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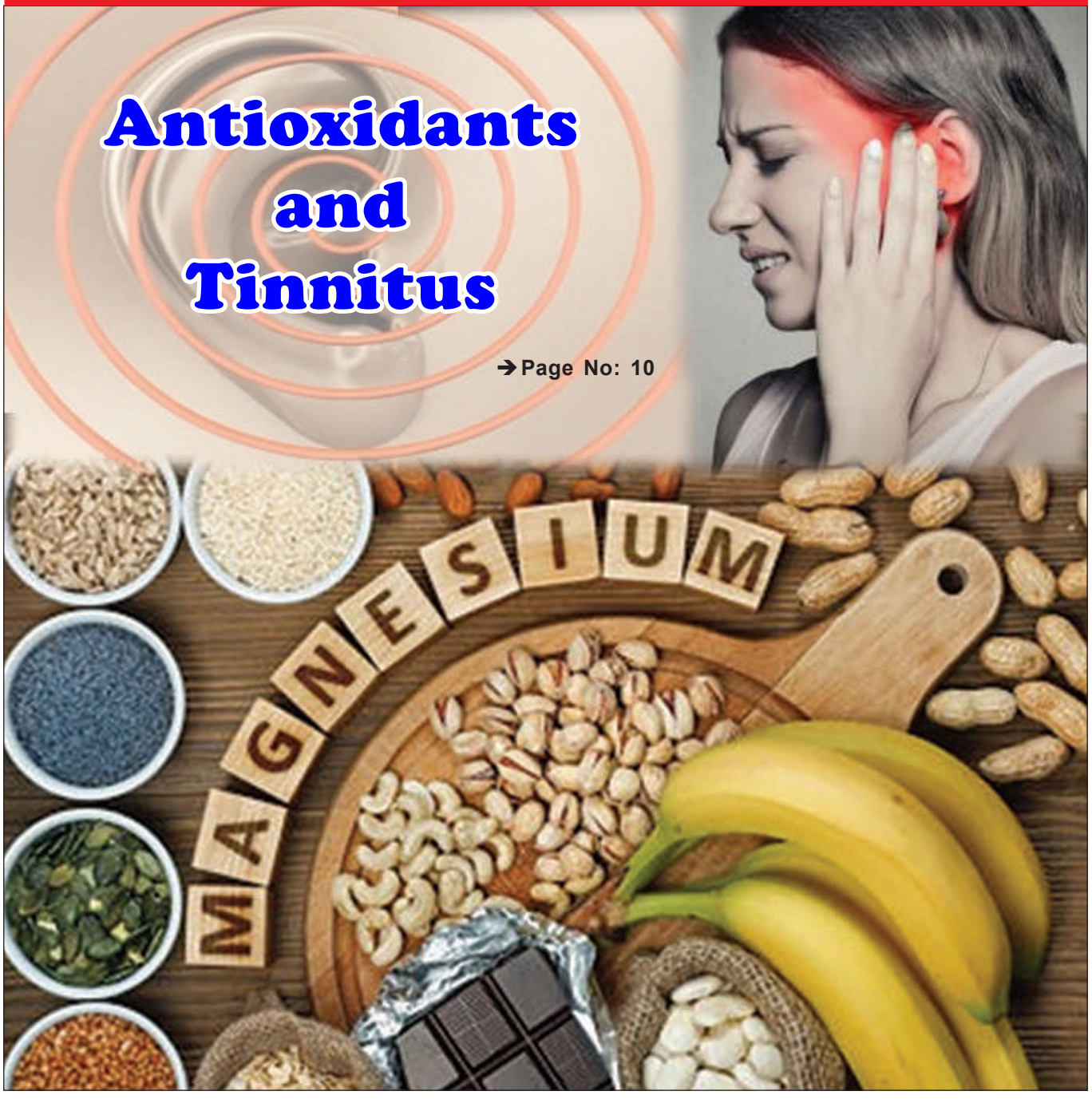

GENERAL

Antioxidants and Tinnitus

SANJAY AGRAWAL

Risk Factors and Markers of Hearing Loss

In order to develop an effective antioxidant strategy, it is essential to know about agents that can induce hearing disorders and the mechanisms by which they cause damage to hearing-related structures. Dispensing professionals are well aware that there are many agents and conditions that cause hearing disorders, and a comprehensive list of hearing loss risk factors is beyond the scope of this article. Some occupations with high risks for hearing loss include musicians, industrial workers, and military personnel in training and in combat who are exposed to high intensity noise and vibration.

High noise intensities and vibrations, cancer chemotherapeutic agents (eg, cisplatin), and antibiotics (eg, gentamicin) can damage hearing-related structures like cochlear hair cells, sensory hair cells, and vestibular hair cells. Injury to these hair cells can cause hearing loss, tinnitus, and balance problems.

When hair cells become damaged, glutamate—an excitatory neurotransmitter responsible for converting vibrational sound into electrical signal—is produced in excessive amounts. Excessive amounts of glutamate are very toxic to neurons. Damage to peripheral auditory and somatosensory systems causes imbalance between excitatory and inhibitory neurotransmitters in the mid-brain auditory cortex and brainstem. This imbalance causes hyperactivity in the auditory cortex leading to the perception of phantom sounds (tinnitus).

Age-related hearing loss (presbycusis) is also an attributed cause of hearing loss in humans, although it is debated whether presbycusis is more closely related to long-term noise exposure or the degeneration of hearing structures due to aging. Meniere's disease (MD) also causes the death of cochlear hair cells and damage to vestibular (motion sensing) hair cells.

Involvement of oxidative stress and chronic inflammation in hearing disorders: Several scientific papers show that increased oxidative stress due to production of excessive amounts of free radicals derived from oxygen and nitrogen, and acute and/or chronic inflammation produced by diverse groups of agents—such as high intensity noise, vibration, cisplatin, gentamicin, aging, and Meniere's disease—are major factors in the initiation and progression of hearing disorders.

Free radicals are atoms or molecules that have an unpaired electron and are therefore very likely to take part in chemical reactions. While free radicals are a natural product of cellular activity, they can also participate in unwanted side reactions that have been implicated in a vast number of diseases, including cancers, liver damage, Parkinson's disease, Alzheimer's disease, and even the process of aging itself. Our bodies have several strategies for minimizing the effects of free radicals, including the production of enzymes such as superoxide dismutase (SOD), catalase, glutathione peroxidase, and glutathione reductase.

The data for the involvement of increased oxidative stress in hearing disorders comes from two sources: 1) directly by measuring oxidative stress, and 2) indirectly by use of antioxidants. Exposure to high intensity noise causes a decrease in serum total antioxidant capacity and an increase in nitric oxide in guinea pigs.[1] Increased nitric oxide causes formation of peroxynitrite, which is very damaging to hair cells. Formation of free radicals following exposure to impulse noise has been reported in some animal studies.[2-8]

Exposure to vibration also produces hearing disorders. In animal models (guinea pig), older animals were twofold more sensitive to vibration-induced hearing loss than younger animals.[9]

In studies, certain chemotherapeutic agents, such as cisplatin, and antibiotics, such as aminoglycosides, induced hearing loss by increasing oxidative stress, and this effect was reduced by antioxidants. Reactive oxygen species are involved in cisplatin-induced hearing loss.[10] Carboplatin depresses significantly the levels of antioxidant enzymes, superoxide dismutase, glutathione peroxidase, glutathione reductase, glutathione transferase, and catalase—all antioxidants that protect cells from toxins such as free radicals. Similarly, carboplatin elevates

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the levels of products of lipid peroxidation,[11] a process in which free radicals degrade the cell membrane. It also depletes the level of glutathione,[4] another important antioxidant.

The levels of nitric oxide, peroxynitrite, oxidative stress, nuclear factor kappa-beta (NF-kappa), glutamate receptor (N-methyl-D-aspartate), and calcium are elevated in patients with tinnitus.[12,13] About 21% to 42% of tinnitus cases are induced by exposure to noise.[14] About 34% of tinnitus patients have post traumatic stress disorder (PTSD), suggesting there may be some linkage of neuronal mechanisms that cause both tinnitus and PTSD.[15] Evidence for increased oxidative stress and chronic inflammation has also been found in patients with PTSD.

The role of oxidative stress in Meniere's disease is supported by the fact that free radical scavengers (ie, rebamipide, vitamin C, and glutathione), when administered orally for 8 weeks to 25 patients with poorly controlled MD, improved tinnitus, hearing loss, and disability.[16]

Age-related cochlear structural alterations and degeneration of sensory and neural cells also occur.[17] Increased oxidative stress and chronic inflammation are likewise associated with aging.

Evidence for Beneficial Effects of Antioxidants in Hearing Disorders

Antioxidants are known to reduce oxidative stress and inflammation; therefore, supplementation with antioxidants appears to be one of the most rational approaches to prevent and improve hearing disorders in combination with standard therapy. Several animal and some human studies show that supplementation with antioxidants produces beneficial effects and improves hearing disorders, including:

- In a prospective, double-blind study, supplementation of vitamin E alone provided better recovery than the standard therapy in patients with idiopathic sudden hearing loss.[18]
- In a prospective double-blind study, vitamin E alone administered orally improved the efficacy of standard therapy[19]
- In a prospective randomized study, intravenous administration of magnesium sulfate improved hearing recovery in patients with idiopathic sudden sensorineural hearing loss.[20]
- Coenzyme Q10 (ubiquinol) delayed the progression of hearing loss in patients with a genetic defect (7445A→G mitochondrial mutation).[21]
- The use of glutamate antagonists, steroids, and antioxidants may also be useful in the management of hearing loss and tinnitus.[22]

Several studies have also looked at the use of antioxidants in the prevention of noise-induced hearing loss, including:

- Vitamin E, when administered intraperitoneally 3 days before and 3 days after noise exposure, reduced noise-induced cochlear damage and hearing loss in guinea pigs.[18,19] It also protected against noise-induced damage to the inner ear in cyrinid fish.[23]
- Alpha-lipoic acid protects against noise-induced hearing loss in guinea pigs.[1]
- An intraperitoneal injection of n-acetylcysteine (NAC) significantly reduced hair cell loss in cochlear cells of rats.[24] NAC attenuated noise-induced hearing disorders in guinea pigs.[25] Acetyl-L-carnitine and NAC administered twice a day for 2 days and 1 hour before and 1 hour after noise exposure for an additional 2 days provided protection against hearing loss.[26]
- Coenzyme Q10 helped in recovery from hypoxia-induced sudden deafness by protecting damage to auditory hair cells as well as preventing respiratory metabolic impairment of hair cells.[27] Idebenone, a synthetic analog of coenzyme Q10 with antioxidant properties, protected guinea pigs against noise-induced hearing loss.[28]
- Vitamin C protected against noise-induced hearing loss in albino guinea pigs.[29]

A number of studies have examined the role of these same antioxidants in reducing the effects of ototoxins related to chemotherapy and antibiotics, including:

- Vitamin E protected against cisplatin-induced damage to cochlear hair cells in rats.[30] Trolox, a water soluble analog of vitamin E, when applied locally reduced cisplatin-induced ototoxicity in guinea pigs.[31] Vitamin E reduced gentamicin-induced hearing loss and vestibular dysfunction.[32] Cisplatin-induced cochlear damage is reduced by vitamin E.[33]
- An in vitro study suggested that NAC protected against cisplatin-induced damage to inner ear auditory sensory cells.[34] NAC protected against amino-glycoside-induced ototoxicity in hemodialysis patients.[35]
- Antioxidants attenuate aminoglycoside-induced hearing loss and vestibular

dysfunction in an animal model (chinchilla).[36]

- **Alpha-lipoic acid protected against carboplatin-induced toxicity in hair cells.[37] Finally, several studies have looked at increased oxidative stress due to aging, MD, and tinnitus, including:**
  - In mice and dogs, a diet rich in antioxidants reduced age-related cochlear degeneration.[17]
  - An antioxidant mixture containing reduced glutathione, alpha-lipoic acid, cysteine, and other antioxidants improved the symptoms of MD.[38]
  - 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.[39]

In addition to increased oxidative stress, inflammation also appears to be a contributing factor in hearing loss. This was demonstrated in a randomized double-blind placebo control study in which aspirin reduced the risk of gentamicin-induced hearing loss.[40]

Noise can damage cochlear function through inflammation in animal models. This is supported by the fact that the levels of intracellular adhesion molecules and migration of leukocytes increased after exposure to noise.[41] Anti-inflammatory drugs reduced inflammation and improved hearing loss.[42] It has been proposed that repeated inflammatory reactions can produce sac dysfunction and eventual production of MD.[43]

Although physical ear protection can reduce the impact of noise and vibration some what, the energy generated from high levels of noise intensity and vibration can penetrate the inner ear in spite of earplugs and earmuffs, causing damage to hair cells. Further, physical protection of the ear plays no role in chemical-induced hearing loss or hearing loss that is truly related to the aging auditory system. Therefore, the authors suggest that physical protection should be supplemented with biological protection using appropriate doses and type of antioxidants and their derivatives via a dose-schedule.

Antioxidants: The Why

Increased oxidative stress and chronic inflammation are involved in hearing disorders. Since antioxidants reduce oxidative stress by neutralizing free radicals and reducing inflammation, supplementation with antioxidants may improve current prevention programs that use physical devices and improve the efficacy of standard therapy in patients with hearing disorders. Several studies with antioxidants and hearing disorders discussed above support this rationale.

Although supplementation with a single antioxidant in these studies has produced some beneficial effects in improving hearing disorders, this is not recommended for optimal results. This is due to the fact that an individual antioxidant, when oxidized, acts as a free radical. In addition, the use of a single antioxidant, such as vitamin E or beta-carotene in humans with a high internal oxidative environment (eg, heavy tobacco smokers), has produced harmful effects. This is consistent with the fact that individual antioxidants in high oxidative environments acted as a pro-oxidant. It is interesting to point out that, unlike studies on high-risk human populations, animal studies with individual antioxidants consistently produced beneficial effects.

Antioxidants: The When and How

In addition to physical protection, antioxidants should be consumed daily prior to exposure to agents or conditions that induce hearing disorders to reduce the risk of developing tinnitus, hearing loss, or a balancing problem. People suffering from hearing disorders should take antioxidants in combination with standard therapy.

However, the selection of the appropriate type of antioxidant preparation and dose-schedule is critical for enhancing their effectiveness. The authors recommend supplementation with multiple micronutrients containing dietary and endogenous antioxidants for reducing the risk of hearing disorders and improving the efficacy of standard therapy to improve the management of hearing disorders.

A closer look at specific antioxidants.

Almost all antioxidants can act as pro-oxidants (free radicals) when oxidized. Therefore, as mentioned earlier, the use of single antioxidants is not recommended. Multiple antioxidants are necessary because their organ and cellular distributions, as well as mechanisms of actions, are different.

For example, beta-carotene (BC) is more effective in quenching oxygen radicals than most other antioxidants. BC can perform certain biological functions that cannot be produced by its metabolite vitamin A, and vice versa. It has been reported that BC treatment enhances the expression of the connexin gene, which codes for a gap junction protein in mammalian fibroblasts

in culture, whereas vitamin A treatment does not produce such an effect. Vitamin A induces differentiation in certain normal cells and cancer cells, whereas BC and other carotenoids do not. Thus, BC and vitamin A have, in part, different biological functions. The gradient of oxygen pressure varies within cells. Some antioxidants, such as vitamin E, are more effective as quenchers of free radicals in reduced oxygen pressure, whereas others, such as BC and vitamin A, are more effective in higher atmospheric pressures. Vitamin C is necessary to protect cellular components in aqueous environments, whereas carotenoids and vitamins A and E protect cellular components in lipid environments. In addition, vitamin C is necessary for the activity of tyrosine hydroxylase, which is the rate-limiting enzyme in the synthesis of catecholamines.

Oxidized forms of vitamin C and vitamin E can also act as radicals; therefore, excessive amounts of any one of these forms, when used as a single agent, could be harmful over a long period of time. Vitamin C also plays an important role in maintaining cellular levels of vitamin E by recycling vitamin E radical (oxidized) to the reduced (antioxidant) form. Also, oxidative DNA damage produced by levels of vitamin C could be protected by vitamin E.

The form of vitamin E used is also important in any clinical trial. It has been established that d-alpha-tocopheryl succinate (a-TS) is the most effective form of vitamin E both in vitro and in vivo. This form of vitamin E is more soluble than a-tocopherol and enters cells more readily. Therefore, it is expected to cross the blood-brain barrier in greater amounts than a-tocopherol. However, this has not yet to be demonstrated in animals or humans.

We have reported that oral ingestion of aTS (800 IU/day) in humans increased plasma levels of not only a-tocopherol, but also a-TS, suggesting that a-TS can be absorbed from the intestinal tract before hydrolysis to a-tocopherol. This observation is important because the conventional assumption, based on rodents, has been that esterified forms of vitamin E such as a-tocopheryl acetate, a-tocopheryl nicotinate, and a-TS can be absorbed from the intestinal tract only after they are hydrolyzed to a-tocopherol. Our data show that this assumption may not be true for the absorption of a-TS in humans.

Another antioxidant is glutathione, which is effective in catabolizing H_2O_2 and anions. However, oral supplementation with glutathione failed to significantly increase plasma levels of glutathione in human subjects, suggesting that this tripeptide is completely hydrolyzed in the gastrointestinal (GI) tract. N-acetylcysteine and alpha-lipoic acid (glutathione-elevating agents by different mechanisms) can be used as an antioxidant in combination with others.

Besides well-characterized antioxidants—such as vitamin A, carotenoids, vitamin C, and vitamin E—other antioxidants are also important in protecting against cellular damage in the ear, including coenzyme and glutathione. A study has shown that ubiquinol (coenzyme Q10) scavenges peroxy radicals faster than a-tocopherol and, like vitamin C, can regenerate vitamin E in a redox cycle. However, it is a weaker antioxidant than a-tocopherol. Selenium is a co-factor of glutathione peroxidase, and Seglutathione peroxidase also acts as an antioxidant. Therefore, selenium supplementation together with other antioxidants is also essential. In addition to antioxidants, B-vitamins, vitamin D, and certain minerals are essential for optimal health. The pertinent references for this section are described in recent reviews.[44,45]

An antioxidant formulation containing iron or copper is not recommended, because these components interact with vitamin C and generate excessive amounts of free radicals. In addition, these trace minerals in the presence of vitamin C are absorbed better than in its absence, and nature has provided no significant mechanisms of excretion of iron or copper in men of all ages and women after menopause. Increased free iron or copper stores in the body increase the risk of many chronic diseases. The addition of heavy metals such as molybdenum, zirconium, and vanadium is also not recommended, because there are no significant mechanisms of removal of these heavy metals from the body. An accumulation of these metals after long-term consumption could be toxic to nervous tissue including the brain.

The inclusion of herbs or herbal antioxidants into a multiple dietary and endogenous antioxidant preparation is not recommended, because they do not produce any unique beneficial effects that cannot be produced by standard antioxidants. In addition, certain herbs are known to interact with prescription and non-prescription drugs in an adverse manner. These issues have been discussed in detail in two review papers.[44,45]

How much? Doses are very important because, at certain low

doses, antioxidants may reduce free radicals but may not decrease chronic inflammation. At higher doses (totally safe in humans), they reduce oxidative stress as well as inflammation. These issues have been discussed in detail in a recent review paper.[44]

A dose-schedule of twice a day (half in the morning and half in the evening) is equally important for increasing effectiveness. Taking antioxidants once a day may not be adequate, because of the resultant fluctuations of antioxidant levels in the body. For example, if antioxidants are consumed in the morning, at least half have been eliminated from the body by evening, and at least another half by the next morning. This can create significant fluctuations in antioxidant levels; only a twofold change in the level of vitamin E succinate is known to cause marked alterations in gene expression. Thus, the genetic machinery of the cell constantly has to readjust to cope with this fluctuation in the levels of antioxidants, and this could create cellular stress over a long period of time.[45]

Clinical Trial of Antioxidant Formulation for Hearing Health

Using the concepts of antioxidant formulation described above, PMC has prepared a formulation referred to as Hearing Health for preventing and improving hearing disorders in combination with standard therapy.

PMC antioxidant formulation was tested in a clinical study in troops returning from Iraq with mild to moderate traumatic brain injury. A total of 34 patients with post-traumatic dizziness were admitted to the Naval Medical Center San Diego Clinic over a 2-month period and the patients agreed to participate in the study under the supervision of Dr Michael Hoffer and his colleagues.

All patients had received their injury 3 to 20 weeks prior to admission, and they received identical treatment consisting of medical therapy (for any migraines), supportive care, steroids, and vestibular rehabilitation therapy. A total of 15 of the 34 patients also received a dose of an antioxidant and micronutrient formula (two capsules by mouth twice a day). At the onset of therapy, all patients were evaluated in outcome measures, which included the Sensory Organization Test (SOT) by Computerized Dynamic Posturography (CDP), the Dynamic Gait Index (DGI), the Activities Balance Confidence (ABC) scale, the Dizziness Handicap Index (DHI), the Vestibular Disorders Activities of Daily Living (VADL) score, and the Balance Scoring System (BESS) test.

The study was carried out for 12 weeks. The therapist who graded these outcomes and performed the testing was blinded as to whether the patient was receiving antioxidant therapy or not. The pretrial test scores did not differ significantly between the two groups on any of the tests.

Both groups of patients showed trends toward significant improvement on all tests after the 12 weeks of therapy, but the combination treatment trend was stronger than that of the standard therapy alone group. After only 4 weeks, the SOT score by CDP was 78 for the antioxidant group as compared to 63 for the non-antioxidant group. This difference was statistically significant at the $P < 0.05$ level. The improvement noted by the antioxidant group on the other tests was also greater than the non-antioxidant group, although these differences did not reach statistical significance because of the short trial period and small sample size.

In addition to the above clinical trial, several consumers who are on PMC Hearing Health formulation are showing improvement in hearing disorders. Almost all previous studies using primarily one, and occasionally two, components showed some beneficial effects in improving hearing disorders, but the PMC Hearing Health formula is very comprehensive and includes (at the proper dose, type, and dose schedule) dietary and endogenous antioxidants, B-vitamins, vitamin D, selenomethionine, and other minerals, but no iron, copper, or manganese or heavy metals or herbal products. This product is available commercially (www.mypmcinside.com).

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