Novel Vibrating Foot Orthoses for Improving Tactile Sensation in Type 2 Diabetes With Peripheral Neuropathy

Wachirayongyot Thimabut, *Graduate Student Member, IEEE*, Natapatchakrid Thimabut, Liang Peng, and Zeng-Guang Hou, *Fellow, IEEE*

***Abstract*— Improving tactile sensation by vibrating insoles was recommended to prevent foot ulcers in diabetic peripheral neuropathy (DPN). Lack of an insole design for diabetics was a challenge. Clinical trials on applying vibrating insoles with noise and stochastic resonance (SR) stimulating tactile were also required. In this study, vibrating foot orthoses (VFO) with a total contact design based on orthotics were proposed to provide proper insoles for diabetes. This study aimed to determine if VFO were beneficial at enhancing tactile in DPN. VFO were developed in combination with individual's custom-made foot orthoses and stimulation signals—integrating random 0–100 Hz square wave pulse signals with pseudorandom white noise by a SR approach. Sixty patients with mild-to-severe DPN were randomized to conduct crossover experiments: using and without VFO for 60 minutes stimulation at 90% of individuals' vibration perception threshold (VPT) level. VPT values when using VFO at the 1st and 5th metatarsophalangeal joints of the left foot decreased by 9.35% (P <.001); 9.04% (P <.001), and of the right foot decreased by 7.63% (P <.001); 7.24% (P <.001), respectively. Without VFO, there was no significant difference. Subgroups of mild and moderate DPN tended to benefit greatly from utilizing VFO. VFO can improve tactile in DPN. VFO may contribute to restoring/prolonging tactile and protective sensations, also decreasing peripheral nervous system deterioration. VFO might be useful for neurorehabilitation, and help prevent foot ulcers and disabilities.**

***Index Terms*— Diabetes, noise, peripheral neuropathy, stochastic resonance, tactile.**

I. Introduction

DIABETES-RELATED foot ulcers are one of the leading causes of disability globally [1]. 96% of all instances of diabetes in the world—which affected more than half a billion people—were type 2 diabetes (T2D) [2]. DPN, or diabetic peripheral neuropathy, is the most typical diabetes consequence [3] that causes disorders, e.g., increasing the risk of foot ulceration and lower limb amputation by contributing to nearly 50% of T2D cases [4], [5]. 85% of diabetic foot ulceration can progress to nontraumatic lower limb amputation [6]. As a result of DPN, the development of foot ulcers is reportedly arisen by a lack of protective sensation [7]; for instance, gradual vibrotactile sensitivity impairments [8] raise vibration perception threshold (VPT) and cause foot complications [9]. VPT is an effective parameter for identifying the risk of diabetic foot ulceration, and has served as a quantitative sensory test for DPN [10], [11], [12], [13], [14]. When compared to VPT <15V, VPT >25V increased the incidence of foot ulceration nearly sevenfold [10]. For each unit rise in the VPT, the probability of developing a first foot ulcer increased by 5.6 percent [15]. A VPT >25V was associated with recurrent foot ulceration [16], [17].

Regarding the prevention of foot ulcers in diabetes, total contact therapeutic footwear was advised [18], [19], [20], [21]. Using therapeutic footwear has been shown to minimize neuropathy and the recurrence of foot ulcers [22], especially custom-made orthotic insoles that significantly decreased plantar pressure, ulceration, and amputation in diabetes [23]. A vibrating insole (therapeutic footwear combined with noise-based and stochastic resonance (SR) approaches) is a revolutionary medical gadget that can improve tactile sensation in the foot [24].

Manuscript received 9 November 2023; revised 15 March 2024, 17 May 2024, and 24 June 2024; accepted 3 July 2024. Date of publication 29 July 2024; date of current version 21 August 2024. This work was supported in part by the National Key Research and Development Program of China under Grant 2023YFC3603700, in part by the National Natural Science Foundation of China under Grant 62203441 and Grant U21A20479, and in part by Beijing Natural Science Foundation under Grant L232021. *(Corresponding authors: Zeng-Guang Hou; Liang Peng.)*

Wachirayongyot Thimabut is with the State Key Laboratory of Multimodal Artificial Intelligence Systems, Institute of Automation, Chinese Academy of Sciences, Beijing 100190, China, and also with the International College, University of Chinese Academy of Sciences, Beijing 101408, China (e-mail: zhoujiabin2023@ia.ac.cn; wachirayongyot@gmail.com).

Natapatchakrid Thimabut is with the Faculty of Physical Therapy, Srinakharinwirot University, Bangkok, Nakhon Nayok 26120, Thailand (e-mail: natapatchakrid@g.swu.ac.th).

Liang Peng is with the State Key Laboratory of Multimodal Artificial Intelligence Systems, Institute of Automation, Chinese Academy of Sciences, Beijing 100190, China (e-mail: liang.peng@ia.ac.cn).

Zeng-Guang Hou is with the State Key Laboratory of Multimodal Artificial Intelligence Systems, Institute of Automation, Chinese Academy of Sciences, Beijing 100190, China, also with the School of Artificial Intelligence, University of Chinese Academy of Sciences, Beijing 100049, China, and also with the CASIA-MUST Joint Laboratory of Intelligence Science and Technology, Institute of Systems Engineering, Macau University of Science and Technology, Macao, China (e-mail: zengguang.hou@ia.ac.cn).

Digital Object Identifier 10.1109/TNSRE.2024.3435469

In a human neural network, noise can perform significant and beneficial roles in amplifying information transfer via chemical synapses [25], [26]. Some studies demonstrated that optimal noise of high-frequency stimulus combined with a subthreshold low-frequency input and stochastic, coherent, or vibrational resonance might efficiently enhance nerve cell responses in chemical synapses [27], [28], [29], [30], [31].

In the glabrous skin of the human foot, vibrotactile sensation is mediated by mechanoreceptors, especially fast-adapting Type I (FAI) afferent nerve fibers that mediate frequencies 8–64 Hz and fast-adapting Type II (FAII) afferent nerve fibers that mediate frequencies >64 Hz [32]. In elderly people, a weak signal stimulus at the 80% threshold with noise increased vibrotactile sensation [33]. Signal frequencies ≥50 Hz improved vibrotactile sensitivity, which was mediated via FAI and FAII afferent nerve fibers [33].

Additionally, square wave pulses could elicit a threshold response based on the study on the response characteristics of mechanoreceptors in mouse glabrous skin [34].

SR, which is associated with biological systems like human somatosensation, is the existence of a certain amount of nonzero noise that improves a nonlinear system's responsiveness to a weak input signal [35], [36]. In biology, SR was found to function as a threshold mechanism and was found in sensory neurons exposed to noise [37], e.g., information transmission in rat slowly adapting type I (SAI) cutaneous mechanoreceptors is improved by noise through aperiodic SR [38]. In nervous system, noise and SR could enhance information processing in nonlinear systems, as well as in theoretical neural system models and experimental neuroscience [39]. A certain level of noise could improve threshold ability, especially a subthreshold input, which would be very beneficial for SR to be useful [40]. Applying a SR-based technique combined with input noise can improve somatosensation in people [41]. A noise-based approach could improve human tactile perception [42]. Utilizing mechanical stimulus at subthreshold level, electrical noise stimulation increased tactile sensibility [43]. When noise is introduced to subthreshold input, SR occurs, which can improve sensory information processing and perception [35]. Vibrotactile sensitivity and sensorimotor function may be improved by applying a noise-based strategy, according to a previous study that showed a reduction in the threshold for vibrotactile detection at the feet [44].

Previous studies demonstrated: vibrotactile perception was enhanced by vibrating insoles with a low level of mechanical stimulation in T2D with moderate to severe peripheral neuropathy [45]; VPT improvement in moderate to severe DPN could be sustained by SR stimulation of a custom-made vibrating insole with a subsensory level of mechanical noise [46]; by utilizing a vibro-medical insole with noise and SR, T2D patients with mild to moderate peripheral neuropathy reported better vibration sensation of the foot [47]; using a bandage shoe with mechanical noise could enhance the vibration perception of the foot in DPN [48].

Although some studies suggested that using vibrating insoles with noise and SR could improve vibratory and tactile perception on the plantar surface of the foot, there were some drawbacks with them: no insole design for an individual's pathology and foot structure (such as for diabetic feet); no specialty of insole fabrication based on the knowledge of orthotics; no completely total contact design of insoles; no use of medical-grade materials for forming insoles. Additionally, clinical studies are still required to determine how effectively vibrating insoles with noise and SR can stimulate vibratory and tactile sensation in DPN for the purposes of neurological rehabilitation and preventing foot ulceration and lower extremity amputation.

In this present study, vibrating foot orthoses (VFO) were developed. The developed VFO were a noninvasive and medical-grade device. Pseudorandom white noise (PRWN) generated by a linear-feedback shift register (LFSR) was created as a novel approach for tactile stimulation. As a unique technique for stimulating tactile sensation, a random stimulation signal (0–100 Hz) in the form of a square wave pulse was created based on previous research's theoretical and experimental foundations [25], [26], [27], [28], [29], [30], [31], [32], [33], [34], [35], [36], [37], [38], [39], [40], [41], [42], [43], [44]. The random stimulation signal and PRWN were then combined using a SR technique to produce an integrated stimulation signal. This new design differs from other previous studies [44], [46], [47], [48] that used low-level white noise (bandwidth limited between 0 and 100 Hz). In a previous study on employing a vibro-medical insole [47], a low-voltage signal was identified as a stimulation signal; however, other earlier investigations [45], [46], [48] did not disclose the specifics of a stimulation signal applied prior to adding noise. We hope that continuous stimulation for 60 minutes using the VFO may be more beneficial in stimulating tactile sensation than periodic stimulation (20 exposures of 30 Hz vibration stimuli lasting 1 second) [44]. In a previous study [45], no information on a stimulation period was provided; thus, 60 minutes of VFO stimulation may be more relevant for exploration.

In this study, custom-made foot orthoses (CFO) with total contact and an appropriate design for the diabetic foot of each individual were manufactured. In addition, CFO have advantages for foot ulcer management [18], [19], [20], [21], [22], [23]. A flat design of a vibrating insole was inconvenient for usage and outcome measurement, e.g., a custom-made vibrating insole had to be used with a brace resembling a boot configuration [46]; a vibrating insole had to be worn with a bandage shoe [48]. A bandage shoe had holes in its sole at the 1st metatarsophalangeal joint (MTP), 5th MTP, and heel locations for VPT measurement when subjects lied in a prone position [48]. This design of a bandage shoe is cumbersome for outcome measurement. Also, the VFO had been attempted to be designed for ease of use and to facilitate outcome evaluation in a trial.

Furthermore, all the circuits of a vibration generator in this study were low-cost inventions. We anticipate that the developed VFO can gain advantages for neurological therapy; for instance, the VFO can help improve, restore, or prolong tactile and protective sensations, and the VFO may help slow down the deterioration of the peripheral nervous system in DPN patients as well.

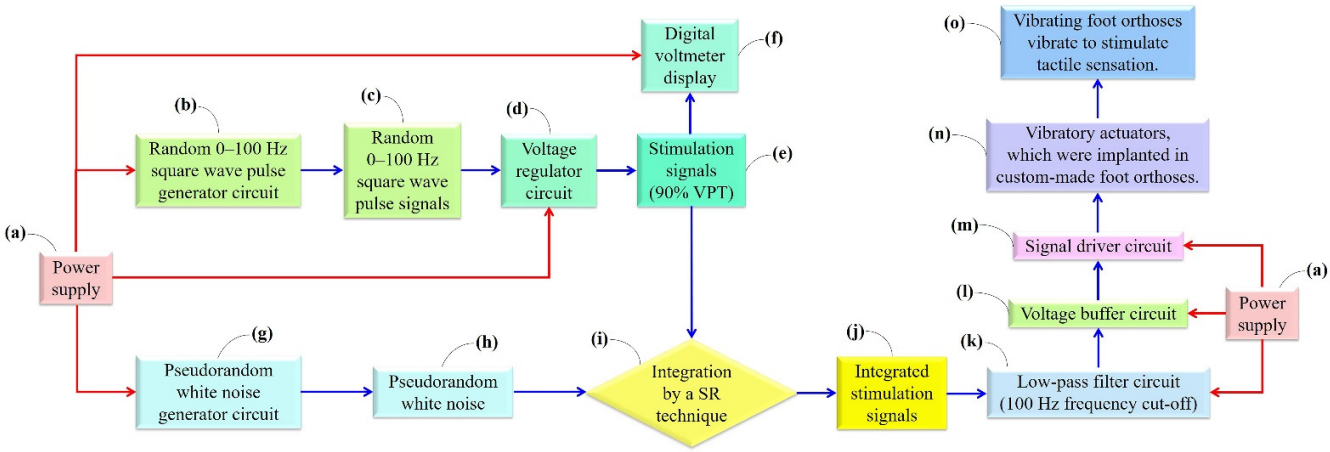

Fig. 1. Invention diagram of VFO: (a) a power supply, (b) a random 0–100 Hz square wave pulse generator circuit, (c) random square wave pulse signals (0–100 Hz), (d) a voltage regulator circuit, (e) stimulation signals, (f) a digital voltmeter display, (g) a pseudorandom white noise (PRWN) generator circuit, (h) pseudorandom white noise, (i) integration of stimulation signals and pseudorandom white noise by a stochastic resonance technique producing integrated stimulation signals, (j) integrated stimulation signals, (k) a low-pass filter circuit (100 Hz frequency cut-off), (l) a voltage buffer circuit, (m) a signal driver circuit, (n) vibratory actuators implanted in custom-made foot orthoses, and (o) vibrating foot orthoses vibrate to stimulate tactile sensation.

Moreover, the developed VFO in this paper might contribute to maximizing benefits in neurorehabilitation and helping prevent diabetic foot ulcers and lower limb disabilities. The purpose of this study was to investigate the efficacy of using the VFO in stimulating the tactile sensation of T2D patients with peripheral neuropathy, including mild to severe conditions of DPN.

II. Methods

A. Development of Vibrating Foot Orthoses (VFO)

VFO were comprised of two major components: a vibration generator and CFO. The vibration generator was composed of two signal generator circuits: a random 0–100 Hz square wave pulse generator circuit (Fig. 1(b)) and a PRWN generator circuit (Fig. 1(g)). A DC power supply powered both circuits (Fig. 1(a)). AD9833 (Analog Devices Inc., USA) and Arduino Nano 3.0 (Arduino SA, Switzerland) micro controllers were used to generate random 0–100 Hz square wave pulse signals (Fig. 1(c)); then, these signals were adjusted to 90% of each subject's VPT level for becoming stimulation signals (Fig. 1(e)) by a voltage regulator circuit (Fig. 1(d)). The intensity of the stimulation signals was shown on a digital voltmeter display (Fig. 1(f)).

A PRWN generator circuit (Fig. 1(g)) was comprised of a pseudorandom binary sequence (PRBS) and a LFSR to produce PRWN. A low-cost design of a PRBS generator was based upon the LFSR implementation using a CD4015BM96 dual quad static shift register (Texas Instruments, USA) and a CD4030BM96 quad exclusive-OR gate (Texas Instruments, USA). 32 D-type flip-flops with feedback taps at the 28th and 31st producing a PRBS31 data pattern were used for this generator. The feedback was connected to an exclusive-OR gate, which was then inverted to form an exclusive-NOR gate to configure the LFSR. The 31-bit pattern had a length of over 2 billion states and a duration of approximately 72 minutes at a 500 kHz clock frequency rate. Consequently, PRWN was generated as output (Fig. 1(h)). Then, the stimulation signals were integrated with PRWN by a SR technique (Fig. 1(i)) to produce integrated stimulation signals (Fig. 1(j)). The integrated stimulation signals were delivered to a low-pass filter circuit at a 100-Hz frequency cut-off (Fig. 1(k)). After that, a voltage buffer circuit helped maintain the level of the integrated stimulation signal voltage (Fig. 1(l)). An IC-LM741 operational amplifier (Texas Instruments, USA) was used for the low-pass filter circuit and the voltage buffer circuit. Next, the integrated stimulation signals were delivered to vibratory actuators (Fig. 1(n)) by a signal driver circuit (Fig. 1(m)) with a 2N2222A transistor (NTE Electronics, Inc., USA). Vibratory actuators were implanted in the CFO, which were fabricated according to the individual's foot structure for total contact purposes. RCA plugs and jacks were used to connect components of the vibration generator and the CFO to become the VFO. When the integrated stimulation signals were delivered to the implanted actuators, the VFO would perform vibration to stimulate across the entire soles of the feet (Fig. 1(o)).

B. Fabrication of Custom-Made Foot Orthoses (CFO)

CFO were fabricated according to each subject's foot structure and pathology by a prosthetist and orthotist (PO). The fabrication of the CFO was composed of six major processes: 1) clinical assessment and imprint of the foot (Fig. 2(a)); 2) foot casting (Fig. 2(b)); 3) molding and sculpting the foot mold (Fig. 2(c)); 4) forming the CFO by suitable materials for diabetic feet (Fig. 1(d)); 5) grinding and fitting the CFO (Fig. 2(e)); 6) finishing the CFO (Fig. 2(f)).

The CFO were formed with three layers: a 5-mm top layer (Fig. 3(a))—Plastazote® (low-hardness material with shore-A 30) [49], [50], [51]; a 10-mm middle layer (Fig. 3(a))—ethyl vinyl acetate (high-hardness material with shore-A 50) [52], [53]; a 0.8-mm bottom layer—PITEX reinforcement sheets. Medial arch support was made of ethyl vinyl acetate

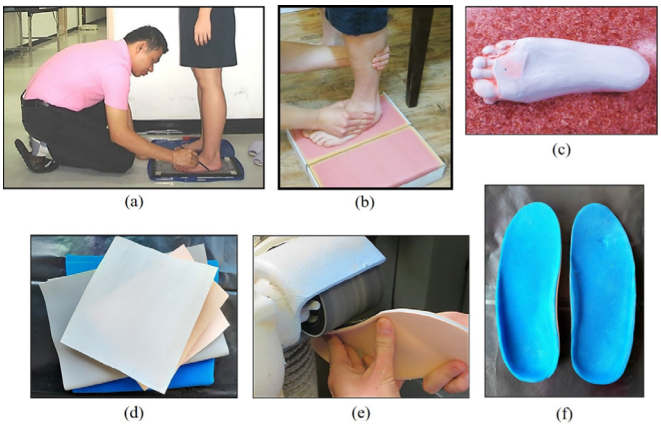

Fig. 2. Fabrication of CFO: (a) clinical assessment and imprint of the foot, (b) foot casting, (c) molding and sculpting the foot mold, (d) forming CFO by employing suitable materials for diabetic feet, (e) grinding and fitting CFO, and (f) finishing CFO.

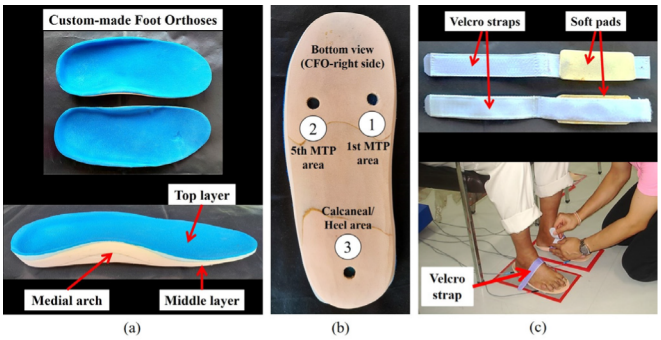

Fig. 3. (a) Forming CFO, (b) embedded positions of vibratory actuators, (c) Velcro straps and soft pads.

(approximately 15 mm thickness, or depending on the individual's medial arch height of the foot) with shore-A 50 [54] (Fig. 3(a)), and the total thickness of the CFO was 10.8 mm. Vibratory actuators were embedded in the middle layer of the CFO at the areas of the 1st MTP, 5th MTP, and calcaneus/heel (Fig. 3(b)). Velcro straps were applied to prevent feet from slipping away while using the VFO, and soft pads were used to relieve pressure from applying the straps to the skin of the dorsum of the foot (Fig. 3(c)).

A vibratory actuator, a DC round-shape vibration motor, 10 mm in diameter and 3 mm in height (Vybronics Inc., USA), was connected with an RCA plug and a coaxial cable (Fig. 4(a)). A single vibratory actuator was embedded in the CFO, following the specific areas as indicated in Fig. 3(b). An RCA plug was used to receive the integrated stimulation signal and connect with an RCA jack. A coaxial cable carried the integrated stimulation signals with tiny losses. All circuits and components of the vibration generator were located inside a plastic waterproof case with an electrical insulator and a closed seal (Fig. 4(b)). When assembling the vibration generator and the CFO by connecting RCA plugs and jacks (Fig. 4(c)), the VFO executed vibration with a random frequency of a random 0–100 Hz bandwidth. Owing to the lack of a lifelong battery without a drop of power supply, a main DC power supply was converted from a 220V residential electrical current to maintain the intensity and voltage levels of the integrated stimulation signals for experimental purposes.

Safety, such as a fuse and residual-current circuit breaker with electrical overload protection, a grounding system, using shield cables, was provided in the development of the VFO. A power supply part was housed within the casing of the vibration generator and was separate from the patient connection section (Fig. 4(b)). Electrical safety testing and risk management for medical devices were performed in accordance with EN IEC 60601-1, ISO 14971, and the protocol for permission on medical devices in Thailand by the Medical Device Control Division of the Food and Drug Administration of Thailand to ensure that the VFO was safe for use in patients and clinical trials.

C. Subjects

Sixty T2D patients with peripheral neuropathy were recruited from the HRH Princess Maha Chakri Sirindhorn Medical Centre (Srinakharinwirot University), Ongkharak, Nakhon Nayok, Thailand. The study protocol was approved by the Human Research Ethics Committee, Srinakharinwirot University (SWUEC-661032), and was registered with the Thai Clinical Trials Registry (TCTR20230530001). Prior to participating in this study, all subjects provided written informed consent.

Inclusion criteria included: 1) aged 18–80 years; 2) diagnosed as T2D and peripheral neuropathy on the feet; 3) no foot problems, such as ulcers, injuries, deformities, etc.; 4) no muscle weakness in the leg and foot; 5) stable vital and neurological signs; 6) adequate language and cognitive abilities to understand and follow instructions; 7) ability to perceive vibration with a graduated 128 Hz tuning fork (Rydel-Seiffer version); 8) capable of sitting for at least 60 minutes.

The aforementioned circumstances precluded subjects from participating: 1) musculoskeletal issues, such as excruciating discomfort in any foot joints; 2) contracture of the foot joints that hinders using the VFO; 3) cognitive impairments; 4) allergy to materials in the VFO.

D. Study Design

A crossover randomized controlled trial was conducted in this study. There were two experiments: using and no using the VFO. Subjects were blinded. Regarding subthreshold stimulation at 90% of each subject's VPT level, each subject did not sense vibration. Subjects could not differentiate between non-vibrational and vibrational interventions. An opaque box was used to cover the vibration generator device to hide the obvious switch-on or switch-off from subjects for 60 minutes of vibration stimulation in each experiment. The PO examined subjects' vibration perceptions at random times throughout the experiment periods by asking them. Subjects were obliged to notify the PO, physician, or researcher immediately if they felt any vibration from the VFO. If subjects report vibration feeling while receiving tactile stimulation, the researcher will terminate the current intervention. Then, subjects have to take a rest for at least 30 minutes for a washout period. The PO will reassess their

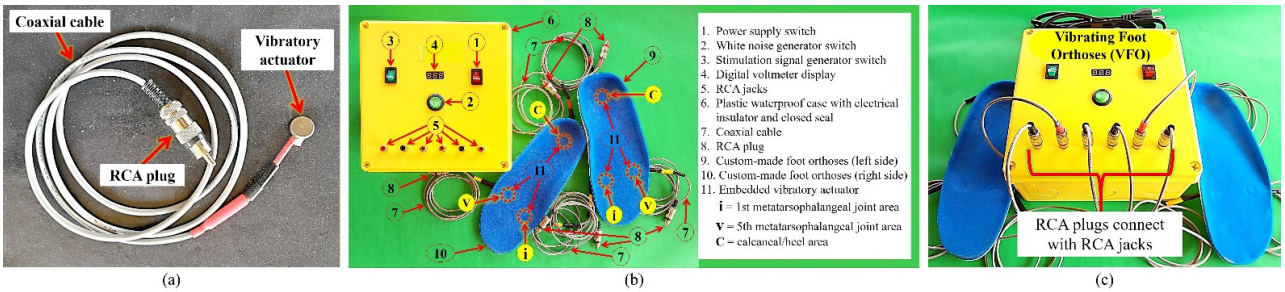

Fig. 4. (a) A vibratory actuator, (b) a vibration generator separates from custom-made foot orthoses with embedded vibratory actuators, (c) vibrating foot orthoses.

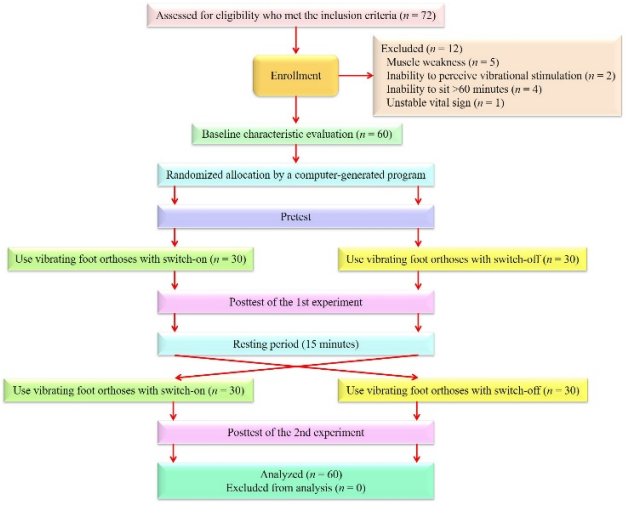

Fig. 5. Consolidated Standards of Reporting Trials flow diagram.

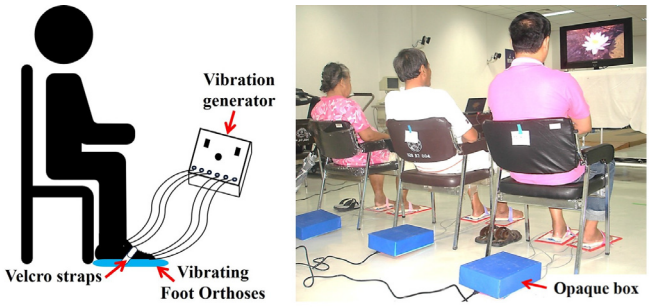

Fig. 6. Sitting position while conducting the experiments.

VPT levels, and the researcher will set a new subthreshold stimulation level for them in a renewed trial.

During the experiments in this study, there were no records regarding subjects' vibration perceptions.

VPT was selected as a parameter, and it was evaluated by the PO using the Vibratory Sensory Analyzer: VSA-3000 (Medoc Ltd., USA) in baseline/pretest and posttests. Subjects received randomized experimental sequences generated by a computer algorithm, and then they performed a crossover. Each subject received a covert envelope, and was instructed by the PO to conduct the assigned experiments. The Consolidated Standards of Reporting Trials flow diagram is shown in Fig. 5.

E. Procedures

Diabetic foot, muscle strength, the Semmes-Weinstein monofilament test (SWMT): a 5.07 monofilament and a 10-site test, the Michigan neuropathy screening instrument (MNSI), vibratory perception, and VPT were assessed as baseline characteristics. Subjects were instructed to abstain from taking any medications that influence the nervous system's upkeep and any vitamins, including vitamin B3, B6, B complex, and no drinking alcohol for 48 hours prior to starting the experiments. Besides, subjects have kept up with their regular regimen of other diabetes medications. Before beginning the experiments for 30 minutes, 200 kcal of food and 110 kcal of drink were provided to subjects, because they needed to keep their blood sugar levels stable to avoid hypoglycemia during the experiments. In the pretest and the 1st and 2nd posttests, VPT was evaluated at the 1st and 5th MTP.

During the experiments (Fig. 6), subjects were assigned to take a seat in a backrest chair, and the angle of their knees to the ground was perpendicular. Then, they put their bare feet on the VFO with fastening Velcro straps. The subjects conducted the crossover experiments: switch-on (vibrating mode) and switch-off (non-vibrating mode), with a comfortable atmosphere by listening to harmonious melodies and watching beautiful natural scenery on a television screen. In switch-on mode, each subject received a vibration stimulus for tactile stimulation from the integrated stimulation signals set at 90% of the individual's VPT level. In each experiment, the posttest was immediately assessed by the PO. Between the experiments, subjects rested for 15 minutes to avoid weariness. The researcher and physician presented with subjects at all times of an experimental period to take care of them.

F. Sample Size Calculation

Based on data from a previous study by Khaodhiar et al. [45], a sample size was calculated by using 100% power and 20% dropout with a 2-sided significance level of 0.05. The calculated sample size was 58; however, we increased the number of recruited subjects to 60 in order to undertake subgroup analysis based on DPN severity levels.

G. Outcome Measurements

The baseline/pretest and immediate posttests for VPT outcomes at the 1st and 5th MTP of the foot were assessed by using the VSA 3000 as an evaluation tool. A subject placed his/her foot on an evaluation tool's pedestal and stylus. When the subject sensed the vibrating stylus, the subject pressed a

TABLE I
DEMOGRAPHIC DATA

	$n = 60$
Age, years; mean±SD (range)	53.0±13.25 (28, 73)
Gender, *n* (%)	
Male	28 (46.7)
Female	32 (53.3)
Condition of DPN, *n* (%)	
Mild	20 (33.33)
Moderate	20 (33.33)
Severe	20 (33.33)
Duration of DPN, months; median (range)	80.5 (25, 194)
BMI, kg/m^2; mean±SD	26.75±2.62
MNSI-A, scores; mean±SD	9.07±1.93
MNSI-B, scores; mean±SD	7.10±0.30
SWMT, sites; mean±SD	6.83±1.88

SD = standard deviation, DPN = diabetic peripheral neuropathy, BMI = body mass index.
MNSI = Michigan neuropathy screening instrument: MNSI-A has a total possible score of 13 points, with a score of 7 deemed abnormal; MNSI-B has a total possible score of 10 points, with a score of 2.5 considered abnormal. At least one of the MNSI assessments (MNSI-A or MSNI-B) was abnormal for each subject.
SWMT = Semmes-Weinstein Monofilament Test (10 g of force and 10-site testing).

stop button in hand to calculate the VPT value. The VPT value was evaluated five times, with the results given as the average VPT value. Notably, the VPT outcome at the calcaneal/heel area could not be examined because the subject weighted the lower limb while pressing the heel against the stylus.

H. Statistical Analysis

A paired sample *t*-test was performed to compare with and without the VFO, as well as to analyze the effectiveness of using the VFO in mild, moderate, and severe DPN conditions. The Bonferroni-adjusted post hoc test (Bonferroni correction) [55] and Holm's sequential Bonferroni procedure [56] were used to analyze the effectiveness of using the VFO in mild, moderate, and severe DPN conditions. Cohen's *d* was used to estimate the effect sizes of the findings. Cohen's d values (*d*) are classified as small (0.0–0.20), medium (0.21–0.50), or large (0.51–0.8) effect sizes [57]. IBM SPSS Statistics for Windows, Version 22.0 (IBM Corp., Armonk, NY) was utilized for statistical analysis, with statistical significance set at two-tailed $P < .05$.

III. RESULTS

Sixty diabetic peripheral neuropathic patients (mild: $n = 20$; moderate: $n = 20$; severe: $n = 20$) completed the study. Demographic data were demonstrated in Table I.

Comparisons of VPT outcomes when using and not using the VFO were summarized in Table II. The VPT values when using the VFO at the 1st and 5th MTP of the left foot significantly decreased by 9.35% (the mean VPT pretest = 27.06±18.06 V, the mean VPT posttest = 24.53±18.72 V, $P < 0.001$, $d = 0.14$); 9.04% (the mean VPT pretest = 28.33±18.56 V, the mean VPT posttest = 25.77±19.28 V, $P < 0.001$, $d = 0.14$), and of the right foot significantly decreased by 7.63% (the mean VPT pretest = 28.95±18.12 V, the mean VPT posttest = 26.74±18.95 V, $P < 0.001$, $d = 0.12$); 7.24% (the mean VPT pretest = 30.36±18.16 V, the mean VPT posttest = 28.16±19.09 V, $P < 0.001$, $d = 0.12$), respectively. There was no significant difference in the VPT values when not using the VFO.

The subgroup consideration of the DPN severity when using and no using the VFO was summarized in Table III and IV.

Subgroup analyses of DPN severity using the paired sample *t*-test demonstrated the following results. For the subgroup of mild DPN, the decreasing VPT values when compared between pretest and posttest in using the VFO demonstrated: the VPT values significantly decreased by 34.60% (the mean VPT pretest = 6.85±1.80 V, the mean VPT posttest = 4.48±1.65 V, $P < .001$, $d = 1.32$, the 1st MTP–left foot); 34.44% (the mean VPT pretest = 7.20±1.59 V, the mean VPT posttest = 4.72±1.52 V, $P < .001$, $d = 1.56$, the 5th MTP–left foot); 29.94% (the mean VPT pretest = 7.85±2.11 V, the mean VPT posttest = 5.50±2.12 V, $P < .001$, $d = 1.11$, the 1st MTP–right foot); 27.56% (the mean VPT pretest = 9.07±2.53 V, the mean VPT posttest = 6.57±2.53 V, $P < .001$, $d = 0.99$, the 5th MTP–right foot). There was no significant change when no using the VFO.

For the subgroup of moderate DPN, the significant decline of the VPT values when using the VFO compared to pre- and post-test showed: the VPT values diminished by 16.38% (the mean VPT pretest = 25.70±6.57 V, the mean VPT posttest = 21.49±6.38 V, $P < .001$, $d = 0.64$, the 1st MTP–left foot); 15.65% (the mean VPT pretest = 27.48±6.78 V, the mean VPT posttest = 23.18±6.51 V, $P < .001$, $d = 0.63$, the 5th MTP–left foot); 13.21% (the mean VPT pretest = 28.77±6.53 V, the mean VPT posttest = 24.97±2.13 V, $P < .001$, $d = 0.58$, the 1st MTP–right foot); 12.51% (the mean VPT pretest = 30.37±5.97 V, the mean VPT posttest = 26.57±5.91 V, $P < .001$, $d = 0.64$, the 5th MTP–right foot). Without the VFO, there was no discernible difference between the pretest and posttest.

For the subgroup of severe DPN, the VPT values in the posttest when using the VFO compared with the pretest represented: the VPT values significantly reduced by 2.06% (the mean VPT pretest = 48.62±5.69 V, the mean VPT posttest = 47.60±6.07 V, $P < .001$, $d = 0.18$, the 1st MTP–left foot); 1.75% (the mean VPT pretest = 50.29±5.35 V, the mean VPT posttest = 49.41±5.72 V, $P < .001$, $d = 0.16$, the 5th MTP–left foot); 0.96% (the mean VPT pretest = 50.23±3.66 V, the mean VPT posttest =

TABLE II
VPT OUTCOMES WHEN USING AND WITHOUT VFO

VPT (V)		Using VFO (n = 30)				Without VFO (n = 30)			
		Mean±SEM (range)	Mean difference (SD)	P* (95% CI)	d	Mean±SEM (range)	Mean difference (SD)	P* (95% CI)	d
Left									
1st MTP	Pretest	27.06±3.30 (4.66, 57.82)	2.53 (1.50)	<.001‡ (1.97, 3.10)	0.14	27.15±3.31 (4.46, 57.84)	-0.0 (0.01)	0.662 (-0.004, 0.002)	0
	Posttest	24.53±3.42 (2.60, 57.50)				27.15±3.31 (4.45, 57.85)			
5th MTP	Pretest	28.33±3.39 (5.32, 57.62)	2.56 (1.57)	<.001‡ (1.97, 3.14)	0.14	28.32±3.39 (5.14, 57.64)	0.0 (0.01)	0.769 (-0.002, 0.003)	0
	Posttest	25.77±3.52 (2.85, 57.53)				28.32±3.39 (5.14, 57.64)			
Right									
1st MTP	Pretest	28.95±3.31 (5.65, 56.24)	2.21 (1.47)	<.001‡ (1.66, 2.76)	0.12	28.95±3.31 (5.65, 56.24)	-0.00 (0.01)	0.702 (-0.004, 0.003)	0
	Posttest	26.74±3.46 (3.26, 56.03)				28.95±3.31 (5.64, 56.25)			
5th MTP	Pretest	30.36±3.32 (6.65, 57.21)	2.20 (1.56)	<.001‡ (1.62, 2.78)	0.12	30.46±3.29 (7.11, 57.12)	0.0 (0.01)	0.823 (-0.003, 0.003)	0
	Posttest	28.16±3.49 (3.76, 57.21)				30.46±3.29 (7.11, 57.12)			

VPT = vibration perception threshold, VFO = vibrating foot orthoses, SEM = standard error of the mean, SD = standard deviation, CI = confidence interval, MTP = metatarsophalangeal joint, V = volt.
* Paired t-test; ‡ Significant at P<0.05.

49.75±3.85 V, P <.001, d = 0.13, the 1st MTP–right foot); 0.58% (the mean VPT pretest = 51.64±3.76 V, the mean VPT posttest = 51.34±3.87 V, P <.001, d = 0.08, the 5th MTP–right foot). With no using the VFO, there was no difference between the pretest and posttest.

By performing the Bonferroni correction for subgroup analysis, when using the VFO in mild, moderate, and severe DPN, the results at the 1st and 5th MTP of the left and right foot revealed: these subgroups had no equivalent variances; the VPT values of the pretest and DPN conditions had a statistically significant influence on the VPT values of the posttest; DPN conditions resulted in a statistically significant difference in the VPT values of the posttest after adjusting for the influence of the VPT values of the pretest. In addition, the posttest outcomes at the 1st and 5th MTP of the left foot and the 1st MTP of the right foot showed there were considerable differences between the mild and moderate subgroups, as well as the moderate and severe subgroups. Except for the outcomes at the 5th MTP of the right foot, only the difference between the moderate and severe subgroups was statistically significant. Furthermore, Holm's sequential Bonferroni procedure represented that all subgroups had posttest outcomes at the 1st and 5th MTP of both feet that differed substantially between each pair of subgroups when using the VFO.

Considering subgroup analysis without using the VFO, the Bonferroni correction revealed that the results at the 1st and 5th MTP of both feet had equality of variances. The posttest VPT values were not significantly affected by DPN severity; however, the pretest VPT values were statistically significant in influencing the posttest outcomes. After impact adjustment on the pretest VPT values, there was no change in the posttest VPT values based on DPN severity. In pairwise comparisons, there was no difference between each pair of subgroups when no using the VFO. Besides, Holm's sequential Bonferroni procedure found no significant difference in all DPN severity subgroups when the VFO was not used.

Neither during the experimentation nor afterward, there were no adverse occurrences reported.

IV. DISCUSSION

In this current study, the VFO were developed to stimulate tactile sensation, and were purposed to use decreasing the VPT on the plantar surface of the foot in T2D patients with mild, moderate, and severe peripheral neuropathy. The combination of a random square wave pulse signal (0–100 Hz) and PRWN by a SR approach was set at subthreshold level (90% VPT of each subject) for tactile stimulation. The novelty of the random square wave pulse signal (0–100 Hz) and PRWN appeared to successfully improve tactile sensitivity.

After utilizing the VFO for 60 minutes, the mean difference of the VPT values was significantly lower than the baseline by an average of 8.32% and was also reduced by more than twofold when compared to those who did not use the VFO.

In subgroups, the findings showed that using the VFO appeared to effectively help decrease the VPT values in mild, moderate, and severe conditions of DPN, i.e., the mean of the VPT values decreased by an average of 31.64% in the mild group, by an average of 14.44% in the moderate group, and by an average of 1.35% in the severe group when compared to the baseline. There was no significant difference in subgroups without the VFO. Fundamentally, multiple comparisons in assessing the effectiveness of the device across various conditions and subgroups of the study should be performed as a prespecified subgroup analysis before setting the study in order to reduce multiplicity and increase the reliability of the findings when compared to a post-hoc subgroup analysis.

In terms of effect sizes, using the VFO had a small impact overall. When the VFO was used at various severity levels of DPN, there was a substantial effect in the mild group, a medium effect in the moderate group, and a modest effect in the severe group.

Considering the association between the severity levels of DPN and the intervention results, we suggest that using the

TABLE III
VPT OUTCOMES OF SUBGROUPS WHEN USING VFO

Bonferroni-adjusted post hoc test: Dependent variable is Posttest; Between-subjects factors are DPN conditions, i.e., Mild (n = 10), Moderate (n = 10), Severe (n = 10).

1st MTP (Left)

Levene's test		Tests of between-subjects effects			
F	P	Source	F	P	R^2 (Adjusted R^2)
9.512	<.001‡	Pretest	1399.364	<.001‡	0.999
		Condition	40.553	<.001‡	(0.999)

Parameter estimates				
Parameter	Mean difference	t	P	95% CI
Pretest	1.0	37.408	<.001‡	0.945, 1.055
Mild DPN	-1.350	-1.162	0.256	-3.737, 1.038
Moderate DPN	-3.202	-4.636	<.001‡	-4.622, -1.782
Severe DPN	0[ǂ]	-	-	-

Pairwise comparisons				
DPN condition: I	DPN condition: J	Mean difference: I-J	P‡	95% CI
Mild	Moderate	1.852	0.014‡	0.326, 3.378
	Severe	-1.350	0.768	-4.322, 1.623
Moderate	Mild	-1.852	0.014‡	-3.378, -0.326
	Severe	-3.202	<.001‡	-4.969, -1.434
Severe	Mild	1.350	0.768	-1.623, 4.322
	Moderate	3.202	<.001‡	1.434, 4.969

DPN condition	VPT (V)	Mean±SD (range)	Mean difference (SD)	P* (95% CI)	d
Mild	Pretest	6.85±1.80 (4.66, 10.22)	2.37 (0.30)	<.001‡ (2.16, 2.58)	1.32
	Posttest	4.48±1.65 (2.60, 7.54)			
Moderate	Pretest	25.70±6.57 (16.25, 35.55)	4.21 (1.07)	<.001‡ (3.45, 4.98)	0.64
	Posttest	21.49±6.38 (13.87, 32.16)			
Severe	Pretest	48.62±5.69 (40.83, 57.82)	1.02 (0.49)	<.001‡ (0.65, 1.36)	0.18
	Posttest	47.60±6.07 (39.59, 57.50)			

Holm's sequential Bonferroni procedure

Stage	P* (DPN condition)	Calculated α level†
1	<.001 (Mild)	0.017
2	<.001 (Moderate)	0.025
3	<.001 (Severe)	0.05

Order the P-values* from smallest to greatest: P_{Mild} = <.001, $P_{Moderate}$ = <.001, P_{Severe} = <.001

5th MTP (Left)

Levene's test		Tests of between-subjects effects			
F	P	Source	F	P	R^2 (Adjusted R^2)
10.00	<.001‡	Pretest	1361.375	<.001‡	0.999
		Condition	45.437	<.001‡	(0.999)

Parameter estimates				
Parameter	Mean difference	t	P	95% CI
Pretest	0.992	36.897	<.001‡	0.936, 1.047
Mild DPN	-1.964	-1.636	0.114	-4.432, 0.504
Moderate DPN	-3.615	-5.238	<.001‡	-5.033, -2.196
Severe DPN	0[ǂ]	-	-	-

Pairwise comparisons				
DPN condition: I	DPN condition: J	Mean difference: I-J	P‡	95% CI
Mild	Moderate	1.651	0.044‡	0.038, 3.264
	Severe	-1.964	0.342	-5.036, 1.108
Moderate	Mild	-1.651	0.044‡	-3.264, -0.038
	Severe	-3.615	<.001‡	-5.381, -1.849
Severe	Mild	1.964	0.342	-1.108, 5.036
	Moderate	3.615	<.001‡	1.849, 5.381

DPN condition	VPT (V)	Mean±SD (range)	Mean difference (SD)	P* (95% CI)	d
Mild	Pretest	7.20±1.59 (5.32, 10.83)	2.48 (0.25)	<.001‡ (2.30, 2.66)	1.56
	Posttest	4.72±1.52 (2.85, 8.02)			
Moderate	Pretest	27.48±6.78 (15.64, 36.54)	4.30 (1.08)	<.001‡ (3.53, 5.08)	0.63
	Posttest	23.18±6.51 (13.36, 32.38)			
Severe	Pretest	50.29±5.35 (42.46, 57.62)	0.88 (0.47)	<.001‡ (0.55, 1.21)	0.16
	Posttest	49.41±5.72 (41.23, 57.53)			

Holm's sequential Bonferroni procedure

Stage	P* (DPN condition)	Calculated α level†
1	<.001 (Mild)	0.017
2	<.001 (Moderate)	0.025
3	<.001 (Severe)	0.05

Order the P-values* from smallest to greatest: P_{Mild} = <.001, $P_{Moderate}$ = <.001, P_{Severe} = <.001

1st MTP (Right)

Levene's test		Tests of between-subjects effects			
F	P	Source	F	P	R^2 (Adjusted R^2)
4.091	0.028‡	Pretest	2131.110	<.001‡	0.999
		Condition	69.877	<.001‡	(0.999)

Parameter estimates				
Parameter	Mean difference	t	P	95% CI
Pretest	1.026	46.164	<.001‡	0.980, 1.072
Mild DPN	-0.770	-0.794	0.435	-2.764, 1.224
Moderate DPN	-2.760	-5.203	<.001‡	-3.850, -1.670
Severe DPN	0[ǂ]	-	-	-

Pairwise comparisons				
DPN condition: I	DPN condition: J	Mean difference: I-J	P‡	95% CI
Mild	Moderate	1.990	0.002‡	0.660, 3.320
	Severe	-0.770	1.0	-3.252, 1.712
Moderate	Mild	-1.990	0.002‡	-3.320, -0.660
	Severe	-2.760	<.001‡	-4.117, -1.403
Severe	Mild	0.770	1.0	-1.712, 3.252
	Moderate	2.760	<.001‡	1.403, 4.117

DPN condition	VPT (V)	Mean±SD (range)	Mean difference (SD)	P* (95% CI)	d
Mild	Pretest	7.85±2.11 (5.65, 12.34)	2.35 (0.33)	<.001‡ (2.11, 2.59)	1.11
	Posttest	5.50±2.12 (3.26, 10.03)			
Moderate	Pretest	28.77±6.53 (20.35, 37.65)	3.80 (0.80)	<.001‡ (3.23, 4.37)	0.58
	Posttest	24.97±2.13 (17.68, 34.17)			
Severe	Pretest	50.23±3.66 (44.56, 56.24)	0.48 (0.27)	<.001‡ (0.29, 0.67)	0.13
	Posttest	49.75±3.85 (43.92, 56.03)			

Holm's sequential Bonferroni procedure

Stage	P* (DPN condition)	Calculated α level†
1	<.001 (Mild)	0.017
2	<.001 (Moderate)	0.025
3	<.001 (Severe)	0.05

Order the P-values* from smallest to greatest: P_{Mild} = <.001, $P_{Moderate}$ = <.001, P_{Severe} = <.001

5th MTP (Right)

Levene's test		Tests of between-subjects effects			
F	P	Source	F	P	R^2 (Adjusted R^2)
3.502	0.044‡	Pretest	1604.667	<.001‡	0.999
		Condition	63.990	<.001‡	(0.999)

Parameter estimates				
Parameter	Mean difference	t	P	95% CI
Pretest	0.993	40.058	<.001‡	0.942, 1.044
Mild DPN	-2.485	-2.291	0.030	-4.715, -0.255
Moderate DPN	-3.634	-6.227	<.001‡	-4.843, -2.435
Severe DPN	0[ǂ]	-	-	-

Pairwise comparisons				
DPN condition: I	DPN condition: J	Mean difference: I-J	P‡	95% CI
Mild	Moderate	1.149	0.179	-0.345, 2.644
	Severe	-2.485	0.091	-5.261, 0.291
Moderate	Mild	-1.149	0.179	-2.644, 0.345
	Severe	-3.634	<.001‡	-5.128, -2.141
Severe	Mild	2.485	0.091	-0.291, 5.261
	Moderate	3.634	<.001‡	2.141, 5.128

DPN condition	VPT (V)	Mean±SD (range)	Mean difference (SD)	P* (95% CI)	d
Mild	Pretest	9.07±2.53 (6.65, 13.94)	2.50 (0.62)	<.001‡ (2.06, 2.95)	0.99
	Posttest	6.57±2.53 (3.76, 11.59)			
Moderate	Pretest	30.37±5.97 (24.42, 38.82)	3.80 (0.70)	<.001‡ (3.30, 4.29)	0.64
	Posttest	26.57±5.91 (20.31, 34.84)			
Severe	Pretest	51.64±3.76 (46.12, 57.26)	0.30 (0.17)	<.001‡ (0.18, 0.42)	0.08
	Posttest	51.34±3.87 (45.68, 57.21)			

Holm's sequential Bonferroni procedure

Stage	P* (DPN condition)	Calculated α level†
1	<.001 (Mild)	0.017
2	<.001 (Moderate)	0.025
3	<.001 (Severe)	0.05

Order the P-values* from smallest to greatest: P_{Mild} = <.001, $P_{Moderate}$ = <.001, P_{Severe} = <.001

VPT = vibration perception threshold, VFO = vibrating foot orthoses, MTP = metatarsophalangeal joint, DPN = diabetic peripheral neuropathy, SD = standard deviation, CI = confidence interval, V = volt.

‡ Significant at P<0.05; ǂ This parameter is set to zero because it is redundant.; * Paired t-test; ‡ Adjustment for multiple comparisons: Bonferroni; † Calculated using α = 0.05

VFO to reduce VPT at the beginning of DPN would be more beneficial.

Obviously, these are acute effects of using the VFO for tactile stimulation, and long-term implications remain unclear.

TABLE IV
VPT OUTCOMES OF SUBGROUPS WHEN NO USING VFO

Bonferroni-adjusted post hoc test: Dependent variable is Posttest; Between-subjects factors are DPN conditions, i.e., Mild (n = 10), Moderate (n = 10), Severe (n = 10).

1st MTP (Left)

Levene's test		Tests of between-subjects effects				Pairwise comparisons				
F	P	Source	F	P	R^2 (Adjusted R^2)	DPN condition: I	DPN condition: J	Mean difference: I-J	$P^{\ddagger}$	95% CI
1.207	0.315	Pretest	10557928.12	<.001‡	1.0 (1.0)	Mild	Moderate	-0.001	1.0	-0.018, 0.017
		Condition	1.590	0.223			Severe	0.010	1.0	-0.024, 0.044
Parameter estimates						Moderate	Mild	-1.852	0.014‡	-3.378, -0.326
Parameter	Mean difference	t	P	95% CI			Severe	-3.202	0.011	0.581
Pretest	1.0	324.297	<.001‡	1.0, 1.001		Severe	Mild	1.350	-0.010	1.0
Mild DPN	0.010	0.752	0.459	-0.017, 0.038			Moderate	3.202	-0.011	0.581
Moderate DPN	0.011	1.335	0.194	-0.006, 0.027						
Severe DPN	0†	-	-	-						

DPN condition	VPT (V)	Mean±SD (range)	Mean difference (SD)	P^* (95% CI)	d	Holm's sequential Bonferroni procedure		
Mild	Pretest	6.87±2.02 (4.46, 11.11)	0.0 (0.01)	0.509 (-0.005, 0.009)	0	Stage	P^* (DPN condition)	Calculated α level†
	Posttest	6.87±2.02 (4.45, 11.12)				1	0.168 (Moderate)	0.017
Moderate	Pretest	25.82±6.60 (16.32, 36.02)	-0.0 (0.01)	0.168 (-0.01, 0.002)	0	Order the P-values* from smallest to greatest: $P_{Moderate}$ = 0.168, P_{Mild} = 0.509, P_{Severe} = 1.0		
	Posttest	25.82±6.61 (16.32, 36.04)						
Severe	Pretest	48.76±5.55 (41.14, 57.84)	0.0 (0.01)	1.0 (-0.005, 0.005)	0			
	Posttest	48.76±5.55 (41.14, 57.85)						

5th MTP (Left)

Levene's test		Tests of between-subjects effects				Pairwise comparisons				
F	P	Source	F	P	R^2 (Adjusted R^2)	DPN condition: I	DPN condition: J	Mean difference: I-J	$P^{\ddagger}$	95% CI
2.245	0.125	Pretest	17556699.37	<.001‡	1.0 (1.0)	Mild	Moderate	-0.001	1.0	-0.016, 0.013
		Condition	0.784	0.467			Severe	-0.008	1.0	-0.035, 0.019
Parameter estimates						Moderate	Mild	0.001	1.0	-0.013, 0.016
Parameter	Mean difference	t	P	95% CI			Severe	-0.007	0.874	-0.022, 0.009
Pretest	1.0	4190.072	<.001‡	0.999, 1.0		Severe	Mild	0.008	1.0	-0.019, 0.035
Mild DPN	-0.008	-0.738	0.467	-0.030, 0.014			Moderate	0.007	0.874	-0.009, 0.022
Moderate DPN	-0.007	-1.077	0.291	-0.019, 0.006						
Severe DPN	0†	-	-	-						

DPN condition	VPT (V)	Mean±SD (range)	Mean difference (SD)	P^* (95% CI)	d	Holm's sequential Bonferroni procedure		
Mild	Pretest	7.13±1.45 (5.14, 9.66)	0.0 (0.01)	0.591 (-0.003, 0.005)	0	Stage	P^* (DPN condition)	Calculated α level†
	Posttest	7.13±1.45 (5.14, 9.65)				1	0.168 (Moderate)	0.017
Moderate	Pretest	27.54±6.51 (15.61, 35.55)	0.0 (0.004)	0.168 (-0.001, 0.005)	0	Order the P-values* from smallest to greatest: $P_{Moderate}$ = 0.168, P_{Severe} = 0.443, P_{Mild} = 0.591		
	Posttest	27.53±6.51 (15.61, 35.55)						
Severe	Pretest	50.30±5.54 (42.64, 57.64)	-0.0 (0.01)	0.443 (-0.008, 0.004)	0			
	Posttest	50.30±5.53 (42.65, 57.64)						

1st MTP (Right)

Levene's test		Tests of between-subjects effects				Pairwise comparisons				
F	P	Source	F	P	R^2 (Adjusted R^2)	DPN condition: I	DPN condition: J	Mean difference: I-J	$P^{\ddagger}$	95% CI
0.272	0.764	Pretest	5685580.807	<.001‡	1.0 (1.0)	Mild	Moderate	0.009	1.0	-0.016, 0.034
		Condition	0.429	0.656			Severe	0.015	1.0	-0.032, 0.062
Parameter estimates						Moderate	Mild	-0.009	1.0	-0.034, 0.016
Parameter	Mean difference	t	P	95% CI			Severe	0.006	1.0	-0.019, 0.032
Pretest	1.0	2384.446	<.001‡	0.999, 1.001		Severe	Mild	-0.015	1.0	-0.062, 0.032
Mild DPN	0.015	0.836	0.411	-0.022, 0.053			Moderate	-0.006	1.0	-0.032, 0.019
Moderate DPN	0.006	0.622	0.539	-0.014, 0.027						
Severe DPN	0†	-	-	-						

DPN condition	VPT (V)	Mean±SD (range)	Mean difference (SD)	P^* (95% CI)	d	Holm's sequential Bonferroni procedure		
Mild	Pretest	7.85±2.11 (5.65, 12.34)	-0.00 (0.01)	0.555 (-0.009, 0.005)	0	Stage	P^* (DPN condition)	Calculated α level†
	Posttest	7.85±2.11 (5.64, 12.34)				1	0.555 (Mild)	0.017
Moderate	Pretest	28.77±6.53 (20.35, 37.65)	0.0 (0.01)	0.726 (-0.005, 0.007)	0	Order the P-values* from smallest to greatest: P_{Mild} = 0.555, $P_{Moderate}$ = 0.726, P_{Severe} = 0.758		
	Posttest	28.77±6.53 (20.35, 37.65)						
Severe	Pretest	50.23±3.66 (44.56, 56.24)	0.01 (0.01)	0.758 (-0.006, 0.008)	0			
	Posttest	50.22±3.67 (44.56, 56.25)						

5th MTP (Right)

Levene's test		Tests of between-subjects effects				Pairwise comparisons				
F	P	Source	F	P	R^2 (Adjusted R^2)	DPN condition: I	DPN condition: J	Mean difference: I-J	$P^{\ddagger}$	95% CI
1.540	0.233	Pretest	7583382.872	<.001‡	1.0 (1.0)	Mild	Moderate	0.004	1.0	-0.018, 0.025
		Condition	0.301	0.742			Severe	0.002	1.0	-0.038, 0.042
Parameter estimates						Moderate	Mild	-0.004	1.0	-0.025, 0.018
Parameter	Mean difference	t	P	95% CI			Severe	-0.001	1.0	-0.023, 0.021
Pretest	1.0	2753.794	<.001‡	0.999, 1.001		Severe	Mild	-0.002	1.0	-0.042, 0.038
Mild DPN	0.002	0.139	0.891	-0.030, 0.035			Moderate	0.001	1.0	-0.021, 0.023
Moderate DPN	-0.001	-0.161	0.873	-0.019, 0.016						
Severe DPN	0†	-	-	-						

DPN condition	VPT (V)	Mean±SD (range)	Mean difference (SD)	P^* (95% CI)	d	Holm's sequential Bonferroni procedure		
Mild	Pretest	9.49±2.60 (7.11, 15.20)	0.0 (0.01)	1.0 (-0.006, 0.006)	0	Stage	P^* (DPN condition)	Calculated α level†
	Posttest	9.49±2.61 (7.11, 15.21)				1	0.555 (Moderate)	0.017
Moderate	Pretest	30.29±6.19 (23.25, 39.25)	0.0 (0.01)	0.555 (-0.005, 0.009)	0	Order the P-values* from smallest to greatest: $P_{Moderate}$ = 0.555, P_{Severe} = 0.591, P_{Mild} = 1.0		
	Posttest	30.29±6.19 (23.24, 39.25)						
Severe	Pretest	51.59±3.85 (45.56, 57.12)	-0.0 (0.01)	0.591 (-0.005, 0.003)	0			
	Posttest	51.59±3.84 (45.57, 57.12)						

VPT = vibration perception threshold, VFO = vibrating foot orthoses, MTP = metatarsophalangeal joint, DPN = diabetic peripheral neuropathy, SD = standard deviation, CI = confidence interval, V = volt.
‡ Significant at P<0.05; † This parameter is set to zero because it is redundant.; * Paired t-test; ‡ Adjustment for multiple comparisons: Bonferroni; † Calculated using α = 0.05

Actually, the blinding approach in this study may not have completely blinded the subjects. Despite the fact that the stimulation was set below 90% VPT and used the conceal techniques, the subjects might distinguish the stimulation as switch-on or switch-off. A parallel trial design may be appropriate for improving the blinding strategy's efficacy.

Even though the PO carried out the studies using a concealed envelope containing computer-generated randomization of the interventions and performed the outcome assessment, the researchers should be kept away from the standby throughout the experiments to minimize bias.

As in the previous study, VPT can predict diabetic patients' greater risk of foot ulceration, with VPT >25V carrying a sevenfold risk compared to VPT <15V [10]. This clinical study may suggest that utilizing the VFO may help lower the occurrence of foot ulcers; however, the effects of using the VFO in reducing the mean baseline VPT >25V compared to VPT <15V may differ from the previous study [10]. Therefore, further investigation is required to be clarified. With regard to the chance of developing the first foot ulceration [15], applying the VFO may help reduce a first foot ulcer by 5.6% in every unit of the decreased VPT. When VPT is greater than 25V [16], [17], using the VFO may lessen the likelihood of recurrent foot ulcers. Based on prior investigations [25], [26], [27], [28], [29], [30], [31], the integrated stimulation signals generated by the VFO might help optimize information transfer and nerve cell responses in chemical synapses. Random 0–100 Hz square wave pulses generated by the VFO at subthreshold stimulation may improve FAI and FAII afferent nerve fibers, resulting in greater vibrotactile responsiveness, according to earlier studies [32], [33]. In accordance with previous findings [37], [38], [39], [40], PRWN and a SR method for tactile stimulation via the VFO may enhance SAI cutaneous mechanoreceptors and threshold abilities. Vibration stimulation by the VFO in conjunction with a pseudorandom noise-based technique was as successful as using a noise-based technique in improving tactile sensation and somatosensation [35], [37], [41], [42], [43], [44]. The addition of PRWN to vibrotactile stimulation at 90% VPT level, as well as noise to subthreshold stimulation [35], [36], [37], has the potential to increase the intensity of a stimulus signal. Random 0–100 Hz square wave pulse signals integrated with PRWN by a SR approach demonstrated a substantial effect in enhancing tactile sensibility in diabetic patients with mild, moderate, and severe peripheral neuropathy. This differs from prior studies [45], [46], [47], which indicated that a vibrating insole may effectively stimulate tactile sensation in mild-to-moderate or moderate-to-severe DPN.

As lack of blood flow and skin oxygenation in diabetic feet is associated with foot ulcer risk, therapeutic whole-body vibration (TWBV) could increase skin blood circulation and muscle force in the lower extremities [58], [59], [60]. Based on TWBV, vibration stimulation using the VFO may improve cutaneous blood flow, glycemic profile, and foot blood perfusion in diabetic patients. Thus, the VFO may contribute to decreasing the risk of foot ulceration.

According to repetitive sensory stimulation [61], [62], [63], [64], utilizing the VFO in stimulating tactile sensation could potentially increase the sensitivity of mechanoreceptors and corticomuscular synchronization on the plantar surface of the feet. As a result, the efficiency of the VFO may help protect the foot from ulcers.

Similar to previous studies [41], [42], [43], the findings of this study showed that a novel design for tactile stimulation at subthreshold by the VFO could enhance human sensibility and perception. Regarding the development of the integrated stimulation signals in this present study, the outcomes showed a positive effect on stimulating vibratory perception, the same as in previous studies [45], [46], [47], [48]. Determining a 0–1,000 arbitrary unit of vibration level [44] or a 0–100 Hz white noise vibratory signal [46], [47], [48] could decrease the VPT level, similar to applying PRWN in this research. In order to reduce VPT level by adding white noise and SR [46], [47], [48], PRWN may also offer a potential phenomenon with SR. Continual improvement in tactile sensation after employing the VFO may be attributed to the use of a square wave form and a SR strategy, which is the same as using a vibro-medical insole [47]. This contrasts with the findings of Cloutier et al. [46], who found that tactile sensation improvement could not be measured following SR removal.

In comparisons with previous studies, the absolute changes in VPT at the right big toe in the study of Cloutier et al. [46] decreased by 11.91% when an outlier was removed for statistical significance ($n = 20$, moderate-to-severe DPN, the mean VPT baseline = 31.9±13.0 V, the mean VPT posttest = 28.1±11.0 V, $P < .001$, $d = 0.29$). This finding seems to improve tactile sensation more than using the VFO. In fact, the VPT measurement at the superficial layer of skin on the big toe might differ from the measurement at the 1st MTP location.

In a study of 40 DPN by Zwaferink et al. [48], the absolute changes in VPT when considering the median value of all differences decreased by 6.89% (the median $VPT_{actuator-off} = 43.5$ V, the median $VPT_{actuator-on} = 39.3$ V, $P < .001$, $d = 0.43$, the 1st MTP–left foot); 6.47% (the median $VPT_{actuator-off} = 41.7$ V, the median $VPT_{actuator-on} = 37.5$ V, $P < .001$, $d = 0.57$, the 5th MTP–left foot); 5.87% (the median $VPT_{actuator-off} = 42.6$ V, the median $VPT_{actuator-on} = 39.0$ V, $P < .001$, $d = 0.48$, the 1st MTP–right foot); 9.80% (the median $VPT_{actuator-off} = 40.8$ V, the median $VPT_{actuator-on} = 34.5$ V, $P < .001$, $d = 0.53$, the 5th MTP–right foot). In comparison to the findings of this study, employing the VFO may be more effective in reducing VPT. In terms of effect sizes, this prior study showed that using a vibrating insole provided larger effect sizes than utilizing the VFO. The prior study's data did not have a normal distribution; hence, the median values may not equal the mean values, and the data differences might be ambiguous.

A total contact design of the CFO manufactured by the PO with orthotic experience could deliver stimulation to the entire plantar area of the individual's foot, potentially resulting in good tactile improvement. Also, the fabricated CFO could benefit foot ulcer prevention and recurrence. A total contact design of the VFO may provide superior vibrotactile stimulation than a flat-design vibrating insole, as employed in those earlier studies [45], [46], [47]. A random square wave pulse (0–100 Hz) mixed with PRWN using a SR approach might produce greater tactile improvement than a stimulus with the combination of SR and low-frequency white noise (0–100 Hz bandwidth limitation) in those previous

studies [45], [46], [47]. In reference to plantar pressure, DPN typically results in undetected plantar pressure ulcers [16]. An orthotic design of the VFO could provide pressure relief and help avoid ulcers. As previously reported [65], [66], the CFO may help protect diabetic feet and prevent plantar ulcers. In people at high risk of foot ulceration [67], the CFO may help reduce the recurrence of foot ulcers by 46%. As stated in a prior analysis of a clinical result [68], diabetics who are at risk of developing foot ulcers may presume that the VFO could help prevent foot ulcers and their recurrence.

As previously stated, the improvements in VPT achieved by using the VFO may be beneficial for preventing foot ulceration, lowering foot ulceration risk, and minimizing the probability of foot ulceration recurrence. However, more studies and measurements on the impact of applying the VFO on ulcer prevention are required. In addition, VPT enhancements with the VFO may have significant implications for neurorehabilitation benefits such as restoring or prolonging tactile and protective sensations in DPN and slowing the deterioration of the peripheral nervous system in diabetic feet. From the point of view of prior research [1], [69], [70], [71], improving VPT through the use of the VFO might provide important contributions to the management of foot ulcer complications, avoiding lower limb amputation and disability, improving the quality of life of diabetic foot ulcer patients and their caregivers, and reducing hospitalization expenses related to diabetic foot ulcers.

Low-cost invention of all components of the VFO was determined in order to achieve the goal of an affordable device. The vibration generator component could be developed for low cost, but the CFO component could not due to expensive medical-grade materials. If the CFO were produced in commercial quantities, cheapness of the materials may be possible.

In this research, the VFO are a noninvasive device. A 3-layer design of the CFO may allow for embedding a vibratory actuator and preventing heat from the actuator's oscillation; as a result, foot skin is unharmed. Additionally, the physician and PO monitored all subjects for abnormalities (including heat from vibration stimulation) throughout the experiments. If subjects were harmed by heat during vibration stimulation, they had to notify the physician or PO immediately. There is no mention of heat from vibration stimulation in this present study, but heat prevention testing is required to verify accuracy in a further study.

Although the VFO were designed to enable noninvasive intervention and were manufactured with medical quality, user safety has to be validated before dissemination and implementation in clinical practices.

The final vibration frequency may differ from the input frequency since the vibration frequency will be determined by the rotation of the vibration motor. It is necessary to test the ultimate frequency generated by the vibration motor. A new type or design of a vibration motor is also suggested. Furthermore, it is possible that VPT enhancements may be greater than the current findings, particularly when a vibratory actuator configuration capable of generating an optimal potential of the integrated stimulation signals is adopted.

Importantly, this study investigated the efficiency of employing the VFO for tactile stimulation while seated. Assessing the usability of active wear insoles is still required.

Improving the device's portability by redesigning electronic circuitry may further bolster the VFO's substantial effectiveness.

For further development, a wireless design with long-lasting batteries, walking usage, and usability in everyday life is necessary.

Validation of the VFO in ergonomics when static and dynamic usage is required for an additional study.

From a clinical standpoint, investigating the efficacy of long-term VFO use is recommended.

In this study, it is obvious that the VFO can offer advantages in neurological therapy for diabetes and peripheral neuropathy. Further research on the effectiveness of using the VFO on other types of neuropathies and neurological illnesses is suggested.

V. Conclusion

In this study, the development of the VFO consists of an orthotic design for an individual's diabetic foot and a noninvasive purpose, including fabrication with medical-grade materials. The VFO with a total contact design could provide vibratory stimulation to the entire plantar area of the foot. A 3-layer design of the CFO might address the problem of heat when using a vibrating actuator. The creation of the integrated stimulation signals (random 0–100 Hz square wave pulse signals supplemented with PRWN using a SR technique) could help tactile enhancement. The vibration generator component of the VFO could be manufactured at a low cost for a wide range of applications, but the CFO component required inexpensive medical-grade materials.

In a clinical aspect, this study indicated that using the VFO could greatly improve tactile sensibility in T2D patients with peripheral neuropathy. In mild and moderate DPN, the VFO could offer effective tactile stimulation. For the excellent benefits of neurorehabilitation, employing the VFO in the early stages of DPN is advised. Utilizing the VFO may be an alternative strategy to help improve, restore, or prolong tactile sensation in DPN patients in order to prevent foot ulcers, reduce the recurrence of foot ulceration, and lower the risk of lower extremity amputation and disability. Applying the VFO might help slow down the deterioration of the peripheral nervous system. Employing the VFO may aid DPN patients and caregivers improve their quality of life while also lowering hospitalization expenditures associated with foot ulcers.

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