The impact of vestibular dysfunction on falls and postural instability in individuals with type 2 diabetes with and without diabetic polyneuropathy (#83386)

First submission

Guidance from your Editor

Please submit by **19 Jun 2023** for the benefit of the authors (and your token reward) .

Structure and Criteria
Please read the 'Structure and Criteria' page for general guidance.

Raw data check
Review the raw data.

Image check
Check that figures and images have not been inappropriately manipulated.

If this article is published your review will be made public. You can choose whether to sign your review. If uploading a PDF please remove any identifiable information (if you want to remain anonymous).

Files
Download and review all files from the materials page.

3 Table file(s)
3 Raw data file(s)

Structure and Criteria

Structure your review

The review form is divided into 5 sections. Please consider these when composing your review:

1. **BASIC REPORTING**
2. **EXPERIMENTAL DESIGN**
3. **VALIDITY OF THE FINDINGS**
4. General comments
5. Confidential notes to the editor

You can also annotate this PDF and upload it as part of your review

When ready submit online.

Editorial Criteria

Use these criteria points to structure your review. The full detailed editorial criteria is on your guidance page.

BASIC REPORTING

- Clear, unambiguous, professional English language used throughout.
- Intro & background to show context. Literature well referenced & relevant.
- Structure conforms to PeerJ standards, discipline norm, or improved for clarity.
- Figures are relevant, high quality, well labelled & described.
- Raw data supplied (see PeerJ policy).

EXPERIMENTAL DESIGN

- Original primary research within Scope of the journal.
- Research question well defined, relevant & meaningful. It is stated how the research fills an identified knowledge gap.
- Rigorous investigation performed to a high technical & ethical standard.
- Methods described with sufficient detail & information to replicate.

VALIDITY OF THE FINDINGS

- Impact and novelty not assessed. *Meaningful* replication encouraged where rationale & benefit to literature is clearly stated.
- All underlying data have been provided; they are robust, statistically sound, & controlled.
- Conclusions are well stated, linked to original research question & limited to supporting results.

Standout reviewing tips

The best reviewers use these techniques

Tip	*Example*
Support criticisms with evidence from the text or from other sources	*Smith et al (J of Methodology, 2005, V3, pp 123) have shown that the analysis you use in Lines 241-250 is not the most appropriate for this situation. Please explain why you used this method.*
Give specific suggestions on how to improve the manuscript	*Your introduction needs more detail. I suggest that you improve the description at lines 57- 86 to provide more justification for your study (specifically, you should expand upon the knowledge gap being filled).*
Comment on language and grammar issues	*The English language should be improved to ensure that an international audience can clearly understand your text. Some examples where the language could be improved include lines 23, 77, 121, 128 – the current phrasing makes comprehension difficult. I suggest you have a colleague who is proficient in English and familiar with the subject matter review your manuscript, or contact a professional editing service.*
Organize by importance of the issues, and number your points	*1. Your most important issue* *2. The next most important item* *3. …* *4. The least important points*
Please provide constructive criticism, and avoid personal opinions	*I thank you for providing the raw data, however your supplemental files need more descriptive metadata identifiers to be useful to future readers. Although your results are compelling, the data analysis should be improved in the following ways: AA, BB, CC*
Comment on strengths (as well as weaknesses) of the manuscript	*I commend the authors for their extensive data set, compiled over many years of detailed fieldwork. In addition, the manuscript is clearly written in professional, unambiguous language. If there is a weakness, it is in the statistical analysis (as I have noted above) which should be improved upon before Acceptance.*

The impact of vestibular dysfunction on falls and postural instability in individuals with type 2 diabetes with and without diabetic polyneuropathy

Ina Ejsing Hunnerup Jørgensen [1], **Louise Devantier** [2], **Hatice Tankisi** [3], **Henning Andersen** [1], **Karolina Snopek Khan** [1]
Corresp. 1

[1] Department of Neurology, Aarhus University Hospital, Aarhus, Denmark
[2] Department of Otorhinolaryngology, Department of Clinical Medicine, Aarhus University Hospital, Aarhus, Denmark
[3] Neurophysiology, Department of Clinical Medicine, Aarhus University Hospital, Aarhus, Denmark

Corresponding Author: Karolina Snopek Khan
Email address: kasnop@rm.dk

Aim This study aimed to determine the association between vestibular dysfunction, falls and postural instability in individuals with type 2 diabetes (T2D) with and without diabetic polyneuropathy (DPN) compared to healthy controls. **Methods** This cross-sectional study included individuals with T2D with DPN (n=43), without DPN (n=32) and healthy controls (n=32). Cervical and ocular Vestibular Evoked Myogenic Potentials (VEMP) were recorded, and latencies and amplitudes were determined. DPN was diagnosed based on nerve conduction studies and clinical scores. Postural instability was examined using a static posturographic balance system and falls were recorded retrospectively during the past year.

Results Individuals with T2D experienced more falls (T2D with DPN 12[38%], T2D without DPN 15[35%], controls 5[16%], p=0.04) and had decreased postural stability (T2D with DPN 52[33; 77], T2D without DPN 31[24; 39], controls 26[19; 33]), compared to controls. Individuals with T2D had a greater number of no-responses in oVEMP compared to controls (T2D with DPN, 15[46.9%] T2D without DPN 25[58.1%], controls 9[28.1%], p=0.04). Irrespectively of DPN, fallers with T2D had decreased oVEMP latencies on the right ears when comparing to non-fallers, but not for the left ears (n10[fallers 11±6ms vs non-fallers 20±10ms], p15[fallers 16±7ms vs non-fallers 26±11ms non-fallers), $p<0.05$.

Conclusion Falls and postural instability was more frequent in individuals with T2D compared to controls. Fallers with T2D had vestibular end-organ impairments based on the oVEMP latencies on the right, but not the left ears, irrespective of DPN. Individuals with T2D had more frequent no-response of the oVEMP indicating impaired vestibular nerve function.

PeerJ Journals- Original Article

The impact of vestibular dysfunction on falls and postural instability in individuals with type 2 diabetes with and without diabetic polyneuropathy.

Short running title: Vestibular dysfunction in diabetes

Authors:

Ina Ejsing Hunnerup Jørgensen[1], Louise Devantier[2], Hatice Tankisi[3], Henning Andersen[1], Karolina Snopek Khan[1]

Affiliations:

[1] Department of Neurology, Aarhus University Hospital, Aarhus N, Denmark

[2] Department of Oto-Rhino-Laryngology, Regional Hospital West Jutland, Denmark

[3] Department of Clinical Neurophysiology, Aarhus University Hospital, Aarhus N, Denmark

Corresponding author: Karolina S. Khan, Department of Neurology, Aarhus University Hospital, Palle Juul-Jensens Boulevard 1, DK-8200 Aarhus N, Phone: +45 30279233, Fax: +45 78454242.

email: kasnop@clin.au.dk

Word count: Short running title character count (spaces included): 34, Number of references: 32, Number of tables: 2, Word count abstract: 250, Word count manuscript: 3138 (max 4,000) excluding references and abstract.

23

Abstract

Aim

This study aimed to determine the association between vestibular dysfunction, falls and postural instability in individuals with type 2 diabetes (T2D) with and without diabetic polyneuropathy (DPN) compared to healthy controls.

Methods

This cross-sectional study included individuals with T2D with DPN (n=43), without DPN (n=32) and healthy controls (n=32). Cervical and ocular Vestibular Evoked Myogenic Potentials (VEMP) were recorded, and latencies and amplitudes were determined. DPN was diagnosed based on nerve conduction studies and clinical scores. Postural instability was examined using a static posturographic balance system and falls were recorded retrospectively during the past year.

Results

Individuals with T2D experienced more falls (T2D with DPN 12[38%], T2D without DPN 15[35%], controls 5[16%], p=0.04) and had decreased postural stability (T2D with DPN 52[33; 77], T2D without DPN 31[24; 39], controls 26[19; 33]), compared to controls.

Individuals with T2D had a greater number of no-responses in oVEMP compared to controls (T2D with DPN, 15[46.9%] T2D without DPN 25[58.1%], controls 9[28.1%], p=0.04). Irrespectively of DPN, fallers with T2D had decreased oVEMP latencies on the right ears when comparing to non-fallers, but not for the left ears (n10[fallers 11±6ms vs non-fallers 20±10ms], p15[fallers 16±7ms vs non-fallers 26±11ms non-fallers), $p<0.05$.

Conclusion

Falls and postural instability was more frequent in individuals with T2D compared to controls. Fallers with T2D had vestibular end-organ impairments based on the oVEMP latencies on the

47 right, but not the left ears, irrespective of DPN. Individuals with T2D had more frequent no-
48 response of the oVEMP indicating impaired vestibular nerve function.

49

50 **Key Words**

51 Type 2 diabetes, Diabetic polyneuropathy, Vestibular Evoked Myogenic Potential, Falls,
52 Postural instability

Introduction

Individuals with diabetes have an increased risk of falls and postural instability [1,2], which may result in impaired mobility, fall-related injuries, and increased mortality [3]. To prevent falling and maintaining postural stability, proper function of the sensory, motor, visual and vestibular system is required [4,5]. Individuals with type 2 diabetes have a higher incidence of vestibular dysfunction, and even more so in individuals with diabetic polyneuropathy [6–9]. Therefore, the influence of dysfunction of the vestibular system and diabetic polyneuropathy on falls is of great importance.

Vestibular dysfunction may present as a subclinical vestibular neuropathy [10]. In diabetes, function of the vestibular system has been studied using cervical and ocular Vestibular Evoked Myogenic Potential (VEMP) including individuals both with and without symptoms of vestibular dysfunction. cVEMP reflects ipsilateral sacculus and inferior vestibular nerve function whereas oVEMP reflects contralateral utriculus and superior vestibular nerve function [11].

Studies have previously examined vestibular function in individuals with diabetes using VEMP, but with conflicting results. Bektas et al. found no difference in cVEMP responses between individuals with diabetes with and without diabetic polyneuropathy (DPN) and healthy controls [12]. Other studies found decreased cVEMP and oVEMP amplitudes in individuals with diabetes compared to healthy controls [9,13], whereas others found prolonged cVEMP [10,14] and oVEMP latencies [10].

To date, no study has investigated vestibular dysfunction and the possible association to DPN and an increased risk of falls and postural instability in individuals with type 2 diabetes.

Therefore, the aim of our study was to assess the association between vestibular dysfunction and falls as well as postural instability in individuals with type 2 diabetes with and without diabetic polyneuropathy compared to healthy control individuals.

Methods

This study was cross-sectional including data from a subpopulation of individuals evaluated and described in an earlier published study conducted at Aarhus University Hospital in Denmark between August 2017, and November 2018 [2]. The study protocol was registered with the Danish Data Protection Agency (approval no.:1-16-02-563-16) and approved by the Central Denmark Region Committees on Health Research Ethics (approval no.: 1-10-72-282-16). Written informed consent was acquired from all participants, and all work was done in accordance with the Declaration of Helsinki (1964).

Individuals with type 2 diabetes were included if they were between 18-80 years and had a diagnosis of type 2 diabetes based on the 1999 WHO criteria [15]. This is described in more detail elsewhere [2].

Participants were excluded if they had a history of transplantation, stroke or ischemic heart disease, or other causes of polyneuropathy, amputation or severe deformity of the lower extremities, musculoskeletal disease, peripheral vascular disease (including abnormal pedal pulses, cool skin, and abnormal skin color), blindness, other neurological or endocrine diseases, and symptomatic osteoarthritis.

The control group was composed of healthy volunteers who were recruited by local advertising. Healthy controls had normal glucose tolerance, normal blood pressure and normal lipid profiles.

DPN assessment

Individuals with diabetes were assigned to the DPN group if meeting the Toronto diagnostic criteria for confirmed DPN [16] defined as an abnormality in nerve conduction studies (NCS) and a symptom and/or a sign of DPN based on the validated Toronto Clinical Neuropathy Score [17]. Motor NCS in peroneal and tibial nerves and sensory NCS in sural nerves, including the distal

segment, were performed using standard surface electrodes techniques [18]. The results were compared with laboratory controls. At least two abnormal nerves, of which one was the sural nerve, were required for abnormality in NCS [18].

Clinical and biochemical assessment

All participants were screened by a physician, including evaluation of the previous medical history. Information concerning body height, weight, and waist circumference was collected, and body mass index (BMI) was calculated. Information on disease duration, use of insulin, and oral anti-diabetes agents was obtained. Furthermore, blood samples were collected and analyzed for HbA_{1c}. A physician assessed visual acuity using Snellen's test. Sway was measured at eight sessions of 32 seconds using a validated static posturographic balance system (Tetrax, IA, Israel) [2,19].

Information on fall history was collected by a physician and a fall was defined as "an event that results in a person coming to a rest unintentionally on the ground or another level" [20]. All participants reported the frequency of falls over the past year. The physician ensured that all participants concurred on the definition of a fall excluding the following causes of falling: vasovagal and cardiogenic syncopal episodes, hypoglycemia, mechanical or external forces.

VEMP

Eclipse EP25 Evoked Potential System (Interacoustics A/S, Denmark) was used for all examinations. Before attaching the electrodes, the skin was carefully cleansed, securing a skin impedance below 10 kΩ.

Cervical VEMP (cVEMP)

Subjects were seated upright with the head rotated opposite to the side of stimulation. The active electrode (Neuroline 720 Single Patient Surface Electrodes, 8500060, Ambu•, Denmark) was

placed on the upper third part of the sternocleidomastoid muscle. The reference electrode was placed on the jugular notch and the ground electrode on the forehead.

To ensure and maintain a tonic contraction of 50-150 μV of the sternocleidomastoid muscle throughout the trials, electromyography information was displayed on a computer monitor, aiding in controlling the contraction intensity. EMG scaling (amplitude correction) was performed. In-earphone plugs (3M^{TM} E-A-RLINK Insert Eartips) were used for air-conducted rarefaction stimulation and one control trial was run at 80 dB nHL, and a minimum of two trials were run at 100 dB nHL. The latencies and amplitudes for p13 and n23 peaks were recorded for each ear.

Ocular VEMP (oVEMP)

Subjects were seated upright and asked to keep a 30° upward gaze. The active electrode was placed 0.5 cm below the eye, parallel to the lateral half of the lower eyelid, and the medial corner of the active electrode was placed below the eye at the midline of the eye. A reference electrode was placed on the upper part of the forehead and the ground electrode below the reference electrode. A bone conductor (B-81 modified with a double headband to deliver more energy to the bone, Interacoustics®, Denmark) was placed on the mastoid process and used for alternating polarity stimulation in one control trial at 50 dB nHL and a minimum of two trials at 70 dB nHL. The latencies and amplitudes for n10 and p15 peaks were recorded for each ear.

Statistical analysis

Statistical analyses were conducted using Stata I/C version 14.2. (StataCorp, USA). The level of significance was set at $p<0.05$. Baseline data concerning the characteristics of individuals are presented as medians (interquartile interval) and compared across the groups by Kruskal-Wallis test. Data were compared by ANOVA if presented as frequencies and proportions for categorical variables. The sum of sway was calculated for all eight positions and as the sum of the four neutral

(no pillow eyes open stability index (ST), no pillow eyes closed ST, pillow eyes open ST, pillow eyes closed ST) and four head tilt/turn (head right, head left, head back, head forward).

Results

A total of 107 individuals were included in the present study and consisted of three groups: type 2 diabetes individuals with DPN (n=43), type 2 diabetes individuals without DPN (n=32), and healthy control individuals (n=32). Clinical and biochemical characteristics are shown in Table 1. There was no difference in age between the three groups. Individuals with type 2 diabetes were heavier, had an increased BMI, waist circumference and had increased postural instability when compared to healthy control. Individuals with DPN had an increased diabetes duration, HbA1c levels, use of insulin and postural instability compared to individuals with diabetes without DPN. Within the past year, individuals with type 2 diabetes reported a higher number of falls with compared to healthy controls (p=0.04), however there was no significant difference in the number of reported falls when comparing individuals with and without DPN (p=0.71) Table 1.

Individuals with diabetes had increased amplitudes in cVEMP in the left ears when compared to healthy controls. Comparing all individuals with diabetes to healthy controls, as well as comparing individuals with diabetes with and without DPN, no difference was found for the other cVEMP and oVEMP measurements (Table 2).

Comparing all individuals with diabetes to healthy controls there was a greater number of no-responses in oVEMP (p=0.04), irrespective of DPN. No difference was found in the number of no responses in cVEMP (Table 2).

Fallers vs. non-fallers

In Table 3, VEMP parameters for left and right ears from individuals with type 2 diabetes and with falls (n=27) versus no falls (n=48) are presented. Fallers had shorter oVEMP (n10 and p15)

latencies compared to non-fallers, significant for right ears and with similar tendency for left ears, however not significant. In contrast, no significant difference was found in cVEMP (p13-n23) and oVEMP (n10-p15) amplitudes, nor in cVEMP (p13 and n23) latencies. No difference was found in the number of no responses in cVEMP and oVEMP when comparing fallers and non-fallers.

Discussion

This cross-sectional study examined the association between vestibular dysfunction, falls and postural instability in individuals with type 2 diabetes with and without DPN compared to healthy controls. Individuals with diabetes reported a higher number of falls within the previous year, irrespective of DPN. Individuals with diabetes had increased postural instability, which was even more pronounced in individuals with DPN. In individuals with type 2 diabetes, fallers had shorter oVEMP (n10 and p15) latencies on right ears compared to non-fallers irrespective of DPN. Similar tendencies were seen for left ears, however not significant. Individuals with type 2 diabetes had a greater number of no-responses in oVEMP compared to healthy controls, irrespective of DPN.

To our knowledge, this is the first study examining vestibular dysfunction using cVEMP and oVEMP in relation to falls and postural instability in individuals with type 2 diabetes with and without diabetic polyneuropathy compared to healthy controls.

In previous studies of falls and postural instability, individuals with diabetes and DPN had more vestibular dysfunction combined with an increased risk of falls [7,8]. Additionally, individuals with diabetes with and without DPN had more postural instability compared to healthy controls, and in contrast to our findings fallers with diabetes had a greater incidence of peripheral neuropathy [2,22–25]. Balance is a complex skill requiring cooperation of somatosensory, vestibular, and visual systems together with muscular and cognitive systems [4]. In individuals with diabetes, the cause of

falls is most likely multifactorial as diabetes may affect one or more of these systems [4]. In our study, individuals with diabetes had a greater number of no-responces on the Ovemp. No-responses can be an indicator of impaired nerve function, which is seen in more advanced stages of nerve dysfunction [21], however, the number of no-responses was not greater in the DPN group.

Several studies have examined vestibular function using VEMP in individuals with type 2 diabetes [9,10,13], in individuals with type 1 diabetes [14], and in individuals with non-insulin-dependent diabetes mellitus [12]. Some of these studies only examined the vestibular function using cVEMP and not oVEMP which is inadequate as cVEMP is believed to reflect the ipsilateral sacculus and inferior vestibular nerve function, whereas oVEMP reflect the contralateral utriculus and superior vestibular nerve function [11].

Studies on VEMP responses in individuals with diabetes show conflicting results. This might be attributed to the smaller sample sizes and a lack of homogeneity of clinical and biochemical characteristics including age, diabetes duration, and HbA1c levels. Some studies [9,13] reported decreased cVEMP and oVEMP amplitudes in individuals with diabetes compared to healthy controls. Contrary to their findings, but in line with other previous studies [10,12,14], we found no differences in cVEMP (p13-n23) and oVEMP (n10-p15) amplitudes. Other studies [10,14] found prolonged cVEMP (p13-n23) latencies in individuals with diabetes compared to healthy controls. In contrast to these findings, but in line with previous studies [9,12,13], we found no differences in cVEMP (p13 and n23) latencies. Many of our study participants have newly diagnosed diabetes with only a mild degree of DPN. This can possibly explain, why we found no differences in any

of the VEMP-parameters when comparing all three groups and when comparing individuals with diabetes with and without DPN.

In diabetic animals, various structural and functional changes in the vestibular system have been found, including overproduction of extracellular matrix and increased lipid droplets in the otolith organs, degeneration of type 1 hair cells, thinning of the myelin covering the vestibulocochlear nerve and smaller diameter of the axonal fibers [26,27]. Human studies have shown abnormalities of the vestibulo-ocular and optokinetic reflex, and deficits in gaze-holding in individuals with type 2 diabetes compared to individuals without type 2 diabetes [28]. These structural and functional changes may compromise vestibular information leading to inadequate motor responses and thereby ultimately a fall. Vestibular dysfunction was more prevalent in individuals with diabetes [7], and vestibular dysfunction was shown independently to increase the odds of falling more than two times, even after adjusting for diabetic polyneuropathy (DPN) [8]. In our study, fallers with diabetes exhibited poorer vestibular function compared to non-fallers with diabetes.

Limitations and strengths

There are several limitations to our study: 1) Due to the cross-sectional design, we cannot determine if the association between diabetes and vestibular function is causal, 2) Numbers of falls within the past year were based solely on the recollection of participants. This might have introduced recall bias leading to incorrect numbers of falls. However, we chose one year to rule out seasonal influence on fall incidences [29], 3) Only individuals fending for themselves and living relatively close to Aarhus University Hospital were included, which probably has left out individuals with more severe diabetes thereby introducing selection bias.

Main strengths of our study are: 1) The same physician examined all individuals regarding VEMP-testing, measuring of sway, clinical and DPN assessment, which secured consistency in the examinations, 2) DPN diagnosis was confirmed by both nerve conduction studies and clinical examination and 3) reliable and validated methods were applied in the examination of the vestibular function and postural stability [19,30,31]. Furthermore, a significant strength of our study is the use of VEMP-testing for measuring vestibular function being a direct assessment of the vestibular function. Other studies [7,8] have used the modified Romberg Test of Standing Balance. This testing tool compared to VEMP-testing, is a poor screening tool for vestibular dysfunction [32]. Contrary to our study, some previous studies assessing falling and postural instability in individuals with diabetes and DPN did not include a healthy control group or did not compare results between individuals with diabetes with and without DPN, which impairs the evaluation of the impact of both diabetes and DPN per se. Other studies did not clearly define a fall or did not exclude other causes of falls.

Future studies should include larger sample sizes with a prospective study design. Furthermore, future studies should consider using VEMP-testing for evaluation of vestibular function and its relation to fall incidents in individuals with longer diabetes duration and more severe disease.

In summary, falls and postural instability was more frequent in individuals with type 2 diabetes compared to healthy controls. No-responses for the oVEMP latencies were more frequent in individuals with type 2 diabetes compared to healthy controls, demonstrating impaired vestibular end nerve function, irrespective of DPN.

Declaration of interest

None of the authors has any conflict of interest to disclose. Research reported in this publication is part of the International Diabetic Neuropathy Consortium (IDNC) research programme, which is supported by a Novo Nordisk Foundation Challenge Programme grant (Grant number NNF14OC0011633) and Aarhus University. Aarhus University receives funding for other studies from companies in the form of research grants to (and administered by) Aarhus University. None of these studies has any relation to the present study.

Disclosure of ethical statement

Approval of the research protocol: The study protocol was registered with the Danish Data Protection Agency (approval no.:1-16-02-563-16) and approved by the Central Denmark Region Committees on Health Research Ethics (approval no.: 1-10-72-282-16).

Informed consent: Written informed consent was acquired from all participants.

Approval date: The Danish Data Protection Agency and the Central Denmark Region Committees on Health Research Ethics approved the study in august 2017.

Conflicts of interest: The authors declare no conflicts of interest

References

1. Yang, Y., Hu, X., Zhang, Q. & Zou, R. Diabetes mellitus and risk of falls in older adults: a systematic review and meta-analysis. *Age Ageing* **45**, 761–767 (2016).
2. Khan, K. S. *et al.* Falls in individuals with type 2 diabetes; a cross-sectional study on the impact of motor dysfunction, postural instability and diabetic polyneuropathy. *Diabetic medicine.* e14470 (2020) doi:10.1111/dme.14470.
3. Tilling, L. M., Darawil, K. & Britton, M. Falls as a complication of diabetes mellitus in older people. *J. Diabetes Complications* **20**, 158–162 (2006).
4. Hewston, P. & Deshpande, N. Falls and Balance Impairments in Older Adults with Type 2 Diabetes: Thinking Beyond Diabetic Peripheral Neuropathy. *Can. J. diabetes* **40**, 6–9 (2015).
5. Grace Gaerlan, M., Alpert, P. T., Cross, C., Louis, M. & Kowalski, S. Postural balance in young adults: the role of visual, vestibular and somatosensory systems. *Journal of the American Academy of Nurse Practitioners.* vol. 24 375–381 (2012).
6. Li, J., Jiang, J., Zhang, Y., Liu, B. & Zhang, L. Impairment of Vestibular Function and Balance Control in Patients with Type 2 Diabetes. *Audiology & neuro-otology.* vol. 24 154–160 (2019).
7. Agrawal, Y., Carey, J. P., Della Santina, C. C., Schubert, M. C. & Minor, L. B. Disorders of balance and vestibular function in US adults: data from the National Health and Nutrition Examination Survey, 2001-2004. *Archives of internal medicine.* vol. 169 938–944 (2009).
8. Agrawal, Y., Carey, J. P., Della Santina, C. C., Schubert, M. C. & Minor, L. B. Diabetes, vestibular dysfunction, and falls: analyses from the National Health and Nutrition

Examination Survey. *Otology & neurotology.* vol. 31 1445–1450 (2010).

9. Ward, B. K. *et al.* Characterization of Vestibulopathy in Individuals with Type 2 Diabetes Mellitus. *Otolaryngology--head and neck surgery.* vol. 153 112–118 (2015).

10. Konukseven, O. *et al.* Electrophysiologic vestibular evaluation in type 2 diabetic and prediabetic patients: Air conduction ocular and cervical vestibular evoked myogenic potentials. *International journal of audiology.* vol. 54 536–543 (2015).

11. Rosengren, S. M. & Kingma, H. New perspectives on vestibular evoked myogenic potentials. *Current opinion in neurology* vol. 26 74–80 (2013).

12. Bektas, D. *et al.* VEMP responses are not affected in non-insulin-dependent diabetes mellitus patients with or without polyneuropathy. *Acta oto-laryngologica* vol. 128 768–771 (2008).

13. Kalkan, M., Bayram, A., Gökay, F., Cura, H. S. & Mutlu, C. Assessment of vestibular-evoked myogenic potentials and video head impulse test in type 2 diabetes mellitus patients with or without polyneuropathy. *European archives of oto-rhino-laryngology.* vol. 275 719–724 (2018).

14. Kamali, B. *et al.* Effects of diabetes mellitus type I with or without neuropathy on vestibular evoked myogenic potentials. *Acta medica iranica.* vol. 51 107–112 (2013).

15. American Diabetes Association. Diagnosis and classification of diabetes mellitus. *Diabetes Care* **34 Suppl 1**, S62–S69 (2011).

16. Tesfaye, S. *et al.* Diabetic neuropathies: update on definitions, diagnostic criteria, estimation of severity, and treatments. *Diabetes Care* **33**, 2285–2293 (2010).

17. Bril, V. & Perkins, B. A. Validation of the Toronto Clinical Scoring System for Diabetic Polyneuropathy. *Diabetes Care* **25**, 2048 LP – 2052 (2002).

18. Tankisi, H., Pugdahl, K., Beniczky, S., Andersen, H. & Fuglsang-Frederiksen, A. Evidence-based recommendations for examination and diagnostic strategies of polyneuropathy electrodiagnosis. *Clin. Neurophysiol. Pract.* **4**, 214–222 (2019).

19. Christensen, I. K. *et al.* Validation of Posturographic Measurements in Adolescents. *Otol. Neurotol.* **39**, e568–e574 (2018).

20. WHO. WHO global report on falls prevention in older age. (2008).

21. Taylor, R. L., Welgampola, M. S., Nham, B. & Rosengren, S. M. Vestibular-Evoked Myogenic Potential Testing in Vestibular Localization and Diagnosis. *Semin. Neurol.* **40**, 18–32 (2020).

22. MacGilchrist, C. *et al.* Lower-limb risk factors for falls in people with diabetes mellitus. *Diabet. Med.* **27**, 162–168 (2010).

23. Allet, L., Kim, H., Ashton-Miller, J., De Mott, T. & Richardson, J. K. Step length after discrete perturbation predicts accidental falls and fall-related injury in elderly people with a range of peripheral neuropathy. *J. Diabetes Complications* **28**, 79–84 (2014).

24. Emam, A. A., Gad, A. M., Ahmed, M. M., Assal, H. S. & Mousa, S. G. Quantitative assessment of posture stability using computerised dynamic posturography in type 2 diabetic patients with neuropathy and its relation to glycaemic control. *Singapore Med. J.* **50**, 614–618 (2009).

25. Vaz BSc, M. M. *et al.* Postural Control and Functional Strength in Patients With Type 2 Diabetes Mellitus With and Without Peripheral Neuropathy. *Arch. Phys. Med. Rehabil.* **94**, 2465–2470 (2013).

26. Myers, S. F. & Ross, M. D. Morphological evidence of vestibular pathology in long-term experimental diabetes mellitus. II. Connective tissue and neuroepithelial pathology. *Acta*

oto-laryngologica vol. 104 40–49 (1987).

27. Myers, S. F., Tormey, M. C. & Akl, S. Morphometric analysis of horizontal canal nerves of chronically diabetic rats. *Otolaryngol. - Head Neck Surg.* **120**, 174–179 (1999).

28. Nicholson, M., King, J., Smith, P. F. & Darlington, C. L. Vestibulo-ocular, optokinetic and postural function in diabetes mellitus. *Neuroreport : an international journal for the rapid communication of research in neuroscience.* vol. 13 153–157 (2002).

29. Magota, C. *et al.* Seasonal ambient changes influence inpatient falls. *Age Ageing* **46**, 513–517 (2017).

30. Nguyen, K. D., Welgampola, M. S. & Carey, J. P. Test-retest reliability and age-related characteristics of the ocular and cervical vestibular evoked myogenic potential tests. *Otol. Neurotol.* **31**, 793–802 (2010).

31. Isaradisaikul, S. *et al.* Reliability of vestibular evoked myogenic potentials in healthy subjects. *Otology & neurotology : an international forum for otology, neurotology, and skull base surgery : official publication of the American Otological Society, American Neurotology Society, European Academy of Otology and neurology.* vol. 29 542–544 (2008).

32. Jacobson, G. P. *et al.* Insensitivity of the 'Romberg test of standing balance on firm and compliant support surfaces' to the results of caloric and VEMP tests. *Ear and hearing : the official journal of the American Auditory Society.* vol. 32 e1–e5.

Table 1(on next page)

Clinical and biochemical characteristics

NA: Not Applicable †p-value comparing individuals with diabetes and healthy controls, p-value§ comparing individuals with diabetes without DPN and individuals with DPN. Categorical data are frequencies (%) and compared by ANOVA. Continuous data are medians (p25; p75) and compared across the groups by Kruskal-Wallis test. *DPN* diabetic polyneuropathy *BMI* body mass index, *ST* stability index

Table Legends

Table 1:
NA: Not Applicable
†p-value comparing individuals with diabetes and healthy controls, p-value§ comparing individuals with diabetes without DPN and individuals with DPN.
Categorical data are frequencies (%) and compared by ANOVA.
Continuous data are medians (p25; p75) and compared across the groups by Kruskal-Wallis test.
DPN diabetic polyneuropathy *BMI* body mass index, *ST* stability index

Table 2:
†p- value comparing individuals with diabetes and healthy controls §p-value comparing individuals with diabetes without DPN and individuals with DPN.
Continuous data are means (SD) and compared across the groups by ANOVA.
DPN diabetic polyneuropathy, *cVEMP* cervical vestibular-evoked myogenic potential, *oVEMP* ocular vestibular-evoked myogenic potential, *ms* millisecond, *μV* microvolts, SCALED: The VEMP amplitude is scaled/normalized in proportion to the tonic EMG activity. (Averaged VEMP response amplitude (μV) divided by root mean square of pre-stimulation EMG activity (μV))

Table 3:
Continuous data are mean (SD)
cVEMP cervical vestibular-evoked myogenic potential, *oVEMP* ocular vestibular-evoked myogenic potential, *ms* millisecond, *μV* microvolts, SCALED: The VEMP amplitude is scaled/normalized in proportion to the tonic EMG activity. (Averaged VEMP response amplitude (μV) divided by root mean square of pre-stimulation EMG activity (μV))

42
43
44
45 **Table 1. Clinical and biochemical characteristics**
46

	Control Individuals	Individuals with type 2 diabetes			
	n=32	without DPN n=32	with DPN n=43	p-value†	p-value§
Age, years	64 (56; 67)	65 (58; 70)	64 (60; 68)	0.37	0.87
Female gender (n,(%))	14 (44)	17 (53)	13 (30)		
Height (cm)	175 (170; 179)	169 (164; 175)	177 (164; 180)	0.23	0.01
Weight (kg)	84 (75; 96)	94 (75; 102)	105 (93; 116)	0.01	0.01
BMI (kg/m2)	28 (25; 31)	31 (27; 36)	35 (30; 37)	0.01	0.01
Waist circumference					
Females (cm)	90 (80; 110)	105 (95; 113)	116 (106; 127)	0.03	0.03
Males (cm)	103 (96; 110)	109 (106; 124)	120 (112; 126)	0.01	0.07
Diabetes profile					
Diabetes duration (years)	NA	7 (6; 10)	10 (6; 18)		0.02
HbA1c, (mmol/mol)	37 (34; 39)	48 (45; 55)	56 (48; 68)	0.01	0.02
Insulin (Yes) (n,(%))	NA	3 (9)	22 (51)		0.01
Oral anti-diabetes agents (n,(%))	NA	27 (84)	38 (88)		0.65
Fallers (n,(%))	5 (16)	12 (38)	15 (35)	0.04	0.71
Instability index					
Average ST in neutral positions	23 (17; 28)	28 (22; 33)	41 (29; 64)	0.01	0.01
Average ST in tilt/turn positions	28 (22; 38)	34 (25; 42)	60 (38; 94)	0.01	0.01
Average ST in all positions	26 (19; 33)	31 (24; 39)	52 (33; 77)	0.01	0.01

47
48
49
50
51
52
53
54
55
56

Table 2. Vestibular-evoked myogenic potential parameters for right and left ears in each group

	Control Individuals	Individuals with type 2 diabetes			
	n=32	without DPN n=32	with DPN n=43	p-value†	p-value§
Right ear					
cVEMP p13 (ms)	15 (10)	15 (9)	14 (9)	0.63	0.62
cVEMP n23 (ms)	23 (13)	23 (12)	21 (12)	0.72	0.52
oVEMP n10 (ms)	14 (9)	16 (10)	20 (10)	0.16	0.32
oVEMP p15 (ms)	19 (10)	21 (12)	25 (11)	0.14	0.35
cVEMP (p13- n23) (μV)	64 (48)	62 (40)	48 (41)	0.30	0.17
cVEMP (p13- n23) SCALED	1 (1)	1 (0)	1 (2)	0.33	0.13
oVEMP (n10-p15) (μV)	12 (9)	15 (14)	14(18)	0.64	0.14
Left ear					
cVEMP p13 (ms)	15 (9)	14 (5)	13 (7)	0.23	0.74
cVEMP n23 (ms)	23 (13)	21 (9)	20 (11)	0.23	0.56
oVEMP n10 (ms)	14 (9)	17 (10)	14 (12)	0.62	0.37
oVEMP p15 (ms)	19 (11)	23 (13)	18 (15)	0.72	0.32
cVEMP (p13- n23)(μV)	73 (58)	56 (31)	47 (37)	0.02	0.25
cVEMP (p13- n23) SCALED	1 (1)	1 (0)	1 (2)	0.76	0.96
oVEMP (n10-p15) (μV)	12 (9)	15 (14)	14 (18)	0.51	0.80
No response in total oVEMP (n, (%))	9 (28)	15 (47)	25 (58)	0.04	0.33
No response in total cVEMP (n, (%))	4 (13)	4 (13)	7 (16)	0.78	0.65

Table 3. Vestibular-evoked myogenic potential parameters for left and right ears in fallers and non-fallers with diabetes

	Individuals with type 2 diabetes		
	No Falls n=48	≥1 Fall n=27	p-value
Right ears			
cVEMP p13 (ms)	15 (9)	13 (9)	0.18
cVEMP n23 (ms)	23 (12)	19 (12)	0.22
oVEMP n10 (ms)	20 (10)	11(6)	0.02
oVEMP p15 (ms)	26 (11)	16 (7)	0.02
cVEMP (p13- n23) (μV)	56 (37)	51 (47)	0.62
cVEMP (p13- n23) SCALED	1 (1)	1 (1)	0.53
oVEMP (n10-p15) (μV)	14 (13)	11 (7)	0.40
No response in oVEMP (n, (%))	23 (48)	19 (68)	0.09
No response in cVEMP (n, (%))	11(15)	7 (21)	0.40
Left ears			
cVEMP p13 (ms)	14 (6)	12 (7)	0.41
cVEMP n23 (ms)	21 (9)	19 (11)	0.44
oVEMP n10 (ms)	17 (12)	9 (5)	0.07
oVEMP p15 (ms)	23 (15)	13 (8)	0.09
cVEMP (p13- n23) (μV)	49 (31)	53 (41)	0.62
cVEMP (p13- n23) SCALED	1 (1)	1 (1)	0.63
oVEMP (n10-p15) (μV)	14 (14)	14 (22)	0.98
No-responses			
oVEMP (n, (%))	27 (56)	20 (71)	0.19
cVEMP (n, (%))	10 (13)	7 (21)	0.30

Table 2(on next page)

Vestibular-evoked myogenic potential parameters for right and left ears in each group

†p- value comparing individuals with diabetes and healthy controls §p-value comparing individuals with diabetes without DPN and individuals with DPN. Continuous data are means (SD) and compared across the groups by ANOVA. *DPN* diabetic polyneuropathy, *cVEMP* cervical vestibular-evoked myogenic potential, *oVEMP* ocular vestibular-evoked myogenic potential, *ms* millisecond, *μV* microvolts, SCALED: The VEMP amplitude isscaled/normalizedin proportion to the tonicEMGactivity. (Averaged VEMP response amplitude (μV) divided by root mean square of pre-stimulationEMG activity (μV))

Table 2. Vestibular-evoked myogenic potential parameters for right and left ears in each group

	Control Individuals	Individuals with type 2 diabetes			
	n=32	without DPN n=32	with DPN n=43	p-value†	p-value§
Right ear					
cVEMP p13 (ms)	15 (10)	15 (9)	14 (9)	0.63	0.62
cVEMP n23 (ms)	23 (13)	23 (12)	21 (12)	0.72	0.52
oVEMP n10 (ms)	14 (9)	16 (10)	20 (10)	0.16	0.32
oVEMP p15 (ms)	19 (10)	21 (12)	25 (11)	0.14	0.35
cVEMP (p13- n23) (μV)	64 (48)	62 (40)	48 (41)	0.30	0.17
cVEMP (p13- n23) SCALED	1 (1)	1 (0)	1 (2)	0.33	0.13
oVEMP (n10-p15) (μV)	12 (9)	15 (14)	14(18)	0.64	0.14
Left ear					
cVEMP p13 (ms)	15 (9)	14 (5)	13 (7)	0.23	0.74
cVEMP n23 (ms)	23 (13)	21 (9)	20 (11)	0.23	0.56
oVEMP n10 (ms)	14 (9)	17 (10)	14 (12)	0.62	0.37
oVEMP p15 (ms)	19 (11)	23 (13)	18 (15)	0.72	0.32
cVEMP (p13- n23)(μV)	73 (58)	56 (31)	47 (37)	0.02	0.25
cVEMP (p13- n23) SCALED	1 (1)	1 (0)	1 (2)	0.76	0.96
oVEMP (n10-p15) (μV)	12 (9)	15 (14)	14 (18)	0.51	0.80
No response in total oVEMP (n, (%))	9 (28)	15 (47)	25 (58)	0.04	0.33
No response in total cVEMP (n, (%))	4 (13)	4 (13)	7 (16)	0.78	0.65

Table 3(on next page)

Vestibular-evoked myogenic potential parameters for left and right ears in fallers and non-fallers with diabetes

Continuous data are mean (SD) *cVEMP* cervical vestibular-evoked myogenic potential, *oVEMP* ocular vestibular-evoked myogenic potential, *ms* millisecond, *μV* microvolts, SCALED: The VEMP amplitude isscaled/normalizedin proportion to the tonicEMGactivity. (Averaged VEMP response amplitude (μV) divided by root mean square of pre-stimulationEMG activity (μV))

Table 3. Vestibular-evoked myogenic potential parameters for left and right ears in fallers and non-fallers with diabetes

	Individuals with type 2 diabetes		
	No Falls n=48	≥1 Fall n=27	p-value
Right ears			
cVEMP p13 (ms)	15 (9)	13 (9)	0.18
cVEMP n23 (ms)	23 (12)	19 (12)	0.22
oVEMP n10 (ms)	20 (10)	11(6)	0.02
oVEMP p15 (ms)	26 (11)	16 (7)	0.02
cVEMP (p13- n23) (μV)	56 (37)	51 (47)	0.62
cVEMP (p13- n23) SCALED	1 (1)	1 (1)	0.53
oVEMP (n10-p15) (μV)	14 (13)	11 (7)	0.40
No response in oVEMP (n, (%))	23 (48)	19 (68)	0.09
No response in cVEMP (n, (%))	11(15)	7 (21)	0.40
Left ears			
cVEMP p13 (ms)	14 (6)	12 (7)	0.41
cVEMP n23 (ms)	21 (9)	19 (11)	0.44
oVEMP n10 (ms)	17 (12)	9 (5)	0.07
oVEMP p15 (ms)	23 (15)	13 (8)	0.09
cVEMP (p13- n23) (μV)	49 (31)	53 (41)	0.62
cVEMP (p13- n23) SCALED	1 (1)	1 (1)	0.63
oVEMP (n10-p15) (μV)	14 (14)	14 (22)	0.98
No-responses			
oVEMP (n, (%))	27 (56)	20 (71)	0.19
cVEMP (n, (%))	10 (13)	7 (21)	0.30