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Characteristics of ageing skin

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1. Summary

1.1. Abstract (English)

Introduction Skin cancer, especially in elderly patients, is one of the most fatal skin diseases. However, the prevalence in institutional long-term care (ILTC) facilities is mostly unknown. Transepidermal Water Loss (TEWL) is considered as an important parameter in skin research, which is associated with the integrity of stratum corneum. Characteristics of the skin are not only indicators of skin, but are also associated with other health conditions e.g. dehydration. A relationship between fluid intake and skin hydration is hypothesized, but have not been investigated so far. This is especially relevant in elderly patients since dehydration is a major health risk in aged populations.

Methods A systematic review and a meta-analysis update aimed to summarize TEWL values in young and aged adults. A systematic literature review aimed to summarize available empirical evidence about associations between fluid intake and skin barrier. To evaluate whether skin barrier characteristics are associated with fluid intake and hydration status in geriatric patients on a clinical level, an explorative observational study was performed. An observational, cross-sectional prevalence study was conducted in ten ILTC facilities to measure the prevalence of skin cancer and to explore possible associations with demographic and other characteristics.

Results The meta-analysis update identified TEWL estimates for 86 skin areas in 212 studies. TEWL in aged adults was either similar or lower than in the younger group. The systematic literature review resulted in six analyzed full texts. Forty patients were included in the exploratory study. Seventeen patients showed a current or impending dehydration according to serum osmolality thresholds. Serum osmolality was associated with epidermal hydration of the leg and the pH of the face. Skin pH showed the strongest association with fluid intake. In ILTC residents, the prevalence of non-melanoma skin cancer (NMSC) was 7.2% (95% CI 4.5 to 11.3). Female sex and smoking was associated with NMSC.

Discussion TEWL is highly skin area dependent and shows a symmetrical pattern between right and left body parts. Additional water intake may increase skin hydration. However, empirical evidence supporting this observation is weak. Results of the exploratory study indicate that epidermal hydration of the lower leg might play a role in the diagnosis of

dehydration but most probably in combination with other tests. The most frequent skin tumors in the ILTC facilities are NMSC. With respect to the worldwide growing aging population, it is important to screen also ILTC residents for skin cancer. Thus, all primary health care professionals in ILTC settings should be trained for this task.

1.2. Abstrakt (German)

Einleitung Hautkrebs ist, insbesondere bei älteren Patienten, eine der schwerwiegendsten Hauterkrankungen. Genaue epidemiologische Zahlen in institutionellen Pflegeeinrichtungen (ILTC) fehlen. Transepidermaler Wasserverlust (TEWL) wird als ein wichtiger Parameter in der Hautforschung angesehen, welcher mit der Integrität des Stratum corneums assoziiert ist. Werte für einen „normalen" TEWL gibt es jedoch nicht. Eigenschaften der Haut sind nicht nur Indikatoren für die Haut an sich, sondern sind auch mit anderen Gesundheitszuständen assoziiert, z.B. mit der Dehydratation. Ein Zusammenhang zwischen der Flüssigkeitszufuhr und dem Zustand der Haut wird vermutet, ist aber bislang nicht untersucht worden. Diese ist vor allem im höheren Lebensalter relevant, denn Dehydratation stellt in der älteren Bevölkerung ein großes Gesundheitsrisiko dar.

Methoden Mit dem Update einer systematischen Übersichtsarbeit und einer Meta-Analyse, sollten TEWL-Werte bei jungen und älteren Erwachsenen zusammengefasst werden. Eine systematische Literaturrecherche zielte daraufhin ab, verfügbare empirische Evidenz für mögliche Zusammenhänge zwischen Flüssigkeitszufuhr und der Hautbarriere zusammenzufassen. Eine explorative Beobachtungsstudie wurde durchgeführt, um bei geriatrischen Patienten auf klinischer Ebene zu untersuchen, ob Parameter der Hautbarriere mit der Flüssigkeitszufuhr und dem Hydratationsstatus in Zusammenhang stehen. Weiterhin wurde eine deskriptive Prävalenzstudie in zehn ILTCs durchgeführt, um die Prävalenz von Hautkrebs bei Pflegeheimbewohnern zu messen und mögliche Zusammenhänge zu untersuchen.

Ergebnisse In der Meta-Analyse wurden in 212 Studien TEWL-Schätzungen für 86 Hautbereiche ermittelt. TEWL war bei älteren Patienten entweder ähnlich oder niedriger als in der jüngeren Gruppe. Die systematische Literaturrecherche ergab sechs analysierte Volltexte. Vierzig Patienten wurden in die explorative Studie einbezogen, davon zeigten siebzehn Patienten entweder eine bevorstehende oder eine bestehende Dehydratation laut der Serumosmolalität. Die Serumosmolalität war mit der epidermalen Hydratation der Beine sowie mit dem pH-Wert der Hautoberfläche des Gesichts verbunden. Der pH-Wert der Hautoberfläche zeigte den stärksten Zusammenhang mit der Flüssigkeitszufuhr. Die Prävalenz

des nichtmelanozytären Hautkrebs (NMSC) betrug 7,2% (95% CI 4.5 to 11.3). Das weibliche Geschlecht und Rauchen wurde mit NMSC in Verbindung gebracht.

Diskussion TEWL ist stark von der untersuchten Körperregion abhängig und zeigt ein symmetrisches Muster zwischen rechten und linken Körperregionen. Eine zusätzliche Flüssigkeitszufuhr kann die Hautfeuchtigkeit erhöhen. Allerdings ist die empirische Evidenz, die diese Betrachtung unterstützt, schwach. Die Ergebnisse der explorativen Studie weisen darauf hin, dass die Hautdurchfeuchtung (epidermale Hydratation) des Unterschenkels bei der Diagnose von Dehydratation eine Rolle spielen könnte, höchstwahrscheinlich jedoch in Kombination mit anderen Verfahren. In den institutionellen Pflegeeinrichtungen stellten NMSC die häufigsten Hauttumore dar. Im Hinblick auf die weltweit wachsende Alterung ist es wichtig, dass auch Hautkrebsscreenings in den ILTCs durchgeführt werden. Demzufolge sollten auch die medizinischen Fachkräfte der primären Gesundheitsversorgung diesbezüglich ausgebildet werden.

2. Background

Age-associated skin conditions and diseases, a loss of functional capacity, impairment of skin barrier and increased risk for pathological changes like skin cancer are dermatological consequences of the growing and ageing world population. Among all dermatological diseases, skin cancer is especially in elderly patients, one of the most fatal skin disease. However, the prevalence in institutional long-term care settings is mostly unknown.

The Stratum Corneum (SC) provides a tight barrier between the internal moist and the dry outer environment. A small proportion of water molecules constantly diffuses from the dermis and epidermis to the skin surface, which is called TEWL. The Transepidermal Water Loss (TEWL) is regarded as one of the most important parameter for measuring the integrity of the skin barrier in a variety of dermatological research contexts. Increased TEWL seems to be associated with skin barrier dysfunction, whereas decreased TEWL is regarded as an indicator for an intact or recovered skin barrier. Empirical evidence indicates that TEWL decreases during ageing, which might be misinterpreted as a skin barrier improvement (1). TEWL is influenced by many environmental and individual factors (2). Whether a "normal" TEWL and possible reference values indicating pathological relevance are a matter of debate. In 2013, covering a search period until May 2012, available TEWL reference values in healthy adults were successfully summarized (1). However, since 2012, numerous new studies reporting TEWL values were published. An update of the existing summary of the TEWL values from different body areas and a comparison of these values between young and aged adults would increase the knowledge and understanding about skin barrier properties and the age-associated changes of skin barrier function.

Clinical characteristics and biophysical properties of the skin are not only indicators of skin function, but are also associated with other systemic health conditions e.g. dehydration. A relationship between fluid balance (e.g. fluid intake) and skin hydration is repeatedly hypothesized but has not been investigated so far. This question is especially relevant in elderly patients since dehydration is a major health risk in aged populations.

The SC barrier function can be further characterized by different other parameters, such as stratum corneum hydration (SCH), skin surface pH and sebum content. The mechanical properties of the SC, including elasticity and extensibility are essential to maintain a physiological functioning. Numerous strategies have been proposed to treat dry skin such as topical leave-on

products, which are widely used to improve skin barrier function and hydration (3). Adequate fluid intake is commonly believed to play an important role to ensure an adequate skin hydration (4). For instance drinking 1.5 to 2 litres of water a day is recommended to help to maintain a proper skin hydration (5). However, assuming that the diffusion of water molecules through the SC is a rather passive physical process and that the water transport and holding properties are mainly determined by SC properties, such relationship seems not to be obvious.

Water does not only play a role for the skin barrier integrity but also plays a crucial role in all other biological processes (e.g. growth, metabolism, movement, signaling) at every stage of life. Due to physiological changes associated with aging (e.g. decreased thirst responses, changes in renal function, altered vasopressin levels, polypharmacy, diuretics, decreased cognitive function) older patients have an increased risk of dehydration. Interventions to improve fluid intake in aged care receivers and geriatric patients are considered of utmost importance. Especially in geriatric patients, dehydration is associated with poor health outcomes, including falls, fractures, drug toxicity, confusion and death (6). Various clinical tests and methods have been proposed to diagnose dehydration (e.g. skin turgor test, expressing fatigue, dry mouth and tongue furrows), but a recent Cochrane review indicated that the evidence supporting the diagnostic accuracy of these tests is extremely week (6). There is a need for simple non-invasive but accurate diagnostic procedures to identify geriatric patients at risk for or with dehydration. Empirical evidence suggests relationships between fluid intake and skin properties. An additional intake of water seems to influence skin barrier parameters especially in individuals with prior water consumption (7). Associations between fluid intake and skin surface pH has been also described (8). Such associations might also exist in aged and geriatric patients but have never been investigated so far.

The aging population is also associated with an increase of aging-related skin conditions and cutaneous diseases. One of the most especially in elderly patients fatal skin diseases, is skin cancer with a steady increase in incident rates (9). There are two primary groups of skin cancer: melanoma and non-melanoma skin cancer (NMSC). Basal cell carcinoma (BCC) and cutaneous squamous cell carcinoma (cSCC) are referred to NMSC. Additionally, actinic keratosis (AK) is characterized by atypical epidermal keratinocytes, and represents a preinvasive “in-situ” lesion of cSCC. Both genetic and environmental factors, mainly chronic exposure to ultraviolet (UV) radiation, ionizing radiation, exposure to chemical carcinogens such as arsenic exposure contribute to the development of NMSC (10). Empirical evidence also shows a strong association between androgenetic alopecia and NMSC (11). Smoking has been reported as an independent modifiable

risk factor by some authors. However, the results of these studies are conflicting, reporting both positive and negative associations (12, 13). Latest epidemiological figures indicate that the prevalence of skin cancer is 0.6% to 13.5% in acute or chronic geriatric units or hospitals (14, 15). According to Nursing Care Statistics in Germany in 2015, about 800.000 residents receive care in long-term care institutions. However, the skin cancer prevalence in institutional long-term care facilities is unknown (14). Representing a fragile group, a detailed knowledge about the load of the skin cancer in this sub-population is extremely relevant, because the regular dermatological examination in these care settings is not common.

2.1. Objectives

1. What are the TEWL reference values in young and aged healthy individuals? Are there differences between young and elderly individuals? (Project 1, Publication 1)

2. What are the possible associations between fluid intake, skin hydration and the skin barrier function? (Project 2, Publication 2)

3. Are skin barrier parameters associated with fluid intake and hydration status in geriatric patients? (Project 3, Publication 3)

4. What is the prevalence of skin cancer in residents living in institutional long-term care facilities? What are the possible associations between skin cancer and demographic, and functional characteristics? (Project 4, Publication 4)

3. Materials and Methods:

3.1. Project 1: Transepidermal water loss in healthy adults: A systematic review and meta-analysis update

In 2013 a systematic review and meta-analysis covering a search period from 1947 to May 2012 was published (1). A systematic review and meta-analysis was conducted to update this existing review summarizing and comparing TEWL values in adults. A review protocol was registered on 26.04.2016 in advance in the PROSPERO database (CRD42016037977).

3.1.1. Search strategy and the eligibility criteria

For this update a concurrent search in the databases MEDLINE and Embase (6 May 2012 to 14 April 2016) via OvidSP was conducted and last updated on 13th April 2017. This update covers therefore the search period from 1947 to 13th. April 2017. The websites of all TEWL probe manufactures were visited, and three (Biox Systems Ltd, London, U.K.; Delfin Technologies Ltd, Kuopio, Finland and Courage + Khazaka, Cologne, Germany) provided publication lists. These publication lists were screened for additional primary studies. Forward searches using all studies meeting the inclusion criteria in Web of Science were conducted for possible additional literatures. Studies had to meet the following inclusion criteria: (i) primary empirical studies providing quantitative estimates of TEWL measurements; (ii) clear reporting of skin areas; (iii) clear reporting of mean age; (iv) TEWL measurements conducted on healthy human skin in vivo; (v) TEWL measured and reported, including measures of spread such as SDs; and (vi) publication language: English or German. Types of studies and references to be excluded were: (i) skin diseases; excised skin or other diseases that might have an impact on TEWL; (ii) unclear reporting of measurement areas; (iii) systemic or topical treatments affecting skin barrier function; (iv) humans under 18 years of age or no reporting of age; (v) in vitro or ex vivo measurements; (vi) animal studies; and (vii) reviews or comments.

3.1.2. Study selection, data collection process and the synthesis of the results

Results from the database search and publication lists were imported into a reference manager (EndNote X7; Clarivate Analytics, Philadelphia, PA, U.S.A.). The following variables were extracted: author(s), year, country, season, sample size, sex, mean age, skin phototype, ethnic origin, smoking status, health status, TEWL device, skin area, measured mean TEWL and corresponding spread values [SD, SE, 95% confidence interval (CI)]. If only the SD was given, we converted this to the SE according to the formula $SE = SD/\sqrt{(\text{sample size})}$. For the new studies, we extracted the following variables in addition: smoking status, room temperature, relative humidity, acclimatization, calibration of the instrument, avoidance of air turbulence and number of measurements.

A risk-of-bias assessment for studies reporting TEWL measurements is not available. The latest assessment and the reporting guideline by du Plessis et al. (16) was used to create a custom-

made risk-of-bias tool. We considered the following items as important for accurate and reproducible measurements: (1) Was there an acclimatization period of at least 15 min before measurements (yes, no)? (2) Was calibration of the instrument conducted before the study (yes, no, not applicable)? (3) Was undesirable air turbulence avoided during the measurements if open-chamber systems were used (yes, no, not applicable)? (4) Were two or three measurements conducted at the same skin area and the results averaged (yes, no)?

The mean TEWL value per skin area was regarded as the primary outcome per study. A random effects model was used to combine the TEWL measurements per skin area of all studies for the meta-analysis. For each site-specific summary measure 95% CIs were given. We have focused on the description of TEWL values. Non-overlapping 95% CIs of TEWL summary measures per skin area were interpreted as showing statistically significant differences. We also measured the extent of between study heterogeneity based on the I^2-statistic. The software SPSS Statistics version 22 (IBM, Armonk, NY, U.S.A.) was used to perform descriptive summary statistics such as mean age, and StatsDirect version 280 (StatsDirect, Altrincham, U.K.) was used to calculate the meta-analysis.

A subgroup analysis was performed to measure possible differences between participants aged 18-64 years and those aged ≥ 65 years. In order to measure possible influences of different TEWL measurement instruments and measurement conditions, further subgroups were compared. This was done only for the right volar forearm because it was the most frequently measured skin area. Non-overlapping 95% CIs were interpreted as showing statistically significant differences.

3.2. Project 2: A systematic literature review to summarize available empirical evidence about possible associations between fluid intake and skin hydration and skin barrier function

The aim of this systematic literature review was to summarize available empirical evidence about associations between fluid intake, skin hydration and barrier function.

3.2.1. Search strategy, study selection and the eligibility criteria

A search in the database PubMed was conducted on June 7, 2016. Reference lists of all full text publications were screened, forward searches in Web of Science for additional literature were

conducted, the results from the data base search were imported into a reference manager (Endnote X7) and screened. The following inclusion criteria were applied: (1) primary study report, (2) studies in humans, (3) disease-free skin, (4) no systematic or topical treatments affecting the skin barrier function, (5) skin physiological parameters measured and reported, (6) 18+ years and clear reporting of age, (7) Language English, German, Spanish and Portuguese. Exclusion criteria were: (1) reviews, (2) animal studies, (3) measurements on excised skin, (4) diseased skin, (5) 17 years or younger or unclear reporting of age. No publication date restrictions were imposed.

3.2.2. Methodological appraisal, data collection, items, and synthesis of the results

The Cochrane Risk of Bias tool was used for appraising intervention studies. Each item was judged high or low risk of bias or "unclear" when there was insufficient evidence (17) . Author, year, region/country, study period, sex, mean age, study procedures and measurement instruments, skin areas, skin parameter estimates including spread values were extracted as variables.

3.3. Project 3: Effect of fluid intake on hydration status and skin barrier characteristics in geriatric patients: An explorative study

3.3.1. Study design and setting

An explorative observational comparative study was conducted in the Evangelic Geriatric Center of Berlin, Germany, between April and June 2016. The study protocol and the informed consent forms and procedures were approved by the Ethics Committee of Charité – Universitätsmedizin Berlin. Due to the explorative nature of the study, a formal sample size determination was not conducted. We regarded n = 40 patients as sufficient to detect possible differences and/or associations between variables. Patients who were 65+ years old, who has signed written informed consent (or by a legal representative) and has assumed ability that skin measurements can be performed were included to the study. Following exclusion criteria were applied: patients at the end of life, any dermatological condition or skin affection, or skin treatment which may interfere with the study assessments, any unstable acute or chronic pathology or condition that may interfere with the study conduct at the discretion of the investigator, any use of topical drugs on the investigational areas 2 weeks prior to inclusion, systemic applications of corticosteroids

3.3.2. Variables and data collection

Demographics and variables characterizing medical and functional conditions were measured. The Mini-Mental State Examination (MMSE) was used to measure the mental status. The Barthel Index was used to assess the dependency in the activities of daily living. The Geriatric Depression Scale was used to measure depression. All these scores were extracted from the medical records including medications and documented signs of dehydration. Fluid intake was recorded by the nurses and/or by the patients themselves, and the volume of intravenous medication was obtained from the clinical records for 3 consecutive days. At day 3, blood samples were drawn and serum osmolality was measured. Hydration status was classified as normally hydrated (275 to < 295 mOsm/kg), impending dehydration (295 to ≤300 mOsm/kg), and current dehydration (> 300 mOsm/kg). The clinical assessment of the presence or severity of skin dryness (xerosis) was performed by a physician using the Overall Dry Skin Score (ODS) on a five-point scale from 0 to 4 which was separately assessed for arms, face, trunk and legs. The skin barrier function was characterized by TEWL in $g/m^2/h$, skin surface pH, epidermal hydration in percentage of local tissue water, SCH in arbitrary units on the three skin areas: forehead, outer forearm, and outer lower leg. All instrumental skin measurements were performed in the patient rooms in the morning between 08:00 and 10:00 am while patients were resting and before any topical products to the test sites were applied. Relative humidity and the room temperature were recorded.

3.3.2. Statistical methods

Characteristics of the subjects were described using mean and spread parameters and proportions. Bivariate associations were described in a correlation matrix using Spearman correlation coefficients. A correlation of 0.2 or higher or –0.2 or lower was regarded as minimum strengths to indicate possible associations. The sample was divided into tertiles according to fluid intake and the number of patients with normal (< 295 mOsm/kg) and high (≥295 mOsm/kg) osmolality. Multiple linear regression analysis with LASSO (Least Absolute Shrinkage and Selection Operator) selection was applied to identify those variables (from the entire potential set of medical variables and skin parameters) that were most strongly related to fluid intake and osmolality. Importantly, obtained parameter estimates in this model cannot be interpreted as such because we reversed dependent and independent variables by modelling fluid intake/osmolality as single dependent variable and the various skin parameters as independent variables. This was done because it was not possible to simultaneously model numerous skin parameters as dependent

variables with only one independent variable (fluid intake/osmolality predicting skin parameters). This approach enabled us to identify those skin parameters that are most likely associated with fluid intake/osmolality. All p values were two-sided. All analyses were performed in SAS (version 9.4, Enterprise Guide 4.3, SAS Institute Inc., Cary, NC, USA).

3.4. Project 4: Prevalence and associated factors of skin cancer in aged nursing home residents: a multicenter prevalence study

The aim of the study was to measure the prevalence of skin cancer and precursor lesions in residents living in institutional long-term care facilities and to explore possible associations with demographic, biographic and functional characteristics.

3.4.1. Study design and setting

An observational, cross-sectional prevalence study was conducted from September 2014 to May 2015 in ten institutional long-term care facilities in Berlin, Germany (18). A study protocol was published before (https://clinicaltrials.gov/ct2/show/NCT02216526) and approved by the ethics committee of Charité-Universitätsmedizin Berlin (EA1/190/14). In order to reduce selection bias, institutional long-term care facilities from a list of all existing facilities (n = 291 in 2014) in the federal state of Berlin were contacted in a random order and invited to participate. Assuming a prevalence of 0.5 of skin diseases, we regarded approximately n = 280 residents as sufficient to measure this proportion with a desired width of a 95% CI of ± 0.06. According to the Nursing Care Statistics (2013), the size of the long-term care population in Berlin was approximately n = 30.000. Assuming n = 80 residents per institution and a participation rate of 50% (n = 40), it was planned to include seven institutions which results in n = 280 (7 x n = 40) cases. Measurements and clinical procedures were performed by trained board certified dermatologists and study assistants according to standard operating procedures. To reduce the risk of detection bias, the dermatologists had no access to medical history of the residents prior and during examinations. Participants had to meet the following inclusion criteria: (1) being resident of the respective nursing home facility, (2) being 65+ years. Residents at the end of life were excluded. All residents living in the nursing home facility at the time of data collection were invited to participate by study assistants and investigators. Written informed consent was obtained from the residents or their legally authorized representatives on their behalf.

3.4.2. Variables and data collection

Skin malignancies, pre-malignancies, androgenetic alopecia and melanocytic nevi were classified according to the International Classification of Diseases (ICD-10). Demographics (age, sex and BMI), biographic (qualification and occupation), physical and functional (Barthel Index) characteristics were measured. The Barthel Index (BI) was used to assess the dependency in the activities of daily living (19). The educational level was classified into six categories: (1) no school qualification, (2) primary school, (3) secondary school, (4) grammar school/A-level, (5) vocational training and (6) university qualification. The smoking status was classified into three categories: (1) smoker, (2) former smoker, (3) never smoked. The history of employment was classified into two categories: (1) indoor, (2) outdoor. The clinical dermatological examination was performed by board certified dermatologists for each participating nursing home resident. Clinical examinations and evaluations were performed with dermatoscopes (Dermogenius basic, DermoScan GmbH, Germany). Demographic, biographic and functional characteristics were obtained from the medical records or assessed by a study assistant via interview of the responsible nurse or the resident were interviewed if possible (depending on the cognitive abilities).

3.4.2. Statistical methods

Depending on the level of measurement (nominal, ordinal and continuous), demographic characteristics, functional assessment scores and dermatological diseases were described using means, medians, proportions, frequencies and associated spread estimates such as standard deviations and (interquartile) ranges. The 95% CIs were calculated around point estimates of dermatological diseases. Exploratory data analysis to investigate possible bivariate associations were conducted using logistic regression analysis for skin diseases and odds ratios (OR) were calculated. 95% CIs of the ORs excluding 1 were considered statistically significant. ORs being statistically significant or with values lower than 0.5 or higher than 2.0 were considered to be likely associated.

4. Results

4.1. Project 1: Transepidermal water loss in healthy adults: A systematic review and meta-analysis update

After removal of duplicates, 366 publications in MEDLINE and Embase and 113 publications from other sources were screened. Finally, 195 studies were assessed in full text and 45 studies were included. The previous original review included 167 studies, and the results of the 45 new studies were added to the existing meta-analysis. Based on in total all 212 studies, 86 skin areas were identified and TEWL values were extracted and pooled, with sample sizes ranging from n = 4 (forehead middle left middle) to n = 4013 (right mid volar forearm). Thirty-six new skin areas were identified in addition to the existing results. The lowest TEWL of 2.3 (95% CI 1.9-2.7) g/m²/h was reported for the breast skin and the highest TEWL of 44.0 (95% CI 39.8-48.2) g/m²/h for the axilla. TEWL estimates were extracted and/or calculated for 82 skin areas in the 18 to 64-year-old subjects. In this younger group pooled mean ages range between 21.8 and 44.8 years. TEWL estimates for 65+ years subjects were calculated for 27 skin areas with pooled mean ages ranged from 68.3 to 78.8 years. Comparisons between both age groups were possible for 24 skin areas. Mean TEWL in the elderly group was generally lower compared to the middle-aged group. In 13 cases the differences were statistically significant. Additionally, pooled TEWL estimates for the right midvolar forearm (n = 4013) were compared per measurement instrument. The lowest TEWL of 3.1 (95% CI 1.0-5.2) was calculated for the Model H 4300 (Japan), whereas the highest value of 11.4 (95% CI 10.7-12.0) was found for the AquaFlux (UK), which uses the condenser-chamber method of measurement.

4.2. Project 2: A systematic literature research to summarize available empirical evidence about possible associations between fluid intake and skin hydration and skin barrier function

After removal of duplicates, 202 publications in PubMed and 14 publications from other sources were screened. Finally, 23 articles were assessed in full text and six were included. In context of skin barrier function and hydration; TEWL, SCH, deep skin hydration (depth unknown), clinical evaluation of dryness, roughness and elasticity, skin relief parameter, the average roughness, evaluation of skin surface morphology, skin smoothness (SEsm) and roughness (SEr), extensibility (U_f and the ability of the skin to return to its original state $U_f - U_a$), sebum content, skin surface pH were reported. Overall, the risk of bias was high in the experimental studies. In an observational study there was a weak positive association between fluid intake and SCH (8). Additional daily water intake of 2 L over a period of 30 days showed an increase in both SC and “deep” skin hydration, especially when the individual’s regular diet included low amounts of water (7). Results

consistently showed, that there were no associations between TEWL at any skin area and an additional intake of mineral water of 1 L over 42 days, or 2 L over 30 days.

4.3. Project 3: Effect of fluid intake on hydration status and skin barrier characteristics in geriatric patients: An explorative study

4.3.1. Participants and descriptive data

The mean age was 79 (SD 6.7) years and 65% were female. Mean BMI was 26.2 (SD 4.3) kg/m^2. Mean MMSE score was 24. Mean BI was 45 and mean Geriatric Depression Scale Score was 3. Mean fluid intake was 1,747 ml daily and five patients had documented clinical signs of dehydration (12.5%). The mean number of prescribed medications was 10.6 (SD 3.6), and 67.5% of the complete listing of medications was diuretics.

Mean serum osmolality was 294 (SD 9.9) mOsm/kg; 23% had impending dehydration, and 20% had current dehydration according to current reference ranges. The highest ODS was 1.7 recorded on the legs, and the lowest was 0.3 on the face. Facial skin also showed highest TEWL, SCH, and epidermal hydration values. Skin surface pH values varied slightly between 5.0 and 5.3.

4.3.2. Associations and multivariate analysis

According to the tertiles of fluid intake, fluid intake seems to be unrelated to serum osmolality, but patients with diuretics nearly always were dehydrated. The fluid intake showed the highest positive association with epidermal hydration at the forehead ($r_s = 0.33$). Serum osmolality was positively associated with the ODS at the face ($r_s = 0.31$) and with serum natrium ($r_s = 0.51$). A negative correlation was observed between MMSE and the use of diuretics ($r_s = -0.43$) and between serum, osmolality and MMSE ($r_s = -0.35$).

Highest associations overall were observed between intra-individual skin barrier parameters. For instance, skin surface pH at the arm was strongly associated with the pH at the leg ($r_s = 0.64$) and the face ($r_s = 0.70$). Similarly, the correlation between SCH at the arm and the face was positive ($r_s = 0.61$). An association was observed between SCH at the leg and epidermal

hydration at the leg (r_s = 0.57). A positive association was observed between ODS at the leg and ODS at the arm (r_s = 0.55).

In total, ten variables appeared to be relevant for predicting fluid intake (R^2 = 0.13). Except age, all selected variables were related to skin properties. Skin surface pH at the face showed the strongest association with fluid intake. Eight predictors were selected for the dependent variable osmolality (R^2 = 0.38). Higher osmolality was significantly associated with epidermal hydration and skin surface pH at the leg.

4.4. Project 4: Prevalence and associated factors of skin cancer in aged nursing home residents: a multicenter prevalence study

4.4.1. Participants and descriptive data

In order to achieve the planned number of participants, three additional long-term care facilities were recruited. In total, 10 from 55 contacted long-term care facilities agreed to participate. In total n = 811 long-term care residents were living within the nursing homes at time of data collection and therefore potentially suitable for participation. N = 252 residents provided written informed consent by themselves or by their legal representative. Twenty-nine residents declined participation prior examination resulting in n = 223 included long-term care residents.

The mean age was 83.6 (SD 8.0) years and the most of the residents were female (67.7%) and the mean BMI was 25.3 (SD 5.1) kg/m2. Mean BI was 45.1 (SD 23.8). A vocational training was the highest educational level for the majority (48.9%). Seventeen residents (8.5%) had an outdoor work history. Fifty-two residents (51.0%) have never smoked, whereby 37 residents (36.3%) were former and 13 residents (12.7) were current smoker. Androgenetic alopecia was diagnosed in n = 112 residents (50.2%). Twenty-nine residents (13.0%) were diagnosed with melanocytic nevi. The most common pre-cancerous skin lesion was actinic keratosis, the precursor lesions of cSCC (n = 47; 21.1%). Sixteen residents (7.2%) were diagnosed with NMSC. BCC was detected in 15 residents (6.7%) and was the most common NMSC. Only one resident (0.4%) was diagnosed with cSCC. Bowen's disease (SCC in situ) was diagnosed in seven residents (3.1%). One resident (0.4%) was diagnosed with lentigo maligna. None of the residents had malignant melanoma.

4.4.2. Associations

Female sex showed a significant negative association with the presence of actinic keratosis (OR 0.321, 95% CI 0.165 to 0.622) and an increased occurrence of NMSC (OR 2.167, 95% CI 0.597 to 7.857). Female sex was also associated with a decreased occurrence of androgenetic alopecia (OR 0.187, 95% CI 0.099 to 0.354). Age and care dependency (BI) seem not to be associated with non-melanoma skin cancer. Having an outdoor occupation history was associated with an increased occurrence of melanocytic nevi (OR 2.140, 95% CI 0.643 to 7.127). Having a university qualification was associated with an increased occurrence of Bowen´s disease (OR 3.200, 95% CI 0.588 to 17.409). Smoking or being a former smoker was associated with an increased occurrence of NMSC (OR 2.223, 95% CI 0.766 to 6.451).

Regarding the associations between skin diseases: An increased occurrence of Bowen´s disease was associated with an increased occurrence of NMSC (OR 2.233, 95% CI 0.252 to 19.777). There was also an association between the increased occurrence of melanocytic nevi and increased occurrence of actinic keratosis (OR 2.682, 95% CI 1.166 to 6.169).

5. Limitations

For the systematic review and meta-analysis, we applied a broad search strategy and screened hundreds of studies including publication lists created by TEWL device manufacturers and conducted forward searches in Web of Science. Nevertheless, there might be publications that we could not identify. Language bias might have occurred, since we have focused on publications in English and German. In addition, it was impossible to perform a formal assessment for risk of publication bias. The sample sizes for some skin sizes were small and an accepted method for evaluating the risk-of-bias assessment of TEWL estimates in empirical research designs are unknown. Therefore, the generalizability might be limited. Another limitation might be the commonly used term “healthy volunteers” in included studies. Some of these individuals might have had a dermatological disease, which might have an influence on the skin barrier function.

During the conduction of the systematic literature review, no authors were contacted. The database search was performed only in one database (PubMed) and in one citation database (Web of Science). Therefore, some studies or data may not have been identified.

The small sample size might be a possible limitation of the exploratory study by geriatric patients. The short-term monitoring of the fluid intake might be another limitation, since it did not allow us the predictive value of fluid intake monitoring on dehydration in the longer term in older people. Due to the geriatric setting, fluid intake showed a limited range. This might have decreased the chance to detect possible associations with other variables. The fluid intake was recorded by the study participants, nurses or extracted from the medical reports. Therefore, measurement errors may have occurred.

The exclusion of residents at the end of life and the lower participation rate than expected of n = 223/811 residents may have caused a selection bias. It is well known that UV-exposure plays an important role in the development of AK and NMSC but the intensity and the duration of UV exposure was not measured. Furthermore, other indicators for cumulative UV exposure such as outdoor hobbies, sunburns in the childhood or sun protection habits were not assessed. Likewise, we have not evaluated the intensity and the duration of the smoking history, which might be another important modifiable risk factor.

6. Discussion

Our overall aim was to improve the knowledge and understanding about skin barrier characteristics and age-associated changes of skin barrier function, to gain a detailed knowledge about the load of the skin cancer in the elderly, which is one of the most fatal consequences of skin ageing by constantly growing and ageing world population. Furthermore, we aimed to investigate possible associations between hydration status, and the biophysical characteristics of the skin, especially in elderly patients since dehydration is a major health risk in this fragile subpopulation.

In the context of the systematic review and meta-analysis we were able to extract and to calculate estimates for 86 skin areas of the human body. As seen in the sensitivity analysis the different measurement instruments and conditions provide slightly different results. Overall, the interpretation of TEWL is challenging. It is well known that TEWL measurements are influenced by many factors as age, sex, geographical region etc. (16) Most probably, it is not the absolute TEWL that matters but relative changes over time or differences between treatment periods. On the other hand, there is an ongoing discussion whether baseline TEWL values might be used as a predictive value for atopic dermatitis (20). Our study results indicate that, there is an important heterogeneity between the study results. The results also show a wide intra-individual heterogeneity of the skin in healthy adults. According to results, skin ageing reduces or does not

change TEWL. The reason for decreasing TEWL in elderly individuals is unclear. The slowdown of epidermal cell proliferation leading to larger corneocyte sizes, a reduction of natural moisturizing factors (NMFs) might play a role (21).

One of the major findings of the literature review was that, there is a paucity of high quality evidence to answer the question, whether fluid intake affects skin hydration and skin barrier function. The results indicate that an additional intake of water might be able to increase the stratum corneum hydration, especially in individuals with lower prior water consumption. Water accumulates in the dermis and an increased water content in the dermis may increase the water content in the epidermis. A higher epidermal water content may change the concentration of water between the stratum granulosum and the SC intercellular lipids. The water content of the SC is largely determined by the NMF, the structure of the corneocytes and the SC intercellular lipids. It is unlikely that these parameters change due to the fluid intake. Therefore, the possible underlying biological mechanism remains unclear. There seems to be no associations between TEWL and the increased fluid intake, which means that the water transport properties of the SC do not change (E.g. diffusion coefficient). This observation is at odds with the increased SC hydration indicating that possible barrier changes have occurred. The results indicates that an additional intake of water was able to increase “deep” skin hydration which can be explained with the capacity of the dermal layers to store water (22). Review results indicate an association between fluid intake and skin surface or sebum pH as unlikely. One study showed that the long-term mineral water intake improved the clinical signs of dryness and roughness (23). Whereas this was not observed in the study of Willams et al. (24) Our results show that an additional water intake seem to increase the the extensibility (Uf) and the ability of the skin to return to its original state (U_f-U_a). A higher proportion cutaneous water may decrease skin stiffness and increase elasticity, eventhough it is not clear, whether rather dermal or epidermal structures influenced the readings.

We aimed to investigate whether skin barrier parameters were associated with fluid intake and hydration status in geriatric patients. The measured median fluid intake of approximately 1,700 mL per day may be considered as appropriate for the geriatric population and the interquartile range from 1,500 to 1,900 mL/day shows a small variation. In accordance to the conducted systematic review and meta-analysis, from face to arm there was a decrease in TEWL, indicating increasing skin dryness, which is also supported by increased ODS. Fluid intake was associated with epidermal hydration of the face and leg. These results are consistent with the results of the systematic literature review, indicating an additional intake of water may be able to

increase the SC hydration in younger populations. However, the underlying biological mechanisms are not clear and younger healthy populations are not comparable with geriatric patients. No other bivariate correlations have been observed between fluid intake and skin barrier parameters, whereas in the multivariate analysis fluid intake showed a positive association with pH on the face. The multivariate analysis of the study results indicate that skin properties are directly or indirectly associated with fluid intake, since age and 9 skin related variables were identified to explain fluid intake. However, this model was able to explain less than 13% of the variance, indicating that there are many more other factors predicting fluid intake, which were not considered. According to current reference standard of dehydration, nine patients showed an impending and eight patients showed a current water-loss dehydration. Negative bivariate associations were observed between serum osmolality and epidermal hydration of the leg and the pH of the leg. Abnormally raised osmolarity implies cell dehydration as intracellular fluid moves to extracellular space which results shrinking in cells. This might have also occurred in the epidermal cells, but biological explanations are challenging. Another explanation might be the anatomical location. It is well known that the most common site for xerosis cutis in the elderly are the lower legs (25) . Hydration changes might be more noticeable in less hydrated areas. In the multivariate model, five of the eight identified variables to explain serum osmolality were related to skin properties, and this model explained nearly 40% of variance. Lower epidermal hydration at the leg was significantly associated with higher osmolality.

An interesting finding of our study was that there was no association between fluid intake and serum osmolality, indicating that other factors (e.g. chronic diseases or hormonal changes, polypharmacy) might play a more important role controlling serum osmolality than the fluid intake itself. This leads to question whether increased serum osmolality should automatically lead to increase the fluid intake by geriatric patients, since the current guidelines and clinical practice recommendations widely propose to ensure an adequate hydration of elderly patients (26). At the same time, it is also unlikely that long-term chronic dehydration may be reversed by increased fluid intake in geriatric or long-term settings (27). Disregarding all limitations of other symptoms and tests for water-loss dehydration in the elderly, only five patients showed clinical signs diagnosed by a geriatrician. According to our findings, use of diuretics seems to be related to dehydration (assessed with serum osmolality), which supports previous studies, indicating that diuretic use can increase the risk of developing dehydration (28).

The results of the prevalence study indicate that every fifth nursing home resident was affected by actinic keratosis and 7.2% were affected by non-melanoma skin cancer, which shows a high load of skin malignancies in this population. Chronic sun exposure is a major risk factor for the development of these lesions and the usual detection of AKs in frequently sun-exposed areas (e.g. balding scalp, face, distal upper extremities). Expectedly, AKs were detected on frequently sun-exposed areas; head and arms. Actinic keratosis was most strongly associated with male sex, which is most probably resulting from the increased prevalence of alopecia. NMSC was most strongly associated with smoking and female sex. It is well-known that UV-exposure and older age play important roles in the development of NMSC and AK. Interestingly, our results did not indicate an association between outdoor occupation and the occurrence of AK or NMSC, which might be resulting from the lack of data regarding the intensity and the duration of outdoor working activity. Furthermore, our study population had a mean age of 83.6 years. Ageing and cancer is a known biological phenomenon (29). However, several earlier studies also reported that immune senescence might paradoxically reduce tumor growth rate with aging (30).The same mechanism might also apply for NMSC. In contrast to previous studies, our results demonstrates a lack of association between androgenetic alopecia and NMSC (11) Our findings also indicated a higher risk for female residents to develop NMSC compared to males which is in contrast to previous findings (31). Several studies suggest an association between smoking and the occurrence of BCC, whereas some studies have shown no relationship (12, 32). Our results indicate a positive association between smoking and the overall risk of NMSC. Therefore, the clinical relevance of the results remain unclear. Lentigo maligna was detected only in one resident whereas none of the residents had a malignant melanoma. However, BCC was detected in 15 residents, whereas cSCC was detected in one resident only. BCC is a common seen NMSC in the elderly with a good prognosis and rare metastasis in the majority of cases and can be managed with both surgical and non-surgical modalities. Depending on the anatomical location, therapeutical challenges may still occur (e.g. ear, periorbital, and nose). Early detection of BCC, the choice of best age adapted therapy depending on co-morbidities and frailty of patients is important. Although cSCC is less common than BCC, unlike to BCC high-risk-cSCC can metastasize to distant sites, which makes an early diagnosis highly important. A complete surgical excision with histopathological control of excision margins is the gold standard treatment for primary invasive cSCC. Limitations can occur in very large and thick tumours, especially in the elderly population.

An oncogeriatric approach for screening and assessment of the nursing home residents with NMSC is generally lacking. Financial limitations, lack of time in clinical practice and insufficient

numbers of dermatologists are important challenges. It is very unlikely that regular dermatology visits in nursing homes can be performed by worldwide growing older population. Future clinical practice guidelines should ideally focus on easy to administer methods and should be adaptable to daily life conditions of dermatological and nursing home care settings. Effective education of primary care physicians using easily reproducible, generalizable training programs, dermoscopy courses for skin cancer might increase the early detection of skin cancer (33). Nurses can also take a more active role in the early diagnoses of skin cancer by questioning the date of last skin examination, by being capable to detect and triage atypical skin lesions. Web-based applications can train healthcare professionals to detect skin cancer or precancerous skin lesions and suspicious clinical and dermoscopic images can be shared immediately with skin cancer consultants to detect skin cancer at the right time and get the nursing home residents to a dermatologist (34).

The results of this dissertation provides reference values for TEWL in young and aged individuals for 86 skin areas, which are useful for future study planning and interpretation of the results in the context of skin barrier characteristics. It contributes to scientific evidence for answering the question whether skin barrier parameters are associated with fluid intake and hydration status, especially in aged populations. It also expands the understanding and knowledge to the load of precursor lesions and skin cancer in the elderly population living in institutional long-term care facilities and to exploring further possible associations.

Conclusions

1. There is a substantial heterogeneity between reported TEWL values and TEWL is also highly skin area dependent. There seem to be a symmetrical pattern between right and left body parts. TEWL in elderly patients seems to be lower than younger individuals, but the clinical relevance remains unclear.

2. Additional dietary water intake seems to increase skin hydration. However, empirical evidence supporting this observation is weak and the clinical relevance is unclear. There seems to be no associations between TEWL, sebum content, skin surface pH at any skin area and an additional fluid intake. A higher proportion of fluid intake may decrease skin stiffness and increase elasticity, even though it is not clear, whether rather dermal or epidermal structures influence the readings.

3. There seems to be no association between fluid intake and serum osmolality. Epidermal hydration of the lower leg might play a role but most probably in combination with other tests. There is an urgent need to develop novel easy to use tests of dehydration in the aged, but the empirical evidence supporting associations between skin barrier parameters and fluid intake and serum osmolality is weak. Especially in aged populations further research is needed to provide scientific evidence in this debate.

4. Nearly every fifth nursing home resident was affected by actinic keratosis. 7.2% of the residents were affected by NMSC. Malignant melanoma does not seem to be a frequently occurring tumor in the elderly and very elderly residents living in the institutional long-term care facilities at this age at least in the investigated population. Our results indicate an association between male sex and actinic keratosis and an association between female sex and NMSC. Previous smoking seems to be associated with an increased incidence of NMSC.

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8. Statutory Declaration

"I, *Akdeniz Merve*, by personally signing this document in lieu of an oath, hereby affirm that I prepared the submitted dissertation on the topic „*Characteristics of ageing skin*", 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.

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; www.icmje.org) on authorship. In addition, I declare that I am aware of the regulations of Charité – Universitätsmedizin Berlin on ensuring good scientific practice and that I commit to comply with these regulations.

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	Merve Akdeniz

9. Declaration of your own contribution to any publications

Merve Akdeniz contributed the following to the below listed publications:

Publication 1:

Akdeniz, M*., Gabriel, S*., Lichterfeld-Kottner, A., Blume-Peytavi, U., Kottner, J., Transepidermal water loss in healthy adults: a systematic review and meta-analysis update. British Journal of Dermatology, 2018, 179: 1049-1055.

Impact Factor: 6.714

Contribution: Planning of the design, selection of the assessment tools, conduction of the systematic review of the literature, evaluation of the studies, data extraction, analysis and synthesis of the results, statistical evaluation and creation of all tables in collaboration with S. Gabriel, leading role in writing of the publication, including the submission and the revision of the manuscript.

Publication 2:

Akdeniz M., Tomova-Simitchieva T., Dobos G., Blume-Peytavi U., Kottner J.
Does dietary fluid intake affect skin hydration in healthy humans? A systematic literature review. Skin Research and Technology. 2018;24(3):459-465.

Impact Factor: 1.657

Contribution: Planning of the design, selection of the assessment tools, conduction of the systematic literature review, evaluation of the studies, data extraction, interpretation and representation of the data in all tables, writing of the publication, including submission and the revision of the manuscript.

Publication 3:

Akdeniz M., Boeing H., Müller-Werdan U., Aykac V., Steffen A., Schell M., Blume-Peytavi U. Kottner J.
Effect of fluid intake on hydration status and skin barrier characteristics in geriatric patients: an explorative Study. Skin Pharmacology and Physiology. 2018;31(3):155-162.

Impact Factor: 1.974

Contribution: Recruitment of the patients, data collection and conduction of the study, interpretation and representation of the data, significant participation in the statistical evaluation of the data, creation of all tables, writing the publication, including submission and the revision of the manuscript.

Publication 4:

Akdeniz M.*, Hahnel E*., Ulrich C., Blume-Peytavi U. & Kottner J.

Prevalence and associated factors of skin cancer in aged nursing home residents: A multicenter prevalence study. PLoS ONE. 2019;14(4):e0215379.

Impact Factor: 2,776

Contribution: Data extraction, analysis and the synthesis of results, representation of the results in all tables. Writing the publication, including submission and the revision of the manuscript.

*shared first authorship

PD Dr. rer. cur. Jan Kottner	Merve Akdeniz

10. Printed copies of selected publications

Publication 1:

Akdeniz, M. Gabriel, S. , Lichterfeld-Kottner, A. , Blume-Peytavi, U. and Kottner, J. (2018), Transepidermal water loss in healthy adults: a systematic review and meta-analysis update. Br J Dermatol, 179: 1049-1055.

Impact Factor: 6.714

https://doi.org/10.1111/bjd.17025

Publication 2:

Akdeniz, M, Tomova-Simitchieva, T, Dobos, G, Blume-Peytavi, U, Kottner, J.

Does dietary fluid intake affect skin hydration in healthy humans? A systematic literature review.

Skin Res Technol. 2018; 24: 459– 465.

Impact Factor: 1.657

https://doi.org/10.1111/srt.12454

Publication 3:

Akdeniz M, Boeing H, Müller-Werdan U, Aykac V, Steffen A, Schell M, Blume-Peytavi U, Kottner J:

Effect of fluid intake on hydration status and skin barrier characteristics in geriatric patients: an explorative study. Skin Pharmacol Physiol 2018;31:155-162.

Impact Factor: 1.974

https://doi.org/10.1159/000487403

Publication 4:

Akdeniz M, Hahnel E, Ulrich C, Blume-Peytavi U, Kottner J (2019)

Prevalence and associated factors of skin cancer in aged nursing home residents: A multicenter prevalence study. PLoS ONE 14(4): e0215379.

Impact Factor: 2,776

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11. Curriculum Vitae

Mein Lebenslauf wird aus datenschutzrechtlichen Gründen in der elektronischen Version meiner Arbeit nicht veröffentlicht.

12. List of publications

Original papers

1. **Akdeniz, M***, Gabriel, S*, Lichterfeld-Kottner A, Blume-Peytavi U., Kottner J (2018): Transepidermal water loss in healthy adults: a systematic review and meta-analysis update. British Journal of Dermatology. 179: 1049-1055. (IF: 6.714)

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3. **Akdeniz M**., Boeing H, Müller-Werdan U, Aykac V, Steffen A, Schell M, Blume-Peytavi U and Kottner J (2018): Effect of fluid intake on hydration status and skin barrier characteristics in geriatric patients: an explorative study. Skin Pharmacology and Physiology. 2018;31(3):155-162. (IF: 1.974)

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5. **Akdeniz M***, Hahnel E*, Ulrich C, Blume-Peytavi U, Kottner J (2019): Prevalence and associated factors of skin cancer in aged nursing home residents: A multicenter prevalence study. PLoS ONE. 14(4): e0215379. (IF: 2,776)

6. Lechner A, **Akdeniz M**, Tomova-Simitchieva T, Bobbert T, Moga A., Lachmann N., Blume-Peytavi U, Kottner J (2019): Comparing skin characteristics and molecular markers of xerotic foot skin between diabetic and non-diabetic subjects: An exploratory study. Journal of Tissue Viability. 2019. doi: 10.1016/j.jtv.2019.09.004. [Epub ahead of print] (IF: 2,831)

*shared authorship

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