This suggests that eight weeks of treatment increased dermoepidermal adhesion. Higher SCH value in the intervention arm also supports the hydrating effect of urea containing leave-on product on dry skin (59, 61). However, the mechanism of how the treatment influence dermoepidermal junction is not fully understood. Urea improves barrier integrity (113), regulates epidermal proliferation (114, 115) and enhance the expression of filaggrin (FLG) (59). Research has shown that applying formulations containing urea can increase the expression of genes like loricrin (LOR) and FLG in the suction blister roof extract, which are important for skin cell differentiation and maintaining the skin barrier function (113, 116). Notably, LOR tends to be more abundant in skin sites where the dermis and epidermis interdigitate, a characteristic feature of a healthy DEJ (117). TEWL values observed in this study are consistent with previously reported findings (59, 116, 118). Furthermore, the reduction in pH observed in our study aligns with findings from previous research (39, 59). Urea's enhances filaggrin biosynthesis which contributes to the increase of NMFs, which help maintain the skin's acidic pH (119). Notably, skin roughness was reduced in the treatment arm in comparison with the control arm. Studies involving the use of leave-on products have reported similar improvements in the Rz parameter (120, 121). Subjective clinical assessment using the ODS scale also revealed an improvement in skin dryness in the treatment arm.

Urea exhibits keratolytic effect, aiding in the removal of the top layer of dry skin and enhancing the skin's texture (61). Measurements of epidermal thickness were consistent with previously reported result; there were no difference observed after the treatment (55). Eight weeks of topical treatment did not show any effect on structural skin stiffness. IL-1α levels at week 8 were notably higher in the samples taken from the control forearm when compared to the treatment forearm. IL-1α is a proinflammatory cytokine found in the epidermis and is a major contributor to IL-1 activity associated with the skin (122). High levels of IL-1α are often linked to reduced SCH (123) and worsened symptoms in various skin conditions (124). Aging skin may also exhibit signs of inflammation (107). This suggests that the intervention may have decreased potential subclinical inflammation caused by dryness. A study by Legiawati et al. in 2020 found that, IL-1α levels in the lower extremities of the control group did not decrease compared to the treatment group after the skin was treated 29 days with a leave-on product. However, they extracted the SC sample followed by cyanoacrylate skin surface stripping. In this analysis, IL-1α extraction was done from the entire epidermis sample, which possibly have produced more analytes additionally from the lower part of the epidermis. One more relevant feature of IL-1α could be its role in the suction blistering process, which creates wounds. Following an incision, cellular recruitment and activation initiate within wounds, leading to the production of IL-1α by keratinocytes (125). However, since blisters were generated on both the treatment and control forearms, blistering should have similarly influenced the presence of IL-1α in both of the arms. Therefore, the observed difference may indeed be attributed to the treatment itself. Previous studies reported that IL-6 expression can be heterogeneous depending on sample material or gender (123, 126). A study by Schweiger et al. in 2013 found that following a tonic treatment, higher level of IL-8 was found in dry scalp in comparison with the hydrated scalp (98). In this analysis, the high concentration of TP in the blister fluid led to very low normalized amounts of IL-6 and IL-8 (as low as 0.2 fg/µg TP). Nevertheless, signals from IL-6 and IL-8 were detectable within the assay's detection range. Levels of IL-6 and IL-8 exhibited no differences between the intervention and control arms, suggesting they may not be suitable markers for the endpoint chosen for this study (64).

4.3 Embedding the results into the current state of research

Results from the systematic review indicates substantial heterogeneity in selection, sampling and analysis of the molecular markers. Quantifying molecular markers is pivotal for

delineating biological processes, pathogenic mechanisms, or pharmacological reactions, but the optimal molecular markers for xerosis cutis are currently unclear (62).

Results from the cluster-RCT with the nursing home residents indicate that there were no or minor group differences between mild and severe dry skin, except for some skin physiological measurements. Our findings regarding the frequent use of leave-on products in care-dependent residents indicates the immense importance of care providers in dry skin management and emphasizes the need of evidence based, person-centered skin care practices (63).

Regularly applying a humectant-containing leave-on product appeared to strengthen dermoepidermal adhesion. This finding adds to our knowledge of how application of leave-on products helps prevent skin tears (64).

4.4 Strengths and weaknesses of the studies

A notable strength of the systematic review is that it summarized an unexpectedly large number of molecular markers and presented the significant heterogeneity in this field. However, the selection of top markers was based on the number of publications those reported the markers, which might have not considered the importance of other markers analyzed in only one study. Another limitation to this study arises from the reliance on arbitrary evaluation of patterns in defining associations of molecular markers with xerosis cutis. Additionally, instead of relying on reported p-values, differences in the marker's quantity for comparing groups was considered, as p-values can be influenced by sample size and were often clinically irrelevant in the included studies. Another limitation is the potential bias in group comparisons of the skin of healthy individuals with those having underlying medical conditions. These groups may differ in various characteristics beyond just skin dryness which could confound the results and limit the ability to attribute observed differences solely to xerosis cutis. Furthermore, this review did not include xerosis cutis resulting from temporary seasonal changes, as seasonal xerosis cutis was not within its scope (62).

The cluster-RCT with the nursing home residents encountered challenges in achieving the initially expected participation of 500 subjects from 20 nursing homes. Recruitment efforts were hindered by the beginning of the COVID-19 pandemic in early 2020, since residents in institutional long-term care were among the highly vulnerable groups. Nevertheless, the attained sample size of 314 participants appears sufficient for comparing groups. The voluntary participation of residents may have introduced the potential for

selection bias. To address the prevalence of dry skin, ODS 0 was combined with ODS 1. This categorization was based on the assumption that it is possible to perceive very mild forms of dryness as absent. However, group comparison results may have been influenced by this categorization. Lastly, because of the cross-sectional design of the study, it is not possible to establish causal association between the severity of xerosis cutis and related factors (63).

As the RCT regarding the effect of leave-on product on the dry skin's dermoepidermal adhesion was of exploratory in nature, results should be considered as descriptive and hypotheses generating. The results are not generalizable because the inclusion and exclusion criteria were much restricted as well as the conditions regarding intervention and measurements were very controlled (64).

4.5 Implications for practice and/or future research

Despite the heterogeneity regarding the association of the molecular markers and xerosis cutis, future research on total ceramides, total free amino acids, cholesterol, and urea could help in establishing their role as potentially useful markers in xerosis cutis research as they showed consistency in terms of the pattern of association, as reported by some studies. Markers like histamine and pyrrolidone carboxylic acid, which were studied in dry skin induced by certain internal conditions (e.g., diabetes), are worth of validation in well-controlled clinical trials. The consideration of marker panels may provide valuable insights, particularly in cases of xerosis cutis with underlying conditions (62).

The findings suggest that sufficient application of leave-on products by professional caregivers appears to be beneficial in mitigating dry skin severity among nursing home residents. This practice may also aid in preventing more severe skin issues such as skin tears. Moreover, the consistently high occurrence of xerosis cutis across long-term care facilities emphasize the need for implementing skin care practice based on standardized guidelines which should be aimed, implemented and coordinated by nursing professionals. In addition, which factors potentially play important role in exaggerating skin dryness especially in highly care dependent population, could be researched further (63).

The results from the RCT with the older adults with xerosis cutis shows that regular application of humectant containing leave-on product strengthens the dermoepidermal adhesion and consequently, it may contribute in preventing skin tears. Future research can investigate whether the treatment also improves the structural aspects of DEJ. IL1-α

seemed to be a relevant marker in this study. In depth research on the markers related to DEJ would be useful in understanding mechanism and treatment response related to skin tears (64).

5 Conclusions

I. A high number of molecular markers are investigated in xerosis cutis research. Among these, ceramides, total free fatty acids, total free amino acids, triglycerides, urocanic acid, and serine have been used most often in research. However, the evidence regarding whether the amount of these markers reliably represent the severity of xerosis is quite heterogenous. Moreover, 31 markers were reported only from single studies. Despite the considerable interest in molecular markers for xerosis cutis research, it remains confusing which of these markers are clinically relevant (62).

II. Nearly all residents of the included nursing homes were affected by dry skin, with severe dryness observed at distal body areas. Residents who depended on the nurses for their skin care, received leave-on products more frequently. They also had mild dryness on the skin. Care provided by the professional caregivers seemed to be beneficial for managing dry skin than self-care. Treatment and prevention of dry skin in long-term care facilities can be enhanced through evidence-based, individually tailored skin care provided by professional caregivers following standardized guidelines. Awareness among the residents about recommended application frequency of the leave-on products may also help in improving skin dryness in this population (63).

III. Applying a humectant containing leave-on product to the dry skin in the older people seems to improve functional, structural, and clinical aspects of skin dryness, and to strengthen dermoepidermal adhesion. The results partly explain how leave-on products contribute to the prevention of skin tears (64).

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Statutory Declaration

“I, Ruhul Amin, by personally signing this document in lieu of an oath, hereby affirm that I prepared the submitted dissertation on the topic [Dry skin in older care dependent people; Trockene Haut bei älteren pflegebedürftigen Menschen], independently and without the support of third parties, and that I used no other sources and aids than those stated.

All parts which are based on the publications or presentations of other authors, either in letter or in spirit, are specified as such in accordance with the citing guidelines. The sections on methodology (in particular regarding practical work, laboratory regulations, statistical processing) and results (in particular regarding figures, charts and tables) are exclusively my responsibility.

Furthermore, I declare that I have correctly marked all of the data, the analyses, and the conclusions generated from data obtained in collaboration with other persons, and that I have correctly marked my own contribution and the contributions of other persons (cf. declaration of contribution). I have correctly marked all texts or parts of texts that were generated in collaboration with other persons.

My contributions to any publications to this dissertation correspond to those stated in the below joint declaration made together with the supervisor. All publications created within the scope of the dissertation comply with the guidelines of the ICMJE (International Committee of Medical Journal Editors; http://www.icmje.org) on authorship. In addition, I declare that I shall comply with the regulations of Charité – Universitätsmedizin Berlin on ensuring good scientific practice.

I declare that I have not yet submitted this dissertation in identical or similar form to another Faculty.

The significance of this statutory declaration and the consequences of a false statutory declaration under criminal law (Sections 156, 161 of the German Criminal Code) are known to me.”

Date Signature

Declaration of your own contribution to the publications

Ruhul Amin contributed the following to the below listed publications:

Publication 1:
Amin R, Lechner A, Vogt A, Blume-Peytavi U, Kottner J. Molecular characterization of xerosis cutis: A systematic review. Plos one. 2021 Dec 16;16(12):e0261253. https://doi.org/10.1371/journal.pone.0261253

Contribution: Significant contribution in title/abstract screening and assessment of full texts as well as data extraction. Leading the synthesis and presentation of the results, writing original draft of the manuscript and significant involvement in the design and collaboration on the manuscript during initial submission and its revision.

Publication 2:
Amin R, Völzer B, El Genedy-Kalyoncu M, Blume-Peytavi U, Kottner J. The prevalence and severity of dry skin and related skin care in older adult residents in institutional long-term care: A cross-sectional study. Geriatric Nursing. 2023 Nov 1;54:331-40. https://doi.org/10.1016/j.gerinurse.2023.10.032

Contribution: Significant involvement in visualization and data curation. Leading statistical analysis, evaluation and interpretation of the data, presentation of the results and content (Tables 1 to 5, and figure 1), writing the manuscript including submission and revision of the article.

Publication 3:
Amin R, Rancan F, Hillmann K, Blume-Peytavi U, Vogt A, Kottner J. Effects of a leave-on product on the strength of the dermoepidermal junction: an exploratory, intraindividual, randomized controlled trial in older adults with dry skin. Health Sci Rep. 2024;7:e1985. https://doi.org/10.1002/hsr2.1985

Contribution: Significant contribution in visualization, project management, data acquisition and curation. Leading statistical analysis, evaluation and interpretation of the data, presentation of the results and content (Tables 1 to 2, and figure 1), writing the manuscript including submission and revision of the article.

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Signature, date and stamp of first supervising university professor / lecturer

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Signature of doctoral candidate

Excerpt from Journal Summary List

Publication 1:

Amin R, Lechner A, Vogt A, Blume-Peytavi U, Kottner J. Molecular characterization of xerosis cutis: A systematic review. Plos one. 2021 Dec 16;16(12):e0261253.

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Publication year: 2021

Impact factor: 2.740

Rank: 27, out of 73 in the category 'multidisciplinary sciences' (among the top 50 percent; according to 2019 ranking).

Journal Data Filtered By: **Selected JCR Year: 2019** Selected Editions: SCIE,SSCI Selected Categories: **"MULTIDISCIPLINARY SCIENCES"** Selected Category Scheme: WoS

Gesamtanzahl: 71 Journale

Rank	Full Journal Title	Total Cites	Journal Impact Factor	Eigenfactor Score
1	NATURE	767,209	42.778	1.216730
2	SCIENCE	699,842	41.845	1.022660
3	National Science Review	2,775	16.693	0.009760
4	Science Advances	36,380	13.116	0.172060
5	Nature Human Behaviour	2,457	12.282	0.014190
6	Nature Communications	312,599	12.121	1.259510
7	Science Bulletin	5,172	9.511	0.014150
8	PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA	676,425	9.412	0.931890
9	Journal of Advanced Research	3,564	6.992	0.005470
10	GigaScience	4,068	5.993	0.016410
11	Scientific Data	5,761	5.541	0.028720
12	Research Synthesis Methods	2,572	5.299	0.006440
13	ANNALS OF THE NEW YORK ACADEMY OF SCIENCES	45,596	4.728	0.026370
14	FRACTALS-COMPLEX GEOMETRY PATTERNS AND SCALING IN NATURE AND SOCIETY	2,156	4.536	0.002210
15	iScience	1,410	4.447	0.004140
16	GLOBAL CHALLENGES	481	4.306	0.001440
17	Scientific Reports	386,848	3.998	1.231180
18	JOURNAL OF KING SAUD UNIVERSITY SCIENCE	1,640	3.819	0.002020
19	Journal of the Royal Society Interface	13,762	3.748	0.027670

Rank	Full Journal Title	Total Cites	Journal Impact Factor	Eigenfactor Score
20	Frontiers in Bioengineering and Biotechnology	2,770	3.644	0.007650
21	NPJ Microgravity	346	3.380	0.001210
22	PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY A-MATHEMATICAL PHYSICAL AND ENGINEERING SCIENCES	20,609	3.275	0.027840
23	PROCEEDINGS OF THE JAPAN ACADEMY SERIES B-PHYSICAL AND BIOLOGICAL SCIENCES	1,669	3.000	0.001980
24	Advanced Theory and Simulations	432	2.951	0.000700
25	SCIENCE AND ENGINEERING ETHICS	2,129	2.787	0.003760
26	PROCEEDINGS OF THE ROYAL SOCIETY A-MATHEMATICAL PHYSICAL AND ENGINEERING SCIENCES	19,218	2.741	0.018450
27	PLoS One	688,763	2.740	1.388860
28	Royal Society Open Science	7,222	2.647	0.027340
29	Symmetry-Basel	4,888	2.645	0.005390
30	INTERNATIONAL JOURNAL OF BIFURCATION AND CHAOS	7,115	2.469	0.007090
31	COMPLEXITY	4,413	2.462	0.007160
32	PeerJ	17,984	2.379	0.062850
33	MIT Technology Review	871	2.357	0.001810
34	Science of Nature	673	2.090	0.002400
35	SCIENCE PROGRESS	499	1.906	0.000340
36	SOUTH AFRICAN JOURNAL OF SCIENCE	2,631	1.866	0.001800
37	Journal of Taibah University for Science	1,126	1.863	0.001470
38	Journal of Radiation Research and Applied Sciences	1,127	1.804	0.002280

Selected JCR Year: 2019; Selected Categories: "MULTIDISCIPLINARY SCIENCES"

RESEARCH ARTICLE

Molecular characterization of xerosis cutis: A systematic review

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Abstract

Background

Xerosis cutis or dry skin is a highly prevalent dermatological disorder especially in the elderly and in patients with underlying health conditions. In the past decades, numerous molecular markers have been investigated for their association with the occurrence or severity of skin dryness. The aim of this review was to summarize the molecular markers used in xerosis cutis research and to describe possible associations with different dry skin etiologies.

Methods

We conducted a systematic review of molecular markers of xerosis cutis caused by internal or systemic changes. References published between 1990 and September 2020 were searched using 'MEDLINE', 'EMBASE' and 'Biological abstracts' databases. Study results were summarized and analyzed descriptively. The review protocol was registered in PROSPERO database (CRD42020214173).

Results

A total of 21 study reports describing 72 molecules were identified including lipids, natural moisturizing factors (NMFs), proteins including cytokines and metabolites or metabolic products. Most frequently reported markers were ceramides, total free fatty acids, triglycerides and selected components of NMFs. Thirty-one markers were reported only once. Although, associations of these molecular markers with skin dryness were described, reports of unclear and/or no association were also frequent for nearly every marker.

Conclusion

An unexpectedly high number of various molecules to quantify xerosis cutis was found. There is substantial heterogeneity regarding molecular marker selection, tissue sampling and laboratory analyses. Empirical evidence is also heterogeneous regarding possible associations with dry skin. Total free fatty acids, total ceramide, ceramide (NP), ceramide (NS), triglyceride, total free amino acids and serine seem to be relevant, but the association

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with dry skin is inconsistent. Although the quantification of molecular markers plays an important role in characterizing biological processes, pathogenic processes or pharmacologic responses, it is currently unclear which molecules work best in xerosis cutis.

1. Introduction

Xerosis cutis or asteatosis is caused by reduced hydration of the stratum corneum and characterized by clinical signs such as small to large scales, cracks, and inflammation [1]. This is often accompanied by pruritus and risks for secondary infections [2, 3]. Besides external causes and environmental triggers [4, 5], there are endogenous or intrinsic causes of xerosis cutis such as aging, internal health conditions, dermatological and psychiatric diseases, diet and drugs [6, 7]. For example, aging related physiological changes, hormonal alteration [8], disease induced stress and inflammatory response [9] or off-target activities of drugs [10] can affect skin hydration. Although the clinical signs and symptoms are similar, it can be assumed that, as different causes are involved, there are different underlying molecular mechanisms and pathways leading to xerosis cutis. In xerosis cutis, the stratum corneum (SC) fails to maintain an adequate water concentration gradient between the living epidermal cells and the skin surface [11]. The changes may also include a decreased sebum and sweat production, inadequate cell replacement [12], disturbed skin barrier function [1] and increased transepidermal water loss [13].

The SC consists of terminally differentiated and unnucleated keratinocytes, namely corneocytes, and a lipid matrix surrounding the cells [14]. The lipid matrix contains cholesterol, ceramides, fatty acids, cholesterol sulfate, glucosyl ceramides, phospholipids, proteins and enzymes [15–17]. Ceramides, which are essential for an optimal lipid structure, play an important role in determining water permeability and maintaining skin barrier function [15]. In addition, natural moisturizing factors (NMFs), mainly located in corneocytes [18], contribute to maintaining SC hydration [11]. Changes in the structure, arrangement or composition of any of these components may lead to decreased SC hydration and may affect the processes regulating skin integrity [43] and normal desquamation [32].

Today, biomarkers play important roles in clinical research and in dermatology. A biomarker is considered as "a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes or pharmacologic responses to a therapeutic intervention" [19]. From the early 1990's, there has been growing interest in molecular markers or compounds which are associated with the occurrence and/or the severity of skin dryness. Advances in analytical methods and instrumentations facilitated the laboratory analysis of molecules and the discovery of new markers [17, 20]. However, up to present time, diagnosis of xerosis cutis is largely based on clinical methods of visual assessment using scores or classifications [21, 22]. Whether the measurement of molecular markers is useful in dry skin assessment, is unclear. It may help to diagnose the underlying cause of xerosis cutis. In addition, changes of molecular markers may help to understand and/or to measure (early) treatment responses.

However, despite the wide range of markers used in xerosis cutis research [34, 37, 41, 43], there is no agreement yet about the most accurate and useful candidates. Therefore, the aim of this systematic review was to describe and summarize molecular markers of dry skin and to describe possible associations with clinical signs and/or the severity of xerosis cutis and possible underlying etiologies.

2. Methods

2.1. Eligibility criteria

We included primary studies in humans (all age groups and all languages) reporting quantitative data of molecular markers of dry skin along with performed analytical methodologies. Xerosis caused by intrinsic processes (e.g., due to aging) or underlying internal diseases (e.g. diabetes mellitus) was in our focus. The included studies had to include the participants' age, skin areas and symptoms and/or severity of dry skin. We excluded articles that described xerosis due to external causes, such as exposures to irritants, allergens, pathogens, topical treatments and inflammatory dermatological diseases such as dermatitis, psoriasis, eczema or comparable conditions. Reviews, letters, editorials, personal opinions, posters, conference abstracts as well as pre-clinical or animal studies and in vitro studies were not included in this review.

2.2. Information sources

'MEDLINE', 'EMBASE' and 'Biological Abstracts' databases were searched concurrently via OvidSP on 29 September 2020. We also conducted an updated database search on 1 January 2021 with exactly the same search criteria.

2.3. Search strategy

We searched the above-mentioned databases with combinations of key words covering xerosis cutis, humans and molecular markers. The search was conducted for articles published between 1990 and 29 September 2020. The reference lists of all interesting articles were also searched manually to identify any additional studies that fit the focus of our review. The detailed search strategy is presented in S1 Appendix.

2.4. Selection process

The retrieved titles and abstracts were independently screened by two reviewers (RA and AL) Any difference in opinions between the two reviewers was resolved by consensus or by the third reviewers (JK, AV). Full text articles of all potentially eligible studies were independently checked for eligibility by the reviewers (RA and AL) and then finalized by discussion with a third author.

2.5. Data collection process

From the included studies, two reviewers extracted data regarding main outcomes of the primary studies, details about study, study participants, intervention (if any) and quantification methods. A standardized data extraction form was used. If needed, quantities of molecular markers were extracted from graphs or figures. Study results were summarized descriptively.

2.6. Data items

The following items were extracted: author's name, publication year, study design, country/ethnicity, signs of dry skin and scoring method, analyzed material, sampling technique, method of analysis, number of participants, age, sex, skin areas, severity of dry skin, molecular markers, results and quantification units (S2 Appendix).

2.7. Risk of bias assessment

There are no accepted standards or methodological guidance how to best quantify molecular markers in skin research. In Addition, the objective of this review was to describe the occurrence and characteristics of the molecular markers. Therefore, a formal risk of bias assessment was not conducted.

2.8. Effect measures

Differences between groups and the degree and strength of associations were considered as effect measures.

2.9. Synthesis methods

Extracted study results were analyzed descriptively. In order to detect possible group differences, a simplified evaluation scheme was applied: differences between proportions or quantities of molecular markers between normal and dry skin of more than 10% were considered to indicate possible associations ('Yes, higher/ lower in dry skin'). Differences between 5% to 10% were considered unclear and indicated with a question mark (?). Any difference lower than 5% was considered as biological variation ('No').

When molecular markers were presented for at least three or more different dry skin severities, a consistent increase or decrease of the marker quantity with the corresponding category was considered as a possible association. One or two deviated values in the 'trend pattern' were considered as unclear association. If there were no differences among the markers' values in relation to different dry skin severities, an association was considered unlikely. A summary of possible association was made for all the markers presented in each included article. A list of top markers was prepared considering the numbers of studies reported the corresponding markers (at least two studies). Markers analyzed once were listed separately.

3. Results

3.1. Study selection

A total of 1858 records were yielded from electronic searches in 'Medline', 'Embase' and 'Biological Abstracts' databases via OvidSP. Based on title and abstract screening, 1675 records were excluded. The remaining 183 publications were retrieved for full text evaluation along with 13 more articles which were found while searching in reference lists. Out of these 196 references, 175 publications were excluded as they did not meet the inclusion criteria. Finally, 21 articles were included for data extraction [23–43] (Fig 1).

3.2. Study characteristics

Thirteen studies were designed as cross-sectional, four as randomized control trials, two as controlled clinical trials, two as case controls and the remaining one as pre-post study. Four studies were conducted in America, nine in Asia and eight in Europe. The sample size ranged from 13 to 159 and the age of the subjects ranged from 23 to 94 years. Two studies did not report the participant's age, six did not report participant's sex and six studies did not assessed the severity of dry skin using a classification or scoring method.

Different forms of xerosis cutis were investigated. Among the included articles, five examined elderly participants whose dry skin conditions were indicated either to be associated with aging [26] or as senile xerosis [25, 28, 33, 38] where especially older people had dry skin. Here, we represented this condition as 'senile xerosis'. Skin dryness of persons with diabetes is described as diabetic xerosis which may be considered as one particular form of xerosis cutis.

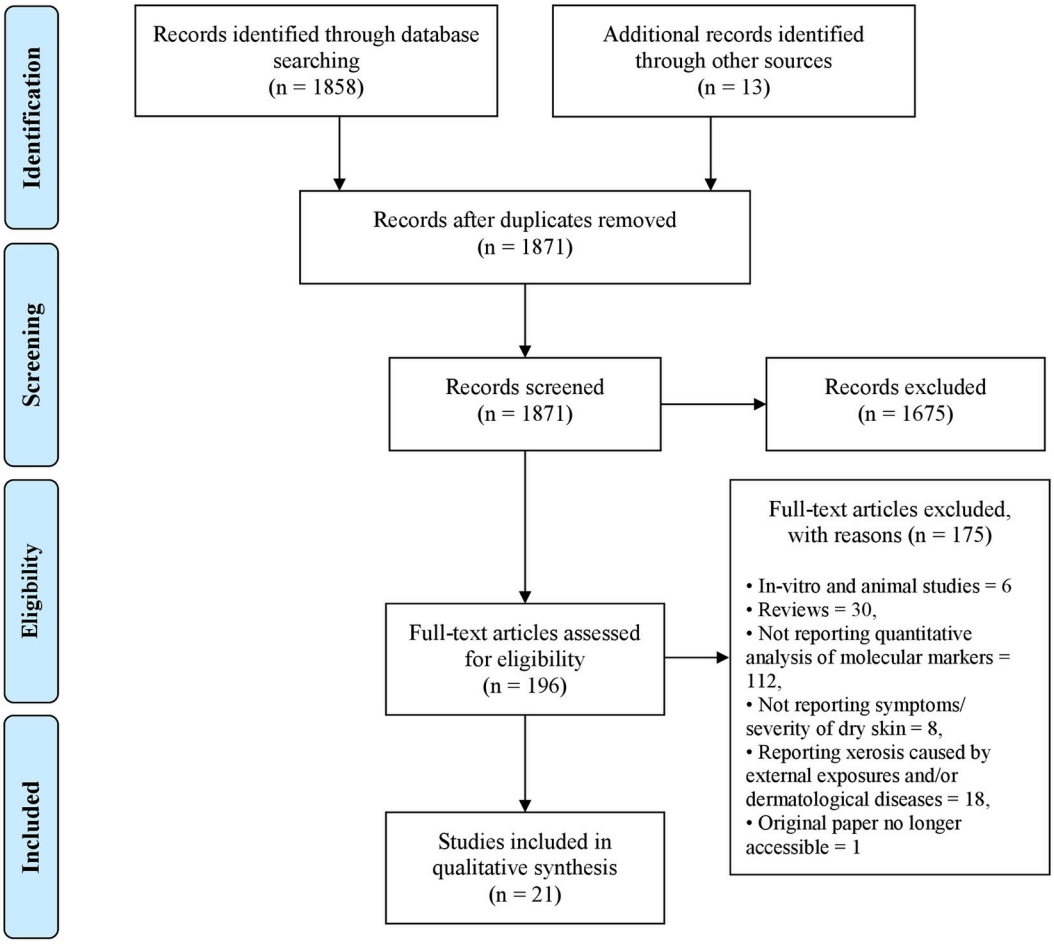

Fig 1. Flow diagram of the literature search and study selection process.

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One study, which investigated dry skin in cancer patients whose skin dryness was induced by oral intake of erlotinib drug, is reported as drug-induced xerosis [43]. Two studies analyzed markers in the dry skin of patients undergoing hemodialysis [23, 29]. In all other articles, where studies were conducted on apparently healthy participants (not mentioning any underlying internal condition), the subject's skin dryness was referred to as 'general skin dryness'.

3.3. Results of individual studies

Study details and results of the data extraction are shown in S2 Appendix. A summary of results is shown in Table 1. Overall, 72 markers were identified. They were sampled from eight skin areas. Most often, liquid chromatography was used as the analytical method. Molecular markers were inductively categorized into (1) lipids, (2) NMFs, (3) proteins and (4) metabolites or metabolic products.

3.3.1. Lipids. In different types of dry skin, 25 lipid and lipid like markers were reported. The markers include ceramides (14 parameters), free fatty acids (four parameters), triglyceride, cholesterol, cholesterol sulfate, total lipid, sterol esters, free sterol and wax.

3.3.1.1. Total ceramide. All the three studies which analyzed total ceramide in dry skin of patients affected by senile xerosis and diabetic xerosis [24, 28, 41], found this marker to be

Table 1. Summary of main findings (n = 21 studies).

Author	Year	Sample	Age (years)	Skin areas	Method of analysis	Molecular markers analysed	Associations
Hanada et. al. [23]	1984	Haemodialysis patients with dry skin and sweat suppression (n = 5); and healthy volunteers (n = 8)	Not reported	Forearm	Atomic absorption spectrophotometry	Aluminium level in the epidermis	Yes, higher in dry skin of haemodialysis patients
						Aluminium level in the dermis	
Saint-Léger et. al. [24]	1988	Subjects with xerosis and subjects with normal skin (in total, n = 50)	25 to 75	Lateral mid-calf	Photodensitometry	Sterol esters in stratum corneum	Yes, lower in dry skin.
						Triglycerides in stratum corneum	Yes, lower in dry skin.
						Polar lipids in stratum corneum	Higher in dry skin.
						Free fatty acid in stratum corneum	Unclear, higher in dry skin(?)
						Cholesterol in stratum corneum	No
Horii et. al. [25]	1989	Subjects with mild xerosis (n = 10), moderate xerosis (n = 8), severe xerosis (n = 5) and subjects with normal skin (n = 7)	59 to 94	Outer aspect of the lower legs	Amino acid analyser	Amino acid in stratum corneum	Unclear
Saint-Léger et. al. [26]	1989	Subjects with xerosis (n = 52) and subjects with normal skin (n = 12)	30 to 40	Outer aspect of the lower legs	Photodensitometry	Wax esters and sterol esters in stratum corneum	Yes, lower in dry skin.
						Triglycerides in stratum corneum	Unclear, lower in dry skin(?)
						Free Fatty Acids in stratum corneum	Yes, higher in dry skin.
						Free sterols in stratum corneum	No
						Ceramide I in stratum corneum	No
						Ceramide II in stratum corneum	No
						Ceramide III in stratum corneum	No
						Ceramide IV and V in stratum corneum	No
						Ceramide VI in stratum corneum	No
						Cholesteryl sulfate in stratum corneum	No
						Total stratum corneum lipids	No
Jacobson et. al. [27]	1990	Old subjects with dry skin (n = 13) and non-dry skin (n = 7); young subjects with dry skin (n = 8) and non-dry skin (n = 18)	60 years or older	Outer aspect of the lower legs	High performance liquid chromatography	Aspartic acid in stratum corneum	Unclear, lower in dry skin(?)
						Threonine in stratum corneum	Unclear
						Serine in stratum corneum	No
						Glutamic acid in stratum corneum	Unclear, lower in dry skin(?)
						Glycine in stratum corneum	Unclear, higher in dry skin(?)
						Alanine in stratum corneum	Unclear, lower in dry skin(?)
						Valine in stratum corneum	No
						Methionine in stratum corneum	No
						Isoleucine in stratum corneum	Unclear, higher in dry skin(?)
						Leucine in stratum corneum	Unclear, higher in dry skin(?)
						Tyrosine in stratum corneum	Unclear, higher in dry skin(?)
						Phenylalanine in stratum corneum	No
						Lysine in stratum corneum	No
						Histidine in stratum corneum	Unclear, lower in dry skin(?)
						Tryptophan in stratum corneum	No
						Arginine in stratum corneum	No
						Ornithine in stratum corneum	No

(*Continued*)

Table 1. (Continued)

Author	Year	Sample	Age (years)	Skin areas	Method of analysis	Molecular markers analysed	Associations
Akimoto et. al. [28]	1993	Older subjects with xerosis (n = 25), their age matched control (n = 20) and young control group (n = 29)	24.3 to 71	Outer aspect of the lower legs	Thin layer chromatography	Total lipid in stratum corneum	Yes, higher in dry skin
						Total ceramide in stratum corneum	Yes, higher in dry skin
						Ceramide I in stratum corneum	Yes, higher in dry skin
						Ceramide II in stratum corneum	Yes, higher in dry skin
						Ceramide III in stratum corneum	Yes, higher in dry skin
						Hydro- ceramide I in stratum corneum	Yes, higher in dry skin
						Ceramide IV and V in stratum corneum	Yes, higher in dry skin
						Ceramide VI in stratum corneum	Yes, higher in dry skin
						Cholesterol sulfate	Yes, higher in dry skin
						Cholesterol Ester	Unclear, lower in dry skin(?)
						Wax in stratum corneum	Yes, lower in dry skin
						Triglyceride in stratum corneum	Yes, higher in dry skin
						Free fatty acid in stratum corneum	Yes, lower in dry skin
						Cholesterol in stratum corneum	Yes, higher in dry skin
Park et. al. [29]	1995	Patients with xerotic skin undergoing maintenance haemodialysis (n = 10) and healthy volunteers (n = 18)	30 to 68	Ventral forearm	Spectrophotometry	Urea in stratum corneum	Yes, higher in dry skin of haemodialysis patients.
Rawlings et. al. [30]	1996	Subjects with dry skin (n = 24)	23 to 45	Ventral forearm	Densitometric analysis	Cholesterol in stratum corneum	Yes, lower in dry skin
					Gas chromatography	Fatty acid levels in stratum corneum	Yes, lower in dry skin
						Ceramide levels in stratum corneum	Yes, lower in dry skin
Schreiner et. al. [31]	2000	Aged subject with dry skin (n = 4), young with dry skin (n = 5) and young with normal skin (n = 10)	25.5 (SD 2.5) to 66 (SD 3)	Lower leg	High performance thin layer chromatography and Photodensitometry	Total Ceramide in stratum corneum	No
						Free Sterols in stratum corneum	Yes, lower in dry skin
						Free fatty acids in stratum corneum	Unclear, higher in dry skin(?)
						Ceramide (EOS) in stratum corneum	Unclear, higher in dry skin(?)
						Ceramide (NS) in stratum corneum	Yes, higher in dry skin
						Ceramide (NP) in stratum corneum	Yes, lower in dry skin
						Ceramide (EOH) in stratum corneum	Yes, lower in dry skin
						Ceramide (AS) in stratum corneum	Unclear, higher in dry skin(?)
						Ceramide (AP) in stratum corneum	Yes, lower in dry skin
						Ceramide (AH) in stratum corneum	No
Simon et. al. [32]	2001	Xerotic skin (n = 30) and normal skin (n = 26)	22 to 49	Outer aspect of the legs	SDS-PAGE, western blotting	Desmoglein 1 in stratum corneum	Yes, higher in dry skin
						Plakoglobin in stratum corneum	Yes, higher in dry skin
						Corneodesmosin in stratum corneum	Yes, higher in dry skin
					Transmission electron microscopy	Corneodesmosome density in the inner stratum corneum	Yes, higher in dry skin
						Corneodesmosome density in the outer stratum corneum	Yes, higher in dry skin

(*Continued*)

Table 1. (Continued)

Author	Year	Sample	Age (years)	Skin areas	Method of analysis	Molecular markers analysed	Associations
Takahashi et. al. [33]	2004	Aged senile xerosis (n = 12), aged normal (n = 5) and young normal group (n = 10)	18 to 81	Lower leg	High performance liquid chromatography	Total amino acid in stratum corneum	Yes, higher in dry skin
						Aspartic acid in stratum corneum	Unclear, higher in dry skin(?)
						Glutamic acid in stratum corneum	Unclear, higher in dry skin(?)
						Citrulline in stratum corneum	Yes, higher in dry skin
						Serine in stratum corneum	Yes, higher in dry skin
						Threonine in stratum corneum	Yes, higher in dry skin
						Arginine in stratum corneum	Yes, lower in dry skin
						Glycine in stratum corneum	Yes, lower in dry skin
						Alanine in stratum corneum	Yes, higher in dry skin
						Proline in stratum corneum	Yes, higher in dry skin
						Valine in stratum corneum	Yes, higher in dry skin
						Isoleucine in stratum corneum	Yes, higher in dry skin
						Leucine in stratum corneum	Yes, higher in dry skin
						Tryptophan in stratum corneum	Unclear, lower in dry skin(?)
						Phenylalanine in stratum corneum	Yes, higher in dry skin
						Urocanic acid in stratum corneum	Yes, higher in dry skin
						Ornithin in stratum corneum	Yes, higher in dry skin
						Lysine in stratum corneum	Yes, higher in dry skin
						Histidine in stratum corneum	Unclear, lower in dry skin(?)
						Tyrosine in stratum corneum	Unclear, higher in dry skin(?)
Delattre et. al. [34]	2012	Postmenopausal women and young women with dry skin (n = 10); postmenopausal women and young women with normal skin (n = 10)	30 to 60	Upper leg skin	Electrophoresis, western blot, Liquid chromatography mass spectrometry	Corneodesmosin in stratum corneum	Yes, higher in dry skin
						Annexin A2 in stratum corneum	Yes, higher in dry skin
						Phosphatidylethanolamine-binding protein 1 (PEBP1) in stratum corneum	Yes, higher in dry skin
Ishikawa et. al. [35]	2013	Patients with dry skin (n = 20)	32 to 57	Outer aspect of the legs	Liquid Chromatography mass spectrometry	Ceramide (NP) in stratum corneum	Yes, lower in dry skin
Schweiger et. al. [36]	2013	Volunteers with dry and itchy scalp skin (n = 30)	26 to 73	Sides of the scalp	Direct analysis in real-Time mass spectrometry	Urea in stratum corneum	Yes, lower in dry scalp skin
						Lactate in stratum corneum	Yes, lower in dry scalp skin
					Fourier-transformed middle-infrared spectroscopy	Amide band ratio I/II in scalp site	Unclear, lower in dry scalp skin(?)
						Triglyceride in scalp site	Yes, lower in dry scalp skin
						Free fatty acid in scalp site	Yes, higher in dry scalp skin
						Total lipid in stratum corneum	Unclear, lower in dry scalp skin(?)
					Enzyme-linked immunosorbent assays	IL-1ra/IL-1β in stratum corneum	Yes, higher in dry scalp skin
						IL-8 in stratum corneum	Yes, higher in dry scalp skin

(*Continued*)

Table 1. (Continued)

Author	Year	Sample	Age (years)	Skin areas	Method of analysis	Molecular markers analysed	Associations
Son et. al. [37]	2015	Dry skin and hydrated skin (total n = 22)	Men: 33.8 (5.6), Women: 31.3 (4.1)	Ventral forearm	Western blotting and densitometric analyses	(Pro)filaggrin in stratum corneum	No
						Bleomycin hydrolase in stratum corneum	Yes, lower in dry skin
					High performance liquid chromatography	Total NMFs (as free amino acid) in stratum corneum	Yes, lower in dry skin
						Histidine in stratum corneum	Yes, lower in dry skin
						Serine in stratum corneum	Yes, lower in dry skin
						Arginine in stratum corneum	Yes, lower in dry skin
						Glycine in stratum corneum	Yes, lower in dry skin
						Aspartic acid in stratum corneum	Unclear, lower in dry skin(?)
						Glutamic acid in stratum corneum	Yes, lower in dry skin
						Threonine in stratum corneum	Yes, lower in dry skin
						Alanine in stratum corneum	Yes, lower in dry skin
						gamma-Aminobutyric acid in stratum corneum	Unclear, lower in dry skin(?)
						Proline in stratum corneum	Unclear, lower in dry skin(?)
						Lysine in stratum corneum	No
						Tyrosine in stratum corneum	Yes, lower in dry skin
						Methionine in stratum corneum	Yes, lower in dry skin
						Valine in stratum corneum	Unclear, lower in dry skin(?)
						Leucine in stratum corneum	Yes, lower in dry skin
						Isoleucine in stratum corneum	Unclear, lower in dry skin(?)
						Phenylalanine in stratum corneum	Yes, lower in dry skin
						Tryptophan in stratum corneum	Yes, lower in dry skin
						Pyrrolidone carboxylic acid in stratum corneum	Yes, lower in dry skin
						Urocanic acid in stratum corneum	Unclear, lower in dry skin(?)
Danby et. al. [38]	2016	Volunteers with dry skin (n = 21)	60 to 89	Ventral forearm	Protease assay	Caseinolytic activities in stratum corneum	Yes, higher in dry skin
						Chymotrypsin-like activities in stratum corneum	Yes, higher in dry skin
						Trypsin-like activities in stratum corneum	Yes, higher in dry skin
					Fluorometric l -lactate assay	Lactate in stratum corneum	Yes, lower in dry skin
					Not found	Pyrrolidone carboxylic acid (PCA) in stratum corneum	Yes, lower in dry skin
					Fourier transform infrared spectroscopy	Carboxylic acid in stratum corneum	Yes, lower in dry skin
Tamura et. al. [39]	2016	Subjects having heavily desquamated lips, slightly desquamated lips and subjects having no desquamation on lips (total n = 40)	22 to 52	Lips	Liquid chromatography mass spectrometry	Ceramide (NH) in stratum corneum	Yes, lower in dry lip skin
						Ceramide (NP) in stratum corneum	Yes, lower in dry lip skin
Vyumvuhore et. al. [40]	2018	Subjects with mild xerosis (n = 19) and subjects with normal skin (n = 15)	57 and 58 (mean)	On outside arms or the calf	Liquid Chromatography Mass Spectrometry	Ceramide (NdS) in stratum corneum	Yes, lower in dry skin
						Ceramide (NS) in stratum corneum	Yes, lower in dry skin
						Ceramide (EOP) in stratum corneum in stratum corneum	Yes, lower in dry skin

(*Continued*)

Table 1. (Continued)

Author	Year	Sample	Age (years)	Skin areas	Method of analysis	Molecular markers analysed	Associations
Lechner et. al. [41]	2019	Diabetic subjects with xerosis (n = 30) and non-diabetic subjects with xerosis (n = 15)	63.5 (7.8) and 56.2 (9.3)	Foot dorsum and Plantar heel	Liquid chromatography mass spectrometry	Ceramides	Yes, higher in dry skin of diabetics
						Natural Moisturising Factors in stratum corneum	Yes, higher in dry skin of diabetics
						Amino Acid in stratum corneum	Yes, higher in dry skin of diabetics
						Serine in stratum corneum	Yes, higher in dry skin of diabetics
						Pyrrolidone carboxylic acid in stratum corneum	Yes, higher in dry skin of diabetics
						Urocanic acid trans in stratum corneum	Yes, higher in dry skin of diabetics
						Urocanic acid cis in stratum corneum	No
						Histamine in stratum corneum	Yes, higher in dry skin of diabetics
						Total proteins in stratum corneum	Yes, higher in dry skin of diabetics
						Glutathione in stratum corneum	Unclear
						Melondialdehyde in stratum corneum	Yes, lower in dry skin of diabetics
Legiawati et. al. [42]	2020	Type 2 diabetes mellitus patients with dry Skin (total n = 159)	26 to 59	Right lower extremities	Enzyme-linked immunosorbent assays	N(6)-carboxymethyl-lysine (CML) activity in stratum corneum	Yes, lower in dry skin of diabetics
						Interleukin-1α (IL-1α) activity in stratum corneum	Unclear
						Superoxide dismutase (SOD) activity in stratum corneum	Unclear, lower in dry skin of diabetics(?)

(*Continued*)

Table 1. (Continued)

Author	Year	Sample	Age (years)	Skin areas	Method of analysis	Molecular markers analysed	Associations
Uchino et. al. [43]	2020	Patients with non-small lung cancer receiving oral Erlotinib administration having dry skin (n = 18) and healthy subjects (n = 6)	50 to 85	Ventral forearm	Ultra performance liquid chromatography combined with time-of-flight mass spectrometry	Cholesterol Sulfate in stratum corneum	Yes, higher in dry skin of patients receiving oral Erlotinib
						Total free fatty acids in stratum corneum	Unclear, lower in dry skin of patients receiving oral Erlotinib(?)
						Saturated free fatty acids in stratum corneum	Unclear, lower in dry skin of patients receiving oral Erlotinib(?)
						Hydroxy free fatty acids in stratum corneum	Unclear, lower in dry skin of patients receiving oral Erlotinib(?)
						Unsaturated free fatty acids in stratum corneum	No
						Total Ceramide in stratum corneum	Unclear
						Ceramide (NdS) in stratum corneum	Unclear, lower in dry skin of patients receiving oral Erlotinib(?)
						Ceramide (NS) in stratum corneum	Unclear, lower in dry skin of patients receiving oral Erlotinib(?)
						Ceramide (NP) in stratum corneum	Unclear, lower in dry skin of patients receiving oral Erlotinib(?)
						Ceramide (NH) in stratum corneum	Unclear, lower in dry skin of patients receiving oral Erlotinib(?)
						Ceramide (AdS) in stratum corneum	No
						Ceramide (AS) in stratum corneum	Unclear, lower in dry skin of patients receiving oral Erlotinib(?)
						Ceramide (AP) in stratum corneum	Yes, lower in dry skin of patients receiving oral Erlotinib
						Ceramide (AH) in stratum corneum	Unclear, lower in dry skin of patients receiving oral Erlotinib(?)
						Ceramide (EOdS) in stratum corneum	Unclear, lower in dry skin of patients receiving oral Erlotinib(?)
						Ceramide (EOS) in stratum corneum	Unclear, lower in dry skin of patients receiving oral Erlotinib(?)
						Ceramide (EOP) in stratum corneum	Unclear, lower in dry skin of patients receiving oral Erlotinib(?)
						Ceramide (EOH) in stratum corneum	Unclear, lower in dry skin of patients receiving oral Erlotinib(?)

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higher in those subjects. However, in drug-induced xerosis, association of total ceramide with skin dryness was unclear [43]. In general skin dryness, one study found lower level of total ceramide in the dry skin [30]. Another cross sectional study, conducted in smaller sample size (n = 5 and 10), found no association [31].

3.3.1.2. Ceramide (NP). Ceramide (NP), previously known as ceramide III, was found to be lower in three studies regarding general skin dryness [31, 35, 39]. In contrast, one study in older subjects found ceramide (NP) to be remained in higher amount in senile xerosis [28]. Saint léger et. al., 1989 did not found any association of this marker with general skin dryness [26]. In drug-induced xerosis, the association was unclear [43].

3.3.1.3. Ceramide (NS). In subjects with senile xerosis, the amount of ceramide (NS), previously ceramide II, was found in lower amounts than their age matched control [28]. Two studies on general skin dryness also found this marker to be associated with dry skin but they reported opposite results to each other [31, 40]. Another study with similar setting did not find any association [26], while in the case of drug-induced xerosis, an association was unclear [43].

3.3.1.4. Ceramide (EOS), ceramide (NH) and ceramide (EOH). These three members of ceramide subclasses were found to be positively associated with senile xerosis [28] but negatively associated with general skin dryness [31, 39, 40]. However, one study showed no association of these ceramides with general skin dryness [26] and another study showed it to be unclear [43].

3.3.1.5. Ceramide (AS) and hydroceramide I. Ceramide (AS) and hydroceramide I were only found to be associated with senile xerosis and the reported amount was higher in the aged dry skin [28]. However, additional studies which analyzed ceramide (AS) in other dry skin conditions (general skin dryness and drug-induced xerosis), reported either unclear or no association [26, 31, 43].

3.3.1.6. Ceramide (AP) and ceramide (NdS). All the studies that analyzed the quantitative amounts of these two ceramides, reported these markers to be present in lower amounts in different dry skin conditions. Ceramide (AP) was investigated both in general skin dryness and drug-induced xerosis [31, 43] while ceramide (NdS) was only analyzed in general skin dryness [40].

3.3.1.7. Ceramide (AH), ceramide (AdS), ceramide (EOdS) and ceramide (EOP). No study reported any positive or negative association of these four ceramides with any type of xerosis cutis.

3.3.1.8. Total free fatty acids. Seven studies published between 1988 and 2020 analyzed total free fatty acids, of which four reported associations of this marker with different dry skin conditions [26, 28, 30, 36]. Akimoto et. al., 1993 found the amount of free fatty acid to be lower in older subjects with xerosis than their age matched control [28]. Two studies on general skin dryness (one cross sectional, another, randomized controlled trial) found opposite results to each other; higher [26] and lower [30]. The amount of free fatty acids were found higher in dry and itchy scalp skin compared to the side of the scalp which achieved reduced dryness after a tonic treatment [36]. Results reported by other three studies were found to be unclear [24, 31, 43]. Uchino et. al., 2020 [43] also analyzed three categories of free fatty acids in the dry skin of patients receiving erlotinib drug. Unsaturated free fatty acids were not associated with drug-induced xerosis while saturated and hydroxyl free fatty acids revealed unclear association.

3.3.1.9. Triglycerides. Two studies on senile xerosis reported the association of triglycerides with skin dryness. One study found this to be higher in aged dry skin compared to the control sample while another study found the opposite [24]. In general skin dryness, one study found no association [26] but in dry scalp skin, the amount of triglycerides was comparatively lower when the scalp was found to be drier [36].

3.3.1.10. Cholesterol and cholesterol sulfate. Studies, where an association was present, both of these two markers were shown to be in lower amounts in general skin dryness [30] and in higher amounts in senile xerosis and drug-induced xerosis [28, 43]. However, there is also one

study per marker, which reported no association of cholesterol and the sulfate ester of this compound with dry skin.

3.3.1.11. Free sterols, sterol esters and wax. Like cholesterol, total free sterols and total sterol esters were also found to be in lower amounts in general skin dryness [26, 31], but unlike the sulfate ester, total sterol esters [24] and wax [28] were found to be in lower amounts in senile xerosis [24, 28]. There are also other studies in this review, which reported unclear association of sterol esters in senile xerosis [28] and no association of free sterols in senile xerosis [26].

3.3.1.12. Total lipids. Three studies reported this marker, one study described an association [28], one described an unclear association [36] and the remaining study described no association [26] with skin dryness. In the study where an association was found, a higher amount of total lipid in senile xerosis was reported [28].

3.3.2. Natural moisturizing factors (NMFs). Twenty-five NMFs components were reported in different dry skin etiologies, which include most standard amino acids, ornithin, citrulline, gamma-aminobutyric acid, urocanic acid, carboxylic acids and pyrrolidone carboxylic acid.

3.3.2.1. Total free amino acids (FAAs) and NMFs. Total FAA was found to be higher in the dry skin of patients with underlying conditions like senile xerosis [33] and diabetic xerosis [41]. Analysis of NMFs also revealed the same pattern [41]. Inversely, in general skin dryness, the amount of FFAs was found to be lower than the control samples [37]. One study, however, found unclear association of FAAs in senile xerosis [25].

3.3.2.2. Serine, alanine, leucine, phenylalnine and threonine. These five amino acids followed the similar pattern as total FAAs. Amounts of these amino acids were higher in senile xerosis and diabetic xerosis [33, 41] and were lower in general skin dryness [37]. However there is at least one study which found either 'unclear' or 'no' association of these amino acids with general skin dryness [27].

3.3.2.3. Glycine and arginine. In both senile xerosis and general skin dryness, glycine and arginine was negatively associated [33, 37], hence, amounts were found to be lower than in the control group. Unclear or no association of these two amino acids were also reported [27].

3.3.2.4. Histidine, tyrosine, glutamic acid, tryptophan and methionine. For these five amino acids, association was reported only in case of general skin dryness and the amounts were lower compared to the control group [37]. One study on senile xerosis [33] and another study on general skin dryness [27], both worked on small control groups (n = 5 and 7), reported either 'unclear' or 'no' association of these amino acids with xerosis cutis.

3.3.2.5. Isoleucine, valine, lysine, proline, ornithin and citrulline. All these six amino acids were reported to be associated with only senile xerosis [33]. The association was positive; that means in aged skin, these amino acids were found to be in higher amounts than the control samples. Except citrulline, other five amino acids were showed to have either 'unclear' or 'no' association with general skin dryness [27, 37].

3.3.2.6. Aspartic acid and gamma-aminobutyric acid. Only unclear associations were found in general skin dryness [27, 37] and senile xerosis [33].

3.3.2.7. Urocanic acid, carboxylic acids and pyrrolidone carboxylic acid (PCA). Urocanic acid was reported to be present in higher amounts in senile xerosis [33] and also in diabetic xerosis [41]; as trans urocanic acid. However, in case of cis urocanic acid, no association was found with diabetic xerosis [41]. In general skin dryness, the association was not clear [37]. Carboxylic acids (total) followed different pattern- 'negative association' with senile xerosis [38]. When only pyrrolidone carboxylic acid was investigated, it was reported to be present in lower amounts in general skin dryness and senile xerosis [37, 38] but in higher amounts in diabetic xerosis [41].

3.3.3. Proteins/ enzymes. Described below are the 17 protein, enzyme, cytokines and similar markers which were reported in the included articles in this review.

3.3.3.1. Corneodesmosin, desmoglein 1, plakoglobin, annexin A2 and phosphatidylethanolamine-binding protein 1. These five protein markers were found to be positively associated with general skin dryness. Corneodesmosin was investigated in two studies [32, 34] while the others were studied once [32] or [34]. In all cases, the amount of these proteins where quantified in higher amounts in dry skin compared to the subjects' age-matched control. It is to be noted that in the study by Delattre et. al. 2012, who analyzed corneodesmosin, annexin A2 and phosphatidylethanolamine-binding protein 1, about half of the study population was postmenopausal women [34].

3.3.3.2. Caseinolytic activities, chymotrypsin-like activities, trypsin-like activities and total proteins. These four protein markers were found to be in elevated amounts in dry skin of patients with underlying conditions. Caseinolytic activities, chymotrypsin-like activities and trypsin-like activities were measured in senile xerosis [38]. These markers were positively associated with skin dryness. Total protein was shown to be increased in diabetic xerosis [41].

3.3.3.2. N(6)-carboxymethyl-lysine activity and bleomycin hydrolase. Being negatively associated with dry skin, N(6)-carboxymethyl-lysine activity was reported in diabetic xerosis [42] and bleomycin hydrolase was reported in general skin dryness [37]. In both cases, amount of these markers were found to be in lower amount in dry skin compared to the control groups.

3.3.3.3. Glutathione, (pro)filaggrin and superoxide dismutase activity. Glutathione, a tri-peptide, was detected in non-diabetics with dry skin though it was not found in diabetics with dry skin [41]. The association seems unclear. (Pro)filaggrin was also reported to have no association in general skin dryness [37]. The association of superoxide dismutase was unclear with diabetic xerosis as reported by Legiawati et. al., 2020 [42].

3.3.3.4. Cytokines (Interleukin (IL)-8, IL-1ra/IL-1β and Interleukin-1α). In scalp skin (general skin dryness), the amount of interleukin-8 was found to be higher in the dry scalp compared to the amount of this marker found in the hydrated scalp after tonic treatment. The ratio of IL-1ra/IL-1β was also positively associated with scalp dryness [36]. Another study which measured interleukin-1α activity in diabetic xerosis, found its association with the skin dryness to be unclear [42].

3.3.4. Metabolites or metabolic products. Five metabolites/ metabolic products including lactate, urea, histamine, melondialdehyde and aluminium were reported to be associated with dry skin.

3.3.4.1. Lactate. Both of the two studies which investigated on the amount of lactate in the skin, found this marker to be negatively associated with skin dryness. One study was on dry scalp skin (general skin dryness) [36] and another was on senile xerosis [38].

3.3.4.2. Urea. In the dry skin of patients undergoing hemodialysis, the amount of urea was found to be higher compared to control subjects [29]. The opposite was found in case of dry scalp skin (general skin dryness) where the amount of urea was negatively associated with dryness of scalp [36].

3.3.4.3. Histamine and melondialdehyde. Both of these markers were shown to be associated with the dry skin of diabetic patients compared to skin dryness in non-diabetics. Histamine, a neurotransmeter, was positively associated with diabetic xerosis while melondialdehyde, a marker of oxidative stress, was decreased in diabetic xerosis [41].

3.3.4.4. Aluminium. In the dry skin of hemodialysis patients, aluminium levels in the epidermis and dermis were higher than in the control group and seemed to be positively associated with the skin dryness [23].

3.4. Number of markers and possible associations with dry skin

Table 2 presents a summary of all molecular markers, which were reported at least in two studies (top markers). Additionally, S3 Appendix is for the markers which was analyzed only in one study. Total free fatty acids, total ceramide, ceramide (NP), ceramide (NS), ceramide (NH), ceramide (EOS), ceramide (EOH), ceramide (AS), triglyceride, total free amino acids, serine and urocanic acid were measured in at least four studies. From those, the number of studies suggesting associations between molecular markers and dry skin compared to the number of studies of unclear or no associations was higher for total free fatty acids, total ceramide, ceramide (NP), ceramide (NS), triglyceride, total free amino acids and serine.

4. Discussion

This systematic review identified more than 70 molecular markers that were measured in dry skin research. In addition, various sampling and analytical methods were used. Overall, only 12 molecular markers were reported in at least four studies. The majority of markers was reported only once or twice. This indicates substantial heterogeneity in this field and makes the intended comparisons nearly impossible.

When considering the markers, which were reported at least four times, seven seemed to be associated with skin dryness in at least two or more studies (total ceramide, ceramide (NP), ceramide (EOS), ceramide (NH), ceramide (EOH), free amino acids and serine). If associated, they were always found to be lower in general skin dryness but higher in xerosis induced by any internal condition. Additional markers, which seem to show a similar pattern are cholesterol, cholesterol sulfate, alanine, leucine, phenylalanine, threonine and urea. Though these were analyzed in less number of studies, associations with xerosis cutis were reported in at least two studies. In addition, the independent association of ceramide (NP), ceramide (NH) and cholesterol sulfate was demonstrated by statistical analysis in corresponding studies [35, 39, 43].

Total free fatty acids, ceramide (NS) and triglycerides were also analyzed in four or more studies but the associations of these markers with xerosis cutis seemed unclear. For example, in general skin dryness, total free fatty acids were shown to have both positive [26, 36] and negative associations [30]. Same was also seen for ceramide (NS) [31, 40]. Triglycerides in senile xerosis also showed conflicting results [24, 28]. Moreover, for nearly every marker there were also studies showing unclear or no association. In addition to the wide variety of reported markers, this may indicate substantial biological variability. Variations may be caused by the analytical methods (e.g., SC or compounds dissolved from SC) used. In addition, use of different sampling methods (tape-stripping, varnish stripping, solvent extraction, etc) might contribute to the variability in results. Sensitivity differences among individual methods of analysis may produce remarkable variability as only six recent studies used unambiguous quantitation technology like mass spectrometry while others used different spectrophotometric techniques such as photodensitometry, thin layer chromatography, liquid chromatography, gas chromatography or other biomolecular tools depending on the analyte characteristics. Moreover, variations in study design, number of samples and reported quantitative units might also have contributed to observed heterogeneity and variability to some extent.

We also found four markers (pyrrolidone carboxylic acid, corneodesmosin, lactate and urea) which were associated with dry skin in all the few studies they were reported. PCA was analyzed in three studies with both negative [37, 38] and positive [41] association. Corneodesmosin was found to be positively associated [32, 34] while lactate [36, 38] and urea [29, 36]

Table 2. Top markers (compounds analysed more than once).

Molecular markers	Number of studies	Analysed material	Sampling technique	Method of analysis	Association with skin dryness (number of studies)
Total free fatty acids [24, 26, 28, 30, 31, 36, 43]	7	Compounds dissolved from stratum corneum/ stratum corneum/ direct measurement of skin area	Hexane- methanol extraction/ stripping with cyanoacrylate resin / tape stripping/ shave biopsy/ direct measurement	Photodensitometry/ thin layer chromatography/ fourier-transformed middle-infrared spectroscopy/ high performance thin layer chromatography/ liquid chromatography mass spectrometry	Yes: 4 Unclear: 3
Total ceramide [24, 28–31, 41, 43]	6	Compounds dissolved from stratum corneum/stratum corneum	Hexane- methanol extraction/ stripping with cyanoacrylate resin / tape stripping/ shave biopsy/ collecting swabs.	Photodensitometry/ thin layer chromatography/ high performance thin layer chromatography/ liquid chromatography mass spectrometry	Yes: 4 No: 1 Unclear: 1
Ceramide (NP); also called Ceramide III. [19, 26, 28, 31, 35, 39, 43]	6	Compounds dissolved from stratum corneum/stratum corneum	Hexane- methanol extraction/ stripping with cyanoacrylate resin / shave biopsy/ varnish stripping/ tape stripping	Photodensitometry/ thin layer chromatography/ high performance thin layer chromatography/ liquid chromatography mass spectrometry	Yes: 4 No: 1 Unclear: 1
Ceramide (NS); also called Ceramide II. [19, 26, 28, 31, 40, 43]	5	Compounds dissolved from stratum corneum/stratum corneum	Hexane- methanol extraction/ stripping with cyanoacrylate resin / shave biopsy/ collecting swabs/ tape stripping.	Photodensitometry/ thin layer chromatography/ high performance thin layer chromatography/ liquid chromatography mass spectrometry	Yes: 3 No: 1 Unclear: 1
Ceramide (EOS); also called Ceramide I. [19, 26, 28, 31, 40, 43]	5	Compounds dissolved from stratum corneum/stratum corneum	Hexane- methanol extraction/ stripping with cyanoacrylate resin / shave biopsy/ collecting swabs/ tape stripping.	Photodensitometry/ thin layer chromatography/ high performance thin layer chromatography/ liquid chromatography mass spectrometry	Yes: 2 No: 1 Unclear: 2
Triglyceride [24, 26, 28, 36]	4	Compounds dissolved from stratum corneum/ stratum corneum/ direct measurement of skin area	Hexane- methanol extraction/ stripping with cyanoacrylate resin / direct measurement	Photodensitometry/ thin layer chromatography/ fourier-transformed middle-infrared spectroscopy	Yes: 3 Unclear: 1
Serine [27, 33, 37, 41]	4	Scraped cells from stratum corneum/ stratum corneum/ compounds dissolved from stratum corneum.	Scraping off the skin with a glass slide/ tape stripping/ collecting swabs	High performance liquid chromatography/ liquid chromatography mass spectrometry	Yes: 3 No: 1
Total free amino acids [25, 33, 37, 41]	4	Stratum corneum/ compounds dissolved from stratum corneum	Tape stripping/ scraping off the skin with a glass slide/ collecting swabs	Amino acid analyzer/ high performance liquid chromatography/ liquid chromatography mass spectrometry	Yes: 3 Unclear: 1
Ceramide (NH); also called Ceramide VI [19, 26, 28, 39, 43]	4	Compounds dissolved from stratum corneum/stratum corneum	Hexane- methanol extraction/ stripping with cyanoacrylate resin/ tape stripping	Photodensitometry/ thin layer chromatography/ liquid chromatography mass spectrometry	Yes: 2 No: 1 Unclear: 1
Urocanic acid (UCA) [27, 33, 37, 41]	4	Stratum corneum/ compounds dissolved from stratum corneum	Scraping off the skin with a glass slide/ tape stripping/ collecting swabs	High performance liquid chromatography/ liquid chromatography mass spectrometry	Yes: 2 (1 as UCA trans) No: 1 (as UCA cis) Unclear: 1
Ceramide (EOH); also called Ceramide IV. [26, 28, 31, 43]	4	Compounds dissolved from stratum corneum/stratum corneum	Hexane- methanol extraction/ stripping with cyanoacrylate resin / shave biopsy/ tape stripping.	Photodensitometry/ thin layer chromatography/ high performance thin layer chromatography/ liquid chromatography mass spectrometry	Yes: 1 No: 1 Unclear: 2
Ceramide (AS) [26, 28, 31, 43]	4	Compounds dissolved from stratum corneum/stratum corneum	Hexane- methanol extraction/ stripping with cyanoacrylate resin / shave biopsy/ tape stripping.	Photodensitometry/ thin layer chromatography/ high performance thin layer chromatography/ liquid chromatography mass spectrometry	No: 1 Unclear: 3
Pyrrolidone carboxylic acid [37, 38, 41]	3	Stratum corneum/ compounds dissolved from stratum corneum	Tape stripping/ collecting swabs	High performance liquid chromatography / liquid chromatography mass spectrometry	Yes: 3

(*Continued*)

Table 2. (Continued)

Molecular markers	Number of studies	Analysed material	Sampling technique	Method of analysis	Association with skin dryness (number of studies)
Glycine [27, 33, 37]	3	Stratum corneum	Scraping off the skin with a glass slide/ tape stripping	High performance liquid chromatography	Yes: 2 Unclear: 1
Alanine [27, 33, 37]	3	Stratum corneum	Scraping off the skin with a glass slide/ tape stripping	High performance liquid chromatography	Yes: 2 Unclear: 1
Leucine [27, 33, 37]	3	Stratum corneum	Scraping off the skin with a glass slide/ tape stripping	High performance liquid chromatography	Yes: 2 Unclear: 1
Phenylalaine [27, 33, 37]	3	Stratum corneum	Scraping off the skin with a glass slide/ tape stripping	High performance liquid chromatography	Yes: 2 No: 1
Arginine [27, 33, 37]	3	Stratum corneum	Scraping off the skin with a glass slide/ tape stripping	High performance liquid chromatography	Yes: 2 No: 1
Threonine [27, 33, 37]	3	Stratum corneum	Scraping off the skin with a glass slide/ tape stripping	High performance liquid chromatography	Yes: 2 Unclear: 1
Cholesterol [24, 28, 30]	3	Compounds dissolved from stratum corneum/stratum corneum	Hexane- methanol extraction/ stripping with cyanoacrylate resin / tape stripping	Photodensitometry/ thin layer chromatography	Yes: 2 No: 1
Cholesterol sulfate [26, 28, 43]	3	Compounds dissolved from stratum corneum/stratum corneum	Hexane- methanol extraction/ stripping with cyanoacrylate resin / tape stripping	Photodensitometry/ thin layer chromatography/ liquid chromatography mass spectrometry	Yes: 2 No: 1
Corneodesmosin [32, 34]	2	Stratum corneum	Varnish stripping	Electrophoresis, western blot and liquid chromatography mass spectrometry.	Yes: 2
Lactate [36, 38]	2	Compounds dissolved from stratum corneum	Skin surface material collected by DIP-it sampler/ collecting swabs	Real-time mass spectrometry/ fluorometric L -lactate assay.	Yes: 2
Urea [29, 36]	2	Stratum corneum/ compounds dissolved from stratum corneum	Cyanoacrylate adhesive stripping/ skin surface material collected by DIP-it sampler	Spectrophotometry/ real-time mass spectrometry	Yes: 2
Ceramide (AP) [31, 43]	2	Stratum corneum	Shave biopsy/ tape stripping.	High performance thin layer chromatography and photodensitometry/ liquid chromatography mass spectrometry	Yes: 2
Histidine [27, 33, 37]	3	Stratum corneum	Scraping off the skin with a glass slide/ tape stripping	High performance liquid chromatography	Yes: 1 Unclear: 2
Tyrosine [27, 33, 37]	3	Stratum corneum	Scraping off the skin with a glass slide/ tape stripping	High performance liquid chromatography	Yes: 1 Unclear: 2
Glutamic acid [27, 33, 37]	3	Stratum corneum	Scraping off the skin with a glass slide/ tape stripping	High performance liquid chromatography	Yes: 1 Unclear: 2
Isoleucine [27, 33, 37]	3	Stratum corneum	Scraping off the skin with a glass slide/ tape stripping	High performance liquid chromatography	Yes: 1 Unclear: 2
Tryptophan [27, 33, 37]	3	Stratum corneum	Scraping off the skin with a glass slide/ tape stripping	High performance liquid chromatography	Yes: 1 No: 1 Unclear: 1
Valine [27, 33, 37]	3	Stratum corneum	Scraping off the skin with a glass slide/ tape stripping	High performance liquid chromatography	Yes: 1 No: 1 Unclear: 1
Total lipid [26, 28, 36]	3	Compounds dissolved from stratum corneum/ stratum corneum/ direct measurement of skin area	Hexane- methanol extraction/ stripping with cyanoacrylate resin / direct measurement	Photodensitometry/ thin layer chromatography/ fourier-transformed middle-infrared spectroscopy	Yes: 1 No: 1 Unclear: 1

(*Continued*)

Table 2. (Continued)

Molecular markers	Number of studies	Analysed material	Sampling technique	Method of analysis	Association with skin dryness (number of studies)
Lysine [27, 33, 37]	3	Stratum corneum	Scraping off the skin with a glass slide/ tape stripping	High performance liquid chromatography	Yes: 1 Unclear: 2
Sterol esters [24, 26, 28]	3	Compounds dissolved from stratum corneum/ stratum corneum	Hexane- methanol extraction/ stripping with cyanoacrylate resin	Photodensitometry/ thin layer chromatography	Yes: 1 Unclear: 2
Proline [33, 37]	2	Stratum corneum	Scraping off the skin with a glass slide/ tape stripping	High performance liquid chromatography	Yes: 1 Unclear: 1
Ceramide (NdS) [40, 43]	2	Compounds dissolved from stratum corneum/stratum corneum	Collecting swabs/ tape stripping.	Liquid chromatography mass spectrometry	Yes: 1 Unclear: 1
Methionine [27, 37]	2	Stratum corneum	Scraping off the skin with a glass slide/ tape stripping	High performance liquid chromatography	Yes: 1 No: 1
Ornithin [27, 33]	2	Stratum corneum	Scraping off the skin with a glass slide	High performance liquid chromatography	Yes: 1 No: 1
Free sterols [26, 31]	2	Compounds dissolved from stratum corneum/stratum corneum	Hexane- methanol extraction/ shave biopsy	Photodensitometry/high performance thin layer chromatography	Yes: 1 No: 1
Aspartic acid [27, 33, 37]	3	Stratum corneum	Scraping off the skin with a glass slide/ tape stripping	High performance liquid chromatography	Unclear: 3
Ceramide (AH) [31, 43]	2	Stratum corneum	Shave biopsy/ tape stripping.	High performance thin layer chromatography and photodensitometry/ liquid chromatography mass spectrometry	No: 1 Unclear: 1

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were found to be negatively associated with skin dryness. More studies are required to evaluate the significance of these markers.

Quantitative expressions of several markers were found to be consistently changing with multiple clinical score values of skin dryness in corresponding samples. Triglycerides, ceramide (NH), ceramide (NP), ceramide (AP), urea and lactate showed gradual increase; while total free fatty acids and cholesterol sulfate were found to be gradually decreased with the reported severities of dry skin assessed according to the scoring methods. However, except urea and lactate (though reported in only two studies), other studies reported unclear or no associations of these markers which indicates heterogeneity in overall expression.

In case of dry skin induced by internal diseases, markers of diabetic xerosis was studied exhaustively in two recent studies by Lechner et. al., 2019 [41] and Legiawati et. al., 2020 [42]. Among the markers, pyrrolidone carboxylic acid was higher in diabetic xerosis; but in other dry skin conditions (general skin dryness and senile xerosis), there were negative associations. Trans-urocanic acid was positively associated but cis-urocanic acid was not associated with diabetic xerosis. Total ceramide, NMFs and histamine were positively associated while N(6)-carboxymethyl-lysine and melondialdehyde was negatively associated.

It is also well known, that the occurrence and severity of xerosis cutis is skin area specific, for example in senile xerosis the legs are drier than the arms [2]. However, the heterogeneity of the reviewed evidences makes these intended comparisons almost impossible. In addition, we did not include any study that compared skin dryness or markers from both the arms and leg skin areas.

Further research in this field is necessary to facilitate the discovery of evidence of associations of the molecular markers with skin dryness and to help in guiding clinical practice. The status of certain markers may even help clinicians in more precise understanding of the underlying causes of the disease. However, for translating the research findings into clinical practice, as recommended by Hammond and Taube [44], the markers should be validated in prospective, well-controlled clinical trials of various patient participants across different institutions with established standard for sample preparations, data collection, statistical analysis and scoring. Many studies analyzed multiple markers simultaneously. Besides considering the individual markers, a panel of markers might also provide a better inside in disease prognosis especially in xerosis cutis with underlying conditions, which merits further investigation.

One of the limitations of this systematic review is that we selected the top markers primarily based on the number of articles in which they were analyzed. We searched for particular patterns regarding the occurrence of the markers with the presence or severity of skin dryness. That is why the markers, which were analyzed only in one study, could not be placed as top markers though some might have potential as important markers. The objective of this review was to describe possible associations of molecular markers based on their quantitative patterns related to skin dryness. To define the association, an arbitrary evaluation of the patterns was used which is another limitation of this study. In addition, as the p-values are affected by the sample size, we considered the difference between the quantitative amounts of the markers found in the comparing groups rather than the reported p-values which were actually present only in few articles and unlikely to be clinically relevant. Additional limitation of this study is that, group comparisons between the skin of healthy people and the skin of people with underlying conditions might be biased as they also differ in other characteristics beyond skin dryness (diabetes, hemodialysis, hormonal imbalance, drug effects, etc.). Also, we did not include temporary skin dryness due to seasonal changes which is more logical to be described as rough skin as stated by De Paepe et.al., 2009 [45]. As we were interested in reviewing the markers studied in pathological xerosis, seasonal dry skin was not in our focus.

5. Conclusion

Seventy-two molecular markers for measuring xerosis cutis were identified. Total free fatty acids, ceramides, triglycerides, total free amino acids, serine and urocanic acid have been reported most often, but the evidence whether the quantity of these molecular markers indicates the status of skin dryness is heterogeneous. Thirty-one molecular markers were reported only once. Although there is a huge interest in molecular markers in dry skin research, it is currently unclear which are the most relevant.

Supporting information

S1 Appendix. Search strategy.
(PDF)

S2 Appendix. Study details and results of the data extraction.
(DOCX)

S3 Appendix. Molecular markers analyzed only once.
(DOCX)

S4 Appendix. PRISMA checklist. A review protocol has been registered in the PROSPERO database (https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42020214173).
(DOCX)

S1 File.
(PDF)

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S1 Appendix 1: Search Strategy.

Manuscript title: “Molecular characterization of xerosis cutis: a systematic review”.

Databases: ‘MEDLINE’, ‘EMBASE’ and ‘Biological abstracts’.

Search conducted on: 29.09.2020

Xerosis cutis

1	(xerosis or xerotic).m_titl.
2	(astea* or xero*).m_titl.
3	(skin adj1 dry*).m_titl.
4	1 or 2 or 3
5	(subject or participa* or patient*).mp.
6	4 and 5

Markers

7	(biomarker or biologic* or new $marker or mediat* or express* or activat* or pathway or inflam*).mp.
8	(prote* or enzyme or cytokine or chemokine or IL$$ or TRL$ or TNF$ or inter*).mp.
9	(MMP$ or involucrin or Loricrin or prosta* or HAS$ or plako*).mp.
10	(corneodesmosin or aquaporin or filaggrin or keratin* or elasti*).mp.
11	(Lipid or ceramide or cholesterol or humec* or trigly* or endogen*).mp.
12	(Urocanic or Hyaluron* or malondialdehyde or glutathione or PCA$ or histamin or amino).mp.
13	7 or 8 or 9 or 10 or 11 or 12
14	6 and 13
15	Remove duplicates from 14
16	Limit 15 to yr= ‘1990 –Current’

S2 Appendix: Study details and results of the data extraction of all included studies in the manuscript “Molecular characterization of xerosis cutis: a systematic review”.

Hanada et. al., 1984

Author	Hanada et. al. [23] (Title: Relationship between dry skin and aluminium in hemodialysis patients.)
Year	1984
Study design	Cross sectional study
Country/ ethnicity	Japan (ethnicity: not reported)
Signs of dry skin and scoring method	Dry skin (hyperkeratosis, atrophy of eccrine sweat glands and stenosis of sweat ducts).
Analysed material	Epidermis and dermis
Sampling technique	Separation of the epidermis from the dermis (described in Baumberger et. al., 1942).
Method of analysis	Atomic absorption spectrophotometry.

	Healthy volunteers (no further information about skin status)	Haemodialysis patients (with dry skin and sweat suppression)		Comments
Number of participants	8	5		
Age (mean)	Not reported			
Sex	Not reported			
Skin areas	Forearm	Forearm		
Severity of dry skin	Normal skin (presumably)	Dry skin (strong suppression of sweating)		
Molecular marker			Quan. units	
Aluminium level in epidermis (mean, SD)	55.6 (38.4)	63.2 (20.3)	µg/g tissue	
	p value not reported			
Aluminium level in dermis (mean, SD)	5.6 (4.8)	22.5 (12.3)		
	$p < 0.05$			

Saint-Léger et. al., 1988

Author	Saint-Léger et. al. [24] (Title: Age-associated changes in stratum corneum lipids and their relation to dryness)
Year	1988
Study design	Cross sectional study
Country/ ethnicity	France and USA (ethnicity: Caucasian)
Signs of dry skin and scoring method	Dryness was visually evaluated according to a scale scoring from 0 to 4 as previously described in Kligman 1978. Grade 0: Surface smooth (normal skin) Grade 1: slight dryness; some sparse uplifted scales;

	Grade 2: moderate dryness; uplifted scales more numerous. Grade 3: extreme dryness; prominent large scales, densely covering the surface. Grade 4: extreme dryness; prominent large scales, densely covering the surface with cracking and/or fissuring.
Analysed material	Compounds dissolved from stratum corneum.
Sampling technique	Using a turbine device containing a chamber placed on the skin in which 1 ml of hexane-methanol (2/3) was agitated for 1 min.
Method of analysis	Photodensitometry

	Subjects with normal skin	Subjects with xerosis							Comments
Number of participants	50 in total								
Age (mean)	Not reported	25	35	45	55	65	75		
Sex	45 females, 5 males								
Skin areas	The lateral mid-calf								
Severity of dry skin (grade)	Not reported	1	1.2	2	2	1.5	3.1		Quantity extracted from graph
Molecular markers								Quan. units	
Sterol esters (mean)	Not reported	15.1	14.2	11.3	9.9	9.8	8.7	Percentage	Quantity extracted from graph
		r = -0.41 (p = 0.0037)							
Triglycerides (mean)	Not reported	14.4	9.8	7.1	5.7	5.7	3.5	Percentage	Quantity extracted from graph
		r = -0.39 (p = 0.0002)							
Polar lipids (mean)	Not reported	40.9	46.2	49.0	50.9	50.3	52.8	Percentage	Quantity extracted from graph
		r and p values not reported							
Increase in the index of sterol esterification (metric not reported)	Not reported	0.48	0.54	0.60	0.62	0.64	0.66	Index	Quantity extracted from graph
		r and p values not reported							
Free Fatty Acid (metric not reported)	Not reported	15	12.8	13.5	14.6	14.8	16.5	Percentage	Quantity extracted from graph
		r and p values not reported							
Cholesterol (metric not reported)	Not reported	14.3	15.8	16.5	16.9	18.8	17.3	Percentage	Quantity extracted from graph
		r and p values not reported							

Horii et. al., 1989

Author	Horii et. al., [25] (Title: Stratum corneum hydration and amino acid content in xerotic skin)
Year	1989
Study design	Part 1: cross sectional study Part 2: pre-post study
Country/ ethnicity	Japan (ethnicity: not reported)

Signs of dry skin and scoring method	Senile xerosis was graded as follows: Grade 0: normal appearing skin, Grade 1: mild xerosis, Grade 2: moderate xerosis, Grade 3: severe xerosis.
Analysed material	Stratum corneum
Sampling technique	Serial adhesive tape-stripping (10 strippings).
Method of analysis	Amino acid analyser.

Study part 1

	Subjects with normal skin	Subjects with mild xerosis	Subjects with moderate xerosis	Subjects with severe xerosis		Comments
Number of participants	7	10	8	5		
Age	59 to 94 years					
Sex	Not mentioned					
Skin areas	The extensor surfaces of the lower leg					
Severity of dry skin	Grade 0	Grade 1	Grade 2	Grade 3		
Molecular marker					Quan. units	
Amino acid (metric not reported)	1.22	0.96	0.89	0.55	µmol/mg protein	Quantity extracted from graph
	p < 0.05					
	p < 0.01					

Study part 2

	Pre-treatment	Post-treatment		Topical application of 10% urea-containing cream
Number of participants	10			
Severity of dry skin	Average grade 2.3	Average grade 0.2		
Molecular marker			Quan. units	
Amino acid content (metric not reported)	0.80	0.77	µmol/mg protein	Quantity extracted from graph
	p value not reported			

Saint-Léger et. al., 1989

Author	Saint-Léger et. al., [26] (Title: Stratum corneum lipids in skin xerosis)
Year	1989

Study design	Cross sectional study
Country/ ethnicity	France and USA (ethnicity: not reported)
Signs of dry skin and scoring method	The dryness of skin was visually evaluated according to a scale scoring from 0 to 6 as previously described in Kligman 1978. Grade 0: Normal; no sign of dryness Grade 1: mild dryness; dusty, ashy appearance or an occasional minute skin flake. Grade 2: mild dryness; dusty, ashy appearance or presence of many particles or minute skin flakes. Small lines or crevices were occasionally present filled with nondescript material. Grade 3: moderate dryness with definite scaling (usually circular); borders of the scales were flat including characteristics of grade 1 and 2. Grade 4: moderate dryness with well-defined scaling with raised edges; size of the scales were larger than in grade 3. Grade 5: severe dryness with heavy scaling and/or fissuring. The scale plates were large with an increased lifting of the edges. Small fissures were occasionally seen between some scale plates. No erythema was evident. Grade 6: Large scale plates with high lifting of the scale edges. Small fissures accompanied by erythema.
Analysed material	Compounds dissolved from stratum corneum
Sampling technique	Using a turbine device containing a chamber in which 5 ml of hexane-methanol (2/3) was agitated for 1 min.
Method of analysis	Photodensitometry

	Subjects with normal skin	Subjects with xerosis (Grade 1 to 6)						Comments
Severity of dry skin (grade)	0	1	2	3	4	5 to 6		
Number of participants	12	None	8	22	14	8		
Age	30 to 40 years							
Sex	Females							
Skin areas	The outer aspect of the lower legs							
Molecular markers							Quan. units	
Wax esters and sterol esters (mean, SE)	17.8 (1.3)	Not reported	14.4 (1.2)	15 (1)	14.3 (1)	11.6 (1.2)	µg/cm^2	
			r = -0.31 (p = 0.027)					
Triglycerides (mean, SE)	17 (1.8)	Not reported	14.0 (2.3)	14.7 (1.6)	13.2 (1.7)	9.6 (1.5)	µg/cm^2	
			r = -0.28 (p = 0.046)					
Free Fatty Acids (mean, SE)	20.5 (2.8)	Not reported	28.5 (3.2	27.7 (1.5)	30.7 (1.5)	41.5 (3.8)	µg/cm^2	
			r = +0.45 (p = 0.011)					
Free sterols (mean, SE)	15.8 (1.0)	Not reported	16.8 (1.85)	15.9 (0.8)	15.0 (1.0)	14.0 (1.3)	µg/cm^2	
			r = -0.05 (p = 0.730)					
Ceramide I (mean, SE)	1.74 (0.18)	Not reported	2.2 (0.25)	2.0 (0.3)	1.75 (0.1)	2.0 (0.26)	µg/cm^2	
			r =-0.09 (p = 0.540)					
Ceramide II (mean, SE)	5.0 (0.54)	Not reported	4.9 (0.4)	4.75 (0.3)	5.6 (0.7)	4.7 (0.76)	µg/cm^2	
			r = +0.09 (p= 0.530)					
Ceramide III (mean, SE)	6.8 (0.5)	Not reported	6.8 (1.0)	6.7 (0.5)	5.8 (0.7)	5.4 (0.6)	µg/cm^2	

			r = -0.09 (p = 0.550)					
Ceramide IV and V (mean, SE)	6.25 (0.7)	Not reported	5.75 (0.4)	5.5 (0.3)	5.6 (0.4)	5.0 (0.3)	µg/cm^2	
			r = -0.06 (p = 0.660)					
Ceramide VI (mean, SE)	6.6 (0.6)	Not reported	5.4 (0.5)	5.6 (0.35)	6.0 (0.6)	5.6 (0.4)	µg/cm^2	
			r = +0.06 (p = 0.660)					
Cholesteryl sulfate (mean, SE)	2.8 (0.5)	Not reported	1.6 (0.2)	2.0 (0.17)	2.0 (0.26)	1.6 (0.2)	µg/cm^2	
			r = +0.07 (p = 0.670)					
Total Stratum corneum lipids (mean, SE)	22.0 (1.8)	Not reported	25.0 (2.5)	22.8 (1.50)	23.4 (1.9)	26.3 (2.9)	µg/cm^2	
			r = -0.15 (p = 0.310)					

Jacobson et. al., 1990

Author	Jacobson et. al., [27] (Title: Effects of aging and xerosis on the amino acid composition of human Skin.)
Year	1990
Study design	Cross sectional study
Country/ Ethnicity	USA (Ethnicity: Caucasian)
Signs of dry skin and scoring method	The dryness of the skin was not evaluated according to a clinical scale. "Dry" refers to subjects diagnosed as having typical dry skin syndrome (xerosis), and "non-dry" refers to controls with skin judged to be normal.
Analysed material	Scraped cells from stratum corneum.
Sampling technique	An 8 x 8 cm area of the skin of each leg was scraped with a glass microscope slide and the cells were collected.
Method of analysis	High performance liquid chromatography.

	Old subjects with non-dry skin	Old subjects with dry skin	Young subjects with dry skin	Young subjects with non-dry skin		Comments
Number of participants	7	13	8	18		
Age	60 years or older	60 years or older	30 years or younger	30 years or younger		
Sex	Females	Females	Females	Females		
Skin areas	The shins of both legs	The shins of both legs	The shins of both legs	The shins of both legs		
Severity of dry skin	Normal	Dry skin (characterized by desquamating cells)	Dry skin (characterized by desquamating cells)	Normal		
Molecular markers					Quan. units	
Aspartic acid (mean)	4.8	4.4	4.5	4.8	Percent of total amino acids	Quantity extracted from graph
	p value not reported					
Threonine (mean)	6.4	5.9	6.4	6.2		

	p ≤ 0.05					
		p ≤ 0.05				
Serine (mean)	28.7	28.2	27	26.7		
	p value not reported					
Glutamic acid (mean)	10.8	9.6	8.4	9.2		
	p value not reported					
Glycine (mean)	15.2	15.9	14.3	13.9		
	p ≤ 0.05					
		p ≤ 0.05				
Alanine (mean)	9.1	8.9	7.6	8.2		
		p ≤ 0.05				
Valine (mean)	3.0	3.0	2.9	2.9		
	p value not reported					
Methionine (mean)	0.5	0.4	0.5	0.5		
	p value not reported					
Isoleucine (mean)	1.6	1.7	1.9	1.8		
	p value not reported					
Leucine (mean)	1.4	1.6	1.8	1.7		
	p ≤ 0.05					
Tyrosine (mean)	1.6	1.8	2.0	1.7		
	p ≤ 0.05					
Phenylalanine (mean)	0.9	1.0	1.0	1.0		
	p ≤ 0.05					
Lysine (mean)	1.5	1.7	1.7	1.8		
	p ≤ 0.05					
Histidine (mean)	6.6	6.2	6.5	7		
	p value not reported					
Tryptophan (mean)	2.4	2.8	3.0	3.3		
	p value not reported					
Arginine (mean)	1.5	1.5	2.2	2.1		
	p value not reported					
Ornithine (mean)	3	2.6	4.6	3.8		
		p ≤ 0.05				

Note: Data of free amino acids from the water extract of skin sample. Data from soluble hydrolysate and whole cell hydrolysate were not extracted.

Akimoto et. al., 1993

Author	Akimoto et. al. [28] (Title: Quantitative analysis of stratum corneum lipids in xerosis and asteatotic eczema)
Year	1993

Study design	Cross sectional study
Country/ ethnicity	Japan (ethnicity: not reported)
Signs of dry skin and scoring method	Scoring method not reported. In this study, "xerosis" was diagnosed as aged leg skin with dryness, itching and scales. The controls were healthy individuals who showed no dryness, scaling or itching in the winter season.
Analysed material	Stratum corneum.
Sampling technique	Stratum corneum sheet was removed from the skin area by a single stripping with cyanoacrylate resin.
Method of analysis	Thin layer chromatography.

	Control (young) group	Age-matched control (older) group	Xerosis (older) group		Comments
Number of participants whose total lipids and total ceramides were analysed	29	20	25		
Number of participants whose sebum-derived lipids (cholesterol ester, wax, triglyceride, free fatty acid, cholesterol sulfate) were analysed	15	11	18		
Age of participants whose total lipids and total ceramides were analysed (metric not reported)	24.3 years	71.6 years	71.0 years		
Age of participants whose sebum-derived lipids (cholesterol ester, wax, triglyceride, free fatty acid, cholesterol sulfate) were analysed (metric not reported)	27 years	72 years	71.4 years		
Sex	Not reported	Not reported	Not reported		
Skin areas	The extensor surfaces of the lower legs	The extensor surfaces of the lower legs	The extensor surfaces of the lower legs		
Severity of dry skin	No dryness, scaling or itching	No dryness, scaling or itching	Skin with dryness, itching and scales		
Molecular markers				Quan. units	
Total lipid (metric not reported)	76.9	49.9	62.2	µg/mg	-Quantity extracted from graph.
	p < 0.01				
Total ceramide (metric not reported)	18.3	12.2	15.7		
		p < 0.01			
Ceramide 1 (metric not reported)	0.91	0.63	0.86		
	P value not reported				
Ceramide 2 (metric not reported)	3.20	2.11	3.31		
		p < 0.01			
Ceramide 3 (metric not reported)	3.46	1.89	2.69		
		p < 0.01			

Hydro- ceramide 1 (metric not reported)	0.63	0.41	0.54		
	p value not reported				
Ceramide 4 and 5 (metric not reported)	3.20	2.97	3.35		
	p < 0.01				
Ceramide 6 (metric not reported)	5.52	3.79	4.97		
		p < 0.05			
Cholesterol sulfate (metric not reported)	3.94	2.48	3.26		
	p < 0.05				
Cholesterol ester (metric not reported)	1.0	0.9	0.8		
	p value not reported				
Wax (metric not reported)	3.20	0.9	0.6		
	p value not reported				
Triglyceride (metric not reported)	3.20	3.1	3.8		
		p < 0.01			
Free fatty acid (metric not reported)	6.8	8.7	6.2		
		p < 0.01			
Cholesterol (metric not reported)	3.20	2.8	3.1		
	p value not reported				

Park et. al., 1995

Author	Park et.al. [29] (Title: Dry skin (xerosis) in patients undergoing maintenance haemodialysis: the role of decreased sweating of the eccrine sweat gland)
Year	1995
Study design	Case control
Country/ Ethnicity	Country: Korea (Ethnicity: Not reported)
Signs of dry skin and scoring method	1. Normal skin. 2. Dry skin (appearing rough with or without scaling), 10 patients had pruritus (56%), while eight patients did not (44%).
Analysed material	Stratum corneum.
Sampling technique	Cyanoacrylate adhesive was attached to a defined area of 2.5 cm^2on the ventral forearm and the horny layer was stripped off.
Method of analysis	Spectrophotometry.

	Healthy volunteers (no further information about skin status)	Patients with xerotic skin undergoing maintenance haemodialysis		Comments
Number of participants	10	18		
Age (mean)	55 years Age range: 41 to 62 years	50 years Age range: 30 to 68 years		
Sex	4 Males, 6 Females	10 Males, 8 Females		
Skin areas	Ventral forearm	Ventral forearm		

Severity of dry skin	Normal skin (presumably)	Dry skin		
Molecular marker			Quan. units	
Urea (mean)	5.04	28.2	µg/cm^2	
	P < 0.05			

Rawlings et. al., 1996

Author	Rawlings et al., [30] Title: Effect of lactic acid isomers on keratinocyte ceramide synthesis, stratum corneum lipid levels and stratum corneum barrier function.
Year	1996
Study design	Double blind paired-comparison study (first study)
Country/ ethnicity	USA (ethnicity: Caucasian)
Signs of dry skin and scoring method	Clinical dryness and erythema scoring on a scale of 0 to 4.0.
Analysed material	Stratum corneum.
Sampling technique	Tape stripping (8 consecutive strips were collected with adhesive tapes)
Method of analysis	For lipids: densitometric analysis using a densitometer, For fatty acid methyl esters (FAMEs): gas chromatography. For protein: plate reading technique.

	Control	Treatments				Comments
	Vehicle treated skin	D-Lactic acid treated skin	D, L-Lactic acid treated skin	L-Lactic acid treated skin		Treatment: 4% active formulations.
Number of participants	24 subjects with dry skin	6 Subjects (Same participants from control)	6 Subjects (Same participants from control)	12 Subjects (Same participants from control)		Treatment duration 4 weeks.
Age	23 to 45 years	Same participants	Same participants	Same participants		
Sex	Male and female	Same participants	Same participants	Same participants		
Skin areas	Volar surface of one forearm	Volar surface of contralateral forearm	Volar surface of contralateral forearm	Volar surface of contralateral forearm		
Severity of dry skin at baseline	No greater than 1.0					
Severity of dry skin after 4 weeks	Not reported					
	After 4 weeks treatment					
Molecular markers					Quan. Units	
Increase in ceramide level (metric not reported)	Not reported	0%	25%	38%	Percentage	Quantity extracted from graph

	p value not reported					
Cholesterol levels (metric not reported)	16.9	Not reported	Not reported	18.8	ng lipid/µg protein	Quantity extracted from graph
	p value not reported					
Fatty acid levels (metric not reported)	35.8	Not reported	Not reported	42.3	ng lipid/µg protein	Quantity extracted from graph
	p value not reported					
Ceramide levels (metric not reported)	27.6	Not reported	Not reported	38.8	ng lipid/µg protein	Quantity extracted from graph
	$p < 0.05$					
Total ceramide 1 esterified fatty acid (16:0) ; metric not reported	16.7	Not reported	Not reported	23.5	Percentage	Quantity extracted from graph
	$p < 0.05$					
Total ceramide 1 esterified fatty acid (18:0) ; metric not reported	26.4	Not reported	Not reported	21.2	Percentage	Quantity extracted from graph
	p value not reported					
Total ceramide 1 esterified fatty acid (18:1) ; metric not reported	35.9	Not reported	Not reported	28.1	Percentage	Quantity extracted from graph
	$p < 0.05$					
Total ceramide 1 esterified fatty acid (18:2) ; metric not reported	17.9	Not reported	Not reported	24.3	Percentage	Quantity extracted from graph
	p value not reported					
Total ceramide 1 esterified fatty acid (20:0); metric not reported	4.9	Not reported	Not reported	5.5	Percentage	Quantity extracted from graph
	p value not reported					
Improvement in ratio of ceramide 1 linoleate to ceramide 1 oleate (metric not reported)	0.51	Not reported	Not reported	0.83	Ratio	Quantity extracted from graph
	$p < 0.05$					

Schreiner et. al., 2000

Author	Schreiner et. al., [31] (Title: Barrier characteristics of different human skin types investigated with x-ray diffraction, lipid analysis and electron microscopy imaging.)
Year	2000
Study design	Cross sectional study
Country/ ethnicity	Germany and the Netherlands (ethnicity: Caucasian)

Signs of dry skin and scoring method	The dryness of the skin was visually evaluated according to a clinical scale. Visual score of scaliness: 1= no scale, 4= very scaly. Sensory score of suppleness: 1= very smooth, 7= extremely rough.
Analysed material	Stratum corneum
Sampling technique	Shave biopsy
Method of analysis	High performance thin layer chromatography and photodensitometry.

	Young with normal skin	Young with dry skin	Skin of aged participants		Comments
Number of participants	10	5	4		
Age	25.5 (SD 2.5) years	30 (SD 6) years	66 (SD 3) years		
Sex	Not reported	Not reported	Not reported		
Skin areas	The skin of the lower leg	The skin of the lower leg	The skin of the lower leg		
Severity of dry skin (scaliness score) (mean, SD)	0.7 (0.5)	3.1 (0.2)	2.5 (1.2)		
Severity of dry skin (suppleness score) (mean, SD)	2.5 (0.8)	6.0 (0.4)	4.5 (0.8)		
Molecular markers				Quan. units	
Total ceramide (mean, SEM)	21 (4)	20 (2)	26 (11)	µg lipid per mg SC protein	
	p value not reported				
Free sterols (mean, SEM)	17 (4)	15 (1)	23 (6)		
	p value not reported				
Free fatty acids (mean, SEM)	17 (3)	18 (5.5)	38 (12)		
	p value not reported				
Ceramide (EOS)/ total ceramide (mean, SD)	0.08 (0.03)	0.09 (0.05)	0.10 (0.05)	Quantity of analysed ceramide	
	p value not reported				
Ceramide (NS)/ total ceramide (mean, SD)	0.16 (0.03)	0.21 (0.01)	0.17 (0.03)		

	p < 0.01			/quantity of total ceramide	
Ceramide (NP)/ total ceramide (mean, SD)	0.18 (0.04)	0.16 (0.02)	0.16 (0.04)		
	p value not reported				
Ceramide (EOH)/ total ceramide (mean, SD)	0.08 (0.02)	0.07 (0.04)	0.05 (0.03)		
	p value not reported				
Ceramide (AS)/ total ceramide (mean, SD)	0.21 (0.02)	0.23 (0.04)	0.23 (0.02)		
	p value not reported				
Ceramide (AP)/ total ceramide (mean, SD)	0.10 (0.02)	0.07 (0.02)	0.11 (0.01)		
	p value not reported				
Ceramide (AH)/ total ceramide (mean, SD)	0.18 (0.03)	0.18 (0.02)	0.19 (0.01)		
	p value not reported				

Simon et. al., 2001

Author	Simon et. al. [32] (Title: Persistence of both peripheral and non-peripheral corneodesmosomes in the upper stratum corneum of winter xerosis skin versus only peripheral in normal skin)
Year	2001
Study design	Case control
Country/ ethnicity	Country: France (ethnicity: Caucasians)
Signs of dry skin and scoring method	1. Normal skin. 2. Moderate to well-defined xerosis, i.e. dry skin characterized by roughness and papyraceous appearance of the skin, presence of raised squames and/or scales, and irritation.
Analysed material	Stratum corneum.
Sampling technique	Superficial stratum corneum extracts were obtained from the volunteers by three consecutive varnish-stripping (following Guerrin et al, 1998).
Method of analysis	Protein concentrations: protein assay (SDS-PAGE, western blotting). The immunoblotting reactivities, related to the detectable amounts of proteins, were quantified by densitometry using a software. Corneodesmosome density (corneodesmosome area divided by total area): transmission electron microscopy.

	Normal skin	Xerotic skin		Comments
Number of participants	n=26	n= 30		
Age	22 to 49 years	22 to 49 years		
Sex	Females	Females		
Skin areas	External parts of the legs	External parts of the legs		
Severity of dry skin	Normal skin	Moderate to well-defined xerosis		
Molecular markers			Quan. units	

Desmoglein 1 (median)	11.1	27.1	Arbitrary scale	Quantity extracted from graph. Amount was elevated in xerotic skin
	p < 0.02			
Plakoglobin (median)	18.5	31.1	Arbitrary scale	Quantity extracted from graph. Amount was elevated in xerotic skin.
	p < 0.02			
Corneodesmosin (median)	16.1	21.3	Arbitrary scale	Quantity extracted from graph. Amount was elevated in xerotic skin.
	p = 0.05			
Corneodesmosome density in the inner SC (n=2); metric not reported	30.0	34.6	Corneodesmosome surface/ μm^2 (arbitrary scale)	Quantity extracted from graph.
	p value not reported			
Corneodesmosome density in the outer SC (n= 3); metric not reported	2.3	19.2		Quantity extracted from graph. Amount was elevated in xerotic skin.
	p < 0.001			

Takahashi et. al., 2004

Author	Takahashi et. al., [33] (Title: The content of free amino acids in the stratum corneum is increased in senile xerosis.)
Year	2004
Study design	Cross sectional study
Country/ Ethnicity	Japan (Ethnicity: Not reported)
Signs of dry skin and scoring method	Not reported
Analysed material	Stratum corneum
Sampling technique	Several layers of the stratum corneum were scraped off with a knife or glass microscope slide and stratum corneum cells were collected.
Method of analysis	High performance liquid chromatography

	Aged senile xerosis	Aged normal group	Young group		Comments
Number of participants	12	5	10		
Age	60 to 81 years	60 to 74 years	18 to 29 years		
Sex	Not reported	Not reported	Not reported		
Skin areas	The skin of the lower leg	The skin of the lower leg	The skin of the lower leg		
Severity of dry skin	Not reported	Not reported	Not reported		
Molecular markers				Quan. units	
Total Amino acid (metric not reported)	581.4	497.7	322.4	Pmol/ 1000 SC cells	-Quantity ex-tracted from graph
	p < 0.01				
Aspartic acid (metric not reported)	31.5	29.0	10.8		
	p value not reported				
Glutamic acid (metric not reported)	8.0	7.0	4.0		
	p value not reported				
Citrulline (metric not reported)	54.5	48.0	43.9		
	p value not reported				
Serine (metric not reported)	132.0	116.2	64		
	p < 0.05				
Threonine (metric not reported)	37.4	27.5	24		
	p < 0.05				
Arginine (metric not reported)	13.0	23.0	8.0		
	p value not reported				
Glycine (metric not reported)	102.5	118.8	52.5		
	p < 0.05				
Alanine (metric not reported)	45.0	39.8	26.0		
	p < 0.05				
Proline (metric not reported)	14.3	11.0	8.0		
	p value not reported				
Valine (metric not reported)	20.2	15.0	9.0		
	p value not reported				
Isoleucine (metric not reported)	15.6	11.0	6.9		
	p < 0.05				
Leucine (metric not reported)	9.7	6.9	6.9		
	p value not reported				
Tryptophan (metric not reported)	5.5	6.0	3.5		
	p value not reported				

Phenylalanine (metric not reported)	6.0	5.2	2.9		
	p < 0.05				
Urocanic acid (metric not reported)	20.0	4.8	12.0		
	p value not reported				
Ornithine (metric not reported)	14.0	4.8	4.8		
	p < 0.05				
Lysine (metric not reported)	9.7	7.2	5.3		
	p < 0.05				
Histidine (metric not reported)	33.2	36.0	17.6		
	p < 0.05				
Tyrosine (metric not reported)	12.2	11.4	6.0		
	p < 0.05				

Delattre et. al., 2012

Author	Delattre et. al. [34] (Title: Proteomic analysis identifies new biomarkers for postmenopausal and dry skin)
Year	2012
Study design	Cross sectional
Country/ ethnicity	France and Canada (ethnicity: Caucasian)
Signs of dry skin and scoring method	0: normal skin – regular cutaneous relief and smooth aspect; 1: dehydrated skin –streaked cutaneous relief and rather rough aspect; 2: dry skin – streaked cutaneous relief, some scales and rough aspect; 3: very dry skin – numerous scales and rough aspect; 4: extremely dry skin – very numerous scales and very rough aspect.
Sample	Stratum corneum
Sampling technique	Varnish stripping sampling
Method of analysis	(2D) Electrophoresis, western blot, liquid chromatography mass spectrometry.

	Normal skin	Dry Skin		Comments
Number of participants	27 (13 postmenopausal women, 14 young women)	31 (15 postmenopausal women, 16 young women)		In total, 58 (28 postmenopausal women, 30 young women)
Age	30 to 60 years	30 to 60 years		28 postmenopausal women aged between 55 and 60 years, and 30 young women between 30 and 35 years.
Sex	Female	Female		
Skin areas	Upper leg skin	Upper leg skin		
Severity of dry skin	Normal skin hydration levels (clinical score 0 to1)	Dry-skin phenotype (score 3 to 4)		
Molecular markers			Quan. units	
	1555	3560	Arbitrary unit	Quantity extracted from graph.

Corneodesmosin (metric not reported)				Amount is increased with xerosis (129%)
	p < 0.001			
Annexin A2 (metric not reported)	142	323		Quantity extracted from graph. Amount is increased with xerosis (127%)
	p = 0.006			
phosphatidylethanolamine-binding protein 1 (PEBP1) (metric not reported)	375	915		Quantity extracted from graph. Amount is increased with xerosis (144%)
	p = 0.002			

Ishikawa et. al., 2013

Author	Ishikawa et. al. [35] (Title: Dry skin in the winter is related to the ceramide profile in the stratum corneum and can be improved by treatment with a Eucalyptus extract)
Year	2013
Study design	Controlled clinical trial
Country/ ethnicity	United States of America (ethnicity: not reported)
Signs of dry skin and scoring method	Visual dryness 0= Normal skin – no signs of dryness, 2= Mild dryness – slight, but definite roughness; fine scaling present; may have a powdery or ashy appearance, 4= Moderate dryness – moderate roughness; somewhat coarser scaling; some cracking as evidenced by uplifted scales, 6= Marked dryness – marked roughness, coarse scaling; cracking evident as uplifted scales; some thickening may be present, 8= Severe dryness – verify marked roughness; very coarse scaling; cracking progressing to fissuring; erythema may be present; marked thickening may be present. Tactile roughness 0= normal –smooth soft supple (yield without wrinkling) resilient 2= mild roughness –papery/parchment like feel; slight wrinkling upon manipulation 4= moderate roughness –slight sandy/grainy feel; skin wrinkles upon manipulation 6= marked roughness–coarse, rigid feel; somewhat brittle 8= severe roughness–rough feel, brittle; inflexible upon manipulation
Analysed material	Stratum corneum
Sampling technique	Skin surface sampling using D-Squame discs; lipid sampling by tape-stripping
Method of analysis	Liquid chromatography mass spectrometry

	Test moisturizer (containing extract of *Eucalyptus globulus*)	Control moisturizer		Comments
Number of participants	20 female patients with dry skin	Same participants		
Age (mean, SD)	47 years. Age range: 32 to 57 years	Same participants		

Sex	Female		Same participants			
Skin areas	Outer calf of one leg		Outer calf of the other leg			
	Day 0		Day 28			
Severity of dry skin	Moderate to severe (visual dryness score >4)	not reported	Moderate to severe (visual dryness score >4)	not reported		
Visual Dryness, mean difference from Day 0		-4.81		-4.83		
	$p < 0.001$		$p < 0.001$			
Molecular markers					Quan. units	
	Day 0	Day 28	Day 0	Day 28		
Ceramide [NP] (mean, SD)	3.1	3.5 Mean difference from day 0 is 0.42	3.1	3.4 Mean difference from day 0 is 0.35	µg/mg protein	Quantity extracted from graph.
	$p < 0.05$		$p < 0.05$			
Total Ceramide, mean difference from day 0		0.79		-0.09		
Correlation between Ceramide levels and dryness	Day 0 (based on the average of both calves)					Quantity of the analysed markers were not reported.
Ceramide [NP] (metric not reported)	$r = -0.501$ ($p < 0.05$)					
Total ceramide (metric not reported)	$r = -0.471$, ($p < 0.05$)					
Ceramide [NH] (metric not reported)	$r = -0.445$, ($p < 0.05$)					
Ceramide [NS] (metric not reported)	$r = -0.433$					
Ceramide [NDS] (metric not reported)	$r = -0.429$					
Ceramide [EOS] (metric not reported)	$r = -0.401$					
Ceramide [AH] (metric not reported)	$r = -0.389$					
Ceramide [EOH] (metric not reported)	$r = -0.380$					
Ceramide [AS] (metric not reported)	$r = -0.376$					
Ceramide [EOP] (metric not reported)	$r = -0.361$					
Ceramide [ADS] (metric not reported)	$r = -0.274$					
Ceramide [AP] (metric not reported)	$r = -0.239$					

Schweiger et. al., 2013

Author	Schweiger et. al. [36]

	(Title: efficacy of a new tonic containing urea, lactate, polidocanol, and *Glycyrrhiza inflata* root extract in the treatment of a dry, itchy, and subclinically inflamed scalp)
Year	2013
Study design	Randomized controlled trial, split-body comparison
Country/ ethnicity	Germany (ethnicity: not reported)
Signs of dry skin and scoring method	The various symptoms, scalp itching, tautness, and oiliness were determined based on the following assessment scale: 0 = no characteristic symptom; 1 = weak, even visible/perceivable symptom; 2 = mild symptom; 3 = moderate symptom; 4 = strong symptom; 5 = very strong (severe) symptom. The approval rates (%) for following statements were determined using a self-assessment questionnaire: A: scalp condition was improved perceivably B: regular use reduces scalp dryness C: regular use diminishes scalp itching D: regular use perceivably reduces scalp tautness
Analysed material	For urea and lactate: Compounds dissolved from stratum corneum. For free fatty acids, triglycerides, amide band ratio (I/II): direct analysis from scalp site For cytokines: compounds dissolved from stratum corneum.
Sampling technique	For Urea and Lactate: The DIP-it sampler was rubbed 10 times with the enclosed end of the glass capillaries, while applying slight, constant pressure. The adherent skin surface material was directly analyzed without further sample preparation. For free fatty acids, triglycerides, amide band ratio (I/II): to record a spectrum, the volunteer's hair was parted; a N_2 -cooled diamond measuring head was placed vertically on the test site. Five measurements consisting of 40 scans were carried out. For cytokines: prewetted cotton buds was rubbed against the skin.
Method of analysis	For Urea and Lactate: direct analysis in real-time mass spectrometry (DART-MS). For free fatty acids, triglycerides, hydration: fourier-transformed middle-infrared spectroscopy (FTMIR) For cytokines: enzyme-linked immunosorbent assays (ELISA)

				Comments
	Untreated	**Tonic treated**		Test tonic: aqueous tonic containing licochalcone A as main active ingredient.
Number of participants	30 volunteers with dry and itchy scalp skin.	Same participants		8 of the 21 participants (38%) reported a previous history of AD
Age	26 to 73 years.	Same participants		
Sex	17 women, 13 men	Same participants		

Skin areas	The one side of the scalp			The other side of the scalp				
	Baseline (t_0)	After 2 weeks (t_1 untreated)	After 4 weeks (t_2 untreated)	Baseline (t_0)	After 2 weeks of treatment (t_1 tonic treated)	After 4 weeks of treatment (t_2 tonic treated)		
Severity of dry skin	Skin conductivity: <20 µS; Scalp oiliness score: <2.5 (by expert visual asessment); Scalp itching and/or tautness score: ≥ 2 (by self-assessment of volunteers)	Not reported	Not reported	Skin conductivity: <20 µS; Scalp oiliness score: <2.5 (by expert visual asessment); Scalp itching and/or tautness score: ≥ 2 (by self-assessment of volunteers)	72% Volunteers (of 25) reported reduction in their scalp dryness by self-assessment.	88% Volunteers (of 24) reported reduction in their scalp dryness by self-assessment.		
Molecular markers							Quan. units	
Amide band ratio I/II (metric not reported)	100.3	105.5	99.0	100.3	113.2	105.0	Percent relative to baseline	Amide band ratio I/II was measured as a second method for assessing the scalp moisturization. Quantity extracted from graph.
				$p \leq 0.05$				
Urea (n=29); median	102.8	99.6	80.1	102.8	264.1 $p \leq 0.05$ compared to baseline and t_1 untreated	160.2 $p \leq 0.05$ compared to baseline, t_1 tonic treated and t_2 untreated	Percent relative to baseline	Quantity extracted from graph.
Lactate (n=29); median	103.2	80.4	81.4	103.2	223.5 $p \leq 0.05$ compared to baseline and t_1 untreated	124.5 $p \leq 0.05$ compared to baseline, t_1 tonic treated and t_2 untreated	Percent relative to baseline	Quantity extracted from graph.
Triglyceride (n=30); median	100.2	91.1	80.9	100.2	112.4	114.7	Percent relative to baseline	Quantity extracted from graph.

					p ≤ 0.05 compared to baseline and $t_{1\ untreated}$			
Free fatty acid (median)	99.2	126.2	108.7	99.2	65.9 p ≤ 0.05 compared to baseline and $t_{1\ untreated}$	57.1 p ≤ 0.05 compared to baseline, $t_{1\ tonic\ treated}$ and $t_{2\ untreated}$	Percent relative to baseline	Quantity extracted from graph.
Total lipid (median)	100.3	105.4	97.1	100.3	115.9	109.6	Percent relative to baseline	Quantity extracted from graph.
	p value not reported							
IL-1ra/IL-1β (median)	101.2	102.5	95.0	101.2	78.1 p ≤ 0.05 compared to baseline and $t_{1\ untreated}$	76.1 p≤0.05 compared to $t_{2\ untreated}$	Percent relative to baseline	Quantity extracted from graph.
IL-8 (median)	99.6	67.4	74.0	99.6	38.3	55.1	Percent relative to baseline	Quantity extracted from graph.
				p ≤ 0.05				

Son et. al., 2015

Author	Son et. al. [37] (Title: Skin dryness in apparently healthy human skin is associated with decreased expression of bleomycin hydrolase in the stratum corneum)
Year	2015
Study design	Cross sectional study, split-body comparison
Country/ ethnicity	Korea (ethnicity: Asian)
Signs of dry skin and scoring method	Not reported (The capacitance values for hydrated skin and for dry skin were > 29 AU and < 25 AU, respectively. The most hydrated area of the volunteer's right forearm was classified as 'hydrated skin' and the least hydrated area of the left forearm of the same volunteer was classified as 'dry skin'.
Analysed material	Stratum corneum.
Sampling technique	Tapes were attached to the volar forearm skin using a disc pressure applicator, and five sequential tape strippings with five different tapes were performed on each hydrated and dry skin region.
Method of analysis	For natural moisturizing factors: high performance liquid chromatography, For (pro)filaggrin and proteases: western blotting and densitometric analyses.

	Hydrated skin	Dry skin	Quan. units	Comments

Number of participants	22 (15 provided samples)	Same participants		
Age (Mean, SD)	Men: 33.8 (5.6) years Women: 31.3 (4.1) years	Same participants		Age is presented for the participants who provided samples
Sex	11 men (8 provided samples), 11 women (7 provided samples)	Same participants		
Skin areas	The volar forearm (right)	The volar forearm (left)		
Severity of dry skin	capacitance value > 29 AU	capacitance value < 25 AU	Arbitrary unit	
Molecular markers				
(Pro)filaggrin expression (Average)	100.0	101.4	percent of ratio	Quantity extracted from graph
	p value not reported			
Relative bleomycin hydrolase expression (Average)	106.0	86.2	Percent	
	p < 0.05			
Total NMFs (as free amino acid) (Average)	173.6	143.4	µg/ mg SC proteins	
	p < 0.05			
Histidine (Average)	12.0	9.3		
	p < 0.05			
Serine (Average)	43.0	35.0		
	p < 0.05			
Arginine (Average)	6.8	4.8		
	p value not reported			
Glycine (Average)	14.8	12.3		
	p < 0.05			
Aspartic acid (Average)	8.3	7.6		
	p value not reported			
Glutamic acid (Average)	35.3	28.0		
	p < 0.05			
Threonine (Average)	11.3	9.0		
	p value not reported			
Alanine (Average)	15.5	13.3		
	p value not reported			
gamma-Aminobutyric acid (Average)	8.5	8.0		
	p value not reported			
Proline (Average)	4.0	3.5		

	p value not reported			
Lysine (Average)	3.5	3.5		
	p value not reported			
Tyrosine (Average)	3.5	2.8		
	p value not reported			
Methionine (Average)	0.8	0.4		
	p value not reported			
Valine (Average)	4.5	4.0		
	p value not reported			
Leucine (Average)	3.0	2.3		
	$p < 0.05$			
Isoleucine (Average)	2.5	2.3		
	p value not reported			
Phenylalanine (Average)	2.0	1.5		
	$p < 0.05$			
Tryptophan (Average)	2.0	1.3		
	p value not reported			
Pyrrolidone carboxylic acid (Average)	7.0	6.0		
	p value not reported			
Urocanic acid (Average)	2.0	1.8		
	p value not reported			

Danby et. al., 2016

Author	Danby et. al. [38] (Title: The effect of an emollient containing urea, ceramide NP, and lactate on skin barrier structure and function in older people with dry skin)
Year	2016
Study design	Randomized controlled clinical trial (intra-individual comparison)
Country/ ethnicity	United Kingdom (ethnicity: not reported)
Signs of dry skin and scoring method	Skin dryness on a 5-point scale. 1 = no dryness. 5= severe dryness with cracking and lifting scales.
Analysed material	For stratum corneum protease activity and PCA: stratum corneum, For Lactate: compounds dissolved from stratum corneum
Sampling technique	Tape-stripping (strips 4–6 pooled), Prewetted cotton swab was rubbed against the skin and then transferred to 1 ml PBS.
Method of analysis	For stratum corneum protease activity: caseinolytic, chymotrypsin-like and trypsin-like activities were determined using corresponding substrates. For PCA: it was referred to a previous publication, however no statement of any analytical procedure was found there.

	For lactate: fluorometric L -lactate assay. For carboxylic acid levels : fourier transform infrared spectroscopy

						Comments Test emollient: lactate
Cohort 1	Test emollient		No treatment			
Number of participants	21 volunteers with dry skin		Same participants			8 of the 21 participants (38%) reported a previous history of AD
Age (mean)	69 years. Age range: 60 to 89 years		Same participants			
Sex	17 women, 4 men		Same participants			
Skin areas	One forearm (volar side, 3 cm below elbow flexure to 3 cm above the wrist)		The other forearm			
	Day 0	After 28 days	Day 0	After 28 days		
Severity of dry skin	Mean score 3	Not reported	Mean score 3	Not reported		It was reported that the test emollient hydrated the skin.
Molecular markers					Quan. units	
Caseinolytic activities (metric not reported)	Not reported	0.86	Not reported	1.48	nU/µg	Quantity extracted from graph.
		p = 0.0023				
Chymotrypsin-like activities (metric not reported)	Not reported	1.09	Not reported	2.68	nU/µg	Quantity extracted from graph.
		p < 0.0001				
Trypsin-like activities after (metric not reported)	Not reported	1.71	Not reported	2.62	nU/µg	Quantity extracted from graph.
		p value not reported				

Cohort 3	**Test emollient**	**Control emollient**		

Number of participants	21 volunteers with dry skin; 18 completed the study.		Same participants			6 of the 18 participants (33%) reported a previous history of AD
Age (mean, SD)	68 years. Age range: 60 to 79 years		Same participants			
Gender	14 women, 7 men		Same participants			
Skin areas	One forearm (volar side, 3 cm below elbow flexure to 3 cm above the wrist)		Another forearm (volar side, 3 cm below elbow flexure to 3 cm above the wrist)			
	Day 0	After 28 days	Day 0	After 28 days		
Severity of dry skin	Mean score 3	Not reported	Mean score 3	Not reported		
Molecular markers						
Caseinolytic activities (metric not reported)	Not reported	1.20	Not reported	1.54	nU/µg	Quantity extracted from graph.
		p < 0.05				
Chymotrypsin-like activities (metric not reported)	Not reported	1.36	Not reported	1.54		
		p value not reported				
Trypsin-like activities (metric not reported)	Not reported	2.82	Not reported	4.00		
		p < 0.05				
Lactate (metric not reported)	406.7	690.0	383.3	350.0	nmol/sample	
		p < 0.05				
Pyrrolidone carboxylic acid (PCA) (metric not reported)	513.3	733.3	559.9	600.0	µmol/g protein	
	p < 0.05					
		p = 0.0002				
Carboxylicacidlevels (metric not reported)	0.32	0.40	0.32	0.31	Absorbance	Quantity extracted from graph. FTIR-determination based on absorbance at 1,410 cm^{-1} /amide II.
	p < 0.05					

		$p \leq 0.0001$		

Tamura et. al., 2016

Author	Tamura et. al. [39] (Title: The roughness of lip skin is related to the ceramide profile in the stratum corneum)
Year	2016
Study design	Cross sectional study
Country/ ethnicity	Japan (ethnicity: Asian)
Signs of dry skin and scoring method	The degree of lip roughness in each subject was classified according to the criteria described below: Score 0: no desquamation, Score 1: slightly desquamated, Score 2: heavily desquamated
Analysed material	Stratum corneum received from each lip side
Sampling technique	Tape stripping with polyphenylsulphide film tape.
Method of analysis	Liquid chromatography mass spectrometry.

	Subjects having no desquamation on lips	Subjects having slightly desquamated lips	Subjects having slightly desquamated lips	Quan. units	Comments
Number of participants	41				Data regarding the distribution of participants in different groups was not provided
Age (mean)	34.1 years Age range: 22 to 52 years				
Sex	Female				
Skin areas	Lips				
Severity of dry skin	Score 0	Score 1	Score 2		
Molecular markers					
Ceramide (NH) (metric not reported)	2.5	2.3	1.9	µg/mg	
	r = -0.371 ($p < 0.05$)				
Ceramide (NP) (metric not reported)	1.6	1.4	1.2		
	r = -0.420 ($p < 0.01$)				

Vyumvuhoreet. al., 2018

Author	Vyumvuhore et. al., [40] (Title: Lipid organization in xerosis: the key of the problem?)
Year	2018
Study design	Cross sectional study
Country/ ethnicity	France (ethnicity: not reported)

Signs of dry skin and scoring method	The dryness was visually evaluated according to a scale scoring from 1 to 4 as previously described in Byrne 2010. Grade 1: healthy skin, no visible signs of dryness and a healthy sheen and glow. Grade 2: indicates mild xerosis, characterized by small flakes of dry skin and whitening of dermatoglyphic triangles. Grade 3: moderate xerosis; appearance of small, dry flakes causing a powdery appearance. Corners of the dermatoglyphic triangles start to uplift. Grade 4: well-defined xerosis with the entire length of a number of dermatoglyphic triangles uplifted to generate large, dry flakes. Roughness and redness are readily apparent.
Analysed material	Compounds dissolved from stratum corneum.
Sampling technique	Cotton swabs wetted with extraction agent.
Method of analysis	Liquid chromatography mass spectrometry.

	Subjects with normal skin	Subjects with mild xerosis		Comments
Number of participants	15	19		
Age (mean)	58 years	57 years		
Sex	Not mentioned	Not mentioned		
Skin areas	On outside arms or the calf	On outside arms or the calf		
Severity of dry skin	Grade 1	Grade 3 to 4		
Molecular markers			Quan. units	
$C_{65}H_{126}NO_{6;}$ presumably, ceramide (NdS) (metric not reported)	11801	1985	Intensity (Arbitrary unit)	Quantity extracted from graph
	P < 0.05			
$C_{66}H_{128}NO_{6;}$ presumably, ceramide (NS) (metric not reported)	4595	1191		
	p value not reported			
$C_{67}H_{130}NO_{6;}$ presumably, ceramide (EOP) (metric not reported)	6695	1305		
	P < 0.05			

Lechner et. al., 2019

Author	Lechner et al. [41] (Title: Comparing skin characteristics and molecular markers of xerotic foot skin between diabetic and non-diabetic subjects: an exploratory study)
Year	2019
Study design	Cross sectional
Country/ ethnicity	Germany (ethnicity: not reported)
Signs of dry skin and scoring method	0 = Normal skin; no sign of dryness. 1= Dusty appearance. 2= Presence of many particles of minute skin flakes.

	3= Defined (usually circular) scaling. 4= Well-defined scaling with larger raised edges Size. 5= Large-scale plates 6= Large-scale plates with high lifting of scale edges. Deep erythematous fissures between scale plates. Moderate dryness: Met the criteria of grades 3 and 4 in regard of scaling and/or showed only superficial fissures limited to the epidermis. Severe dryness: Met the criteria of grade 5 in regard of scaling and/or showed deep heel fissures extending to dermis. (Please see Rogers et al., 1989 and Oe et al., 2012)
Analysed material	Compounds dissolved from stratum corneum
Sampling technique	Cotton swabs wetted with chelating agents and non ionic surfactants
Method of analysis	Liquid chromatography mass spectrometry

	Non-diabetic xerosis		Diabetic xerosis			Comments
Number of participants	n = 20 (Samples collected from: 15)		n = 40 (Samples collected from: 30)			
Age (mean, SD)	56.2 (9.3)		63.5 (7.8)			
Sex	Females =15, Males =5		Females =13, Males =27			
Skin areas	Foot dorsum	Plantar heel	Plantar heel	Foot dorsum		
Severity of dry skin	Moderate = 7, Severe = 13	Moderate = 7, Severe = 13	Moderate = 20, Severe = 20	Moderate = 20, Severe = 20		
Molecular markers					Quan. units	
Ceramides (mean, SD)	95.1 (35.4)	430.4 (97.1)	824.5 (550.7)	283.6 (146.2)	UA/cm^2	Amount is increased in diabetics
		p = 0.003				
	p < 0.001					
NMFs (mean, SD)	65.0 (37.1)	148.4 (86.0)	199.0 (113.2)	101.7 (70.4)	µg/cm^2	
	p value not reported					
Amino Acid (mean, SD)	39.8 (12.7)	90.9 (42.2)	139.0 (67.4)	67.5 (40.1)	UA/cm^2	Amount is increased in diabetics
		p = 0.01				
	p = 0.02					
Serine (mean, SD)	42.4 (25.5)	99.1 (60.6)	145.8 (72.5)	67.3 (41.2)	µg/cm^2	Amount is increased in diabetics
		p = 0.02				
	p = 0.04					
Pyrrolidone carboxylic acid (mean, SD)	54.1 (31.2)	125.5 (75.4)	172.3 (96.8)	86.1 (57.4)	µg/cm^2	Amount is increased in diabetics
	p value not reported					
Urocanic acid trans (mean, SD)	6.0 (4.6)	16.4 (9.7)	20.2 (13.2)	10.3 (10.0)	µg/cm^2	Amount is increased in diabetics
	p = 0.03					
Urocanic acid cis (mean, SD)	4.9 (2.6)	6.5 (5.5)	6.5 (5.8)	5.3 (4.7)	µg/cm^2	Amount is increased in diabetics
	p value not reported					

Histamine (mean, SD)	5.3 (2.9)	9.0 (5.2)	23.3 (15.0)	13.5 (11.5)	ng/cm^2	Amount is increased in diabetics
		p < 0.001				
	p = 0.005					
Total proteins (mean, SD)	28.7 (15.2)	66.5 (56.2)	101.5 (43.8)	42.2 (17.7)	µg/ml	Amount is increased in diabetics
		p = 0.003				
	p = 0.02					
Glutathione (mean, SD)	31.5 (8.0)	35.9 (9.4)	Not detected	Not detected	ng/cm^2	Not detected in diabetics
Melondialdehyde (mean, SD)	60.8 (7.2)	66.7 (12.5)	58.7 (14.9)	47.7 (8.6)	ng/cm^2	Amount is decreased in diabetics
		p = 0.03				
	p < 0.001					

Legiawati et al 2020

Author	Legiawati et. al. [42] (Title: Oral and topical *Centella asiatica* in type 2 diabetes mellitus patients with dry skin: a three-arm prospective randomized double-blind controlled trial)
Year	2020
Study design	Randomized controlled trial
Country/ ethnicity	Indonesia (ethnicity: Asian)
Signs of dry skin and scoring method	The status of skin dryness was assessed by specified symptom sum score (SRRC) system with grading of scaling, roughness, redness and cracks as the main signs of dry skin (xerosis). Scaling (visual evaluation) *0 = absent* 1 = *slight;* Small scales only, surface lightly dull in colour, *2=moderate;* Small scales in combination with larger scales (>0.05 mm), surface opaque or whitish, *3 =severe;* Larger and large scales (flakes >1 mm) are prominent, surface whitish 4 =*extreme;* Larger flakes covering almost the entire skin surface in the examination field Roughness (tactile evaluation) *0 =absent;* Perfectly smooth and pliable 1 =*slight;* Slightly irregular and scratchy on tangential tactile evaluation *2=moderate;* Definitely irregular and scratchy and possibly slightly stiffened on vertical tactile evaluation *3 =severe;* Advanced irregularly and scratchy feeling associated with some stiffening. 4 =*extreme;*Gross irregularity and major disturbance of skin markings and definite stiffening. Redness (visual) 0 =*absent* 1 =*slight;* Small areas of minimal redness or diffuse faint redness *2=moderate;* Limited areas of definite redness or diffuse and obvious redness

	3 = *severe;*Larger areas of definite redness or diffuse and more pronounced redness. *4 =extreme;* Advanced redness in entire examination field (redness of cracks not included) Cracks fissures (visual evaluation) *O=absent* 1 = *slight;* Single and superficial cracks in the examinationfield *2=moderate;* Single or grouped superficial and more deep cracks 3=*severe;* As *2* but with deep cracks *4=extreme;*Dominated by deep cracks. (Serup et al 1995)
Analysed material	Stratum corneum
Sampling technique	Cyanoacrylate skin surface stripping using a transparent foil of 3.75 cm × 2.5 cm with 20 µL cyanoacrylate adhesive.
Method of analysis	Enzyme-linked immunosorbent assays (ELISA)

											Comments
	Oral treatment and Topical treatment (CAo andCAt)			Oral placebo and Topical treatment (Plo andCAt)			Oral placebo and Topical placebo (Plo andPlt)				CAo= Oral dose of *Centellaasiatica* (2 ×1100 mg) CAt= 1% ointment of *Centellaasiatica* Plt= Vaseline album
Number of participants	53 T2DM patients with dry skin on low extremities (SRRC score above 3)			53 T2DM patients with dry skin on low extremities (SRRC score above 3)			53 T2DM patients with dry skin on low extremities (SRRC score above 3)				43, 42, 36, respectively, reported previous histories of atopy
Age (median, min to max)	52 (34 to 58)			54 (26 to 59)			53 (34 to 59)				
Sex	13 Males, 40 Females			14 Males, 39 Females			12 Males, 41 Females				
Skin areas	Right lower extremities			Right lower extremities			Right lower extremities				
	Day 1	Day 15	Day 29	Day 1	Day 15	Day 29	Day 1	Day 15	Day 29		
Severity of dry skin (SRRC); median (min to max)	4 (3 to 10)	2 (0 to 6)	2 (0 to 6)	4 (3 to 8)	3 (0 to 7)	2 (0 to 7)	5 (3 to 8)	3 (0 to 7)	2 (0 to 6)		
Molecular markers										Quan. units	
N(6)-carboxymethyl-lysine activity; median (min to max)	87.2 (20.12 to 14559.42)	Not analyzed	119.8 (24.2 to 615.9)	77.2 (4.1 to 385.7)	Not analyzed	119.4 (25.2 to 1731.4)	93.9 (14 to 407.8)	Not analyzed	104.8 (22 to 748.1)	pg/mg protein	

	p = 0.76 (on day 1), p = 0.41 (on day 29)										
Interleukin-1α activity; median (min to max)	16.5 (2.9 to 167.3)	Not analyzed	19.7 (3.2 to 167.3)	16.0 (2.1 to 110.5)	Not analyzed	18.2 (4.9 to 69.6)	17.6 (4.4 to 114.6)	Not analyzed	17.6 (4.9 to 114.5)		
	p = 0.60 (on day 1), p = 0.68 (on day 29)										
Superoxide dismutase activity; median (min to max)	4.6 (0.3 to 59.4)	Not analyzed	5.9 (1 to 59.4)	3.4 (0.3 to 41.5)	Not analyzed	4.3 (0.2 to 18.7)	3.9 (0.2 to 35)	Not analyzed	4.9 (0.1 to 23.6)	U/mg protein	
	p = 0.31 (on day 1), p = 0.07 (on day 29)										

Subgroup Analysis in partially controlled blood glucose subgroup:											
	Cao and CAt			Plo and CAt			Plo and Plt				
	Day 1 n=13	Day 15	Day 29 n=13	Day 1 n=9	Day 15	Day 29 n=7	Day 1 n=14	Day 15	Day 29 n=14		
Severity of dry skin (SRRC value)	4	2	3	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported		
Molecular markers											
N(6)-carboxymethyl-lysine activity; median (min to max)	73.9 (26.7 to 219.9)	Not analyzed	158 (26 to 524.6)	153 (35.5 to 179.6)	Not analyzed	82.7 (44.3 to 270.1)	70.9 (27.5 to 279.4)	Not analyzed	91.8 (22 to 422.1)	pg/mg protein	
	p = 0.55 (on day 1), p = 0.42 (on day 29)										
Interleukin-1α activity; median (min to max)	17.3 (7 to 32)	Not analyzed	21.6 (7.9 to 65.9)	17.9 (4.4 to 96.2)	Not analyzed	17 (6.2 to 32.2)	16.7 (6.8 to 47.1)	Not analyzed	14.5 (4.9-to 80)		
	p = 0.67 (on day 1), p = 0.51 (on day 29)										
Superoxide dismutase activity; median (min to max)	3.9 (0.3 to 11.2)	Not analyzed	8.4 (1.3 to 25)	6 (0.4 to 25.3)	Not analyzed	2.4 (1.3 to 10.5)	2.7 (0.2 to 16.4)	Not analyzed	3.5 (0.2 to 8.1)	U/mg protein	
	p = 0.28 (on day 1), **p = 0.03** (on day 29)										

Subgroup Analysis in well controlled, partially controlled and poorly controlled blood glucose subjects of the CAo+CAt treatment group:											
	well controlled			partially controlled *			poorly controlled				
	Day 1	Day 15	Day 29	Day 1	Day 15	Day 29	Day 1	Day 15	Day 29		
Severity of dry skin (SRRC value)	4	2	1	4	2	3	4	3	3		-Quantity extracted from graph.
Molecular markers											
	103.7	Not analyzed	125.9	71.6	Not analyzed	153.0	76.5	Not analyzed	118.5	pg/mg protein	-Quantity extracted from graph.

N(6)-carboxymethyl-lysine activity (metric not reported)	p value not reported										
Interleukin-1α activity (metric not reported)	18.5	Not analyzed	22.0	17.2	Not analyzed	22.0	16.6	Not analyzed	14.3		-Quantity extracted from graph.
	p value not reported										
Superoxide dismutase activity (metric not reported)	4.6	Not analyzed	6.6	4.1	Not analyzed	8.6	5.5	Not analyzed	5.3	U/mg protein	-Quantity extracted from graph.
	p value not reported										

*****These values differ a little bit from above, as they were extracted from the graphs.

Uchino et. al., 2020

Author	Uchino et. al. [43] (Title: Association of dry skin with intercellular lipid composition of stratum corneum after erlotinib administration)
Year	2020
Study design	Controlled clinical trial
Country/ ethnicity	Japan (ethnicity: not reported)
Signs of dry skin and scoring method	The condition of dry skin was assessed according to the 'Common Terminology Criteria for Adverse Events (CT-CAE)' version 4.0; term definition: a disorder characterized by flaky and dull skin; the pores are generally fine, the texture is a papery thin texture. Grade 1: mild; asymptomatic or mild symptoms; covering <10% Body surface area and no associated erythema or pruritus, Grade 2: moderate; covering 10 - 30% BSA and associated with erythema or pruritus; limiting instrumental activities of daily living (ADL) Grade 3: severe or medically significant; covering > 30% BSA and associated with pruritus; limiting self-care ADL.
Analysed material	Stratum corneum.
Sampling technique	Tape-stripping. Each tape was pressed against the skin for 10 s using a standardized pressurizer to minimize the pressure associated with sampling. Each of the fifth tape-stripped tapes corresponding to each sampling time point was cut into half and used for extraction of compounds.
Method of analysis	For lipids: ultra performance liquid chromatography combined with time-of-flight mass spectrometry. For proteins: ortho-phthalaldehyde (OPA) fluorescent protein assay.

	Healthy Subjects			Patients with non-small lung cancer receiving oral erlotinib administration (150 mg/day)						Comments
Number of participants	6			18						
Age	50-60 years			62-85 years						Median= 74
Sex	Not mentioned			10 Males, 8 Females						
Skin areas	Inner forearm			Inner forearm						
	Day 0	Day 28	Day 56	Day 0	Day 7	Day 14	Day 28	Day 56		

Severity of dry skin	Not reported	Not reported	Not reported	Grade 0 = 66.5%, grade 1 = 33.5%	Grade 0 = 94%, grade 1 = 6%	Grade 0 = 43.6%, grade 1 = 37.6%, grade 2 = 6%, grade 3 = 12.8%	Grade 0 = 16.3%, grade 1 = 72.8%, grade 2 = 10.9%	Grade 0 = 13.9%, grade 1 = 21.5% grade 2 = 64.6%	Percentage	Quantity extracted from graph. Dry skin increased with increasing time after the initiation of erlotinib administration.
Molecular markers									Quan. units	
Cholesterol sulfate (metric not reported)	1.00	1.05	0.82	1.00	0.87	0.87	1.50	1.82	Enhancement ratio	Quantity extracted from graph
				p < 0.05, between day 0 and day 56, day 7 and day 56, day 14 and day 56						
Total free fatty acid (metric not reported)	0.062	0.066	0.062	0.077	0.076	0.054	0.050	0.041	Ratio of free fatty acid abundance to protein concentration	
	p value not reported									
Saturated free fatty acid (metric not reported)	0.009	0.008	0.009	0.018	0.018	0.013	0.012	0.010		
	p value not reported									
Hydroxyfree fatty acid (metric not reported)	0.052	0.056	0.052	0.059	0.058	0.040	0.036	0.030		
				p < 0.05, between day 0 and day 56, day 7 and day 56						
Unsaturated free fatty acid (metric not reported)	0.00057	0.00063	0.00060	0.00079	0.00113	0.00066	0.00070	0.00080		
	p value not reported									
Total ceramide (metric not reported)	0.30	0.37	0.35	0.58	0.49	0.34	0.38	0.38	Ratio of CER abundance to protein concentration	
	p value not reported									
Ceramide [NdS] (metric not reported)	0.024	0.024	0.024	0.038	0.035	0.022	0.026	0.031		
	p value not reported									
Ceramide [NS] (metric not reported)	0.017	0.019	0.019	0.032	0.026	0.016	0.031	0.031		
	p value not reported									
Ceramide [NP] (metric not reported)	0.073	0.070	0.071	0.140	0.124	0.091	0.092	0.092		
	p value not reported									
Ceramide [NH] (metric not reported)	0.035	0.034	0.034	0.077	0.065	0.046	0.052	0.054		
	p value not reported									
Ceramide [AdS] (metric not reported)	0.005	0.005	0.005	0.013	0.010	0.010	0.013	0.012		
	p value not reported									

Ceramide [AS] (metric not reported)	0.013	0.015	0.015	0.029	0.022	0.014	0.030	0.022		
	p value not reported									
Ceramide [AP] (metric not reported)	0.052	0.052	0.048	0.107	0.084	0.066	0.066	0.052		
				p < 0.05, between day 0 and day 56						
Ceramide [AH] (metric not reported)	0.051	0.050	0.048	0.092	0.076	0.054	0.061	0.056		
				p < 0.05, between day 0 and day 56, day 0 and day 14						
Ceramide [EOdS] (metric not reported)	0.003	0.004	0.003	0.005	0.004	0.001	0.002	0.003		
	p value not reported									
Ceramide [EOS] (metric not reported)	0.011	0.012	0.012	0.019	0.013	0.008	0.009	0.011		
	p value not reported									
Ceramide [EOP] (metric not reported)	0.003	0.004	0.003	0.010	0.006	0.004	0.005	0.005		
	p value not reported									
Ceramide [EOH] (metric not reported)	0.011	0.012	0.012	0.023	0.019	0.011	0.013	0.015		
	p value not reported									

Reported only for patients after erlotinib administration:														
	Day 14				Day 28				Day 56					
Dry skin grade	0	1	2	3	0	1	2	3	0	1	2	3		
Molecular markers														
Increase of cholesterol sulfate (mean)	0.62	1.18	0.50	0.78	0.81	1.64	2.25	Non-existent	0.88	1.04	2.08	non-existent	Ratio	Quantity extracted from graph
	p value not reported													
Reduction of hydroxy free fatty acid (mean)	0.65	0.89	0.52	0.92	0.60	0.71	0.86	Non-existent	0.62	0.52	0.70	non-existent		
	p value not reported													
Reduction of ceramide (mean)	0.63	0.78	0.52	0.78	0.65	0.75	1.18	Non-existent	0.68	0.52	0.96	non-existent		
	p value not reported													

S3 Appendix: Molecular markers analyzed only once.

Manuscript title: “Molecular characterization of xerosis cutis: a systematic review”.

Molecular markers	Analysed material	Sampling technique	Method of analysis	Association
Aluminium level in the epidermis and dermis [23]	Epidermis and dermis	Separation of the epidermis from the dermis	Atomic absorption spectrophotometry	Yes
Saturated free fatty acids [43]	Stratum corneum	Tape stripping	Liquid chromatography mass spectrometry	Unclear
Hydroxy free fatty acids [43]	Stratum corneum	Tape stripping	Liquid chromatography mass spectrometry	Unclear
Unsaturated free fatty acids [43]	Stratum corneum	Tape stripping	Liquid chromatography mass spectrometry	No
Ceramide (AdS) [43]	Stratum corneum	Tape stripping	Liquid chromatography mass spectrometry	No
Ceramide (EOdS) [43]	Stratum corneum	Tape stripping	Liquid chromatography mass spectrometry	Unclear
Ceramide (EOP) [43]	Stratum corneum	Tape stripping	Liquid chromatography mass spectrometry	Unclear
Hydroceramide [28]	Stratum corneum	Stripping with cyanoacrylate resin	Thin layer chromatography	Yes
Wax [28]	Stratum corneum	Stripping with cyanoacrylate resin	Thin layer chromatography	Yes
Desmoglein 1[32]	Stratum corneum	Varnish stripping	SDS-page, western blotting	Yes
Plakoglobin [32]	Stratum corneum	Varnish stripping	SDS-page, western blotting	Yes
N(6)-carboxymethyl-lysine activity [42]	Stratum corneum	Cyanoacrylate skin surface stripping	Enzyme-linked immunosorbent assays	Yes
Interleukin-1α activity [42]	Stratum corneum	Cyanoacrylate skin surface stripping	Enzyme-linked immunosorbent assays	Unclear
Superoxide dismutase activity [42]	Stratum corneum	Cyanoacrylate skin surface stripping	Enzyme-linked immunosorbent assays	Unclear
Caseinolytic activities [38]	Stratum corneum	Tape stripping	Protease assay	Yes
Chymotrypsin-like activities [38]	Stratum corneum	Tape stripping	Protease assay	Yes
Trypsin-like activities [38]	Stratum corneum	Tape stripping	Protease assay	Yes
Histamine [41]	Compounds dissolved from stratum corneum	Collecting swabs	Liquid chromatography mass spectrometry	Yes
Glutathione [41]	Compounds dissolved from stratum corneum	Collecting swabs	Liquid chromatography mass spectrometry	Unclear

Melondialdehyde [41]	Compounds dissolved from stratum corneum	Collecting swabs	Liquid chromatography mass spectrometry	Yes
Natural moisturising factors [41]	Compounds dissolved from stratum corneum	Collecting swabs	Liquid chromatography mass spectrometry	Yes
Citrulline [33]	Stratum corneum	Scraping off the skin with a glass slide	High performance liquid chromatography	Yes
Gamma-aminobutyric acid [37]	Stratum corneum	Tape stripping	High performance liquid chromatography	Unclear
Carboxylic acid [38]	Compounds dissolved from stratum corneum	Collecting swabs	Fourier transform infrared spectroscopy	Yes
IL-1ra/IL-1β [36]	Compounds dissolved from stratum corneum	Collecting swabs	Enzyme-linked immunosorbent assays	Yes
Interleukin-8 [36]	Compounds dissolved from stratum corneum	Collecting swabs	Enzyme-linked immunosorbent assays	Yes
(Pro)filaggrin [37]	Stratum corneum	Tape strippings	Western blotting and densitometricanalyses	No
Bleomycin hydrolase [37]	Stratum corneum	Tape strippings	Western blotting and densitometricanalyses	Yes
Total proteins [41]	Compounds dissolved from stratum corneum	Collecting swabs	Liquid chromatography mass spectrometry	Yes
Annexin A2 [34]	Stratum corneum	Varnish stripping	Electrophoresis, western blot, liquid chromatography mass spectrometry	Yes
Phosphatidylethanolamine-binding protein 1 [34]	Stratum corneum	Varnish stripping	Electrophoresis, western blot, liquid chromatography mass spectrometry	Yes

S4 Appendix: PRISMA 2020 checklist.
Title of the manuscript: Molecular characterization of xerosis cutis: a systematic review

Section and Topic	Item #	Checklist item	Location where item is reported	
TITLE			Pages	Lines
Title	1	Identify the report as a systematic review.	1	1
ABSTRACT				
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	2, 3	13 to 41
INTRODUCTION				
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	3, 4	43 to 79
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	4, 5	81 to 85
METHODS				
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	5	88 to 97
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	5	99 to 102
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	6	104 to 109
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	6	111 to 116
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	6	118 to 122
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	6, 7	124 to 128
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.		
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Risk of bias assessment was not conducted	
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	7	136 to 138
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)	7, 8	140 to 154
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.		
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.		
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Meta-analysis was not done.	
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	Not applicable	

S4 Appendix: PRISMA 2020 checklist.
Title of the manuscript: Molecular characterization of xerosis cutis: a systematic review

Section and Topic	Item #	Checklist item	Location where item is reported	
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	Not applicable	
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Not applicable	
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Not applicable	
RESULTS				
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	8	157 to 164
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Not applicable	
Study characteristics	17	Cite each included study and present its characteristics.	9	166 to 172
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Not applicable	
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	9 to 28	174 to 390
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Not applicable	
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	29 to 32	391 to 392
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Not applicable	
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	Not applicable	
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Not applicable	
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Not applicable	
DISCUSSION				
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	33 to 36	393 to 448
	23b	Discuss any limitations of the evidence included in the review.	36	461 to 477
	23c	Discuss any limitations of the review processes used.		
	23d	Discuss implications of the results for practice, policy, and future research.	35	450 to 459
OTHER INFORMATION				
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	37	499 to 500
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.		
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	Not applicable	
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	37	487 to 492
Competing interests	26	Declare any competing interests of review authors.	Not applicable	
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	As supporting information.	

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

For more information, visit: http://www.prisma-statement.org/

Publication 2:

Amin R, Völzer B, El Genedy-Kalyoncu M, Blume-Peytavi U, Kottner J. The prevalence and severity of dry skin and related skin care in older adult residents in institutional long-term care: A cross-sectional study. Geriatric Nursing. 2023 Nov 1;54:331-40.

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Impact factor: 2.7 (according to the latest available data from 2022)

Rank: 25 out of 126 in the category 'nursing' (among the top 25 percent; according to 2022 ranking).

Journal Data Filtered By: **Selected JCR Year: 2022** Selected Editions: SCIE, Selected Categories: **"NURSING"** Selected Category Scheme: WoS

Gesamtanzahl: 126 Journale

Rank	Full Journal Title	Total Cites	Journal Impact Factor	Eigenfaktor
1	INTERNATIONAL JOURNAL OF NURSING STUDIES	16,189	8.1	0.01362
2	International Journal of Mental Health Nursing	4,154	5.6	0.00531
3	Journal of Nursing Management	8,500	5.5	0.00739
4	Intensive and Critical Care Nursing	2,882	5.3	0.00311
5	NURSING OUTLOOK	3,028	4.3	0.00322
6	Worldviews on Evidence-Based Nursing	2,315	4.3	0.00214
7	JOURNAL OF CLINICAL NURSING	18,779	4.2	0.01845
8	NURSING ETHICS	4,594	4.2	0.00404
9	INTERNATIONAL NURSING REVIEW	2,945	4.1	0.00228
10	NURSE EDUCATION TODAY	13,538	3.9	0.01052
11	JOURNAL OF ADVANCED NURSING	23,672	3.8	0.01212
12	Women and Birth	3,901	3.8	0.00467
13	JOURNAL OF NURSING SCHOLARSHIP	4,404	3.4	0.00339
14	Australian Critical Care	1,675	3.3	0.00229
15	BMC NURSING	3,229	3.2	0.00342
16	Nurse Education in Practice	4,564	3.2	0.00481
17	Journal of Family Nursing	1,064	3.1	0.00084
18	Nursing in Critical Care	1,654	3.0	0.00183
19	European Journal of Cardiovascular Nursing	2,670	2.9	0.00299

Rank	Full Journal Title	Total Cites	Journal Impact Factor	Eigenfaktor
20	European Journal of Oncology Nursing	3,868	2.8	0.00347
21	HEART & LUNG	3,448	2.8	0.00349
22	Journal of Pediatric Health Care	1,771	2.8	0.00198
23	AMERICAN JOURNAL OF CRITICAL CARE	2,829	2.7	0.00208
24	AMERICAN JOURNAL OF NURSING	2,648	2.7	0.00180
25	Geriatric Nursing	2,785	2.7	0.00321
26	JOURNAL OF MIDWIFERY & WOMENS HEALTH	2,796	2.7	0.00271
27	Journal of Nursing Research	1,510	2.7	0.00128
28	Journal of Psychiatric and Mental Health Nursing	3,329	2.7	0.00235
29	MIDWIFERY	6,701	2.7	0.00605
30	Nursing & Health Sciences	3,244	2.7	0.00202
31	CANCER NURSING	4,414	2.6	0.00301
32	Clinical Simulation in Nursing	2,502	2.6	0.00240
33	JOURNAL OF HUMAN LACTATION	2,786	2.6	0.00296
34	Journal of Wound Ostomy and Continence Nursing	2,352	2.6	0.00123
35	Nurse Educator	1,751	2.6	0.00193
36	Workplace Health & Safety	1,336	2.6	0.00153
37	Biological Research for Nursing	1,824	2.5	0.00177
38	BIRTH-ISSUES IN PERINATAL CARE	2,995	2.5	0.00253
39	JOURNAL OF PROFESSIONAL NURSING	2,514	2.5	0.00246
40	Journal of Tissue Viability	1,331	2.5	0.00135

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Featured Article

The prevalence and severity of dry skin and related skin care in older adult residents in institutional long-term care: A cross-sectional study

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ABSTRACT

Objectives: To identify possible factors associated with different severities of xerosis cutis and to describe possible associations between (skin) care dependency and application of moisturizers.
Design: Cross-sectional study using baseline data from a cluster-randomized controlled trial. Demographic and health characteristics, skin physiological measurements, functional abilities and application of moisturizers were compared between the participants with mild and severe dry skin. Frequency of moisturization were also compared based on the participants' skin care dependency.
Results: The more distal the body area, the more severe xerosis were observed. There were no or minor differences between the groups, except for the stratum corneum hydration and skin surface pH. Participants with severe xerosis received moisturizers less often. Skin care dependent residents received moisturizers frequently.
Conclusion: There is under-application regarding xerosis cutis treatment in long-term care. Skin care provided by nurses, in adequate frequencies, might be helpful compared to skin care performed by the residents themselves.

Introduction

Xerosis cutis or dry skin is a common phenomenon in the older adult population. Depending on different settings, prevalence estimates range from 41.2 to 99.1%.[1-3] A recent large scale study reported a prevalence of 78% in nursing homes in China.[4] At the general population level, dry skin also has a considerable prevalence, e.g., 60%, as reported in a population-based cohort of older adult participants in the Netherlands.[5] Dry skin maybe caused by external factors (e.g., cold environment, low humidity, intense sunlight or hot water exposures), as well as various endogenous causes, such as intrinsic aging and the associated structural and functional changes of the skin, dermatological diseases, internal health conditions, psychiatric conditions, diet or drugs.[6-8] Impaired function of the skin barrier is one of the underlying conditions of dry skin.[9] In dry skin, the stratum corneum (SC) cannot maintain sufficient water concentration gradient between the epidermal cell layers and the surface of the skin, which leads to decreased stratum corneum hydration (SCH).[10] The changes may also include increased transepidermal water loss (TEWL).[11]

Xerosis is represented by dry skin surface with rough and scaly appearance. There are various ways to classify dry skin which include visual analogue scales, scoring systems with grading of scaling, roughness, redness and cracks e.g., the overall dry skin score (ODS) or the specified symptom sum score (SRRC).[12,13] A recent systematic review found that, for assessing skin dryness, 14 different instruments were used in the included articles.[8] The European Group on Efficacy Measurement of Cosmetics and other Topical Products (EEMCO) described a scoring system where the severity of dryness is evaluated from 'slight' to 'extreme' xerosis using the ODS. Slight xerosis is characterized by faint scaling and roughness, while in moderate xerosis scaling can be seen with rough, whitish appearance. In severe dryness, scales are uniform and roughness is definite. When xerosis symptoms are extreme, it is dominated by large scales, advanced roughness, cracks and redness.[12] The ODS is widely used today[14] and measurement properties have been investigated.[15]

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Dry skin related problems may affect patients' quality of life; dryness related itching or pruritus may cause sleep and emotional distress and affects patients' wellbeing.[16,17] Scratching can lead to further damage of the skin as well as painful wounds, which require efforts to heal.[18] Pruritus is also found to be increased with age.[19] Because of weakening of the skin barrier function,[20] sensitivity to external irritants is increased, and there is an increased risk of secondary infection.[21] This may also facilitate the development of inflammatory skin disorders e.g., contact dermatitis or eczema.[22] Dry skin is considered as a risk factor for pressure ulcer, and as a modifiable risk factor for skin tear development.[23] Especially older adults with dry skin have elevated risk of developing pressure ulcers/injuries.[24,25] Managing xerosis cutis by regular application of adequate skin care products is very important for the prevention and treatment of dry skin.[21,26] There is a substantial heterogeneity regarding the labels of skin care products including creams, lotions, emollients, and many other. In the EU Cosmetics Regulation, the umbrella term 'leave-on product' is used and defined as "a cosmetic product which is intended to stay in prolonged contact with the skin".[27] However, the term 'skin moisturizer' is commonly used and it refers to a wide range of leave-on products. Therefore, the term 'moisturizer' is used in this paper.

There is a huge body of evidence that moisturizers e.g., lipophilic products containing humectants are helpful in decreasing skin dryness, reducing pruritus and improving skin barrier function in the older adults.[26] These interventions were also found to be efficient in reducing the severity of skin dryness in terms of clinical scores, when compared with control groups.[28,29]

Interestingly, there seems to be an association between skin dryness and skin care interventions provided by nurses. Results from a prevalence study conducted in German nursing homes and hospitals indicate, that there might be an under-application, because not all participants with dry skin receive moisturizers.[1] One reason might be that clinical signs of dry skin, which may range from mild and faint scaling to severe asteatotic eczema, might remain overlooked by health care providers. This may happen especially in case of early signs of xerosis cutis.[30] However, nursing practices related to skin care, regarding the severity of xerosis cutis has never been investigated. Although numerous associations between dry skin and demographic and health characteristics have been described in long-term care,[1-4] the severity of dry skin was never considered so far. Therefore, the overall aim of this analysis was to compare participants with regard to the severity of skin dryness. A secondary aim was to describe possible associations between (skin) care dependency and application of moisturizers.

Methods

Study design and setting

Baseline data from a representative cluster-randomized controlled trial conducted in nursing homes was analyzed (ClinicalTrials.gov Identifier: NCT03824886, registration date: 31st January 2019).[31] The long-term care institutions were randomly selected from all eligible nursing homes located in the federal state of Berlin, Germany. Baseline data considered for this analysis were collected before randomization. The study took place from April 2019 to June 2021. It was approved by the ethics committee of Charité - Universitätsmedizin Berlin (ethics application number EA1/243/18).

Participants

Main inclusion criteria for the participating nursing homes were: location within the federal state of Berlin, Germany, with a capacity of at least 70 beds. Residents were considered eligible for participating in the study if they were 65+ years old, living in the nursing home during data collection, having at least care level II according to the German Code Book (Sozialgesetzbuch or SGB) XI, and provided a written informed consent (from the resident or a legal representative).

Variables

Demographic characteristics

Data on sex (female, male), age (years), body mass index (kg/m^2), and duration of residency in nursing home (months) were extracted from the participants' medical and nursing records. The levels of care (care level II to V) according to the German Code Book XI were used to indicate the degree of care dependency, whereas higher care dependency is associated with higher care levels.[32] Information on smoking status (never/current/former smoker), if applicable, duration of smoking in years and amount of smoking (expressed in pack years; 1 pack year is equal to smoking 20 cigarettes per day for 1 year) were collected. To describe possible influence of continuous sun exposure during any outdoor professional activity, outdoor occupation was assessed, which applies to the participants, who had an outdoor occupation for at least one year, anytime in life.

Health characteristics

Main medical diagnoses were extracted from the participants' medical files and recorded following the International Classification of Diseases (ICD) −11.[33] Presence of incontinence (urinary, fecal or double incontinence) was recorded, along with the occurrence of diarrhea, if applicable. Regular medications were recorded and coded according to the Anatomical Therapeutic Chemical (ATC) classification system.[34] 'Polypharmacy' was defined as intake of five or more different pharmaceutical agents by a participant on daily basis. Regular oral intake of cortisone (or an affiliating derivative) was recorded as cortisone intake.

Dry skin

Xerosis cutis per skin area (face, trunk, arms, legs and feet) was assessed by dermatologists by visual examinations in accordance with the ODS using a five-point scale.[12] A score of 0 indicates no skin dryness, 1 indicates slight xerosis, 2 indicates moderate xerosis, 3 indicates severe xerosis and a score of 4 indicates extreme xerosis, which is seen as advanced skin roughness, inflammation, large scales and cracks.

Other skin conditions

Skin tears (ST) were assessed according to the International Skin Tear Advisory Panel,[35] Incontinence-associated dermatitis (IAD) was assessed following the Ghent Global IAD categorization Tool (GLOBIAD)[36] and pressure ulcers (PUs) were assessed according to the National Pressure Injury Advisory Panel, European Pressure Ulcer Advisory Panel and Pan Pacific Pressure Injury Alliance (NPIAP/EPUAP/PPPIA).[37] Intertrigo was assessed by following the ICD −11[33] and, to evaluate itch, the 5-D itch scale was followed in case of the residents with GDS (Global deterioration scale) stage 1.[38,39]

Functional abilities

Barthel Index was used to measure the functional abilities related to the activities of daily living, whereas the score ranges from zero (very dependent) to 100 (independent).[40] This index uses ten items of activities regarding 'standing up and mobility', 'help during bathing', etc. Skin self-care ability was assessed in three categories: fully independent, need some assistance, and dependent. GDS was used to evaluate cognitive function, and the participants were assigned to seven possible stages (GDS 1 to 7).[39] Participants having no cognitive

impairments or memory deficits are categorized in stage 1, and participants having severe cognitive decline are categorized in stage 7.

Skin measurements

TEWL, SCH, skin surface pH and skin surface temperature were measured by using Tewameter TM 300, Corneometer CM 825, Skin-pH-meter pH 905 and Skin-Thermometer ST 500, respectively. The manufacturer of these instruments was Courage + Khazaka, Cologne, Germany. The measuring probe for TEWL estimates the constant permeation of water through the SC. The probe, which contains a pair of sensors located at different distances from the skin surface, determine temperature and relative humidity above the skin surface. The humidity gradient between both the sensors is used for calculating the TEWL in grams per hour per square meter, where higher values indicate higher TEWL.[41] SCH measurement is based on the differences of the dielectric constant of water and other substances present on the skin surface. The moisture content in the stratum corneum was measured in arbitrary units (AU) and ranges from 0 to 120. Higher readings indicate higher SCH.[42] Skin surface pH was measured using a combined glass electrode with a selective hydrogen ion sensitivity. pH values indicate the concentration of the hydrogen ions in an aqueous solution. However, in case of skin pH measurement, the values are expressed as skin surface pH due to extraction of water soluble components of the SC into the aqueous interface between the skin and the pH measuring electrode.[43] Reference values of human skin surface pH have been reported as in a range from 4 to 6.[44] The skin surface temperature of the skin area was recorded in degrees Celsius (°C). The reliability of these measurements in this setting was supported previously.[45]

All skin measurements were performed in duplicate on the upper part of the right ventral lower leg, and the mean was calculated. In case this area could not be assessed, e.g. due to wounds or wound dressings, the contralateral extremity was taken. It was instructed not to moisturize the skin of the participants on the measurement day. The participants were requested also to avoid caffeinated beverages on that day.

Application of moisturizers

Data about the application of moisturizers was assessed using questionnaires and chart reviews. The following frequencies were distinguished: two to three times daily, once daily, two to three times per week, and once per week or more rarely. Data was collected for the following skin areas: face/ neck, arms/ hands, trunk, legs/ feet and whole body.

Data sources and measurement

A paper-based case report form (CRF) was used for data regarding demography, medical history, current health characteristics, functional and cognitive abilities, clinical examination of skin, skin functional parameters and application of moisturizers. The participants were interviewed, and relevant data was extracted from the participants' medical records by the researchers and study assistants, head-to-toe skin examination was performed by trained dermatologists.

Bias

To support external validity, nursing homes were randomly selected from a comprehensive list of all nursing homes located in the federal state of Berlin, Germany. All residents living in the participating nursing homes were invited to take part in the study. To ensure internal validity, standardized CRFs and definitions were used. Dermatologists assessed the skin using standardized definitions of the categories and possible types of the skin condition of interest. The affected body areas were documented. All investigators and dermatologists were instructed how to use the ODS and data collection forms. In addition, images per ODS category were provided to ensure consistent evaluation and data collection. The skin parameters TEWL, SCH, pH, and temperature were measured according to standard operating procedures by trained study personnel. To maintain data accuracy and to ensure protocol adherence, external monitoring was performed.

Study size

The analyzed baseline data were obtained from an exploratory cluster randomized controlled trial. Based on pragmatic considerations, it was estimated to include 20 nursing homes. Assuming a participation rate of up to 25% from about 100 residents living in each nursing home, on average 25 residents were expected to participate in the study, resulting in an expected sample size of n = 500. Because of the exploratory nature of this study, this sample size was considered sufficient to describe possible associations.

Quantitative variables

Demographic characteristics

Participants' year of birth was recorded and the age in years was calculated. Duration of residency in months was calculated from the admission date to the nursing home. Participants were categorized into underweight (BMI < 18.5 kg/m^2) and overweight (BMI $>$ 25.0 kg/m^2).[46] Participants, who were current smokers or smoked at least once during their lifetime, were categorized as smokers/former smokers. Pack-years were calculated by multiplying the numbers of packs of cigarettes smoked per day (each pack containing 20 cigarettes) by the number of years spent as active smoker.

Health characteristics

From the ICD 11 coding of diseases, the first three letters were used for statistical analysis to identify the five most frequent medical diseases present in the participants. In order to present the most frequent medication consumed by the study population, the Anatomical Therapeutic Chemical Codes (ATC) was used. The ATC codes consists of up to seven letters and numbers, first three of which indicate the main active substance.

Presence and severity of xerosis cutis

If at least one skin area (face, trunk, arms, legs, feet) was affected with an ODS of at least 1, the participant was considered as prevalent case for xerosis cutis. At extremities, at least one side (left or right) must have been graded with ODS 1 or higher. Mean of the two sides were used for the analysis. If the two sides were graded with different ODS values, the higher value was considered for the categorization of severity of skin dryness. Number of cases and proportions were used to present dry skin severity per skin area. As nearly every participant was affected with xerosis cutis and some very mild forms of dryness might be perceived as no dryness, participants with ODS 0 (no xerosis) were grouped with ODS 1 (slight xerosis). This group (described here as mild xerosis) was compared with another group, described here as having severe forms of xerosis, consists of ODS 2 (moderate xerosis), ODS 3 (severe xerosis), and ODS 4 (extreme xerosis).

Statistical methods

Categorical variables were described using frequencies and proportions, metric variables by using means and standard deviations. Group comparisons were done between the two groups: 'no xerosis to slight xerosis' and 'moderate to severe/extreme xerosis' based on the ODS values assessed on the legs and the feet. The legs and feet were chosen because, on these body parts 'moderate to severe/ extreme xerosis' was most distinct and the number of participants was sufficient for group comparison. During statistical analysis for moisturizer application on legs and feet, participants applied

products on their 'whole body' were considered to have applied products to their legs and feet as a part of their body. The participants who applied moisturizers (or received product application by the nurses) 'two to three times daily' were grouped with the participants who had 'once daily' application. The new group was named as 'one to three times daily'. For metric variables group comparisons were described using mean differences and independent samples *t*-tests with corresponding 95% confidence intervals (CIs). Categorical variables were compared using odds ratios (OR) including 95% CIs. Because this was an exploratory study, all p-values were considered descriptively indicating strengths of associations. All calculations were conducted by using IBM SPSS Statistics for Windows, version 29 (IBM Corp., Armonk, N.Y., USA).

Results

Participants and descriptive data

From 17 nursing homes, n = 314 residents participated in the study. On average, *n* = 18 participants per nursing home were included. Fig. 1 represents a flowchart of nursing homes and participants of this study. Details on demographic characteristics and skin conditions have been published previously; among *n* = 314 participants, *n* = 301 (95.9%, 95% CI 93.6 to 97.8) had skin dryness on at least one of the following skin areas of their body: face, trunk, arms, legs or feet.[30]

Main results

Table 1 shows the proportions and severity of xerosis cutis at different skin areas of the participants. The majority of participants was affected by mild forms of dry skin. 'Moderate' to 'severe/extreme' xerosis was most frequently found at the feet (24.7%) and the legs (19.1%). The arms were also affected by 'moderate to severe' xerosis, as seen in 13.7% of the participants. A minor proportion of participants had severe to extreme dryness (ODS 3 to 4) at the arms, legs and feet. Extreme xerosis (ODS 4) was present on a foot of only one participant.

Table 2 represents the frequencies of moisturizer application on the legs and feet. In case of 63% of the participants, moisturizers were found to be applied once per week or more rarely, while once daily application occurred in 23% participants.

Comparisons between participants with 'no xerosis to slight xerosis' and 'moderate to severe xerosis' at the legs are shown in table 3. Participants with moderate to severe xerosis on the legs were older (mean difference −1.84; 95% CI −3.84 to 0.16), had a slightly longer length of stay (mean difference −1.05; 95% CI −9.94 to 7.84), and considering their smoking habit, they had a higher number of pack years (mean difference −0.64; 95% CI −9.48 to 8.20) compared to participants with 'no xerosis to slight xerosis'. Sex of the participants, being under- or overweight, care levels, being smoker or not, or being employed in an outdoor occupation in the past, presence of frequent diseases was not associated with the presence of moderate to severe xerosis on the legs. Less dryness of the legs was associated with urinary incontinence (OR 0.45; 95% CI 0.24 to 0.85, $p = 0.012$). Fecal and double incontinence (OR 0.63; 95% CI 0.34 to 1.15 and OR 0.58; 95% CI 0.31 to 1.07, respectively) showed similar results. Participants with moderate to severe xerosis on the legs were less dependent in terms of functional ability (higher Barthel index, mean difference −10.72; 95% CI −17.39 to - 4.05, $p = 0.002$). However, abilities related to bathing, mobility and cognitive function were not associated. Participants who were dependent on care givers in case of skin care, tended to have lower prevalence of moderate to severe xerosis on the legs (OR 0.60; 95% CI 0.32 to 1.13). Other dermatological conditions seemed not to be associated with the severity of xerosis cutis on the legs.

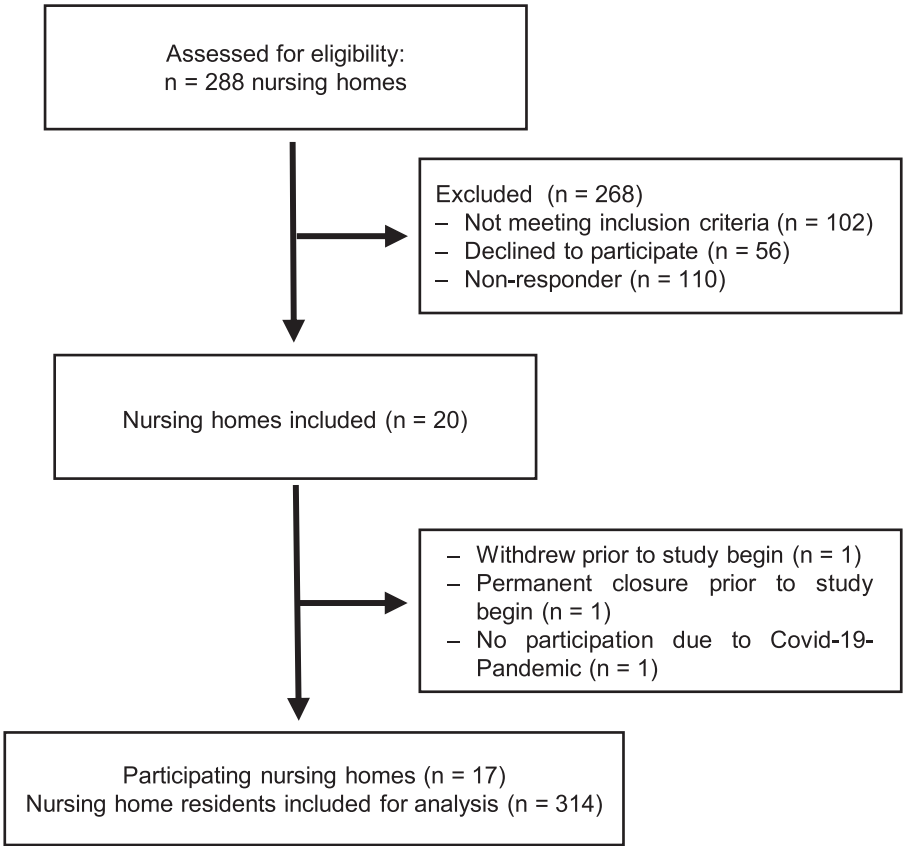

Fig. 1. Flowchart of nursing homes and participants.

Table 1
Severity of dry skin on different skin areas.

	Face (*n* = 313)	Trunk (*n* = 313)	Arms (*n* = 314)	Legs (*n* = 314)	Feet (*n* = 312)
Overall dry skin score 0, n (%)	131 (41.9)	152 (48.6)	59 (18.8)	45 (14.3)	43 (13.8)
Overall dry skin score 1, n (%)	174 (55.6)	146 (46.6)	211 (67.2)	209 (66.6)	192 (61.5)
Overall dry skin score 2, n (%)	8 (2.6)	14 (4.5)	39 (12.4)	55 (17.5)	73 (23.4)
Overall dry skin score 3, n (%)	0	1 (0.3)	4 (1.3)	5 (1.6)	3 (1.0)
Overall dry skin score 4, n (%)	0	0	0	0	1 (0.3)
Overall dry skin score 0 to 1, n (%)	305 (97.4)	298 (95.2)	271 (86.3)	254 (80.9)	235 (75.3)
Overall dry skin score 2 to 4, n (%)	8 (2.6)	15 (4.8)	43 (13.7)	60 (19.1)	77 (24.7)
Overall dry skin score 3 to 4, n (%)	0	1 (0.3)	4 (1.3)	5 (1.6)	4 (1.3)

TEWL seemed to be similar between the two groups. Participants with moderate to severe xerosis on the legs had lower SCH (mean difference 5.43; 95% CI 1.89 to 8.97, p = 0.003) and a higher skin pH value (mean difference −0.23; 95% CI -0.47 to − 0.001, p = 0.051). Skin temperature was not different between the groups. In case of the participants with moderate to severe skin dryness, daily moisturizer application on the legs occurred less often compared to the participants with mild dry skin (OR 0.56; 95% CI 0.26 to 1.21). Instead, they received product application rather with a frequency of once per week or more rarely (OR 1.63; 95% CI 0.86 to 3.09). Showering/bathing frequency was not associated with the severity of skin dryness on the legs.

Table 4 represents the comparison between the participants with 'no xerosis to slight xerosis' and 'moderate to extreme xerosis' on the feet. The proportion of females was lower in the group with moderate to extreme xerosis on the feet (OR 0.58; 95% CI 0.38 to 0.99, p = 0.045). Age of the participants, being under- or overweight, duration of residency, smoking habits, being employed in an outdoor occupation in the past, and most frequent medical diagnoses were not associated with the presence of moderate to extreme xerosis on the feet. Less dryness was associated with participants with urinary and/or fecal incontinence (OR 0.41; 95% CI 0.23 to 0.73, p = 0.002 for double incontinence). Participants with moderate to extreme xerosis on the feet were less dependent regarding functional ability (higher Barthel Index; mean difference −12.48; 95% CI −18.53 to −6.43, $p <$ 0.001). Bathing ability and mobility was not associated. Participants who were dependent on care givers in case of skin-care, had lower prevalence of moderate to extreme xerosis on the feet (OR 0.47; 95% CI 0.26 to 0.85, p = 0.011). Cognitive ability and other dermatological conditions was not associated. Infrequent application of moisturizer on the feet seemed to be associated with severe forms of xerosis (OR 1.88; 95% CI 0.92 to 3.85). The participants who showered/bathed once per week or more rarely had less dryness on the feet (OR 0.27; 95% CI 0.09 to 0.83, p = 0.016).

Other analysis

The association between (skin) care dependency and receiving moisturizers is presented in Table 5. Participants who were dependent on care providers for skin self-care, received more applications daily and more often (OR 2.59; 95% CI 1.47 to 4.56).

Table 2
Frequency of moisturizer application on legs and feet.

Frequencies	Moisturizer application on the legs (*n* = 279)	Moisturizer application on the feet (*n* = 278)
Two to three times daily, n (%)	3 (1.1)	3 (1.1)
Once daily, n (%)	63 (22.6)	63 (22.7)
Two to three times per week, n (%)	38 (13.6)	38 (13.7)
Once per week or more rarely, n (%)	175 (62.7)	174 (62.6)
Never, n (%)	0 (0.0)	0 (0.0)

Discussion

Key results

Several studies showed that the majority of nursing home residents was affected by different forms of skin dryness.[3,4,47] The current analysis is based on a study which also showed a prevalence of 95.9%.[30] The majority of the participants had slight dryness, which was common across different skin areas of the body. The more distal the body areas, the more prevalent were moderate to severe/extreme forms of skin dryness, showing the highest severity on the feet. Every fourth participants had at least moderate form of dryness on the feet. However, nearly no extreme dryness (ODS 4) was present.

Participants who had moderate to severe/extreme dryness on the legs and the feet, were likely to be less dependent on the care providers in terms of functional abilities related to activities of daily living, indicated by a higher Barthel Index. In addition, nursing home residents, who were dependent on caregivers for skin care, had lower prevalence of moderate to extreme dryness on the legs and feet. Moreover, participants with incontinence, who are more likely to be dependent on nursing staff, were in the group who had less dryness on the legs and the feet. These results support that receiving care from the nurses might had positive influence for severity of xerosis.

As expected, daily moisturizer application compared to weekly application seemed to be associated with less occurrence of moderate to severe xerosis on the legs and the feet. These results indicate that there was an under-application of moisturizers among the participants with moderate to severe dry skin. Infrequent showering/bathing, as expected, also seemed to be associated with less dryness on the feet.

Participants with moderate to severe xerosis on the legs had lower SCH and a higher pH indicating skin barrier dysfunction.

Limitations

The anticipated participation of n = 500 participants from n = 20 nursing homes was not achieved. Due to the onset of COVID-19 pandemic in March 2020, recruitment was hampered, as nursing home residents were one of the most vulnerable groups. However, the achieved sample size of n = 314 seems to be adequate to compare groups. COVID-related mandatory measures (e.g., use of hand sanitizers, masks) might have influenced skin hygiene routine but the impact on regular skin care practice was negligible. In addition, due to voluntary participation of residents, a selection bias cannot be ruled out. Nevertheless, institutions and/ or residents might have been systematically excluded due to unknown selection principle. As dry skin is one of the most common aging related skin manifestation in older people, we combined ODS 0 with ODS 1 assuming that some

Table 3
Comparison between 'no xerosis to slight xerosis' and 'moderate to severe xerosis' on the legs.

	Total number of participants (n = 314)	Participants with no xerosis to slight xerosis (n = 254)	Participants with moderate to severe xerosis (n = 60)	Mean difference (95% CI)	Odds Ratio (95% CI)	p-value	Missing, n
Demographic characteristics							
Female, n (%)	216 (68.8)	178 (70.1)	38 (63.3)	n.a.	0.74 (0.41 to 1.33)	0.310	
Age (years), mean (SD)	85.4 (7.1)	85.0 (7.2)	86.8 (6.2)	−1.84 (−3.84 to 0.16)	n.a.	0.071	
Underweight (BMI < 18.5 kg/m^2), n (%)	13 (4.1)	12 (4.7)	1 (1.7)	n.a.	0.34 (0.04 to 2.68)	0.285	
Overweight (BMI > 25.0 kg/m^2), n (%)	181 (57.6)	150 (59.1)	31 (51.7)	n.a.	0.74 (0.42 to 1.30)	0.298	
Care levels							
Care level II, n (%)	99 (31.5)	80 (31.5)	19 (31.7)	n.a.	1.01 (0.55 to 1.85)	0.980	
Care level III, n (%)	115 (36.6)	93 (36.6)	22 (36.7)	n.a.	1.00 (0.56 to 1.80)	0.994	
Care level IV, n (%)	74 (23.6)	56 (22.0)	18 (30.0)	n.a.	1.52 (0.81 to 2.84)	0.192	
Care level V, n (%)	26 (8.3)	25 (9.8)	1 (1.7)	n.a.	0.16 (0.02 to 1.17)	0.039	
Duration of residency in months, mean (SD)	30.44 (31.43)	30.24 (28.64)	31.28 (41.50)	−1.05 (−9.94 to 7.84)	n.a.	0.817	
Current or former smoker, n (%)	129 (45.6)	105 (46.1)	24 (43.6)	n.a.	0.91 (0.50 to 1.64)	0.747	31
Pack-years, Mean (SD)	17.57 (17.07)	17.46 (16.93) n = 84	18.10 (18.21) n = 18	−0.64 (−9.48 to 8.20)	n.a.	0.886	
Outdoor occupation, n (%)	26 (8.3)	21 (8.3)	5 (8.3)	n.a.	1.01 (0.36 to 2.80)	0.987	
Health Characteristics							
Hypertension, n (%)	235 (74.8)	191 (75.2)	44 (73.3)	n.a.	0.91 (0.48 to 1.72)	0.765	
Dementia, n (%)	101 (32.0)	79 (31.1)	22 (36.7)	n.a.	1.28 (0.71 to 2.31)	0.407	
Renal insufficiency, n (%)	99 (31.1)	79 (31.1)	20 (30.9)	n.a.	1.11 (0.61 to 2.02)	0.738	
Diabetes mellitus, n (%)	88 (28.0)	70 (27.6)	18 (30.0)	n.a.	1.13 (0.61 to 2.09)	0.705	
Heart arrhythmia, n (%)	72 (22.9)	61 (24.0)	11 (18.3)	n.a.	0.71 (0.35 to 1.45)	0.346	
Urinary incontinence, n (%)	247 (78.7)	207 (81.5)	40 (66.7)	n.a.	0.45 (0.24 to 0.85)	0.012	
Fecal incontinence, n (%)	121 (38.5)	103 (40.6)	18 (30.0)	n.a.	0.63 (0.34 to 1.15)	0.131	
Double incontinence, n (%)	120 (38.2)	103 (40.6)	17 (28.3)	n.a.	0.58 (0.31 to 1.07)	0.080	
Diarrhea, n (%)	1 (0.3)	1 (0.4)	0	–	0.81 (0.77 to 0.85)	0.626	
Functional abilities							
Barthel Index, mean (SD)	45.16 (23.96)	43.11 (23.89)	53.83 (22.44)	−10.72 (−17.39 to −4.05)	n.a.	0.002	
Bathing ability: completely independent, n (%)	14 (4.5)	11 (4.4)	3 (5.0)	n.a.	1.15 (0.31 to 4.25)	0.836	
Standing up and mobility: completely dependent, n (%)	52 (16.6)	46 (18.1)	6 (10.0)	n.a.	0.50 (0.20 to 1.24)	0.129	
Skin self-care ability							
Fully independent, n (%)	10 (3.2)	8 (3.1)	2 (3.3)	n.a.	1.06 (0.22 to 5.13)	0.942	
Need some assistance, n (%)	198 (63.1)	155 (61.0)	43 (71.7)	n.a.	1.62 (0.87 to 2.99)	0.124	
Dependent, n (%)	106 (33.8)	91 (35.8)	15 (25.0)	n.a.	0.60 (0.32 to 1.13)	0.111	
Global Deterioration Scale (GDS)							
GDS 1, n (%)	159 (50.6)	130 (51.2)	29 (48.3)	n.a.	0.89 (0.51 to 1.57)	0.691	
GDS 2, n (%)	55 (17.5)	41 (16.1)	14 (23.3)	n.a.	1.58 (0.80 to 3.14)	0.187	
GDS 3, n (%)	19 (6.1)	16 (6.3)	3 (5.0)	n.a.	0.78 (0.22 to 2.78)	0.704	
GDS 4, n (%)	18 (5.7)	13 (5.1)	5 (8.3)	n.a.	1.69 (0.58 to 4.92)	0.335	
GDS 5, n (%)	32(10.2)	27 (10.6)	5 (8.3)	n.a.	0.76 (0.28 to 2.08)	0.597	
GDS 6, n (%)	21 (6.7)	18 (7.1)	3 (5.0)	n.a.	0.69 (0.20 to 2.42)	0.561	
GDS 7, n (%)	10 (3.2)	9 (3.5)	1 (1.7)	n.a.	0.46 (0.06 to 3.71)	0.457	
Other skin conditions							
Skin tears, n (%)	33 (10.5)	25 (9.8)	8 (13.3)	n.a.	1.41 (0.60 to 3.30)	0.428	
Itch at lower legs, n (%)	18 (5.7)	13 (5.1)	5 (8.3)	n.a.	1.69 (0.58 to 4.92)	0.335	
Incontinence associated dermatitis, n (%)	59 (18.8)	43 (16.9)	16 (26.7)	n.a.	1.78 (0.92 to 3.45)	0.082	
Pressure ulcers, n (%)	25 (8.0)	22 (8.7)	3 (5.0)	n.a.	0.56 (0.16 to 1.92)	0.346	
Intertrigo, n (%)	110 (35.0)	83 (32.7)	27 (45.0)	n.a.	1.69 (0.95 to 2.99)	0.072	
Most frequent medication							
Diuretics, n (%)	170 (54.1)	135 (53.1)	35 (58.3)	n.a.	1.23 (0.70 to 2.18)	0.469	
Antithrombotic medication, n (%)	198 (63.1)	158 (62.2)	40 (66.7)	n.a.	1.22 (0.67 to 2.20)	0.520	
Beta-Adreno- receptor antagonists, n (%)	173 (55.1)	138 (54.3)	35 (58.3)	n.a.	1.18 (0.67 to 2.08)	0.575	
Medication influencing the renin-angiotensin system, n (%)	162 (51.6)	129 (50.8)	33 (55.0)	n.a.	1.18 (0.67 to 2.08)	0.557	
Analgesic, n (%)	132 (42.0)	108 (42.5)	24 (40.0)	n.a.	0.90 (0.51 to 1.60)	0.722	
Psychoanaleptics, n (%)	144 (45.9)	125 (49.2)	19 (31.7)	n.a.	0.48 (0.26 to 0.87)	0.014	
Cortisone intake, n (%)	14 (4.5)	13 (5.1)	1 (1.7)	n.a.	0.31 (0.04 to 2.45)	0.244	
Polypharmacy (≥ 5 medications), n (%)	274(87.3)	223 (87.8)	51 (85.0)	n.a.	0.79 (0.35 to 1.76)	0.559	
Skin parameters							
Transepidermal water loss	9.04 (5.90); n = 313	9.16 (6.42)	8.51 (2.74)	0.65 (−1.02 to 2.31)	n.a.	0.447	1
Stratum corneum hydration	36.27 (12.69); n = 313	37.31 (12.59)	31.87 (12.29)	5.43 (1.89 to 8.97)	n.a.	0.003	1
Skin surface pH	5.29 (0.83) n = 313	5.24 (0.78)	5.48 (1.02)	−0.23 (−0.47 to −0.001)	n.a.	0.051	1
Skin temperature	31.24 (1.33) n = 313	31.25 (1.37)	31.20 (1.12)	0.05 (−0.33 to 0.42)	n.a.	0.811	1
Application of moisturizers							
One to three times daily, n (%)	66 (23.7)	57 (25.6)	9 (16.1)	n.a.	0.56 (0.26 to 1.21)	0.135	35
Once per week or more rarely, n (%)	175 (62.7)	135 (60.5)	40 (71.4)	n.a.	1.63 (0.86 to 3.09)	0.132	35
Showering/bathing frequency							
Once per week or more rarely, n (%)	265 (95.3)	214 (95.5)	51 (94.4)	n.a.	0.80 (0.21 to 3.00)	0.733	36

Table 4
Comparison between 'no xerosis to slight xerosis' to 'moderate to extreme xerosis' on the Feet.

	Total number of participants (n = 312)	Participants with no xerosis to slight xerosis (n = 235)	Participants with moderate to extreme xerosis (n = 77)	Mean difference (95% CI)	Odds Ratio (95% CI)	p-value	Missing, n
Demographic characteristics							
Female, n (%)	215 (68.9)	169 (71.9)	46 (59.7)	n.a.	0.58 (0.38 to 0.99)	0.045	2
Age (years), mean (SD)	85.4 (7.1)	85.3 (7.2)	85.8 (6.6)	−0.56 (−2.39 to 1.27)	n.a.	0.545	2
Underweight (BMI < 18.5 kg/m^2), n (%)	13 (4.2)	12 (5.1)	1 (1.3)	n.a.	0.26 (0.03 to 1.91)	0.147	2
Overweight (BMI > 25.0 kg/m^2), n (%)	180 (57.7)	138 (58.7)	42 (54.5)	n.a.	0.84 (0.50 to 1.42)	0.520	2
Care levels							
Care level II, n (%)	99 (31.7)	70 (29.8)	29 (37.7)	n.a.	1.42 (0.83 to 2.44)	0.198	2
Care level III, n (%)	114 (36.5)	84 (35.7)	30 (39.0)	n.a.	1.15 (0.68 to 1.95)	0.611	2
Care level IV, n (%)	73 (23.4)	57 (24.3)	16 (20.8)	n.a.	0.82 (0.44 to 1.53)	0.532	2
Care level V, n (%)	26 (8.3)	24 (10.2)	2 (2.6)	n.a.	0.23 (0.05 to 1.02)	0.036	
Duration of residency in months, mean (SD)	30.49 (31.50) Line 43	30.45 (28.96)	30.61 (38.43)	−0.16 (−98.31 to 7.99)	n.a.	0.969	2
Current or former smoker, n (%)	127 (45.2)	95 (45.5)	32 (44.4)	n.a.	0.96 (0.56 to 1.65)	0.882	33
Pack-years, mean (SD)	17.70 (17.21)	17.75 (18.21) n = 75	17.58 (14.11) n = 25	0.17 (−7.76 to 8.09)	n.a.	0.967	
Outdoor occupation, n (%)	26 (8.3)	21 (8.9)	5 (6.5)	n.a.	0.71 (0.26 to 1.95)	0.501	2
Health Characteristics							
Hypertension, n (%)	233 (74.7)	175 (74.5)	58 (75.3)	n.a.	1.05 (0.58 to 1.90)	0.881	2
Dementia, n (%)	100 (32.1)	78 (33.2)	22 (28.6)	n.a.	0.81 (0.46 to 1.41)	0.451	2
Renal insufficiency, n (%)	98 (31.4)	75 (31.9)	23 (29.9)	n.a.	0.91 (0.52 to 1.59)	0.737	2
Diabetes mellitus, n (%)	88 (28.2)	65 (27.7)	23 (29.9)	n.a.	1.11 (0.63 to 1.96)	0.708	2
Heart arrhythmia, n (%)	71 (22.8)	55 (23.4)	16 (20.8)	n.a.	0.86 (0.46 to 1.61)	0.633	2
Urinary incontinence, n (%)	245 (78.5)	191 (81.3)	54 (70.1)	n.a.	0.54 (0.30 to 0.97)	0.039	2
Fecal incontinence, n (%)	120 (38.5)	102 (43.4)	18 (23.4)	n.a.	0.40 (0.22 to 0.72)	0.002	2
Double incontinence, n (%)	119 (38.1)	101 (43.0)	18 (23.4)	n.a.	0.41 (0.23 to 0.73)	0.002	2
Diarrhea, n (%)	1 (0.3)	1 (0.4)	0	–	0.75 (0.71 to 0.80)	0.566	2
Functional abilities							
Barthel Index, mean (SD)	45.08 (24.01)	42.00 (23.67)	54.48 (22.68)	−12.48 (−18.53 to −6.43)	n.a.	< 0.001	2
Bathing ability: completely independent, n (%)	14 (4.5)	10 (4.3)	4 (5.3)	n.a.	1.24 (0.38 to 4.07)	0.724	5
Standing up and mobility: completely dependent, n (%)	52 (16.7)	44 (18.7)	8 (10.4)	n.a.	0.50 (0.23 to 1.12)	0.089	2
Skin self-care ability							
Fully independent, n (%)	10 (3.2)	7 (3.1)	3 (3.3)	n.a.	1.32 (0.33 to 5.24)	0.692	2
Need some assistance, n (%)	196 (62.8)	139 (59.1)	57 (74.0)	n.a.	1.97 (1.11 to 3.49)	0.019	2
Dependent, n (%)	106 (34.0)	89 (37.9)	17 (22.1)	n.a.	0.47 (0.26 to 0.85)	0.011	2
Global Deterioration Scale (GDS)							
GDS 1, n (%)	158 (50.6)	117 (49.8)	41 (53.2)	n.a.	1.15 (0.69 to 1.92)	0.598	2
GDS 2, n (%)	55 (17.6)	40 (17.0)	15 (19.5)	n.a.	1.18 (0.61 to 2.28)	0.623	2
GDS 3, n (%)	19 (6.1)	14 (6.0)	5 (6.5)	n.a.	1.10 (0.38 to 3.15)	0.864	2
GDS 4, n (%)	18 (5.8)	13 (5.5)	5 (6.5)	n.a.	1.19 (0.41 to 3.44)	0.753	2
GDS 5, n (%)	31 (9.9)	26 (11.1)	5 (6.5)	n.a.	0.56 (0.21 to 1.51)	0.245	2
GDS 6, n (%)	21 (6.7)	17 (7.2)	4 (5.2)	n.a.	0.70 (0.23 to 2.16)	0.535	2
GDS 7, n (%)	10 (3.2)	8 (3.4)	2 (2.6)	n.a.	0.76 (0.16 to 3.64)	0.727	2
Other skin conditions							
Skin tears, n (%)	33 (10.6)	21 (8.9)	12 (15.6)	n.a.	1.89 (0.88 to 4.03)	0.100	2
Incontinence-associated dermatitis, n (%)	59 (18.9)	44 (18.7)	15 (19.5)	n.a.	1.05 (0.55 to 2.02)	0.883	2
Pressure ulcer, n (%)	25 (8.0)	18 (7.7)	7 (9.1)	n.a.	1.21 (0.48 to 3.01)	0.688	2
Pressure ulcer at any foot, n (%)	4 (1.3)	2 (0.9)	2 (2.6)	n.a.	3.1 (0.43 to 22.44)	0.237	2
Pressure ulcer at sacral area, n (%)	19 (6.1)	14 (6.0)	5 (6.5)	n.a.	1.10 (0.38 to 3.15)	0.864	2
Intertrigo, n (%)	108 (34.6)	73 (31.1)	35 (45.5)	n.a.	1.85 (1.09 to 3.13)	0.021	2
Most frequent medication							
Diuretics, n (%)	169 (54.2)	126 (53.6)	43 (55.8)	n.a.	1.09 (0.65 to 1.84)	0.734	2
Antithrombotic medication, n (%)	197 (63.1)	144 (61.3)	53 (68.8)	n.a.	1.40 (0.81 to 2.42)	0.233	2
Beta-Adreno- receptor antagonists, n (%)	172 (55.1)	131 (5.7)	41 (53.2)	n.a.	0.90 (0.54 to 1.52)	0.702	2
Medication influencing the renin-angiotensin system, n (%)	161 (51.6)	118 (50.2)	43 (55.8)	n.a.	1.25 (0.75 to 2.10)	0.391	2
Analgesic, n (%)	131 (42.0)	99 (42.1)	32 (41.6)	n.a.	0.98 (0.58 to 1.65)	0.930	2
Psychoanaleptics, n (%)	144 (46.2)	115 (48.9)	29 (37.7)	n.a.	0.63 (0.37 to 1.07)	0.085	2
Cortisone intake, n (%)	14 (4.5)	10 (4.3)	4 (5.2)	n.a.	1.23 (0.38 to 4.05)	0.730	2
Polypharmacy (≥ 5 medications), n (%)	272 (87.2)	202 (86.0)	70 (90.9)	n.a.	1.63 (0.69 to 3.86)	0.259	2
Application of moisturizers							
Once to three times daily, n (%)	66 (23.7)	55 (26.3)	11 (15.9)	n.a.	0.53 (0.26 to 1.09)	0.079	34
Once per week or more rarely, n (%)	174 (62.6)	126 (60.3)	48 (69.6)	n.a.	1.51 (0.84 to 2.70)	0.167	34
Showering/bathing frequency							
Once per week or more rarely, n (%)	263 (95.3)	200 (97.1)	63 (90.0)	n.a.	0.27 (0.09 to 0.83)	0.016	36

Table 5
Association between being dependent in 'skin self-care' and receiving moisturizers on the legs/feet.

	Total (n = 279)	Once to three times per week or more rarely (n = 66)	Once to three times daily (n = 213)	Odds Ratio (95% CI)	p-value	Missing, n
Dependent on 'skin care', n (%)	96 (34.4)	62 (29.1)	34 (51.5)	2.59 (1.47 to 4.56)	< 0.001	35

very mild forms of skin dryness might have been perceived as no xerosis. This categorization may have affected the results of the group comparisons. Due to the cross-sectional design, causal relationships between the severity of dryness and the associated factors cannot be made.

Interpretation

Almost every older resident was affected by some form of dry skin, a finding which has been supported by previous research.[3,4,47] In contrast, some other studies in this setting reported lower proportions (41.2 to 52.6%) of participants with dry skin.[1,2] In these studies nurses conducted structured skin assessments which may indicate that, compared to dermatologists, nurses might have overlooked the early signs of xerosis cutis.[30] Although this phenomenon is relevant to nursing[48] and the concept of 'dry skin' is for example, listed as a defining characteristic for skin integrity in the latest NANDA International Nursing Diagnoses,[49] there seems to be no particular focus on dry skin in nursing practice.[50,51]

Moderate to severe/extreme xerosis was mainly located on the arms, legs and the feet. This is similar to previous studies which showed that the presence and severity of xerosis is most prevalent at distal extremities; arms and legs are more affected by xerosis than the skin of face or trunk.[1,2,4] The presence of fewer sebaceous glands on the lower legs, feet and forearms might be one reason why these body sites are usually more frequently affected by xerosis.[7] Other less likely explanations include that declines in physical activities with aging decrease the blood supply, leading to reduced stratum corneum hydration.[4]

Several studies showed associations between dry skin and demographic characteristics,[1-5,52] health conditions,[2-5,52] various skin diseases,[3,5,52,53] medical treatments,[52] functional abilities,[2,4] nutrition[4] and skin care practices[1] in nursing homes,[1-4] hospitals,[2,4] primary care,[52] and other settings.[5,53] However, limited information is available concerning factors associated with different severities of xerosis cutis in the older adults. Paul et al., 2011 reported skin dryness appeared to be more severe in older patients in primary care facilities.[52] Our results seem to support this finding that more severe dry skin is observed in older nursing home residents. However, overall group comparisons indicate that there were negligible group differences regarding demographic and health characteristics. Dry skin etiology and pathogenesis is a complex process and closely associated with skin aging.[54] This also seems to be independent from other skin conditions relevant for nursing practice including incontinence-associated dermatitis, skin tears, pressure ulcers and intertrigo.[30]

Participants with moderate to severe xerosis on the legs had lower SCH and a slightly higher skin surface pH. These results support the internal validity of this study, because the more clinically severe the dry skin, the less the SCH. There is substantial evidence supporting that application of moisturizers decrease signs of dry skin and increase the SCH.[16,55,56] Dry skin is closely associated with impaired skin barrier function leading to a higher pH.[10] In the so called 'senile xerosis', lower amount of carboxylates e.g., lactate and pyrrolidone carboxylic acid results into increased pH.[57,58] This is in line with our findings (a higher skin pH in severe forms of dryness). TEWL was slightly lower in the more severe dry skin group. In comparison to younger participants, older adult participants show lower values for TEWL at leg skin areas.[11] However, in diseased skin, TEWL is increased due to defective barrier function and the defective water retention capacity in the SC reveals lower water content.[59] The results of these two parameters usually show an inverse relationship in diseased skin e.g., in pathologically dry skin. On the other hand, dry skin in older adult participants seems to be different from pathologically dry skin.[60]

In the present study, we focused on the frequency of the moisturizer application. The study results indicate, the drier the skin, the less frequently the application of moisturizers took place. This strongly points out the under-application in participants with severe dry skin (mostly once per week or more rarely). A possible under-application was also reported by Lechner et al., 2019 suggesting that residents do not get adequate moisturizers and quantity they require.[1] Our participants, who showered/bathed only once per week or more rarely seemed to had less dryness. Dry skin can worsen if management (use of moisturizers or frequency of bathing) is inappropriate.[61] For prevention and management of dry skin and further complication, skin should not be cleansed daily.[62] Our results also suggest that, participants, who were more dependent on the care providers in terms of functional abilities or skin self-care, were likely to receive moisturizers on a daily basis (others seemed to receive two to three times per week or in more rare frequencies) and had less severe dryness on the legs and the feet. In other words, they had lower prevalence of moderate to extreme skin dryness. Moisturizer use was higher in the (skin) care dependent residents. This is also supported by the result from Lechner et al., as they reported skincare-dependent participants to be more affected by a mild form of xerosis (24.1%) than the moderate to severe form of xerosis (15.5%) on the legs and feet.[1] The present study confirms the occurrences in similar proportions, 35.8% for 'no xerosis to slight xerosis' group and 25.0% for 'moderate to severe xerosis' group, regarding the skin dryness on the legs.

The role of healthcare professionals is becoming more and more important in the skin care of the older adults.[63] Our results indicate that, application of moisturizers done by professional caregivers in adequate frequency, seems to be helpful regarding dry skin severity in the residents living in nursing homes. This might also help regarding prevention of further severe skin damages like skin tears.[23] However, considering the consistent high prevalence of xerosis cutis (of all severity grades) across the long-term care institutions, in-depth research regarding the effects and possible side-effects of the used moisturizers should be carried out.

Generalizability

Selection bias was reduced by randomly choosing nursing homes from a list of all available nursing homes in the region. Detailed information on the generalizability regarding demography, functional impairment, care dependency, etc. have been published elsewhere.[30] The sample characteristics are comparable with the skilled nursing facilities in the US, in terms of health characteristics and cognitive status.[64,65] Considering the long-term care provided, including dressing, nutrition, taking care of personal hygiene, rehabilitation, wound

care, skin care and maintaining psychosocial well-being, the included nursing homes are also comparable to the similar facilities in the US.[66]

Conclusion

Results from the current study indicate that nearly every resident living in long-term care institutions was affected by xerosis cutis, with severe forms of dryness being more prevalent at distal body areas. Participants being dependent on care-givers regarding (skin) care were likely to have less severe forms of dryness (no xerosis to slight xerosis) on the legs and feet. Participants in this group also received application of moisturizers more frequently than the others. Considering the severity of dry skin, care provided by the nurses seemed to be more helpful compared to skin care done independently. Comprehensive whole body examinations, as well as individually tailored evidence based skin care provided by nurses or other care providers, can improve the prevention and treatment of xerosis cutis in nursing home residents in long-term care facilities. Awareness of the necessity and application frequency of moisturizers among the residents who perform skin care independently, might also play a role in improving dry skin condition.

Trial registration information

ClinicalTrials.gov Identifier: NCT03824886, registration date: 31st January 2019

Ethical approval information

Charité - Universitätsmedizin Berlin (ethics application number EA1/243/18)

Declaration of Competing Interest

None.

CRediT authorship contribution statement

Ruhul Amin: Writing – original draft, Data curation, Formal analysis, Writing – review & editing, Visualization. **Bettina Völzer:** Validation, Investigation, Data curation, Visualization, Formal analysis, Writing – review & editing. **Monira El Genedy-Kalyoncu:** Investigation, Data curation, Writing – review & editing, Project administration. **Ulrike Blume-Peytavi:** Conceptualization, Resources, Writing – review & editing, Supervision. **Jan Kottner:** Conceptualization, Methodology, Investigation, Resources, Writing – review & editing, Supervision, Project administration, Funding acquisition.

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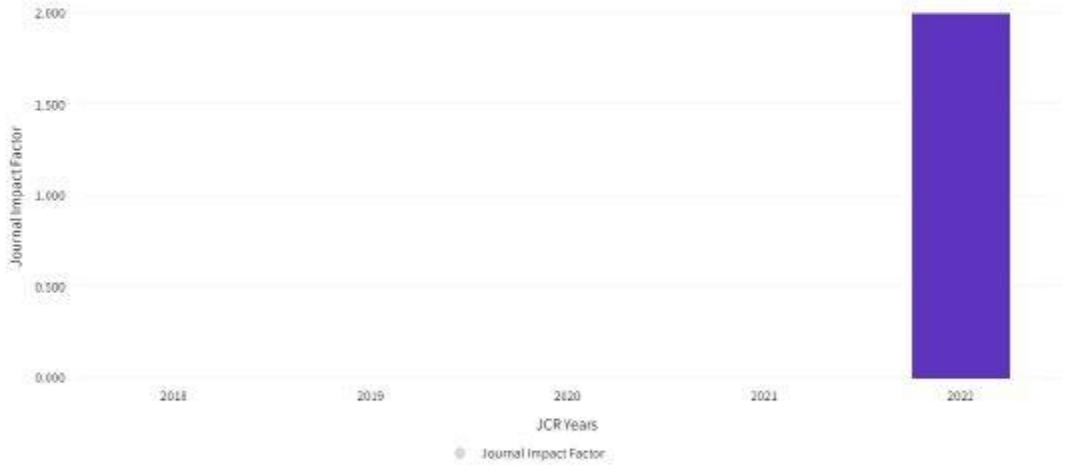

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ORIGINAL RESEARCH

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Effects of a leave-on product on the strength of the dermoepidermal junction: An exploratory, intraindividual, randomized controlled trial in older adults with dry skin

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Abstract

Background and Aims: Skin aging is associated with dry skin and a decrease of the strength of the dermoepidermal adhesion, which increases the risk for lacerations (skin tears). Application of leave-on products improves dry skin and seems to reduce skin tear incidence. The aim of this study was to measure the effects of a humectant containing leave-on product on the strength of the dermoepidermal junction in older adult participants with dry skin.

Methods: A randomized controlled trial using a split body design was conducted. One forearm was randomly selected and treated with a lipophilic leave-on product containing 5% urea for 8 weeks. The other forearm was the control. The parameters stratum corneum hydration (SCH), transepidermal water loss, pH, roughness, epidermal thickness and skin stiffness were measured at the baseline, Weeks 4 and 8. At Week 8, suction blisters were created and time to blistering was measured. Blister roofs and interstitial fluid were analyzed for Interleukin-1α, 6 and 8.

Results: Twelve participants were included. After 8 weeks treatment, SCH was higher (median difference 11.6 AU), and the overall dry skin score (median difference −1) and median roughness (Rz difference −12.2 µm) were lower compared to the control arms. The median group difference for Interleukin-1α was −452 fg/µg total protein (TP) in the blister roofs and −2.2 fg/µg TP in the blister fluids. The median time to blister formation was 7.7 min higher compared to the control arms.

Conclusion: The regular application of humectant containing leave-on products improves dry skin and seems to lower inflammation and contribute to the strengthening of the dermoepidermal adhesion. This partly explains how the use of topical leave-on products helps to prevent skin tears.

KEYWORDS

dermoepidermal junction, dry skin, older adults, senile xerosis, suction blister

Trial registration: German Clinical Trials Register ID: DRKS00031151.

1 | INTRODUCTION

Aging is associated with physiological and morphological changes of the skin, increasing the susceptibility to many dermatological conditions and skin injuries.[1] Dry skin (xerosis cutis) is associated with intrinsic aging and prevalence estimates in older adults range between 41.2 and 99.1%.[2-6] The prevalence of skin dryness increases with increasing age.[7] In xerosis cutis, decreased stratum corneum hydration (SCH),[8] increased pH,[9,10] increased roughness, decreased elasticity,[7] possible subclinical inflammation[11] and altered molecular markers[12] have been reported. Dry skin related pruritus might affect patients' quality of life.[13] Scratching can lead to painful wounds.[14] There are various visual analogue scales and scoring systems to assess the severity of skin dryness. One widely used system, described by the European Group on Efficacy Measurement of Cosmetics and other Topical Products, is the "overall dry skin score" (ODS) where the severity of dryness is evaluated from "slight" to "extreme" xerosis.[15,16]

Ageing related changes also affect the dermoepidermal junction (DEJ). DEJ is an anchoring system formed by interdigitation of epidermal protrusions downward into the dermis and dermal papilla projections upward into the epidermis.[17] In older adults, DEJ is gradually disorganized, epidermal protrusions and dermal papillae are reduced,[18] which lead to significant thinning and flattening of DEJ and resulting in increased fragility.[19-21] Though a direct relationship between a fragile DEJ and skin tears has not been established in clinical research, in-vitro studies show DEJ damage by inflammatory cytokines and subsequent formation of skin tears.[22] Interestingly, skin dryness is also one of the strongest predictors of skin tear development[23] and the risk factor is considered modifiable.[24] Especially in care dependent populations the skin tear prevalence is up to 22%.[5,25,26] For measuring the strength of DEJ adhesion in clinical research, suction blistering can be used.[20,27] Suction blistering is an artificial and controlled technique[28,29] and is widely used in dermatology, for example, for studying wounds or epidermal grafting.[30,31] A constant negative pressure (suction) is applied on the skin surface, and after time sub-epidermal vesicles arise and eventually coalesce to form a single cavity filled with interstitial fluid, as the complete dermoepidermal separation along the DEJ occurs.[32] The parameter "time to blistering" was suggested as a clinically relevant outcome, which reflects the resistance and mechanical integrity of DEJ.[20,27,33]

Basic leave-on products are helpful in decreasing skin dryness, improving skin barrier function, as well as reducing the risk of skin tear development in the older adults.[34,35] Humectants in combination with basic leave-on products are effective in this regard and any effect on the skin is due to the total composition of the product.[36] Urea is widely accepted as a potent humectant and is one of the most extensively studied product ingredient for the treatment of dry skin,[7] which was found to improve hydration, barrier function, to reduce transepidermal water loss (TEWL), skin pH[37,38] and roughness.[39] Urea added to lipophilic leave-on products was associated with stronger hydrating effect.[40] Products containing 5% urea are considered tolerable on moderately scaly skin.[7] Previously we have shown, that the application of petrolatum in skin healthy older people improved DEJ adhesion.[33] Since dry skin is one prognostic factor for skin tear development,[23] we hypothesized that the effect might be stronger in dry skin; in terms of increased DEJ adhesion and subsequent reduction of the risk of skin tears. Thus, the main aim of this study was to investigate the effects of a 5% urea containing leave-on product on the adhesion of the DEJ in older adult participants with dry skin.

2 | METHODS

2.1 | Trial design

An exploratory, within person randomized controlled trial was conducted from January to April 2023 at the Clinical Research Center for Hair and Skin Science (CRC) at Charité - Universitätsmedizin Berlin, Germany (German Clinical Trials Register ID: DRKS00031151, registration date: 30 January 2023).[41] Using a split-body design, the volar surface of one forearm of the participants was randomly selected for applying a leave-on product. The other forearm was considered as control arm on which no product was used for the entire trial period. The study was approved by the ethics committee of Charité - Universitätsmedizin Berlin (application number: EA1/228/22, date of approval: December 12, 2022). No changes were made after the commencement of the study.

2.2 | Participants

Inclusion criteria were 65–85 years old males or females, having skin phototype I–III according to the Fitzpatrick classification, body mass index between 20 and 30 kg/m^2, nonsmoker since at least 1 year and provided written informed consent. Eligibility criteria for the body sites were slight to moderate skin dryness (ODS category 1–2) on the volar surface of the forearms according to the ODS system,[15] absence of skin diseases and lesions including atopic dermatitis, urticaria, psoriasis, scars, wounds or tattoos on the investigational skin areas. Major exclusion criteria were severe or extreme dryness (ODS category 3 or 4) on the skin area of interest, diabetes mellitus, unstable chronic condition, current skin malignancy, known defect of healing, use of anti-inflammatory drugs, retinoids, etc on the forearms within the past 4 weeks, hormone replacement therapy within last 3 months and any known allergy to the compounds of the investigational product and band-aids.

2.3 | Intervention

The study participants applied a 5% urea containing lipophilic product (Lipophile Harnstoff-Creme 5% NRF 11.129; containing urea, (S)-lactic acid, sodium-(S)-lactate and hydrophobic base cream

DAC) which was prepared by the hospital pharmacy. The study personnel demonstrated application of the product and the recommended amount (two-fingertip units, approximately equivalent to 1 g). The participants were instructed to apply the product to the selected intervention forearm twice daily (in the morning and evening) at home for 8 weeks; after washing, showering or before going to sleep. To assess adherence to the intervention, study personnel checked participants' diaries during visits. The product bottles were also weighed at Weeks 4 and 8. The participants were asked not to apply any other leave-on product and not to change their currently used cleansing product. The other forearm remained untreated (control arm), hence use of any leave-on product on the control arm was not allowed. No placebo group was used because we did not intend to measure the effect of urea as an active ingredient, but rather the effect of topical application of a hydrating leave-on product. Furthermore, the participants were requested not to have physical therapies (e.g., massages, laser applications) or strong natural or medical UV-exposure on the forearms. Intake of systemic anti-inflammatory drugs, retinoids, vitamin C, vitamin A derivatives more than five consecutive days was also discouraged while participating in the study.

2.4 | Outcomes

Due to the exploratory nature of the study, no distinction was made between primary and secondary outcomes. No change regarding the trial outcomes was made after commencement of the trial. Outcomes for both the treatment and control skin areas were the blistering time, SCH, TEWL, skin surface pH, skin structural parameters (ODS, Rz, epidermal thickness, stiffness) and molecular markers Interleukin-1α (IL-1α), 6 (IL-6), and 8 (IL-8). The occurrence of adverse events was monitored during the study period on participant's reporting and diary entries and was rated based on their intensity and causal relationship to the intervention.

2.4.1 | Time to blistering

"Time to blistering" (minutes) was defined as (a) time to first vesicles (from the start of suction pressure until the appearance of first macroscopically visible vesicles), (b) time to full blister (from the start of suction pressure until the development of a full blister). Suction blisters were raised at Week 8 (end of treatment). Room temperature ranged from 20 to 24°C and relative humidity from 40 to 60%. Skin areas were marked on similar locations on the right forearm (A, B, and C) and the left forearm (D, E, and F), and the inter-area distances were recorded. Hairy skin areas were avoided. Participant's forearms were positioned comfortably on arm supports of examination chairs and the skin areas were disinfected. A styrofoam block served as a stable housing for six upside-down positioned syringe barrels, assembled with tubes connected to a vacuum pump (MEDAP BORA UP 2080, FALK MedizinTechnik). Upon starting the vacuum pump, the syringe bases (8 mm in diameter) were simultaneously placed on the skin areas in the same direction, and the initiation time of the blistering process was recorded. Vesicle formation was continuously and closely monitored and duration was recorded. When a blister was fully formed, the corresponding tube was closed to halt negative pressure, and the time was noted. Upon completion, the syringe barrels were removed, and the blister fluids (from three blisters on each side) as well as the blister roofs (two on each side; A and B, D, and E) were collected and stored at −80°C for subsequent laboratory analysis. Vaseline and band-aids were applied on the wounds. Successful wound healing was checked after 2 weeks.

2.4.2 | Skin barrier parameters

SCH, TEWL and skin surface pH were measured by using Corneometer CM 825, Tewameter TM 300, and Skin-PH-meter pH 905 (Courage + Khazaka electronic GmbH). SCH was measured in arbitrary units (AU) and ranges from 0 to 120; where higher value indicate higher SCH.[42] The measuring probe for TEWL detects the continuous permeation of water through a defined surface of the SC per unit time and is expressed as grams per square meter per hour ($g/m^2/h$).[43] Skin surface pH is expressed as the concentration of the hydrogen ion detected by the pH measuring electrode due to the extraction of water soluble constituents from the skin surface.[44] The reliability of the above-mentioned measurements was supported in previous studies.[45,46] Measurements were performed in duplicate on the upper part of the volar forearms. SCH and TEWL measurements were conducted at baseline as well as at Weeks 4 and 8, while pH measurement was done at baseline and Week 8. The participants were instructed not to bath, sauna or apply products locally 12 h before the measurements and also not to drink caffeinated beverages 3 h beforehand. Before the measurements, the participants were acclimatized for 30 min in a room temperature adjusted to 22 ± 2°C and a relative humidity to 50% (±10).

2.4.3 | Clinical and structural parameters

ODS categories included no skin dryness (category 0), faint scaling, faint roughness and dull appearance (category 1), small scales with few larger ones, along with roughness and whitish appearance (category 2), small and larger scales uniformly distributed with definite roughness with a few superficial cracks and possible slight redness (category 3) and large scales, advanced roughness, redness, eczematous changes and cracks (category 4).[15] ODS of the forearms was evaluated by visual examination at baseline, at Weeks 4 and 8 by an investigator who was blinded to the treatment allocation.

Mean roughness was measured as Rz using the Visioscan VC 98 USB (Courage & Khazaka) which assesses the grayscale photograph of the epidermis surface.[47,48] Rz is expressed in μm as arithmetic mean of the maximum peak-to-valley height of five successive sections of the sampling line of the skin surface.

Epidermal thickness (ET) was measured by optical coherence tomography (OCT) using the OCT imaging system from Thorlabs, Germany according to standard operating procedures. Images were analyzed using the ImageJ software.[49] ET was expressed in micrometer (μm). Structural skin stiffness was measured with the Cutometer MPA 580 (Courage & Khazaka) following standard operating procedures. The measuring probe (2 mm in diameter) was placed on the skin surface and by means of a defined intake pressure (450 mbar), skin surface was pulled into the probe (suction on, for 2 s) and released again (suction off, for 2 s) for five repetitions, evaluating the maximum extensibility, Uf (in mm).[50,51]

2.4.4 | Molecular inflammatory markers

IL-1α, IL-6 and IL-8 were analyzed from the epidermal blister roofs and the interstitial fluid samples. Blister roofs were cut into small pieces, incubated with extraction buffer (100 mM Tris, pH 7.4; 150 mM NaCL, 1% Triton-X-100, 1 mM EDTA) and then sonicated in ice-water to extract the analytes. Blister fluid diluted in assay buffer was used for analysis. Total protein (TP) measurement was done in triplicates by colorimetric method using Pierce™ 660 nm Protein assay reagent from Thermo Scientific™, Rockfeld. The ILs were quantified in duplicates using commercial kits for specific enzyme-linked immunosorbent assay (ELISA) (Human IL-1 alpha/IL-1F1 DuoSet ELISA from R&D Systems, Minneapolis, USA; Human IL-6 and IL-8 CytoSet™ from Invitrogen by Thermo Fisher Scientific and Bender Medsystems GmbH) according to the manufacturer's protocols. Absorbance was measured with EnSpireTM multilabel reader (Perkin Eimer Singapore Pte. Ltd., Singapore). TP values were expressed as μg/mL. The concentrations of the inflammatory markers were calculated from the standard curve (pg/mL) and normalized by dividing the values by the concentration of TP of the corresponding sample. The normalized values were expressed as fg/μg TP.

2.5 | Sample size

Due to the explorative character of the study, a formal sample size estimation was not performed. Following the recommendation by Julious et al. regarding pilot studies,[52] it was planned to include 12 participants.

2.6 | Randomization and blinding

There was a concealed random allocation of the treatment arms. A simple computer generated randomization table having 1:1 allocation left versus right was created by a statistician not involved in the study conduct. Sequentially numbered, opaque, sealed envelopes containing the allocation were prepared and opened after confirming eligibility, inclusion and baseline skin measurements. The treatment allocation procedure, product dispensation and instructions for use was performed by a study nurse independently from the investigators. Due to the nature of the intervention, blinding of the participants was not possible. The investigators and outcome assessors were blinded throughout the study. Participants were requested not to reveal any information regarding the allocation of the treatment arm during clinical assessments and skin measurements.

2.7 | Statistical analysis

Participant characteristics were described using mean and spread estimates. Comparisons between intervention and treatment arms were done descriptively using parametric (mean, standard deviation) and nonparametric (median, 25%–75% interquartile ranges; IQR) statistics and group differences were presented. Because of the exploratory design of the trial, statistical hypothesis testing was not conducted. However, *p* values based on Wilcoxon signed-rank tests (related-samples, 2-sided test) between the treatment and control arms were provided, considering all *p* values to be descriptive. Calculations were performed by using IBM SPSS Statistics for Windows, version 29 (IBM Corp.).

3 | RESULTS

3.1 | Participant flow

Thirteen participants were screened for eligibility whereas one subject was excluded for not meeting inclusion criteria. Twelve participants were included in the study. For all included participants, one forearm was randomly allocated for intervention while the other forearm was considered as control arm. All participants adhered to the study protocol, wrote regular diary entries and completed all the study visits. A participant flow diagram is shown in Figure 1.

3.2 | Recruitment

Recruitment took place between January and February 2023. By April 2023, all participants had completed the final visits.

3.3 | Baseline data

Mean age of the participants was 77.9 (SD 5.6) years, with a mean BMI of 24.7 (SD 2.4) kg/m^2. Most of them had skin phototype II according to Fitzpatrick scale. Participant characteristics in detail are shown in Supporting Information: Table 1.

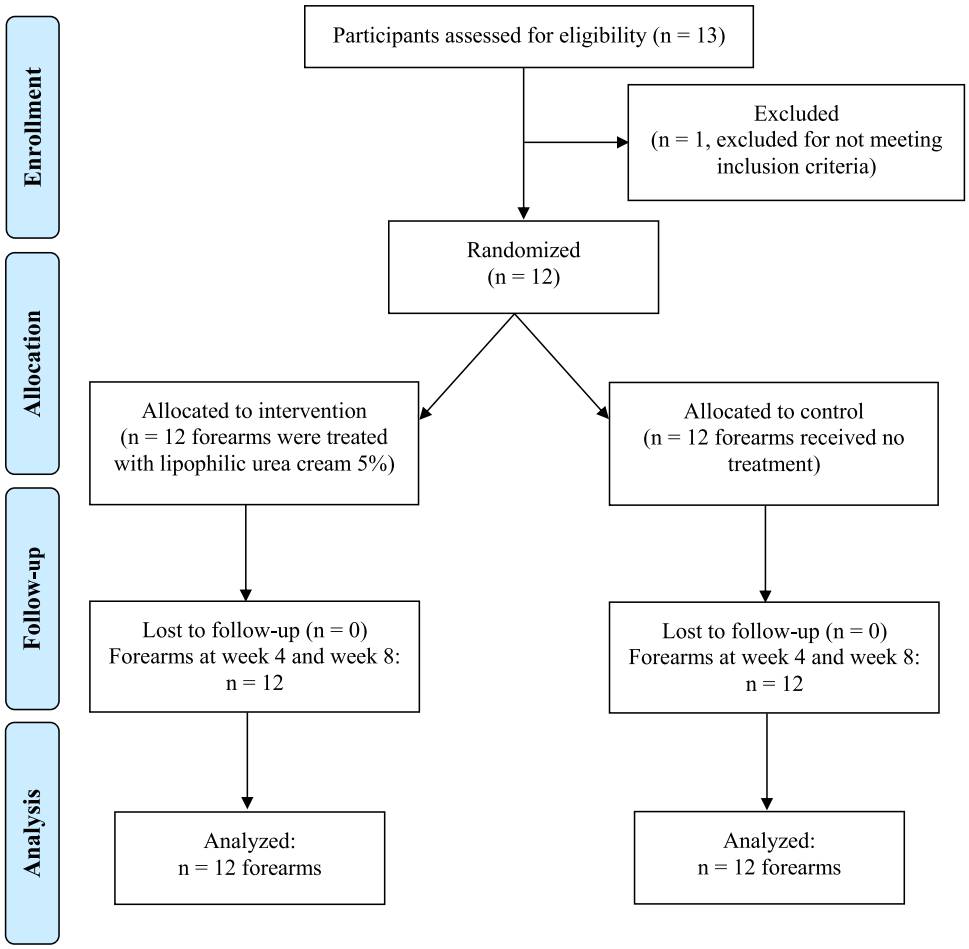

FIGURE 1 Flow diagram outlining the participant flow during the study.

3.4 | Outcomes and estimation

The results for time to blistering, skin barrier characteristics and clinical and structural parameters are shown in Table 1. "Time to first vesicles" and "time to full blister" for the treatment forearms was longer compared to the control forearms (median difference 2.3 min and 7.7 min, respectively).

At baseline, SCH, TEWL and pH values were similar between groups. At Weeks 4 and 8, SCH in the intervention group was higher, with a median difference of 11.6 AU at Week 8. At Weeks 4 and 8 TEWL was lower with a median difference of −2.8 g/m^2/h at Week 8. pH values were also lower in the treatment group at Week 8 (median difference −0.14).

Baseline ODS was similar in both groups. At Weeks 4 and 8, the median ODS was one point lower in the intervention group. At Week 8, the median roughness (Rz) was 12.2 µm lower in the intervention group. Median ET and Uf were slightly higher in the intervention group at Week 8.

Table 2 displays the results of the molecular markers analyzed at Week 8. There were small differences in the amount of TP measured in the samples from different participants and no differences were measured between treatment and control arms. Concentration of IL-1α were measured in the blister roofs in pg and in blister fluids in fg range. IL-1α was lower in treatment arms in the blister roofs and fluid samples (median difference −452.4 and −2.2 fg/µg TP, respectively). For IL-6 and 8, lower concentrations were measured which were close to the lower sensitivity limit of the assay. Group differences between IL-6 and IL-8 were minor. The difference in molecular inflammatory markers between men and women from the intervention arm are presented in Supporting Information: Table 2.

3.5 | Harms

No harms or unintended effects were observed. The wounds created by suction blistering process healed and there was no remarkable difference in wound healing between the intervention and control arm.

4 | DISCUSSION

4.1 | Interpretation

The overall aim of this study was to investigate the effects of a urea containing lipophilic leave-on product on the strength of the dermoepidermal adhesion in older adults with dry skin. Time to

TABLE 1 Time to blistering, skin barrier characteristics, clinical, and structural parameters.

		Intervention	Control	Difference
Time to first vesicles (min)				
	Mean (SD)	52.8 (26.8)	50.1 (23.7)	2.7 (9.4)
	Median (IQR)	47.3 (37.0–58.9)	46.5 (34.1–54.7)	2.3 (−5.4 to 9.0), $p = 0.27$
Time to full blister (min)				
	Mean (SD)	88.7 (25.1)	82.8 (24.0)	5.9 (11.4)
	Median (IQR)	83.8 (71.2–99.0)	77.3 (70.8–89.8)	7.7 (−1.7 to 12.2), $p = 0.07$
Stratum corneum hydration (AU)				
Baseline (Week 0)	Mean (SD)	35.5 (8.7)	35.4 (7.7)	0.1 (5.5)
	Median (IQR)	36.3 (26.9–45.5)	36.3 (29.8–41.3)	2.5 (−5.4 to 4.7)
Week 4	Mean (SD)	49.2 (10.4)	32.6 (7.1)	16.6 (9.5)
	Median (IQR)	46.7 (42.1–56.9)	35 (26.4–36.5)	20.1 (7.1–25.6), $p = 0.002$
Week 8	Mean (SD)	45.3 (7.1)	32.6 (4.2)	12.7 (6.0)
	Median (IQR)	45.1 (40.3–48.8)	33.0 (29.6–34.4)	11.6 (9.1–15.1), $p = 0.002$
Transepidermal water loss ($g/m^2/h$)				
Baseline (Week 0)	Mean (SD)	7.7 (2.1)	7.5 (1.8)	0.2 (2.0)
	Median (IQR)	7.8 (5.7–8.4)	7.6 (5.8–9.5)	0.2 (−1.4 to 1.5)
Week 4	Mean (SD)	7.4 (5.0)	7.8 (1.8)	−0.4 (3.8)
	Median (IQR)	7.0 (4.3-7.7)	7.6 (6.7-8.8)	−1.3 (−2.3 to 0.2), $p = 0.12$
Week 8	Mean (SD)	5.6 (1.1)	8.3 (1.4)	−2.7 (1.5)
	Median (IQR)	6.0 (4.3–6.4)	8.3 (7.4–8.6)	−2.8 (−3.7 to −1.3), $p = 0.002$
Skin surface pH				
Baseline (Week 0)	Mean (SD)	5.43 (0.58)	5.36 (0.64)	0.07 (0.31)
	Median (IQR)	5.55 (4.90–5.97)	5.47 (4.47–5.97)	−0.01 (−0.12 to 0.27)
Week 8	Mean (SD)	5.38 (0.50)	5.54 (0.60)	−0.15 (0.33)
	Median (IQR)	5.41 (5.13–5.79)	5.71 (5.03–6.01)	−0.14 (−0.22 to 0.04), $p = 0.06$
Overall dry skin score				
Baseline (Week 0)	Mean (SD)	1.0 (0.4)	1.1 (0.3)	−0.1 (0.3)
	Median (IQR)	1.0 (1.0–1.0)	1.0 (1.0–1.0)	0.0 (0.0–0.0)
Week 4	Mean (SD)	0.1 (0.3)	0.8 (0.6)	−0.8 (0.5)
	Median (IQR)	0.0 (0.0–0.0)	1.0 (0.3–1.0)	−1.0 (−1.0 to −0.3), $p = 0.003$
Week 8	Mean (SD)	0.1 (0.3)	0.7 (0.5)	−0.6 (0.7)
	Median (IQR)	0.0 (0.0–0.0)	1.0 (0.0–1.0)	−1.0 (−1.0 to 0.0), $p = 0.02$
Mean roughness (Rz in µm)				
Baseline (Week 0)	Mean (SD)	51.2 (11.0)	46.7 (9.9)	4.5 (9.7)
	Median (IQR)	49.5 (42.8–57.3)	43.2 (40.8–53.8)	7.2 (−0.6 to 9.2)
Week 8	Mean (SD)	47.9 (7.0)	50.0 (8.2)	−7.1 (11.1)
	Median (IQR)	47.7 (41.4–53.2)	54.9 (47.1–59.3)	−12.2 (−15.8 to 4), $p = 0.04$

TABLE 1 (Continued)

		Intervention	Control	Difference
Epidermal Thickness (μm)				
Baseline (Week 0)	Mean (SD)	88.2 (11.6)	97.1 (13.0)	−8.9 (14.9)
	Median (IQR)	87.0 (77.7–96.4)	94.8 (89.3–107.5)	−7.0 (−16.5 to 1.2)
Week 8	Mean (SD)	101.6 (15.7)	92.6 (15.3)	9.0 (15.7)
	Median (IQR)	96.1 (90.4–110.8)	87.4 (81.4–105.2)	8.4 (−2.5 to 25.9), $p = 0.07$
Skin stiffness (Uf in mm)				
Baseline (Week 0)	Mean (SD)	0.273 (0.028)	0.294 (0.028)	−0.022 (0.027)
	Median (IQR)	0.279 (0.256–0.290)	0.291 (0.256–0.290)	−0.023 (−0.049 to −0.000)
Week 8	Mean (SD)	0.295 (0.037)	0.283 (0.036)	0.011 (0.030)
	Median (IQR)	0.296 (0.275–0.320)	0.284 (0.250–0.314)	0.008 (−0.017 to 0.037), $p = 0.27$

Abbreviations: AU, arbitrary units; IQR, interquartile ranges.

blistering in the treatment arm was longer compared to the control arm. Especially "time to full blister" (median difference 7.7 min) was similar to the results reported by El Genedy-Kalyoncu et. al.[33] in a slightly different sample and after a slightly different treatment. This suggests that the application of a topical leave-on product increases the dermoepidermal adhesion in older adults.

Results further indicate that the treatment decreased skin dryness in terms of clinical, functional and structural parameters. Baseline SCH and TEWL values are comparable with results in similar populations.[9,37,53,54] Especially the substantially higher SCH in the intervention group indicates the well-known hydrating effects of topical leave-on products containing urea.[37,39,55,56] However, how exactly the treatment may influence dermoepidermal adhesion, is not fully understood. Urea regulates epidermal proliferation[57] and was found to enhance filaggrin (FLG) expression.[37] Previous reports on relative gene expression in the suction blister roof showed that application of urea containing formulation resulted in upregulation of genes like loricrin (LOR) and FLG, which are involved in skin cell differentiation and barrier function.[55,58] LOR was found to be enriched in skin areas where the interdigitation of the epidermis and dermis are more prominent[59] which is a characteristic of healthy DEJ. However, because the difference in time to blistering was observed previously by treating with petrolatum only, the overall physiological and structural changes caused by application of leave-on products may also induce changes in the underlying epidermal tissue and the DEJ, hence improving the resistance against mechanical loads.

Values of skin surface pH in our sample are also comparable to previous studies.[9,37,53,54] As urea enhance FLG biosynthesis, increased natural moisturizing factors (NMFs) in SC due to catabolic degradation of FLG into NMFs components contributes to the maintenance of skin's acidic pH.[60] Beside reducing dryness, topical application of urea containing products exert keratolytic effect, facilitating the removal of top layer of dry skin and improves the dry and rough texture,[39] which might also have contributed the reduction of ODS in the treatment arm in our study. Similar to our study, improvement in Rz parameter have also been reported in studies involving leave-on product use.[61,62] ET measurements were also comparable with previously reported results[63,64] and there were no difference after the treatment.[33] Previous studies reported improvements in the structural stiffness (Uf) in young participants by using topical formulations.[65] Stiffness is mainly influenced by stretching of the collagen and elastic fiber networks.[66] This dermal network, which provides mechanical support also for the epidermis[67] and therefore, may also influence epidermal stiffness, degenerates with intrinsic aging[68] and our results seems to indicate that 8 weeks topical treatment has no effect.

IL-1α, a proinflammatory cytokine capable of inducing neutrophil and macrophage recruitment, is accounted for the vast majority of epidermal-associated IL-1 activity.[69] Overexpression of IL-1α is positively correlated with reduced SCH as well as symptom exacerbation in many skin diseases.[70,71] Our result suggest that, the treatment might have reduced possible subclinical inflammation induced by dry skin, as the aged skin may exhibits signs of continuous inflammation.[72] Legiawati et al. reported that after 29 days of treating the lower extremities with a leave-on product, IL-1α levels in the control group were not lower than the treatment groups.[73] The authors used cyanoacrylate skin surface stripping for analyzing SC extract. IL-1α is expressed by keratinocytes in epidermis and is retained as intracellular stores.[74,75] In our analysis, IL-1α was extracted from the whole epidermis which might have provided analytes also from the lower epidermal cell layers. Another aspect of IL-1α might be relevant in suction blistering process as this produces wounds. Immediately after an incision, cellular recruitment and activation starts within wounds and keratinocytes produce IL-1α.[76] However, as blisters were created both on control and treatment arm, blistering should effect the production of IL-1α similarly on both arms. Hence, the lower levels of IL-1α might be due to the treatment. Topical application was reported to normalize serum IL-6 level.[77] However, increased serum IL-6 level was significantly correlated with reduced SCH only in the females participants.[71] In our study, the value of epidermal IL-6 was not affected by the treatment. This

TABLE 2 Total protein (TP) and Interleukins/TP in the blister roof and blister fluid samples.

	Units		Blister roofs Intervention	Control	Difference
Total protein	µg/mL	Mean (SD)	166.6 (45.9)	183.0 (38.6)	−16.4 (46.6)
		Median (IQR)	166.3 (126.5–202.4)	184.2 (144.1–218.3)	−11.5 (−57.7 to 13.6), $p = 0.31$
IL-1α	fg/µg TP	Mean (SD)	3541.1 (1172.8)	4374.2 (2034.3)	−833.1 (1113.7)
		Median (IQR)	3338.2 (2755.7–4728.9)	3947.9 (2988.3–5427.9)	−452.4 (−923.3 to −239.4), $p = 0.002$
IL-6	fg/µg TP	Mean (SD)	195.8 (79.9)	149.3 (82.7)	46.5 (111.4)
		Median (IQR)	181.7 (126.7–250.1)	142.9 (71.8–229.4)	37.8 (−15.6 to 111.9), $p = 0.14$
IL-8	fg/µg TP	Mean (SD)	164.2 (48.7)	155.0 (68.8)	9.2 (71.1)
		Median (IQR)	161.1 (113.9–208.0)	137.5 (96.9-205.8)	−5.7 (−32.3 to 63.3), $p = 0.81$
			Blister fluid		
Total protein	µg/mL	Mean (SD)	21,079.2 (2803.4)	21,242.4 (2835.9)	−163.2 (2189.1)
		Median (IQR)	21,058.3 (19,506.3–22797.9)	21,183.3 (19,485.4–23,433.3)	0.0 (−2187.5 to 510.4), $p = 0.97$
IL-1α	fg/µg TP	Mean (SD)	9.6 (5.4)	14.3 (11.4)	−4.8 (7.4)
		Median (IQR)	8.2 (5.5–12.7)	9.9 (5.7-22.8)	−2.2 (−4.7 to −0.1), $p = 0.01$
IL-6	fg/µg TP	Mean (SD)	2.3 (5.3)	2.1 (4.7)	0.2 (0.7)
		Median (IQR)	0.8 (0.5–1.1)	0.7 (0.6–1.1)	0.0 (−0.1 to 0.1), $p = 0.88$
IL-8	fg/µg TP	Mean (SD)	2.1 (2.4)	1.6 (1.8)	0.5 (0.9)
		Median (IQR)	1.3 (0.8–2.3)	1.0 (0.6–1.6)	0.2 (−0.1 to 0.9), $p = 0.16$

Note: Blister roof: Average values of two blister locations (A, B or C, D) on the same forearm; Blister fluid: all fluids from each forearm pooled together.

indicates heterogeneity in IL-6 expression depending on gender or analyzed sample material. Schweiger et. al., 2013 reported the amount of IL-8 to be higher in the dry scalp compared to the hydrated scalp after a tonic treatment.[11] Our result show that for dry forearm skin (not the scalp region) the marker was not affected by dryness or hydration. Due to very high concentration of TP in the blister fluid, the normalized amount of IL-6 and IL-8 were very low (as low as 0. 2 fg/µg TP). Nevertheless, in our analysis, the amounts of IL-6 and IL-8 in the blister roof extract and the blister fluid were located in the range measurable by the assay. The values of IL-8 and IL-6 were not significantly affected by the treatment and probably they are not proper markers for the endpoint chosen in this study.

4.2 | Limitations

We included only Fitzpatrick skin type I-III to reduce heterogeneity. Due to the exploratory nature of the trial, results should be regarded as descriptive and hypotheses generating. Because of the restricted in- and exclusion criteria and the controlled intervention and measurement conditions, results are not generalizable.

5 | CONCLUSION

The use of a urea containing leave-on product improves clinical, functional and structural aspects of dry skin and seems to reduce inflammation and to strengthen the dermoepidermal adhesion in older adults. Our result contributes to the understanding of how topical leave-on products help in the prevention of skin tears in older adults.

AUTHOR CONTRIBUTIONS

Ruhul Amin: Data curation; formal analysis; visualization; writing—original draft; writing—review and editing. **Fiorenza Rancan**: Formal analysis; investigation; validation; visualization; writing—review and editing. **Kathrin Hillmann**: Conceptualization; data curation; methodology; project administration; writing—review and editing. **Ulrike**

Blume-Peytavi: Conceptualization; funding acquisition; methodology; project administration; resources; software; supervision; writing—review and editing. **Annika Vogt**: Conceptualization; investigation; methodology; resources; supervision; writing—review and editing. **Jan Kottner**: Conceptualization; funding acquisition; investigation; methodology; resources; software; supervision; writing—review and editing.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The corresponding author had full access to all of the data in this study and takes complete responsibility for the integrity of the data and the accuracy of the data analysis. The authors confirm that the data supporting the findings of this study are available within the article and its Supporting Information Material. If requested, anonymized data will be shared by the corresponding author.

TRANSPARENCY STATEMENT

The lead author Jan Kottner affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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Additional supporting information: Participant characteristics of the sample.

Manuscript title: Effects of a leave-on product on the strength of the dermoepidermal junction: an exploratory, intraindividual, randomized controlled trial in older adults with dry skin.

Participant characteristics	
Age (years) mean (SD); median (IQR)	77.9 (5.6); 78.5 (75.3-82.8)
Sex, n	
Female	7
Male	5
Skin phototype according to Fitzpatrick scale, n	
Type I	1
Type II	10
Type III	1
BMI (kg/m^2) mean (SD); median (IQR)	24.7 (2.4); 24.4 (23.3-26.3)
Body temperature (°C) mean (SD); median (IQR)	36.4 (0.2); 36.4 (36.3-36.5)
Blood pressure (mmHg) mean (SD); median (IQR)	
Systolic	145 (9.6); 145.5 (139.3 - 150.0)
Diastolic	89.2 (5.5); 89 (84.0-94.5)
Heart rate (beats per minute) mean (SD); median (IQR)	73.1 (12.4); 73.0 (62.3-79.8)

Curriculum Vitae

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Publication list

Amin R, Lechner A, Vogt A, Blume-Peytavi U, Kottner J. Molecular characterization of xerosis cutis: A systematic review. Plos one. 2021 Dec 16;16(12):e0261253. https://doi.org/10.1371/journal.pone.0261253. Impact Factor: 2.740

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