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Effect of whole-body vibration training on transcutaneous oxygen levels of the foot in patients with type 2 diabetes: A randomized controlled trial

Gerardo Rodríguez-Reyes [a,1], Ana Cristina García-Ulloa [b,1], Sergio Hernández-Jiménez [b,2], Aldo Alessi-Montero [c], Lidia Núñez Carrera [c], Francis Rojas-Torres [b], Héctor Infanzón-Talango [b], Patricia Clark [d], Antonio Miranda-Duarte [e], Rita A. Gómez-Díaz [f,2,*]

[a] Laboratorio de Ortesis y Prótesis, Instituto Nacional de Rehabilitación Luis Guillermo Ibarra Ibarra, Mexico City, Mexico
[b] Centro de Atención Integral del Paciente con Diabetes (CAIPaDi), Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico
[c] Laboratorio de Análisis de Movimiento Humano e Ingeniería de Rehabilitación, Instituto Nacional de Rehabilitación Luis Guillermo Ibarra Ibarra, Mexico City, Mexico
[d] Unidad de Epidemiología Clínica, Hospital Infantil de México Federico Gómez and National University of Mexico-UNAM, Mexico City, Mexico
[e] Laboratorio de Genética, Instituto Nacional de Rehabilitación Luis Guillermo Ibarra Ibarra, Mexico City, Mexico
[f] Unidad de Investigación Médica en Epidemiología Clínica, UMAE Hospital de Especialidades, Centro Médico Nacional Siglo XXI. Instituto Mexicano del Seguro Social, Mexico City, Mexico

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ABSTRACT

Whole body vibration (WBV) has been suggested as improving skin and blood flow. This study aimed to determine the effect of exposure to WBV on levels of partial transcutaneous oxygen pressure (TcPO2) in the foot of patients with type 2 diabetes (T2D) within the metabolic control goals. A block randomized, open, two-arm, parallel and controlled clinical trial was conducted. Participants recruited from the Center of Comprehensive Care for the Patient with Diabetes were assessed at the National Institute of Rehabilitation, Mexico City. Control group underwent multidisciplinary care for T2D; experimental group, in addition to the comprehensive diabetes care, was exposed to WBV through an exercise program, attending three times a week for a period of 3 months. TcPO2 was measured in the feet of the participants at baseline and after 12 weeks. A sample of 50 volunteers with recently-diagnosed T2D and similar baseline characteristics (demographic, cardiovascular risk, presence of diabetic polyneuropathy, and indicators of glycemic control and TcPO2) was recruited. The experimental group ($n = 27$) showed a mean value of 47.7 ± 6.1 mmHg in TcPO2, significantly higher ($p = 0.028$) than the 44.3 ± 7.5 mmHg of control group ($n = 23$), at the end of intervention. In conclusion, exposure to WBV promoted an increase and a significant 3 mmHg difference in the foot TcPO2 levels between those subjects with T2D that underwent the 12-week exercise program and those not exposed to the treatment.

1. Introduction

Whole body vibration (WBV) is a well-tolerated procedure that can substitute for physical exercise, especially for people with motor limitations. It has been used effectively in various therapies, such as for fibromyalgia (Mingorance et al., 2021) and lumbar spine fusion (Wang et al., 2021), and has been suggested in treatment for obesity (Zago et al., 2018). Administered for short periods at low frequencies (20–30 Hz), it may improve cutaneous blood flow, peripheral lymphatic flow, and venous drainage of the lower extremity. In one study, WBV accelerated pressure ulcer healing in mice (Wano et al., 2021). WBV may also influence factors involved in angiogenesis induction and can assist in glycemic control and type 2 diabetes (T2D)–associated complications, such as dyslipidemia and neuropathic pain (Behboudi et al., 2011; Robinson et al., 2018; Dominguez-Muñoz et al., 2020; del-Pozo-Cruz et al., 2014; Sañudo et al., 2013; Mahbub et al., 2019; Kitamoto et al., 2021; Suhr et al., 2007; Robinson et al., 2016). Correctly applied, vibration stimulus can improve plantar skin blood flow in T2D volunteers

* Corresponding author at: Unidad de Investigación Médica en Epidemiología Clínica, UMAE Hospital de Especialidades, CMN-SXXI, IMSS, Av. Cuauhtémoc #330, Col. Doctores, Deleg. Cuauhtémoc, Mexico City 06720, Mexico.
E-mail address: ritagomezdiaz@yahoo.com.mx (R.A. Gómez-Díaz).
[1] These authors contributed equally to this work.
[2] These authors jointly supervised this work.

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(Ren et al., 2019). Since patients with T2D should avoid weight-bearing physical activity, which inhibits plantar skin blood flow (Duan et al., 2021), WBV may allow the exercise that such patients need, without detrimental effects.

Vascular supply, blood circulation and adequate local oxygen concentrations are key in wound healing. Improvement in tissue perfusion that promotes normalization of O_2 concentrations could be effective in the treatment and management of wounds (Gordillo and Sen, 2003; Niinikoski, 2004). Partial transcutaneous oxygen pressure (TcPO2) is a non-invasive measurement that assesses skin microcirculation, tissue perfusion and oxygen delivery (Eleftheriadou et al., 2019). It can detect altered blood flow in the presence of micro– and macrovascular disease (Yip, 2015), and its usefulness for chronic wounds (Weir et al., 2016) and as a predictor for short-term survival in T2D patients has been demonstrated (Eleftheriadou et al., 2018). It is considered the best method for assessing diabetic foot (Lopez-Moral et al., 2021; Wang et al., 2016).

Diabetic neuropathy and peripheral arterial disease (PAD), indicative of micro- and macrovascular dysfunction respectively, constitute risk factors for diabetic foot ulcers, a common complication that diminishes quality of life (Khunkaew et al., 2019; Eleftheriadou et al., 2019; Armstrong et al., 2017). Ulcer remission is feasible, but recurrence is common, since many precipitating factors (peripheral neuropathy and vascular disease, increased plantar pressure and foot deformity) are still present after healing; up to 40% recurrence is expected within the first year, and up to 60% within the next 3 years (Armstrong et al., 2017). Around 50% of patients with T2D may present neuropathy and 19–34% will suffer ulcers. Over 50% of those ulcers will become infected and 20% will require some level of amputation (Armstrong et al., 2017; Zhang et al., 2020).

The objective of this study was to identify if WBV may improve foot perfusion, as reflected in TcPO2 registries, in a sample of T2D patients.

2. Methods

2.1. Experimental design

A block randomized, open, two-arm, parallel, controlled clinical trial was conducted at the National Institute of Medical Sciences and Nutrition and at the National Institute of Rehabilitation (INCMNSZ and INRLGII, respectively – for their Spanish initials) in Mexico City. Ethics and Research Committees of both institutions approved the study (Ref 2234–INCMNSZ, 2416–INRLGII), and it was registered in ClinicalTrials.gov (NCT03957811). The study complied with all relevant laws and institutional guidelines. All participants signed an informed consent.

2.2. Study population

Volunteers with T2D treated at the Center of Comprehensive Care for the Patient with Diabetes (CAIPaDi, for its name in Spanish) of INCMNSZ (Hernandez-Jimenez et al., 2014, 2019) were invited to participate. Inclusion criteria: both genders 40–70 years of age, with < 6 years from diagnosis of diabetes, without disabling complications, without ulcers, non-smokers, with HbA1c 6–9%, blood pressure $\leq$ 130/80 mmHg, total cholesterol $\leq$ 240 mg/dL, triglycerides $\leq$ 300 mg/dL, with stable body weight over the last 6 months (variation $< 10\%$ of body weight) and residence within Mexico City. Exclusion criteria: pregnancy, deep venous thrombosis, severe motor disability, amputations of the lower extremity and/or diabetic foot (Wagner ≥ 3) or intermittent claudication; presence/history of < 2 episodes of severe hypoglycemia, balance alterations, discopathy, myocardial ischemia or recent surgeries, active neoplasia in the last 5 years, recently-placed orthopedic/cosmetic implants, pacemakers, hepatic failure (Child-Pugh "C") and/or heart failure (Functional class –NYHA-: III-IV), chronic kidney disease (estimated creatinine clearance < 60 ml/min); severe non-proliferative retinopathy, proliferative retinopathy or uncontrolled macular edema, hemoglobinopathies, severe anemia ($\leq$7.5 g/dL) and known hemolytic disease.

2.3. Allocation

Participants were assigned to two groups (WBV or control) using block randomization method (block sizes: 6 and 8). Control group participants were encouraged to attend the CAIPaDi protocol recommendations, which include an intervention with education and empowerment techniques. Initial intervention consists of four monthly visits followed by an annual one. At each visit, patients spend six hours in the center receiving comprehensive support from different specialists, including in endocrinology, nutrition, dentistry, ophthalmology, psychology, physical training or foot care (Hernández-Jimenez et al., 2014). Experimental group additionally attended WBV sessions three times a week, for 12 weeks.

2.4. Outcome measurements

At baseline and after 12-weeks, demographic and clinical data were obtained for each participant from internal records generated by CAIPaDi and by direct measurement: age, duration of T2D, weight, BMI, body composition (bioelectrical impedance analysis using a JAWON ioi 353 Body Composition Analyzer), calories and macronutrient intake (three-day food record), lipid profile, HbA1c, fasting blood glucose, presence of small fiber neuropathy (electrochemical skin conductance, Sudoscan™ equipment), functional exercise capacity via the six-minute walk test (T6MW) using a treadmill (Laskin et al., 2007), and TcPO2 registered at the dorsum of both feet as the outcome variable. The presence of comorbidities and pharmacological framework was recorded prior to intervention. Symptomatic diabetic polyneuropathy was assessed either through the Semmes-Weinstein 10-g monofilament or the 128 Hz tuning fork test (Pop-Busui et al., 2017). An altered result in either test was considered presence of diabetic polyneuropathy. Peripheral arterial disease (PAD) was considered when ankle-brachial index (ABI) values were $\leq$ 0.9 or $\geq$ 1.4 mmHg. Visual analogue scale (VAS) was used to assess lower extremity pain (where 0 indicated "no pain" and 10 "worst sensed pain").

2.5. Sample size determination

To detect an increase of 7 mmHg in foot TcPO2 after WBV intervention, as per the study of (Rodriguez-Reyes et al., 2017), with two-sided 5% significance and power of 80%, a sample size of 20 patients/group was necessary, anticipating a dropout rate of 20%.

2.6. Procedures

WBV. Commercial platform model Pro5 (Power Plate North America Inc., Northbrook, IL, USA) was used to deliver vertical WBV, according to the guidelines proposed by van Heuvelen et al (2021). The device consisted of a plate coated with non-slip material 86 $\times$ 94 cm (overall dimensions: 87 $\times$ 109 $\times$ 155 cm; mass: 150 kg), equipped with a handrail and twin motor system that can deliver sinusoidal vibration of 25–50 Hz (with 1 Hz increment) and a peak-to-peak (PP) displacement of 2 or 4 mm (according to manufacturer's specifications). Selected stimulation parameters were fixed at 30 Hz and "low" amplitude displacement (2 mm PP) in an attempt to match those proposed by Sañudo et al. (2013) and within the range that promotes peripheral blood flow according to Mahbub et al. (2019).

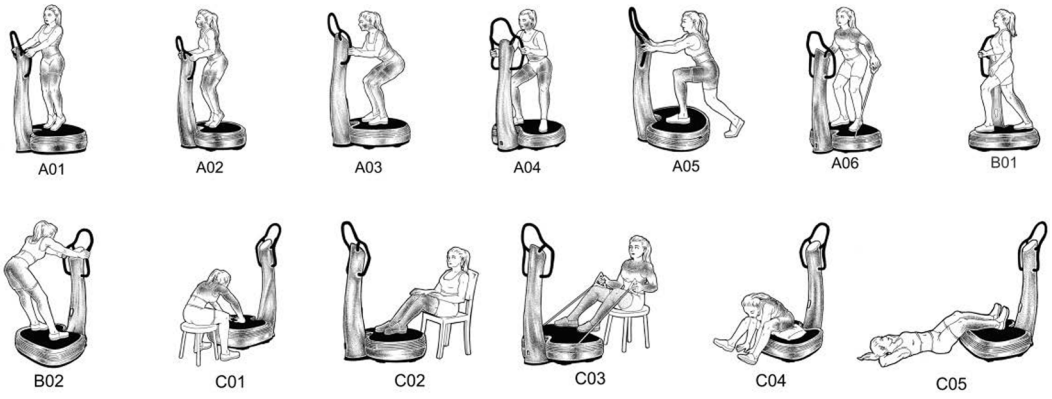
To verify real vibration parameters, 3D accelerometers were used: an Adafuit MPU-6050, (Adafruit, USA) – firmly attached at the center of the plate and directly on the surface, and two Shimmer 3 EXG UNIT (Shimmer, Ireland) – attached with a strap on the lateral malleolus of the right leg and another to the center of the forehead, of a 100 kg volunteer. Measurements yielded a vibration frequency of 30.8 $\pm$ 0.01 Hz at the

plate surface and 30.6 ± 0.14 Hz on the leg. Measured PP accelerations were 14.13 ± 0.43 m/s2 r.m.s. in the platform, 6.32 ± 0.30 m/s2 r.m.s. in the external malleolus and 0.2 ± 0.16 m/s2 r.m.s. in the forehead. The latter represents an attenuation of 99.5% of the vibration that reaches the head. Frequency-weighted acceleration delivered was approximately 13.68 m/s2 r.m.s. (Mahbub et al. 2019). Sessions took place at the Rehabilitation Engineering Laboratory of the INRLGII every third day, three times a week (only weekdays), for 12 weeks following the exercise program used by Rodriguez-Reyes et al. (2017), where improvement of TcPO2 would be observed. Duration and intensity of the routines and rest laps between WBV bouts were progressive. The program included strengthening, stretching, massage and relaxation exercises. The exercise program and positioning is presented in Fig. 1. Participants were instructed to perform WBV training with shock-absorbing sport footwear and to maintain their weight, when possible, on the forefoot to reduce vibration transmission to the head. Prior to WBV-based training sessions participants took a 150-step walk.

TcPO2. Transcutaneous oxygen monitor (model TCM400, Radiometer Copenhagen, Copenhagen, Denmark) was calibrated following manufacturer's specifications. To reduce oxygen diffusion resistance and improve TcPO2 reading reliability, volunteers reclined in decubitus supine position for 10 min prior to recording procedure. At the dorsum of the foot, the skin between the first and second metatarsal was thoroughly cleaned with an alcohol swab and the self-adhesive, ring-shaped plastic support was placed. Five-ten drops of buffer solution were added inside and the electrode was attached into it. Patients were asked to remain immobile and relaxed. A signal-stabilization period of 20 min was given and immediately after, recording session began and lasted for another 20 min. The procedure was conducted on both feet. Ambient temperature was recorded since it may influence the TcPO2 readings (Marcoccia et al., 2020). The final reported value of the TcPO2 was the arithmetic mean of the last 20 readings. Qualified personnel, blinded to the study, performed the assessments and processed the data.

2.7. Statistical analysis

Demographic characteristics are described as arithmetic means ± SD, percentages and frequencies. Kolmogorov-Smirnov test confirmed normality of the data. Student *t*-test was performed for independent data between groups and for paired samples within groups. For qualitative variables, X^2 was used. Multivariate analysis was performed through lineal regression and two-way ANCOVA to adjust for confounding



Exercise Program

Week 1 & 2		Week 3		Week 4		Week 5		Week 6 & 7		Week 8		Week 9		Week 10		Week 11 & 12	
Exercise	Sets/ time	Exercise	Sets/ time	Exercise	Sets/ time	Exercise	Sets/ time	Exercise	Sets/ time	Exercise	Sets/ time	Exercise	Sets/ time	Exercise	Sets/ time	Exercise	Sets/ time
A01	2/30s	A01	2/30s	A01	2/30s	A01	2/30s	A01	2/30s	A01	2/30s	A01	2/30s	A01	2/30s	A01	2/30s
B01	2/30s	A02	2/30s	A02	2/30s	A02	2/30s	A02	2/30s	A02	2/30s	A02	2/30s	A02	2/30s	A02	2/30s
C02	1/60s	B01	2/60s	A03	2/30s	A03	2/30s	A03	2/30s	A03	2/30s	A03	2/30s	A03	2/30s	A03	2/30s
C03	1/60s	C02	2/60s	B01	2/30s	B01	2/30s	A04	2/30s	A04	2/30s	A04	2/30s	A04	2/30s	A04	2/30s
		C03	2/60s	C02	2/60s	A05	1/60s	B01	2/30s	B01	2/30s	B01	2/30s	B01	2/30s	B01	2/30s
				C03	2/60s	C02	2/60s	A05	2/60s	A05	2/60s	A05	2/60s	A05	2/60s	A05	2/60s
						C03	2/60s	B02	2/30s	B02	2/30s	B02	2/30s	B02	2/30s	B02	2/30s
								C02	2/60s	C02	2/60s	C02	2/60s	C01	2/60s	A06	2/60s
								C03	2/60s	C03	2/60s	C03	2/60s	C02	2/60s	C01	2/60s
										C04	2/60s	C05	2/60s	C03	2/60s	C02	2/60s
												C04	2/60s	C04	2/60s	C03	2/60s
														C05	2/60s	C04	2/60s
																C05	2/60s

Fig. 1. Positioning and execution of the 12-week WBV exercise program. Strengthening –A01: with the feet placed in the middle of the platform, balance on the ball of the foot with knees lightly bent, keep the back straight while tensing abdominals and calves; –A02: with the feet placed slightly apart in the middle of the platform, bend the knees lightly, keep the back straight and balance on the ball of the foot; –A03: in the middle of the platform, with the feet flat, slightly apart and in line with the toes, bend the knees 100°, keep the back straight, move the upper body slightly forward and bounce; –A04: with the feet flat, the toes outward, the knees bent 100°, the back straight and the knee aligned directly above each foot bounce lightly; –A05: with one foot placed direct on the floor, the counterlateral in the middle of the platform, the knee bent about 90° and in line with toes, keep upper body in straigh position and push down the front leg and bounce lightly; –A06: with the feet placed slightly back to the center area of the platform, seize the straps and tense them constantly by abducing both shoulders simultaneously. Stretching –B01: Place the feet lengthwise over platform and wide apart, one behind the other, bend forward one leg and keep back leg extended, push hips and torso forward and observe straight posture of the upper body; alternate sides and legs; –B02: with the feet placed wide apart in the middle of the plate, seize the handlebar, keep the knees slightly bent, the hips up and stretch backward, then bend the upper body forward; Massage and Relaxation –C01: Seated on a chair, place the hands on the plate, slightly bent the elbows and keep the back straight; –C02: Seated on a chair place the feet on the plate and the hands over the knees; relax; –C03: Seated on a chair, seize the straps, place the feet against the edge of the plate and pull towards it while flexing the elbows, keep the back and the neck straight; –C04: Place a pad/pillow on the plate and sit, with the knees slightly bent allow upper body to hang forward with back rounded; –C05: In supine position lie down over the floor in front of the plate, rest the legs on the platform and relax. Rest time between excercises: 15 sec. during the first two weeks; 10 sec. from week 3 to 6; and no rest time from week 7 to 12.

variables. Relative percent change (Δ) was computed as Δ = [(final value – baseline value)/baseline value) × 100]. SPSS package v.25 was used for data analysis. $p < 0.05$ was considered significant.

3. Results

3.1. Outcomes

Fifty-six patients with T2D were recruited (Fig. 2). Six volunteers did not meet the selection criteria and were excluded. The 50 remaining participants were randomly assigned to the control (n = 27) and WBV (n = 23) groups. Six participants from control group were lost to follow-up: one expressed no interest in continuing and five were removed due to COVID-19 (loss rate: 22%). In WBV group, three participants were excluded: one could not continue attending WBV program, two did not attend the final evaluation due to COVID-19 (loss rate: 13%). WBV participants attended a mean of 32.6 ± 5.4 WBV sessions out of a possible 36.

Average age in control group (n = 21) was 58.1 years, and in the WBV group 60.0 ($p = 0.414$). BMI was comparable: 27.3 ± 3.9 vs. 28.9 ± 6.1, respectively ($p = 0.687$). Baseline homogeneity was observed between the groups in all variables of interest, and in the pharmacological framework indicated by CAIPaDi staff; only mean dose of diuretics significantly differed between groups ($p = 0.001$), while two participants per group received insulin (Table 1). Regarding physical activity, all participants in both groups reported being consistent with the daily 10,000 steps in the CAIPaDi protocol. Only six participants of each group ($p > 0.05$) indicated additional sporadic exercise no more than three days per week (jogging, gym, cycling, yoga and Zumba) besides the daily 10,000-step walk. In WBV group, this physical activity was performed in addition to the WBV sessions received.

Table 2 shows the effects after 12 weeks of WBV intervention. Regarding body composition, the WBV group showed more lean mass than the controls, although not significant (control: 41.5 kg, WBV: 48.2 kg; $p = 0.064$). In lipid profile, the control group registered a significant increase in high-density lipoproteins ($p = 0.011$), but final values were not different between groups (control: 53.1, WBV: 52.5 mg/dL; $p = 0.888$).

Baseline TcPO2 records did not differ among groups (control: 45.17 ± 8.24, WBV 46.31 ± 6.65 mmHg; $p = 0.492$). After 12-week follow-up, a % change of Δ = -0.83 was observed in the control group and Δ = 4.40 in the WBV group, almost significant ($p = 0.059$), that yielded 44.37 ±

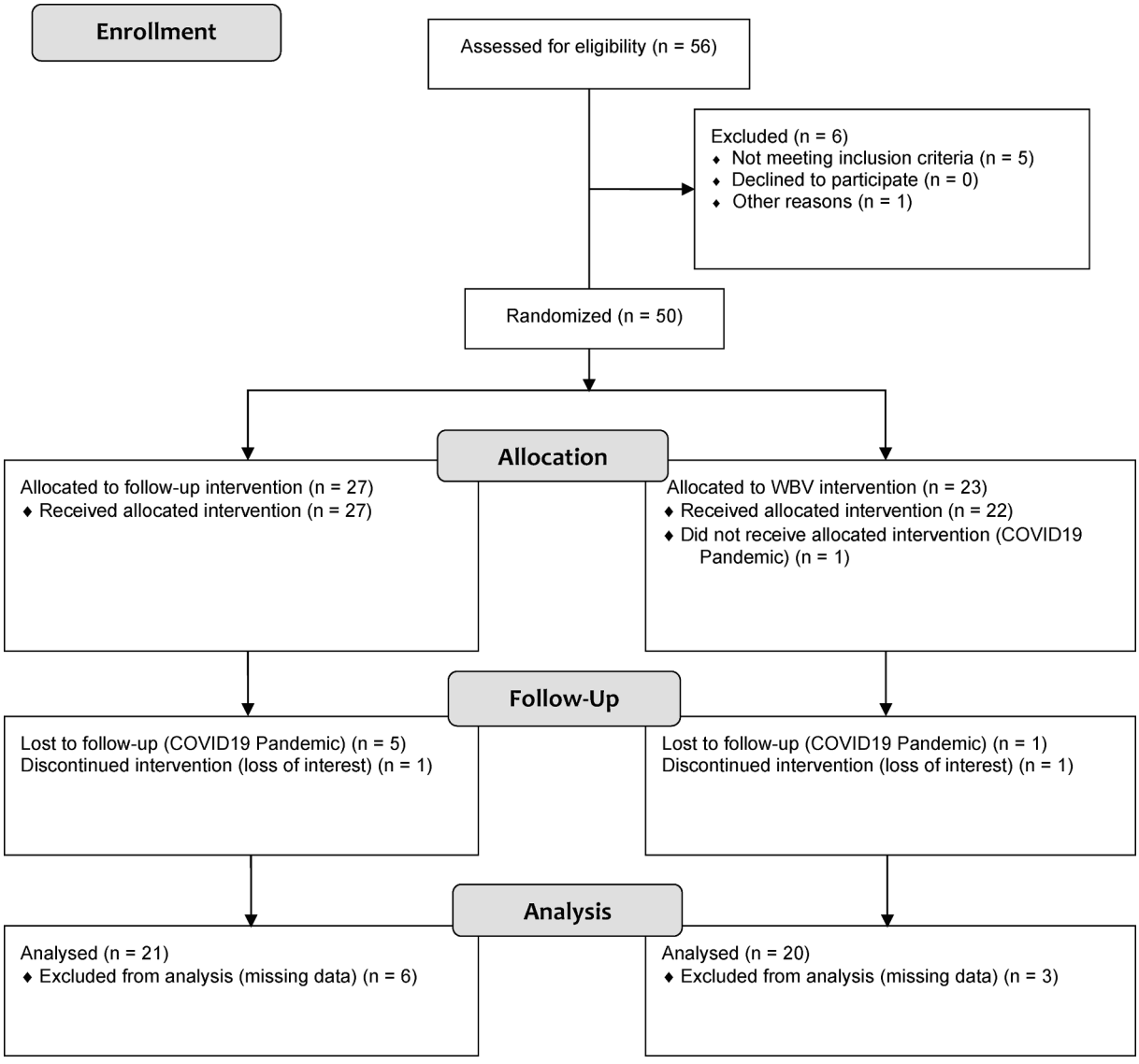


Fig. 2. Title: "Recruitment and follow-up". Explanation: this figure shows the flow of recruited participants and observed losses at each stage of the study. Of the 56 eligible subjects, 41 completed the study succesfully.

Table 1
Baseline characteristics and pharmacological framework of participants.

	Control group	WBV group	*p*-Value
n=	21	20	
Age (years)	58.1 ± 8.1	60.0 ± 6.1	0.414
Gender (male/female)	4/17	6/14	0.484
Diabetes duration (years)	2.95 ± 1.7	2.85 ± 1.6	0.845
Calorie intake (Kcal)	1333.3 ± 257.1	1379.6 ± 195.8	0.522
Carbohydrate intake (%)	39.8 ± 5.5	40.5 ± 6.3	0.692
Protein intake (%)	21.1 ± 2.6	21.4 ± 2.1	0.734
Fat intake (%)	39.0 ± 4.9	38.1 ± 5.5	0.568
Triglycerides (mg/dL)	130.1 ± 41.9	125.1 ± 32.4	0.672
Total cholesterol (mg/dL)	164.9 ± 43.3	157.6 ± 15.9	0.480
HDL (mg/dL)	47.8 ± 13.8	51.4 ± 8.9	0.340
LDL (mg/dL)	96.24 ± 36.1	90.7 ± 16.3	0.528
Non-HDL (mg/dL)	117.5 ± 40.4	106.2 ± 17.05	0.271
Fasting blood glucose (mg/dL)	116.2 ± 41.8	108.9 ± 27.9	0.520
HbA1c (%±SD, mmol)	6.6 ± 1.1, 48.6	6.5 ± 0.9, 47.5	0.572
Dyslipidemia n (%)	16 (76.2)	13 (65.0)	0.657
Dysthyroidism n (%)	3 (14.3)	2 (10.0)	0.524
Hypertension n (%)	8 (38.1)	4 (20.0)	0.306
Blood Pressure (mmHg)	115.7 ± 8.8	117.1 ± 12.1	0.676
Systolic Diastolic	71.1 ± 6.3	70.3 ± 5.1	0.681
Ankle-brachial index	1.06 ± 0.08	1.08 ± 0.25	0.560
PAD n (%)	2 (4.8)	5 (12.5)	0.259
Loss of vibratory sensation n (%)	7 (16.7)	6 (15.0)	0.836
Loss of pressure sensation n (%)	1 (2.4)	1 (2.5)	0.972
Feet ESC (μS)	68.9 ± 6.9	63.4 ± 12.7	0.086
Hands ESC (μS)	58.4 ± 15.0	56.5 ± 16.7	0.699
Cardiovascular autonomic neuropathy risk (%)	36.1 ± 10.5	37.4 ± 9.8	0.661
T6MW distance (m)	449.9 ± 82.4	415.4 ± 107.5	0.225
TcPO2 (mmHg)	45.17 ± 8.24	46.31 ± 6.65	0.495
Metformin (n; mg/day)	21; 1495.0 ± 785.3	20; 1669.7 ± 726.1	0.476
SGL T2 inhibitors (n; mg/day)	1; 10 ± 0.0	2; 17.5 ± 10.6	0.667
Sulphonylureas (n; mg/day)	3; 7.2 ± 1.04	4; 5.7 ± 3.3	0.514
DPP-IV inhibitors (n; mg/day)	3; 51.7 ± 47.5	4; 63.7 ± 45.7	0.747
Insulin (n; IU/day)	2; 42.0 ± 8.5	2; 24.5 ± 16.3	0.310

WBV: whole body vibration; BMI: Body Mass Index; HDL: High-Density Lipoprotein; Non-HDL: Non High-Density Lipoprotein; LDL: Low-Density Lipoprotein; HbA1c: Glycosylated haemoglobin; PAD: Peripheral artery disease; ESC: Electrochemical skin conductance (<40: High risk, ≥40 and ≤ 60: Moderate risk, > 60: No risk); T6MW: Six-minute walk test; TcPO2: Transcutaneous oximetry; SGLT2: Sodium-glucose cotransporter 2; DPP-IV: Dipeptidyl peptidase IV; ACE: Angiotensin-converting enzyme; ARB: Angiotensin II receptor blocker; CCB: Calcium channel blockers; *Significance level: $p < 0.05$ (independent samples *t*-test and Chi square tests).

7.51 and 47.76 ± 6.08 mmHg, respectively. Final figures differed significantly ($p = 0.028$). Mean ambient temperature at which TcPO2 measurements were conducted showed a significant decrease ($p = 0.022$) from baseline (24.3 ± 2.3 °C) to final (23.4 ± 2.2 °C).

Finally, lower extremity pain VAS score at baseline was higher ($p = 0.001$) in the controls (6.1 ± 1.7 pts) than in the WBV group (3.5 ± 1.5 pts). Scores decreased ($p < 0.001$) towards the final assessment (control: 3.7 ± 1.5 pts, WBV: no pain).

3.2. Multivariate models

To identify basal TcPO2 predictors, multivariate linear regression analysis was conducted; triglycerides, HDL and LDL cholesterol, HbA1c, presence of diabetic polyneuropathy and of PAD were entered in the model. HbA1c proved the only significant, negatively-correlated covariate with baseline TcPO2 ($\beta = -2.08$, $p = 0.047$, $R^2 = 0.169$). To adjust for the intervention and confounders, a second multivariate lineal regression model was proposed and the Δ of the aforementioned variables were introduced as covariates. Variables with potential impact on the outcome variable (ΔTcPO2), such as insulin, statins and sulfonylureas doses, adherence to exercise and to diet, were introduced (enter method). Covariates that were maintained were: ΔHDL-cholesterol ($\beta = -0.647$, $p = 0.031$), ΔHbA1c ($\beta = -0.647$, $p = 0.031$), diabetic polyneuropathy ($\beta = -0.647$, $p = 0.031$) and exposure to WBV ($\beta = -0.647$, $p = 0.031$). The final model explained up to 65.5% of the total variance.

Additionally, two-way ANCOVA was conducted to assess the effectiveness of WBV in increasing foot TcPO2 by the degree of glycemic control achieved by participants. Independent variables were exposure to WBV and glycemic control (HbA1c < 7). End-line TcPO2 measurement was the dependent variable. Since ambient temperature can influence TcPO2 readings (Marcoccia et al., 2020), its respective Δ - together with the baseline TcPO2 values – were used as covariates to control for individual differences. Assumptions of independence, normality, homoscedasticity, linearity and homogeneity of regression slopes were fulfilled. After adjusting for the baseline TcPO2 assessment ($p = 0.003$) and the relative change in ambient temperature ($p = 0.497$), WBV intervention ($p = 0.043$) and glycemic control ($p = 0.039$) were statistically significant, with no interaction between them ($p = 0.656$). WBV group maintained higher TcPO2 levels than controls despite glycemic control (Fig. 3). The adjusted final figures were 43.6 mmHg (95% CI: 41.5–45.8) and 47.1 mmHg (95% CI: 44.7–49.5) for the control and WBV groups, respectively.

Raw data analysis revealed that end-line TcPO2 were 3.4 mmHg higher ($p = 0.028$) in the WBV group (47.7 ± 6.1 mmHg) compared with controls (44.3 ± 7.5 mmHg). The multivariate regression model also supports that exposure to WBV constituted a significant, positively-associated independent variable with a subtle effect on TcPO2 that could help explain the slight improvement observed in WBV group. ANCOVA analysis reinforces the statistical difference observed in TcPO2 between groups, with mean adjusted values of 43.6 mmHg and 47.1 mmHg ($p = 0.043$) for control and WBV groups, respectively. Two-way ANCOVA analysis revealed that lower levels of TcPO2 may associate with non-controlled HbA1c (≥7%) and that despite this, WBV may promote higher TcPO2 figures.

4. Discussion

A randomized controlled trial was conducted to assess the effectiveness of a 12-week WBV-based intervention, in addition to multidisciplinary care for T2D, to modify foot TcPO2. No adverse effects were observed throughout the study. Glycemic control and lipid-related markers, functional capacity, neuropathy indicators and body mass composition experienced no changes with WBV intervention, but a significant difference was found in foot TcPO2 levels in those subjects who underwent WBV-exercise program vs. controls.

In a previous work that involved a T2D sample with a mean time of diagnosis of 12.3 years and less glycemic control (mean HbA1c 8.82%), we were able to register significant ($p \leq 0.001$) increase of 7.0 mmHg in foot TcPO2 (baseline: 28.7 mmHg, end-line: 35.7 mmHg) with the same WBV-intervention maneuver (Rodriguez-Reyes et al., 2017). From these findings, we hypothesize that the behavior of TcPO2 can resemble an S-shaped curve, which under normobaric, non-pathological conditions can reach 60–70 mmHg as blood perfusion increases, and in T2D, tends to asymptotically approach 60 mmHg. Given this, we can suggest that in decreased levels of TcPO2 (associated with less T2D control), major increases in TcPO2 could be expected with a WBV-based maneuver. Early diagnosis of T2D, good glycemic control and good self-care habits should associate with high TcPO2 levels and only small increases can be expected with the WBV intervention maneuver used here. Further studies involving populations with different degrees of T2D control should be conducted.

It is worth mentioning that throughout this study, WBV TcPO2 levels consistently remained above those in controls; nevertheless, it is impossible to discard the possibility that the significant difference between groups might be attributed to a slight improvement in the WBV

Table 2
12-weeks whole body vibration training effects on variables of interest.

	Control Group			WBV Group			Between Group *p* value
	Basal	Final	*p* value	Basal	Final	*p* value	
Weight (kg)	72.2 ± 10.6	72.3 ± 10.0	0.921	76.7 ± 13.9	76.9 ± 11.4	0.909	0.350
BMI (kg/m2)	27.3 ± 3.9	27.5 ± 4.2	0.291	28.9 ± 6.1	29.4 ± 5.9	0.210	0.430
Free fat mass (kg)	39.5 ± 3.4	41.5 ± 4.9	**0.007***	45.4 ± 7.8	48.2 ± 8.7	0.078	0.064
Fat mass (kg)	23.9 ± 5.1	24.6 ± 6.0	0.234	27.0 ± 8.6	28.1 ± 9.1	0.131	0.318
Fat (%)	35.3 ± 3.7	36.3 ± 4.8	0.137	34.9 ± 6.3	34.9 ± 6.5	0.952	0.598
Triglycerides (mg/dL)	130.1 ± 41.9	120.59 ± 44.7	0.566	125.1 ± 32.4	118.3 ± 33.3	0.432	0.854
Total cholesterol (mg/dL)	164.9 ± 43.3	170.9 ± 38.6	0.555	157.6 ± 15.9	161.2 ± 25.9	0.579	0.480
HDL (mg/dL)	47.8 ± 13.8	53.1 ± 12.33	**0.011***	51.4 ± 8.9	52.5 ± 11.6	0.452	0.888
LDL (mg/dL)	96.24 ± 36.1	108.4 ± 41.7	0.273	90.7 ± 16.3	88.88 ± 30.8	0.793	0.106
Non-HDL (mg/dL)	117.5 ± 40.4	120.4 ± 37.4	0.730	106.2 ± 17.05	108.7 ± 28.3	0.697	0.281
Fasting blood glucose (mg/dL)	116.2 ± 41.8	120.0 ± 40.9	0.305	108.9 ± 27.9	109.8 ± 28.3	0.975	0.378
HbA1c (%±SD, mmol)	6.6 ± 1.1, 48.6	6.5 ± 1.2, 47.5	0.504	6.5 ± 0.9, 47.5	6.3 ± 0.8, 45.4	0.357	0.597
Feet ESC (μS)	68.9 ± 6.9	67.3 ± 11.6	0.953	63.4 ± 12.7	67.0 ± 7.2	0.261	0.936
Hands ESC (μS)	58.4 ± 15.0	64.3 ± 19.9	0.531	56.5 ± 16.7	62.9 ± 12.1	0.942	0.848
Cardiovascular autonomic neuropathy risk (%)	36.1 ± 10.5	36.7 ± 7.1	0.098	37.4 ± 9.8	38.0 ± 9.6	0.148	0.738
T6MW distance (m)	449.9 ± 82.4	447.4 ± 39.9	0.835	415.4 ± 107.5	425.0 ± 54.3	0.784	0.255
TcPO2 (mmHg)	45.17 ± 8.24	44.37 ± 7.51	0.579	46.31 ± 6.65	47.76 ± 6.08	0.114	**0.028***

WBV: whole body vibration; BMI: Body Mass Index; HbA1c: Glycosylated haemoglobin; HDL: High-Density lipoprotein; Non-HDL: Non-High-Density lipoprotein; LDL: Low-Density lipoprotein; PAD: Peripheral artery disease; ESC: Electrochemical skin conductance; T6MW: Six-minute walk test; TcPO2: Transcutaneous oxygen pressure;
*Significance level: $p < 0.05$ (paired and independent samples *t*-test).

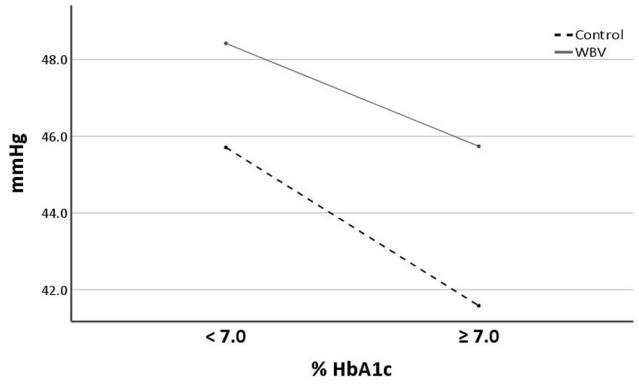


Fig. 3. Title "Estimated marginal mean of TcPO2 after 12-week follow-up". Leyend: Figure depicts TcPO2 ANCOVA-adjusted levels observed in both groups. The intervention group, even in a glucemic non-controlled scenario (HbA1c ≥ 7%), denoted higher values ($p = 0.043$) when compared with the controls.

group and a small deterioration in controls. Lack of statistical significance observed within groups may be explained by the large change considered for calculating the sample size (7 mmHg). A larger sample is needed to observe statistical significance over time.

In an attempt to standardize WBV stimulation parameters that promote lower limb peripheral circulation, Mahbub et al. (2019) proposed that improvement in distal blood flow may be observed within the range of 20–30 Hz and 8-hour-normalized frequency-weighted accelerations (Aw_{8h}) – that describes daily vibration exposure – in the range of 0.29–7.23 m s^{-2} r.m.s. Our study adhered to these guidelines: low amplitude (peak to peak displacement ~ 2 mm) and 30 Hz frequency yielded a mean Aw_{8h} of 1.65 m s^{-2} r.m.s. This reinforces our findings since our experimental group received an intervention focused on increasing lower extremity blood flow. However, the achievements of our work are described in terms of TcPO2, a more accurate surrogate for tissue perfusion and oxygen delivery than local quantification of blood flow using ultrasound techniques.

It has been proposed that exposure to WBV activates muscle spindle receptors that induce tonic vibration reflexes and promote muscle activity, increasing its metabolic demand and oxygen consumption (Mahbub et al., 2019; Robinson et al., 2016). The vasodilator effect has been explained through two pathways: 1) the shear stress generated by blood tissue directly onto vessel endothelia that releases nitric oxide (NO) and unleashes microvascular vasodilation, and 2) the mechanical stress that stimulates cutaneous polymodal receptors, which triggers an axonal reflex that directly promotes vasodilation and mediates NO release (Ren et al., 2019).

T2D, however, entails a set of adverse factors that modify blood tissue rheology: glucose oxidation and protein glycosylation caused by hyperglycemia modify the mechanical and rheological properties of erythrocyte's membrane, reducing its flexibility and deformability properties and promoting its binding to vessel endothelium. Hypercholesterolemia, on the other hand, increases blood viscosity. Together, these affect blood perfusion and change shear stress on vessel endothelium, affecting NO production (Helms et al., 2018). Glucosylation also affects hemoglobin structure, increasing its affinity for oxygen (Ye et al., 2016). The combination of these factors and capillary rarefaction may promote the aggregation of red blood cells and increase the peripheral vascular resistance often observed in T2D (Ren et al., 2019). From this, restriction in the flow of the erythrocyte through the capillaries, with its consequent affectation in local oxygen supply, can be inferred. Hence, our hypothesis is that vertical acceleration, reflex muscle contraction, and the mediating pathways for NO release induced by WBV may help modulate vascular resistance and improve blood rheology by promoting pulsatile blood flow, by reducing the degree of adherence of the erythrocyte to the vascular endothelium and by mechanically forcing its flow through the capillaries. This may explain the slight improvement observed in the WBV group and depicted in Fig. 2, that poses the possible positive effect that the intervention maneuver could have on TcPO2 levels in both volunteers who followed strict glycemic control and those who did not.

It has been noted that a TcPO2 cut-off point of 40 mmHg has been established as a favorable predictor in the wound-healing process (Weir et al., 2016). From our findings, we believe that WBV could stand as a complementary non-pharmacological tool that can help bring/maintain foot TcPO2 close to 40 mmHg. This could aid in preventing the appearance or recurrence of ulcers, in accelerating the healing process of chronic wounds or in assisting when blood perfusion may be compromised by T2D complications.

Unlike other groups who reported significant improvement ($p < 0.05$) in BMI, HbA1c, lipid profile markers body fat, weight, HbA1c, and aerobic capacity with exposure to WBV (Sañudo et al., 2013; Del Pozo et al., 2014; Domínguez-Muñoz et al., 2020), our sample did not

experience major changes in these variables. It is worth noting that the WBV figures achieved by these authors closely resemble those observed throughout this study.

Regarding physical activity, all participants were encouraged to strictly follow CAIPaDi indications. It was impossible to accurately determine the level of adherence to the 10,000-steps daily walk recommended by the CAIPaDi protocol, nor was it possible to quantify the amount of additional exercise performed by each group. The amount of aerobic exercise by the volunteers appeared to be equivalent in each group, as reflected by the T6MT ($p = 0.255$). While WBV training implies additional physical activity, the T6MW may not have enough sensitivity to detect it.

Regarding the sudomotor function test, non-significant improvement was observed in ESC of feet and hands ($p > 0.05$). Observed figures ended within the normal range. This test assesses diabetic neuropathy and cardiovascular function by measuring the chloride ion current present at the sweat glands through electrodes attached to the soles of the feet, and palms of the hands. It ranges from normal to severe dysfunction (Vinik et al., 2015; Gin et al., 2011; Calvet et al., 2013).

Due to the fact that preventive orthotic management (insoles) was provided to all participants, no conclusion could be drawn about the effect of WBV on the VAS pain score other than that it does not appear to worsen it and that no WBV–related discomfort was reported. However, the lower extremity-centered VAS pain score registered a significant improvement in both groups. Initial reported conditions such as metatarsalgia, plantar fasciitis, heel pain, or knee pain improved, as reflected by the end-line score.

Caution must be taken when drawing clinical conclusions, since "no-exercise, no-WBV" and "WBV only" arms were not possible to include, for ethical considerations. Also, determination of the temporality of the residual effect of WBV on TcPO2 (or blood flow, which is not reported in literature) improvement was unavailable due to the cost and time-consuming procedure that TcPO2 measurement implies. Finally, the availability of the WBV equipment used here, which may comprise the proposed method to improve peripheral blood flow, may represent the main limitations of the present work. Given the potential usefulness of low-cost side–alternating–type commercial WBV platforms, that according to Mahbub et al. (2019) may be effective for this purpose, and which might be an economically-affordable alternative to more users, future research and treatment strategies must explore them. Finally, WBV residual effect duration should be understood and poses a possible research line.

Future work could focus on reducing WBV daily exposure and maximizing the effect on peripheral circulation. This could be attained by identifying which type of exercise (strengthening, stretching or massage and relaxation) exerts more impact on TcPO2 and simplifying the exercise program by just keeping those routines that exert the highest stimulation of the lower extremity.

Foot ulceration associated to T2D needs different conservative approaches. WBV could offer a non-invasive approach to improve peripheral circulation and foot health in this population even if physical activity is restricted. To conclude, these results support the idea that WBV can help maintain or even increase lower extremity peripheral circulation, as reflected in the slight increase observed in the TcPO2 of the foot, even in the absence of strict glycemic control. In addition to standard clinical practice, this form of stimulation can stand as a viable non-pharmacologic tool to prevent or aid in foot complications associated with restricted blood perfusion.

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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