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EFFECTS OF DIABETES ON HEARING AND COCHLEAR STRUCTURES

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Abstract

Diabetes mellitus (DM) is a chronic systemic disease characterized by hyperglycemia, with various pathogenic mechanisms. From absolute or relative insulin deficiency, patients with DM often demonstrate various levels of metabolic disorders. Major clinical manifestations of DM include metabolic disorders, vascular lesions, circulatory disturbances and neurologic complications. Along with advances in DM research, reports of DM related tinnitus and hearing impairment have increased continuously. Research on DM related auditory system dysfunction has focused on cochlear microcirculation, cellular homeostasis, genetics and aging. Cochlear microcirculation plays an important role in cochlear physiology and its disorders are associated with many inner ear diseases. Ischemia and subsequent reperfusion seen in cochlear microcirculation disorders are important factors in hearing damage. Understanding cochlear microcirculation and structural as well as functional changes in DM patients with hearing loss and their causal factors will help reveal pathogenic mechanisms in diabetic hearing loss and provide new ideas in developing interventions and preventing damages caused by diabetes.

Key words: diabetes mellitus; complications; hearing loss; cochlea; cochlear hair cell; microcirculation; ischemia; inner ear; capillaries; microvascular lesions; neuropathy; metabolic abnormalities

Introduction

Studies have since long indicated a close relation between diabetes mellitus (DM) and hearing loss [1,2]. The main clinical manifestation of DM is glucose, lipid and protein metabolism disorders, for the body is unable to produce or use insulin properly[3]. Metabolic disorders in DM include decreased lipid synthesis and increased lipid breakdown, which lead to elevated blood lipid levels and contribute to arthrosclerosis. With sustained high levels of blood glucose, increased amount of glycated hemoglobin is produced and deposited in the walls of small blood vessels. Together with injury to the endothelium by immune complex, this leads to increased vessel permeability, thickened basement membrane and abnormal growth of endothelial cells, resulting in reduced lumen size. With constricted or blocked supplying vessels and sustained high glucose levels, nerves become malnourished and their cellular membrane demonstrate dysplasia or necrosis changes from metabolic disorders, leading to the so called diabetic peripheral neuropathy which can also involve the autonomous nerves and can happen at an early stage of diabetes. Microcirculation disorders and hemodynamic changes (including that in the cochlea) are common in DM[4], which can also contribute to diabetic neuropathy. Involvement of the immune system has also

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been shown to be an important etiology and mechanism of DM and its complications. In addition to systemic effects, there have been increasing reports of compromised inner ear functions in DM, including dizziness, tinnitus and hearing loss. Along with advances in research on DM and its complications, there has been an increasing attention to hearing disorders in patients with DM[5]. Studies have indicated that vascular and neural changes in the cochlea are likely the cause of hearing changes in DM, including thickening of capillary walls (especially in the stria vascularis) and loss of outer hair cells[6]. Blood vessels supplying the cochlea carry no collateral circulation once inside the cochlea. Cochlear microcirculation provides the cochlea with energy and substrates, carries away metabolic wastes, and helps maintain cochlear homeostasis. The functions of the inner ear depend on the stability of its internal environment supported by microcirculation. While it is clear that compromised cochlear blood supply can lead to cochlear dysfunction[7-9], details of injury mechanisms in diabetic hearing loss such as regulation of cellular transduction signals and neural, humoral and autonomous regulation of microcirculation are subject to debate and yet to be thoroughly studied. This paper aims at reviewing and summarizing existing literature on DM-related inner ear disorders, as well as discussing their possible etiology and pathogenesis.

Effects of DM on the audiotry system

Cochlear microcirculation plays a very important role in cochlear physiology. Hyperglycemia and hyperlipidemia are associated with increased blood viscosity and circulation disorders. Studies have indicated that inner ear diseases are often associated with microcirculation disorders, especially involving the stria vascularis. The associated tissue ischemia and hypoxia can cause damage to single or multiple neural units and/or hair cells. The deep location and complex structures of the inner ear makes its morphological studies difficult. Research on cochlear microcirculation therefore lacks behind microcirculation studies of other organs, despite researchers' efforts and some recent advances. Lipid metabolic disorders can lead to lipid deposit in cochlear hair cells and damage of cochlear neural cells, followed by impeded neural transduction. The high dependence on glucose as the source for its high energy consumption makes the cochlea a target of damage in DM.

Basic research on DM effects on the auditory system

The labyrinthine artery comes from the basal artery or from the anterior inferior cerebellar artery. Labyrinthine artery gives rise to the common cochlear artery and vestibular artery, the former giving rise to the vestibulocochlear artery and spiral modiolar artery that supply the cochlea [10]. Blood pressure can affect cochlear microcirculation[11], although the correlation between cochlear blood flow and systemic blood pressure is relatively weak. It is believed that there is an autonomous regulation mechanism in cochlear microcirculation, although it is not as obvious as that with cerebral blood flow. Such regulation has not been seen in muscles[12]. Autonomous regulation in cochlear microcirculation refers to a local regulatory activity within the cochlear micro vessels and is an important factor in maintaining normal cochlear blood supply. Among the multiple complex regulatory mechanisms of cochlear blood flow, the local regulation of cochlear micro vessels plays an important role. Studies show that lateral cochlear wall micro blood vessels are not fully open under normal circumstances but open in alteration, indicating certain levels of reserve in blood [13]. Regulation of cochlear blood vessels is dominated by local metabolites. The responsiveness of endothelial cells is critical in local vessel changes, although neural control is also at play[14]. Auto-rhythmic activities have been observed with normal arterioles in the cochlea. L-arginine significantly increases the frequency and magnitude of these activities and may enhance cochlear microcirculation and increase cochlear blood flow[15]. Study evidence indicates that regulation of blood flow in cochlear lateral wall relies on the tropomyosin-like immune active materials near the endothelial and peripheral cells in the spiral ligament, supporting the notion that there are active local regulatory materials in cochlear micro blood vessels[16]. Under certain pressure or anoxic conditions, endothelium releases ATP, acetylcholine and endothelin, which, upon interacting with their receptors, produce an endothelium-dependent factor, now called nitric oxide, which causes smooth muscle relaxation[17].

Cochlear microcirculation changes with age. In 1990, Prazma[18] reported greatly decreased cochlear blood flow in old gerbils, especially in the lateral stria vascularis. In 2000, Seidman[19] showed in Fischer rats that blood flow slowed or was blocked as the animal aged, resulting in insufficient local perfusion and cochlear microcirculation dysfunction, followed by cochlear and vestibular malfunctions.

Cochlear microcirculation changes have also been reported in pathological conditions. Masutani[20] found decreased blood vessels in the stria vascularis and correlated stria vascularis atrophy under Meniere's disease condition. DM can also change cochlear microcirculation. In 2006, Wang[21] reported changes in ultrastructure of inner ear capillaries in a rat model of DM, including thickened basement membrane. In 2000, Tomisawa[22] com-

pared temporal bone stria vascularis sections from 16 DM patients with those from 16 non-DM patients and found atrophy and thickening changes. He concluded that capillary lumen changes from basement membrane thickening and atrophy of the stria vascularis are important factors in hearing loss in DM patients.

In addition to changes in the vascular structures, other morphological changes in the inner ear in DM have also been reported. In rats, DM was reported to cause pathological changes in outer hair cells (OHCs), spiral ganglion cells and nerve fibers, primarily mitochondria damages[23]. When compounded with noise exposure at 95 dB SPL, significantly increased OHC loss was found in rats with streptozotocin-induced diabetes as compared to normal controls[24]. Other diabetes-related metabolic disorders can also result in morphological abnormalities in the cochlea. Lipid metabolism disorders have been found to lead to deposit of fatty droplets in hair cells and are thought to be a direct cause of deafness in DM, with microvascular changes having probably a secondary influence on inner ear functioning and spiral ganglion dysplasia being a subsequent change[25]. In fact, high frequency hearing loss and increased susceptibility to noise damage have been reported in mice on high cholesterol diet, with hyperlipidemia and vascular abnormalities being blamed as the cause[26].

One important consequence of cochlear microvascular and morphological changes is auditory dysfunction. In middle aged and old mice, increased auditory brainstem response (ABR) thresholds were found to be associated with type I and, especially, type II DM modeling, with decreased distortion product otoacoustic emission (DPOAE) amplitudes[27]. The latency of ABR wave I was found to be delayed in gerbils with high sugar diet induced diabetes, although without changes in amplitudes[28]. Changes in otoacoustic emissions (OAEs) were found to take place before abnormal ABRs in a rat DM model, with oxidation injury to the OHC related to inner ear damage and metabolic disorders blamed as the underlying cause [29].

Clinical studies on diabetes-related hearing impairment

Along with advances in DM research, hearing function in DM patients has attracted increasing attention from clinicians including audiologists, with increasing reports on DM related hearing damage. It has been reported that prevalence of hearing loss in DM patients is twice that in normal individuals and that vertigo, tinnitus and hearing loss in DM patients are likely from inner ear diseases related to glucose metabolism disorders[30]. Susceptibility to hair cell damage and hearing loss in noise exposure has been found to be increased in insulin dependent DM, probably related to dysplasia changes in the inner ear[31]. Research shows that hearing loss in most DM patients has little to do with noise exposure, can take place gradually or suddenly, and is usually high frequency sensorineural loss. Many patients may not realize the relation between their hearing impairment and their diabetic condition. Clinicians (especially endocrinologists) therefore need to monitor hearing in DM patients, in addition to other common diabetic complications, to ensure timely interventions.

In as early as 1975, Friedman[32] evaluated hearing in 20 DM patients with peripheral neuropathy and showed that hearing thresholds were elevated in at least one frequency in 11 of these patients (55%), higher than normal individuals of the same age. Snashall proposed in 1977 that DM might lead to premature hearing deterioration [33]. Sieger (1983) compared pure tone audiometry and ABRs between 51 insulin dependent DM patients and 13 non-DM patients and found no difference, although insufficient sensitivity of testing methodology was thought to be the reason[34]. In 1989, Kurien found that average hearing thresholds in 30 DM patients younger than 50 years were worse than those in 30 non-DM patients[35]. In 1993, Cullen[36] compared hearing in 44 insulin dependent DM patients with 38 healthy individuals and found hearing was worse in DM patients, especially in males, which was not affected by dose of insulin or family history. A study by Tay in 1995[37] that compared 102 DM patients with 102 healthy individuals demonstrated significantly deteriorated mid and low frequency hearing in DM patients that seemed to be correlated with disease duration but not with stages of retinopathy. Similar relation between hearing impairment and DM duration was also shown in a study by Lasisi in 2003[38], in which bone conduction thresholds in 13 DM patients were higher than non DM patients and correlated to DM duration, especially in those longer than 10 years. Based upon evaluation, including hearing assessment, of 59 DM patients with retinal and nephritic complications in comparison to 20 DM patients without complications, Bayazit[39] concluded that diabetic peripheral neuropathy and encephalopathy are the cause of sensorineural hearing loss in DM. Zhao[40] showed significantly worse hearing thresholds in 50 DM patients (type II = 46, type I = 4) with complications compared to those without complications, and concluded that mechanisms of diabetic hearing loss are the same for other diabetic complications and that treatment should focus on controlling diabetic complications. In 2008, Loader found significant differences in pure tone audiometry results between DM patients and normal individuals at all frequencies and believed that cochlear microvascular as the cause of hearing impairment should be further studied[41].

In addition to audiometry, other test modalities have al-

so been used to study effects of DM on the auditory system. In 1990, Parving[42] found that, in a group of 20 insulin dependent DM patients, ABRs were abnormal in 40% of those with long disease history, suggesting possible presence of diabetic encephalopathy. In 1998, Wang[43] tested DPOAEs in 19 patients with well controlled DM and 19 normal adults and found that DPOAEs might reveal early stage mild damage and dysfunction in the cochlea and efferent nervous system and might be useful for early diagnosis of diabetic hearing impairment. Orts[44] studied DPOAEs in 20 insulin dependent DM patients in 1998 and concluded that diabetic cochlear diseases might be related to OHC injury. Lisowska[45] compared DPOAEs between 42 young and middle aged insulin dependent DM patients and 33 age/gender matched non DM patients and found reduced DPOAE amplitudes among the DM patients. It was concluded that OHC injury might be responsible for early stage diabetic hearing impairment. In 2002, Ottaviani[46] studied OAEs in 60 type I DM patients and 58 normal volunteers and found that OAEs were either unilaterally or bilaterally absent in some diabetic patients. Reproducibility and magnitudes of OAEs across speech frequencies (1-4 kHz) were reduced compared to normal volunteers. The authors concluded that OAEs might be useful in detecting early stage cochlear damage. Zhang[47] found that latencies of ABR waves III and V and I-III and III-V interwave latencies were delayed in 50 DM patients compared to 50 healthy individuals, indicating increased transduction time from the brainstem to the mid brain. In another study in 2005, Diaz[48] tested pure tone and speech audiometry and ABRs in 92 patients with type II DM in comparison to 94 age and gender matched healthy subjects and identified subclinical hearing loss and impaired ABRs in the diabetic patients which appeared to increase with age.

Other potential pathogenic factors in diabetic hearing loss in human have also been studied. Gutmanns in 1993[49] analyzed ultrasound results from 150 patients with vertigo, hearing loss and tinnitus and identified arterial diseases of various degrees, suggesting early stage cerebral ischemia. In 2002, Callejo[50] found significantly increased blood viscosity and erythrocyte adhesion in DM patients with hearing loss compared to normal hearing individuals. Niiya[51] studied effects of age factor on up-regulation of thrombocianase in the aortic endothelial cells in 29 diabetic patients in comparison to 19 healthy individuals. The results showed that up-regulation in endothelial cells of cerebral microvessels was more affected by the age factor and there were increased levels of radical oxidation species (ROS) in these endothelial cells. In the same year, Fukushima[52] conducted a morphological study in 18 patients with type II DM who were randomly selected to receive insulin (n=11) or oral anti-diabetic agents (n=7) in comparison to 26 normal controls. The results indicated that microvascular changes were likely the main mechanisms in diabetic hearing loss. Such changes included disorders in the cochlear micro vessels, dysplasia of the stria vascularis and of cochlear OHCs. Microcirculation disorders as a mechanism in diabetic hearing loss is also supported by serology studies. Serum creatinine is found to be elevated in diabetic patients with hearing loss as compared to non diabetic patients and correlated to the degree of hearing loss and blood glucose levels[53, 54]. In addition to comorbid vascular diseases, and probably associated with endothelial cell injury, platelet activation, enhanced coagulating factor activities and reduced fibronolytic system function have also been reported in patients with type II DM, indicating their potential values in early diagnosis of diabetic hearing loss and comorbid vascular diseases [55].

DM has been suspected to be a hereditary condition. DM patients may carry related genes at the time of birth. The interaction of these genetic factors with other environmental factors may eventually lead to clinical DM manifestation. Mitochondria DNA mutations have been identified in patients with maternally inherited DM and hearing loss. mDNA mutations can affect mitochondrial functions, leading to inner ear structural and functional changes and hearing loss.

Potential significances of such reseach in management of diabetic hearing loss

Microcirculation disorders are important pathological basis in diabetic hearing loss and hemodynamic changes are important indicators of microcirculation. Improving microcirculation is therefore an important approach in treating related hearing loss. Lin[56] studied the effects of atrial natriuretic factor (ANF) on cochlear microcirculation in guinea pigs and found that, despite lowering systemic blood pressure, ANF effectively increased cochlear blood flow when given intravenously in a dose-dependent fashion. Jiang[57] separated and cultured cochlear cells in neonatal SD rats to examine cell proliferation with 5-bromine-2-deoxyuracil and to determine cell differentiation via immunofluorence. Results indicated that there were proliferative cells in neonatal rat cochlea, which were able to differentiate in vitro into cells with hair cell or neuron markers. This may provide a new approach in treating sensorineural hearing loss using cell transplantation. Liu[58] studied expression of nerve growth factor (NGF) and its changes in the cochlea in rapidly aging mice using immunohistochemical methodology. The findings showed that NGF was expressed in mouse cochleae and the expression levels decreased as the mice aged, indicating its role in maintaining cochlear functions and possible application in treating cochlear hearing loss.

Summary

DM is closely linked to hearing damage. Both large and microscopic size blood vessels are affected in DM. Metabolic disorders, atherosclerotic changes and micro vessel diseases result in ischemia and hypoxia in neural tissues, leading to nerve damage. When such pathological changes involve the cochlea and auditory nerve, cochlear and/or neural hearing loss follows. Due to the often high frequency nature of DM related hearing loss, it commonly goes undetected and unreported. A hearing monitoring approach is therefore important clinically. Interventions aimed at controlling factors that may cause morphological and functional changes in the cochlea are critical in managing diabetic hearing damage. Further studies are needed to develop effective treatment for inner ear diseases caused by cochlear microcirculation disorders related to DM.

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