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Vincent Serantoni, Franck Jourdan, Hervé Louche, Antoine Avignon, Ariane Sultan. Definition of thermal indicators for the study of thermoregulation alterations in the foot of people living within diabetic peripheral neuropathy: A proof of concept. *Journal of Thermal Biology*, 2023, 118, pp.103729. 10.1016/j.jtherbio.2023.103729 . hal-04293842

HAL Id: hal-04293842

<https://hal.science/hal-04293842>

Submitted on 19 Nov 2023

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Definition of thermal indicators for the study of thermoregulation alterations in the foot of people living within diabetic peripheral neuropathy: A proof of concept

Vincent Serantoni a,* , Franck Jourdan a, Hervé Louche a, Antoine Avignon b, Ariane Sultan c

a *LMGC, Univ. Montpellier, CNRS, Rue St-Priest, 34095, Montpellier, France*

b *Unit of Nutrition and Diabetes, Department of Endocrinology-Nutrition and Diabetes, Univ. Montpellier, INSERM, CHRU Montpellier, Montpellier, France*

c *PHYMEDEXP, Univ. Montpellier, INSERM, CNRS UMR, CHRU, Montpellier, Montpellier, France*

Keywords:

Diabetic foot Peripheral neuropathy Six-minute walk test Wavelet analysis Thermoregulation Infrared camera

*** Corresponding author.**

E-mail address: vincent.serantoni@gmail.com (V. Serantoni).

ABSTRACT

Aims:

This study investigates how diabetic peripheral neuropathy is linked to impairment of thermoregulatory mechanisms using a thermal camera, spectral thermal analysis and a physical test.

Methods:

The plantar skin temperature of all participants was measured using a thermal camera following a 6- min walking exercise. The data were subjected to frequency decomposition, resulting in two frequency ranges corresponding to endothelial and neurogenic mechanisms. Then, 40 thermal indicators were evaluated for each participant. ROC curve and statistical tests allowed to identify indicators able to detect the presence or absence of diabetic peripheral neuropathy.

Results:

The study included 33 participants living with diabetes. The results revealed that a 6-min walk exercise increased plantar foot temperature and highlighted a significant difference between people living with diabetes with and without peripheral neuropathy ($p < 0.01$). The results also revealed the advantages of using thermal images rather than single point measurements.

Conclusions:

Diabetic peripheral neuropathy is linked to impairment of thermoregulatory mechanisms. This link can be highlighted after a dedicated 6-min walk exercise, enabling to activate these mechanisms, and measuring with a thermal camera the temporal plantar skin temperature. Assessment of this link gave best results by filtering the thermal signal in the neurogenic range.

1. Introduction

Diabetes mellitus (DM) is a chronic disease that has now become a huge public healthcare issue, concerning about 463 million patients worldwide in 2019, with an estimated increase to 700 million by 2045 (Saeedi et al., 2019). Among the DM complications, diabetic foot is of major importance as this complication affects nearly 25% of patients with diabetes (Uçkay et al., 2015), it can lead to lower limb amputation, and it is associated with reduced life expectancy (Armstrong et al., 2017). The

core mechanisms involved are peripheral neuropathy (PN) and peripheral arterial disease. It is assumed that thermoregulatory pathways may be altered in these conditions (Jan et al., 2013).

Thermoregulatory mechanisms enable the human body to rapidly cope with heat generation and dissipation to prevent damage. They involve a regulation in skin blood flow (SkBF), thus controlling heat exchange with the environment through the skin. However, presence of diabetes act on thermoregulatory mechanisms. Indeed, Stansberry et al. (1996) revealed that patients living with diabetes (Type 1 or 2) have a lower blood perfusion amplitude capacity compared to healthy volunteers, especially regarding low frequency signals. Meanwhile, other authors have established a clear link between SkBF oscillations and thermoregulatory mechanisms (Stefanovska et al., 1999; Jo Geyer et al., 2004; Podtaev et al., 2008). In these studies, five frequency bands of interest were identified (0.008–0.02 Hz, 0.02–0.05 Hz, 0.05–0.15 Hz, 0.15–0.4 Hz, and 0.4–2.0 Hz), respectively corresponding to endothelial, neurogenic, myogenic, respiratory, and cardiac activity. The endothelial range corresponds to the rhythmic regulation of vessel resistance initiated by metabolic substances released by endothelial cells. The neurogenic range corresponds to the rhythmic regulation of vessel size resulting from neurogenic activity. The myogenic range is attributed to the continuous response of smooth muscle cells to intravascular pressure changes. Last, respiratory and cardiac ranges are linked to lung and heart activity.

The link between diabetic foot disorder and the amplitude of thermoregulatory mechanisms was demonstrated by Jan et al. (2013), who showed a lower amplitude of SkBF in the first metatarsal head after local heating and mechanical stress in patients with diabetes compared to healthy volunteers. These findings narrowed the research area to three main frequency ranges: endothelial, neurogenic and myogenic. Further, Liao and Jan noted that local heating seemed to be more relevant than mechanical stress, especially in the myogenic range. All these data argue in favor of a clear link between skin temperature (SkT) and SkBF (Nilsson, 1987; Wilson and Spence, 1989; Francis, 2010). Based on this knowledge, and using a thermal probe, Parshakov et al. (2017), (Parshakov et al., 2016) showed that low frequencies (i.e., endothelial, neurogenic and myogenic ranges) on SkT oscillations (i.e. weak temporal temperature variations) had a lower thermal amplitude in patients with diabetes compared to healthy volunteers, before and after a local heating of the big toe at 42 °C. The endothelial range seemed to be especially relevant regarding laboratory markers of endothelial dysfunction. These results were obtained on a single point (probe location). Few works have tried to obtain these results not only on a single point, but on an area of interest.

Among these works, Sagaidachnyi et al. (2017) performed spectral analysis of thermoregulatory activities based on infrared images (thermal camera), but not on DM participants. The team of Soliz et al. (2016) worked on DM participants after a cold provocation, using principal component analysis and independent component analysis. They found significant differences between DM and PN participants. However, they highlighted the need for multiple indicators to classify PN patients. To our knowledge, no study has involved spectral analysis of SkT oscillations following a dedicated physical test to ensure the activation of thermoregulatory mechanisms in DM patients.

Based on these observations, this paper has two main objectives: i) study the effects of PN on thermoregulatory mechanisms in the feet of patients with diabetes and ii) assess whether the thermal measurement protocol could be readily implemented in a clinical environment. The first point was done by quantifying the amplitude of temperature variations beneath the foot sole, using a thermal camera and wavelet analysis, for DM people with or without PN after a physical exercise. The second point involve the creation of a small, not expensive and contactless protocol recording the temperature beneath the foot sole of DM people.

2. Materials and methods

From April 2019 to July 2019, an observational study was conducted at the Endocrinology-Nutrition-Diabetes Unit of the University Hospital of Montpellier, France. All diabetic patients over 18 years old who came for their routine diabetes follow-up and were treated for Type 1 or 2 diabetes were eligible if they were classified in risk group 0 or 1, as defined by the International Working Group on the Diabetic Foot (Schaper et al., 2019), and therefore diagnosed with or without PN. However, patients with PAD, history of foot ulceration, amputation, active foot wounds, expectant mothers and patients unable to walk for 6 min were excluded from this study. Foot deformities were not an exclusion criterion and were not investigated. The total number of included participants was 33. Based on actual recommendations (Schaper et al., 2019), PAD was diagnosed by palpating the dorsalis pedis and the posterior tibial arteries and PN was assessed using a 10-g Semmes-Weinstein monofilament, based on the actual recommendation (Schaper et al., 2019). Age, sex, diabetes duration and type of DM (as well as current medication) were recorded.

All enrolled participants included in the study received an informational document describing the study and provided written informed consent. This study followed the World Medical Association's Declaration of Helsinki and was approved by the local ethics committee (CPP Sud-Méditerranée IV, Montpellier, France, clinical trials NCT03872089).

2.1. Skin temperature measurement and protocol

Skin temperature measurement consisted of thermal imaging of both plantar foot soles before and after a 6-min walk exercise.

The 6-min walk exercise was originally designed to evaluate the functional capacity of patients and is used here to activate thermoregulatory mechanisms. As indicated by the American Thoracic Society (ATS) (Thoracic Society, 2002), this simple test was originally a 12-min walk exercise aiming to evaluate the level of physical fitness of healthy individuals. In an attempt to accommodate patients with medical conditions for whom walking 12 min was too exhausting, a 6-min walk was found to perform as well as the 12-min walk. The ATS concluded that the 6-min walk exercise was easier to perform, better tolerated, and more reflective of activities of daily living than the 12-min walk exercise. To perform this exercise, participants were instructed to cover the longest distance possible (walking only) in 6 min. It

was assumed that thermoregulatory activation would occur during exercise or during the post-exercise hyperemia phase.

The plantar foot sole temperature was measured using a microbolometer (MB) camera (Device-ALab, SmartIR640, 16-bit resolution, 640×480 pixels and thermal sensitivity of 50 mK). The choice of a MB infrared camera enables to select a small and not-expensive thermal camera. These two points are important to create an affordable and easily transportable protocol. The whole procedure was contactless and a full article (Serantoni et al., 2019) describes the accurate metrology done on this MB camera and the tests done on healthy participants.

Patients were placed barefoot in the semi-Fowler's position for 5 min in a hospital room with a controlled temperature of 25 °C for thermal acclimation. The MB camera was placed in front of the foot soles (Fig. 1). The initial 10-min thermal recording of both plantar foot soles served as a baseline, and participants were then asked to put their shoes back on and perform the 6-min walk test (Thoracic Society, 2002). Putting the shoes back on during exercise affects the absolute temperature of the feet but it was assumed that the thermal oscillations generated by the thermoregulatory mechanisms were independent of the local absolute temperature of the feet. Finally, participants were again placed barefoot in the semi-Fowler position and recorded for another 10 min following the exercise period and after removing their shoes. In each case, foot SkT oscillations were closely monitored using the MB camera and thermal indicators described in section 2.2. Details of the image processing are available in (Serantoni et al., 2019). The interested reader will find a video showing these thermal oscillations in supplementary data.

2.2. Analysis plan

The field of view of the thermal camera encompassed the two entire plantar foot soles, then thermal oscillations were investigated under an area of interest that included the five metatarsal heads and the big toe. Thermal indicator evaluated in each pixel within the area of interest (AOI), differed in the time duration of the analysed signal (2, 4, 6, 8 or 10 first minutes of the total signal), the frequency range of interest (raw signal: R, endothelial range: E, or neurogenic range: N), as well as the oscillation measurements (maximum amplitude: AM, mean wavelet: MW, and standard deviation: SD). A total of 40 thermal indicators, described in Appendix A, were built. For ease of reading, results are presented using the above abbreviations. For example, the thermal indicator of the mean wavelet evaluated within the endothelial range during the first 6 min is written MW-E□ 6. Evaluation of this thermal indicator is illustrated in Appendix B. The extracted indicator was the one from the area of interest located in the pixel with the highest value, allowing us to monitor a so-called active area, i.e., an area that is highly active under the foot. The exact location of this active area is expected to vary from depending on each participant due to the heterogeneity of the vascular network. Thermal indicators were expected to quantify the amplitude of the thermoregulatory mechanisms through thermal oscillations. If this assumption is correct, then the presented protocol could be used in routine consultation as a quantitative warning of PN,

completing the monofilament evaluation. The increase in the mean plantar foot temperature, assessed by the thermal difference at the end of the two thermal recordings, was also measured in this active area. All types of results are expressed as mean $\pm$ SD.

Evaluation of statistical tests and AUC through ROC curve on all the extracted thermal indicators enables the selection of the best thermal indicator able to discriminate the two groups of participants with or without PN, before and after performing the 6-min walk exercise. Due to the small number of participants included, the non-parametric Kruskal-Wallis test was selected, but p values were only used to validate the thermal indicator with high AUC values able to discriminate participants with or without PN. All p-values were extracted using R software (R Core Team, 2020) while AUC were evaluated using Matlab®.

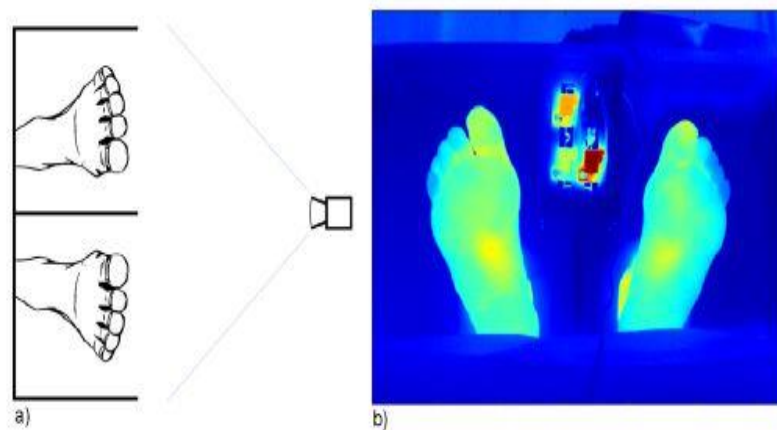


Fig. 1. (a) Illustration of the thermal recording procedure. A box was placed all around the feet to prevent external radiations from altering the foot temperature. (b) Thermal image recorded by the MB camera. Hot spots in the middle are needed for live thermal calibration.

Table 1

Subject characteristics for participants with no complications (NC) and with peripheral neuropathy (PN). Data are mean $\pm$ SD.

Population	NC	PN
No. of participants	23	10
Men/women (n)	19/4	7/3
Age (years)	62.13 $\pm$ 13.65	58.3 $\pm$ 13.3
Diabetes Type (1/2)	8/15	7/3
Diabetes duration	15.44 $\pm$ 8.56	21 $\pm$ 11.19

3. Results

3.1. Subject characteristics

Thirty-three patients were enrolled during the total duration of the study, 26 men and 7 women, 15 participants with Type 1 and 18 with Type 2 diabetes mellitus. The mean age was 61 ± 13.5 years and the mean diabetes duration was 17.1 ± 10 years. Among them, 10 were diagnosed with PN and 23 had no complications (NC). The proportion of diabetic women

worldwide is slightly lower than that of men (Magliano and Boyko, 2021), but the number of women included in this work was really small ($n = 7$) compared to men ($n = 26$). No restrictions other than the previously mentioned exclusion criteria were applied, and such a small number was not expected. Table 1 summarizes the subject characteristics with respect to the complication groups. Regarding the feasibility of using thermal imaging in clinical practice, we were able to set up a contactless protocol using a MB camera and achieved an experimental sensitivity of 25 mK with a dedicated setup, as previously described (Thoracic Society, 2002).

3.2. Effects of physical exercise on plantar foot temperature

Mean plantar foot temperature was assessed on the AOI of each foot and for the two full thermal recordings, i.e. before and after the 6-min walk exercise. Local warming of the feet was observed with a mean increase in planter foot temperature of 0.66 ± 1.38 °C for all included participants. However, when examining the increase in plantar foot temperature following exercise as a function of the initial mean plantar foot temperature, a threshold effect was observed. Participants with an initial plantar foot temperature below 33 °C had an important increase in temperature of 1.69 ± 1.58 °C, while those with an initial plantar foot temperature of more than 33 °C had a small increase in temperature of 0.04 ± 0.75 °C.

3.3. Location of the active area and interest of thermal imaging

Extraction of the thermal indicators for each participant was performed on the most active area, i.e. the pixel with the highest indicator value within the AOI. Results revealed that the most active areas were often under the big toe (63% of patients had an active area in this location) or under the first metatarsal head (in 37% of patients). Moreover, a decrease of up to 50% in the extracted thermal indicator was observed when the indicator value was extracted within less than 5 mm of the exact location.

3.4. Thermal indicators regarding the presence or absence of PN

The AUC and p-values calculated for the 40 indicators are shown in Fig. 2a. The thermal indicator with the best AUC value able to discriminate the presence or absence of PN after exercise was the mean wavelet expressed in the neurogenic range during 8 min, with an AUC of 0.841 ($p < 0.01$; sensitivity: 85%; specificity: 76.3%).

Fig. 2a reveals that the neurogenic range always provides better AUC and p-values compared to those obtained in the endothelial range or with the raw data. Moreover, the best AUC and p-values for each range were obtained by observing the first 4–8 min of the signal, which allowed to shorten the recording time. The worst AUC and p-values were obtained when the thermal indicators were evaluated using the raw signal. Endothelial range gave better AUC and p-values compared to those obtained with the raw signal, but lower than those obtained with the neurogenic range. Evaluating the AUC and p-values using either the maximal amplitude, the standard deviation, or the mean wavelet in the endothelial range showed no difference. However, when the AUC and p-values were evaluated using the neurogenic range, the mean wavelet gave the best result (AUC = 0.841; $p = 2.3e-5$), followed

by the maximum amplitude (AUC = 0.81; $p = 1e-4$) and the standard deviation (AUC = 0.785; $p = 3.5e-4$). All exact AUC and p-values are available in Appendix C. Fig. 2b highlights that the 6-min walk exercise enables to emphasise the difference between NC and PN participants using a thermal indicator evaluated in the neurogenic range.

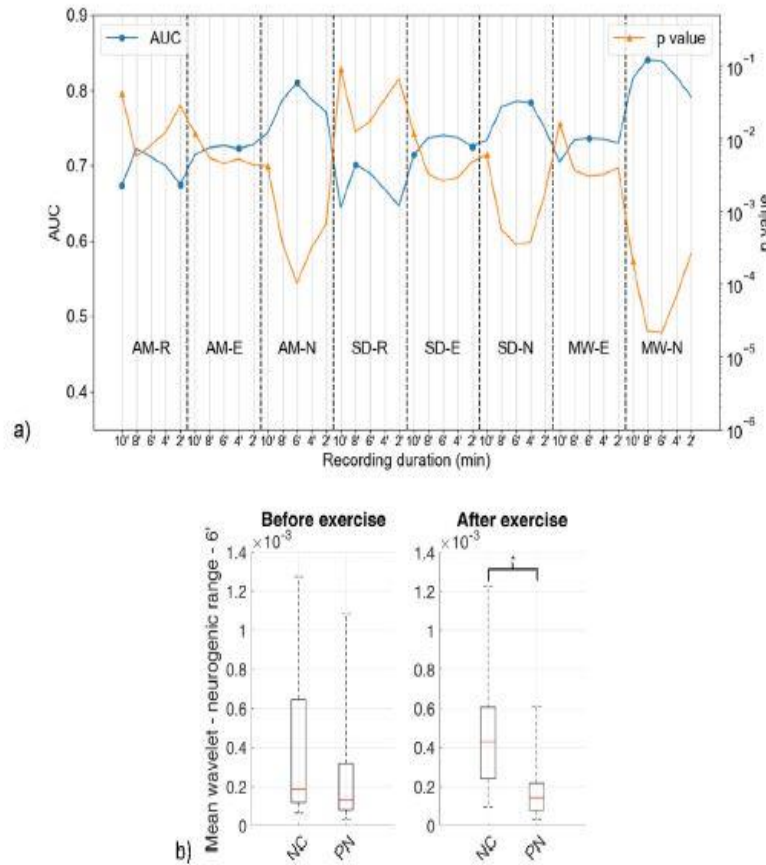


Fig. 2. (a) Plot of all (40) AUC values (best theoretical value: AUC = 1) and p-values. The recording duration represents the first minutes of the signal used to evaluate the indicator (maximum amplitude: AM, mean wavelet: MW, standard deviation: SD - raw signal: R, endothelial range: E, neurogenic range: N). (b) Indicator MW-N-6 before and after a 6-min walk exercise based on the presence or absence of the PN complication (*: $p < 0.05$).

4. Discussion

4.1. Impact of physical exercise on thermoregulatory mechanisms

Since heat activates thermoregulatory mechanisms while cold reduces them (Johnson et al., 2014), a global warming of the body was necessary to trigger thermal oscillations induced by thermoregulatory mechanisms. As already described by P. Kenny et al. (2016), reaching a minimum mean body temperature threshold is one of the main conditions for thermoregulatory activation. The two most common ways to increase inner body temperature are increasing ambient room temperature (at least 30 min) and physical activity. Both of which are quite difficult to achieve in clinical practice. However, the 6-min walk exercise was an easily achievable choice capable of producing a global warming of the body.

This increase in temperature must be interpreted with caution. Indeed, since participants put their shoes back on for the 6-min walk exercise, the confinement of the feet in the shoes had an effect on the local absolute temperature of the feet that was not studied here. Due to the

nature of this exercise as a global stimulus of the whole body, these increases can be interpreted as the effect of the hyperemia phase observed after performing a physical exercise and are interpreted here as an activation of thermoregulatory mechanisms.

A minimum foot skin temperature of 33 °C, either spontaneously or after physical activity, appears to be essential for the activation thermoregulatory mechanisms. Indeed, participants with an initial foot temperature below this threshold showed an important increase in foot temperature after the exercise, whereas this temperature increase was not observed in participants with an initial foot temperature above this threshold. It is trusted that thermoregulatory mechanisms were not activated in the case of low skin temperature and that the 6-min walk exercise enables to activate them (Thoracic Society, 2002), whereas in the second case they were already activated and the exercise had little effect. This confirms the interest of the walking exercise in the study of thermoregulatory mechanisms, enabling to activate them.

4.2. Complication characterization

The best thermal indicator enabling to compare PN participants with NC participants was expressed in the neurogenic range using the mean wavelet tool. This result was expected because PN represents an alteration in nerve function. Indeed, the neurogenic range is assumed to reflect rhythmic variations in vessel size induced by nerve activity (Kastrup et al., 1989).

In this study, a lower AUC value was always obtained when evaluating the temporal thermal signal in the endothelial range compared to the neurogenic range, suggesting that the neurogenic range is of greater interest than the previously studied endothelial range (Parshakov et al., 2016), (Podtaev et al., 2014). These conflicting findings with the literature could be explained by the small number of patients in the PN group, the sensitivity of the thermal sensor, the lack of laboratory markers of endothelial dysfunction, or intra-individual variability. Indeed, the boundary used in this study between the endothelial and neurogenic frequency domains is 0.02 Hz and, due to intra-individual variability, patients with diabetes may have endothelial activity at a frequency higher than 0.02 Hz, thus falling in the neurogenic range and vice-versa.

4.3. Interest of thermal imaging

Many studies have shown that thermography can be a useful tool for studying DM complications (Nilsson, 1987; Wilson and Spence, 1989; Francis, 2010; Podtaev et al., 2014), but these results were generally obtained with a local thermal probe. Based on the presented work, it seems that the results varied markedly depending on the location of the probe (Serantoni et al., 2019) and need to be evaluated in the most active area. The latter can be precisely located using the thermal field generated by an infrared camera. However, these studies used a localized thermal stimulus, in contrast to the global stimulus used in this study. Consequently, given the disparity between these two stimuli, additional research is required to evaluate the influence of data extraction location.

4.4. Limitations

This study had three shortcomings: the small number of participants, the efficiency of the 6-min walk exercise, and the thermal sensitivity of the infrared camera. The small number of participants, had an impact on the results, leading to caution in data interpretation. Moreover, only the PN complication was studied here, it would be interesting to also monitor the effect of the peripheral arterial disease on the thermoregulatory mechanisms. Regarding the 6-min walk exercise, even though the sensitivity of this protocol was relatively good, its specificity was quite low, suggesting that the exercise performed was not always sufficient to activate the thermoregulatory mechanisms. Solutions would be to repeat the exercise or to make it longer when the thermal indicator is low. However, the latter is not recommended by the ATS (Thoracic Society, 2002). Performing another type of exercise (e.g., treadmill) that can be easily monitored could also be an interesting choice, even if it is complicated to perform due to the installation of the machine in the hospital. Finally, the camera sensitivity enabled to analyse data in the endothelial and neurogenic ranges but not in the myogenic range. A thermal camera with a higher sensitivity, able to detect activity in the myogenic range, would be worth investigating.

5. Conclusion

The presented results highlight that peripheral neuropathy in patients with diabetes is associated with alterations in foot thermoregulatory mechanisms. These results were obtained using a contactless and non-invasive experimental protocol involving a 6-min walk exercise, thermal camera and wavelet analysis. The neurogenic range revealed significant differences between thermal indicators of DM people with or without PN. It also seemed essential to obtain the result specifically at the location of the most active area. The thermal camera was effective in accurately selecting this exact location.

However, due to the small number of participants, the data are sparse to readily support the implementation of this protocol in clinical environment. Further work with a meaningful sample size of participants is needed to confirm the interesting results presented in this proof of concept.

Deepening this link between diabetic peripheral neuropathy and impairment of thermoregulatory mechanisms can provide an opportunity to expand the binary Semmes-Weinstein monofilament test. The proposed expand would involve incorporating an additional assessment to quantitatively measure the severity of the peripheral neuropathy using a thermal indicator, as described in this study. This additional assessment would provide practitioners with a warning signal on the peripheral neuropathy complication through the evaluation of thermoregulatory mechanisms.

CRedit authorship statement

Vincent Serantoni: Conceptualization; Investigation; Methodology; Software; Roles/Writing - original draft, Franck Jourdan: Conceptualization; Funding acquisition; Supervision; Validation; Writing - review & editing, Hervé Louche: Conceptualization; Funding acquisition; Supervision; Validation; Writing - review & editing, Antoine Avignon: Writing - review & editing, Ariane Sultan: Conceptualization; Supervision; Validation; Writing - review & editing.

Funding

This study was carried out thanks to the support of the LabEx NUMEV project (n° ANR-10-LABX-20) funded by the *Investissements d'Avenir* program managed by the French National Research Agency (ANR). We reported no potential conflict of interest relevant to this article.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

We would like to thank all the participants with diabetes who contributed to the study.

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