



Antioxidant Therapy in Tinnitus

Oguz Kadir Egilmez¹ and M. Tayyar Kalcioğlu^{1*}

¹Department of Otorhinolaryngology, Faculty of Medicine, Istanbul Medeniyet University, Istanbul, Turkey.

Authors' contributions

This work was carried out in collaboration between all authors. Author OKE designed the study, wrote the protocol, and wrote the first draft of the manuscript. Authors OKE and MTK managed the literature searches, analyses of the studies performed previously. All authors read and approved the final manuscript.

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ABSTRACT

Oxidative stress and reactive oxygen species (ROS) have been working in the pathophysiology of various chronic diseases. Under normal circumstances, the human cochlea has some antioxidant molecules which can scavenge the oxidant substances and ROS to avoid the possible damage into the inner ear. In tinnitus therapy, several forms of complementary and alternative medicine (CAM) are increasingly popular but they are generally selected with or without professional guidance. Although several antioxidant agents like vitamin A, C, E and glutathione can be used in the treatment of tinnitus as CAM, melatonin, N-acetyl cysteine (NAC) and coenzyme Q10 (CoQ10) were especially used as alternative for classic antioxidants. According to the literature, it seems antioxidant therapy in patients with idiopathic tinnitus may reduce oxidative stress and damage to the inner ear. And also it can reduce the intensity and discomfort of tinnitus. Further clinical studies are necessary to determine antioxidants' protective role and to choose the appropriate therapeutic protocol.

Keywords: Antioxidant; tinnitus; alternative medicine.

*Corresponding author: Email: mtkalcioğlu@hotmail.com;

1. INTRODUCTION

Tinnitus, also referred as 'ringing in the ears' is defined as a perceived sound without definite acoustic stimulation. Ten to fifteen percent of general population are affected by tinnitus but approximately 2-3% are estimated to suffer from intense disabling tinnitus and consider to be an important problem interfering with work, sleep and decreasing the quality of life [1,2].

Tinnitus is mainly classified into two categories; which are subjective and objective tinnitus. Because this disorder is mainly subjective in nature and there is limited knowledge about its pathophysiology, treatment of tinnitus has been limited, yet, quite often unsuccessful [3]. Several strategies including, habituation therapy, electrical stimulation, dietary modification, antidepressants, anxiolytics, surgical intervention, herbal therapies and tinnitus management program have been tried to treat tinnitus and reduce its severity and improve patients' quality of life [4]. Some pharmacological treatment has been studied and some used to reduce tinnitus severity, but there are no specific agents recommended to this purpose [3]. Most common prescribed and used drugs for tinnitus include sedatives, antidepressants, anticonvulsants, antihistaminics, antipsychotics, local anesthetics and botulinum toxin [5,6].

Oxidative stress and reactive oxygen species (ROS) have been working in the pathophysiology of various chronic diseases and aging [7]. The major impact of radical-induced lesions is on the endothelium and the damage is mostly seen in microcirculation, particularly in the kidney and brain [7,8]. It has been recently established that ROS play an important role also in the pathology of the inner ear microcirculation and peripheral and central pathways [7]. Under normal circumstances, the human cochlea has some molecules like vitamins, glutathione, reactive transcription factors and enzymes which can work together to scavenge the oxidant substances and ROS to avoid the possible damage [7,9].

In tinnitus therapy, several forms of complementary and alternative medicine (CAM) are increasingly popular in western countries and they are generally selected with or without professional guidance [3]. According to National Institutes of Health in US, CAM has been defined as 'a group of diverse medical and health care systems, practices and products that are not

presently considered to be part of conventional medicine' [10]. Some factors, such as the feeling of despair about the problem, dissatisfaction with conventional medicine, the wish to play a major role in own treatment, poorer health status, anxiety and chronic pain are the reasons for using CAM as an alternative care. In this review, PUBMED database search was done and the articles related with antioxidant therapy used in tinnitus treatment were evaluated and discussed.

2. HOW CAN THE OXIDATIVE STRESS AFFECT THE EAR?

Oxidative stress can be involved in the pathogenesis of several diseases such as autoimmune, endocrine, cardiovascular and metabolic diseases, and also associated with intense muscular activity and tobacco smoking and treatment with progestagens [7]. Lesions induced by free radicals are seen mostly in the endothelium and microcirculation, especially the terminal type. The red blood cells are important for oxygen and carbonic anhydrase transport and also removing toxic substances. The inactivation of cascade of the red blood cells can cause membrane peroxidation and hemoglobin denaturation leading to cell damage [7]. When they are damaged by ROS, their cellular membranes could be injured, membrane lipids could be damaged and there could be membrane instability and increased permeability. So one important component of antioxidant system is blocked by ROS.

Under physiological conditions, ROS and free radicals are components of normal cellular redox state which comes from two reactions related with electron transfer; reduction and oxidation. And their toxicity is controlled by antioxidant system [11]. In such conditions, like ischemia-reperfusion injury, free radicals and ROS can affect the tissue by overcoming the antioxidant capability and induce damage to biological structures and leads to cell death [12].

In inner ear, ROS can damage the planum semilunatum (which is located near the crista ampullaris of the semicircular canal) and stria vascularis (which is located on the upper portion of the spiral ligament and contains several capillary loops and small blood vessels) [7]. In some reports, it was noted that oxidative stress could impair the labyrinth's sensorineural epithelium and also acoustic and vestibular nervous system [13,14]. ROS produced by oxidative stressors interacts with the

phospholipidic structures of the sensorial cells and aldehyde lipids like the 4-hydroxynonenal are produced and induce the apoptosis for auditory neurons and hair cells [7].

Oxidative harm can emerge during treatment with aminoglycoside antibiotics and platinum-based chemotherapeutic drugs. Also it was reported that some psychological and emotional stress could increase the production of ROS and cause oxidative damage to the inner ear [15,16]. Because of correlation between oxidative stress and the relevant pathology, using antioxidants in tinnitus treatment was suggested in several studies [1,3,7]. Particularly, antioxidants can protect the biological structures from oxidative damage by playing a role as reducing agent and counteracting overproduction of reactive species [3].

3. ANTIOXIDANTS IN TINNITUS

Although several antioxidant agents like vitamin A, C, E and glutathione i.e. can be used for treatment of tinnitus, especially melatonin, N-acetyl cysteine (NAC) and coenzyme Q10 (CoQ10) were used as alternative for classic antioxidants.

From 1950's to present day, vitamin deficiencies and replacement treatment had been the subject of research in the field of tinnitus. Particularly, known as the antioxidant vitamins A, C and E were used in many studies and significant results in the treatment of tinnitus had been reported [17-29]. In a study reported by Baron SH, 36 patients with deafness and 17 with tinnitus were given 50,000 to 100,000 units of vitamin A and at the end of the study, 4 of 17 patients with tinnitus had improved and lessened tinnitus but Anderson et al. reported that 50% of patients in their study had hearing improvement and better tinnitus reduction [17,19]. In recent years, although there have been some publications about B12 deficiency that might induce tinnitus [30,31], Berkiten et al. reported that some patients had improved tinnitus after B12 treatment but that result was statistically insignificant and they emphasized the etiology of tinnitus is multifactorial [32].

Also, Savastano et al. used vitamin A, C and E as antioxidants in their study and they measured the ROS values before and after the antioxidant treatment at the level of jugular vein of patients [7]. They found that ROS levels were significantly reduced and tinnitus perception in patients were decreased after antioxidant treatment. Reduction

of tinnitus were evaluated with tinnitus intensity measurements which were visual analog scale (VAS) and tinnitus loudness. And they suggested that using antioxidant therapy in patients with idiopathic tinnitus reduced oxidative stress and probably damage to tissues in the inner ear [7].

Interest in using melatonin to treat tinnitus was initiated by a study of Rosenberg et al. [33] instead of they prescribed patients with a dose of 3 mg melatonin daily for 30 days. They found significant reduction in tinnitus especially in patients with bilateral tinnitus and sleep disturbance because of tinnitus. As a result, the authors recommended melatonin usage in treating subjective tinnitus [33].

A prospective, randomized, double-blind, placebo controlled study was reported by Lopez-Gonzalez et al. [34]. They showed the alleviation of subjective tinnitus by using melatonin. In this report, melatonin (3 mg, daily) was compared with sulpiride- D₂ dopamine receptor antagonist (50 mg, daily) or combination of both for perception of tinnitus. The duration of treatment was 30 days and at the end of the treatment, it was found that melatonin reduced tinnitus by 40%, sulpiride lowered it by 56% and combination caused an 81% drop in subjective tinnitus [34].

In another study reported by Neri et al. [1], combination of melatonin and sulodexide treatment received by 34 patients improved the quality of life and reduced the severity of subjective tinnitus. In that study, sulodexide was used because it's ability to improve blood flow in the labyrinthine microcirculation [1].

Megwalu et al. reported a prospective study in which patients took 3 mg melatonin, daily for 4 weeks and observed 4 weeks [35]. Severity of tinnitus and sleep quality was assessed using Tinnitus Handicap Inventory (THI) and Pittsburgh Sleep Quality Index (PSQI). The authors suggested some association between improvements in tinnitus and sleep quality and they reported that melatonin might be a safe treatment modality for patients with idiopathic tinnitus who had sleep disturbance because of severe tinnitus [35].

Pirodda et al. reported that melatonin had ability to relieve tinnitus by reducing sympathetic drive, causing a reduction in skeletal muscle tone limiting tinnitus resulting from tonic contraction of tensor tympani muscle and inducing a more stable hemodynamic condition which results in a

regular labyrinthine perfusion [36]. It was also reported that melatonin had antidepressive actions and via indirect means, it reduced tinnitus or perception of tinnitus severity and it played a role as a direct regulator of inner ear immunity [36].

In another prospective, randomized, double-blind, placebo controlled study from Albu & Chirtes [2], patients with unilateral acute idiopathic tinnitus were allocated into two groups and one group received melatonin and intratympanic (IT) dexamethazone and the other group received melatonin alone for 3 months totally. After treatment, tinnitus severity was assessed using tinnitus loudness score, THI, PSQI, tinnitus awareness score and Beck Depression Inventory (BDI). As a result, they found that melatonin plus IT dexamethazone group had significant better outcomes about tinnitus perception and efficient improvement of idiopathic tinnitus [2].

Hurtuk et al. [4] also used melatonin in tinnitus patients. In that study, 61 patients with chronic tinnitus were randomized to 3 mg melatonin or placebo nightly for one month followed by a 1 month washout period. Then, each group crossed into the opposite treatment for one month. Tinnitus severity was evaluated with tinnitus matching (TM), TSI, Self Rated Tinnitus (SRT), BDI and PSQI. A significant reduction in tinnitus severity was observed in the group treated with melatonin. The authors were suggested that melatonin was most effective in some conditions like, male gender, noise exposure, bilateral tinnitus, absence of depression and anxiety, no prior tinnitus treatment and greater pre-treatment TSI scores [4].

In several studies mentioned above, short-term melatonin usage up to 3 months looked like safe for the majority of adults (1,2,4,33-40). But, it may cause nausea, headache, daytime sleepiness, short term feelings of depression, stomach cramps, dizziness, irritability and low body temperature [38]. Otherwise, melatonin can interact with some medications like immunosuppressants, anticoagulants, hypoglycemic agents and oral contraceptives. In addition, it may worsen symptoms of orthostatic hypotension and may exacerbate neurodegeneration in Parkinson disease and Parkinsonian symptoms [41].

One component of antioxidant system- glutathione, is the free radical scavenger in the brain and NAC increases the cysteine level and promotes endogeneous production of glutathione. It is used to counter paracetamol poisoning and treat schizophrenia and bipolar disorders [39], but there is no published data about using NAC in the treatment of tinnitus. In a scientific letter by Dean et al. [39] a 47-year-old woman patient with unipolar depression was treated with NAC and her pre-existing tinnitus was strikingly reduced after that treatment. The authors were suggested that there was correlation between reduction in depressive symptoms and decrease in subjective tinnitus which was achieved by reducing the inflammation and oxidative stress. And they also recommended further placebo controlled trials for understand the exact mechanism of NAC.

To determine the effects of CoQ10 on the antioxidative status and tinnitus expression, Khan et al. [40] reported a prospective, non-randomized clinical trial in which 20 patients were evaluated for plasma concentrations of CoQ10, malendialdehyde and antioxidant status with Tinnitus and Short Form-36 Questionnaires (TQ/SF-36). They found that CoQ10 might decrease the tinnitus expression in patients with a low levels of plasma CoQ10 concentrations [40].

4. CONCLUSION

Tinnitus is considered to be an important problem and approximately 2-3% of general population are estimated to suffer from intense disabling tinnitus. Several strategies have been tried to treat tinnitus but there are no specific agents recommended to this purpose. Oxidative stress and reactive oxygen species (ROS) have been working in the pathophysiology of various chronic diseases and also tinnitus. According to the literature, it seems antioxidant therapy in patients with idiopathic tinnitus may reduce oxidative stress and damage to the inner ear. And also it can reduce the intensity and discomfort of tinnitus. They may be an additional therapy option for patients with tinnitus and considered as a supplement for patients undergoing treatment with ototoxic drugs. Further clinical studies are necessary to determine antioxidants' protective role and to choose the appropriate therapeutic protocol.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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