

## The role of vitamin C and E in improving hearing loss in patients with type 2 diabetes

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(Ann Coll Med Mosul 2019; 41 (1):184-189).

Received: 16<sup>th</sup> Feb. 2019; Accepted: 15<sup>th</sup> May 2019.

### ABSTRACT

**Objective:** to evaluate the effect of antioxidant vitamins on hearing loss in diabetic patients.

**Patients and methods:** Sixty type 2 diabetic patients with positive pure tone audiogram (PTA) enrolled in the study and divided into two groups: each group consists of thirty patients, group one was put on antioxidant therapy, and group two on placebo therapy, for 2 months duration. Thirty healthy individuals were kept as a control. Fasting blood sugar (FBS), and malondialdehyde (MDA) were measured in all groups. MDA and PTA were repeated after therapy.

**Results:** The FBS and MDA are higher in diabetic patients, and beneficial effects of the administration of vitamin E and C combination on the oxidative stress and significant improvement, with mean differences of  $12.5 \pm 7.79$  decibel (dB), in the sensorineural hearing loss (SNHL) in diabetic patients were obtained.

**Conclusion:** the present study demonstrated that diabetic patients have exaggerated oxidative stress, and administration of vitamin E and C combination had beneficial effect on the oxidative stress, and on the SNHL in diabetic patients with mean differences of  $12.5 \pm 7.79$  dB ( $p < 0.001$ ).

**Keywords:** diabetes, oxidative stress, hearing deficit, antioxidants.

## دور فيتامين سي و اي في علاج عطب السمع لدى مرضى السكري من النوع الثاني

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### الخلاصة

**الهدف من الدراسة :** هو تقييم تأثير الفيتامينات المضادة للأكسدة على عطب السمع لمرضى السكري .

الطرق المتبعة والأشخاص : أجريت هذه الدراسة على مرضى السكري من النوع الثاني، حيث دخل الدراسة 60 مريضاً مصاباً بعطب السمع، تم تقسيمهم الى مجموعتين، كل مجموعة تتألف من 30 مريضاً. وتم اعطاء المجموعة الاولى فيتامينات مضادة للأكسدة والمجموعة الثانية عولجو بعلاج الغفل ولمدة شهرين، وشملت الدراسة ايضاً 30 شخصاً سليماً كمجموعة ضبط. تم قياس سكر المصل والملوندايالديهايد عند المجموعات الثلاثة .

اعيدت الفحوصات الثلاثة ( فحص سكر المصل والملوندايالديهايد وفحص عتبة السمع ) بعد العلاج .

**الاستنتاجات:** أظهرت النتائج ارتفاعاً في نسبة السكر ومستوى الملوندايالديهايد عند مرضى السكري، وان تعاطي فيتامينات المضادة للأكسدة له دور فعال على الأكسدة وتحسين معنوي في عطب السمع عند مرضى السكر وبمعدل تحسن وصل الى 12.5 ديسيبل.

**الكلمات المفتاحية :** مرض السكري، جهد الأكسدة، عطب السمع، مضادات الأكسدة.

## INTRODUCTION

Diabetes mellitus in all its varieties has become an important issue as one of the crucial health obstacles. The complications of this disease are the main cause of morbidity and mortality. Oxidative stress plays a great role in diabetic complications<sup>1,2</sup>. Recent studies conducted on diabetic patients have investigated that hyperglycaemia is associated with glycosylation of proteins and overproduction of free radical and more reactive oxygen species (ROS). These deleterious impacts can induce dramatical damage to cellular biomolecules, such as, DNA, carbohydrate, lipid, and protein<sup>3</sup>.

There is a debate whether hearing deficit is more predominant in type 2 diabetes than in non-diabetic patients<sup>4</sup>. Some researchers suggest that there is negative correlation between diabetes mellitus and hearing deficit; several clinical trials have demonstrated a direct relationship between hearing deficit and diabetes mellitus<sup>5</sup>, but the nature of the relationship between diabetes and hearing deficit is still uncertain<sup>6</sup>. The free radical generation and production of ROS is regarded as an important pathways in auditory damage, a common reason of neurogenic hearing loss, and high levels of oxidative stress-related molecules, such as, the hydroxyl radical, hydrogen peroxide, and superoxide anion, have been found in the cochlea of industrial-workers exposure to various threshold of noise<sup>7</sup>.

The aetiology of underlying cochlear damage is still unknown. Nevertheless, different studies have suggested that they are associated with the generation of ROS, which provide a damage to cellular components in the cochlear structure resulting in sensorineural hearing loss (SNHL)<sup>8</sup>. These results suggest that oxidative stress may play an important role in hearing impairment in diabetic patients<sup>9</sup>. The aim of the present study is to evaluate the effects of antioxidant vitamins on the oxidative stress and on hearing threshold in diabetic patients.

## PATIENTS AND METHODS

The study had ethical approval from Mosul college of medicine. A known cases of type 2 diabetes mellitus with a positive Pure Tone Audiogram (PTA) enrolled in this study, and divided into two groups: each group consists of thirty patients, group one received the antioxidants therapy (Vitamin C 500mg twice daily, and vitamin E 400IU once daily)<sup>10</sup> and group two was put on placebo therapy, for 2 month duration. Another group involved thirty apparently healthy individuals kept as a control for comparing oxidative stress. PTA is the paper-based result obtained from pure tone audiometer following application of standard procedure of different frequencies and intensities on exposed subject.

Fasting blood sugar (FBS) was measured for each patient and control by using enzymatic colorimetric kit supplied by (Randox, UK). Malondialdehyde (MDA), a product of oxidative stress was measured for each patient and control using thiobarbituric acid (TBA) assay<sup>11</sup>. Pure tone audiometry (PTA) was done for diabetic patients by measurement of intensities at frequency of 250, 500, 1000, 2000 and 4000 hertz (Hz). The intensities measured in decibels (dB). The PTA was measured and interpreted by Ear, Nose, Throat specialist in Alzahrawy hospital, department of ENT according to the American-speech-language-hearing association (ASLHA)<sup>12</sup>. The hearing loss was calculated at these frequencies and the average of them to derive a pure tone threshold average (PTTA). PTA and MDA were repeated after therapies.

Paired t-test was used to compare the results of various parameters among the studied groups. All values were expressed as mean±SD and p value of <0.05 was considered to be statistically significant.

## RESULTS

1. Demographic characteristics of patients and control groups:

**Table 1:** shows the age, Body Mass Index (BMI) and duration of diabetes in the diabetic patients included in the study. There were non-significant differences between the groups.

	Control group	Antioxidant group	Placebo group	p-value
Age (year)	50.83±5.82	49.33±7.03	50.33±4.83	0.31
BMI (kg/m <sup>2</sup> )	30.65±4.06	29.41±5.5	29.99±3.47	0.53
Duration (year)	.....	8.92±7.96	8.65±8.26	0.43

2. Biochemical parameters measured in diabetic patients before treatment:

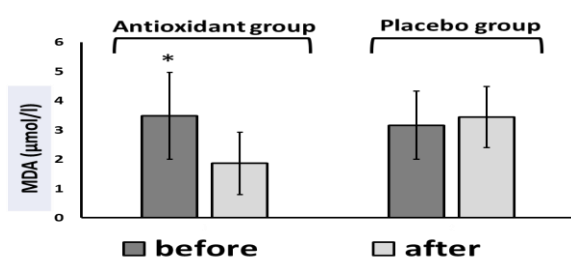
Table 2 shows the FBS and MDA of all studied groups. FBS and MDA of the control subjects were within normal range while those of diabetic patients were high when compared with the control group ( $p=0.001$ ).

**Table 2:** the MDA and FBS of the all studied groups before treatment.

	Control group	Antioxidant group	Placebo group	p-value
MDA ( $\mu\text{mol/l}$ )	1.48±0.33	3.48±1.13	3.16±0.8	0.001
FBS (mmol/l)	5.62±0.75	14.54±5.27	11.79±5.04	0.001

3. Biochemical parameters measured before/after antioxidant therapy in diabetic patients:

Figure 1 shows the results of the comparison of MDA of the antioxidant and placebo groups before and after the therapy. There is a highly significant reduction in MDA; after antioxidant therapy, and no significant differences in the MDA after placebo therapy.



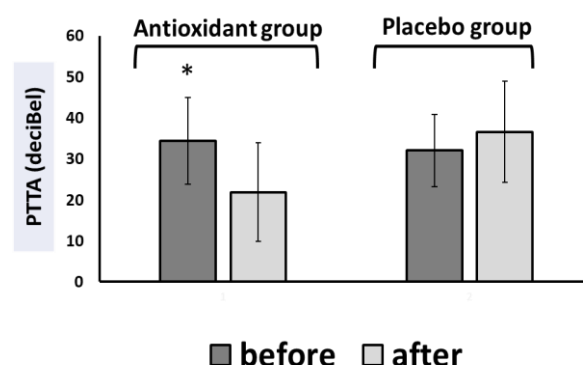
**Figure 1.** The levels of Malondialdehyde (MDA) in both antioxidant and placebo groups.

The results indicated that the antioxidant therapy was significantly reduce the oxidative stress marker indicated by measurement of

MDA in antioxidant group compared to placebo group. Data expressed as mean±SD,  $*p<0.05$ .

Auditory parameters measured before/after antioxidant therapy in diabetic

Figure 2 shows a statistical difference (improvement) in PTTA after antioxidant therapy with mean difference( $12.58\pm7.79\text{dB}$ )( $p=0.001$ ), while in the placebo group shows worsening differences.



**Figure 2.** The levels of pure tone threshold average (PTTA) in both antioxidant and placebo groups.

The results showed that the antioxidant therapy was significantly reduce the hearing loss indicated by measurement of auditory function in comparison to placebo group. Data expressed as mean $\pm$ SD, \* $p$ <0.05.

## DISCUSSION

The FBS reported in this study was high in diabetic patients as compared with the control. These results were in agreement with the data of previous studies which also reported a high level of FBS indicating a poor glycaemic control in diabetic patients<sup>13-15</sup>. A higher significant levels of serum MDA were found in this study in diabetic patients. Increased MDA level is an evidence of exaggerated oxidative stress in diabetic patients. Serum MDA levels were found significantly higher in diabetic patients than the healthy control subjects in some of previous studies, its worthy to mention that Vessby *et al.* 2002, and Yilmaz *et al.* 2004, have reported an elevated oxidative stress parameter including MDA in diabetic patients<sup>16-19</sup>.

In this study serum MDA levels were decreased significantly after antioxidant therapy with vitamin E and C. The impact of antioxidant compounds such as vitamin E, vitamin C, and Beta-caroten have been reported in many studies, including, a study conducted by Hatano *et al.* 2008, Firuzi *et al.* 2011, and Dakhale *et al.* 2011 which were reported improved oxidative stress parameters following antioxidant therapy, and positive effects of these compound on oxidative stress have been reported<sup>10,20,21</sup>.

Data obtained from the present study demonstrated positive effects of a combination of vitamin E and C on the SNHL in diabetic patients. At the end of the study and after repeating the pure tone audiogram test, the frequencies obtained by pure tone audiometry including pure tone threshold average PTTA, showing highly significant improvement (from 34.4 $\pm$ 10.5 dB to 21.9 $\pm$ 12dB) with mean differences of 12.5 $\pm$ 7.79dB. Review of literature provides limited information on the usefulness of vitamin E and vitamin C in diabetic neuropathies<sup>10</sup>. Many studies dealt with management of SNHL due to other reasons that anticipated the same mechanism, depending on free radical induced damage. A preclinical study done on laboratory animal model, investigated the effectiveness of hydrogen in

protecting the auditory hair cell from overproduced ROS induced damage, demonstrated that hydrogen notably reduced the oxidative stress by scavenging ROS, and protected auditory cochlear cells against oxidative stress<sup>9</sup>. A study conducted by Dallan *et al.*, 2006 base on transtympanic administration of Methylprednisolone; in patients with sensorineural hearing loss-nonresponsive to classical therapy had a significant improvement (significant improvement= PTA improvement  $\geq$ 15) was obtained in 70% of patients included in the study<sup>22</sup>.

Recent studies reported that all hyperglycaemia-induced injuries; including increases in aldose reductase, advanced glycation end products, and protein kinase C, are reversible by suppression of high-glucose induced ROS production<sup>23</sup>. In the present study the beneficial mechanism of the vitamin E and C on the diabetic SNHL may be related to improved neuronal pathophysiology caused by chronic hyperglycaemia induced oxidative stress by improving antioxidant status and reversing all hyperglycaemia-induced changes.

Recent studies have reported toxic effects of free radicals, reactive oxygen species and nitric oxide in the hearing system<sup>24,25</sup>. The prevalence of hearing loss caused by cisplatin, aminoglycoside, loud noise and presbycusis is significantly reduced by free radical scavengers, such as vitamin E and edaravone, in preclinical animal models<sup>26,27</sup>. Vitamin E is a potent fat-soluble antioxidant and is thought to be an important free radical scavenger that protects cell membranes from oxidative stresses and lipid peroxidation. Its function is believed to be mediated by the antioxidant action as a membrane stabilizer. These results indicate that free radical scavengers may be useful in protecting the outer haircell function from ototoxicity, noise-induced hearing loss (NIHL) and presbycusis. It was also demonstrated that the application of vitamin E was beneficial against ISSHL<sup>28</sup>. Some studies suggest that vitamin C is also effective in reducing susceptibility to NIHL and presbycusis<sup>27,29</sup>. Although the pathophysiology of ISSHL is unknown, a similar pathological mechanism to free radical production might occur in ISSHL. We carried out this study to determine whether the administration of free

radical scavenger's vitamin E and vitamin C is useful for the treatment of ISSHL.

## CONCLUSION

Data obtained from the present study demonstrated overproduction of MDA; an oxidative stress-related molecule; in diabetic patients, and beneficial effects of administration of vitamin E and C combination on the oxidative stress and the SNHL in diabetic patients were obtained. Therefore, it is necessary to consider the hearing status as a long-term complication of diabetes. It is wisely advised to conduct a clinical and audiometry assessment initially for all diabetic patients and to keep this as initial record of auditory examination of patient. Supplementation of vitamin E and C to diabetic patients can be a routine practice to avoid complication of hearing loss.

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