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ORIGINAL ARTICLE

Clinical, haematological and biochemical profiling of podoconiosis lymphoedema patients prior to their involvement in a clinical trial in the Northwest Region of Cameroon

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Background: Prior to carrying out clinical trials, it is important to assess the health status of the study participants to be able to interpret subsequent changes that may be related to the effects of the treatments during the follow-up of patients. This study presents the clinical, haematological and biochemical profiles of podoconiosis patients prior to their involvement in the PodoLEDoxy clinical trial.

Methods: All lower limb lymphoedema patients visiting the centre were screened and a podoconiosis diagnosis was based on clinical manifestation and detailed medical history. Patients who satisfied the eligibility criteria were enrolled in the study and their demographic data, vital signs and medical history were collected followed by biochemical and haematological examinations.

Results: Of the 222 participants enrolled in the study, 55.4% and 41.4% had either stage 3 or 2 podoconiosis as their highest stages, respectively. On physical examination, gastritis (46%) and poor vision (2.7%) were the most prevalent health issues identified. The majority of haematological and biochemical values were within the normal range except for mean platelet volume (47.7%), plateletcrit (58.1%), platelet distribution width (66.2%), mean corpuscular volume (67.6%) and red cell distribution width-standard deviation (79.3%), where >40% of the study participants had values out of the normal.

Conclusion: The clinical, haematological and biochemical profiles of the study participants were largely within the normal range except for certain haematological parameters that might be worth investigating.

Keywords: biochemical, clinical, haematological, lymphodema, podoconiosis, profiling

Introduction

Lower limb lymphoedema is caused by several neglected tropical diseases such as podoconiosis, lymphatic filariasis (LF) and leprosy. While the latter two conditions are caused by a parasite and bacterium, respectively, podoconiosis is a non infectious disease associated with the exposure of bare feet to irritant alkaline red clay soils.[1–4]

Podoconiosis is locally known as 'mossy foot' and causes massive swelling of the lower legs and feet resulting in heavy aching discomfort, which limits a person's ability to use his or her legs.[5] It increases the risk to certain infections, causes emotional distress, depression and stigmatisation in the affected person. This imposes huge burdens on affected individuals, their families and communities, resulting in a loss of economic productivity.[6–10]

Podoconiosis arises mostly in barefoot subsistence farmers after long-term exposure to irritant red clay soils.[11,12] Swelling occurs on the lower limbs and ascends, starting in the foot and progressing to the knee. It has been classified into five stages based upon severity, with stage 5 being the most severe stage.[13]

Podoconiosis was identified as a neglected tropical disease by the WHO in 2011.[14] Approximately 20 million people worldwide are thought to be affected by lymphoedema, 4 million cases of which are due to podoconiosis.[15,16] It is a major health problem in developing countries and has been reported in more than 32 countries in Africa, Latin America and South East Asia.[11,15] It affects people of all ages, but is more prevalent among older age groups. However, females are more affected due to the nature of their activities, such as farming.[4] The recent nationwide mapping of podoconiosis in Cameroon reported a 0.5% prevalence of lower limb lymphoedema, of which 62.7% were podoconiosis cases. This also highlighted the Northwest Region of Cameroon as an endemic area recording the highest prevalence (1.7%) among all 10 regions.[17,18]

To date, there is no specific diagnostic tool for defining podoconiosis; the diagnosis is made solely on the basis of medical history and clinical examination, coupled with the exclusion of other causes of lower limb lymphoedema.[19] Although there has been a significant improvement over the last few years in the management of podoconiosis cases,[20] much has still to be learned to improve on its diagnosis and treatment. Knowledge of the clinical and laboratory patterns of people with lower limb lymphoedema due to podoconiosis is of interest because it presents opportunities for the diagnosis of podoconiosis, but interestingly, to date no studies have been conducted to investigate the clinical and laboratory features of podoconiosis patients. There is, therefore, a need to understand the clinical, haematological and biochemical profiles of patients with lymphoedema of non-filarial origin (podoconiosis) with the aim of identifying patterns unique to the disease. In addition, some of the measurements can also be indicative of the burden of other non-communicable diseases among podoconiosis patients that have clinical and programmatic implications.[21,22] These patterns can open up avenues that might serve as biomarkers to discriminate podoconiosis from other diseases that cause lymphoedema.

The aim of this study was to describe the clinical, haematological and biochemical profiles of podoconiosis patients in the Northwest Region of Cameroon screened prior to their involvement in the Doxycycline for treatment of non-filarial lymphoedema due to podoconiosis (TAKeOFF PodoLEDoxy) clinical trial. This was a randomised, double-blind, placebo-controlled, phase II trial to determine if a doxycycline treatment regimen of 6 wk will improve lymphoedema in patients with stage 2 and/or 3 podoconiosis.

Materials and Methods

Study area

This study was conducted at a lymphoedema clinical trial centre (PodoLedoxy clinical trial centre) situated at Foncha Street Nkwen (with the coordinates 5.9811374 and 10.1706479) in Bamenda, the headquarters of the Northwest Region of Cameroon. It is located 366 km northwest of the capital, Yaoundé. Participants in the study resided in 11 of 19 health districts in the North West Region of Cameroon that had the highest prevalence (1.7%) of podoconiosis.[17] The health districts were Bafut, Bali, Bamenda, Batibo, Fundong, Kumbo, Ndop, Ndu, Nkambe, Santa and Tubah, which have an estimated total population of approximately 1 548 926 people.

Study design and period

A cross-sectional study was conducted from April to December 2019. Figure 1 presents the flowchart of recruitment and the number of individuals who were excluded and eligible for the clinical trial.

Study population

The study population consisted of all lymphoedema patients clinically suspected of podoconiosis when visiting the lymphoedema clinical trial centre within the study period.

Inclusion and exclusion criteria

The following inclusion criteria were used: people with stage 2 and/or 3 podoconiosis in at least one leg, age 18–60 y, body weight $\geq$40 kg, residing in a podoconiosis-endemic district for $\geq$2 y and testing negative for LF using Filarial Test Strip. The following exclusion criteria were used: individuals who do not fulfil the inclusion criteria, pregnant women and breastfeeding mothers, lymphoedema due to other causes, HIV, podoconiosis patients with alanine aminotransferase (ALT) >80 U/L, aspartate aminotransferase (AST) >80 U/L, gamma-glutamyl transferase (γ-GT)>100 U/L, serum creatinine >2.8 mg/dL, neutrophil <1100/mm^3, haemoglobin <8 g/dL and platelets <100 000/mm^3.

Study variables

The following key variables were measured in the study:

- Sociodemographic variables: gender, age, occupation and duration in the community (endemicity);
- Clinical variables: blood pressure, pulse rate, temperature, weight, physical examination and medical history;
- Haematological variables: white (WBC) and red blood cell (RBC) count, haemoglobin (HGB), haematocrit (HCT), mean corpuscular volume (MCV), mean corpuscular haemoglobin concentration (MCHC), mean corpuscular haemoglobin (MCH), red cell distribution width (RDW), platelet count (PLT), mean platelet volume (MPV), plateletcrit (PCT) and platelet distribution width (PDW).
- Biochemical variables: ALT, AST, γ-GT and serum creatinine. Urinalysis: specific gravity, protein, blood, glucose, nitrite, pH, ketone, bilirubin, urobilinogen and leucocytes.

Case identification

A total of 222 podoconiosis patients were screened for enrolment to the clinical trial after obtaining their informed consent. All lower limb lymphoedema patients who visited the centre were screened for podoconiosis by two trained personnel with

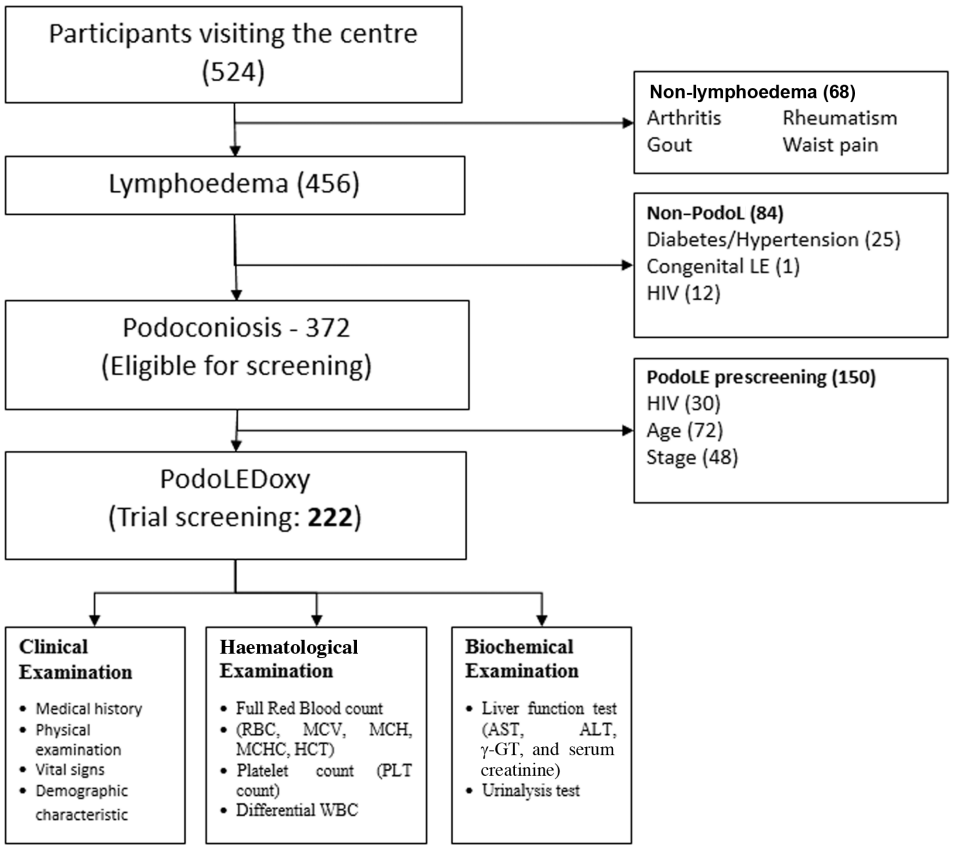

Figure 1. Flowchart of activities.

experience in podoconiosis diagnosis. Diagnosis was based on clinical manifestation and detailed medical history, followed by staging using the five-point scale of Tekola et al.[13] Confirmed podoconiosis participants who satisfied all the eligibility criteria were retained and enrolled in the study. Patient's demographic data were recorded; their vital signs were measured and medical history recorded.

Sample collection, processing and transportation

Samples (blood and urine) were collected in the laboratory unit of the centre and labelled with the date of collection and participant code. In the centre, 50–60 mL of midstream urine was collected in sterile urine cups for urinalysis with a urinalysis dip stick (URIT 11G; Urit Medical Electronic Co., Ltd, Guangxi); pH, glucose, protein, blood, nitrite, ketone, bilirubin, urobilinogen, specific gravity and leucocytes were the parameters assessed using the collected urine samples.

A total of 6 mL of venous blood was collected through venepuncture from each study participant. Next, 4 mL of blood was collected into an EDTA tube for biochemical analysis and 2 mL into a clot activator tube (BD Vacutainer, UK) for haematological analysis. The laboratory request form was completed and the sample collection time noted. Whole blood and serum samples were transported to the Bamenda Regional Hospital Laboratory for analysis. The 2 mL blood samples collected in the clot activator tubes were centrifuged at a speed of 2000x g for 10 min and 500 µL of serum was extracted and aliquoted into labelled Eppendorf tubes. To exclude LF as a possible cause of lymphoedema in lymphoedema individuals, 75 µL of capillary blood was collected to perform the Alere filarial test (Alere Scarborough, Inc., USA) according to the manufacturer's instructions.

Laboratory examination

The EDTA tube containing 4 mL whole blood and the Eppendorf tube containing 500 µL were packaged into iceboxes (4°C) and transported within 4–5 h to the Bamenda Regional Hospital Laboratory, which is situated approximately 6.2 km from the centre. The samples were received and documented by the laboratory reception staff along with the test request forms upon arrival.

The samples were forwarded to the various laboratory units (biochemistry and haematology) and analyses were performed immediately. ALT, AST, γ-GT and serum creatinine were measured using an automated biochemical analyser (BIOSMART 240; Bionline S.R.L, Chile) according to the manufacturer's instructions. Result outputs were projected onto the screen, verified then printed out.

The haematological parameters were determined using an automated haematology analyser (URIT 3300; URIT Medical

Table 1. Sociodemographic characteristics of study population

	Podoconiosis subjects (n=222)		
	Class	Frequency	%
Age, y	18–30	40	17.9
	31–40	54	24.1
	41–50	58	25.9
	51–60	72	32.1
Gender	Female	192	85.7
	Male	32	14.3
Occupation	Farmer	100	44.64
	Business	40	17.86
	Student	15	6.70
	Teacher	12	5.36
	Tailor	11	4.91
	Others	32	14.29
	Farmer + (other)	14	6.25
Podoconiosis stage	Stage 2	92	41.07
	Stage 3	123	54.91
	Stage 4	07	3.42

Electronic Group Co., Ltd, China), which performs full blood counts. To determine the differential WBC count, two experienced personnel independently counted the blood cells and the average for each cell type was calculated and recorded. After analysis, the results for each participant were validated by the laboratory head, placed in sealed envelopes then made available for collection at reception.

Quality control

Biochemical and haematological analysis were performed in accordance with the standard operating protocol and the manufacturer's instructions. The test was conducted in a certified laboratory by trained and certified laboratory technologists with experience in the use of automated analysers. For every automated machine, daily quality assurance checks were performed in accordance with the manufacturer's recommendations.

Ethical considerations

Ethical approval was obtained from the National Ethics Committee for Health Research on Humans (CNERSH) and the clinical trial is registered under International Standard Randomised Controlled Trial Number (ISRCTN) 11881662. Individual informed consent was obtained from each participant. Patient information sheets, assent and consent forms were printed in French and English, the official languages of Cameroon. Confidentiality was assured by assigning unique codes to all participants and their identification files were kept in a secured locker.

Data analysis

Data were entered by two data clerks using REDCap software secure web application (REDCap 7.0.6 -Vanderbilt University, Nashville, Tennessee USA. https://www.project-redcap.org), compared, then any inconsistencies corrected. The validated data were then exported to Excel 2013 (Microsoft Corporation, Redmond, Washington, USA) and analysed using SPSS version 20 (IBM SPSS Statistics, Armonk, NY, US). Summary frequency tables were generated and parameters were categorised into normal and abnormal based on reference ranges set by the trial and the reference laboratory of the Bamenda Regional Hospital.

Results

Sociodemographic data

In total, 222 individuals with podoconiosis were included in the study, of whom 191 (86%) and 31 (14%) were females and males, respectively. One hundred and thirty of the participants were aged >40 y and the occupation of 113 (50.9%) was farming. The majority of participants had either stage 3 (55.4%) or stage 2 (41.4%) podoconiosis as their highest stages (Table 1).

Vital signs and comorbidities

Clinically, most of the participants had vital signs within the normal range, with five of them being hypertensive (Table 2). Upon physical examination, the most prevalent health issues identified were gastritis (21/222; 9.46%) and poor vision (6/222; 2.7%). Evidence of surgery was also observed in 12 participants (5.41%) (Supplementary Table 1). The following reported comorbidities

Table 2. Vital sign presentation of study participants

	Reference ranges	Class	Frequency	%
Temperature	36.5–37.5	Normal	220	99.1
		High	2	0.9
Pulse	60–100	Normal	220	99.1
		Low	2	0.9
Blood pressure	<120/80	Normal	169	76.1
	>130/80–120	High blood pressure	48	21.6
	>180/>120	Hypertensive crises	5	2.3

Table 3. Haematological profiles of study participants

Parameter	Classification	Stage 2 n (%)	Stage 3 n (%)	Stage 4 n (%)	Total n (%)	Reference range
WBC (x 10^2 µl)	Normal	69 (75.0)	95 (77.20)	5 (71.40)	169 (76.10)	4.0–10.0
	Abnormal	23 (25.0)	27 (22.0)	2 (28.60)	52 (23.40)	
HCT(%)	Normal	71 (77.20)	75 (61.00)	5 (71.40)	151 (68.00)	36.0–48.0
	Abnormal	21 (22.80)	47 (38.20)	2 (28.60)	70 (31.50)	
HBG (g/dL)	Normal	92 (100.00)	122 (99.20)	7 (100.00)	221 (99.50)	11.0–15.0
MCV	Normal	32 (34.80)	37 (30.10)	2 (28.60)	71 (32.00)	80.0–99.0
	Abnormal	60 (65.20)	85 (69.10)	5 (71.40)	150 (67.60)	
Eosinophil (%)	Normal	63 (68.50)	79 (64.20)	3 (42.90)	145 (65.30)	1–6
	Abnormal	29 (31.50)	44 (35.80)	4 (57.10)	77 (34.70)	
Monocytes (%)	Normal	75 (81.50)	94 (76.40)	7 (100.00)	176 (79.30)	2–10
	Abnormal	17 (18.50)	28 (22.80)	0 (0.00)	45 (20.30)	
Lymphocytes (%)	Normal	53 (57.60)	77 (62.60)	4 (57.10)	134 (60.40)	21–45
	Abnormal	39 (42.40)	45 (36.60)	3 (42.90)	87 (39.20)	
Neutrophil (%)	Normal	90 (97.80)	119 (96.70)	7 (100.00)	216 (97.30)	45–75
	Abnormal	2 (2.20)	3 (2.40)	0 (0.00)	5 (2.30)	
PCT (%)	Normal	33 (35.90)	55 (44.70)	4 (57.10)	92 (41.40)	0.10–0.28
	Abnormal	59 (64.10)	67 (54.50)	3 (42.90)	129 (58.10)	
PDW	Normal	30 (32.60)	42 (34.10)	2 (28.60)	74 (33.30)	10.0–14.0
	Abnormal	62 (67.40)	80 (65.00)	5 (71.40)	147 (66.20)	
MPV (fL)	Normal	43 (46.70)	66 (53.70)	6 (85.70)	115 (51.80)	7.4–10.4
	Abnormal	49 (53.30)	56 (45.50)	1 (14.30)	106 (47.70)	
MCHC (g/dL)	Normal	76 (82.60)	101 (82.10)	5 (71.40)	182 (82.00)	32.0–36.0
	Abnormal	16 (17.40)	21 (17.10)	2 (28.60)	39 (17.60)	
PLT (10^3uL)	Normal	92 (100.00)	122 (99.20)	6 (85.70)	220 (99.10)	100–300
	Abnormal	0 (0.00)	0 (0.00)	1 (14.30)	1 (0.50)	
RDWSD (fL)	Normal	20 (21.70)	24 (19.50)	1 (14.30)	45 (20.30)	39.0–46.0
	Abnormal	72 (78.30)	98 (79.70)	6 (85.70)	176 (79.30)	
RDWCV (%)	Normal	66 (71.70)	78 (63.40)	5 (71.40)	149 (67.10)	11.5–14.5
	Abnormal	26 (28.30)	44 (35.80)	2 (28.60)	72 (32.40)	
MCH (pg)	Normal	67 (72.80)	88 (71.50)	2 (28.60)	157 (70.70)	26.0–32.0
	Abnormal	25 (27.20)	34 (27.60)	5 (71.40)	64 (28.80)	

HCT, haematocrit; HGB, haemoglobin; MCH, mean corpuscular haemoglobin; MCHC, corpuscular haemoglobin concentration; MCV, mean corpuscular volume; MPV, mean platelet volume; PCT, plateletcrit; PDW, platelet distribution width; PLT, platelet count; RDWSD, red cell distribution width-standard deviation; RDWCV, red blood cell distribution coefficient of variation; WBC, white blood cell.

were identified: gastritis (10), hypertension (9), diabetes mellitus (2), leg ulcer (2), asthma (1), cataract (1) and tinea versicolor (1) (Supplementary Table 2).

Haematological profiles

The haematological parameters were within the normal range (Table 3). However, for MPV (47.7%), PCT (58.1%), PDW (66.2%), MCV (67.6%) and RDWSD (79.3%), >40% of the study participants had values outwith the normal range (Supplementary Table 3). Similar observations were made regarding RBC, WBC and the platelet picture, as no abnormalities were prevalent within a particular group of study participants. The abnormalities recorded for RBC, WBC and platelets are presented in Table 4. For the blood picture, 17.6% of study participants had microcytic red blood cells; 10.4% of the participants had neutropenia and 22.5% had thrombocytosis.

Biochemical profiles

The biochemical profiles of blood serum were within the normal range for most participants. Less than 3% of the study participants had abnormal ALT, AST and γ-GT values while 9% had abnormal creatinine (Table 5). Biochemical measurements of urine for a majority of participants were also within the normal range (Supplementary Table 4).

Discussion

The PodoLEDoxy clinical trial aims to test the efficacy of a 6-wk doxycycline regimen as a treatment option for non-filarial

Table 4. Red blood cell, white blood cell and platelet picture of study subjects

	Cell type	Frequency	%
RBC size	Macrocytic	4	1.8
	Microcytic	39	17.6
	Normocytic	170	76.6
	Other	9	4.2
RBC HB conc.	Hyperchromic	3	1.4
	Hypochromic	58	26.1
	Normochromic	153	68.9
	Other	8	3.7
RBC shape	Burr cell	8	3.6
	Rouleux formation	9	4.1
	Ovalocyte	16	7.2
WBC	Normal	123	55.4
	Scanty	48	21.6
	Left shift of neutrophils	8	3.6
	Lymphopenia	4	1.8
	Monocytosis	7	3.2
	Neutropenia	23	10.4
	Basophils	3	1.4
	Eosinophilia	11	5
	Leucopenia	2	0.9
	Lymphocytosis	5	2.3
Platelet	Normal	164	73.9
	Thrombocytosis	50	22.5
	Giants	48	21.6
	Large forms	14	6.3

HB, hemoglobin; RBC, red blood cells; WBC, white blood cell.

lymphoedema caused by podoconiosis. This is a phase II trial involving the administration of 200 mg/d of doxycycline treatment for 6 wk that has been shown to halt or improve disease severity in filarial lymphoedema.[23] Building on the successes of the regimen in filarial lymphoedema, the trial seeks to determine if a similar outcome can be observed with non-filarial lymphoedema. Prior to carrying out clinical trials, it is important to assess the health status of participants. This study therefore presents the clinical, haematological and biochemical profiles of podoconiosis study participants screened for enrolment in the trial.

To the best of our knowledge, this is the first study attempting to investigate and document the clinical, haematological and biochemical profiles of podoconiosis patients. Because of the long duration of the treatment regimen, which exerts significant pressure on liver function, profiling these individuals with a health condition that has no specific diagnostic and treatment tool is important.

On clinical examination, most of the participants were clinically fit except for stage 2 and 3 lymphoedema, which was of interest in the PodoLEDoxy clinical trial. This is clearly demonstrated by the fact that 75.7% and 69.0% had no comorbidities or health issues upon physical examination, respectively. This is important because it ensures that the values measured in our study largely reflected effects due to the podoconiosis condition and were not attributable to any other comorbidity that could have significantly affected the parameters investigated. In addition, it also ensures that during trial follow-ups, it is easier to identify any effect of the doxycycline treatment.

With respect to the haematological profiles, a significant proportion of the participants had values outwith the normal range. The most noticeable abnormality was the size and proportion of platelets (PDW and PCT) and red blood cells (RDW and MCV). The blood picture also revealed a considerable percentage of microcytic RBC in participants. This abnormality is associated with several diseases or a clinical state such as thalassemia, anaemia of chronic inflammation, lead poisoning, iron deficiency anaemia or sideroblastic anaemia.[24,25] Since the major morbidity in our study participants is podoconiosis, abnormalities in the parameters mentioned may be a consequence of lymphoedema and thus may merit further investigation. Examining the biochemical profiles, the liver and kidney function parameters measured were largely within the normal range, indicating that the liver and kidney might not be implicated in podoconiosis disease.

This study was limited to profiling the clinical, haematological and biochemical profiles of podoconiosis patients who satisfied

Table 5. Biochemical parameters of blood serum in between control and all podoconiosis participants

Parameter	Classification	Stage 2 n (%)	Stage 3 n (%)	Stage 4 n (%)	Total n (%)	Reference range
Creatinine (mg/dl)	Normal	88 (95.70%)	106 (86.20)	7 (100.00)	201 (90.50)	0.7–2.8
	Abnormal	4 (4.30)	16 (13.00)	0 (0.00)	20 (9.00)	
γ-GT (U/L)	Normal	90 (97.80)	118 (95.90)	7 (100.00)	215 (96.80)	11–100
	Abnormal	2 (2.20)	4 (3.30)	0 (0.00)	6 (2.70)	
AST (U/L)	Normal	91 (98.90)	119 (96.70)	7 (100.00)	217 (97.70)	0–80
	Abnormal	1 (1.10)	3 (2.40)	0 (0.00)	4 (1.80)	
ALT (U/L)	Normal	90 (97.80)	121 (98.40)	7 (100.00)	218 (98.20)	0–80
	Abnormal	2 (2.20)	1 (0.80)	0 (0.00)	3 (1.40)	

ALT, alanine transaminase; AST, aspartate transaminase; γ-GT, gamma-glumyltransferase.

the baseline eligibility criteria for participating in the PodoLEDoxy clinical trial. Thus, it did not include podoconiosis patients with underlying comorbid conditions, which could have significantly affected the parameters measured. By contrast, this strengthened the study because its results could be related more directly to podoconiosis as, in large part, the participants did not have any other comorbid conditions that could significantly affect the results.

With large gaps still remaining in the understanding of the immunology and pathophysiology of podoconiosis, studying the clinical and laboratory profiles of podoconiosis participants screened for the clinical trial was an opportunity to explore potential patterns associated with people with podoconiosis. Therefore, the information presented might identify and open avenues for further clinical studies or research.

Conclusion

Upon physical examination, 68.92% of the enrolled participants presented with no medical condition, while gastritis (9.46%), poor vision (4.05%) and hypertension (2.25%) were the most recorded comorbid conditions. The haematological profiles were within the normal range for most study participants. High proportions of participants with abnormal haematological values were recorded for MPV (47.7%), PCT (58.1%), PDW (66.2%), MCV (67.6%) and RDWSD (79.3%). For the biochemical parameters, >97% of the study participants had measurements within the normal range.

Supplementary data

Supplementary data are available at *Transactions* online.

Authors' contributions: Conceptualisation: SW and AH; study protocol: UKS, MR, AH and SW; clinical assessment: INN, BLN and GTN; sample analysis and interpretation of data: RTM, TY, GNA, RAA, MEE, JFC BLN, GTN and CAK; manuscript drafting: BLN, GTN, CAK, RTM, AJN, SW and FFF; critically revising the manuscript for intellectual content: KD, AJN, MR and PE; and guarantors of the paper: AH and SW.

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