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Changes in Mechanical Skin Properties as a Compensatory Mechanism of Sensory Impairment in Diabetes Patients

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Abstract

Aim: We hypothesized, that there is no relationship between the mechanical skin properties and vibration perception thresholds (VPT) in individuals with (DPN) and without(DM) diabetic neuropathy.

Methods: 33 healthy controls (CG), 20 DM and 13 DPNparticipated in this cross-sectional study. VPTs (30Hz, 200Hz), skin hardness and skinthickness were measured at the heel and first metatarsal head.

Results: General linear models showed no effects of mechanical skin properties on VPTs at either frequency or location. DPN showed significantly higher VPTs compared to DM and CG at both frequencies and locations. Skin was harder in DPN compared to CG (heel). No differences were observed in skin thickness. VPTs at 30Hz correlated negatively with skin hardness for DPN, and with skin thickness for DM.

Conclusion: Mechanical skin properties change as a compensatory mechanism to sensitivity loss and should be considered in future studies.

Keywords: Skin hardness; Skin thickness; Vibration perception threshold; Mechanoreceptors;Sensory perception; Diabetic neuropathy

Introduction

Recent studies have shown that in addition to clinically established high-frequency vibrations, low-frequency vibrations (4Hz-30Hz) also show a strong relation to diabeticneuropathic symptoms and diabetic foot ulcers. [1,2] Besides these changes in the sensory system, plantar skin becomes thinner and stiffer in patients with diabetic neuropathy (DPN)[3]Piaggesi et al.[4] found that harder skin in DPN significantly correlates withthe measured vibration perception thresholds. Unfortunately, the measurements ofskin hardness and vibration perception thresholds (VPT) did not take place at the sameanatomical locations. In contrast, Chatzistergos et al. [5] found no relationship betweenthe mechanical properties of the heel-pad and VPTs. However, it remains unclearwhether measurements were taken at the same anatomical locations or not.5 Further-more, both studies measured VPTs using a biothesiometer, the application of whichas a research tool is controversial, because of poor repeatability[6], and, therefore, doesnot present reliable results. [4,5] In a recently published study with healthy subjects, norelationship between plantar callus thickness and vibration sensitivity was found inusually shod and usually barefoot subjects [7] Therefore, we hypothesized that there isno relationship between mechanical skin properties (MSP) and vibration perceptionthresholds (VPT) in individuals with and without DPN

Materials and methods

33 healthy controls (CG; 56.3±9.9yrs) and 33 patients [without (DM; n=20,53.3±15.1yrs) and with DPN (DPN; n=13, 61.0±14.5yrs)] participated in this study. Patients were classified as DPN based on a fuzzy decision support system [8,9] All participants gave their written consent. This study was performed in accordance with the recommendations of the Declaration of Helsinki and approved by the Ethics Committee of the University of São Paulo (Protocol 1.464.870). To quantify and compare the influence of MSP in the participants, we applied the same methodology for evaluating VPTs, skin hardness and skin thickness at the heel andvfirst metatarsal head (MTH) as described in Holowka et al.[7].To achieve normality and correct the naturally skewed distribution for statistical analysis, VPTs were log-transformed [10]Kruskal-Wallis rank sum tests and ANOVAs were performed to analyze differences between groups. Post hoc tests for pairwise comparisons were performed with appropriate Bonferroni corrections. Spearman's rank-order and Pearson's product-moment correlation coefficients were used to test for relationships within the MSP and between VPTs and MSP. General linear models (GLM) were used to test the relationship between VPTs and skin thickness, with age and skin hardness set as covariates, and gender and group (CG, DM and DPN) set as fixed effects.

Results

VPTs of DPN at 30Hz were significantly higher ($p<0.001$) compared to at 200Hz (Table1). Additionally, DPN VPTs were significantly higher (all $p<0.001$) compared to DM and CG at both frequencies and locations. Interestingly, we found no difference betweenDM and CG (Table 1).

Skin hardness at the heel was significantly higher for DPN compared to CG ($p<0.001$). Skin thickness showed no significant differences between groups (Table 1). Considering groups together, skin hardness and thickness correlated significantly at the heel ($p<0.001$, $rs=0.45$),

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but not at the MTH (p=0.13, rs=0.23).Furthermore, 30Hz VPTs at heel and MTH showed moderate to high negative correlations (p=0.020 and p=0.187, respectively) with skin hardness for DPN (Figures 1a and 1b). For 200Hz VPTs at heel and MTH, moderate negative correlations with skin thickness (p=0.181 and p=0.120, respectively) were found for DM (Figures 1c and1d). Additionally,200Hz VPTs at the heel showed a moderately positive correlation with skin thickness for DPN (Figure 1c). No other correlations were foundGLMs found no effects of MSP on VPT at either location or frequency. The significanceof model effects was tested using type-3 ANOVAs on model variance.

Table 1: Vibration sensitivity data and mechanical skin properties in healthy and diabetic subjects.

	Variable	CG	DM	DPN	statistics	d.f.	p-value
	VPT 30Hz [µm]	23.4 ± 19.9#	35.6 ± 29.5§	155.6 ± 160.1#§	18.72	2	4e-7
	VPT 200Hz [µm]	5.2 ± 7.1#	4.6 ± 7.5§	23.7 ± 23.2#§	9.52	2	2e-4
Heel							
	thickness [mm]	0.78 ±0.17	0.94 ±0.41	0.86 ±0.40	5.18	2	0.08
	hardness [Shore 00]	28.6 ±7.9*	33.4 ±8.3	39.0 ±8.8*	7.89	2	9e-4
	VPT 30Hz [µm]	15.6 ± 15.0#	20.7 ± 21.6§	172.3 ± 199.5#§	21.29	2	6e-8
	VPT 200Hz [µm]	5.8 ± 8.2#	4.6 ± 8.6§	33.2 ± 25.7#§	12.82	2	2e-5
MTH							
	thickness [mm]	0.72 ±0.10	0.78 ±0.41	0.71 ±0.40	1.56	2	0.46
	hardness [Shore 00]	29.1 ±14.0	27.1 ±7.5	31.3 ±8.4	0.56	2	0.57

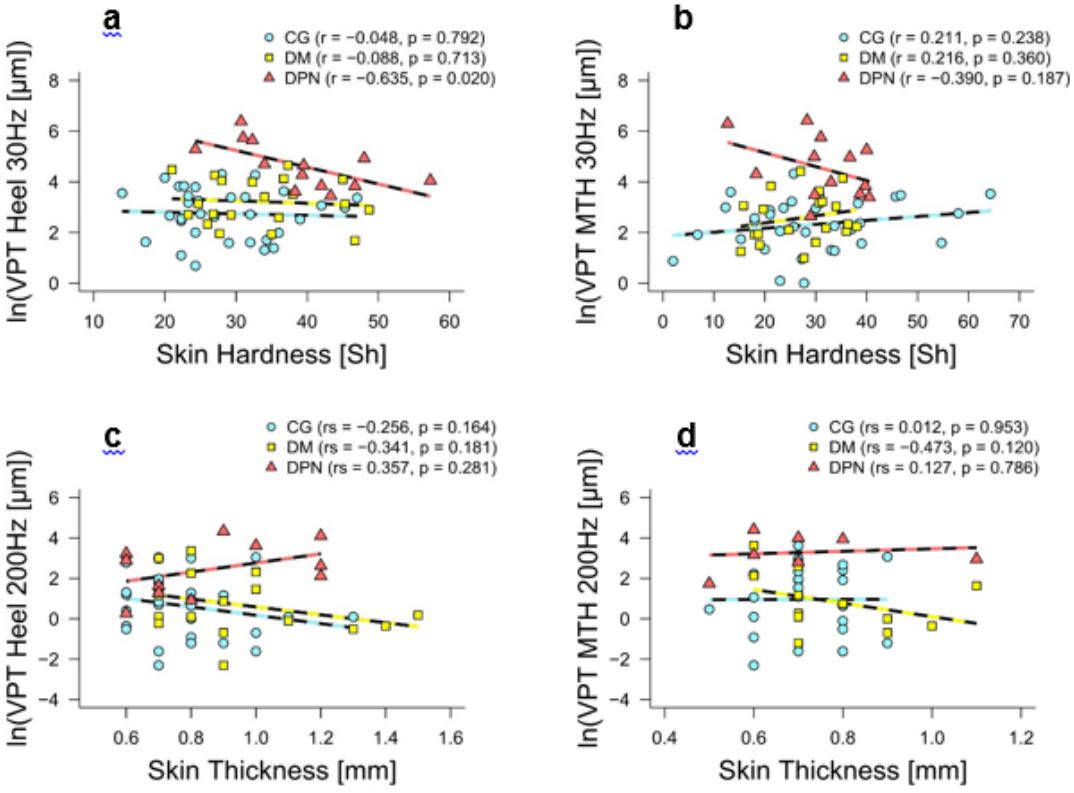

Figure 1: Correlations between vibration perception thresholds (VPT) and mechanical skin properties (MSP). a, b, Scatter plot of skin hardness versus VPT at 30Hz at heel and first metatarsal head (MTH) for control group (blue), diabetes patients without diabetic neuropathy (yellow) and diabetes patients with diabetic neuropathy (red). c, d, Scatter plot of skin thickness versus VPT at 200Hz at heel and first metatarsal head (MTH)

Discussion

In contrast to Chatzistergos et al.[5], MSP of patients with diabetes in our study had aninfluence on their VPTs. Similar to the results of Piaggesi et al.4, DPN had the hardestskin compared to DM and CG (Table 1). Interestingly, Piaggesiet al.4 found a positivecorrelation between skin hardness and VPT. As already mentioned, the measurementsof skin hardness and VPTs in Piaggesi et al.[4] did not take place at the same anatomicallocations. Our study measured skin hardness and VPT at the same locations, resultingin moderate to high negative correlations with skin hardness for VPTs at 30Hz. Thismeans, the harder the skin, the better the perception (Figures 1a, and 1b). In DPN, earlierepidermal denervation compared to deeper dermal layers could result in structuralchanges and might explain the correlations found [11]Consequently, sensitivity loss insuperficial Meissner corpuscles (FAI) may occur earlier and stronger than in Paciniancorpuscles (FAII) in deeper tissues. Thus, FAII and their pathways seem to be influenced less than FAI. Hardening the skin may be the body's attempt to compensate thisloss of sensitivity. Recent studies showed that increasing contact force and/or stimulation area improved VPTs even at lower frequencies [12,13]. Hardening the skin couldlead to a wider spread of vibrations, stimulating a higher quantity of remaining mechanoreceptors and their afferences. Furthermore, we observed moderate negative but not significant correlations between 200Hz VPTs and skin thickness for DM (Figure 1c,d), which showed the thickest skin compared to DPN and CG. Again, the thicker the skin in DM, the better the perception. At the onset of diabetes, FAI show hypertrophic and structural changes, while FAII only show structural changes [14] Furthermore, fibrous collagen networks show a strongercross-linking15, leading to skin thickening.3 The Durometer measured the superficialstiffness of the skin. Deeper plantar stiffness could not be measured, but possibly wasquantified indirectly via skin thickness measurements. Skin thickness is directly relatedto skin stiffness due to the accumulation of glycolysis end products [15]. An increasedspatial summation of FAII due to the increased plantar stiffness could therefore providean explanation for the enhancement of high-frequency VPTs in DM [16]. To confirm thistheory, further studies measuring the thickness and stiffness of the total plantar softtissue, like Chao et al.[3], are necessary. Furthermore, our theory is based on changes that occur in the early stages of diabetes.14 Our range in diabetes duration in DM ishigh (11.9±10.3yrs), which is why further studies should compare newly diagnosedpatients with long-term patients.Besides MSP, VPTs may be influenced by other factors, such as age or gender. Toquantify the influence of MSP in relation to these parameters, we calculated differentGLMs. Similar to previous findings7, only a significant influence of age and group werefound for all VPT conditions, and of gender under 30Hz conditions. Studies have shownthat older subjects are less sensitive to VPT and men are less sensitive at lower VPTfrequencies than women.From the age of 50, men have higher VPTs than women,because of the assumed faster degeneration of the peripheral nervous system [17]. Thisgender effect was only measured at 30Hz, which could be a further indication thatafferent degeneration in diabetes patients already starts at 30Hz rather than at200Hz.1,2 Consequently, men with diabetes are even more affected than healthy subjects. Furthermore, DPN consistently had higher VPTs at both frequencies and locations. This is consistent with the results of the GLMs.From an evolutionary point of view, calluses protect the sole of the foot without causing a loss of vibration sensitivity. From a pathological perspective, in patients with diabetes, the changes in MSP may be a compensatory mechanism in response to theloss of sensitivity up to a certain progression of the disease. The positive correlationbetween skin thickness and 200Hz VPT in DPN (Figure 1c) may indicate a reversalpoint of compensation: tissue disappears, thickness decreases, hardness increases.These changes could affect the functionality of FAII by affecting the compression oftheir lamellar structure. Nevertheless, these changes do not have as great an influence on sensory perception as other parameters (e.g. age), but should be consideredin further studies with larger samples. Although the relationship between skin hardness and VPT in DPN and skin thickness and VPT in DM appear conclusive from a sensory point of view, these pilot-results still need to be tested in larger samples. Partially blurred ultrasound images thinned out the already small samples of DM and DPN (12/20, 7/13 respectively). Furthermore, the cross-sectional design of the study limits conclusions to the cause-and-effect relationship. Nevertheless, we presume that MSP in diabetes patients are related to VPTs.

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Conflict of Interest

The authors declare that there are no conflicts of interest.

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