

# Potential diagnostic biomarkers for early detection of idiopathic sensorineural hearing loss in type 2 diabetes mellitus patients



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## ABSTRACT

**Background:** Sensorineural hearing loss (SNHL) is a hearing loss that accounts for almost 90% of all hearing loss. Various factors can cause this disorder, one of which is diabetes mellitus (DM). However, few studies still discuss biomarkers to detect the incidence of SNHL in patients with DM as early as possible. The purpose of this paper is to determine the potential of biomarkers to detect SNHL in type 2 diabetes mellitus (T2DM) patients.

**Methods:** The author uses a database in the form of PubMed, Cochrane, and ScienceDirect used to search for articles using the Boolean operator "AND" or "OR" using the keywords "hearing loss," "diabetes," "biomarkers," "Prestin," "lipid profile," and "Nox2". A total of 276 studies were obtained, followed by the title and abstract screening and feasibility assessment (eligibility) to get inclusion studies included in the qualitative analysis (systematic study).

**Result:** A total of 10 inclusion studies consisted of 2 cross-sectional studies, 2 case controls, and six preclinical studies with 105 and 101 patients in the cross-sectional and case-control studies, respectively. A total of 5, 3, and 2 studies reported associations between hearing loss and Prestin, Nox2, and lipid profile values, respectively.

**Conclusion:** The biomarkers such as Prestin, Nox2 and lipid profile have a role in the early diagnosis of SNHL, but no related studies discuss T2DM. Therefore, basic and clinical studies are still needed to determine its effectiveness.

**Keywords:** Biomarkers, Early diagnostics, Sensorineural hearing loss, Type 2 Diabetes Mellitus (T2DM).

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## INTRODUCTION

Sensorineural hearing loss (SNHL) is a hearing loss that accounts for about 90% of all hearing loss.<sup>1</sup> Based on data from the World Health Organization (WHO) in 2021, it is reported that the prevalence of hearing loss (deafness) worldwide is around 466 million people, with nearly 1 billion young adults at risk of hearing loss.<sup>2</sup> Sensorineural deafness indicates a lesion of the cochlea or the 8th cranial nerve. Various factors influence the incidence of SNHL, such as old age, gender, family history, smoking and diabetes.<sup>1,3</sup> Sensorineural deafness in a previous study was more common in patients with diabetes than in non-diabetics, with the degree of hearing loss correlated with disease progression. This may be due to the occurrence of microangiopathic complications in the inner ear.<sup>3-5</sup>

The relationship between T2DM and

hearing loss has been recognized for decades<sup>3,5,6</sup>, but there is little evidence to address this issue. This may be due to the lack of medical history records and incomplete data. There may be the influence of confounding factors such as age, gender, duration of hearing loss, glycaemic control, and smoking. When viewed from the International Diabetes Federation data in 2019<sup>7</sup>, the number of adults with diabetes is almost around 463 million people and will continue to increase with age in society.

The current findings suggest that the condition of T2DM can cause inner ear pathology. Horikawa et al.<sup>8</sup> report a meta-analysis of 13 studies involving more than 20,000 participants. The study concluded that people with diabetes were more likely to develop hearing loss than those without the disease, regardless of their age.<sup>8</sup> This is also supported by a study by Bener et al.<sup>5</sup>, which showed a

high risk of SNHL hearing loss in patients with T2DM and hypertension. Similar findings were found by Ghosh et al.<sup>3</sup> that the duration of T2DM and HbA1c levels had a significant relationship with the incidence of SNHL. The conditions that cause SNHL are multifactorial, with early detection will greatly affect the prognosis, quickly making a diagnosis will improve the quality of life of T2DM patients.<sup>9-11</sup>

Clinical trials of several previous studies have attempted to identify biomarkers to determine the early diagnosis of the incidence of SNHL.<sup>1,3,11-14</sup> Biomarkers include changes in either DNA, RNA, protein, or metabolites that distinguish between normal and pathological states or objectively measure the response to the occurrence of a disease.<sup>9</sup> To function as an accurate biomarker, several analyses and clinical trials must continue to be carried out. It must play a role in normal biological processes and indicate disease

progression. The role of these biomarkers in the medical world is especially in establishing a diagnosis, which will determine therapeutic decisions and the prognosis of the disease.<sup>9,11</sup>

Based on this, the authors would like to systematically examine the potential of current biomarkers in establishing an early diagnosis of sensorineural hearing loss in patients with type 2 diabetes mellitus (DMT2).

## METHODS

### Literature search

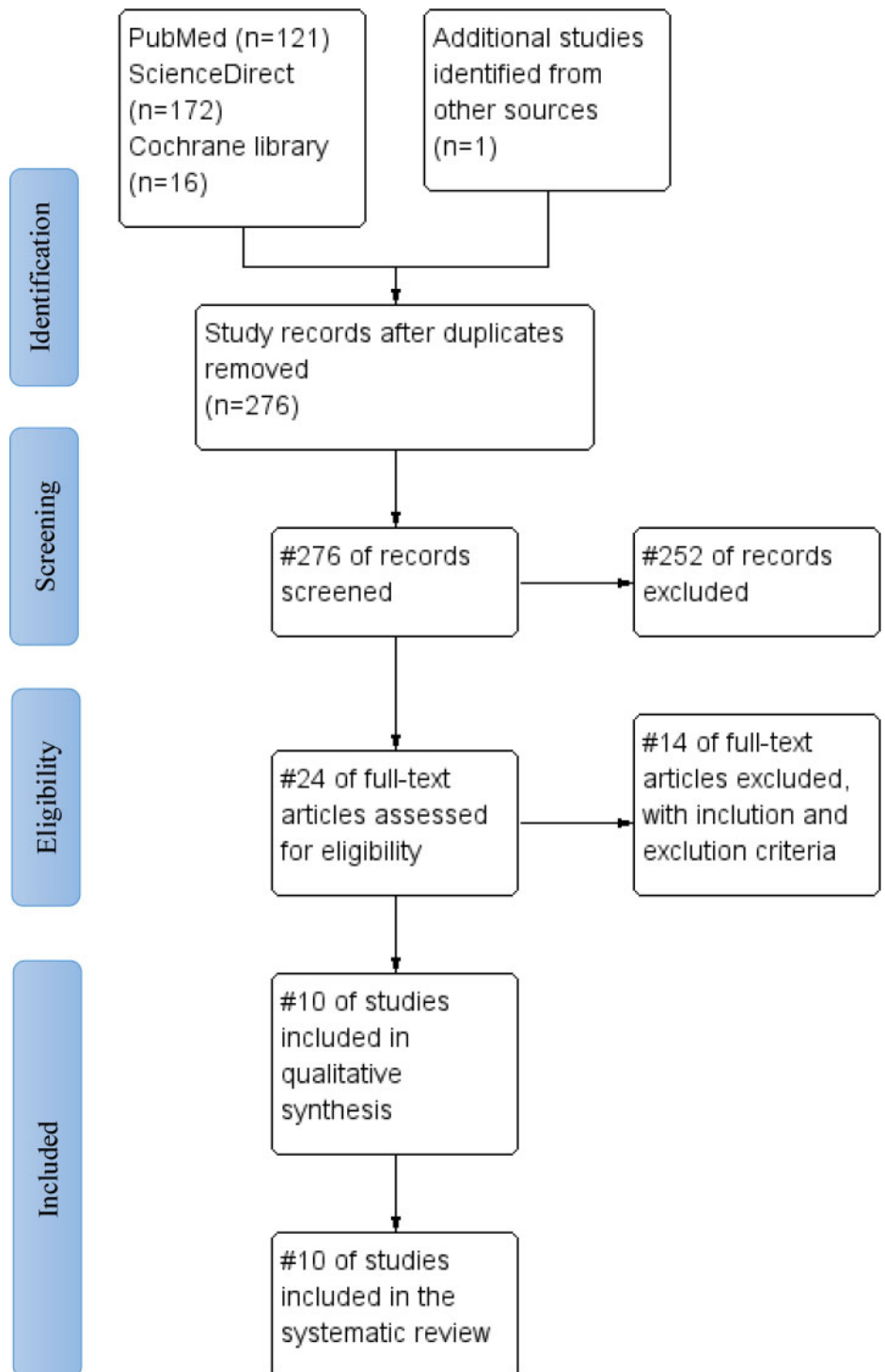
Databases in PubMed, Cochrane, and ScienceDirect were used to search for articles with a timeframe of publication until the end of September 2021. The literature search process used the Boolean operator “AND” or “OR” using the keywords “hearing loss,” “diabetes,” “biomarkers,” “Prestin,” “lipid profile,” and “Nox2”.

### Study selection

Studies that meet the criteria will be included in the inclusion study, with the following criteria: (1) studies that report results regarding the significance of Prestin, NADPH oxidase 2 (Nox2) or lipid profile values in patients with hearing loss in the cohort; (2) studies reporting outcomes between two different groups for both comparators and interventions; (3) a study that reports on the characteristics of the study population in the form of age and type of hearing loss; (4) English studies. Two reviewers independently conducted study selection and data extraction. If there is a disagreement between the two authors, the consensus is reached with the opinion of the third author. The full literature search and selection process followed the (PRISMA) Guideline.

### Data extraction and analysis

Data extraction was carried out independently by noting baseline characteristics and outcomes from included studies using a predefined protocol including first author name, year of publication, study design, age range, diagnosis, sample size, and results. All data results are presented and described descriptively in tabular form.



**Figure 1.** PRISMA Flowchart.

## RESULT

### Literature search

In the literature study search process, 310 studies with 309 originating from online databases (PubMed, ScienceDirect, and Google Scholar) and 1 study originating from data sources previously identified by the authors. A total of 276 studies were

obtained after removing duplicates using computer software (Citation Manager). In the title and abstract screening process, 24 studies were received to be assessed for eligibility (eligibility). Furthermore, 14 studies were excluded because they did not meet the inclusion and exclusion criteria so that ten studies were included in

the qualitative analysis (systematic study). The entire literature search process follows the PRISMA Guideline and is summarized through a flowchart (Figure 1).

### Results Characteristics of Data

All data on the characteristics of the included studies are described in Table

1. All English studies consist of 2 cross-sectional studies, 2 case controls, and six preclinical studies with 105 and 101 patients in the cross-sectional survey and case-control, respectively, described in Table 1.

### Prestin biomarkers in ISNHL

A total of 5 studies reported the association between hearing loss and prestin scores. A total of 4 studies reported increased levels of prestin in the intervention group compared to the control group. On the other hand, one study reported the opposite finding showing no significant

**Table 1. Results of Study Data Characteristics.**

Author, year	Study design	Sample Size			Age
		Intervention	Control	Total	
Xia, 2013	in vivo	7	9	16	5-6 weeks
Sun, 2019	Cross-sectional	14	28	42	57.9 ± 15.4 years
Walton, 2018	in vivo	14	12	26	28.5 ± 1 days (control), 28 ± 1.8 days (intervention)
Parham, 2016	in vivo	21	6	27	6-11 weeks
Tovi, 2019	Cross-sectional	63	-	63	47 ± 16 years
Du, 2014	In vivo	66	22	88	1 month
Du, 2015	In vivo	132	44	176	1 month
Qi, 2018	In vivo and in vitro	12 (in vivo) 10 (in vitro)	6 (in vivo) 5 (in vitro)	18 (in vivo), 15 (in vitro)	N/A
Weng T, 2013	Case control	250	250	500	Range: 15-84 years
Li D, 2020	Case control	100	100	200	Intervention: 38.47±14.36 Control: 36.52±9.86

**Table 2. Findings of Prestin Level in the Hearing Loss Study.**

Author, year	Outcome	Type of Hearing Loss
Xia, 2013	The prestin/GAPDH ratio increased after noise exposure (p=0.017). The percentage of prestin/myosin VIIA also increased with p=0.026	Noise-Induced Hearing Loss
Sun, 2019	Prestin levels were higher in the ISSHL group than in the control group (p<0.001)	Idiopathic Sudden Sensorineural Hearing Loss
Walton, 2018	There was a significant increase in prestin levels (p<0.001)	Noise-Induced Hearing Loss
Parham, 2016	Prestin levels were 56% lower in the control group than in the intervention group with p=0.0003	Noise-Induced Hearing Loss
Tovi, 2019	There is no significant relationship between prestin levels and the incidence of Idiopathic Sudden Sensorineural Hearing (p>0.05)	Idiopathic Sudden Sensorineural Hearing Loss

**Table 3. Findings of Nox2 Levels in the Hearing Loss Study.**

Author, year	Outcome	Type of Hearing Loss
Du, 2014	There was an increase in Nox2 levels in the intervention group with D-galactose induction (p<0.01).	Age-related hearing loss
Du, 2015	There was an increase in Nox2 levels in the intervention group with D-galactose induction (p<0.01).	Age-related hearing loss
Qi, 2018	There was an increase in Nox2 levels in the intervention group with D-galactose induction (p<0.01) in in vitro and in vivo studies.	Neomycin-induced hearing loss

**Table 4. Findings of Lipid Profile Levels in the Hearing Loss Study.**

Author, year	Outcome	Type of Hearing Loss
Li D, 2020	There was a significant difference between lipid profile imbalance and dyslipidemia between the sudden sensorineural hearing loss group and the control group. apo B, apo AI and LDL-C (p<0.05).	Sudden sensorineural hearing loss
Weng T, 2013	apo B and LDL-C levels showed a significant increase in the Sudden sensorineural hearing loss group than the control group (p<0.05).	Sudden sensorineural hearing loss

difference between the two groups in overall prestin levels as described in Table 2.

### Nox2 biomarker on ISSNHL

A total of 3 studies reported an association between hearing loss and the value of Nox2, which is an inflammatory mediator. The comprehensive study reported an increase in Nox2 levels in the intervention group compared to the control group with a strong significance value ( $p < 0.01$ ), which is overall described in Table 3.

### Lipid Profile Biomarkers in ISSNHL

A total of 2 studies reported an association between hearing loss and levels of lipoproteins such as apo B (apolipoprotein B), LDL-C (low-density lipoprotein cholesterol), HDL-C (high-density lipoprotein cholesterol), and apo AI (apolipoprotein AI), and. The two studies that showed a significant difference in lipid profile levels in the sudden sensorineural hearing loss group and the control group showed a substantial increase in the case group ( $p < 0.05$ ), as described in Table 4.

## DISCUSSION

Currently, the etiology and pathogenesis of SNHL are still controversial and found to have a complex pathway of pathogenesis and disease progression. There are many different findings regarding the role of the serological marker, such as autoantibodies and inflammatory cytokines in SSHL progression, particularly idiopathic sudden sensorineural loss (ISSNHL). To date, the immune system and its effect on inner ear tissue have a significant clinical manifestation characterized by high steroid response, which indicates its role in disease pathogenesis.<sup>11,15,16</sup> Serological evidence also supports the involvement of the ISSNHL immune system that may include circulating antibodies in patients with progressive idiopathic bilateral sensorineural deafness.<sup>16</sup> In addition, the limitations of these findings are compounded by the fact that the inner ear immune system is difficult to study because of the difficult-to-access tissue location.

Furthermore, the autoimmune process in the vestibular and cochlea is difficult to determine because there are no specific

tests that can identify problematic antigens in the inner ear. As with another organ-specific autoimmunity, some antigens in the inner ear can become targets of the body's immune response after the onset of infection, trauma, or vascular events. Hence, we could have concluded that prestin, the antigen that has been studied and assessed to play a significant role in the autoimmune process of the inner ear.<sup>16</sup>

### Prestin as a biomarker in ISSNHL

Prestin is found on the lateral/Outer Hair Cells (OHC) cell membrane, where electromotility or auditory processing occurs, the physical process causing cochlear amplification, signifying that it plays a central role in cochlear functioning and sensitivity. Hence, OHC damage is one of the early events leading to deafness; anti-prestin autoantibodies and coenzyme Q10 (prestin-like molecules) are reported prognostic values in ISSNHL patients. Previous *in vivo* studies in mice induced by noise-induced hearing loss and cisplatin ototoxicity or cisplatin-induced hearing loss have shown that prestin (a specific protein X OHC) can be a chemical biomarker for early diagnosis of SNHL.<sup>12,17</sup> Through ELISA measurement, it was found that the serum prestin concentration was significantly higher in patients with ISSNHL patients in comparison to the normal control group ( $p < 0.001$ ). On the other hand, the same study also showed that 60% of patients with ISSNHL had lower prestin concentrations than the post-treatment control group. However, the difference was not statistically significant ( $p > 0.05$ ). Meanwhile, another study shows no significant difference in ELISA analysis of analyzed anti-prestin autoantibodies between the plasma of patients with SSNHL and the control group.<sup>12,17</sup>

The release of prestin from OHC directly through the blood labyrinth barrier or through phagosomes in supporting cells (in the short term) and upregulation of prestin expression in residual OHC (long time) can cause an increase in blood prestin concentration in cases of OHC damage or loss. Another study using wild-type CBA/CaJ mice aged 5 to 6 weeks reported a 32%-58% prestin upregulation in OHC remaining after noise exposure.<sup>11</sup> Other studies with 5-week-

old CBA/CaJ wild-type rats induced by diphtheria toxin SNHL (intraperitoneal diphtheria toxin injection, 50 ng/g for three consecutive days) also reported a similar finding in which the prestin upregulation was regulated locally without feedback involvement. Centrally mediated efferent. A decrease in the concentration of blood prestin in cases of OHC damage or loss may be caused by a dynamic balance of cochlear function in which lower OHC levels release less prestin into the circulation. Decreased blood prestin levels may also be caused by free radicals and antioxidants production disturbance in the cochlea, which could occur after exposure to intense noise or stimulation of other toxic agents.

Oxidative stress can be triggered by the imbalance between free radicals/Reactive Oxygen Species (ROS) and antioxidants. Oxidative stress has a significant contribution to microvascular diabetes complications. Metabolic disturbances in diabetes lead to increased mitochondrial superoxide production in endothelial cells of the myocardium and large and small blood vessels. This increase in superoxide production stimulates the activation of 5 main pathways involved in the pathogenesis of diabetes complications: polyol pathway flux, increased formation of advanced glycation end-products (AGEs), increased expression of AGEs receptors and their activating ligands, activation of protein kinase C (PKC) isoforms, and hexosamine pathway over-activity. Increased superoxide production also directly inactivates two anti-atherosclerotic enzymes (eNOS and prostacyclin synthase). Through this pathway, increased intracellular ROS cause angiogenesis impairment in response to ischemia activates several pro-inflammatory pathways. It causes long-term epigenetic changes that can result in vascularization impairment in sensory organs, particularly auditory.<sup>11</sup>

There is an increase in free radicals, and these mechanisms further enhance cellular mechanisms involving inflammatory mediators. Nox2 is similar to the various inflammatory mediators involved in this process.<sup>18,19</sup>

### Nox2 as a biomarker in ISSNHL

Previous studies have shown that increased Nox2 expression can increase ROS production during the aging process in a mouse model with hearing loss. In addition, another study found that Nox2 overexpression was correlated with increased expression of 8-OHdG, which has been shown as a biomarker of DNA damage caused by oxidative stress. Furthermore, 8-OHdG expression was detected in the cell cytoplasm, showing that oxidative damage to mtDNA in the brain's auditory cortex could be associated with the Nox2 pathway.<sup>20</sup>

The Nox group of molecules has been shown to have a primary function in increasing ROS production, in contrast to the oxidative phosphorylation pathway in mitochondria that produces ROS as a by-product. Previous studies have also shown that Nox2 is a major up regulator of ROS generation in the auditory tissue, especially inner ear tissue. In addition, it has been reported that ROS generation, which Nox2 regulates, is associated with mitochondrial structural damage in the hippocampus *in vivo* (14,20). Therefore, Nox2 levels can be useful target markers for detecting the development of hearing loss, particularly findings in ARHL.<sup>21</sup>

### Lipid profile as biomarkers in ISSNHL

Previous studies have described the lipid profile imbalance as one of the causes of SNHL. The mechanism that plays a role is the condition of dyslipidemia affecting blood circulation in the auditory organ. Blood circulation in the middle ear is directly related to the labyrinth artery. The state of dyslipidemia causes the accumulation of cholesterol and fat in the endothelium of blood vessels. This condition will affect the flow of oxygen-filled blood to the auditory organ.<sup>22</sup>

The results of the analysis of the study comparing 250 patients with ISSNHL with 250 without ISSNHL found that LDL-C and apo B levels ( $p \leq 0.05$ ) were significantly higher in the case group than in the control group. However, this study did not find a significant difference ( $p > 0.05$ ) in other types of lipid profiles such as apo AI and HDL-C (23). A recent study showed similar results, where apo AI, apo B, and LDL-C ( $p \leq 0.05$ ) had a significant

association with the incidence of ISSNHL. The apo B and LDL-C concentrations were higher in the case group than the control group, with the average difference of LDL-C levels in the two groups being 20.08 mg/dL and the difference in apo B levels being 8.66 mg/dL. Meanwhile, apo AI and HDL-C levels were lower in the sudden sensorineural hearing loss group than in controls, with the average difference in HDL-C levels in the two groups being 0.05 mg/dL. The difference between the average concentrations of apo AI between the two groups was 14.5 mg/dL. The apo AI and HDL-C concentrations were assessed as protective factors against sudden sensorineural hearing loss.<sup>22</sup>

Low-density lipoprotein cholesterol (LDL-C) is a lipoprotein particle that carries cholesterol to tissue cells in the periphery. Before LDL-C particles enter the blood vessel wall through endothelial cells, LDL-C will be oxidized in the subendothelial tissue into oxidized LDL-C (ox-LDL-C). When the concentration of ox-LDL-C is excessive in the blood vessels, it directly causes the accumulation of cholesterol in the endothelium of the arteries. This condition causes stiffness of the arterial walls.<sup>22</sup> If this condition persists for a long time, LDL-C will help the formation of atherosclerotic plaques, which are closely related to the incidence of thrombotic and cardiovascular diseases, including sensorineural hearing loss. This process occurs because, in the walls of blood vessels, Ox-LDL-C will be engulfed by macrophages, then converted into xanthoma cells. The fusion and proliferation of xanthoma cells will form the lipid core of the atherosclerotic plaque.<sup>22,24</sup>

Excess cholesterol concentration, in addition to affecting the flow of blood vessels in the organs of hearing, cholesterol also plays a role in the destruction of the structure and activity of the outer hair cells (OHC), which is an important structure in the hearing process. The apolipoprotein of LDL-C is Apo B, a protein particle expressed on the surface of LDL-C. Apo B particles play an important role in recognizing and binding LDL-C particles with their receptors in peripheral tissue cells. Apo B is also important in internalizing LDL-C so that the peripheral

tissue cells can easily absorb cholesterol.

Meanwhile, the apolipoprotein from HDL-C particles was Apo AI. This type of apolipoprotein is synthesized in the liver. About 60% to 70% of the HDL-C structure consists of Apo AI. This protein particle becomes the main structural component of HDL-C. A decrease of apo AI concentration will reflect a reduction in the function of HDL-C to increase cholesterol metabolism and export cholesterol.<sup>22</sup> In addition, if a person has dyslipidemia, there will be an increase in LDL-C concentration, which interferes with the release of nitric oxide. Nitric oxide is a powerful vasodilator that plays an important role in maintaining the blood supply to the organs of hearing. When the release of NO is disturbed, it will directly be affecting the blood flow to the auditory organ system.<sup>23</sup>

### CONCLUSION

Based on this, it can be concluded that biomarkers such as Prestin, Nox2, and lipid profiles such as LDL-C, apo AI, apo B and HDL-C have a role in the early diagnosis of SNHL there are no related studies that discuss T2DM. Therefore, basic and clinical studies are still needed to determine the effectiveness of these biomarkers.

### CONFLICT OF INTEREST

All authors declare that there is no conflict of interest in the preparation and writing of this article.

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### AUTHOR CONTRIBUTION

All authors have the same role in contributing to the writing of this article.

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