



# Auditory and Vestibular Functioning in Individuals with Type-2 Diabetes Mellitus: A Systematic Review

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## Abstract

**Introduction** Diabetes mellitus is a metabolic disease associated with a rise in the level of blood glucose. Individuals with diabetes mellitus are more likely to develop hearing loss, tinnitus, and dizziness due to macro- and microvascular complications. The extent to which auditory and vestibular functions are impaired in individuals with type-2 diabetes mellitus is still under debate.

**Objective** To systematically review studies focusing on auditory and vestibular functions in individuals with type-2 diabetes mellitus.

**Data Synthesis** A search was conducted in the PubMed, MedlinePlus, Ingenta Connect and Google Scholar databases for articles published until June 2019. A total of 15,980 articles were primarily retrieved, 33 of which were shortlisted based on the inclusion criteria set by the investigators for the systematic review. Out of 33 full-length articles, 26 evaluated the functioning of the auditory system, while 7 evaluated the functioning of the vestibular system. Most studies related to auditory functioning reported a significant effect of type-2 diabetes mellitus on the peripheral auditory system, whereas studies on vestibular functioning reported no significant effect of diabetes mellitus on the functioning of the peripheral vestibular end-organ.

**Conclusion** Overall, the results of various audiological and peripheral vestibular tests reveal distinctive peripheral and/or central auditory and vestibular end-organ impairments in individuals with type-2 diabetes mellitus.

## Keywords

- ▶ hearing loss
- ▶ diabetes mellitus
- ▶ cochlea
- ▶ inner ear
- ▶ vertigo

## Introduction

Diabetes is a complex systemic disorder usually characterized by chronic hyperglycemia, with disturbances in the protein, carbohydrate, and fat metabolism that result from irregularities

with the insulin hormone, which maintains the regulation of blood glucose within the body.<sup>1</sup> According to the 8th edition of the International Diabetes Federation's (IDF), Diabetes Atlas,<sup>1</sup> in 2017, 425 million people worldwide had diabetes mellitus (DM), and 352 million people were at risk of developing

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type-2 DM (DM2). It is predicted that diabetes may affect 72.9 million individuals in India by 2045.<sup>1</sup> Diabetes mellitus is usually diagnosed based on the results of tests such as the fasting plasma glucose (FPG) test, the 2-hour postprandial glucose (2-hour PG) test, the oral glucose tolerance test (OGTT), the glycated hemoglobin (HbA1c) test, or a random plasma glucose test.<sup>2</sup> Overall, these tests are equally appropriate for diagnostic purposes; hence, they can be repeated for both screening and diagnosis of individuals. Based on the etiological factors, individuals with DM are classified as having type-1 DM (DM1), also called insulin-dependent DM (IDDM), or DM2, also called non-insulin-dependent DM (NIDDM). Type-1 DM is characterized by  $\beta$ -cell destruction due to autoimmune processes resulting in insulin deficiency,<sup>3</sup> and DM2, the most common form of DM, is characterized by factors that include hyperglycemic crisis, insulin resistance, and relative insulin deficiency.<sup>4</sup> Diabetes has many potential subclinical complications, such as retinopathy, nephropathy, and peripheral neuropathy, which diminish the health-related quality of life of the individuals affected. Disease-specific medical factors, such as the type, the duration, the treatment program, the level of glycemic control, and the presence of additional vascular complications have an effect on the complications that arise as a result of DM.<sup>5</sup>

### Type2 Diabetes Mellitus

Approximately 90% of all individuals with DM have DM2, which makes it a major public health issue.<sup>1</sup> Type-2 DM can be attributed to intra-abdominal obesity and sedentary lifestyle interrelated with insulin resistance. In addition, conditions such as hypertension and dyslipidemia are often present in individuals with DM2. The American Diabetes Association (ADA) recommends the use of validated tools to screen asymptomatic adults or a simple informal assessment regarding the risk factors that cause DM in an individual. Tests such as the FPG, 2-hour PG, and HbA1c are also appropriate for the diagnosis of DM2.

The two main pathological defects in DM2 are impaired insulin secretion by means of dysfunction in the pancreatic  $\beta$  cells, and reduced action over the insulin resistance,<sup>4</sup> which affects the insulin-mediated glucose uptake by the periphery substance, the triglyceride uptake by fat, and causes the suppression of hepatic glucose output. As a result of these changes, insulin secretion is increased by the islet cell, which, in turn, increases the production of endogenous glucose in DM2.<sup>6</sup>

### Diabetes Mellitus and the Auditory System

Diabetes mellitus is a systemic disease; as such, it affects multiple organ systems, including the auditory system. Individuals with diabetes are more likely to develop hearing loss, tinnitus, and dizziness due to macro- and microvascular complications in the inner ear caused by glucose metabolism.<sup>7</sup> The main etiological factors that result in hearing loss and dizziness are those conditions that affect glycosides and lipids.<sup>8</sup> The capillary lumen changes as a result of the thickening of the basilar membrane and atrophy of the stria vascularis, which are some of the other important contributors for the hearing loss in individuals with DM.<sup>9</sup>

The physiology of the cochlea, which is dependent on cochlear microcirculation, is indirectly affected in DM2, since the disease affects the microcirculation.<sup>10</sup> Wang et al.<sup>11</sup> reported a change in the ultrastructure of inner ear capillaries along with the thickening of the basement membrane. Thickening of capillaries in the basal region of the stria vascularis, along the lateral wall of the cochlea, and a decrease in the amount of hair cells present within cochlea are observed in cases of DM.<sup>12</sup>

Moreover, histopathological evidence also suggests that factors such as neuropathy of the VIIIth nerve, microangiopathy of the inner ear, and inflammation and glycemia can result in diabetes-related hearing impairment. For years, many clinical researchers investigated the effect of DM on hearing function, and they found a significant association between diabetes and hearing loss;<sup>13–15</sup> only a small number of studies found no association between diabetes and hearing loss.<sup>16</sup>

### Diabetes Mellitus and Vestibular Dysfunction

The inner ear consists of both hearing and vestibular organs. Hence, DM might also have an effect on vestibular function. Vestibular dysfunction in individuals with DM is found to be the result of compromised inner-ear functioning.<sup>17</sup> The progression of the disease may lead to comorbidity of vestibular symptoms, at least in a few individuals.<sup>18</sup> The prevalence of balance disorder in individuals with diabetes mellitus is reported to be between 60% and 75%.<sup>19</sup> The pathophysiological mechanism by which diabetes affects vestibular function involves parts or all of the vestibular structures, and is not completely understood by the researchers.<sup>20</sup> Animal studies<sup>21,22</sup> on rats with induced diabetes revealed evidences of atrophy of type-I vestibular hair cells and thinning of the myelin sheath present on the vestibular nerves. Thus, it is important to investigate the effects DM2 on vestibular damage beyond the micro- and macrovascular complications.

Since the inner ear consists of the hearing and vestibular systems, the extent to which auditory and vestibular functions are impaired in cases of DM2 remains under debate. So, the main focus of the present systematic review is to perform a quantitative analysis to explore the auditory and vestibular findings in cases of DM2 reported in the literature. The present review exclusively focused on DM2, as it constitutes 90% of all cases of DM, and is a major public health issue.<sup>1</sup> The results of the present systematic review will enhance the understanding of the association with and alterations caused by DM2 regarding auditory and vestibular functions.

## Research Design and Methods

### Study Design

We performed a systematic review of published studies that evaluated auditory and vestibular functioning in DM2. A written study protocol was prepared in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.<sup>23</sup>

## Search Strategy

We systematically searched the Google Scholar, PubMed, MedlinePlus, and Ingenta Connect databases for experimental studies published until June 2019 evaluating DM2 and the functioning of the audio-vestibular system. The search terms used were as follows: *non-insulin dependent diabetes mellitus OR type-2 diabetes mellitus OR adult onset diabetes mellitus, hearing, auditory brainstem response OR brainstem-evoked response audiometry, cochlear function, otoacoustic emission, cortical potentials, balance, vestibular, otolith, vestibular-evoked myogenic potential, video head impulse, and semicircular canals*. Details on the number of articles obtained using the aforementioned terms is reported in ► **Table 1**.

The search was limited to articles published in English. In addition, articles with systematic reviews and meta-analyses related to this particular topic helped us identify additional articles that were missing in our database search.

## Inclusion and Exclusion Criteria

Experimental studies evaluating the effect of DM2 on auditory and vestibular functioning were eligible for inclusion. Inclusion was restricted to controlled trials reporting the measurements that confirm the presence of DM2, such as HbA1c, the fasting blood sugar test (FBS), and the postprandial glucose test (PPBS). Articles that incorporated tests of particular interest mentioned in the present review were included. Studies that addressed only DM1 or without a subgroup analysis matching the required group, presence of other comorbid conditions of diabetes, and review articles not relevant to this particular topic were excluded from the review process.

## Data Extraction and Quality Assessment

For each article that met our inclusion criteria, reviewers extracted information such as study design, sample size, participant characteristics, tests incorporated and results. The literature search was independently conducted by two reviewers. Disagreements about inclusion or exclusion based on the review of titles and abstracts review were resolved by a third reviewer. The general quality of the studies was evaluated based on the external and internal validity, randomized or non-randomized trials, and use of appropriate analytical techniques.

**Table 1** Number of articles on auditory and vestibular tests regarding type-2 diabetes mellitus retrieved in the database search

Database	Auditory-related articles (n)	Vestibular-related articles (n)	Total
PubMed	2,995	1,900	4,895
MedlinePlus	260	336	596
Google Scholar	3,512	6,816	10,328
Ingenta Connect	14	147	161
Total	6,781	9,199	15,980

## Data Synthesis and Analysis

The studies were methodologically and clinically diverse. Therefore, qualitative analyses were performed for the individual studies that addressed similar research questions with different measurements regarding DM2. Based on the methodological focus of this particular review article, a systematic review without a meta-analysis was conducted.

## Results

### Search Results

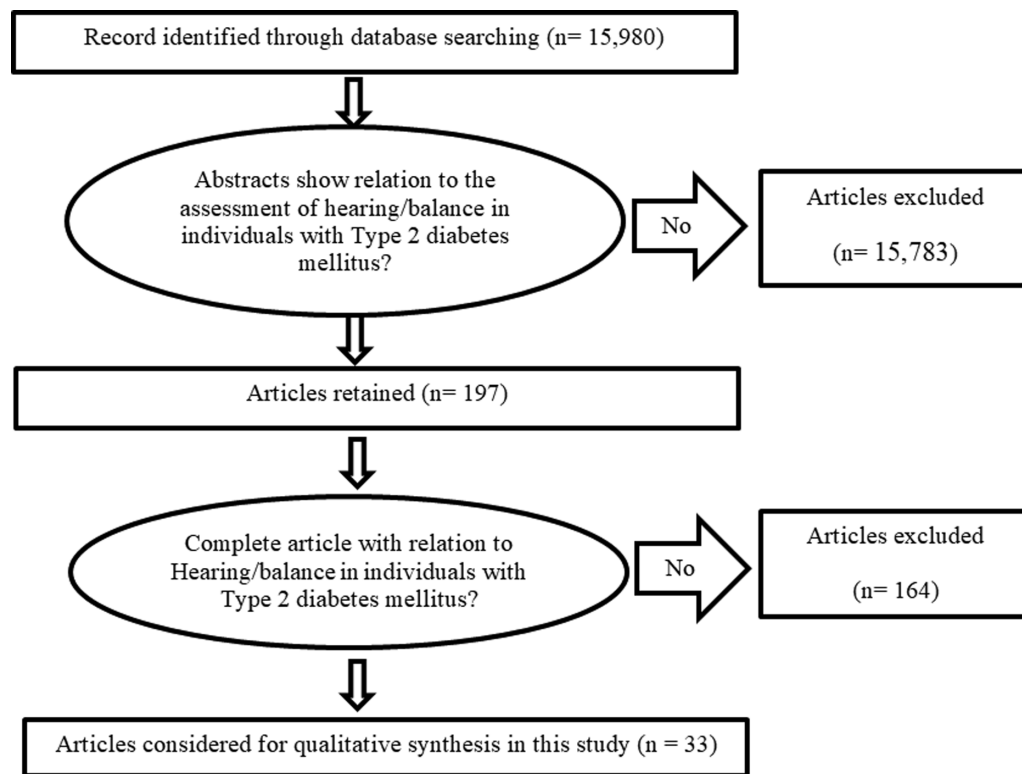
The database search yielded 15,980-potentially relevant articles, 197 of which had the full text available for review. Following our inclusion criteria, 26 articles on the auditory system and 6 on the vestibular system were included in the final systematic review (► **Fig. 1**).

### Audiological Evaluation in Type-2 Diabetes Mellitus

Numerous researches have evaluated the peripheral auditory and central auditory systems in individuals with DM2. ► **Table 2** shows a summary of the studies that dealt particularly with auditory evaluations.

The association between hearing loss and DM2 has been extensively reported in the literature, and a higher prevalence of hearing loss is reported among diabetic individuals. Horikawa et al.<sup>24</sup> observed that the occurrence of hearing loss is 2.1 times higher in individuals with DM2 compared with healthy individuals. Microangiopathy, neuropathy, and mitochondrial damage are considered three multifactorial conditions that lead to and increase the prevalence of hearing impairment in DM. Impaired metabolic functioning due to diabetes might result in deterioration of pure-tone thresholds, speech-recognition thresholds (SRTs), and speech-recognition scores (SISs). An evaluation of 104 DM2 patients and 104 non-diabetic controls revealed significantly poorer air-conduction thresholds, bone-conduction thresholds and speech-recognition scores.<sup>25</sup> However, no significant difference was noted in immittance measures that assessed middle-ear functioning.<sup>25</sup> Similarly, significantly poorer hearing thresholds were observed in two studies<sup>26,27</sup> comparing DM2 individuals and non-diabetic healthy controls; the authors concluded that the metabolic changes caused by diabetes can modify the micromechanics of the inner ear, which affects the hearing function. Increased stromal cell-derived factor 1a (SDF-1a), a microangiopathic marker, was observed in DM individuals who exhibited poorer (higher) hearing threshold levels across all frequencies and more difficulty in speech discrimination.<sup>28</sup>

Reduced perception of sounds, especially at high frequencies, such as those between 4,000 Hz and 8,000 Hz, was observed in individuals with DM2.<sup>15</sup> Similarly, Díaz de León-Morales et al.<sup>13</sup> reported an increased perception threshold at 8,000 Hz. The increase in hearing sensitivity regarding high-frequency signals could be a result of degeneration or loss of outer hair cells predominantly at the basal turn of cochlea in DM2.<sup>29,30</sup> Some investigators<sup>9</sup> have suggested changes in the capillary lumen as a result of thickening of the basilar membrane and atrophy of



**Fig. 1** PRISMA flowchart of the literature review process.

the stria vascularis as important contributors for the hearing impairment in diabetic individuals.

Disruption in glucose metabolism can compromise the functioning of the outer hair cells, since glucose is considered the energy source for the cochlea. One study<sup>31</sup> stated that the odds of failing the distortion-product otoacoustic emissions (DPOAEs) were 7 and 15 times higher for the right and left ears respectively among DM2 participants compared with normal healthy controls. Similarly, decreased signal-to-noise ratio and abnormal DPOAEs were observed in DM2 individuals.<sup>32,33</sup> Studies<sup>15,27</sup> on transient-evoked otoacoustic emissions (TEOAEs) reported reduced reproducibility in both ears and lower mean amplitudes in DM2 individuals. Reduced mean amplitudes of otoacoustic emissions in DM2 individuals indicate that the cochlea can also be a target organ for hyperglycemia, resulting in widespread tissue damage. Changes in the brain metabolites, such as on the concentrations of N-acetyl aspartate and myoinositol might add up to the hearing changes in diabetic patients.<sup>34</sup> Regardless of the type of DM, it is clearly understood from the aforementioned studies that malfunctioning of the outer hair cells might be associated with hyperglycemia.

Studies<sup>35,36</sup> on auditory-evoked potentials (AEPs) and nerve conduction have reported the involvement of central and peripheral neuropathies in DM individuals. A significant delay in the absolute latency of waves I, II, III, IV and V and interpeak latencies (IPLs) of waves I-III, I-V and III-V was observed in DM2 individuals.<sup>37</sup> Other studies<sup>38,39</sup> with DM2 patients and healthy controls have reported a significant increase in the absolute latencies of waves I, III and V and IPLs of waves III-V and I-V. Kannan<sup>40</sup> also reported an increase in

both absolute latencies (of waves III and V) and IPLs (of waves I-III, I-V and III-V) in DM2 individuals compared with healthy controls. Studies<sup>41,42</sup> reporting the effect of stimulus intensity on AEPs in DM2 revealed a significant increase in the absolute latencies of waves III and V and IPLs of waves I-III, III-V and I-V at 70 dBnHL and 80 dBnHL, whereas, at 90 dBnHL, the authors found a significant increase in the absolute latency of wave I compared with that of the other two intensities. It can be inferred from the aforementioned findings, that DM2 can result in reduced conduction velocity in the auditory nerve that occurs secondary to diabetic neuropathy. Some authors<sup>37-40</sup> suggest that the prolongation of wave I could be due to a reduction in the time of peripheral transmission, and that the prolongation of waves III and V could be due to a reduction in the time of central transmission. This can be attributed to the neuronal degeneration that results from the oxidative stress and apoptosis of neurons in DM2. The delay in IPLs reveals retrocochlear and brainstem involvement. Contradicting these findings, Jabbari Moghaddam<sup>16</sup> reported no significant difference in the findings regarding auditory brainstem response (ABR) and otoacoustic emissions (OAEs) among individuals with and without DM2. These outcomes could be due to subjective factors such as age (< 50 years), duration of the diabetes (< 10 years), and glycemic control (good control).<sup>16</sup>

With respect to how speech signals are processed at the subcortical level in DM2, Gupta et al.<sup>43</sup> found that the latency and amplitude for both transient and sustained responses were significantly reduced in DM2 individuals compared with individuals without DM2. A similar trend with respect to latency was reported by Sanju et al.<sup>44</sup> for the transient and

**Table 2** Summary of audiological tests and their findings regarding type-2 diabetes mellitus

Serial Number (Sl. No.)	Author	Year	Tests administered	Number of participants EG/CG	Significance
1. 1	Díaz de León-Morales et al. <sup>13</sup>	2005	PTA/Speech audiometry/ABR	94/94	(++)
2. 2	Manjarrez et al. <sup>45</sup>	2007	ALLR	20/20	(++)
3.	Panchu <sup>56</sup>	2008	PTA	41/41	(++)
4.	Ren et al. <sup>14</sup>	2009	PTA/OAE/ABR	50/50	(++)
5. D	Durmus et al. <sup>57</sup>	2004	ABR	26/20	(++)
6.	Gupta et al. <sup>41</sup>	2010	ABR	25/25	(++)
7.	Vesperini et al. <sup>15</sup>	2011	PTA/OAE/ABR	40/20	(++)
8.	Jabbari Moghaddam <sup>16</sup>	2011	ABR/OAE	50/50	(-)
9.	Özel et al. <sup>25</sup>	2014	PTA/SRS	104/104	(++)
10.	Gupta et al. <sup>35</sup>	2013	ABR	126/106	(++)
11.	Karabulut et al. <sup>32</sup>	2014	PTA/SDS/TEOAE/DPOAE/CLS-TEOAE	50/51	(++) CLS-TEOAE (-)
12.	Mahallik et al. <sup>58</sup>	2014	ABR	25/25	(++)
13.	Gupta et al. <sup>43</sup>	2015	Speech ABR /da/	25/25	(++)
14.	Hemashree and Preetha <sup>26</sup>	2016	PTA	20/20	(++)
15.	Meena et al. <sup>27</sup>	2016	PTA/TEOAE/ABR	50/50	(++)
16.	Paluru et al. <sup>31</sup>	2016	DPOAE	50/50	(++)
17.	Murugesan et al. <sup>38</sup>	2016	ABR	50/50	(++)
18.	Yikawe et al. <sup>59</sup>	2017	PTA	170/170	(++)
19.	Gulati et al. <sup>60</sup>	2017	PTA	50/50	(++)
20.	Kannan <sup>40</sup>	2017	ABR	40/40	(++)
21.	Sanju et al. <sup>44</sup>	2017	Speech ABR /da/	11/11	(++)
22.	Li et al. <sup>33</sup>	2018	PTA/DPOAE	51/43	(++)
23.	Suresh et al. <sup>42</sup>	2018	ABR	15/15	(++)
24.	Victor et al. <sup>39</sup>	2018	ABR	30/30	(++)
25.	Kumar et al. <sup>46</sup>	2018	ALLR /da/	25/25	(++)
26.	Goyal et al. <sup>37</sup>	2019	ABR	50/50	(++)

Abbreviations: ABR, auditory brainstem response; ALLR, auditory late-latency response; CLS, contralateral suppression; CG, control group; DPOAE, distortion-product otoacoustic emission; EG, experimental group; OAE, otoacoustic emission; PTA, pure-tone audiometry; SDS, speech discrimination score; SRS, speech recognition score; TEOAE, transient evoked otoacoustic emission.

Notes: (++) , significant effect of type-2 diabetes mellitus; (-), no significant effect of type-2 diabetes mellitus.

sustained responses of the speech-evoked response. Thus, these findings are ascribed to factors such as reduced outer hair cell activity, impaired neuronal conduction time, and degeneration at the level of the brainstem.

Brain involvement is common in longstanding DM. Reduced serotonergic neurotransmission along the sensory cortex predominantly with the auditory cortex was observed due to metabolic changes in DM. Manjarrez et al.<sup>45</sup> observed that the latency of the N1 and P2 peaks was found to be significantly prolonged in women with DM2 compared with women in the control group. Auditory late-latency response (ALLR) showed prolonged latencies and reduced amplitude of the P1, N1 and P2 peaks in individuals with DM2.<sup>46</sup> These findings have been attributed to the possible change in conductivity of the thalamo-cortical pathways, or the reduced level of activity in

the serotonergic neurons, which affects the lower tolerance threshold of the cortical pyramidal neurons.<sup>47</sup>

### Vestibular Evaluation in Type-2 Diabetes Mellitus

The process by which DM affects vestibular function may involve parts or all of the vestibular structures. Major contributing factors for vestibular impairment in DM2 are the microangiopathic effects, such as ischemia of the vestibular structures, alteration of the metabolism of the inner ear fluid, and loss of type-I hair cells in the saccule.<sup>17</sup> ▶ **Table 3** shows a summary of the DM2 studies that deal with the peripheral vestibular evaluations in particular.

However, there are only a handful of studies<sup>48-53</sup> focusing on the functioning of otolith organs and semicircular canals (SCCs) in DM2 individuals. Ocular and cervical vestibular-

**Table 3** Summary of vestibular tests and their findings regarding type-2 diabetes mellitus

Serial Number (Sl. No.)	References	Year	Tests administered	Number of participants EG/CG	Significance
1.	Bektas et al. <sup>51</sup>	2008	c-VEMP	13/21	(-)
2.	Konukseven et al. <sup>49</sup>	2015	c- VEMP and o- VEMP	30/31	Latency (++); AR and Amp (-)
3.	Sahu et al. <sup>50</sup>	2015	c-VEMP	15/15	(++)
4.	Kanmuri et al. <sup>48</sup>	2018	c- VEMP	40/20	(++)
5.	Kalkan et al. <sup>52</sup>	2018	c- VEMP, o- VEMP and vHIT	33/35	VEMP (++); vHIT (-)
6.	Omar et al. <sup>53</sup>	2018	c- VEMP, o- VEMP and vHIT,	8/8	VEMP, vHIT (-)

Abbreviations: Amp, amplitude; AR, asymmetry ratio; c-VEMP, Cervical vestibular-evoked myogenic potential; o-VEMP, ocular vestibular-evoked myogenic potential; CG, control group; EG, experimental group; VEMP, vestibular-evoked myogenic potential; vHIT, video head impulse test. Notes: (++) ,significant effect of type-2 diabetes mellitus; (-),no significant effect of type-2 diabetes mellitus.

evoked myogenic potentials (o-VEMPs and c-VEMPs) are known to assess the functioning of the otolith organs. The video head impulse test (vHIT) can assess the SCCs in all the three different planes. Kanumuri et al.<sup>48</sup> reported that DM can have an impact on the impairment of the vestibular system. They performed c-VEMPs on 40 DM2 individuals, and compared these results with the 20 controls. The authors reported absence of c-VEMP responses in 10% of the DM2 individuals, and delayed P13 and N23 latencies in 20% of them. Konukseven et al.<sup>49</sup> observed significantly prolonged o-VEMP latencies in DM2 individuals compared with prediabetic and healthy controls without any central or peripheral vestibular pathology.<sup>49</sup> Similarly, reduced amplitudes in both c-VEMPs and o-VEMPs were observed in DM2 individuals.<sup>50</sup> Vestibular dysfunctions in DM2 individuals could be a consequence of sensory or motor polyneuropathy.<sup>49</sup>

Contrary to these findings, a few reports suggest no significant difference between the latency and amplitude of VEMP responses among diabetics and control groups.<sup>51</sup> The authors attribute these findings to the unaltered conduction times in the VEMP pathway. Another reason for the similar VEMP findings in both the groups could also be no vestibular symptoms or complaint reported by the participants in both the groups. Thus, it can be established that peripheral vestibular organs may not experience the same extent of diabetic angiopathic change as other inner-ear structures.

Both studies<sup>52,53</sup> on vHIT in DM2 showed no significant group difference in the gain in vestibulo-ocular reflex (VOR) between the clinical and the control groups. Further, both studies showed unanimous agreement about the lack of refixation saccades in DM2 individuals. These findings point toward the ineffectiveness of the vHIT in identifying pathologies of the SCCs in DM2. This could be attributed to the nature of the pathology. Type-2 DM is a chronic condition which brings about slowly progressive changes. It is well known that the vHIT is not sensitive to slowly-occurring or chronic pathologies.<sup>54,55</sup>

While the studies on the assessment of hearing provide conclusive evidence for damage associated with DM2,

the studies on the assessment of vestibular function in these individuals are less supportive of a cause-and-effect relationship. Based on the studies evaluated, the small sample, the conflicting results, and the different methodologies, it is not possible to conclude that vestibular damage is caused by DM2.

## Conclusion

In summary, the present systematic review is a brief introduction that explains DM2 and its effect on the auditory and vestibular systems. The odds of having hearing loss are found to be higher in diabetic individuals compared with non-diabetic individuals. Studies on AEPs revealed a trend for prolonged latencies and reduced amplitudes of waves in DM2, providing significant differences between diabetic and non-diabetic groups. Hence, DM2 individuals should be counselled regarding the disease and its effect on audition. The studies that performed vestibular assessments show no conclusive evidence for the vestibular damage. Therefore, more studies on vestibular assessment in DM2 patients are needed.

## Conflict of Interests

The authors have no conflict of interests to declare.

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