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Increased exposure to loading is associated with decreased plantar soft tissue hardness in people with diabetes and neuropathy

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ABSTRACT

Aims: Literature indicates that altered plantar loading in people with diabetes could trigger changes in plantar soft tissue biomechanics which, in turn, could affect the risk for ulceration. To stimulate more research in this area, this study uses *in vivo* testing to investigate the link between plantar loading and tissue hardness.
Methods: Tissue hardness and plantar pressure distribution were measured for six plantar areas in 39 people with diabetes and peripheral neuropathy.
Results: Spearman correlation analysis revealed that increased pressure time integral at the 1st metatarsal-head region ($r = -0.354$, $n = 39$, $P = 0.027$) or at the heel ($r = -0.378$, $n = 39$, $P = 0.018$) was associated with reduced hardness in the same regions. After accounting for confounding parameters, generalised estimating equations analysis also showed that 10% increase in pressure time integral at the heel was associated with ≈ 1 unit reduction in hardness in the same region.
Conclusions: For the first time, this study reveals that people with diabetes and neuropathy who tend to load their feet more heavily also tend to have plantar soft tissues with lower hardness. The observed difference in tissue hardness is likely to affect the tissue's vulnerability to overload injury. More research will be needed to explore the implications of the observed association for the risk of ulceration.

1. Introduction

People with diabetes can gradually lose the protective sensation of pain in their feet due to peripheral neuropathy. As a result, they tend to repeatedly overload and seriously injure the soft tissues in the soles of their feet (i.e., plantar soft tissue), causing the development of diabetic foot ulcers [1,2]. Diabetic foot ulcers are open wounds that have limited capacity for healing, they can get infected and even lead to amputation. In the UK 169 people have a toe, foot or limb amputation every week because of diabetes [3].

The main role of plantar soft tissue is to act as a shock absorber, to dampen the effect of ground reaction forces during weight-bearing activities by promoting more even distribution of plantar loads [4]. A recent *in vivo* and computational analysis has revealed that specific changes in the mechanical behaviour of plantar soft tissue can significantly undermine the tissue's ability to fulfil its mechanical role making it more vulnerable to overload injury and ulceration [5]. These findings point to a direct relationship between plantar soft tissue biomechanics and the risk for ulceration and highlight the importance of tissue biomechanics for reliable risk assessment and effective prevention of diabetic foot ulceration [5–12].

In a seminal study on the effect of diabetes on plantar soft tissue biomechanics, Piaggesi et al.(1999) [13] observed that people with diabetes and peripheral neuropathy tend to have harder plantar soft tissues compared to their non-diabetic or diabetic non-neuropathic counterparts. This finding (which was also later independently verified [14]) was explained as a potential "reactive phenomenon" [13] to increased exposure to loading due to the loss of sensation in the neuropathic foot [1,15,16]. Even though, similar phenomena linking loading with tissue biomechanics have been established for other tissues (tendon [17] etc.) the relationship between plantar loading and plantar soft tissue biomechanics remains poorly understood, which could be a barrier for reliable risk assessment for tissue damage. More specifically, increased loading could trigger adaptations in the tissue that make it

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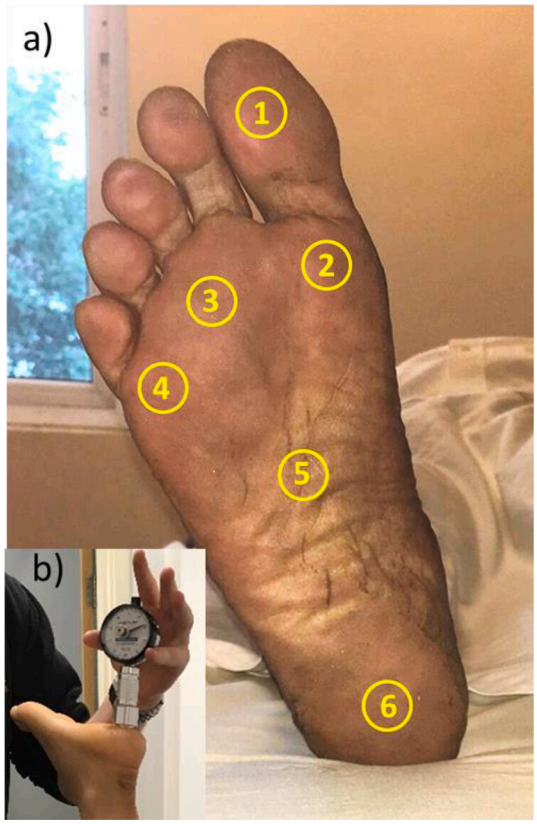

Fig. 1. (a) The anatomical positions used for the measurement of VPT and Shore hardness (1) hallux, (2) 1st metatarsal head, (3) 3rd metatarsal head, (4) 5th metatarsal head, (5) midfoot, (6) heel. (b) The positioning of the Shore hardness durometer on the surface of the foot.

more capable to cope with more intense plantar loading and therefore reduce the risk of injury [18], or cause degenerative changes (e.g., due to repeated overloading) that make diabetic foot ulceration more likely [13].

In this context, the present study explores the relationship between plantar loading and plantar soft tissue hardness in people with diabetes and peripheral neuropathy. It is hypothesised that if increased plantar loading can indeed affect the risk of ulceration by triggering changes in tissue biomechanics (positive or negative), then people who load their feet differently should also have plantar soft tissues that exhibit different biomechanical characteristics.

2. Methods

2.1. Participants

Thirty-nine (M/F: 21/18) participants with diabetes (Type 1,2) and impaired vibration perception due to peripheral neuropathy in both feet were recruited from two outpatient centres in Chennai, India (Dr A. Ramachandran Diabetes Hospital, Chennai, India and Sri Ramachandra University, Chennai, India). Ethical approval for testing at Sri Ramchandra University was obtained through the institutional ethical review committee. (application Ref: IEC-NI/16/APR/52/27). For Dr A. Ramachandran Diabetes Hospital, the study was approved by the independent ethics committee at India Diabetes Research Foundation. All participants provided written informed consent before data collection.

Demographical data were recorded through a patient-led questionnaire including questions related to their general health, diabetes management, and history of foot-related pathologies. The participants' mean(±STDEV) age, body mass and duration of diabetes (DoD) was 63 ± 7 years, 69 ± 11 kg and 15 ± 9 years respectively.

Vibration perception threshold (VPT) was measured using a biothesiometer (Kody Biothezi-VPT, Chennai, India) in six plantar sites on each foot: Hallux, 1st metatarsal head (MetHead), 3rd MetHead, 5th MetHead, midfoot, and heel (Fig. 1a). Impaired vibration perception was defined as having a VPT $\geq$ 15 V in at least one site [19,20]. People with an active foot ulcer or Charcot foot or history of major foot surgery (including amputation) were excluded from the study.

To enable an analysis on the effect of the severity of vibration perception loss participants were also divided into two groups: one for mild loss of vibration perception (15 V $\leq$ VPT $<$ 25 V in all tested sites) [19–21] and another for severe vibration perception loss (VPT $\geq$ 25 V in at least one site) [19–21].

2.2. Biomechanical measurements

Shore hardness was measured using a Shore-00 durometer (AD-100, Checkline Europe B.V, Dennenweg, The Netherlands). Shore hardness is a simple and cost-effective measurement of a material's resistance to indentation and is given a dimensionless value between 0 and 100 with a high value of Shore hardness indicating a high resistance to indentation.

To measure hardness, participants were asked to lie in a prone position on an examination couch with their shank approximately at 90 degrees to the thigh. With the foot relaxed, the durometer was lowered onto each of the plantar sites that were used for VPT testing allowing the tissue to be compressed by the full weight of the device before taking the hardness reading (Fig. 1). Each site was tested three times, and the average value of hardness for each site was calculated [14,22]. The average of left and right for each region was also calculated (regional average). Special attention was given to avoid measuring hardness in areas where there was clear callus formation.

Exposure to loading was assessed by measuring the plantar pressure distribution during walking, at a self-selected pace, using a MatScan 0.5 $\times$ 0.5 m pressure mat (Tekscan, Boston MA, USA). Three stance phases per foot were recorded at 100 Hz using a two-step protocol [23]. Values of maximum peak plantar pressure (PPP) and pressure time integral (PTI) [24] were assessed for the same six regions of the foot. Similar to hardness, the regional average between left and right was also calculated. All biomechanical measurements were performed by the same examiner.

2.3. Statistical analysis

All statistical analyses were conducted using IBM®SPSS®v.26. The Shapiro-Wilk test was used to screen the data for normal distribution. Normally distributed data were represented using their mean(±STDEV) while non-normally distributed data by their median(minimum value, maximum value). Based on the non-normal distribution of the data, Spearman's rank correlation tests were run between hardness and plantar pressure measurements. For this correlation analysis, the regional average values of hardness, PPP and PTI were used [25].

Generalised Estimating Equations (GEE) analysis was used to test whether the relationships between hardness and pressure measurements which were identified by the analysis of correlation remained significant when gender, age, body mass, DoD and VPT were also considered. VPT was included either as a region-specific measurement or averaged across each foot in separate GEE analyses.

GEE is an extension of the generalised linear model that facilitates regression analysis on variables that are not normally distributed. Moreover, GEE accounts for dependent measurements which enables combining, in the same regression analysis, the dependent measures for both limbs. The GEE analysis was performed assuming a gamma distribution and natural-log link function [26,27]:

$$R = e^{(b_0 + \sum_{i=1}^{n} b_i * P_i)} \quad (1)$$

where R, P are the response and predictor parameters respectively, b_0 is

Table 1
The median (minimum value, maximum value) of the regional average of vibration perception threshold (VPT), Shore hardness (Hardness), maximum peak plantar pressure (PPP) and pressure time integral (PTI) for all participants.

Foot region	VPT (V)	Hardness	PPP (kPa)	PTI (kPa*s)
Hallux	28 (16,55)	38 (20,74)	237 (124,393)	0.61 (0.33,0.99)
1st MetHead	25 (11,54)	39 (17,71)	202 (77,385)	0.60 (0.20,1.24)
3^{dr} MetHead	25 (15,55)	35 (11,67)	258 (102,448)	0.82 (0.28,1.26)
5th Methead	25 (13,55)	33 (13,71)	206 (66,361)	0.66 (0.24,1.33)
Midfoot	27 (17,54)	39 (21,76)	129 (59,291)	0.37 (0.20,0.81)
Heel	25 (17,55)	43 (22,71)	218 (33,404)	0.54 (0.07,1.35)

the intercept and b_i the coefficients that describe the relationship between a predictor and the response variable.

Previous applications of Shore hardness in the diabetic foot revealed higher plantar soft tissue hardness in people with diabetes and peripheral neuropathy relative to their non neuropathic counterparts [13,14]. A final between-groups analysis (Mann-Whitney *U* test) was also performed here to test whether people with severe vibration perception loss also tend to have higher plantar soft tissue hardness relative to people with mild vibration perception loss. PPP and PTI were also included in this analysis for completeness.

3. Results

An overview of the collected data for the six regions is presented in Table 1. As expected, PPP and PTI vary across the plantar surface with the midfoot being the least loaded area. An initial comparison of hardness between areas with relatively high or low PPP or PTI did not reveal any specific pattern or link between loading and hardness.

A pattern of negative association between loading and hardness however starts emerging when data from each specific area are analysed separately across all participants. More specifically, Spearman's rank order correlation analysis showed weak [28] but statistically significant ($P < 0.05$) negative correlations between hardness and PTI at the 1st MetHead (r = -0.354, 95% confidence intervals [29,30] for r: −0.124, -0.548, n = 39, $P = 0.027$) and between hardness and PTI at the heel (r = -0.378, 95% confidence intervals [29,30] for r: −0.150, -0.568, n = 39, $P = 0.018$).

After accounting for the effect of gender, age, body mass, DoD and VPT, GEE confirmed a statistically significant association between high PTI at the heel and reduced hardness at the heel (Table 2). A sense of the predicted effect of PTI on heel hardness is given from equation (1). Assuming a person with measurements equal to the participants' median values (Table 1), equation (1) indicates that 10% increase in PTI at the heel will be associated with 3% reduction in hardness (≈1 Shore hardness unit). In the case of the 1st MetHead, the previously found association between exposure to loading and tissue hardness was not confirmed when all confounding variables were considered in the GEE analysis (Table 2). The results of the GEE analysis remained practically the same regardless of which VPT measurement was used (i.e., region-specific or averaged across each foot).

When participants were grouped based on the severity of vibration sensation loss, fifteen participants (M/F: 7/8, age: 63y ± 10y, BM: 65 kg ± 8 kg, DoD: 15y ± 9y) had mild vibration perception loss. The remaining 24 participants (M/F:14/10, age: 63y ± 8y, BM:71 kg ± 13 kg, DoD: 15y ± 9y) had severe vibration perception loss. Mann-Whitney *U* test verified that there was no significant difference between the two groups with regards to age, body mass or DoD. Similarly, no significant difference was found with regards to PPP or PTI (Fig. 2). However, the median heel hardness of the group with mild vibration sensation loss (median hardness = 35) was significantly lower (U = 253.5, z = 2.122, $P = 0.033$) than the group with severe vibration sensation loss (median hardness = 43).

The complete data set of all *in vivo* measurements that were used in

Table 2
The GEE models used to assess the association between Shore hardness and pressure time integral (PTI), gender, age, body mass, duration of diabetes (DoD) and vibration perception threshold (VPT) at the heel and 1st MetHead regions. Results are presented separately for the region-specific VPT (VPT_1stMetHead, VPT_Heel) and for VPT averaged across each foot (VPT_Avg). The values of the coefficients (b) that describe the relationship between a predictor variable and the response variable are also shown with their 95% Wald confidence intervals. Coefficients which are statistically significantly different that zero (Sig. < 0.050) are indicated with (*).

Foot region	Predictor parameter	b	95% Wald Confidence Interval		Sig.
			Lower	Upper	
1st MetHead	(Intercept)*	3.725	3.159	4.290	< 0.0005*
	Gender	0.052	−0.066	0.170	0.385
	Age	−0.001	−0.009	0.006	0.710
	Body mass	0.002	−0.002	0.006	0.402
	DoD*	0.006	< 0.0005	0.012	0.041*
	VPT_1stMetHead	−0.005	−0.011	0.001	0.136
	PTI_1stMetHead	−0.111	−0.393	0.171	0.439
	(Intercept)*	3.733	3.171	4.296	< 0.0005*
	Gender	0.056	−0.064	0.176	0.358
	Age	−0.002	−0.009	0.005	0.666
	Body mass	0.002	−0.002	0.006	0.389
	DoD*	0.006	0.000	0.012	0.043*
	VPT_Avg	−0.005	−0.012	0.001	0.098
	PTI_1stMetHead	−0.087	−0.365	0.192	0.542
Heel	(Intercept)*	3.669	2.923	4.414	< 0.0005*
	Gender	−0.006	−0.163	0.151	0.939
	Age	0.002	−0.006	0.010	0.667
	Body mass	0.003	−0.003	0.010	0.268
	DoD	−0.002	−0.009	0.005	0.530
	VPT_Heel	<0.0005	−0.004	0.004	0.996
	PTI_Heel*	−0.507	−0.880	−0.133	0.008*
	(Intercept)*	0.3829	2.867	4.368	< 0.0005*
	Gender	0.0817	−0.170	0.150	0.905
	Age	0.002	−0.006	0.011	0.615
	Body mass	0.003	−0.003	0.010	0.333
	DoD	−0.002	−0.009	0.005	0.534
	VPT_Avg	0.001	−0.005	0.008	0.711
	PTI_Heel*	−0.496	−0.880	−0.112	0.011*

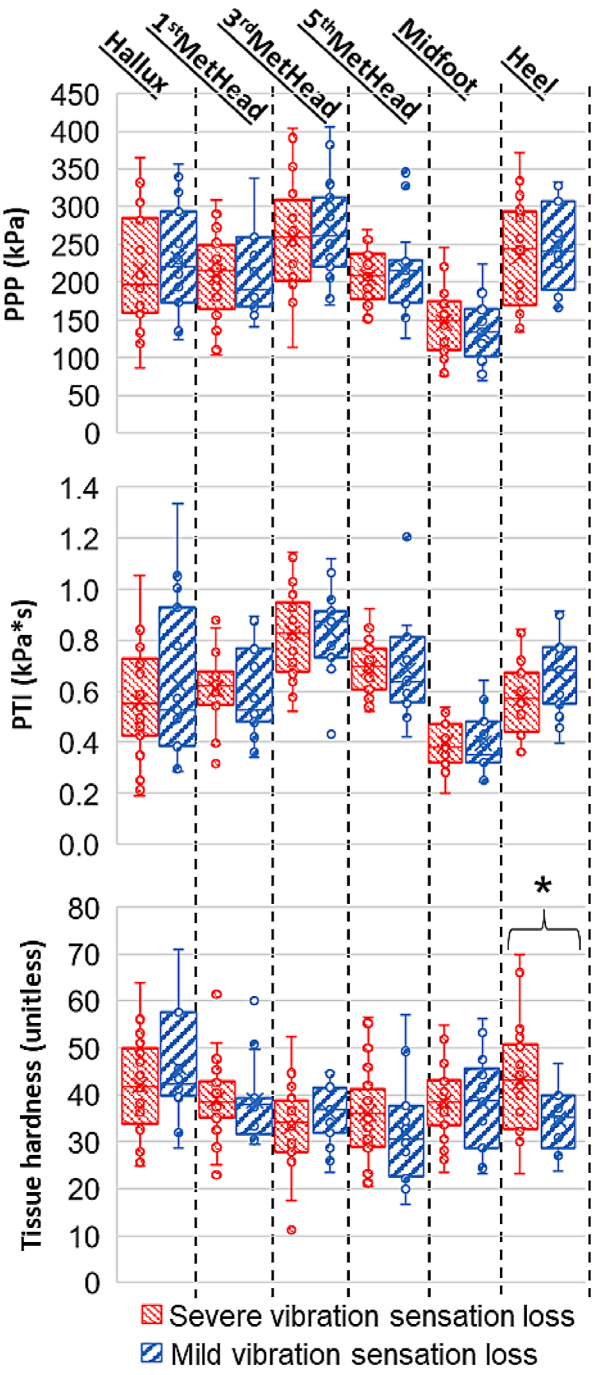

Fig. 2. Comparison between the subgroups with mild vibration sensation loss (15 V ≤ VPT < 25 V in all sites) and severe vibration sensation loss (VPT ≥ 25 V in at least one site). Comparative box-and-whisker plots for peak plantar pressure (PPP), pressure time integral (PTI) and Shore-00 tissue hardness for six plantar regions are presented. Statistically significant differences between groups are indicated with (*).

this study can be found in supplementary material A.

4. Discussion

Although diabetic foot ulceration is a complex and multifactorial condition, the consensus is that it is triggered by mechanical trauma that goes unnoticed due to the lack of sensation of pain in the foot caused by peripheral neuropathy [2]. Because of that, the phenomena that affect the likelihood of mechanical trauma in the tissue can also be significant contributors to ulceration and should be considered during ulceration risk assessment and patient stratification.

People with diabetes and neuropathy tend to load their feet more heavily compared to their non-diabetic, non-neuropathic counterparts [1,15,16]. If nothing else changes in the diabetic foot, then this increase in loading magnitude would on its own directly increase the risk for injury and ulceration. However, along with plantar loading, plantar soft tissue biomechanics are also affected by diabetes [13,31–33] which can also affect the risk for injury in different ways.

These changes in tissue biomechanics can be caused by histological changes due to glycation [31] and/or by increased loading [13,18] and can have either positive or negative effects on ulceration risk [5]. Similar phenomena linking tissue loading to biomechanics and the risk of injury have been established for other tissues [17]. However, in the case of plantar soft tissue a causal link between loading and tissue biomechanics has been hypothesised, but it has not been proven yet [13,18].

Understanding the potential interplay between loading, tissue biomechanics and vulnerability to ulceration is extremely important for reliable ulceration risk assessment. Previous research has demonstrated the link between altered tissue biomechanics and the risk for injury [5]. Demonstrating a significant relationship between loading and biomechanics is therefore a missing prerequisite for the aforementioned causal link between loading, biomechanics and the risk of ulceration to exist.

In the present study, *in vivo* testing in 39 people with diabetes and peripheral neuropathy revealed significant correlations between increased PTI and reduced hardness at the 1stMetHead and heel. The link between increased PTI and reduced hardness was also confirmed by GEE analysis for the heel when the effect of age, body mass, DoD and VPT was considered. These observations are the first to directly demonstrate a link between plantar loading and plantar soft tissue biomechanics in people with diabetes.

Limited indirect evidence on a potential link between plantar loading and plantar soft tissue biomechanics can also be found in the literature for non-diabetic populations [18]. More specifically a comparison between the stiffness of the heel pads of habitual runners and cyclists revealed significantly lower heel pad stiffness in the first group [18]. Assuming that the heel pads of habitual runners are also exposed to higher loads, then this finding also points towards a relationship between increased exposure to loading and reduced plantar soft tissue stiffness. Even though these findings about the effect of different activities are only indirectly linked to the effect of loading they seem to point in the same direction as the findings of the present study [18].

Previous numerical analysis has demonstrated that changes in the plantar soft tissue that increase its capacity to deform can improve the tissues ability to uniformly distribute plantar loads [5]. As a result, this can reduce the risk of soft tissue injury by reducing the magnitude of plantar pressure that is developed for the same externally applied force. At the same time however, excessive deformability could also potentially lead to excessive mechanical strains in the tissue increasing the risk of injury [34]. This is in line with previous findings that indicated a higher risk of future diabetic foot ulcer incident in those with higher deformability at the 1st MetHead area when people with diabetes and peripheral neuropathy were studied using an ultrasound elastography technique [12].

Based on these, and in the absence of thresholds over which deformability can be considered as excessive, no conclusion can be drawn at this point on whether the observed association between increased PTI and increased hardness is a positive adaptive response which reduces the risk of injury or a negative change (e.g. due to tissue degradation) that increases it. Further research, potentially involving more detailed assessments of plantar soft tissue biomechanics will be needed to answer this question [5,6].

The comparison between the two groups of mild and severe vibration sensation loss revealed that the heel pads of the people in the latter group where significantly harder than the first group. This finding appears to complement the results presented by Piaggesi et al.(1999) [13]

where people with diabetes and peripheral neuropathy had significantly harder plantar soft tissues than their non-neuropathic counterparts. No statistically significant difference was found with regards to loading (PPP or PTI) between these two groups (Fig. 2), demonstrating that increased loading may not be a prerequisite for altered plantar soft tissue biomechanics. Histological changes due to glycation could be the main drive behind these differences in tissue biomechanics associated with increased VPT [31].

One of the main limitations of the *in vivo* testing presented here is that skin thickness was not measured. A recent numerical analysis demonstrated that Shore hardness is significantly affected by the stiffness and thickness of skin as well as by the stiffness of subcutaneous tissues [35]. Even though literature indicates that skin thickness might not be affected by the presence of peripheral neuropathy [36], the lack of skin thickness measurements means that Shore hardness can be interpreted only as an assessment of the bulk tissue's (i.e., skin and subcutaneous tissue combined) macroscopic capacity to deform (bulk deformability) [35]. Further research will be needed to clarify which aspects of the complex non-linear mechanical behaviour of plantar soft tissue are affected by exposure to loading and whether different layers (skin or the subcutaneous macro/micro-chamber layer) are equally affected [35].

Shore hardness was used in this study because of its exceptional portability, patient safety, cost-effectiveness and ease-of-use in clinical settings and to facilitate comparisons with relevant literature [13]. Building on the findings that were presented here, more sophisticated methods that are capable of directly quantifying differences in plantar soft tissue stiffness [5,6,37] could be used to explore further the relationship between plantar loading and plantar soft tissue biomechanics. Finally, it should also be noted that in this study the recruited population was relatively older. Considering the effect of age on plantar soft tissue biomechanics [38–40], caution should be exercised when generalising the results presented here for younger populations.

Despite its limitations, the present study was able to demonstrate for the first time that the heel pads of people with diabetes and peripheral neuropathy who tend to load their heels more heavily also tend to have less hard heels. This finding establishes the possibility of altered loading indirectly affecting the likelihood of ulceration by triggering changes in plantar soft tissue biomechanics that make the tissue either more or less vulnerable to overload injury [5]. More research will be needed to assess the implications of this finding for the risk of injury and diabetic foot ulceration.

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.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.diabres.2022.109865.

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