Association of Glycemic Index Using HbA1c and Sensorineural Hearing Loss in Diabetes Mellitus Type 2 Patients: A Systematic Review and Meta-Analysis

ABSTRACT

Objective: To systematically review the available evidence on the association of HbA1c levels and development of sensorineural hearing loss and to quantitatively analyze the available data on HbA1c levels in patients with type 2 diabetes mellitus and sensorineural hearing loss to determine an HbA1c level that may be associated with the risk of having sensorineural hearing loss.

Methods:

Design: Systematic Review and Meta-analysis

Eligibility Criteria: Cross-sectional studies, or cohort studies which were limited to English language that investigated the correlation of glycemic index using HbA1c and sensorineural hearing loss among adult type 2 diabetic patients which were done from January 2010 to December 2021. Studies with no published outcome, incomplete data or that were ongoing as of August 1, 2022 were also excluded.

Information Sources: MEDLINE (through PubMed), Cochrane Library, Scopus, Embase (through OVID@journal), Directory of Open Access Journals (DOAJ), Google Scholar and HERDIN Plus

Risk of Bias: Risk of Bias was assessed using the Guidelines for Cochrane Collaboration

Synthesis of Results: Results were presented using forest plots for representation.

Results: A total of 8 studies were reviewed with 2,103 participants in all. Six articles compared hearing loss incidence between diabetic and non-diabetic patients. Overall, there were a total of 881 diabetic patients and 1222 non-diabetic patients. There was a significantly lower incidence of sensorineural hearing loss in non-diabetic patients with a risk ratio of 1.89, 95% CI [1.65, 2.16]. Three articles compared the HbA1c levels of diabetic patients with or without sensorineural hearing loss. Diabetic patients without sensorineural hearing loss had significantly lower HbA1c levels compared to those with sensorineural hearing loss with mean difference of 1.04, 95%CI [0.82, 1.25].

Conclusion: In conclusion, this meta-analysis showed a higher prevalence rate of sensorineural hearing loss among patients with diabetes mellitus compared to non-diabetic patients. Moreover, poor glycemic control among diabetic patients with a glycemic index based on HbA1c of more than 8.3 (6.97-9.6) is associated with sensorineural hearing loss.

Keywords: diabetes mellitus; T2DM; HbA1c; glycemic index; sensorineural hearing loss; pure tone audiometry; deafness
Diabetes Mellitus (DM) is a multiple-etiologic metabolic disorder characterized by chronic hyperglycemia and other metabolic abnormalities which result in absolute or relative insulin deficiency and is associated with other health disorders such as atherosclerosis manifested in cardiovascular disease, kidney disease, retinopathy, and neuropathy.\(^1\) Hearing impairment is an under-recognized complication of type 2 diabetes mellitus (T2DM); the insulin/glucose signaling pathway that characterizes T2DM may lead to inner ear pathology and accompanying hearing loss.\(^2\) Cochlear changes, such as an increased thickness of the basal membrane and stria vascularis vessel walls, internal auditory artery sclerosis, and inner ear neural system degeneration, are responsible for hearing impairment among DM patients.\(^3\) The prevalence of hearing loss in type 2 diabetic patients varies from 34.4 to 60.2%.\(^4\)

The published literature has conflicting results with regards to the association of sensorineural hearing loss and glycemic index reflected in HbA1c levels in terms of levels of glycemic control and their effects in hearing loss.\(^1,2,3\) Although there is still no consensus on the level of HbA1c at which patients with type 2 DM are predisposed to developing sensorineural hearing loss, different studies have demonstrated that sensorineural hearing loss was associated with control of diabetes mellitus.\(^6-8\)

Our study aims to systematically review the available evidence on the association of HbA1c levels and development of sensorineural hearing loss and to quantitatively analyze the available data on HbA1c levels in patients with T2DM and sensorineural hearing loss to determine an HbA1c level that may be associated with the risk of having sensorineural hearing loss. Data from studies on patients with T2DM diagnosed and assessed with laboratory results of HbA1c with assessment of hearing using pure-tone audiometry done will be included and the association of their HbA1c results and pure tone audiometry will be qualitatively analyzed.

**METHODS**

This systematic review and meta-analysis were conducted from August 1, 2021 to August 20, 2022 with University of Santo Tomas Hospital Research Ethics Committee Exemption Number REC-2022-10-136-TR.

**Eligibility Criteria**

Studies eligible for inclusion were randomized controlled trials (RCTs), cross-sectional studies, or cohort studies in English language that investigated the correlation of glycemic index using HbA1c and sensorineural hearing loss among adult type 2 diabetic patients and had data on the number of hearing-impaired and non-hearing-impaired patients with diabetes, with hearing impairment assessed using pure-tone audiometry that included a frequency range of at least 2KHz. Case reports and case series were excluded. Studies with no published outcome, incomplete data or ongoing as of August 1, 2022 were also excluded as well as studies whose full text was not available through our institutional library. Only studies after January 1, 2010 to December 31, 2021 were included in the search.

**Information Sources**

A search of clinical trials that investigated the correlation of glycemic index using HbA1c and the development of sensorineural hearing loss among adults diagnosed with T2DM were independently performed by the primary investigator (MRRQ) and co-investigator (CECG) using MEDLINE (through PubMed), the Cochrane Library, Scopus, Embase (through OVID@journal), the Directory of Open Access Journals (DOAJ), Google Scholar and HERDIN Plus. These online databases were accessed from February 2022 to August 2022. A final search of each database was done from July 21 to August 20, 2022, to assess if new articles that might be eligible for meta-analysis had been added.

**Search Strategy**

The citations were identified with the use of a combination of the following text MeSH terms: “HbA1c”, “glycemic index”, “Type 2 Diabetes Mellitus”, “T2DM”, “sensorineural”, “hearing loss” “sensorineural hearing loss”, “deafness” “hypoacusis” and “randomized”. A sample search included a line search of the MeSH Term “Diabetes Mellitus” and other terms related to Diabetes Mellitus (Type 2 Diabetes Mellitus; T2DM) under the filter of Title/Abstract using the conjunction “OR”. A second line search of the MeSH Term “glycemic index” and “HbA1c” using the conjunction “OR” was made. These two lines were joined together in one search combined by the conjunction “AND” to obtain all possible articles with this intersection of search terms.

All trials that matched the terms set by the researchers were retrieved. Titles and research abstracts were reviewed individually. No restriction for geographic location was applied but the search was limited to English language articles. Other studies were sought by searching for previous or ongoing trials registered in ClinicalTrials.gov to determine if any unpublished but relevant studies existed. The final database search for each was conducted from July 21 to August 20, 2022. Only studies after January 1, 2010 to December 31, 2021 were included in the search.

**Selection process**

Prior to data abstraction, review of data from article abstracts were done by the primary and co-investigator to assess eligibility of papers...
to be included in the analysis. Those eligible for inclusion were then individually analyzed by the investigators. The researchers settled any inconsistencies by discussion or mediated by a statistician who acted as an arbiter.

**Data collection process**

Standard data extraction templates and operational definitions of outcomes and explanatory variables were prepared prior to abstraction. The researchers independently abstracted data for each study prior to pooling of results. Information on participant characteristics (study inclusion and exclusion criteria), diagnosis and study duration were collected. Information on each of these outcomes were extracted whenever available: incidence of sensorineural hearing loss and incidence of control of diabetes based on HbA1c.

**Data Items**

The researchers extracted the number of events of interest and total number to be analyzed in each group for dichotomous data namely the presence and absence of sensorineural hearing loss in patients with and without DM and extracted the mean and standard deviations (SD) for continuous data such as the levels of HbA1c for those with sensorineural hearing loss. However, in case mean change and SD were not available, calculations were made from presented data such as standard error, confidence intervals, baseline and follow up means and SD to obtain the mean change and SD values.

**Risk of Bias Assessment in Individual Studies**

Guidelines for Cochrane Collaboration were used to assess the risk of bias using the Review Manager (RevMan) Version 5.3, 2014 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark). The statistician reviewed the methods of random sequence generation and allocation concealment, which became the authors’ basis for evaluation of selection bias. The methods of blinding among the participants and investigator of each trial were noted for performance bias. Blinding for outcome assessment was used to calculate detection bias. Completeness of the outcome data was used to evaluate attrition bias. Lastly, publication bias was evaluated using funnel plots.

**Effect Measures**

Risk ratio was used to represent the effect of the number of patients with sensorineural hearing loss among total patients with DM compared to those with sensorineural hearing loss without DM. Mean difference was used to present the data between HbA1c levels of DM patients presenting with or without sensorineural hearing loss.

**Synthesis Methods**

The inclusion of studies for the systematic review and meta-analysis were based on the assessment of the primary investigators in the studies’ completeness in terms of data on the levels of HbA1c and results of pure tone audiometry by tabulating the studies included with the outcomes to be used for comparison and analysis. Data included in the studies which had incomplete or missing data were either excluded or supplemented from other meta-analytic studies and review articles previously done. The complete data of studies included were placed in a table for representation.

Studies included on data abstraction were placed in a software to aid in analysis where Review Manager (RevMan) Version 5.3, 2014 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark) was used to produce the forest plots to represent the data for the analysis. Overall effect was determined using odds ratios (ORs) with 95% confidence intervals set for each parameter. Publication bias was also evaluated by visual inspection of the funnel plots and Egger’s tests which were generated using RevMan and Comprehensive Meta-Analysis Program version 3.3.070, 2014 (Bio stat, Englewood, NJ, USA). Lastly, to summarize information on individual studies and give a visual suggestion of the amount of study heterogeneity and show the estimated common effect, forest plots were used for representation. A fixed effect model was used to represent data granted that the outcome which was sensorineural hearing loss was present in diabetic and non-diabetic patients. The Mantel-Haenzel method was used to calculate odds ratio in the presence of confounders. Test of heterogeneity was done via visual inspection of results and formal computation using Chi² testing.

**RESULTS**

**Study Selection**

Initial literature search from January 1, 2010 to December 31, 2021 yielded 51 citations. Duplicates were eliminated by selecting only the more complete article for each duplicated study. After screening for completeness of the article, case and control groups and final data analysis, 15 full-text articles were screened and 8 articles were included for qualitative and quantitative study. Studies meeting all the requirements were included in the meta-analysis and reported using PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) flowchart. (Figure 1)

**Study Characteristics**

A total of 2,103 study subjects from 8 different articles were included in the study. One thousand seventy-four (1,074) were case subjects and 1,029 were control subjects. One out of the 8 included studies had no
controls\(^9\) while 6 out of the 8 studies had subjects less than 60 years old.\(^9,12,14,15\) Duration of diabetes for subjects were included in 6 out of 8 studies with most of the subjects having more than 10 years of disease process.\(^9,12,15,16\) Other confounding factors such as gender and environmental exposures were not included in the analysis. All studies utilized pure tone audiometry as assessment of sensorineural hearing loss and level of glycemic control was assessed based on laboratory determination of HbA1c. The studies included are described in Table 1.

**Risk of Bias in Studies**

The Cochrane risk of bias assessment tool was used to assess methodological quality and bias in the included studies. The following biases were assessed: selection bias, performance bias, detection bias, reporting bias, attrition bias and other author reported bias. Each criterion was assessed as having low, unclear or high-risk bias. There was low risk of selection bias for studies in references 9, 12, 13, 14, 15, 16, and an unclear risk of bias for studies 10 and 11 as the blinding were not explicitly included in the methodology. Performance bias was also low for studies 14, 15 and 16. Attribution and reporting bias were all low in all studies. Figure 2 shows that the included studies fall within the symmetrical curve of the funnel plot which means the studies included have a low risk for publication bias.

**Results of Individual Studies**

The results of individual studies are described in Table 2.

**Results of Synthesis**

There were 6 articles comparing hearing loss incidence between diabetic and non-diabetic patients. Figure 3 compared the incidence of sensorineural hearing loss between diabetic and non-diabetic patients. There were a total of 305 cases of sensorineural hearing loss out of 1,222 non-diabetic patients compared to 321 cases of sensorineural hearing loss out of 881 diabetic patients. Based on the forest plot, the incidence favors non-diabetic patients. Therefore, the analysis shows that the incidence of sensorineural hearing loss is significantly lower in non-diabetic patients with risk ratio of 1.89, 95% CI [1.65, 2.16].

Figure 4 compared the mean HbA1c levels between diabetic patients with hearing loss vs. those without hearing loss. Among diabetic patients, the mean HbA1c levels of patients with sensorineural hearing loss ranges from 7.88 to 12.2 whereas diabetic patients

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Table 1. Summary of included studies

<table>
<thead>
<tr>
<th>Reference, Title</th>
<th>Authors</th>
<th>Year</th>
<th>Sample size (diabetic/control)</th>
<th>Age (years)</th>
<th>Duration of diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Hearing loss among patients with type 2 diabetes mellitus: a cross-sectional study</td>
<td>Al-Rubeaan K, Al Momani M, Al Gethami A, Darandari J, Alsafi H, Al Naqeeb D, Almogbel E, Almasaari F, Youssef A</td>
<td>2021</td>
<td>157/0</td>
<td>51 (47-54)</td>
<td>1-5 years: 21.7% 6-10 years: 17.8% &gt;10 years: 60.5%</td>
</tr>
<tr>
<td>2. Effect of diabetes mellitus on hearing</td>
<td>Ghosh U, Fakir A, Osmany H, Lodh D, Islam Z, Islam M</td>
<td>2019</td>
<td>55/28</td>
<td>&lt;60</td>
<td>0-5 years: 38.2% 6-10 years: 25.5% &gt;10 years: 32.7%</td>
</tr>
<tr>
<td>6. Correlation between sensorineural hearing loss and HbA1c in diabetes mellitus patients</td>
<td>Sharma R, Choudhary R, Teharia R</td>
<td>2022</td>
<td>150/150</td>
<td>10-50</td>
<td>Not stated</td>
</tr>
<tr>
<td>7. A one year prospective study of hearing loss in diabetes in general population</td>
<td>Thimmasettaiah N, Shankar R, Ragi V, Reddy S</td>
<td>2012</td>
<td>87/105</td>
<td>60.9 ± 10.9 Control: 56.5 ± 15.7</td>
<td>&gt;5 years: 79% First time diagnosis: 42%</td>
</tr>
<tr>
<td>8. Alterations in hearing function of patients with glucose disorders</td>
<td>Vergou Z, Paschou S, Bargiota A, Kouloumis G</td>
<td>2019</td>
<td>221/278</td>
<td>DM: 57.4 ± 9 Control: 51.2 ± 8.9</td>
<td>9.4 ± 8.7 years</td>
</tr>
</tbody>
</table>
without sensorineural hearing loss have mean HbA1c levels of 6.79 to 9.8 (m=8.3). Based on the forest plot, the results favor the group without sensorineural hearing loss. Significantly lower HbA1c levels are observed in diabetic patients without sensorineural hearing loss compared to those with sensorineural hearing loss, with mean difference of 1.04, 95%CI [0.82, 1.25]. This means that diabetic patients without sensorineural hearing loss have better glycemic control.

**Reporting Biases**

Risk of publication bias was reported using funnel plot. Based on Figure 2, all the studies fall within the triangle of the funnel plot showing that the included studies had low risk for reporting bias.

**DISCUSSION**

The current meta-analysis of observational studies shows a 1.8-fold prevalence of sensorineural hearing loss in patients diagnosed with DM than without, showing a significant association between glycemic control and sensorineural hearing loss. This is comparable with the study done by Horikawa et al. in 2013 with a relative risk of 2.1. Based on the combined results of studies, diabetic patients without sensorineural hearing loss have better glycemic control.

With the current meta-analysis, glycemic control as represented by glycosylated hemoglobin (HbA1c) in known diabetic patients was studied and associated with sensorineural hearing loss. A limited number of observational studies directly show continuous data

**Table 2. Results of Individual Studies**

<table>
<thead>
<tr>
<th>Title</th>
<th>Authors</th>
<th>Year</th>
<th>With Diabetes Mellitus</th>
<th>Without Diabetes Mellitus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevalence of sensorineural hearing loss and its association with glycemic control in Filipino patients with diabetes at the Philippine General Hospital</td>
<td>Gutierrez J, Jimeno C, Labra P, Grullo P, Cruz T.</td>
<td>2016</td>
<td>54</td>
<td>120</td>
</tr>
<tr>
<td>Correlation between sensorineural hearing loss and HbA1c in diabetes patients</td>
<td>Sharma R, Choudhary R, Teharia R.</td>
<td>2022</td>
<td>42</td>
<td>150</td>
</tr>
<tr>
<td>Alterations in hearing function of patients with glucose disorders</td>
<td>Vergou Z, Paschou S, Bargiota A, Koutoulis G.</td>
<td>2019</td>
<td>17</td>
<td>278</td>
</tr>
</tbody>
</table>

**Mean Glycemic Index using HbA1c of Diabetes mellitus type 2 patients with or without Sensorineural Hearing Loss**

<table>
<thead>
<tr>
<th>Title</th>
<th>Authors</th>
<th>Year</th>
<th>With Sensorineural Hearing Loss</th>
<th>Without Sensorineural Hearing loss</th>
</tr>
</thead>
</table>
regarding the use of HbA1c to represent glycemic control in diabetic patients and associated these with the degree of sensorineural hearing loss.\textsuperscript{7,8,13} In the studies included in the meta-analysis, those with diagnosed DM with HbA1c levels greater than 8.3 (6.79-9.8) had higher incidence of sensorineural hearing loss. Moreover, poor glycemic control is associated with a higher incidence of sensorineural hearing loss, with a mean difference of 1.04. Glucose levels within the endolymph may affect homeostasis and cause strial damage leading to hearing impairment.\textsuperscript{7,9}

Although stratified and meta-regression analyses were not done on individual demographic profiles of the included population, the confounding factor of aging was mitigated based on the demographic profiles of patients included in the study. The duration of disease process was also stated in the data abstracted from the study, which showed those with disease process of more than 10 years have higher risk of developing sensorineural hearing loss compared to patients with the disease process less than 10 years.\textsuperscript{9,13,16}

Limitations of this meta-analysis should be considered. First, the meta-analysis includes data from mostly observational studies and control of confounding factors within each study which associate impairment of glucose control and the risk of hearing impairment cannot be fully mitigated (i.e., exposure to noise, intake of ototoxic drugs, presence of other comorbidities predisposing subjects to end-organ complications particularly the cochlea). Second, with the literature review done, the dose-response relationship between level of glycemic control in DM patients and their degree of sensorineural hearing loss was not fully established. Ideally, to give weight and supplement the result of the meta-analysis, a stratification of subjects’ demographics complete with meta-regression analysis should be done to qualify the results and to produce a stronger association of the outcome based on patient’s overall demographic and clinical picture. It is recommended for further studies, given that there are already ample amounts of data showing the association of glycemic control and sensorineural hearing loss, to quantify the dose-response relationship between these two variables to be able to create a standardized data for clinicians, ultimately to push for strict glycemic control for prevention of hearing loss. Dose-response associations between severity of DM and sensorineural hearing loss may give a clearer association between the disease and its long-standing effect which may be shown via the relationship of hyperglycemia, glycemic control, duration of disease and the prevalence of sensorineural hearing loss.
In conclusion, this meta-analysis showed a higher prevalence rate of sensorineural hearing loss among patients with DM compared to non-diabetic patients. Moreover, poor glycemic control among diabetic patients with a glycemic index based on HbA1c of more than 8.3 (6.97-9.6) is associated with sensorineural hearing loss. Clinicians should be advised of this finding in managing patients with diabetes mellitus and its chronically debilitating end-organ effects within the inner ear.

REFERENCES


