http://www.cjmb.org

Open Access Original Article

Crescent Journal of Medical and Biological Sciences
Vol. 8, No. 3, July 2021, 174–178
eISSN 2148-9696

Investigation of Effects of Galvanic Vestibular Stimulation on Patients With Type 2 Diabetes

Yones Lotfi[1], Aghil Absalan[1*], Mahmoud Ali Keykhaei[2]

Abstract

Objectives: Autonomic nervous system is one of the most important regulators of insulin secretion in type 2 diabetic patients. Considering the neuronal connections between the vestibular nuclei and this system, this study used galvanic vestibular stimulation (GVS) for evaluating the efficacy of this stimulus in controlling the blood glucose level in such patients.

Materials and Methods: In this randomized clinical trial study, 48 patients with type 2 diabetes mellitus participated in the GVS, sham GVS, and the no-treatment group as the control group (mean age of 50.79 ± 6.65 years). In the GVS group, each subject received electrical stimulation three times a week via two electrodes on mastoid processes throughout the 12-week study period. The current for sham stimuli was reduced to zero after about 10 seconds. The blood samples were used to monitor the blood sugar level and HbA1C changes. Body mass index (BMI) changes were assessed as well. The one-way ANOVA technique and Tukey's test were applied to compare the values between the groups. A paired-samples t-test was applied to individually compare the baseline and 12-weeks values of BMI, fasting blood sugar, and hemoglobin A1C in the groups.

Results: The comparison of the results in the three groups showed a statistically significant reduction in the blood sugar level and BMI in the GVS group ($P<0.05$).

Conclusions: The findings of the current study demonstrated that in patients with diabetes, GVS, along with receiving medical treatment, led to a further reduction in the blood sugar level and BMI, and thus this method can be used to treat patients with treatment-resistant diabetes and lower pharmacotherapy.

Keywords: Electric stimulation, Diabetes mellitus, Treatment outcome, Vestibular nuclei, Obesity

Introduction

Diabetes mellitus is a common endocrine disease which is characterized by chronic hyperglycemia and the impairment of the metabolism of proteins, carbohydrates, and lipids and results from the insufficiency of insulin secretions or target-tissue resistance to insulin function (1).

Hyperglycemia can lead to an increase in the levels of oxidative stress and lower the activity of antioxidant enzymes. This increase in reactive oxygen species (ROS) production in diabetic patients decreases insulin gene expression. Furthermore, studies support the role of oxidative stress in causing chronic hyperglycemia-induced insulin resistance and increasing complications such as micro-vascular and macro-vascular diseases and atherosclerosis development in such patients (2).

The management of patients includes training, healthy diets, weight control, physical activity, blood glucose monitoring by the patient, and if necessary, the use of anti-hyperglycemic agents (1). Diet and exercise are the essential components for the treatment of patients with diabetes (3). However, many diabetes patients fail to control their blood sugar levels thus there is a need for complementary therapies. In recent years, considering the role of the autonomic nervous system, which is one of the most important regulators of endocrine secretion glands, vagal nerve stimulation is used to control blood glucose in these patients (4).

The autonomic nervous system includes parasympathetic and sympathetic sections. The stimulation of the parasympathetic section leads to the stimulation of the secretion of insulin from the pancreas, and the stimulation of the sympathetic section by the norepinephrine secretion affecting adrenergic alpha-receptors inhibits its secretion. Blood glucose levels could be controlled in patients suffering from type 2 diabetes mellitus by stimulating the parasympathetic system and inhibiting the sympathetic system and thus increasing insulin secretion (5).

The vagus nerve which is a part of the autonomic nervous system consists of motor, sensory, and parasympathetic nuclei. Studies have shown that the stimulation of the dorsal motor nucleus of the vagus nerve (DMX) and nucleus tractus solitarius (NTS) can regulate the secretion of endocrine secretion glands. The branches of the right vagus nerve innervate pancreatic islets. The secretion of glucose-dependent insulin is altered by several hormones

Received 5 January 2020, **Accepted** 12 May 2020, **Available online** 28 June 2020

[1]Department of Audiology, University of Social Welfare and Rehabilitation Sciences, Tehran, Iran. [2]Internal Seat, Ali-ibn-Abitaleb Hospital, Zahedan University of Medical Sciences, Sistan and Balouchestan, Zahedan, Iran.
***Corresponding Author:** Aghil Absalan, Tel: +985433295711, Fax: +985433295836, Email: Aghilabsalan@yahoo.com

Key Messages

- As many diabetes patients fail to control their blood sugar levels, this article describes a new way to control blood sugar and weight by GVS.

and neurotransmitters such as acetylcholine. Acetylcholine is secreted by terminals within the parasympathetic pancreatic vagus nerve. This secretion plays an important role in maintaining glucose tolerance (6).

Direct neuronal connections are observed among DMX, NTS, and vestibular nuclei. In the central DMX region, there are cells originating from the vestibular system. The ipsilateral vagus nerve is evoked by stimulating the vestibular system. As a result, the vestibular stimulation by changing the activity of the vagus nerve through the above-mentioned process leads to increased insulin secretions, control of obesity, and ultimately, control of blood glucose (5).

Swinging, rotating chairs, caloric stimulation, and galvanic vestibular stimulation (GVS) are the stimuli which are commonly used to induce vestibular stimulation for clinical and research purposes. It is shown that caloric stimulation and oscillatory movements are effective in controlling blood glucose in diabetes mellitus, indicating the ability of the vestibular stimuli in controlling blood glucose (6,7).

The advantage of GVS is that it is less invasive than caloric stimulation and is not affected by middle ear disorders. On the other hand, it results in a controlled firing in the afferent fibers from the whole parts of the vestibular system without causing a potential change in the intervention in non-vestibular inputs such as oscillatory movements (8). The GVS signal is transmitted by irregular units and can be sent to all areas of the central nervous system receiving vestibular branches (9,10). One of the advantages of this response is that it is highly automated, and despite the stimulation of the mobile visual environment, the GVS response is not habitual even when it is repeated by the individual itself (11). The GVS uniformly activates the initial afferents of all vestibular sensory regions, thus the position of GVS stimulation causes no specific change in stimulating pathways (12). Furthermore, evidence suggests that providing noisy galvanic stimulation below the threshold level can improve motor function and the efficacy of the autonomic nervous system in patients with neurodegenerative lesions (13).

Low treatment and lack of awareness of accompanying problems and disease management are among the main causes of increased mortality due to this disease. For this reason and by considering the effects of vestibular stimulation on increasing the activity of the autonomic nervous system, especially the parasympathetic system and increased insulin secretions, the current study aimed at using these features to control the blood glucose level and hemoglobin A1c (HbA1c) in patients suffering from diabetes. It is recommended that internal medicine specialists utilize the study findings for patients with diabetes and enhance treatment and control of disease progression.

Materials and Methods

The current single-blind randomized clinical trial was registered at the Iranian Registry of Clinical Trials (identifier: IRCT20180228038904N1, https://www.irct.ir/trial/30414). The study protocol was also approved by the institutional Ethics Committee of the University of Social Welfare and Rehabilitation Sciences (IR.USWR.REC.1396.249).

All participants signed the informed consent form prior to enrolment in this study. The study procedures and experiments were carried out at the Diabetes Clinic of Bou-Ali hospital, Zahedan, Iran under the supervision of an endocrinologist and a medical team from February 2017 to January 2019.

The inclusion criteria were the age range of 40-65 years, confirmation of the diagnosis of type 2 diabetes mellitus by an endocrinologist, at least six months of receiving type 2 diabetes diagnosis and treatment for blood glucose, the HbA1c level of 7.5%-9.5%, and the lack of health issues interfering with diabetes or its treatment. The other criteria were the lack of systemic disease such as kidney, liver, and rheumatologic diseases, digestive and balance disorders, pregnancy, and cerebrovascular diseases, no history of intensive infections in the previous month, and a willingness to participate in the study. On the other hand, the exclusion criteria included an unwillingness to participate in the trial and any illness that required medical interventions and could have a negative impact on the study process.

By using random block sampling and according to results of the pilot study, 48 patients were selected and then divided into GVS, sham GVS, and no-treatment groups. Fasting blood sugar (FBS), HbA1c, and body mass index (BMI) were recorded for all participators.

The laboratory used a turbidimetric inhibition immunoassay method to measure HbA1c and the enzymatic glucose oxidase method for the measurement of FBS.

All groups were advised not to stop using their anti-diabetic drugs throughout the study period. Each subject in the GVS group received stimulation three times a week on three different days via two electrodes placed on mastoid processes by a trained clinician. Stimulation sessions lasted 20 minutes and the applied voltage was set just below the threshold of the individual. The stochastic stimulation was applied with the random frequencies of 1-30 Hz.

All conditions of the sham GVS group were similar to those of the GVS group except for the current that was reduced to zero after about 10 seconds. At the end of

the 12th week of the intervention, blood sampling was performed by a laboratory technician in order to check blood sugar and HbA1c level changes.

The SPSS software (version 19) was utilized for statistical data analysis at a significant level ($P<0.05$). The one-way ANOVA technique and Tukey's test were applied to compare the values of BMI, FBS, and HbA1c in three groups of GVS, sham GVS, and no-treatment control group. Then, a paired-samples t-test was used to make a comparison between the baseline and 12-week values of BMI, FBS, and HbA1c individually in GVS, sham GVS, and no-treatment control groups.

Results

The present study was performed on 48 adult patients (with mean age of 50.79 ±6.65 years) who were divided into three groups of intervention (GVS; n = 16, mean age of 52.56 ± 7.02 years), sham GVS (n = 16, mean age of years 49.75 ± 5.65), and the control group (no-treatment; n = 16, a mean age of 50.06 ± 7.23 years).

The results showed no significant differences between the three groups regarding the baseline values of BMI, FBS, and HbA1c (Table 1, $P > 0.05$) and age ($P = 0.433$).

Contrarily, there were statistically significant differences between the three groups with respect to the obtained values at the end of the twelfth week of BMI and FBS although the differences were not significant in terms of HbA1c (Table 2).

Similarly, a significant difference was observed between the baseline and 12-week values of BMI and FBS in the GVS group although the difference was not statistically significant with regard to HbA1c (Table 3).

However, no significant differences were found between the initial values and those obtained at the end of the twelfth week in the sham and no-treatment groups (Tables 4 and 5).

Table 1. Initial BMI, FBS, and HbA1c Values in 3 Groups

	GVS	Sham GVS	Control	*P* Value
FBS	268.31	261.06	271.12	0.923
HbA1c	8.46	8.35	8.33	0.833
BMI	29.43	28.87	29.25	0.503

Note. FBS: Fast blood sugar level (mg/dL); HbA1c: Hemoglobin A1C in percentage; BMI: Body mass index (kg/m^2); GVS: Galvanic vestibular stimulation.

Table 2. Values of BMI, FBS, and HbA1c in Three Groups at the 12th Week

	GVS	Sham GVS	Control	*P* Value
FBS	202.25	259.93	265.68	0.017*
HbA1c	8.52	8.49	8.33	0.673
BMI	27.43	28.68	29.06	0.002*

Note. *$P<0.05$; FBS: Fast blood sugar level (mg/dL); HbA1c: Hemoglobin A1C in percentage; BMI: Body mass index (kg/m^2); GVS: Galvanic vestibular stimulation.

Discussion

Considering the globally increasing prevalence of diabetes, controlling this disease is the core of treatment and providing a simple and cost-effective method in this regard is crucial for public health.

One of the problems of diabetic patients is related to ROS production. The increments in ROS production in diabetic patients decrease insulin gene expression, thus leading to the worsening of the patient's condition and the progression of the disease. Accordingly, breaking this chain can lead to positive results in the management of patients (2).

In the beginning stages, diabetes can be controlled by a diet, physical activity, and weight loss. Nonetheless, the oral medication should be prescribed if these methods are ineffective. However, in many patients, blood glucose levels are not effectively controlled due to drug resistance thus such patients need complementary treatments (3).

In recent years, considering the role of the autonomic nervous system, which is considered as one of the most important regulators of endocrine secretion glands, the use of vagal nerve stimulation in controlling blood glucose and obesity in such patients has raised attention (4).

Huang et al reported that stimulating the vagus nerve with an electrical current through the terminals of the nerve on the auricle, blood glucose, and HbA1c levels may be lowered in subjects with impaired glucose tolerance. The difference between the result of the current study and that of Huang et al was the location of the stimulation, the

Table 3. Comparison of Values in GVS Group

	Initial	12-week	*P* Value
FBS	268.31	202.25	0.001*
HbA1c	8.462	8.525	0.189
BMI	29.43	27.43	0.001*

Note. *$P<0.05$; FBS: Fast blood sugar level (mg/dL); HbA1c: Hemoglobin A1C in percentage; BMI: Body mass index (kg/m^2); GVS: Galvanic vestibular stimulation.

Table 4. Comparison of Values in Sham GVS Group

	Initial	12-week	*P* Value
FBS	261.06	259.93	0.458
HbA1c	8.356	8.493	0.296
BMI	28.87	28.68	0.094

Note. FBS: Fast blood sugar level (mg/dL); HbA1c: Hemoglobin A1C in percentage; BMI: Body mass index (kg/m^2); GVS: Galvanic vestibular stimulation.

Table 5. Comparison of Values in Non-treatment Group

	Initial	12-week	*P* Value
FBS	271.12	265.68	0.332
HbA1c	8.337	8.331	0.469
BMI	29.25	29.06	0.094

Note. FBS: Fast blood sugar level (mg/dL); HbA1c: Hemoglobin A1C in percentage; BMI: Body mass index (kg/m^2); GVS: Galvanic vestibular stimulation.

type of electrical stimulation, and the number of sessions that stimulation was presented over the 12 weeks (4).

The present study investigated the efficacy of GVS in diabetic patients. Due to the extensive association of the vestibular nuclei with the central nervous system, GVS has been so far of interest to researchers. Numerous studies confirmed the positive effects of GVS on a variety of disorders such as unilateral vestibular dysfunction, Parkinson's, and cognitive disorders (13-17).

In the study by Huang et al (4), vagus nerve stimulation was performed through the auricle whereas in the current study, the stimulation of the vagal nucleus was considered to utilize the other features of vestibular stimulation, including the inhibition of the sympathetic system through its synaptic connections with the vestibular nucleus. In both studies, blood sugar levels decreased as a result of the intervention. Compared with the study by Huang et al, the HbA1c results in this study showed no differences between the three groups, which may be due to the difference in the number of sessions of stimulation. In the current study, each patient was stimulated three times a week whereas, it was performed twice daily in the above-mentioned study.

As mentioned earlier, utilizing vestibular stimulation to lower blood sugar in diabetes has been studied in two other studies (6,7). The type of applied vestibular stimulation in the current study was different. In the Athira pilot study on rats, caloric stimulation was used and the results revealed the positive effect of caloric stimulation on lowering blood sugar levels (6), which is in line with the results of the current study. Galvanic stimulation is less invasive than caloric and needs simpler equipment that can be used at home. Moreover, middle ear diseases do not adversely affect its efficiency.

In a case study by Sailesh et al, a diabetic patient received a vestibular stimulation for 26 weeks through a swinging movement. The results showed that medication accompanied with vestibular stimulation could have been better controlled blood glucose levels compared to medication alone (7), which corroborates with the findings of the current study.

Compared with swing motion, GVS results in a controlled firing in the afferent fibers from the whole parts of the vestibular system, and non-vestibular inputs do not interfere with its results (8). On the other hand, Guerraz and Day emphasized that despite the stimulation of the mobile visual environment, responses evoked by GVS were not affected by predictability (11).

The BMI was one variable that was investigated in our study but was not reviewed in the mentioned studies.

Obesity is one of the most important causes of diabetes in patients who are genetically predisposed to this disease (1).

Indicator points in the comprehensive treatment of patients include training, healthy eating, weight control, physical activity, blood glucose monitoring by the patient, and if necessary, the use of anti-hyperglycemic agents (1). Diet and exercise are important components for treating patients with both types 1 and 2 (3).

Stimulating the vagus nerve can regulate the feeding behavior via the connections between NTS and hypothalamic nuclei (4,18), and as a result, the stimulation of the vestibular nuclei can also contribute to weight loss (5).

Our finding on the use of GVS in diabetic patients showed a reduction in BMI, which is consistent with the results of some studies reporting the role of vagus nerve stimulation in losing weight (4,19). According to the results of this study, further studies can be done on this method and lead to the clinical application of GVS in diabetes clinics for controlling blood sugar and weight in patients who are resistant to medical therapy.

Limitations of the Study

One of the limitations of our study was that participants were volunteers. Therefore, some of them were excluded from the study during the three-month stimulation period. The availability of only one device during the study was another constraint of the study. Thus, we suggest larger sample sizes and control of changes over a longer period of stimulation for subsequent studies.

Conclusions

The results of the current study showed that in patients with diabetes, GVS, along with receiving medical treatment, led to a further decrease in blood pressure compared to sham and control groups, and this method can be used to treat patients with treatment-resistant diabetes and lower pharmacotherapy. It also reduces the BMI, which, in turn, reduces the blood sugar in patients.

Authors' Contribution

YL, AA and MAK: Concept and design. AA and MAK: Data collection and interpretation of the data. AA: Performing of the study. YL and AA: Writing of the draft. All authors read and approved the study.

Conflict of Interests

Authors have no conflict of interests.

Financial Support

The authors did not have funding sources in any part of this study.

Acknowledgments

We thank the staff at the Diabetes Center at Bou-Ali Hospital for their sincere cooperation, and especially Zahra Sharafi for assistance with the process of stimulating patients. Finally, we would like to thank all the volunteers for the study.

References

1. Diagnosis and classification of diabetes mellitus. Diabetes Care. 2014;37 Suppl 1:S81-90. doi:10.2337/dc14-S081
2. Oguntibeju OO. Type 2 diabetes mellitus, oxidative stress and inflammation: examining the links. Int J Physiol Pathophysiol Pharmacol. 2019;11(3):45-63.
3. Prasad H, Ramesh V, Balamurali P. Morphologic and cytomorphometric analysis of exfoliated buccal mucosal

cells in diabetes patients. J Cytol. 2010;27(4):113-117. doi:10.4103/0970-9371.73291
4. Huang F, Dong J, Kong J, et al. Effect of transcutaneous auricular vagus nerve stimulation on impaired glucose tolerance: a pilot randomized study. BMC Complement Altern Med. 2014;14:203. doi:10.1186/1472-6882-14-203
5. Sailesh KS, Mukkadan JK. Vestibular modulation of endocrine secretions–a review. Int J Res Health Sci. 2014;2(1).
6. Athira MS, Archana R, Sailesh KS, Mukkadan JK. A pilot study on anti-diabetic effect of vestibular stimulation in alloxan induced diabetic model of Wistar albino rats. Res J Pharm Biol Chem Sci. 2015;6(3):1772-1774.
7. Sailesh KS, Archana R, Mukkadan J. Controlled vestibular stimulation: physiological intervention in diabetes care. Asian J Pharm Clin Res. 2015;8(4):315-318.
8. Wardman DL, Fitzpatrick RC. What does galvanic vestibular stimulation stimulate? In: Sensorimotor Control of Movement and Posture. Springer; 2002:119-128.
9. Goldberg JM, Highstein SM, Moschovakis AK, Fernandez C. Inputs from regularly and irregularly discharging vestibular nerve afferents to secondary neurons in the vestibular nuclei of the squirrel monkey. I. An electrophysiological analysis. J Neurophysiol. 1987;58(4):700-718. doi:10.1152/jn.1987.58.4.700
10. Fitzpatrick RC, Day BL. Probing the human vestibular system with galvanic stimulation. J Appl Physiol (1985). 2004;96(6):2301-2316. doi:10.1152/japplphysiol.00008.2004
11. Guerraz M, Day BL. Expectation and the vestibular control of balance. J Cogn Neurosci. 2005;17(3):463-469. doi:10.1162/0898929053279540
12. Kim J, Curthoys IS. Responses of primary vestibular neurons to galvanic vestibular stimulation (GVS) in the anaesthetised guinea pig. Brain Res Bull. 2004;64(3):265-271. doi:10.1016/j.brainresbull.2004.07.008
13. Yamamoto Y, Struzik ZR, Soma R, Ohashi K, Kwak S. Noisy vestibular stimulation improves autonomic and motor responsiveness in central neurodegenerative disorders. Ann Neurol. 2005;58(2):175-181. doi:10.1002/ana.20574
14. Carmona S, Ferrero A, Pianetti G, Escolá N, Arteaga MV, Frankel L. Galvanic vestibular stimulation improves the results of vestibular rehabilitation. Ann N Y Acad Sci. 2011;1233:E1-7. doi:10.1111/j.1749-6632.2011.06269.x
15. Shaabani M, Lotfi Y, Karimian SM, Rahgozar M, Hooshmandi M. Short-term galvanic vestibular stimulation promotes functional recovery and neurogenesis in unilaterally labyrinthectomized rats. Brain Res. 2016;1648(Pt A):152-162. doi:10.1016/j.brainres.2016.07.029
16. Pal S, Rosengren SM, Colebatch JG. Stochastic galvanic vestibular stimulation produces a small reduction in sway in Parkinson's disease. J Vestib Res. 2009;19(3-4):137-142. doi:10.3233/ves-2009-0360
17. Wilkinson D, Ko P, Kilduff P, McGlinchey R, Milberg W. Improvement of a face perception deficit via subsensory galvanic vestibular stimulation. J Int Neuropsychol Soc. 2005;11(7):925-929. doi:10.1017/s1355617705051076
18. Wilkinson D, Zubko O, Degutis J, Milberg W, Potter J. Improvement of a figure copying deficit during subsensory galvanic vestibular stimulation. J Neuropsychol. 2010;4(Pt 1):107-118. doi:10.1348/174866409x468205
19. Berthoud HR, Neuhuber WL. Vagal mechanisms as neuromodulatory targets for the treatment of metabolic disease. Ann N Y Acad Sci. 2019;1454(1):42-55. doi:10.1111/nyas.14182