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Short title: RCT to evaluate a new skincare regimen for podoconiosis in Ethiopia

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A randomized controlled trial to evaluate the effect of a new skincare regimen on skin barrier function in those with podoconiosis in Ethiopia

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Conflicts of interest

None declared.

Summary

Background Podoconiosis affects an estimated 3 million people in Ethiopia with a further 19 million at risk. Volcanic soil and pathogens enter skin breaches in the feet causing inflammation, lymphoedema and hyperkeratosis. There is no robust evidence on optimal podoconiosis skincare regimens to improve skin barrier function (SBF).

Objectives To evaluate the effectiveness of a new, low-cost, evidence-based intervention to improve SBF in the lower limbs of those with podoconiosis.

Methods A randomized controlled trial (NCT02839772) was conducted over 3 months in two podoconiosis clinics (n = 193). The intervention comprised 2% (v/v) glycerine added to a reduced volume of soaking water. The control group received the current skincare regimen. Primary outcome measures were transepidermal water loss (TEWL) and stratum corneum hydration (SCH) at four specific sites on the lower limbs.

Results Improvement in SBF was observed in both groups across all measurement sites and time points, although this was significantly greater in the experimental group. TEWL reduced in both groups at all sites. For example, on top of the foot the estimated group difference in TEWL at visit 4 was 1.751 [standard error (SE) = 0.0390] in favour of the experimental group [t = 3.15, df = 189.58, P = 0.002, 95% confidence interval (CI) 0.066–2.85], indicating a greater reduction in TEWL in the experimental group. Similarly, at the same site the estimated group difference in SCH at visit 4 was –2.041 (SE = 0.572) in favour of the experimental group (t = –3.56, df = 186.74, P = < 0.001, 95% CI –3.16 to –0.91), indicating a greater increase in SCH in the experimental group. There were also significantly greater reductions in odour, number of wounds and largest foot circumference in the experimental vs. the control group.

Conclusions The addition of 2% (v/v) glycerol to a reduced volume (83% reduction) of soaking water significantly improved SBF.

What's already known about this topic?

- Podoconiosis (nonfilarial elephantiasis, sometimes called 'mossy foot' due to moss-like skin eruptions) is a tropical skin disease caused by irritant soil particles and pathogens entering plantar skin via skin breaches, and affects lower leg lymphatics.
- It is incurable but treatable.
- The current podoconiosis skincare regimen reduces clinical disease stage and oedema, and improves skin condition and quality of life, but may not be optimum and requires 6 L of water, a scarce resource.

What does this study add?

- This is the first published randomized controlled trial to evaluate podoconiosis skin treatment regimens using quantitative measures of skin barrier function (SBF).
- A new treatment regimen, incorporating 2% (v/v) glycerol in one-sixth of the current water volume, significantly improved SBF and clinical disease presentation compared with the current regimen.

Podoconiosis is a non-infectious skin disease that results in bilateral and usually asymmetric lymphoedema below the knee.[1] It is found in over 20 countries across tropical Africa, Central America and northern India.[2] Prevalence data, unavailable in most countries, are available in Ethiopia. Areas of prevalence are associated with the minerals smectite, mica and quartz (crystalline silica) within alkaline volcanic soil.[3] Due to poverty or culture, subsistence farmers and others may wear no shoes or shoes that give inadequate protection. Plantar stratum corneum (SC) thickens, dries and becomes extremely brittle, leading to deep cracks and fissures, allowing soil particles and bacteria to enter, triggering the inflammatory process.[4]

Water is essential to cleanse the skin surface of soil and pathogens, to help maintain healthy skin barrier function (SBF) – a major challenge in the developing world, where water is typically carried to homes from remote standpipes, wells or rivers. Use of this precious resource for washing skin is a relatively low priority, resulting in poor foot hygiene. Subsequent oedema disrupts superficial lymphatic drainage, causing further oedema and stress on deeper lymphatics. If overloaded, this secondary drainage system can fail, causing lymphoedematous feet and legs.[5] The high protein content of static lymph fluid in tissues leads to trophic skin changes, including hair loss, xerosis, hyperkeratosis, adipose tissue deposition and papillomatosis (Fig. 1).[6] Figure 2 proposes a cyclical pathogenic model for podoconiosis induction and propagation. Without therapeutic intervention, the cycle continues, with worsening lymphoedema and skin change. Disease progression has five stages of severity (5 = most severe).[7] Transforming growth factor beta 1 has a pathogenic role in the disease and oxidative stress a lesser role.[8] The disease is thought to be T-cell mediated with high (63%) heritability.[9]

Significant social stigmatization and episodic severe leg pain from adenolymphangitis (ADL) give rise to severe macro- and microeconomic effects.[10] Acute attacks of ADL cause leg inflammation and inguinal lymphadenopathy, which results in lost work days and subsequent loss of family income. The estimated cost in one region of Ethiopia (population 1.5 million) was estimated at US$16 million per year. Stigmatization is widespread due to the appearance of the disease, unpleasant odour and unfounded fear of infection. Patients report that they are unable to marry, are shunned by others and excluded from social events.[11] This ostracism increases as the disease progresses. Wearing shoes provides only partial protection. One large study found heel cracks and foot trauma present regardless of shoe type.[12] Therefore, maintaining SBF health and effective washing of feet and legs are essential in podoconiosis prevention.

The current treatment regimen taught in the Action on Podoconiosis and Integrated Development Organization (APIDO) clinics consists of washing feet and legs daily in soapy water, a 30-min soak in 6 L water with 0.0125% (v/v) sodium hypochlorite (NaOCl), air drying and application of petrolatum jelly to augment SBF and reduce friction.[13] Surfactant action removes pathogens/soil, while the soak hydrates the SC (decreasing its elastic modulus, thus creating a pliable structure less likely to crack or split) and NaOCl reduces pathogen load. Whitfield's ointment is used, where appropriate, to treat fungal infection. A 1-year noncomparative longitudinal study using a similar regimen was effective in reducing disease clinical stage and oedema, and in improving quality of life scores ($n = 27$).[14] No previous randomized controlled trials (RCTs) assessing treatment regimens for this disease were identified.

We hypothesized that addition of low levels of humectant to the regimen would increase SC hygroscopicity, thus improving SBF and, ultimately, clinical outcome. Glycerine was chosen because of its wide range of efficacy, low cost, and availability even in resource-poor settings. In Ethiopia it can be obtained easily in roadside kiosks for around 50 pence per 100 mL). The chosen glycerol concentration of 2% (v/v) was based on a balance between cost and previous studies showing efficacy at this concentration.[15–18] Fluhr *et al.*[15] identified glycerol-related skin benefits as improved SCH, SBF, desmosomal degradation and skin mechanics, inhibition of SC lipid-phase transition, accelerated wound healing, reduced irritation and some antimicrobial efficacy. To conserve glycerol and water, we reduced the wash-water volume by 83%, from 6 L to 1 L.

Materials and methods

Study design and population

The null hypothesis was that an evidence-based skincare intervention that added 2% (v/v) glycerol to the current skin regimen used to treat Ethiopian podoconiosis patients would not improve SBF and disease-related quality of life, compared with the current regimen. The study used an RCT parallel-group design. Data were collected from two APIDO clinics in the Gamo Gofa zone, southern Ethiopia, from January to August 2014. Clinics were chosen within similar socioeconomic populations and geographical areas (with volcanic soil, high rainfall and elevations > 1600 m above sea level). Inclusion criteria were previously untreated patients with podoconiosis (determined by the experienced clinic nurses), > 18 years of age and able to give informed consent.

Sample size and selection

Computerized stratification of the sample ensured similar numbers of each sex and of those with mild/moderate (stages 1–3) to severe disease (stages 4–5);[7] this allowed variance between these factors to be determined. The study was powered to detect a difference between the treatment groups. Based on the pilot study results,[19] an effect size of around 0.72 was expected for TEWL, the primary outcome measure. To achieve a power of 80% (two-sided *t*-test) with a 5% significance level, 64 participants were required, divided equally between the two treatment groups. To allow detection of possible smaller effect sizes on other secondary outcome measures, a target sample size of 200 was chosen. Participants were allocated randomly to groups using a computer-generated sequential system based on clinic, sex and disease severity. Randomization was explained to participants as their allocation to a group using the current effective treatment or another using an extra, harmless product. Four containers were placed in each clinic (labelled by sex/disease severity) containing individually-coded sealed opaque envelopes opened sequentially by the nurse to reveal group allocation.

Ethical approval

Ethical approval for the study was obtained from the University of Hull, U.K. (approval letter reference 125, 29.11.13) and Sodo University, Ethiopia (24/214/2013). An explanation of the study was read out by the clinic nurse to each potential participant and any clarifying questions answered. As most were illiterate, those willing to take part signed or marked their agreement with a cross or ink mark from their index finger, witnessed, signed and dated by the clinic social worker.

Study groups and intervention tested

Each individual was taught (verbally and by demonstration) initially and at each monthly visit how to treat their feet/legs according to their group. Control group subjects continued with the daily skin treatment used currently in APIDO clinics (see above). In the experimental group the treatment was as follows: 1 L water (only) was used for feet soaking and splashing lower legs, and 20 mL glycerol was added to provide a 2% (v/v) dilution.

Measures used

The primary outcome measures of TEWL and SCH were measured using portable, wireless, noninvasive probes. TEWL (water flux across the SC, g m^{-2} h^{-1}) was measured with a VapoMeter® closed-chamber evaporimeter (Delfin Technologies, Kuopio, Finland) and SCH (reflecting SC water content) was measured in arbitrary units using a MoistureMeter SC probe (based on electrical capacitance) (Delfin Technologies). These instruments were used previously by one of the authors (P.M.) to successfully measure SBF in those with podoconiosis in rural Ethiopia.[4] Measurements were taken at three sites: on the outer, lower leg (8 cm below the fibula head (top), 8 cm above the external malleolus (base) at the midpoint between these sites, and the top of the foot (similar to Ferguson *et al.*[4]).

In each site, SCH measures were made in triplicate (recording the mean). Single TEWL measures were recorded. With both of these objective instrumental measurements it is critical to minimize interference from environmental artefacts. Therefore, in line with the manufacturer's[20] and other published guidelines,[21] measurements were restricted to times of the day when ambient temperature was lower, and patients were asked to rest and equilibrate for at least 20 min with measurement sites exposed. This process was aided by the automatic recording of ambient temperature and humidity by the VapoMeter. Measurements of TEWL are particularly challenging in external environments. The use of a closed-chamber evaporimeter proved to be critical in reducing local atmospheric perturbation and resulting measurement noise (as per Ferguson *et al.*[4]).

Other measures recorded were: stage of podoconiosis, trophic changes (mossy/papillomatosis changes present/absent); malodour (if detected on foot/leg by clinic nurse); number of wounds; work days lost due to ADL (defined as an episode of inflammatory pain associated with the lymph nodes within a lymphoedematous leg that led patients to be bedridden/unable to work); and largest leg and foot circumferences. The Amharic Dermatology Life Quality

Index (ADLQI), which has been validated for assessing those with podoconiosis, was used.[22] Its 10 questions rate aspects of an individual's disease-related quality of life. The maximum score of 3 for each question indicates the disease has a high impact, 2 a lot of impact, 1 a little and 0 indicates no impact or the question is irrelevant.

Data collection

The qualified nurses and social workers who had worked at each clinic for at least 1 year received an initial 5-h standardized training session provided by the principal investigator (PI). This included practice in measuring the liquids used in the trial, using the instruments and completing the data forms under the PI's supervision. Due to high rates of illiteracy, ADLQI questions were read out to individual participants by the clinic nurse.

A local nurse (with a master's degree in public health, studying podoconiosis), visited each clinic to monitor and review data collection and participant treatment at least seven times across the 7-month trial period. The PI also directly monitored staff at each clinic, their teaching of participants and data collection at week 1 (each day for 5 days) and then at weeks 10, 17 and 24. Baseline data were collected prior to intervention (visit 1) and data were then collected monthly for three months (visits 2–4).

Data analysis

The data analysis plan was developed a priori. Data were entered into IBM SPSS 22.0 (IBM, Armonk, NY, U.S.A.) and checked for outliers and completeness prior to analysis. Mixed multi-level modelling was used for continuous outcome measures. For each such measure, the change from baseline at visits 2–4 was calculated and used as the dependent variable in the analytic model. Generalized estimating equations were used for discrete, categorical or binary outcome measures. For each such measure, the change from baseline at visits 2–4 was calculated and used as the dependent variable in the model. The variables controlled for each outcome measure model were group, clinic, sex, initial stage of podoconiosis (visit 1), side (right/left) of leg and the value of corresponding measures at visit 1. A group-by-time interaction was included in the model to allow the group difference, if any, to vary in time.

Results

Of the 193 participants enrolled onto the study (97 in the control group and 96 in the experimental group, all completed except one male control group patient with mild/moderate disease who did not attend visit 4 (see CONSORT flow diagram, Fig. 3). Three participants (1.5%) had clinical signs of podoconiosis on only one leg/foot. Legs with clinical signs of podoconiosis were used as the unit for analysis (n = 383), except for the analysis of stage of podoconiosis where all legs (n = 386) were used as the unit of analysis. Twenty-five participants (12.9%) had a different stage of podoconiosis in each leg (moderate/less severe vs. severe). No adverse treatment effects were noted. Table 1 provides a demographic profile of patients at baseline.

Transepidermal water loss

Baseline mean TEWL values in both groups were greatest on the top of the foot (weaker SBF) and decreased progressively up the lower leg (indicating stronger SBF) (Table 2). Mean TEWL values in lower leg/foot sites reduced in both groups at visits 2–4, although the reduction was greater in the experimental group (highly significant group difference for all leg/foot sites at visit 4) (Table 3, Fig. 4). At all points at visits 2–4 TEWL reduction was greater in right legs and highly statistically significant. At the top of the lower leg the difference statistics were: t = –3.42, df = 186.089, P = 0.001, 95% CI –0.57 to –0.15; at the midpoint: t = –2.59, df = 187.075, P = 0.010, 95% CI –0.65 to –0.087; at the base: t = –2.62, df = 189.83, P = 0.010, 95% CI –0.60–0.083; and on the foot: t = –2.57, df = 189.49, P = 0.01, 95% CI –0.63 to –0.082.

Stratum corneum hydration

Baseline mean SCH was lower at the base of the leg and top of the foot, increasing progressively up the lower leg (Table 4). Mean SCH values at all points on the lower legs/feet increased in both groups over visits 2–4, although the increase was greater in the experimental group (highly significant) (Table 5, Fig. 5).There was no significant difference in SCH between right and left legs except at the base of the lower leg (nearing significance) (t = 1.92, df = 180.99, P = 0.057, 95% CI –0.65–0.010).

Stage of podoconiosis of all participants' legs at baseline and at fourth visit

At baseline (n = 386), 176 legs (45.6%) displayed severe disease (stages 4–5). By visit 4 (n = 384), this number had decreased to 50 legs (13.0%). Similarly, at baseline, 207 legs (53.6%) displayed mild/moderate disease (stages 1–3). By visit 4, this number had increased to 340 legs (88.5%). Together, these results indicate clinical improvement due to the two treatment regimens based on the description of stages. There was no significant treatment group difference at visit 4 [log odds ratio (OR) 0.45, standard error (SE) = 0.26; Wald $\chi^2 = 3.14$, df = 1, $P = 0.076$, 95% CI –0.048–0.95] nor stage difference between right/left legs.

Trophic ('mossy') skin changes

At baseline, trophic skin changes were present in 153 (79.3%) right legs/feet and in 156 (80.8%) left legs/feet. By visit 4, trophic changes were reduced and present in 120 (62.5%) right legs/feet and 117 (60.9%) left legs/feet: however, there was neither a significant treatment group difference at visit 4 nor between right/left legs.

Odour

At baseline, odour was present in 114 (59.1%) of legs/feet. By visit 4, odour was reduced and present in only two right legs/feet (1%) and one left leg/foot (0.5%). The odds of leg odour being present at visits 2, 3 and 4 were significantly lower in the experimental group (log OR –0.866, SE = 0.401; Wald $\chi^2 = 4.67$, df = 1, $P = 0.031$, 95% CI –1.652 to –0.080). However, the group difference was not clinically significant because the numbers with leg odour in each group reduced to almost zero.

Number of wounds

At baseline, 105 participants (54.4%) had four wounds (all were skin breaches and all areas of fungal infection were on the legs/feet). The experimental treatment led to significantly fewer wounds on legs/feet at visits 2–4 (for group difference $P < 0.05$). Those in the experimental group were expected to have fewer wounds (group ratio estimate = 2.06, SE = 0.74; Wald $\chi^2 = 7.75$, df = 1, $P = 0.005$, 95% CI 0.61–3.51). As most participants at visit 4 had no wounds, the group difference was clinically insignificant.

Number of days of work lost in previous month due to adenolymphangitis

At baseline, the mean number of work days lost in the previous month due to ADL was 4.56 for the control group and 4.44 for the experimental group. The group ratio in the expected number of days lost at visit 4 was not significant (group ratio estimate = 2.09, SE = 1.10; df = 1, $P = 0.058$, 95% CI –0.069–4.25), nor was the difference clinically significant as no participants lost any work days in the previous month due to ADL.

Correlation between days lost due to adenolymphangitis and number of wounds

The Spearman rank correlation coefficient at baseline was 0.25, at the second visit 0.31, the third 0.29 and the fourth 0.27. This indicated that at all time points there was a weak but highly significant correlation ($P < 0.001$) between the number of lower leg/foot wounds totalled over both legs and the number of days participants were unable to work due to ADL for visits 2, 3 and 4.

Largest lower leg circumference

In the control group the largest lower leg circumference reduced over the study period by 3.8 cm (from 32.1 to 28.3cm) and in the experimental group by 4.2 cm (32.0 to 27.8 cm). The between-group treatment difference was not significant ($t = 1.42$, df = 185.39, $P = 0.16$, 95% CI –0.11–0.69).

Largest foot circumference

In the control group, the mean foot circumference reduced over the study period by 2.4 cm (from 27.5 to 25.1 cm). The reduction was greater in the experimental group by 3 cm, (from 27.7 to 24.7 cm). The treatment group difference was highly statistically significant ($t = 3.55$, df = 169.92, $P < 0.001$, 95% CI 0.26–0.89). The reduction in circumference was significantly greater in the right foot ($t = –3.27$, df = 152.99, $P = 0.001$, 95% CI –0.24–0.059).

Amharic Dermatology Life Quality Index

The mean ADLQI reduced in both groups over the study period, indicating an improved self-assessed disease-related quality of life. In the control group, the mean ADLQI reduced from 21.6 to 4.1 (an improvement of 17.5 points). In the experimental group, the mean ADLQI reduced from 21.1 to 3.9 (an improvement of 17.2 points). The estimated group difference at visit 4 was not statistically significant ($t = –0.12$, df = 178.81, $P = 0.90$, 95% CI (–1.13–1.002).

Discussion

To our knowledge, this is the first RCT to study podoconiosis skincare regimens, and the largest to use a dilution of only 2% glycerol to improve SBF. As hypothesized, the addition of 2% (v/v) glycerol to a significantly reduced volume of soaking water led to significant incremental improvements in SBF in the lower legs and feet of those with podoconiosis. This was evident in the significantly higher recorded values of SCH and lower recorded values of TEWL in skin on legs and feet of those receiving the experimental vs. the current treatment regimen. This was accompanied by significantly greater reductions in malodour, number of wounds and largest circumference of foot in the experimental group vs. the control group. No adverse effects were reported.

Ferguson *et al.*[4] measured SBF in those with podoconiosis vs. matched control subjects in a previous non-intervention study. They reported significantly lower levels of SCH in the feet/lower legs of those with podoconiosis, indicating a greater propensity to SC dryness and cracking for those with the disease (hence, a higher risk of reactive soil/pathogens entering foot tissue). This current study builds on these insights and demonstrates conclusively the central role of compromised SBF in the induction and propagation of podoconiosis. There is no other explanation for the relatively acute significant effect of only 2% (v/v) glycerol, in a simple water soak, on both objective SBF measures and clinical outcome in this chronic lymphoedematous condition.

We propose a therapeutic model centred around increasing SC hygroscopicity and on the cascade of ensuing events, summarized by Rawlings and Matts,[23] including: (i) an immediate reduction in the SC elastic modulus, resulting in a softer, more flexible substrate less prone to cracking/splitting; (ii) longevity of SCH, activating desquamatory enzymes in previously dry SC, leading to a significantly thinner, more compact SC over time; (iii) a reduction in the inflammatory process, leading to a more mature, efficient SC; and (iv) ultimately, restoration of healthy SBF, better able to prevent ingress of irritant soil/pathogens into tissue.

Sikorski *et al.*[14] investigated the effect of a similar skin hygiene regimen in patients with podoconiosis vs. a control group over 1 year. Despite the current study being only 3 months in duration, we report higher reductions in largest lower leg circumference (4.0 cm and 4.1 cm, respectively, in this study vs. 2.0 cm for Sikorski *et al.*[14]) and a greater improvement in ADLQI score (17.1 and 17.5 points, respectively, in this study vs. 15.0 for Sikorski *et al.*[14]). We cannot account for these differences in response but hypothesize that there could be different study populations, locations, climate or skin regimen compliance.

In this current 3-month intervention study, 62.7% of legs/feet still had ‘mossy’ trophic changes evident across the treatment groups, compared with 22.2% reported by Sikorski *et al.* after 1 year of treatment.[14] This indicates that a longer period of continuous treatment is probably needed to reduce trophic changes. It is remarkable that an intervention comprising water, soap and petrolatum can bring about these improvements at all and, once again, indicates the importance of improving and maintaining SBF in the treatment regimen.

In this study, a reduction in the number of wounds in both groups was associated with a reduction in the work days lost due to ADL. This is important, as most of those in this study were subsistence farmers, so any income loss would have significant economic effects. Indeed, it is estimated that Ethiopia loses approximately US$200 million annually through lost work days due to podoconiosis.[10]

The current study and that of Sikorski *et al.*[14] both demonstrate the utility of simple treatment regimens in significantly improving quality of life in those with podoconiosis (evidenced by improved DLQI scores). We hypothesize that this is likely due to a combination of the skincare and attention received in treatment sites, the visible improvement in leg/foot condition, reduction in ADL and odour, and a concomitant decrease in stigma and ostracism. The significant difference in TEWL reduction in right vs. left legs and greater reduction in circumference of the right foot may have been due to more attention being given to the right leg during treatment or to this leg being used more than the left when walking (in those with a right-side preference). Exercise is known to improve circulation and venous return, thus reducing oedema.[6] It could also be explained by anatomical and physiological differences between legs that impair left leg venous and lymphatic drainage.[25]

Finally, in this study, we incorporated 2.0% (v/v) glycerol into only 1 L of wash/soaking water (vs. the current 6 L). Participants were able to follow instructions and use the new treatment protocol effectively. This new regimen not only conserves the precious resource of water, but also minimizes glycerol requirement.

In summary, the results of this study support our hypothesis that current podoconiosis treatment regimens can be enhanced further by increasing the water-binding potential of the SC with the humectant, glycerol, which is widely available in Ethiopia, even in rural settings, at low cost. The addition of glycerol to a water soak may be effective in a wide variety of other skin diseases, including lymphoedematous conditions such as lymphatic filariasis, where compromised SBF is indicated and skincare is critical. Glycerine use in podoconiosis treatment is currently being considered for implementation by APIDO. Further research is needed to investigate lower dilutions of glycerol and different soaking methods (e.g. wrapping technique) to further reduce cost and water usage, and increase efficiency.

There are some study limitations: Podoconiosis diagnosis was based on participants living at high altitude, with volcanic soil, high rainfall, and with clinical manifestations of the disease.

No differential diagnosis was made to exclude those with swelling of the lower leg due to other diseases such as lymphatic filariasis, liver or heart failure. Although groups were matched as far as possible, there may have been other confounding factors influencing the results that are not identified. Although participants were not supervised daily to ensure treatment adherence, improvements in SBF would not have been achieved without some level of compliance.

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Figure legends

Fig 1. Feet of patients presenting with oedema, hyperkeratosis, nodules, fused toes, mossy changes and ulceration due to ill-fitting shoes.

Fig 2. Development and cycle of progression of lymphoedema in podoconiosis.

Fig 3. CONSORT 2010 flow diagram.

Fig 4. Top of foot: difference over time between groups in mean transepidermal water loss (g m^{-2} h^{-1}).

Fig 5. Top of foot: difference over time between groups in mean stratum corneum hydration (arbitrary units).

Table 1 Demographic profile of all participants at baseline (*n* = 193)

Age (years)	*n* (%)	Occupation	*n* (%)	Time to onset (years)	*n* (%)	Shoes worn in previous week	*n* (%)
18–29	54 (28)	Farmers	89 (46.1)	> 1	2 (1)	Barefoot	18 (9.4)
30–39	33 (15.8)	Housewives	82 (42.5)	1–2	47 (24.4)	Hard plastic sandals	120 (62.2)
40–49	47 (22.5)	Students	14 (7.3)	3–4	49 (25.4)	Canvas shoes	24 (12.4)
50–59	32 (15.3)	Others, e.g. servants and merchants	8 (4.1)	5–6	47 (24.4)	Other enclosed shoes	20 (10.4)
60–69	22 (10.5)			7–8	23 (11.9)	Open sandals made with tyres	9 (4.7)
> 70	5 (2.6)			9–10	18 (9.3)	Other sandals	2 (1)
				11–12	4 (2.1)		
				> 12	3 (1.6)		

Table 2 Mean transepidermal water loss (TEWL) across all participants measured at different anatomical sites within podoconiosis-affected legs/feet, at baseline

Site on the lower leg	Mean TEWL right leg, first visit	Mean TEWL left leg, first visit
Top	13.08	13.40
Midpoint	14.29	15.02
Base	16.62	17.17
Top of foot	22.41	22.75

All data are presented in g m^{-2} h^{-1}.

Table 3 Estimated group differences in transepidermal water loss (TEWL) at visits 2, 3 and 4

Anatomical site	Estimated group difference in TEWL ($g m^{-2} h^{-1}$)	SE	*t*	df	*P*	95% CI for the group difference
Top of outer lower leg	1.58	0.30	5.34	89.35	< 0.001	0.10–2.16
Midpoint of outer lower leg	1.68	0.35	4.87	189.79	< 0.001	1.002–2.37
Base of outer lower leg	1.97	0.39	5.11	189.62	< 0.001	1.21–2.73
Middle of top of foot	1.75	0.39	3.15	189.58	0.002	0.66–2.85

SE, standard error; df, degrees of freedom; CI, confidence interval.

Table 4 Mean stratum corneum hydration (SCH) across all participants measured at different anatomical sites within podoconiosis-affected legs/feet at baseline

Site on the lower leg	Mean SCH, right lower leg	Mean SCH, left lower leg
Top	9.33	9.54
Midpoint	9.03	9.23
Base	8.51	8.55
Top of foot	8.49	8.62

All data are presented in arbitrary units, measured using the MoistureMeter (Delfin Technologies, Kuopio, Finland).

Table 5 Estimated group differences in stratum corneum hydration at visits 2, 3 and 4

Site on the lower outer leg	Estimated group difference	SE	*t*	df	*P*	95% CI for the group difference
Top	–2.08	0.52	–4.24	165.31	< 0.001	–3.04 to –1.11
Midpoint	–1.66	0.47	3.55	180.92	< 0.001	–2.58 to –0.74
Base	–1.64	0.47	– 3.47	186.31	0.001	–2.57 to –0.71
Top of foot	–2.04	0.57	–3.57	186.74	< 0.001	–3.17 to –0.91

All data are presented in arbitrary units. SE, standard error; df, degrees of freedom; CI, confidence interval.