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# Multi-center feasibility study of microwave radiometry thermometry for non-invasive differential diagnosis of arterial disease in diabetic patients with suspected critical limb ischemia

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A B S T R A C T

*Aims:* Diagnosis of vascular involvement in diabetic foot ulceration (DFU) remains challenging. We conducted a proof of concept study to investigate the feasibility of microwave radiometry (MWR) thermometry for non-invasive differential diagnosis of critical limb ischemia (CLI) in subjects with DFU.

*Methods:* This prospective, multi-center, study included 80 participants, divided into four groups (group N: normal control subjects; group DN: participants with diabetes and verified neuropathic ulcers without vascular involvement; group DC: participants with diabetes and CLI and group NDC: participants with CLI without diabetes). Vascular disease was confirmed with angiography. All patients underwent MWR (RTM-01-RES:University of Bolton, UK) to record mean tissue temperatures at various pre-determined foot sites. Comparisons of temperature measurements between study groups were performed using one-way ANOVA and Dunn tests. ROC analysis was performed to determine sensitivity, specificity and cut-off value of MWR for CLI diagnosis.

*Results:* Temperatures recorded in vicinity to the foot ulcers of participants with diabetes and CLI were similar to those with CLI without diabetes, but significantly lower than in subjects with neuropathic ulcers without vascular involvement and normal controls (group DC:29.30 °C ± 1.89 vs. group NDC:29.18 °C ± 1.78vs. group N:33.01 °C ± 0.45 vs. group DN:33.39 °C ± 1.37;$P < .0001$). According to ROC analysis, cut-off temperature value to diagnose CLI was <31.8 °C (area under the curve: 0.984; 95% CI: 0.965–1.005;$P < .001$), with a sensitivity of 100.0% (95%CI: 90.26–100.0) and specificity of 88.37% (95% CI: 74.92–96.11).

*Conclusions:* Tissue temperatures in vicinity to ulcers were significantly lower in participants with CLI, with or without diabetes, compared to non-ischemic controls. MWR could be used for differential diagnosis of arterial ischemia in subjects with DFU.



## 1. Introduction

Diabetes mellitus (DM) affects over 380 million people worldwide and is a recognized independent predictor of peripheral arterial disease (PAD) and lower limb loss.[1,2] The latter has been attributed to the fact that progression of atherosclerosis occurs more rapidly in subjects with DM compared to those without, but also to microcirculatory compromise and peripheral neuropathy that contributes to non-healing ulcerations, even after minor trauma.[3] It has been estimated that more 1 million persons with DM each year suffer limb loss due to diabetes.[4] According to the World Health Organization (WHO) and the International Working Group on the Diabetic Foot

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(IWGDF), diabetic foot ulceration (DFU) pathology associated with neurological abnormalities and PAD of various degrees, is defined as "diabetic foot" and although the two main categories of limb tissue loss are neuropathic and ischemic, diabetic foot ulceration is mainly either pure neuropathic or mixed neuro-ischemic.[5] Differential diagnosis between pure neuropathic or mixed neuro-ischemic diabetic foot requires a combination of meticulous clinical examination, medical history and ankle–brachial index (ABI) measurement, which is considered the "gold standard" non-invasive modality for limb blood flow assessment. However, in subjects with diabetes and suspected advanced chronic atherosclerotic arterial ischemia resulting in tissue loss and/or gangrene (e.g.,Rutherford–Becker category 5 or 6 of critical limb ischemia; CLI), false negative ABI results are frequent due to Monckeberg medial calcific sclerosis resulting in partially compressible or in incompressible vessels, while clinical signs are not always accurate and subjective as to pose definite diagnosis of CLI. As a result, the diagnosis of vascular involvement in DFU remains challenging and recent diabetic foot management guidelines recommended that pedal perfusion should be assessed by ABI and Doppler arterial waveforms and either toe systolic pressure or transcutaneous oxygen pressure ($TcPO_2$), to ensure accurate patient selection for revascularization via combined clinical decision and cautious interpretation of objective perfusion assessments.[6,7] Although toe pressure measurement (toe brachial index; TBI) has been proposed as a more appropriate measurement for diabetic patients considering that lack of compressibility is more unlikely in toe arteries, sensitivity values in detecting hemodynamically significant PAD as low as 60% have been reported, while level of evidence regarding its diagnostic accuracy remains weak and does not reduce the number of subsequent diagnostic tests required for diagnosis.[6–8] In everyday clinical practice a considerable number of subjects with DM are referred for further, more objective, imaging evaluation of limb arterial supply by duplex ultrasound (DUS), computed tomography, magnetic resonance angiography or the gold standard imaging modality, invasive, intra-arterial, and digital subtracted angiography (DSA). This is attributed to the fact that prompt and precise diagnosis of ischemic limb compromise in subjects with DFU is essential for treatment planning, as pure neuropathic foot ulcers require specific management but not revascularization.[9] On the other hand, in cases of mixed neuro-ischemic diabetic foot ulceration rapid revascularization is vital in order to improve limb perfusion, accelerate wound healing and prevent from major amputation and associated morbidity and mortality.[9,10]

Measuring tissue temperatures has been previously utilized in the diagnostic approach of various pathologies.[11] While thermography and thermometry have been reported as a useful tool of diabetic foot assessment, their clinical use remains limited and although foot temperatures measurements using skin thermometers are currently being used for the prediction of neuropathic foot ulceration in patients with Charcot's arthropathy, temperature assessment has not been previously utilized in the differential diagnosis of CLI.[12–15]

Microwave radiometry (MWR) is a non-invasive method, which enables accurate measurement of internal tissue temperature, formerly used for the characterization of neoplastic tissue or vulnerable atherosclerotic plaque.[16–18] We conducted a proof of concept study to investigate the feasibility MWR thermometry for non-invasive diagnosis of critical limb ischemia in subjects with DFU.

## 2. Subjects, materials and methods

### 2.1. Study design

This multi-center, prospective study was in accordance with the principles outlined in the Declaration of Helsinki and both protocol and informed consent were approved by the Hospitals' Ethics and Scientific Committee. Informed consent was obtained by all participants prior to enrollment. The study was registered in a public database (www.clinicaltrials.gov: NCT03002116). In total, 80 subjects were included, equally divided into four groups (group N: normal subjects; group DN: participants with DM and verified neuropathic ulcers without vascular involvement; group DC: subjects with DM and CLI and group NDC: subjects with CLI without DM). Group N was formed by healthy volunteers who were considered free of PAD following clinical examination (no medical history and asymptomatic for PAD, normal peripheral pulses, ABI: 0.90–1.39) and normal DUS (absence of bilateral lower limb atheromatous lesions of any degree). Normal pulses were those of grade 3 according to the American Heart Association/American College of Cardiology guidelines recommend grading (scale of 0 to 3, with 0, absent; 1, reduced; 2, normal; and 3, bounding).[19] Group DN was formed by consecutive patients suffering from either insulin-dependent (IDDM) or non-insulin dependent (NIDDM; treated with drugs) DM and diagnosed with lower limb neuropathic ulcer without vascular compromise according to clinical assessment (normal peripheral pulses, no history of intermittent claudication, ABI $>0.9$ to 1.39), normal continuous-wave Doppler (normal triphasic, waveforms) and DUS examination (normal triphasic, waveforms and no evidence of stenosis of any degree).[9] In cases of dubious diagnosis, intra-arterial digital subtraction angiography was performed to assess the arterial system. Groups N, DN and NDC served as controls. Active comparator group DC included consecutive IDDM or NIDDM subjects with tissue loss or gangrene or both due to verified CLI (Rutherford–Becker classification 5 or 6) according to clinical examination and abnormal continuous-wave Doppler or DUS as described above, confirmed with diagnostic intra-arterial DSA indicating at least one significant $\geq 50\%$ stenosis within the arterial vasculature of the affected limb (from the aortic bifurcation to the infrapopliteal arteries). Clinical evaluation, DUS and DSA were performed by three interventional radiologists with over 10 years of experience in diagnostic imaging and endovascular treatment of peripheral vascular disease. Group NDC included subjects without DM with tissue loss or gangrene or both due to verified CLI (Rutherford–Becker classification 5 or 6) as described for group DC. Patients with verified infected ulcer receiving antibiotic therapy, or Charcot's arthropathy, were excluded from the study as to avoid bias from false negative results due to increased tissue temperatures owned to inflammation. Patients' demographics were recorded and are analytically reported in Table 1.

### 2.2. Foot MWR

All participants underwent MWR (RTM-01-RES; University of Bolton, UK; Fig. 1) to record the mean internal tissue temperature of the foot. The principles of MWR have been previously reported.[20] In brief, MWR is based on the principle that the intensity of radiation is proportional to tissue temperature and is capable of detecting temperatures from internal tissues at microwave frequencies using the contrast of dielectric properties of different tissues.[21] The MWR system is consisted of an antenna, which includes one microwave and one infrared sensor, connected to a data processing unit, a monitor and a PC equipped with dedicated software for patient and temperature documentation (Fig. 1). Measurements are performed by applying the antenna on the surface of the tissue under examination at an angle of $90^o$ degrees for approximately 8 to 10 seconds. The system then integrates the microwave emission and a microprocessor converts the measured signal to temperature. The microwave sensor of the antenna is 3.9 cm in diameter and is set to detect microwave radiation ranging from 2 to 5 GHz, which corresponds to 7 cm in depth, with an accuracy of $\pm 0.20$ °C. The sensor also filters all microwave or radiofrequency waves from the environment avoiding signal interference. The infrared sensor is receiving measurements from the skin and is necessary for calibrating