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## Type 2 diabetes and hearing loss

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### Background and significance

Hearing loss is a common public health problem that affects work productivity, functional status, social interactions, personal safety and well-being, and quality of life. In particular, hearing loss is of concern among older adults due to age-related hearing loss and among the working population due to hearing loss associated with noise exposure on the job. In 2009, the Centers for Disease Control and Prevention (CDC) reported that 34.5 million adults in the U.S. experienced “trouble hearing;” a 9% increase since 2000 when 31.5 million U.S. adults reported “trouble hearing.”<sup>1,2</sup> While aging and exposure to loud noise and other ototoxic substances are well-known risk factors for hearing loss, research conducted over the past several decades has brought attention to sensorineural hearing loss among individuals with other health problems such as diabetes.

More than 8% of the population in the U.S. has diabetes mellitus and the incidence is increasing at unprecedented rates; it is expected that by 2050, one in three Americans will suffer from this disease.<sup>3</sup> For those born in 2000, the estimated lifetime risk for developing diabetes is 32.8% for males and 38.5% for females, and the risk is even higher in certain minority groups.<sup>4</sup>

Since 1997, diabetes mellitus has been categorized as either type 1 or type 2. Type 1 diabetes is an autoimmune destruction of pancreatic  $\beta$ -cells and subsequent dependence upon insulin therapy.<sup>5</sup> Type 2 diabetes is a disorder characterized by insulin resistance, pancreas  $\beta$ -cell function decline, impaired glucose tolerance, and hyperglycemia; sometimes the  $\beta$ -cell function destruction is enough to require insulin therapy.<sup>6</sup> Risk factors for type 2 diabetes are complex and include genetic predisposition, lifestyle issues such as insufficient exercise, diet and smoking, as well as environmental components.<sup>7</sup>

Type 2 diabetes accounts for 90% of all cases of the disease, and traditionally it has been a disease of middle-aged or older people.<sup>3</sup> However, since the 1990s, the age of onset has become apparent among younger adults, and even children.<sup>8</sup> This trend is a serious threat to public health, as diabetes is associated with severe and potentially fatal complications and comorbidities, such as cardiovascular disease, kidney disease, visual impairment, neuropathies, and infectious complications.<sup>7</sup> The person living with diabetes can experience symptoms from such comorbidities which may impact function, emotional well-being, and quality of life as

well as morbidity from complications that may limit work productivity, increase absenteeism, and lead to premature loss of employment.<sup>9,10</sup>

Considering both hearing loss and diabetes mellitus are significant health issues, it is worthwhile to examine the relationship between the two. The purpose of this paper is to examine the evidence linking type 2 diabetes with hearing loss and possible causal mechanisms through an extensive review of the literature. In addition, the paper discusses the underlying mechanism responsible for hearing loss occurring with diabetes, specifically, microangiopathy, advanced glycation end products, and reactive oxygen species (oxidative stress).

## Hearing loss in type 2 diabetes

The majority of the studies identified for this review found hearing loss among individuals with diabetes, or identified worse hearing among those with diabetes compared to control participants. Three studies did not find a difference in hearing loss between controls and those with diabetes. The first, a cross-sectional study of 200 adults in 1981, found no evidence of increased prevalence of hearing loss among individuals with diabetes.<sup>11</sup> Although this study tested pure-tone audiometry ranging from 250 to 8000 Hz, including these higher frequencies, the researchers did not measure the smoking history among the participants, and they compared the prevalence of hearing loss in their diabetic study population to data from a population study of hearing loss prevalence from 12 years earlier, making their comparison less valid, as over time the public's hearing likely improved due to factors such as better occupational hearing protection or decreased smoking prevalence.

The next cross-sectional study to find no increased hearing loss amongst individuals with diabetes aimed to describe the relationship between diabetes, noise exposure, and hearing loss among working men between the ages of 40 and 63 years.<sup>12</sup> The participants were divided into high and low-noise exposure groups, and they included 15 individuals with diabetes in the high-noise exposed group and 13 individuals with diabetes in the low-noise exposed group; such low numbers may have reduced the power of the study and increased the chance of missing a difference in hearing loss between participants with diabetes and the control group. Moreover, this study did not ask the participants about their smoking history. Both studies, from Harner and from Hodgson et al. may not have included measurement of smoking history as the connection between smoke exposure and hearing loss was a newly emerging hypothesis in the 1980s when these studies were conducted.

In 1998, among 3373 adults recruited for a large population study including 344 self-reported participants with diabetes, researchers measured hearing loss with pure-tone audiometry at 500, 1000, 2000 and 4000 Hz and defined hearing loss as >25 dB, and found that the association between hearing loss and diabetes was not significant after they controlled for age, and after the researchers controlled for various potential confounders including smoking history, noise exposure and hypertension.<sup>13</sup> However, as Dalton et al. did not measure frequencies higher than 4000 Hz, they may have missed some higher tone hearing loss at 6000 or 8000 Hz frequencies. Of interest is that studies identified for this review completed after the year 2000 found a positive association between hearing loss and diabetes, which suggests that increased knowledge of potential confounders such as tobacco exposure, and changes to study design may mean that there should no longer be any controversy over whether diabetes mellitus is associated with hearing loss; instead, questions remain about the pathology, the prevalence and incidence, the progression of hearing loss, and the ways that healthcare providers and preventative measures can reduce risk of hearing loss for patients with diabetes.

The prevalence of hearing loss among individuals with type 2 diabetes remains unclear, and there have not been any prospective cohort studies to measure incidence. Several studies report higher prevalence of hearing loss among adults, not including elderly participants, which provides evidence that diabetes affects hearing separately from age-related hearing loss, or perhaps that age-related hearing loss occurs sooner among persons with diabetes.

A cross-sectional study of adults under 50 years of age that compared participants with type 2 diabetes diagnosed when less than 40 years of age to control participants without diabetes found that the prevalence of mild to moderate hearing loss among those with diabetes to be 21.7% and significantly higher than among the control group.<sup>14</sup> Bainbridge et al. in a large population study of 5140 adults under 69 years of age found the prevalence of hearing loss to be 21% among adults with diabetes, and that this had significantly higher prevalence than among adults without diabetes, which was found to be 9%.<sup>15</sup> Another population study of 2306 Japanese adults found an increased prevalence of high- and mid-frequency hearing loss in adults between the ages of 40 and 60 years compared to participants without diabetes, but among older adults (aged 65–86 years) they found no significant hearing loss difference between those with diabetes and those without diabetes.<sup>16</sup>

In 2009, Cheng et al. compared data from the National Health and Nutrition Examination Surveys (NHANES) that took place from 1971 to 1973 and from 1999 to 2004.<sup>17</sup> The comparison of cross-sectional data of adults between the ages of 25 and 69 with self-reported diabetes found hearing loss to be greater among individuals with diabetes, and the prevalence increased between the two NHANES data: between 1971 and 1973 the prevalence was 28.5% among individuals with diabetes compared to 24.4% in people without diabetes; and between 1999 and 2004 data, the prevalence was 34.4% among individuals with diabetes compared to 22.3% in people without diabetes.<sup>17</sup> This suggests that there may be a worsening trend of hearing loss among those with diabetes, perhaps this is due to younger age of onset of diabetes in the more recent cohort; the researchers reported a significant difference in mean duration of disease between the groups, with a longer duration of diabetes in the 1999–2004 group. In the earlier time period, 1971–1973, fewer frequencies were measured in pure-tone audiometry testing, whereas higher frequencies of 6000 and 8000 Hz were not tested. This may have resulted in underestimation of the prevalence of hearing loss in the earlier group if the association with diabetes is high frequency in nature. Both Bainbridge et al. and Cheng et al. measured diabetes by self-report which may underestimate the number of individuals with diabetes because it fails to identify undiagnosed cases.

A retrospective chart review of 53,461 age-matched adults without diabetes and 12,575 adults with diabetes recruited from within the Veterans Affairs Healthcare System found a significantly higher prevalence of hearing loss among patients with diabetes, at 23% among those with diabetes compared to 19% among controls.<sup>18</sup> The researchers did not report age range or gender of the adults studied, nor did they specify type of diabetes or duration of disease. Hearing loss was measured with pure-tone audiometry, but only to frequencies of 4000 Hz, and decibels at which hearing loss was defined was not reported. Moreover, there was no mention of noise exposure in the sample, hypertension or smoking history. Noise exposure is particularly likely among the adults included in this study as the medical records they used were from the Veterans Healthcare System.<sup>18</sup>

There are inconsistent findings in various studies regarding the severity of loss, and hearing frequency that is affected in the population with diabetes. Some studies identified high-frequency loss, others low frequency, and some found hearing loss across frequencies. Among those that identified high-frequency loss, Diaz de Leon Morales et al., in a cross-sectional study including 94 type 2 adult males and females with diabetes and 94 controls found high-frequency hearing loss was significantly and positively associated with the duration of disease and the age of the participant.<sup>19</sup> In this study, the mean age was 50 years, the mean duration of disease was 7.2 years, and patients with noise exposure were excluded.<sup>19</sup> In a study from China, Ren et al., compared 50 individuals with type 2 diabetes with 50 control participants, all participants were described as middle-aged men and women, the mean age of participants with diabetes was 40.8 years and the mean duration of disease was 7 years.<sup>20</sup> In the study design, the researchers attempted to control for confounders by screening for and excluding those with neurological conditions, noise damage and middle-ear hearing loss, serious health problems, treatment with ototoxic medications, history of diseases of the inner ear, smokers, regular consumers of alcohol, and those who failed cognitive screening. The researchers identified increased high-frequency hearing loss among the diabetes participants, and as these

were younger patients this is not likely to be the high-frequency hearing loss associated with aging. Vaughan et al.<sup>21</sup> reported on a cross-sectional analysis of a large study of adult military veterans (including 667 men and 27 women), of whom 342 had diabetes and 352 did not have diabetes, and found that those with diabetes with ages under 60 years experienced higher-frequency hearing loss than those without diabetes.<sup>21</sup> This study did not specify diagnosis of type 1 or type 2 diabetes, but the average duration of disease was 12.5 years.<sup>21</sup>

Several studies reported low-frequency hearing loss. In a cross-sectional study of 30 adults between the ages of 59 and 92 years, which examined hearing loss in older individuals with type 2 diabetes compared to controls, Frisina et al., found worse hearing loss at low frequencies in the group with diabetes and the hearing was worse in the right ear than the left.<sup>22</sup> Age-related hearing loss affects high frequencies first, which may explain why the difference between those with diabetes and controls was found at lower frequencies in this study. Hearing loss among individuals with diabetes was also found to be worse in the right ear compared to the left, and with age-related hearing loss, the right ear hearing advantage is lost, suggesting that diabetes may increase presbycusis. In addition to pure-tone audiometry, the researchers measured otoacoustic emissions, which measures sound waves produced by the hair cells of the inner ear, and may detect damage to the cells that could affect hearing, but they were not able to detect a statistically significant difference in the group with diabetes.<sup>22</sup>

In a much larger cross-sectional study of 1740 Mexican American adults between the ages of 20 and 74 years who had participated in the Hispanic Health and Nutrition Examination Survey between 1982 and 1984, Ma et al., found participants with diabetes only had worse hearing at 500 Hz after adjusting for age, gender, employment and marital status (tobacco use was not reported).<sup>23</sup> Unfortunately, in this study, pure-tone audiometry was only tested upto 4000 Hz and so they may not have detected higher frequency losses among the participants with diabetes. In addition, diagnosis of diabetes was self-reported, and may therefore have underestimated the number of participants with diabetes surveyed. A cross-sectional analysis of 102 individuals with insulin and non-insulin dependent diabetes that compared their hearing to control data from three population studies in the United Kingdom detected worse hearing loss among participants with diabetes at low and middle frequencies.<sup>24</sup> Tay et al., included men and women between the ages of 18 and 80 years and they measured pure-tone audiometry between 250 and 8000 Hz. The inclusion of elderly participants may explain why no difference was found at 8000 Hz because age-related hearing loss affects higher frequencies. The researchers excluded those with a history of noise exposure and ototoxic drug use, but did not measure tobacco use.

Mitchell et al., conducted a retrospective analysis of a population survey that followed up the participants for 10 years.<sup>25</sup> The researchers used data from 2334 participants' year-5 follow-up visit and 1952 participants' year-10 follow-up visit, as audiometric testing was done at these two times. After adjusting for age, smoking, gender and noise exposure, type 2 diabetes was independently associated with increased risk of hearing loss, and hearing loss was worse at all frequencies between 250 and 8000 Hz.<sup>25</sup> Bainbridge et al., cross-sectional study, which did not differentiate between diagnosis of type 1 and type 2 diabetes, adjusted for age, and reported increased odds of hearing loss at all the levels of severity and frequency.<sup>15</sup> A further cross-sectional population study of 3853 adults from the NHANES survey between 1999 and 2002 reported that diabetes was associated with hearing loss at low frequencies, 500–1000 Hz, and high frequencies, including 3000–8000 Hz; however, diabetes was self-reported and may have included type 1 and type 2 as well as undiagnosed disease.<sup>26</sup>

## Theories of hearing loss in diabetes

Diabetes is ultimately a disturbance of energy metabolism that involves mitochondrial dysfunction, oxidative stress, and the deposition of glycated products in body tissues, leading to disturbances in metabolic functioning. The disturbed metabolism of diabetes may provide a

pathway to damaging audiologic physiology and ultimately, function. There are a number of physiologically plausible theories about the underlying mechanism responsible for hearing loss occurring with diabetes. Microangiopathy, advanced glycation end products, and reactive oxygen species will be discussed in this article.

### *Microangiopathy*

The cochlea is highly microvascular and considered vulnerable to the effects of microangiopathy as the end result of hyperglycemia of diabetes. Hearing loss in diabetes may be a result of microangiopathy and several studies postulate this.<sup>18,22,27,28</sup> Greater odds (OR 2.28) of hearing loss were found in individuals with non-insulin dependent diabetes (NIDDM) and nephropathy than in those with NIDDM without nephropathy in a population-based longitudinal study.<sup>13</sup> Worsening creatinine levels as a marker for microangiopathy were observed as the hearing worsened in a very large cohort (12,575) of chart reviews of patients with diabetes.<sup>18</sup> Kurt et al.<sup>27</sup> measured factors of microangiopathy such as microalbuminuria and serum creatinine levels along with HgBA1C levels and duration of diabetes and found that poor disease control and duration of diabetes showed significantly worse hearing levels at low-, middle- and high-frequencies, providing support for microangiopathy as a possible pathway to hearing loss in diabetes.

An evaluation of risk factors for hearing loss ( $N = 3527$ ) from the National Health and Nutrition Examination Survey (NHANES) 1999–2002 found that diabetes affected hearing loss across the full-frequency spectrum,<sup>26</sup> a pattern of hearing loss that the authors describe as due to loss of stria vascularis, supporting microvascular disease. Researchers evaluating NHANES 1999–2004 data agree with possible microvascular causation but also state that as yet unidentified genetic susceptibility may play a role for both diabetes and hearing loss.<sup>15</sup>

Loader et al.<sup>28</sup> examined a microangiopathic marker, Stromal cell-derived factor 1a (SDF-1a) in patients with type 2 diabetes and controls. Higher SDF-1a levels occurred in patients with diabetes, with more difficulty in speech discrimination and with higher hearing threshold levels over all frequencies. SDF-1a is a known microangiopathy mediator; this implies a role in audiopathy secondary to diabetes and warrants further research.

Evaluation of auditory brainstem response (ABR) has been conducted by numerous researchers<sup>19,21,29–31</sup> with similar latency prolongation found in multiple waves. The findings suggest a central neuropathy abnormality in diabetes that precedes hearing loss.<sup>29</sup> One group of researchers differed in their opinion; Diaz et al. believe their results are the result of metabolic compromise and that diabetes may aggravate hearing loss related to aging as they found a relationship between patient age and time since diagnosis.<sup>19</sup>

### *Advanced glycation end products*

Peripheral auditory function was more affected in a study by Frisina et al.<sup>22</sup> than central function most likely due to the fact that glycosylation of myelin occurs in the peripheral nervous system but not in the central nervous system. A study by Austin et al.<sup>32</sup> provided evidence for the hypothesis that the level of glucose in the endolymph reflects the ambient blood glucose and can lead to pure tone deficits as the two lowest frequency pure-tone thresholds measured were significantly related to glucose levels measured 1 h before the hearing test. Extending the logic, repeated hyperglycemia may lead to chronic cochlear damage or impaired endolymph homeostasis.

Vascular endothelial damage resulting from diabetes is proposed as a mechanism leading to hearing loss in diabetes. Ren et al., propose that, in type 2 diabetes, this results in accelerated loss of the right ear advantage of greater hearing sensitivity that is normal in young adulthood.<sup>20</sup> Frisina, et al.<sup>22</sup> also found a greater effect of diabetes on the right ear in a cohort of aged type 2 diabetes patients.

## *Reactive oxygen species/oxidative stress*

Frisina et al.<sup>22</sup> cite reactive oxygen species (ROS) as an important factor in type 2 diabetes that may impact hearing loss. Oxidative stress was considered a causative factor in a study of type 2 diabetes patients without microangiopathy or peripheral neuropathy.<sup>33</sup> Higher levels of serum protein oxidation products, nitric oxide and enzymatic antioxidant activity were found with a group of 63 participants with type 2 diabetes compared to a control group of 37 participants without diabetes. Nitric oxide, which is considered protective, was higher in those with diabetes who had normal hearing than in those with hearing loss. The study results suggest a role for oxidative stress in hearing loss in diabetes. Oxidative stress was also considered potentially causative by Sakuta et al.<sup>34</sup> Elevated glucose levels, triglycerides and noise-induced hearing loss are all associated with oxidative stress and were found in their study.

Increased oxidative stress associated with diabetes and lack of antioxidant protection in basal hair cells were proposed by other researchers as explanation for findings in a study where middle-aged individuals with diabetes had an interaction with aging at high frequencies resulting in increased hearing loss.<sup>16</sup>

As suggested by Durmus et al.<sup>29</sup> and Konrad-Martin et al.<sup>31</sup> hearing loss in diabetes is most likely a multifactorial process which may include more than one of the causative factors discussed here. Further research is needed to determine which theory or theories reflect the true cause of hearing loss in diabetes.

## **Conclusion**

Research conducted over the past several decades has brought attention to sensorineural hearing loss among individuals with diabetes. We have moved from hearing loss associated with diabetes being controversial to being accepted. Now, we need to move to the next step—what can we do about it? Before we can answer that question, we need to learn a lot more about what is causing it.

The auditory system requires glucose and high-energy utilization for its complex signal processing. Hearing loss in the context of type 2 diabetes may result from microangiopathic processes that follow deposition of glucoprotein due to hyperglycemia in small blood vessels, impacting neurological function.<sup>35,36</sup> Peripheral neuropathy, nephropathy, and retinopathy in diabetes are known to result from this same microangiopathic process. Coronary artery disease (CAD), cerebrovascular disease, and peripheral vascular disease (PVD), or macrovascular outcomes of diabetes, may also result from this process.

A number of plausible physiological mechanisms that may explain the links between hearing loss and type 2 diabetes have been proposed. These include vascular, neurological etiologies including central nervous system effects of diabetes, mitochondrial abnormalities, and genetic causes.<sup>37</sup> Type 2 diabetes may be an independent risk factor for hearing loss, because its effects of hyperglycemia may damage the cochlea both anatomically and physiologically.<sup>22</sup> Signs and symptoms that commonly occur in type 2 diabetes can be related to immediate effects of hyperglycemia or hypoglycemia (blurred vision and excessive thirst for example), to sustained hyperglycemia that impacts neurological functions (peripheral neuropathy symptoms such as numbness, tingling, hypersensitivity), or to microvascular and/or macrovascular effects accompanying diabetes as a complication. The auditory complications are more closely related in pathophysiology to other microvascular complications, not macrovascular ones, where there may be more of a cumulative effect of dyslipidemia, insulin resistance, and hypertension, along with hyperglycemia at work.

While many prior studies have reported a distinct process of hyperglycemia and its intracellular and extracellular physiological changes in many body systems for individuals with type 2 diabetes, limited studies investigated the effects of type 2 diabetes on the auditory system. As the inner ear is vulnerable to metabolic and circulatory stress, it is a logical

expectation to see the impact of microvascular complications commonly associated with type 2 diabetes on the auditory systems. However, the potential that other processes are at work causing acoustic trauma is as yet unclear, and therefore requires further research. Growing evidence suggests a role for oxidative stress in the pathway leading to acoustic trauma causing hearing loss.

Although the association between diabetes and hearing loss has previously been studied, the majority of studies utilized limited hearing measurement, pure-tone audiometric tests, to assess hearing loss. Therefore, the prevalence and magnitude of association between type 2 diabetes with the peripheral and central auditory systems is as yet unknown. Evaluation of hearing loss associated with type 2 diabetes requires using tests that evaluate the full auditory system, from the cochlea to the higher auditory pathways. To date, there is no “gold standard” audiological-test protocol available for this purpose in regular clinical use.

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