Activity of coenzyme Q_{10} (Q-Ter multicomposite) on recovery time in noise-induced hearing loss

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Abstract

A potential consequence of exposure to noise is a temporary reduction in auditory sensitivity known as temporary threshold shift (TTS), which mainly depends on the intensity and duration of exposure to the noise. Recovery time is related to the amount of initial hearing loss, and the most recovery takes place during the first 15 min following exposure. This study evaluated the efficacy in otoprotection against noise-induced hearing loss of an orally administrated food supplement containing coenzyme Q_{10}-Ter. This water-soluble formulation of coenzyme Q_{10} shows better bioavailability than the native form and has been found to have a protective effect on outer hair cells after exposure to noise in animal models. Thirty volunteers were enrolled, and the right ear of each subject was exposed to a narrow-band noise centered at 3 kHz for 10 min at the intensity of 90 dB HL. In the 30 subjects enrolled, TTS was evaluated after 2, 15, and 30 min and the recovery time was recorded in each subject. The longest recovery time was 45 min. Among the 18 subjects who underwent a second test after treatment with Q-Ter, the mean recovery time was 31.43 min. The results of the present study show that 30 days' treatment with Q-Ter can aid faster recovery after exposure to noise ($P < 0.0001$). The reduction in the recovery time following treatment can be explained by Q-Ter-mediated improvement of the outer hair cells' response to oxidative stress.

Keywords: Coenzyme Q_{10}, hearing protection, noise-induced hearing loss, Q-Ter, recovery time, temporary threshold shift

Introduction

A potential consequence of exposure to noise is a temporary reduction in auditory sensitivity known as temporary threshold shift (TTS). When recovery remains incomplete, this is regarded as a permanent threshold shift (PTS). Noise with intensity lower than 65-70 dB SPL does not cause an elevation of the threshold level, while above 70 dB the TTS increases linearly until 120 dB. Beyond this level, the TTS rises along a logarithmic curve, up to an asymptotic maximum known as "asymptotic threshold shift"[1] Threshold shift is correlated to the noise frequency spectrum: It is more evident in the frequency range between 3 and 5 kHz, probably due to ear canal resonance and the transfer function of the auditory canal, or to the effect of stapedial reflexes.[1,2]

The largest amount of TTS generally occurs from one-half to one octave above the exposure frequency.

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Hearing loss mainly depends on the intensity and duration of exposure to noise.[3-5]

The recovery time is related to the amount of initial hearing loss (being longer the greater the initial hearing loss) and mostly occurs during the first 15 min following exposure.[3,6]

Traditionally, the prevention of noise-induced hearing loss (NIHL) has been addressed by providing wearable hearing protection (earplugs, earphones) and reducing noise emissions.[7]

Clinical and preclinical trials for drugs that could reduce TTS and PTS retrace the understanding of the physiopathology of NIHL.

First vasodilators and vasoactive agents were tested (carbogen, loftyl) in an attempt to re-establish normal vascularization and oxygenation of the organ of Corti.[8-10]

The next drug tested was allopurinol, an inhibitor of xanthine oxidase and scavenger of free radicals that stops the accumulation of reactive oxygen and reactive nitrogen species from causing metabolic exhaustion of the outer hair cells.[11,12]

Magnesium has also been tested, alone or in compounds with other antioxidants (β-carotene, Vitamins E and C) with encouraging results.[13-15]

Supra-physiological administration of Vitamin B12 appears to be efficacious in protecting hearing, especially at the frequencies of 3 and 4 kHz.[16]

Other studies have shown some efficacy in preventing NIHL for glutathione precursors, such as N-acetylcysteine and methionine, or other antioxidants like alpha-lipoic acid.[17-23]

Coenzyme Q_{10}, also known as ubiquinone, is the predominant form of coenzyme Q in humans. It has a potent antioxidant effect either by directly scavenging free radicals or by recycling and regenerating other antioxidants.[24-26] Ubiquinone is a lipid-soluble molecule that acts as a mobile electron carrier in the mitochondrial electron transport chain, which is the major source of adenosine triphosphate in the mitochondria. Within the mitochondria, ubiquinone is reduced by the respiratory chain to its active ubiquinol form, which is an effective antioxidant that prevents lipid peroxidation and mitochondrial damage.[27]

The water-soluble formulation of the coenzyme Q_{10}, Q-Ter, has shown better bioavailability than the native form, as well as a protective effect on outer hair cells after noise exposure in animal models.

Q-Ter consists of an outer case of cyclodextrins, which entrap moieties of the coenzyme $Q_{10,}$ and an aminoacid that acts as a catalyst for the formation of the multicomposite.

This formulation has been proven to be 200 times more soluble and nearly 5 times more antioxidant than native coenzyme Q_{10}.[26,27]

This study evaluated the efficacy in otoprotection against NIHL of an orally administrated food supplement containing coenzyme Q_{10}-Ter, along with Vitamins (E, B1, B2, B6, and B12), choline and *Ginkgo biloba.*

Ginkgo biloba extract is a blood flow-promoting drug that also works as a scavenger of free radicals, stimulates the relaxation of contracted blood vessels and contributes to neuroprotection. It has been tested against gentamicin or cisplatin-induced ototoxicity both *in vitro* and in animal models with encouraging results,[28,29] but has shown no effect on acute NIHL.[30]

While Vitamin E and *G. biloba* can integrate the antioxidant action of Q-Ter, Vitamin B12 and choline have no proven efficacy in NIHL by oral administration.

The aim of this study was to assess the influence of orally administrated Q-Ter on NIHL recovery time in subjects with normal hearing. The resolution of noise exposure-induced tinnitus was also evaluated.

Methods

A total of 30 volunteers were enrolled: 12 females and 18 males, mean age 30.43 ± 4.96 years, range from 20 to 40 years, with no family history of hearing loss and normal otoscopy results. All tests were performed early in the morning, from 8.00 am to 10.00 am, between January and March 2013.

Pure tone audiometry of the right ear was performed in a soundproof cabin using pure tones from 125 Hz to 8000 Hz.

Then, using headphones, the right ear was exposed to a narrow-band noise centered at a frequency of 3 kHz for 10 min, at an intensity of 90 dB HL (which is within the range of the WHO occupational exposure limits and those of Italian legislative decree 195/2006 regarding the risk of exposure to noise in the workplace).[31]

The hearing threshold shift was evaluated 2 min after the end of exposure (TTS_2), then after 15 min (TTS_{15}) and 30 min (TTS_{30}). Subsequent measures were taken every 5 min until complete recovery.

Twenty-five of the subjects (14 males and 11 females, 25-36 years of age) were treated with the Q-Ter compound once a day for 30 days [Table 1]. The second test was performed the day after the 30th day of treatment, following the same methodology as the initial evaluation.

The duration of tinnitus was assessed by a multiple choice questionnaire in which the options, in order of severity, were:

a. Not present in the afternoon after exposure.
b. Not present in the evening.
c. Not present in the following morning.
d. Disappeared within 24 h of exposure.

Comparisons between groups were assessed using the paired *t*-test or Wilcoxon signed-rank test, as appropriate, applying a significance level of $P < 0.05$. To analyze the hearing data, thresholds were compared by one-way analysis of variance

Table 1: Q-Ter compound formulation

Coenzyme Q_{10}-Ter	160 mg
Lactium	150 mg
Melatonin	5 mg
Choline	100 mg
Ginkgo biloba	80 mg
Vitamin E	36 mg
Vitamin B1	1.65 mg
Vitamin B6	2.1 mg
Vitamin B12	3.75 mcg

(ANOVA), followed by Tukey's multiple comparison tests for variance between time intervals at the first assessment. TTS in the untreated and treated subjects was compared using two-way ANOVA, followed by Bonferroni's *post-hoc* test with the variables of time and 30 days of dietary supplementation with Q-Ter compound. Statistical analysis was performed using SPSS software (SPSS, Inc., Chicago, IL, USA).

Results

One-way ANOVA was used to compare hearing levels and TTS after the baseline test. The threshold shift was significant at the frequencies 4000 Hz, 6000 Hz, and 8000 Hz, with recovery still being incomplete after 15 min [Figure 1]; at 3000 Hz no significant difference was observed in the threshold shift after 2 and 15 min.

Next, the recovery time was evaluated in each of the 30 subjects. The longest recovery time was 45 min (mean time 37.67 ± 4.49 min). All of the subjects complained of tinnitus for 24 h.

Five subjects refused to attend the test again and to follow the therapy, so were excluded from the study.

Among the 25 subjects who underwent a second test after treatment with Q-Ter, the mean recovery time was 31.60 ± 2.38 min. Two-way ANOVA showed a significant effect of Q-Ter administration on the thresholds at 4000, 6000, and 8000 Hz, at 2 and 15 min ($P = 0.0267$, 0.0446, 0.0355, respectively); and confirmed that time affects the recovery of the threshold in a significant way ($P < 0.0001$ for 4000, 6000, and 8000 Hz) [Figure 2]. *T*-test statistical analysis showed a significantly shorter full recovery time in treated subjects ($P < 0.0001$) [Figure 3].

Regarding the duration of tinnitus, after the first examination 12/30 subjects reported that it lasted 24 h (answer d), while 18 responded with answer c. At the 1 month control, 8/25 subjects responded with the answer a; eight with b; and nine with answer c. There was a statistically significant difference between the treated and untreated groups according to the Wilcoxon signed-rank test ($P < 0.0001$).

Discussion

On the basis of measurements recorded in the 1960's, Miller developed a diagram, which makes it possible to hypothetically estimate the TTS_2 values from decibel levels (between 70 and 120 dB) after exposures of varying duration.[32]

However, the TTS_2 value represents only one aspect of the problem of noise exposure.

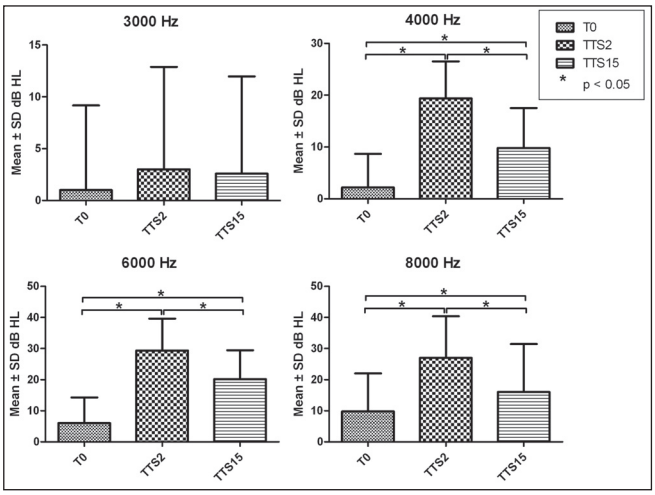

Figure 1: One-way analysis of variance (ANOVA) shows a significant threshold shift at the frequencies 4000 Hz, 6000 Hz, and 8000 Hz (Tukey's multiple comparison test; *$P < 0.0001$)

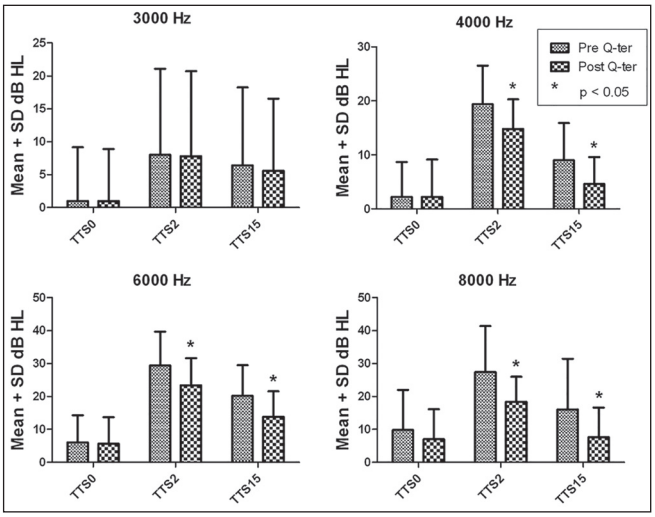

Figure 2: Two-way ANOVA shows a significant effect of Q-Ter in temporary threshold shift (TTS_2) and TTS_{15} variations (Bonferroni's post-test; *$P < 0.05$)

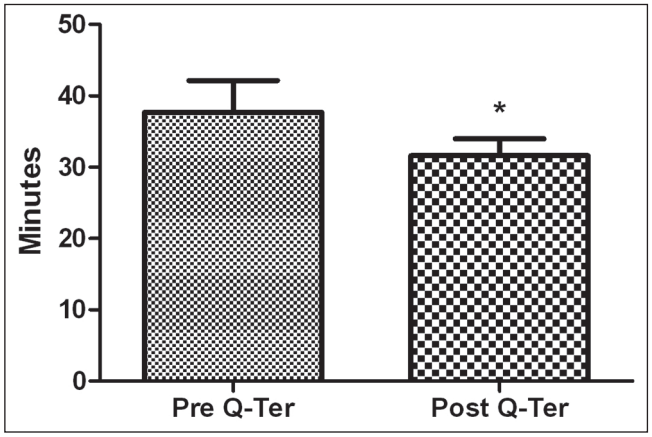

Figure 3: Comparison of the recovery time before and after treatment (Paired *t*-test; *$P < 0.0001$)

In fact, recovery time can be considered an indicator of the psycho-physical cost of noise exposure because, unlike the TTS, it is strongly influenced by the characteristics of the fatiguing stimulation (frequency, intensity, and duration) as well as by interindividual differences.[3,6,33,34]

The threshold shift induced by the stimulus used in this study was significant at high frequencies (4000-8000 Hz) which, due to the tonotopic organization of the cochlea, are received by receptors in the basal turn of the cochlea.

The major limitation of the present study is that we used a food supplement containing not only Q-ter but other components.

Nonetheless, Q-Ter has been proven to be efficacious in the prevention of cell death in the mid-basal turn of the cochlea in animal studies, while there is no clear evidence of efficacy against NIHL for the other individual components of the compound.[16,26-30]

No other studies in the literature consider the effect and the efficacy of a compound containing E and B-complex vitamins together with choline and *G. biloba* in otoprotection. We are, therefore, inclined to believe that Q-Ter plays the leading role in the improvement of the recovery time shown by our data, although we cannot exclude a synergistic effect on the part of the other components of the compound.

Conclusion

Our data show a significant improvement in the recovery time and residual tinnitus after 1 month of treatment with orally administrated Q-Ter compound.

Further studies are needed on a larger population to assess the real importance of Q-Ter in relation to the other components, and to evaluate the possible influence of interindividual variations in recovery time.

The reduction in recovery time following treatment can be attributed to Q-Ter, which is known to be effective in preventing the formation of free radicals and in promoting the recovery of other antioxidant substances, thus, improving the response of the outer hair cells to oxidative stress.

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References

1. Quaranta A, Portalatini P, Henderson D. Temporary and permanent threshold shift: An overview. Scand Audiol Suppl 1998;48:75-86.
2. Borg E. A quantitative study of the effect of the acoustic stapedius reflex on sound transmission through the middle ear of man. Acta Otolaryngol 1968;66:461-72.
3. Chen CJ, Dai YT, Sun YM, Lin YC, Juang YJ. Evaluation of auditory fatigue in combined noise, heat and workload exposure. Ind Health 2007;45:527-34.
4. Ward WD. Temporary threshold shift and damage-risk criteria for intermittent noise exposures. J Acoust Soc Am 1970;48:561-74.
5. Ward WD. Recovery from high values of temporary threshold shift. J Acoust Soc Am 1960;32:497-500.
6. Melnick W. Human temporary threshold shift (TTS) and damage risk. J Acoust Soc Am 1991;90:147-54.
7. Lynch ED, Kil J. Compounds for the prevention and treatment of noise-induced hearing loss. Drug Discov Today 2005;10:1291-8.
8. Joglekar SS, Lipscomb DM, Shambaugh GE Jr. Effects of oxygen inhalation on noise-induced threshold shifts in humans and chinchillas. Arch Otolaryngol 1977;103:574-8.
9. Witter HL, Deka RC, Lipscomb DM, Shambaugh GE. Effects of prestimulatory carbogen inhalation on noise-induced temporary threshold shifts in humans and chinchilla. Am J Otol 1980;1:227-32.
10. Axelsson A, Lindgren F. The effect of buflomedilhydrochloride (Loftyl) on temporary hearing threshold shift. Scand Audiol Suppl 1986;26:37-40.
11. Attanasio G, Cassandro E, Sequino L, Mafera B, Mondola P. Protective effect of allopurinol in the exposure to noise pulses. Acta Otorhinolaryngol Ital 1999;19:6-11.
12. Franzé A, Sequino L, Saulino C, Attanasio G, Marciano E. Effect over time of allopurinol on noise-induced hearing loss in guinea pigs. Int J Audiol 2003;42:227-34.
13. Attias J, Bresloff I, Haupt H, Scheibe F, Ising H. Preventing noise induced otoacoustic emission loss by increasing magnesium (Mg^{2+}) intake in guinea-pigs. J Basic Clin Physiol Pharmacol 2003;14:119-36.
14. Le Prell CG, Johnson AC, Lindblad AC, Skjönsberg A, Ulfendahl M, Guire K, *et al.* Increased vitamin plasma levels in Swedish military personnel treated with nutrients prior to automatic weapon training. Noise Health 2011;13:432-43.
15. Le Prell CG, Dolan DF, Bennett DC, Boxer PA. Nutrient plasma levels achieved during treatment that reduces noise-induced hearing loss. Transl Res 2011;158:54-70.
16. Quaranta A, Scaringi A, Bartoli R, Margarito MA, Quaranta N. The effects of 'supra-physiological' vitamin B12 administration on temporary threshold shift. Int J Audiol 2004;43:162-5.
17. Kramer S, Dreisbach L, Lockwood J, Baldwin K, Kopke R, Scranton S, *et al.* Efficacy of the antioxidant N-acetylcysteine (NAC) in protecting ears exposed to loud music. J Am Acad Audiol 2006;17:265-78.
18. Bielefeld EC, Hynes S, Pryznosch D, Liu J, Coleman JK, Henderson D. A comparison of the protective effects of systemic administration of a pro-glutathione drug and a Src-PTK inhibitor against noise-induced hearing loss. Noise Health 2005;7:24-30.
19. Fetoni AR, Ralli M, Sergi B, Parrilla C, Troiani D, Paludetti G. Protective effects of N-acetylcysteine on noise-induced hearing loss in guinea pigs. Acta Otorhinolaryngol Ital 2009;29:70-5.
20. Cheng PW, Liu SH, Young YH, Hsu CJ, Lin-Shiau SY. Protection from noise-induced temporary threshold shift by D-methionine is associated with preservation of ATPase activities. Ear Hear 2008;29:65-75.
21. Lin CY, Wu JL, Shih TS, Tsai PJ, Sun YM, Ma MC, *et al.* N-Acetyl-cysteine against noise-induced temporary threshold shift in male workers. Hear Res 2010;269:42-7.
22. Ewert DL, Lu J, Li W, Du X, Floyd R, Kopke R. Antioxidant treatment reduces blast-induced cochlear damage and hearing loss. Hear Res 2012;285:29-39.
23. Quaranta N, Dicorato A, Matera V, D'Elia A, Quaranta A. The effect of alpha-lipoic acid on temporary threshold shift in humans: A preliminary study. Acta Otorhinolaryngol Ital 2012;32:380-5.
24. Bhagavan HN, Chopra RK. Coenzyme Q10: Absorption, tissue uptake, metabolism and pharmacokinetics. Free Radic Res 2006;40:445-53.
25. Lenaz G, Fato R, Formiggini G, Genova ML. The role of Coenzyme Q in mitochondrial electron transport. Mitochondrion 2007;7:S8-33.
26. Fetoni AR, De Bartolo P, Eramo SL, Rolesi R, Paciello F, Bergamini C, *et al.* Noise-induced hearing loss (NIHL) as a target of oxidative

stress-mediated damage: Cochlear and cortical responses after an increase in antioxidant defense. J Neurosci 2013;33:4011-23.
27. Fetoni AR, Eramo SL, Rolesi R, Troiani D, Paludetti G. Antioxidant treatment with coenzyme Q-ter in prevention of gentamycin ototoxicity in an animal model. Acta Otorhinolaryngol Ital 2012;32:103-10.
28. Yang TH, Young YH, Liu SH. EGb 761 (*Ginkgo biloba*) protects cochlear hair cells against ototoxicity induced by gentamicin via reducing reactive oxygen species and nitric oxide-related apoptosis. J Nutr Biochem 2011;22:886-94.
29. Cakil B, Basar FS, Atmaca S, Cengel SK, Tekat A, Tanyeri Y. The protective effect of *Ginkgo biloba* extract against experimental cisplatin ototoxicity: Animal research using distortion product otoacoustic emissions. J Laryngol Otol 2012;126:1097-101.
30. Lamm K, Arnold W. The effect of blood flow promoting drugs on cochlear blood flow, perilymphatic pO(2) and auditory function in the normal and noise-damaged hypoxic and ischemic guinea pig inner ear. Hear Res 2000;141:199-219.
31. Johnson DL, Papadopoulos P, Watfa N, Takala J. Exposure criteria, occupational exposure levels. In: Goelzer B, editor. Occupational Health-Occupational Exposure to Noise: Evaluation, Prevention and Control. Dortmund, Germany: World Health Organization Publications; 2001. p. 95. Available from: http://www.who.int/occupational_health/publications/noise4.pdf. (Last accessed on 2014 March)
32. Miller JD. Effects of noise on people. J Acoust Soc Am 1974;56:729-64.
33. Strasser H, Irle H, Legler R. Temporary hearing threshold shifts and restitution after energy-equivalent exposures to industrial noise and classical music. Noise Health 2003;5:75-84.
34. Passàli D, Passàli GC, Passàli FM, Damiani V, Mora R, Bellussi L. Airbags and permanent auditory deficits. A real correlation? Acta Otorhinolaryngol Belg 2003;57:177-81.

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