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Electrical vestibular nerve stimulation as an adjunctive therapy in the management of type 2 diabetes

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Abstract

Objectives: Vestibular nerve stimulation using the portable battery-operated vestibular nerve stimulator is a sophisticated method noninvasive, safe, and easy to operate. It was hypothesized that vestibular nerve stimulation is effective in the management of type 2 diabetes. Hence, the present study was undertaken to determine the effectiveness of vestibular nerve stimulation using portable battery-operated vestibular nerve stimulator in the management of diabetes.

Methods: The present study was a double-blind randomized controlled trial with 1:1 split between the control and experimental groups. A total of 30 participants with type 2 diabetes were part of the study after obtaining the written informed consent. After recording the baseline values, the vestibular nerve stimulation was administered to the participants in the intervention group for 90 days. Sham stimulation was administered to the control group for 90 days. Outcome measures were recorded after 30 days and after 90 days of the intervention in both the groups.

Results: There was significant decrease in the total body weight, fasting, postprandial blood glucose, glycosylated hemoglobin levels, leptin, very low density lipoproteins levels followed by the intervention. There was significant improvement in both spatial and verbal memory scores. Depression and stress scores and systolic blood pressure decreased and remained in normal limits.

Conclusions: The study results have proven multimodal action of vestibular stimulation. It not only acts on regulation of the glucose metabolism but also can regulate the autonomic activity and improve cognition and relieve stress. This is the interesting finding of our study, which needs detailed further research to support implementation of vestibular nerve stimulation as an adjunctive therapy in the management of diabetes.

Keywords: adjunctive therapy; type 2 diabetes; vestibular nerve stimulation.

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Introduction

The raising pandemic of COVID-19 is challenging the entire globe. Though the infection is progressing geometrically, the fatality is the main concern. There is a raise in the fatality rate with 5.67% worldwide. Uncontrolled diabetes is a known contributing factor to the increase in mortality seen in patients with type 2 diabetes [1]. Diabetes is a chronic metabolic disorder, which occurs due to either insufficient production of insulin by pancreas or inability to utilize insulin effectively [2]. Diabetes is a global health issue with 347 million affected individuals with approximately 80% of diabetes deaths occurring in underdeveloped or developing countries with low and average socioeconomic groups [3, 4]. Some of the Asian countries show high diabetic population [5, 6]. Change in life style was reported to be the major cause for this significant increase in the number of cases of type 2 diabetes [7]. In some cases, this condition can be reverted by lifestyle improvements, and it would appear that the combination of a healthy diet and appropriate level of exercise can be effective in preventing the onset of Type 2 diabetes [8].

The relation between obesity and diabetes is well known. The exact mechanism linking obesity with diabetes has still remained uncertain. It was proposed that the insulin resistance causes impairment of glucose metabolism and leads to obesity [9]. The liver, skeletal muscle, and adipose tissue of the obese individual possess fewer insulin receptors when compared to a lean individual [10]. Insulin resistance is mostly due to the hindrances in the signaling pathways those linked to the receptor activation involved in multicellular effects. Impairment in the insulin signaling is associated with toxic effects of lipid accumulation in various tissues such as the liver and skeletal muscle, stands secondary to the excess weight gain. Various pharmacological therapies are available to manage the diabetes, but still the diabetic control is not satisfactory [11]. Hence, there is a need for an effective adjunctive therapy with minimum or no side effects.

Vestibular system is considered as a separate entity since the middle of the 19th century. It is identified that all the five special sense organs terminate into vestibular nuclei [12]. Vestibular apparatus is a part of internal ear and has a role in maintaining equilibrium and postural stability. It has direct connections with vagus (dorsal motor nucleus), locus coeruleus, hypothalamus, tractus solitarius, hippocampal formation, and dorsal raphe nucleus. It is demonstrated that electrical stimulation to the vagal nerve increases the secretion of insulin and glucagon. Various factors increase the risk for the occurrence of type 2 diabetes, namely stress, depression, anxiety, anger, and sleep disorders. Studies have proven the effectiveness of vestibular stimulation in relieving pain, reducing stress, and promoting sleep. There are various methods of vestibular stimulation, one of the traditional and most ancient methods by swing. Vestibular nerve stimulation (VeNS) using the portable battery-operated vestibular nerve stimulator is a sophisticated method noninvasive, safe, and easy to operate. The present study was undertaken to determine the effectiveness of VeNS using portable battery-operated vestibular nerve stimulator in the management of diabetes.

Materials and methods

Study design

The present study was a double-blind randomized controlled trial with 1:1 split between the control and experimental groups. After recording the baseline values, the VeNS was administered to the participants in the intervention group for 90 days. Sham stimulation was administered to the control group for 90 days. Outcome measures were recorded after 30 days and after 90 days of the intervention in both the groups. All subjects were put on a daily diet of 1500 kCal. The trial was registered at The Clinical Trials Registry – India (CTRI) with reference number of CTRI/2019/06/019854.

Study setting

The study was conducted at Vestibular Research Lab, Vishnu Dental College, Andhra Pradesh, India.

Study participants

A total of 30 participants with type 2 diabetes were part of the study after obtaining the written informed consent. After recruiting the participants, they were randomly assigned into control and intervention groups with 15 participants in each group. Treatment assignments were generated via a randomized block procedure, with block sizes randomly chosen in the set (2, 4, 6, 8, 10). There was no exclusion from the study on the basis of race, gender, socioeconomic status, language spoken, or ethnicity. At the screen visit, subjects were requested to complete a questionnaire about their medical history and medications to ensure that they fulfill the inclusion and exclusion criteria for the study. Participants were recruited using the following criteria.

Inclusion criteria: Male and female type 2 diabetic patients within the age group of 35–60 years and willing to participate in the study were included in the study.

Exclusion criteria: Patients with ear infections or any vestibular disturbances or following any other alternative therapy and those with severe complications were excluded from the study.

Sample size

The assumed mean difference was 25% in the variables with standard deviation of 20%. The power of the study is 90% with a significance level of 5%. Fifteen participants in each group were found to be adequate. SigmaPlot Version 13 (systat software) was used for calculation of sample size.

Intervention

VeNS was administered to the participants in the intervention group for 90 days using the portable battery-operated vestibular nerve stimulator (0.1–1 mA, titrated in 0.1 mA steps by subjects according to comfort; 0.5 Hz AC square wave with a 50% duty cycle) (ML 1000, Neurovalens, UK) [14]. Placebo stimulation (sham device that beeped and flashed but didn't deliver an active stimulus) was administered to the participants in the control group for 90 days using similar portable battery-operated vestibular nerve stimulator.

Outcome measures

All the parameters were recorded between 7 and 7:30 am. Blood samples for estimation of postprandial glucose levels were collected after 2 h of the breakfast. All the samples were processed by kit method using dimension RxL 100 fully automated instrument.

Demographic data

Demographic data of the participants including age, height, weight, and body mass index (BMI) were recorded at the time of recruitment. Weight was recorded after 30 and 90 days of the intervention.

Fasting and postprandial blood sugar

Estimation of fasting and postprandial blood sugar was performed using glucose oxidase (GOD)-peroxidase (POD) method [15].

HbA1c

HbA1c was assessed using Diazyme (enzymatic assay) [16].

Serum leptin

Serum leptin levels were assessed using Human Leptin ELISA Kit (ELH-Leptin-1) purchased from Genxbio Health Sciences Pvt. Ltd [17, 18].

Lipid profile

Total cholesterol was estimated by cholesterol oxidase-phenol + aminophenazone (CHOD PAP) method, triglycerides were estimated by glycerol- 3-phosphate oxidase-phenol + aminophenazone (GPO-PAP) method, and high-density lipoprotein (HDL) and low-density lipoprotein (LDL) were estimated by precipitation method.

SGOT and SGPT

Serum Glutamic Oxaloacetic and Glutamic Pyruvic Transaminases were estimated using colorimetric method [19].

Assessment of cardiorespiratory parameters

Blood pressure was recorded by using Diamond digital sphygmomanometers (BPDG024) and P02, pulse rate was recorded by using pulse oximeter (EDAN H100B), respiratory rate was measured manually [20].

Assessment of spatial and verbal memory

Spatial and verbal memory test was used to assess the spatial and verbal memory of the participants [21–23].

Assessment of depression, anxiety, and stress

DASS 21 was used to assess the depression, anxiety, and stress levels [24].

Ethical consideration

The present study protocol was approved by institutional ethics committee (VSR/EC/19/01).

Data analysis

Data was analyzed using SigmaPlot Version 13 (systat software). Two-way analysis of variance (ANOVA) of groups (control and intervention) and the days (0, 30 and 90) with Bonferroni multiple comparison test was applied for quantitative data. Kruskal–Wallis one-way ANOVA on ranks with Student–Newman–Keuls multiple comparison test was applied for qualitative data. Probability value less than 0.05 was considered as significant.

Results

The mean age (years), height (cm), and BMI of participants in control group are 54.60 ± 11.27, 162.47 ± 8.18, 24.72 ± 3.22 and those of participants of intervention group are 51.67 ± 12.99, 163.33 ± 8.33, 26.64 ± 3.74. These baseline demographic values are not statistically significant between the control and intervention groups. The mean total

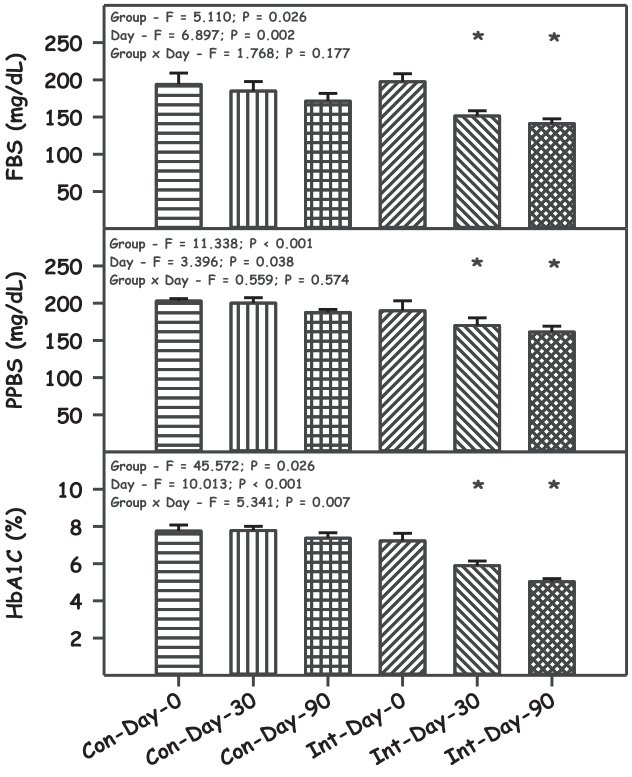

Figure 1: The effect of vestibular nerve stimulation by portable battery-operated vestibular nerve stimulator on fasting blood sugar (FBS), postprandial blood sugar (PPBS), and glycosylated hemoglobin (HbA1c) levels in type 2 diabetics before the intervention (day 0) and after one month (day 30) and three months (day 90). Con, control; Int, intervention.
Values are mean ± SE (n=15 each).
Two-way ANOVA of groups (control and intervention) and the days (0, 30, and 90) with Bonferroni multiple comparison test.
*Significantly different from the respective control group.

body weight loss (TBWL) (%) from baseline of the participants in the control group on days 30 and 90 days of intervention was +0.4 ± 2.3% and +0.1 ± 1.9% and of the participants of intervention group was −1.7 ± 2.8% and −3.6 ± 3.3%. The day 90 difference in TBWL between both groups was statically significant (p=0.0006). Fasting blood sugar (mg/dL), postprandial blood sugar (mg/dL), and glycosylated hemoglobin (%) levels were not significantly different between control and intervention groups before the intervention (day 0). There was a significant decrease in the fasting blood sugar, postprandial blood sugar (mg/dL), and glycosylated hemoglobin (%) levels in the intervention group followed by the VeNS for 30 and 90 days. Multiple comparisons with respective control group showed significant decrease in the fasting blood sugar levels followed by the VeNS (Figure 1). Aspartate aminotransferase (AST) (U/L) and alanine aminotransferase (ALT) (U/L) were not significantly changed followed by the VeNS. Leptin levels were significantly decreased in the intervention group followed by the VeNS for 30 and 90 days (Figure 2). Though there was decrease in the total cholesterol and triglycerides, this was not statistically significant (Figure 3). Very low density lipoproteins (VLDL) levels were significantly decreased in the intervention group followed by the VeNS on day 30 and day 90. No significant change was observed in the LDL and HDL (Figure 4). Systolic blood pressure was significantly decreased in the intervention group followed by the VeNS on day 30 and day 90. No significant change was observed in the diastolic blood pressure (DBP) and heart rate (HR) percentage of oxygen saturation (PO2) (Figure 5).

Spatial memory (p=0.006) and verbal memory (p < 0.001) scores were significantly increased followed by the intervention. Depression (p=0.009) and stress (p=0.004) scores were significantly decreased in the intervention group followed by the intervention. No significant change was observed in the anxiety scores (Table 1).

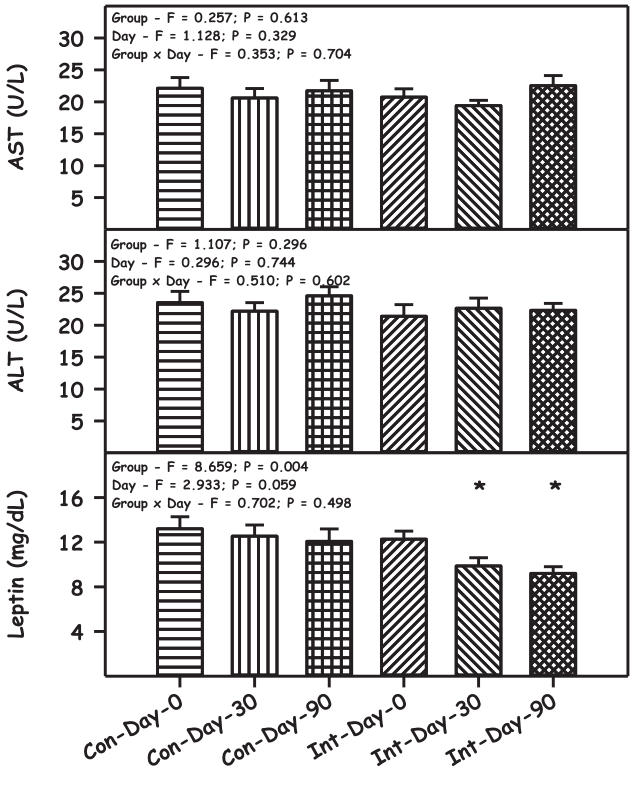

Figure 2: The effect of vestibular nerve stimulation by portable battery-operated vestibular nerve stimulator on aspartate aminotransferase (AST), alanine aminotransferase (ALT), and leptin levels in type 2 diabetics before the intervention (day 0) and after one month (day 30) and three months (day 90).
Con, control; Int, intervention.
Values are mean ± SE (n=15 each).
Two-way ANOVA of groups (control and intervention) and the days (0, 30, and 90) with Bonferroni multiple comparison test.
*Significantly different from the respective control group.

Discussion

Management of diabetes requires multimodal management approach as it affects various body systems.

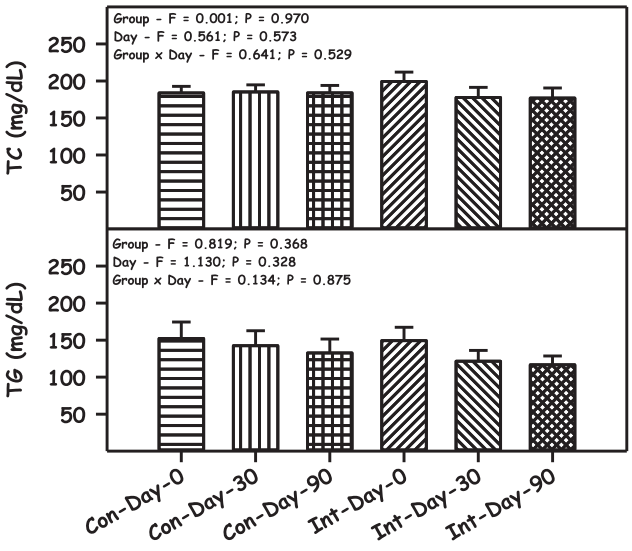

Figure 3: The effect of vestibular nerve stimulation by portable battery-operated vestibular nerve stimulator on total cholesterol (TC), triglycerides (TG) in type 2 diabetics before the intervention (day 0) and after one month (day 30) and three months (day 90).
Con, control; Int, intervention.
Values are mean ± SE (n=15 each).
Two-way ANOVA of groups (control and intervention) and the days (0, 30, and 90) with Bonferroni multiple comparison test.
*Significantly different from the respective control group.

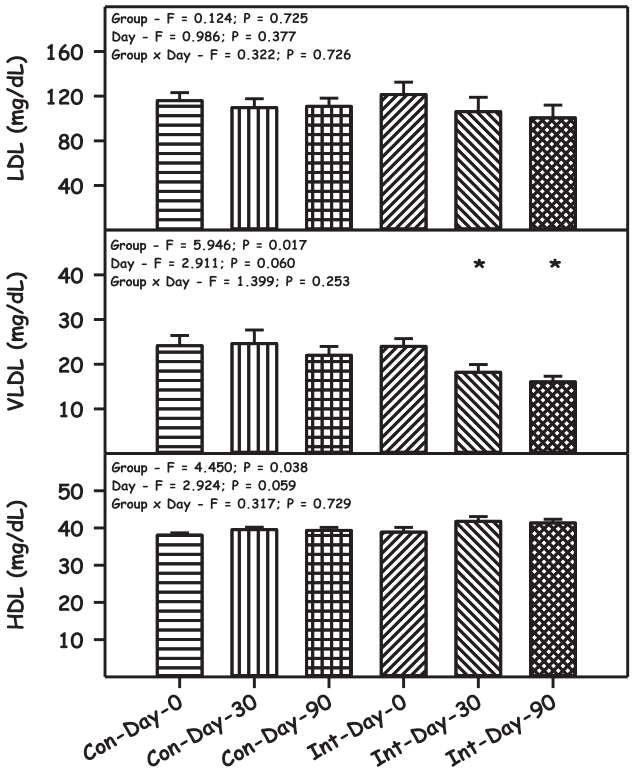

Figure 4: The effect of vestibular stimulation by portable battery-operated vestibular nerve stimulator on low-density lipoproteins (LDL), very low density lipoproteins (VLDL), and high-density lipoprotein (HDL) in type 2 diabetics before the intervention (day 0) and after one month (day 30) and three months (day 90).
Con, control; Int, intervention.
Values are mean ± SE (n=15 each).
Two-way ANOVA of groups (control and intervention) and the days (0, 30, and 90) with Bonferroni multiple comparison test.
*Significantly different from the respective control group.

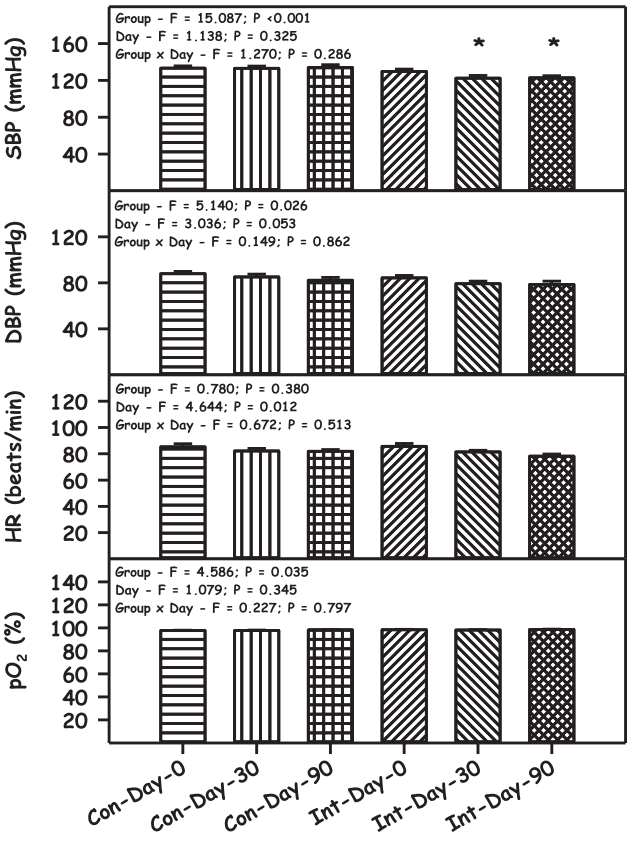

Figure 5: The effect of vestibular stimulation by portable battery-operated vestibular nerve stimulator on systolic blood pressure (SBP), diastolic blood pressure (DBP), and heart rate (HR) percentage of oxygen saturation (PO2) in type 2 diabetics before the intervention (day 0) and after one month (day 30) and three months (day 90).
Con, control; Int, intervention.
Values are mean ± SE (n=15 each).
Two-way ANOVA of groups (control and intervention) and the days (0, 30, and 90) with Bonferroni multiple comparison test.
*Significantly different from the respective control group.

Vestibular system is a unique sensory system that can influence all our body systems and stimulating vestibular system is essential for all age groups. The present study was undertaken to determine the effectiveness VeNS using portable battery-operated vestibular nerve stimulator in the management of diabetes. It was hypothesized that vestibular stimulation modulates the body weight through its connections with the hypothalamus. Vestibular stimulation influences the energy storage mechanism, feeding behavior and also decreases the adipose storage by direct action [25]. The current study results support this hypothesis as there was significant decrease in the body weight and serum leptin levels followed by the VeNS. Earlier studies reported that vestibular stimulation may influence the glucose metabolism [26]. Stimulation of vestibular nerve excites the vagus nerve that supplies to the islets of pancreas and increases the secretion of insulin, which reduces the blood glucose levels. This mechanism is mediated by M_4 receptors [27, 28]. Another hypothesis is that vestibular stimulation may activate AMP-activated protein kinase (AMPK), the enzyme associated with the metabolism of fat and glucose, and contributes to regulation of blood glucose [29]. The present study results support these earlier studies as there was a significant decrease in both the fasting and postprandial blood glucose levels followed by the VeNS. Further, there was a significant decrease in the HbA1c levels followed by the vestibular stimulation. This is beyond our expectations and further detailed research has to be conducted to understand the mechanism.

AST and ALT levels were not altered followed by the vestibular stimulation. This testifies that VeNS is safe procedure and doesn't have any adverse effect on liver

Table 1: The effect of vestibular stimulation by portable battery-operated vestibular nerve stimulator on cognitive and psychological parameters in type 2 diabetics before the intervention (day 0) and after one month (day 30) and three months (day 90).

S.No.	Parameter	Groups	Median	Percentile (25–75)	Statistical analysis
1	Spatial memory	Con-day-0	12	11–13	H=16.150
		Con-day-30	12	11–14	p=0.006
		Con-day-90	13	12–13	
		Int-day-0	11	10–13	
		Int-day-30	13	12–15	
		Int-day-90	14	13–15	
2	Verbal memory	Con-day-0	9	8–10	H=21.706
		Con-day-30	8	6–10	p<0.001
		Con-day-90	9	8–10	
		Int-day-0	9	8–10	
		Int-day-30	11	9–12	
		Int-day-90	11	9–13	
3	Depression	Con-day-0	12	7–14	H=15.253
		Con-day-30	11	8–13	p=0.009
		Con-day-90	11	9–13	
		Int-day-0	12	11–14	
		Int-day-30	10	8–12	
		Int-day-90	9	7–10	
4	Anxiety	Con-day-0	9	8–10	H=7.236
		Con-day-30	9	8–10	p=0.204
		Con-day-90	9	8–10	
		Int-day-0	11	8–12	
		Int-day-30	9	8–10	
		Int-day-90	8	8–10	
5	Stress	Con-day-0	17	12–21	H=17.378
		Con-day-30	16	10–20	p=0.004
		Con-day-90	15	10–19	
		Int-day-0	15	11–20	
		Int-day-30	10	8–16	
		Int-day-90	8*	6–12	

Con, control; Int, intervention. (n=15 each). Kruskal–Wallis one-way ANOVA on ranks with Student–Newman–Keuls multiple comparison test. *Significantly different from the respective control group.

functions. Earlier study by Saritha et al., where vestibular stimulation was administered using a swing in underweight females, reported that there was an increase in the triglycerides and HDL and no change in LDL and total cholesterol followed by vestibular stimulation [30]. Another study by Neethu Sadanandan et al., where caloric vestibular stimulation was administered to the hyperlipidemic model of *wistar* albino rats, showed no significant change in the body weight, significant decrease in the total cholesterol, triglycerides, HDL, and LDL levels [31]. In the present study, no significant change was observed in the total cholesterol, HDL, triglycerides, and LDL levels. However, the VLDL levels are significantly decreased. The exact mechanism for this effect is unclear. This may be due to effect of vestibular stimulation on feeding behavior and set point of fat.

Earlier studies reported that stimulation of vestibular receptors regulates the blood pressure and HR through baroreceptor reflex [32–36]. A study by Archana et al. reported significant decrease in the salivary cortisol, pulse rate, and blood pressure within the normal limits followed by the vestibular stimulation using a swing [13, 37]. In the present study, only the systolic blood pressure was significantly decreased followed by the vestibular stimulation. Whereas no significant change was observed in diastolic blood pressure and heart rate. It was reported that vestibular stimulation can restore the normal respiratory rhythm in preterm infants [38]. In contrast, other studies reported that there is no significant change in the respiratory parameters followed by the vestibular stimulation [39, 40]. In the present study, partial pressure of oxygen was measured as a respiratory parameter. However, there was no significant change observed in the partial pressure of oxygen.

Vestibular influences on memory are well documented. Vestibular stimulation modulates the activity of

hippocampal place cells where the sensory information integrates with the spatial memory [41, 42]. Further, impairment in the spatial memory was reported followed by the vestibular lesions [43, 44]. The present study results support earlier studies as there was a significant increase in the scores of spatial and verbal memory followed by the vestibular stimulation. It was reported that vestibular stimulation is effective in the management of psychological distress. There was significance in the scores of depression and stress followed by the vestibular stimulation in the present study.

Conclusions

The study results have proven multimodal action of vestibular stimulation. It not only acts on regulation of the glucose metabolism but also can regulate the autonomic activity and improve cognition and relieve stress. This is the interesting finding of our study, which needs detailed further research to support implementation of VeNS as an adjunctive therapy in the management of diabetes.

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Author contributions: All authors have accepted responsibility for the entire content of this manuscript and approved its submission.

Competing interests: Authors state no conflict of interest.

Informed consent: Dr. Jason McKeown and Dr. Paul Mcgeoch are cofounders of Neurovalens, a medical device company that provided the VeNS devices used in the study. JM is CEO of Neurovalens and PDM is a nonexecutive director. They were involved in the design of the study but not in its execution.

Ethical approval: The present study protocol was approved by institutional ethics committee (VSR/EC/19/01).

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