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HEARING DISORDERS: RATIONALE FOR USING A MICRONUTRIENT MIXTURE, PROBIOTICS, OMEGA 3 FATTY ACIDS, AND COLLAGEN PEPTIDES TO PREVENT AND IMPROVE THEIR TREATMENT

Kedar N. Prasad*

Engage Global Inc, 245 El Faisan Drive, San Rafael, CA, 94903.

***Corresponding Author: Kedar N. Prasad**
Engage Global Inc, 245 El Faisan Drive, San Rafael, CA, 94903.

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ABSTRACT
Hearing disorders are a complex disease of the ear in which partial or full loss of hearing may occur. In 2023, approximately 60.7 million Americans of age 12 and older were suffering from a mild hearing loss. The prevalence of hearing loss is increasing in USA, and it is expected to rise to 73.5 million by the year 2060. There are different types of hearing disorder which include conductive hear loss, sensorineural hearing loss, tinnitus, Meniere's disease, and congenital hearing loss. The individuals with hearing loss have a poor quality of life such as lack of social interaction, communication problem, mental health issue, and difficulty in personal relationship. Despite rise of incidence of hearing disorders, and poor quality of life of individuals suffering from hearing loss, no effective preventive plan has been developed. Recommendation of changes in diet, lifestyle and exposure to environmental toxins, and use of earplug, the incidence of hearing loss has not declined. At present, only hearing aids, cochlear transplant, and steroids and anti-glutamate medications are available for the treatment of hearing disorders. None of the available preventive or treatment devices and medications addresses the causes of hearing loss. Decades of research have identified external factors such as noise, advancing age, ototoxic agents, and Menieres disease, which increase internal stressors such as oxidative stress and chronic inflammation. There are other internal stressors such as intestinal dysbiosis, and loss of collagen and omega3 which initiate and promote hearing disorders. This review proposes that daily supplementation of a mixture of micronutrients, probiotics with prebiotics, collagen peptides, and omega 3 may prevent and improve the current treatment of hearing disorders.

KEYWORDS: Hearing loss; oxidative stress; inflammation; cochlear damage; intestinal dysbiosis.

1. INTRODUCTION

Hearing disorders are a complex disease of the ear which include partial or full loss of hearing. In 2023, The National Council of Aging reported that 60.7 million Americans of age 12 and older had a mild hearing loss; and 20.8 million of them were 60 years and older. The prevalence of hearing loss is on rise in USA and is expected to increase to 73.5 million by the year 2060. The prevalence of hearing loss among older individuals was further evaluated. Approximately, one-third of adults aged 61-70 years suffer from the hearing loss. Men exhibit more severe hearing loss than women.[1] Furthermore, 65% of adults aged 71 years or older showed hearing loss, while 96.2% of individuals aged 91 years suffer from hearing loss.[2] Approximately, 20% of world population have some degree of hearing loss. Annual Global economic cost of managing hearing loss is $980 billion, while American economic cost of managing this disease of the ear is $105 $billion.

There are different types of hearing loss: (a) conductive hearing loss occurs when sound is not transmitted properly through the outer, middle or both of the ear. It occurs due to ear canal obstruction, damage to tympanic membrane and ossicles of the middle ear, and injury to the inner ear; (b) sensorineural hearing loss is the most common form of hearing disorder and occurs due to the insensitivity of the inner ear to sound, or to impaired function of the auditory nervous system. It can lead to complete deafness; (c) tinnitus, also known as ringing the ear, occurs due to damage to the hair cells that cause excessive production of glutamate which causes hyperactivity in the auditory cortex and brain leading to the perception of phantom sounds; and (d) Meniere's disease (MD) is a disorder of the inner ear that can cause tinnitus, dizziness, vertigo (abnormal sensation), increased sensitivity to noise (hyperacusis), and progressive hearing loss. This disease can occur in one or both ears. Congenital hearing disorder is

primarily due to cytomegalovirus infection during pregnancy or gene mutation.

A recent review has described impact of hearing loss on the quality of life. One-third of American population at the age of over 50 years reported that hearing loss had significant adverse effects on their quality of life such as social interaction, communication, mental health, and personal relationship.[3] Despite importance and rising incidence of hearing loss, there are no effective preventive plan except for reducing exposure to intense noise and using earplug during exposure to intense noise such as musical events and war zone. Only hearing aids, cochlear transplant, and steroids and anti-glutamate medications are available for improving the symptoms of hearing disorders. None of the available preventive or treatment devices and medications addresses the causes of hearing loss. To elucidate the causes of hearing loss, it is essential to identify external stressors which induce internal stressors that initiate and promote hearing disorders. It would be then possible to identify agents that can reduce the levels of internal stressors, and thereby, reduce the risk of developing hearing loss and improve the treatment of this ear disorder.

During decades of research, several external stressors which induce hearing disorders have been identified. They include exposure to chronic and intense noise, vibrations, gentamicin, ionizing radiation, cisplatin, large doses of aspirin, bacterial and viral infection, gene mutations, and advanced age. In addition, health conditions, such as ear canal obstruction, mechanical damage to the tympanic membrane, ossicles of the middle ear, and inner ear also contribute to the hearing loss. Troops in combat zones, musicians or industrial workers are likely to develop varying degrees of hearing loss because of exposure to intense noise. All external stressors enhance the levels of internal stressors which increase the risk of hearing loss.

The internal stressors which participate in the development and progression of hearing loss include increased oxidative stress[4-8], inflammation[28-42], glutamate[43-46], intestinal dysbiosis (increase in the number of harmful bacteria and decline in the number of beneficial bacteria)[9,10], loss of collagen[11-13], and decline in the level of omega 3 fatty acids (omega 3) and its function[14-17], and gene mutations. Approximately, 50% of all cases of hearing loss are due to mutation in genes; the remaining is acquired due to exposure to intense noise, infection, trauma, and ototoxic medications. Among gene defects induced hearing loss, inherited hearing loss referred to as syndromic hearing loss accounts for approximately 30 %; the remaining inherited hearing loss referred to as non-syndromic hearing loss represents about 70%. The internal stressors cause ototoxicity that includes damage to inner ear parts such as cochlear, vestibular, and sensory functions.

Therefore, to develop an effective plan to prevent and improve the treatment of hearing disorders, it is essential to reduce exposure to external stressors as much as possible and to provide safe agents that can decrease all internal stressors at the same time.

This review presents evidence to show that increased oxidative stress, chronic inflammation, excessive release of glutamate, intestinal dysbiosis, loss of omega 3 and collagen, play a central role in the initiation and progression of acquired or inherited hearing disorders. This review also proposes to minimize the exposure to external stressors as much as possible and utilize safe agents which can attenuate all internal stressors at the same time for reducing the incidence of hearing disorders and improving the treatment of hearing loss.

2. External Stressors Increased Oxidative Stress and Chronic Inflammation Causing Hearing Disorders

Ototoxic agents such as intense noise, infection, trauma, and ototoxic medications induce hearing disorders by increasing oxidative stress. If oxidative damage to the ear is not fully repaired, chronic inflammation occurs. Bacterial or viral infection to the ear increases inflammation that releases free radicals, pro-inflammatory cytokines, complement proteins, and adhesion molecules which initiate and promote hearing disorder.

2.1. Intense noise induces hearing loss by increasing oxidative stress: Exposure to high intensity noise increased oxidative stress as evidenced by decreased levels of serum total antioxidant capacity and increased levels of nitric oxide in guinea pigs.[4] Increase nitric oxide levels can form peroxynitrite that damages the hair cells of the ear. Noise exposure induced approximately 21 to 42 % tinnitus in humans.[18-20] The levels of nitric oxide, peroxynitrite, oxidative stress, nuclear factor-kappa-beta (NF-kappaB), glutamate receptor (N-methyl-D-aspartate) and calcium are elevated in patients with tinnitus.[5, 6, 21-25]

Exposure to moderate or intense noise induced hearing loss by enhancing oxidative stress as evidenced by increasing NADPH (nicotinamide adenine dinucleotide) oxidases (NOXs) activity in the cochlea of rats. Treatment of rats with diphenyleneiodonium, an inhibitor of NOX, after noise exposure, prevented hearing loss.[26] Treatment with Pravastatin, a cholesterol lowering drug, also decreased noise-induced hearing loss by inhibiting NOX activity in mice.[27]

Activation of a nuclear transcription factor Nrf2 is one of the factors which protects ear cells from oxidative damage by increasing the levels of antioxidant enzymes. In Nrf2 deleted mice (-/-), hair cells become more sensitive to noise-induced oxidative damage in comparison to wild-type mice. Pre-treatment with an activator of Nrf2 preserved integrity of hair cells and

improved hearing levels in wild-type mice but not in Nrf2 deleted mice (-/-). These results suggest that activation of Nrf2 in the cochlea is essential for protecting against noise-induced hearing loss.[28]

Frequent exposure to vibration also produces hearing disorders. For example, the older guinea pigs were two-fold more sensitive to vibration than younger animals.[29] The combination of noise and vibration during the use of hand-held vibrating tools increases the risk of hearing loss in industrial workers.[8, 30]

2.2. Advancing age induces hearing loss by increasing oxidative stress: Age-related hearing loss (ARHL) or presbycusis is most common among older individuals throughout the world. The external stressors influence the onset and severity of ARHL. Increased oxidative stress, mitochondrial dysfunction, moderate inflammation, immune dysfunction, and depletion of stem cells play a central role in the development and progression of ARHL.[31] Hearing loss occurs with advancing age due to increased oxidative stress and chronic inflammation that are associated with ageing.[32] Cochlear structural alterations and degeneration of sensory and neural cells also occur with advancing age.[33] D-galactose-induced aging rats that resembles normal aging, hearing loss occurs due to increased oxidative stress, and accumulation of mutated mitochondrial DNA in the peripheral and central auditory cells.[34-36]

2.3. Ototoxic drugs induce hearing loss by increasing oxidative stress: Cisplatin, a cancer treatment agent, caused hearing loss by increasing oxidative stress as evidenced by decreased levels of antioxidant enzymes such as superoxide dismutase (SOD), glutathione peroxidase, glutathione reductase, glutathione transferase, catalase, and enhanced levels of lipid peroxidation.[37] Treatment with Carboplatin decreased the level of glutathione.[38] Inhibition of antioxidant and anti-inflammation activities protected against cisplatin-induced ototoxicity.[39]

2.4. Meniere's disease associated hearing loss shows increased oxidative stress: Meniere's disease (MD) is a disorder of the inner ear that can cause tinnitus, dizziness, vertigo (abnormal sensation), increased sensitivity to noise (hyperacusis), and progressive hearing loss. Increased oxidative stress initiates and promotes above listed hearing disorders. This is supported by the fact that free radical scavengers such as rebamipide, vitamin C, and glutathione, when administered orally for 8 weeks to 25 patients with poorly controlled MD, improved tinnitus, hearing loss, and disability.[40]

2.5. Noise induces hearing disorders by enhancing inflammation: Inflammation also plays an important role in hearing disorders induced by noise, drugs, advancing age, and health conditions. Noise exposure can damage cochlear function by inducing inflammation in animal models.[41,42] This is supported by the fact that exposure to noise increased the levels of intracellular adhesion molecules and migration of leukocytes. Intense noise exposure can also activate the nuclear transcription factor-kappaB (NF-kappaB) in the cochlea of mice that causes over-expression of pro-inflammatory products including intracellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), and inducible nitric oxide synthase (iNOS) in the inner ear that contribute to the hearing loss.[43] Polymorphism of interleukin-6 (IL-6) increased the sensitivity of noise-induced hearing disorders in individuals over the age of 60 years.[44]

2.6. Drugs induce hearing disorders by enhancing inflammation: Aspirin and other anti-inflammatory drugs prevented gentamicin-induced hearing loss and improved hearing ability.[45,46] Cisplatin-induced ototoxicity in mice and immortalized cochlear cells in culture[47,48] is due to production of enhanced levels of pro-inflammatory cytokines and activation of NF-kappaB. Bacteria-induced meningitis produces pro-inflammatory cytokines tumor necrosis factor-alpha (TNF-alpha) that induces cochlear degeneration causing hearing loss.[49] Administration of TNF-alpha antibody reduced meningitis-induced hearing loss in Mongolian gerbils. Increased levels of TNF-alpha were also associated with trauma-induced hearing loss. Treatment with an anti-inflammatory drug dexamethasone reduced TNF-alpha-induced toxicity in the organ of Corti explants cultures.[50] A study has reported that otosclerosis-induced sensorineural hearing loss is due to the chronic release of TNF-alpha from the foci of otic capsule.[51,52]

Chronic inflammatory reactions produce sac dysfunction leading to Meniere's disease.[53] Increased inflammation in the elder individuals was associated with age-related hearing loss[54] and sensorineural hearing loss.[55]

2.7. Enhanced glutamate level induces hearing disorders: When the hair cells are injured, glutamate transmission responsible for converting vibration sound into electrical signal is enhanced. Glutamate at high concentrations is neurotoxic. Damage to the peripheral auditory and somatosensory systems causes imbalance between excitatory and inhibitory neurotransmitters in the mid brain auditory cortex and brain stem. This imbalance in neurotransmission can cause hyperactivity in the auditory cortex leading to the perception of phantom sounds (tinnitus). Intense noise causes release of excessive amounts of glutamate that damage the inner hair cells-auditory synapses. Kynurenate, a glutamate antagonist, protected guinea pigs against noise-induced hearing loss (NIHL).[56] Glutamate-aspartate transporter (GLAST) that plays an important role in maintaining the normal levels of glutamate was decreased in the cochlea after exposure to noise leading to increased accumulation of glutamate in perilymph. Increased levels of glutamate

enhanced the rate of progression of hearing loss.[57] Treatment with riluzole, an inhibitor of glutamatergic neurotransmission, protected guinea pigs against NIHL.[58] Treatment with D (-)-2-amino-5-phosphonopentanoic acid (D-AP5), a selective inhibitor of glutamate receptor N-methyl D-aspartate (NMDA) receptor, attenuated noise-induced tinnitus.[59]

3. Effect of Antioxidants on Hearing Disorders

Increased oxidative stress and chronic inflammation are involved in the initiation and progression of hearing disorders irrespective of their causative agents. Since antioxidants are known to attenuate them, treatment with antioxidants may reduce the risk of development and progression of hearing disorders. A few studies on the effects of antioxidants on animal and humans are described here.

3.1. Animal studies: Vitamin E treatment reduced hearing disorders by attenuating cochlear damage, and the damaging effects of noise[60,61], cisplatin[62,63], and gentamicin on inner ear.[64,65] Treatment with alpha-lipoic acid protected against noise- and carboplatin-induced hearing loss in animals.[66-68] The role of N-acetylcysteine (NAC) in reducing noise-induced hearing loss (NIHL) has been reviewed (4). Treatment with (NAC) significantly reduced NIHL in the cochlear cells of rats and guinea pigs.[69] A combination of acetyl-L-carnitine and NAC provided protection against hearing loss induced by noise, cisplatin, and aminoglycoside in animals.[70,71]

Coenzyme Q10[72], Idebenone, a synthetic analog of coenzyme Q10[73], and the soluble form of coenzyme Q10[74] were effective in reducing hypoxia- induced hearing loss and NIHL in animals. The combination of vitamin E and idebenone produced an additive effect in protecting against NIHL, suggesting that these two antioxidants act by different mechanisms.[75] Oral administration of MitQ, a mitochondria-targeted derivative of ubiquinone, reduced gentamicin-induced hearing disorders by protecting the cochlea in animals.[76]

Vitamin C also protected against NIHL in albino guinea pigs.[77] Treatment with resveratrol reduced NIHL by decreasing cyclooxygenase-2 (COX-2) levels.[78] Folic acid deficiency induced premature hearing loss by increasing the levels of oxidative stress and homocysteine in mice.[79] Indeed, supplementation with folic acid reduced hearing disorders by reducing oxidative stress and homocysteine levels.[80]

Caloric restriction and treatment with individual antioxidants, such as vitamin E, vitamin C, acetyl-L-carnitine, alpha-lipoic acid, and melatonin improved auditory sensitivity to sound, reduced mitochondrial DNA deletion, and loss of hair cells in aging rats.[81-83] In a mice model of premature age-related hearing loss, treatment with n-acetyl-L-carnitine failed to protect against hearing loss.[84]

3.2. Human studies: Coenzyme Q10 delayed the progression of hearing loss in patients with a genetic defect, 7445A→G mitochondrial mutation.[85] An oral supplementation with antioxidants (vitamin E, vitamin C, beta-carotene and phospholipids) reduced the subjective discomfort and tinnitus intensity in patients with idiopathic tinnitus.[86] NAC protected against aminoglycoside-induced ototoxicity in hemodialysis patients.[87] An antioxidant mixture containing reduced glutathione, alpha-lipoic acid, cysteine and other antioxidants improved the symptoms of MD.[88] A commercial preparation of multiple micronutrients reduced symptoms of tinnitus in humans.[89]

3.3. Antioxidants in combination with standard therapy: Glutamate antagonists and steroids, are used in the management of hearing loss and tinnitus.[90] A combination of vitamins A, C and E, and selenium in combination with standard therapy improved hearing gain more that produced by standard therapy alone in patients with idiopathic sensorineural hearing loss.[91] Intravenous administration of high dose vitamin C in combination with steroid therapy improved hearing gain more than that produced by steroid therapy alone.[92] Vitamin E supplementation and carbogen (5% Co2 + 95% O2) breathing reduced noise-induced hearing loss.[93] Treatment with the combination of vitamin E and vitamin C together with steroids and/or alprostadil reduced idiopathic sudden sensorineural hearing loss by decreasing oxidative stress compared to control group.[94]

Most human studies have utilized one or a few antioxidants for a short period of time. Such a strategy may not increase the levels of both antioxidant enzymes and dietary and endogenous antioxidant compounds that are essential for attenuating sufficient levels of oxidative stress and chronic inflammation. We have proposed that simultaneous elevation of the levels of antioxidant enzymes through an activation of the Nrf2 pathway and enhancing the levels of dietary and endogenous antioxidant compounds is essential to optimally reduce oxidative stress and inflammation at the same time for improving the symptoms of post-traumatic disorders (PTSDs) and traumatic brain injury (TBI).[95] A similar strategy may be needed for reducing hearing loss in humans. Since activation of Nrf2 is essential for increasing the levels of antioxidant enzymes, the characteristics, location, and activation of Nrf2 processes are briefly described here.

4. Characteristics, Location, and Activation of Nrf2 and its Function

4.1. Characteristics and location of Nrf2: The nuclear transcriptional factor, Nrf2 (nuclear factor-erythroid-2-related factor 2) belongs to the Cap ´N´Collar (CNC) family that contains a conserved basic leucine zipper (bZIP) transcriptional factor.[88] Under physiological condition, Nrf2 is associated with Kelch-like ECH associated protein 1 (Keap1) which acts as an inhibitor of Nrf2.[96] Keap1 protein serves as an adaptor to link Nrf2

to the ubiquitin ligase CuI-Rbx1 complex for degradation by proteasomes and maintains the steady levels of Nrf2 in the cytoplasm. Nrf2-keap1 complex is primarily located in the cytoplasm. Keap1 acts as a sensor for ROS/electrophilic stress.

Overexpression of Keap1 inhibits nuclear accumulation and transcriptional activity of Nrf2, while addition of cytoprotective agents release this inhibition, and thereby, allows migration of Nrf2 to the nucleus where it binds with antioxidant response element (ARE) causing increased expression of genes coding for antioxidant enzymes. On the other hand, in Keap1 knockout mice, both Nrf2 and its target genes are constitutively expressed; therefore, they could not be upregulated upon the addition of cytoprotective agents.[97,98]

Nrf2 is present in the cytoplasm and nuclei of the human Corti organ, including inner hair cells (IHC), outer hair cells (OHC), and supporting cells, but is not present in spiral ganglion cells, and other cochlear structures such as stria vascularis, spiral ligaments and Reissner Membrane.[99]

4.2.ROS (reactive oxygen species) activates Nrf2: Normally, during a short-term moderate oxidative stress, ROS is needed to activate Nrf2 which then dissociates itself from Keap1- CuI-Rbx1 complex and translocates itself in the nucleus where it heterodimerizes with a small Maf protein, and binds with the ARE (antioxidant response element) leading to increased expression of target genes coding for several cytoprotective enzymes including antioxidant enzymes.[100-103] Thus, activation of Nrf2 during a short-term moderate oxidative stress protects the cochlea from oxidative damage.

4.3.Antioxidant compounds activate Nrf2: Activation of Nrf2 by ROS (reactive oxygen species) becomes impaired during chronic oxidative stress found in patients with hearing loss.[104-106] This is evidenced by the fact that increased oxidative stress occurs in hearing disorders despite the presence of Nrf2. However, certain antioxidants activate Nrf2 without ROS. They include vitamin E and genistein.[107], alpha-lipoic acid[108], curcumin[109], resveratrol[110, 111], omega-3-fatty acids, glutathione[112,113], glutathione[114], NAC[35], coenzyme Q10[115], and several plant-derived phytochemicals with antioxidant activities, such as epigallocatechin-3-gallate, carestol, kahweol, cinnamonyl-based compounds, zerumbone, lycopene, and genistein[116,117], allicin, a major organosulfur compound found in garlic[107], genistein.[107]

4.4.Binding of Nrf2 with ARE in the nucleus: An activation of Nrf2 alone may not be sufficient to increase the levels of antioxidant enzymes. Activated Nrf2 must bind with antioxidant response element (ARE) in the nucleus for increasing the expression of target genes codingfor antioxidant enzymes. This binding ability of Nrf2 with ARE was impaired in aged rats and this defect was restored by supplementation with alpha-lipoic acid.[108] It is unknown whether the binding ability of Nrf2 with ARE is impaired in hearing disorders.

4.5.Nrf2 in noise-induced hearing loss (NIHL): Nrf2 is an important factor that protects NIHL by reducing oxidative stress.[28] Nrf2 deficiency aggravates NIHL. This is evidenced by the fact that mice with deleted Nrf2 (-/-) are more susceptible to NIHL than wild-type mice.[28] Nrf2 must be activated before noise exposure to improve hearing loss. After exposure to noise, sufficient amounts of antioxidants must be present to activate Nrf2 for decreasing the progression NIHL.

4.6.Nrf2 in Age related hearing loss (ARHL): Oxidative damage to the cochlea is the most important cause of ARHL. The deficiency of Nrf2 is involved in the development of ARHL. Tubby strain of obese mice with gene mutation developed progressive hearing loss due to the damage to inner hair cells.[118] Homozygous mutant Tubby mice exhibit reduced expression of Nrf2 causing accumulation of ROS in the hair cells leading to their death.[119] Mice with completely knockout Nrf2 exhibit rapid hearing loss with age compared to the rate in wild-type mice. These mice also show faster loss of hair cells and spiral ganglion cells in the cochlea.[120] In addition to reducing oxidative stress, activation of Nrf2 also reduce chronic inflammation.[121,122] Activation of Nrf2 may not be sufficient to optimally reduce oxidative stress and chronic inflammation for improving prevention and improved management of hearing disorders, because the levels of antioxidant compounds are also decreased; therefore, their levels must also be simultaneously elevated.

5. Reducing Glutamate Levels

Since excessive production of glutamate is involved in the development and progression of hearing disorders, reducing its level would be useful in prevention and improved management of hearing disorders. Some antioxidants decrease the release of glutamate as well as its neurotoxicity.[123-125] In addition, certain B-vitamins can also decrease the release of glutamate.[126-127] Reduction of glutamate level and its toxicity alone may not be sufficient to reduce optimally hearing loss in humans.

6. Intestinal Dysbiosis Contributes to Hearing Disorders

In addition to increased oxidative stress, chronic inflammation, and glutamate production, intestinal dysbiosis (increase in the number of toxic bacteria and decline in the number of beneficial bacteria) also contributes to the development and progression of hearing disorders. High Fat diet induces intestinal dysbiosis which causes inflammation that impairs the permeability of the blood-labyrinth barrier in the inner ear that causes damage to the cochlea leading to hearing loss.[9] Intestinal dysbiosis increases inflammation which is considered one of the main causes of various

auditory disorders including sensorineural hearing loss, otitis .media, and tinnitus. Supplementation with probiotics improves the symptoms of hearing disorders.[10] Beneficial bacteria Bifidobacterium produces neurotransmitters such as gamma-amino butyric acid (GABA) and serotonin needed for the ear heath; however, intestinal dysbiosis decreases the production of these neurotransmitters and increases inflammation which then leads to tinnitus.[128]

7. Loss of Omega 3 Contributes to Hearing Disorders

Regular consumption of fish and higher intake of omega3 reduce the risk of hearing loss in women.[14] Inadequate supply of blood to the cochlea may contribute to reduced auditory sensitivity to sound.[16] Higher consumption of omega3 may help in maintaining blood flow to the cochlea.[17]

8. Loss of Collagen Contributes to Hearing Disorders

There are 29 different types of collagens, but the types of collagens are distributed differently from one organ to another. Each cell has genes capable of making the types of collagen that needed for maintaining normal fuction. One of the major role of collagen is to maintain structural integrity of all organs. Any alteration in the structure of organs can influence their function. Collagen type IX plays a crucial role in maintaining normal hearing.[11] Mutation in any one of collagen genes COL9A1, COL9A2, COL9A3 which code for collagen type IX causes autosomal recessive Strickler syndrome associated with sensorineural hearing loss in 50% of patients.[13,129] Collagen type IV is an important component of the inner year structure, particularly in the organ of Coti that transforms sound waves to nerve impulses for the brain. Alteration in function of Collagen IV in the inner year can lead to hearing loss.[13] Mutation in collagen genes COL9A3, COL9A4, COL9A5 which code for collagen type IV can cause sensorineural hearing loss.[130] It has been reported that guinea pig immunized against collagen type II developed sensorineural hearing loss similar to that observed in patients with connective tissue disease.[131] This suggests that collagen type II plays a crucial role in maintaining normal hearing. Thus, loss of collagen type II, collagen type IV, and collagen type IX causes hearing loss.

9. Proposed Recommendations for Reducing and Improving the Treatment of Hearing Disorders

9.1.Reduce exposure to external stressors: The recommendations for reducing exposure to external stressors have been propagated for decades but had no significant impact in reducing the incidence of hearing disorders or improving their treatment. One of the main reasons could be that reducing exposure to age, noise, vibration, heritable gene mutation, and medications are beyond our control. Nevertheless, we must continue to educate public about the value of reducing exposure to external stressors on hearing loss as much as possible.

9.2.Reducing the effects of all internal stressors: The internal stressors such as increased oxidative stress, chronic inflammation, excessive release of glutamate, intestinal dysbiosis, omega 3, and collagen play a central role in the initiation and progression of acquired and inherited hearing disorders. To prevent hearing disorders and improve their treatment, this review proposes that all internal stressors must be simultaneously attenuated by using a micronutrient mixture, probiotics with prebiotics. Omega 3, and collagen peptides.

9.3.Proposed micronutrient mixture on some internal stressors: The proposed micronutrient mixture includes vitamin A (retinyl palmitate), vitamin E (both d- alpha-tocopherol acetate and d-alpha-tocopheryl succinate), natural mixed carotenoids, vitamin C (calcium ascorbate), vitamin D3, all B-vitamins, coenzyme Q10, alpha-lipoic acid, N-acetylcysteine (NAC), curcumin, resveratrol, quercetin, green tea extract, and minerals selenium and zinc. This proposed micronutrient mixture has no iron, copper, or manganese. Although these trace minerals in tiny amounts are essential for the growth and survival, slight excess of free iron or copper can increase the risk of chronic diseases, because these trace minerals when combined with vitamin C produce extensive amounts of free radicals. These trace minerals in the presence of antioxidants are rapidly absorbed and quickly saturate their respective protein, and thereby. allows free iron and copper to interact with molecules like vitamin C to produce large amounts of free radicals. This micronutrient mixture also has no heavy metals such as vanadium, zirconium, and molybdenum, because increased levels of these heavy metals are neurotoxic. There are no methods of elimination of either trace minerals or heavy metals from the body; therefore, taking them with a micronutrient mixture could be harmful after a prolonged consumption.

The proposed micronutrient mixture is expected to reduce the risk of hearing disorders by simultaneously reducing oxidative stress and chronic neuroinflammation by enhancing the levels of antioxidant enzymes such as glutathione peroxidase, catalase, and superoxide dismutase through activating the Nrf2 pathway, and increasing the levels of dietary and body-made antioxidant compounds at the same time. This micronutrient mixture would also attenuate the symptoms of hearing by prevent the toxicity of glutamate on ear structures.

9.4.Proposed probiotics with prebiotics, collagen peptides, and omega 3 on some internal stressors: The suggested probiotics with prebiotic would decrease the risk of hearing disorders by reversing the effects of intestinal dysbiosis. The proposed collagen peptides would prevent hearing defects by enhancing the levels of collagen type II, collagen type IV, and collagen type IX

which are important for maintaining normal hearing. The recommended omega 3 would enhance the auditory sensitivity to sound by maintaining blood flow to the cochlea.

The proposed plan may reduce the incidence of hearing disorders, and in combination with current medications, cochlear transplant or hearing aids may improve their effectiveness in maintaining normal hearing for a long period of time.

10. CONCLUSIONS

Despite decades of research on prevention and development of new treatment modalities, the prevalence of hearing disorders is on rise and patients who are suffering from this disease of the ear continue to have a poor quality of life. One reasons could be that none of these preventive or treatment devices address causes of the disease. To reduce the incidence of hearing disorders and improve their treatment, it is essential to identify internal and external stressors which initiate and promote hearing loss. Extensive research of over 30-40 have identified external factors such as noise, advancing age, ototoxic drugs, Meniere's disease which induce internal stressors such as increase oxidative stress, chronic inflammation. Other internal stressors include excessive production of glutamate. In addition, internal factors such as intestinal dysbiosis, loss of collagen and omega 3 also contribute to the development and progression of hearing disorders. This review has proposed that all external and internal stressors must be addressed at the same time. Treatment with one or a few antioxidants, probiotic with prebiotics, collagen peptides, and omega3 alone produced limited benefits on hearing loss. This review proposes daily use of a micronutrient mixture which would simultaneously reduce oxidative stress and chronic inflammation, and reduce toxicity of glutamate, probiotics with prebiotics which would reverse intestinal dysbiosis, collagen peptides which would enhance the levels of collagen type II, collagen type IV, and collagen type IX in the ear to maintain normal hearing, and omega3 which would allow blood flow to the cochlea to improve sensitivity to sound. Thus, the proposed strategy may reduce the incidence of hearing loss, and in combination with current therapies may improve their effectiveness.

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