B-ENT, 2013, **9**, 111-116

Vitamin B12 levels in patients with tinnitus and effectiveness of vitamin B12 treatment on hearing threshold and tinnitus

G. Berkiten, G. Yildirim, I. Topaloglu and H. Ugras

ENT Department, Okmeydanı Teaching Hospital, Şişli, Istanbul, Turkey

Key-words. Vitamin B12 deficiency; tinnitus; hearing loss; audiometry; therapy

Abstract. *Vitamin B12 levels in patients with tinnitus and effectiveness of vitamin B12 treatment on hearing threshold and tinnitus. Objectives*: The aim of this study was to determine vitamin B12 levels in patients with non-pulsatile tinnitus and to assess the efficacy of replacement treatment in tinnitus and hearing in patients with vitamin B12 deficiency.
Materials and methods: We assessed 100 patients (mean age, 43.87, SD 10.12; 62 females, 38 males) and 20 healthy volunteers (9 females, 11 males). Patients whose blood serum vitamin B12 levels were below 180 pg/mL were deemed to be vitamin B12-deficient. The effect of vitamin B12 replacement treatment on hearing was examined using audiometric tests between 250 and 20000 Hz, and we compared results with a visual analogue scale (VAS) before and after treatment, which helped to produce an objective assessment of the therapeutic results in tinnitus.
Results: Tinnitus was found to be unilateral in 57% of cases (the right ear in 56% and the left ear in 44% of these cases) and bilateral in 43% of cases. Of the patients with tinnitus, 63 had low B12 vitamin levels, and 37 had normal B12 vitamin levels. No statistically significant difference was found with the control group levels ($p = 0.80$, odds ratio = 1.13). No significant change was observed in tinnitus severity after vitamin B12 therapy. Eight of these patients reported some relief in tinnitus on the VAS, but the rate of improvement was not significant ($p>0.05$). In the tinnitus patients with low B12 vitamin levels, audiometric tests conducted after B12 vitamin treatment revealed a significant improvement in hearing levels only at the 250 Hz frequency. No change was observed at other frequencies.
Conclusion: B12 replacement treatment was not effective in these patients with tinnitus. Some patients improved following vitamin B12 supplementation but the results were not significant. More studies are needed to find the reasons for, and effective treatment of, tinnitus since the aetiology of subjective tinnitus is highly variable.

Introduction

Tinnitus is defined as the perception of a sound in the absence of an external stimulus. Tinnitus is also defined as perceiving sound in association with activity in the nervous system that does not match the resonant or mechanical activity in the cochlea.[1] The pathological mechanisms and clinical features are still not fully understood. The prevalence of tinnitus has been variously reported as ranging from 2-32%.[1,2] Tinnitus is more common in men than in women, and its prevalence increases with advancing age. Tinnitus is accompanied by hearing loss in many cases. Furthermore, as hearing loss increases, so does the incidence of tinnitus.[3]

Vitamin B12 is a co-enzyme that has a role in two particularly important metabolic functions in normal cell growth and DNA synthesis. Vitamin B12 is an important co-factor that plays a role in basic myelin protein synthesis. B12 deficiency is associated with axonal degeneration, demyelinisation, and subsequent neuronal death.[4]

Cochlear function is dependent on adequate vascular supply and the normal functioning of nerve tissue. Homocysteine is elevated during deficiencies of vitamin B-12, folate, or both, and homocysteine is believed to be a vascular toxin and a neurotoxin.[5] In electrophysiological studies of vitamin B12 deficiency, an increase in sensorimotor axonopathy and central conduction has been shown.[6] Vitamin B12 deficiency may cause the demyelinisation of neurons in the cochlear nerve, resulting in hearing loss.[6,7] Additionally, low levels of vitamin B12 and folate are associated with the destruction of the microvasculature of the stria vascularis, which might result in decreased

Presented at 30th Turkish National Otorhinolaryngology and Head and Neck Surgery Congress, Antalya, October 8-12, 2008.

endocochlear potential and in hearing loss and tinnitus.[5]

In this study, we sought to understand the connection between vitamin B12 deficiency and non-pulsatile tinnitus and hearing loss.

Materials and methods

This study included 100 patients (38 males, 62 females; age range, 17-66, mean 43.87, SD 10.12). The control group included 20 healthy volunteers (9 males, 11 females; age range, 19-59, mean 33.85, SD 11.16). After a detailed medical history, patients who had suffered head trauma, who had a history of chronic otitis media or a family history of hearing loss and who had a noise induced hearing loss were excluded. A typical otological and audiological examination was carried out in all patients. Computed tomography (CT) and/or magnetic resonance imaging (MRI) were performed when retrocochlear hearing loss was suspected. The sample was divided into three age groups: 17-29, 30-49, and 50-66 years.

Audiometry and high-frequency audiometry were performed in all patients and the control group. The audiometric evaluation was performed using a soundproof AC 40 Audiometry cabin calibrated to ISO 9001 standards. Frequencies at octave intervals from 250 to 20000 Hz were tested for air conduction and from 500 to 4000 Hz for bone conduction (Figures 1, 2 show average audiograms).

Blood samples were taken after overnight fasting, and serum cobalamin levels were evaluated using a Beckman Coulter UniCel DxI 800 Immunoassay Analyser (normal values; 180–914 pg/mL). Subjects were deemed to be vitamin B12 deficient if the serum cobalamin level was below 180 pg/mL. Patients who had serum vitamin B12 deficiency were started on parenteral vitamin B12 treatment: 63 patients with low vitamin B12 levels received parenteral vitamin B12 therapy. Vitamin B12 (1 g/mL) was injected intramuscularly once a day for five days and then once a month for one year. Serum vitamin B12 concentrations increased significantly after this vitamin B12 treatment.

The effects of vitamin B12 treatment on hearing were assessed using audiometry. Pure tone audiometry was repeated after treatment. The severity of patient tinnitus was also assessed using a tinnitus visual analogue scale (VAS).[8] On this scale, the patients stated their own discomfort level using ratings ranging from 0 to 10 (0 = absence of tinnitus; 10 = unbearable tinnitus). Symptoms were deemed to be improved if perceived tinnitus improved by one or more points on this scale.

Statistical analyses of data were conducted using the SPSS 15.0 and Graphpad 5.0 software. For the analysis of values between groups, chi-square testing and paired two-tailed Student's *t*-testing were used. P values <0.05 were deemed to indicate statistical significance. The statistical model used considered gender (male, female), age group (Group 1: 17-29, Group 2: 30-49, Group 3: 50-66 age), tinnitus status (tinnitus present / no tinnitus, normal), response to treatment (yes/no), tinnitus duration, vitamin B12 level (low/normal), and frequency.

Results

The patients complaining of tinnitus had experienced tinnitus for 3 months to 10 years. Patients with normal vitamin B12 had experienced tinnitus for an average of 15.10 (SD 13.51) months, and those with vitamin B12 deficiency had experienced tinnitus for an average of 19.61 (SD 25.12) months. Tinnitus was found to be unilateral in 57% of cases (right ear in 56% and left ear in 44% of these cases) and bilateral in 43% of cases.

Of the patients with tinnitus, 63% had low vitamin B12 levels, and 37% had normal levels. In the control group, 12 had low vitamin B12 levels and eight had normal levels. When tinnitus patients with vitamin B12 deficiency were compared with the control group, no statistically significant difference was found (p = 0.80, odds ratio (OR) =1.13). No significant difference was observed between male and female tinnitus patients with normal B12 levels with regard to age range ($p = 0.377$, chi-square = 1.9470).

No significant difference was observed between male and female tinnitus patients with vitamin B12 deficiency over the age range ($p = 0.7507$, chi-square = 0.573).

No significant difference in age range was observed between patients with vitamin B12 deficiency and those with normal vitamin B12 levels ($p = 0.22$, chi-square = 2.99).

Table 1 lists air conduction thresholds (expressed as means and standard deviations) before and after vitamin B12 treatment for each frequency in the pure tone audiometry of 63 patients between 250 and 20000 Hz. An increase in hearing loss values was observed at frequencies above 8000 Hz. This

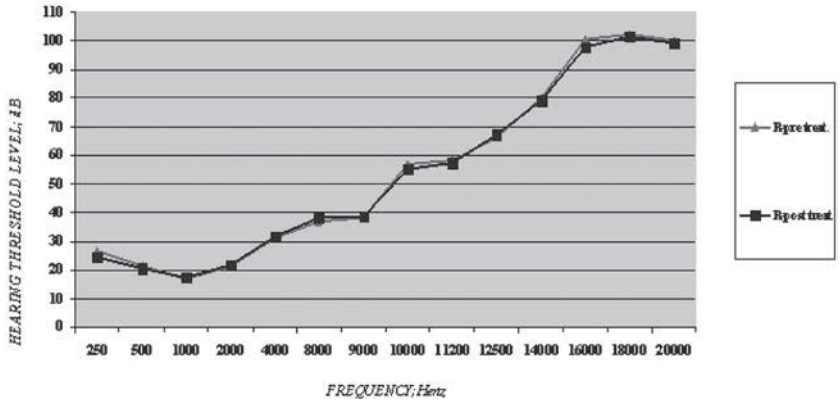

Figure 1
Hearing values at 250-20000 Hz before and after vitamin B12 replacement treatment (right ear)

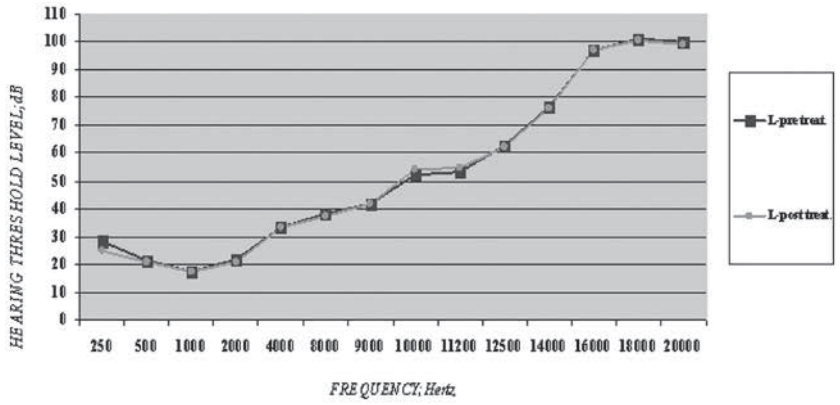

Figure 2
Hearing values at 250-20000 Hz before and after vitamin B12 replacement treatment (left ear)

increase was observed up to 20000 Hz. Hearing loss was higher in ears with tinnitus. Greater hearing loss on the right side was associated with right-side tinnitus, and greater hearing loss in the left ear was associated with left-side tinnitus. However, hearing loss was not proportional to tinnitus severity.

The control audiometry revealed that B12 replacement treatment was effective in the right and left ears at 250 Hz in the 63 patients with vitamin B12 deficiency ($p<0.005$). No change was found at other frequencies in the right (Figure 1) or left ear (Figure 2).

In subjects with vitamin B12 deficiency, the mean VAS values were 6.40 ± 1.58 before vitamin B12 therapy and 6.24 ± 3.05 after vitamin B12 therapy. However, the difference in the severity of tinnitus after vitamin B12 therapy was not significant. Eight of these patients reported some relief on the VAS, but the level of improvement was negligible ($p>0.05$).

Discussion

Tinnitus is a common complaint that can affect a patient's quality of life. Although the cause is usually unknown, tinnitus can be a symptom of almost any ear disorder, including infection, a blocked ear canal (ear wax) or Eustachian tube, otosclerosis, labyrinthitis, and Meniere's disease. Additionally, neurological disorders, metabolic disorders, psychiatric disorders and even the adverse effects of some drugs (e.g., aspirin and some antibiotics) can cause tinnitus symptoms.[1,2]

Table 1

Pure tone air conduction thresholds (dB HL) in 63 patients (grand average)

Hz	Right Ear Pretreatment hearing loss (dB)	Right Ear Posttreatment hearing loss (dB)	Left Ear Pretreatment hearing loss (dB)	Left Ear Posttreatment hearing loss (dB)
250	26.51 (7.44)*	24.37 (7.38)	28.17 (8.67)	24.84 (7.62)
500	21.19 (7.11)	20.32 (7.06)	21.27 (7.46)	20.71 (7.00)
1000	16.90 (7.80)	17.54 (7.77)	17.46 (8.65)	17.22 (8.46)
2000	21.35 (10.25)	21.98 (10.34)	21.67 (11.78)	21.11 (11.69)
4000	31.11 (17.65)	31.83 (17.40)	33.10 (17.61)	33.25 (18.01)
8000	37.14 (20.55)	38.10 (21.62)	38.25 (20.04)	37.14 (20.59)
9000	38.33 (24.38)	38.73 (25.86)	41.75 (25.15)	41.59 (26.38)
10000	57.06 (26.10)	55.24 (26.92)	52.30 (27.16)	54.37 (29.22)
11200	58.17 (27.51)	57.62 (29.81)	53.17 (27.87)	54.68 (29.58)
12500	66.51 (26.98)	67.14 (28.83)	62.54 (27.46)	62.06 (29.60)
14000	80.24 (22.73)	79.13 (24.11)	76.43 (22.69)	76.03 (25.53)
16000	100.8 (14.90)	97.94 (19.54)	97.06 (14.25)	97.30 (16.33)
18000	102.5 (12.04)	101.5 (12.10)	101.1 (10.37)	100.6 (11.05)
20000	100.4 (11.08)	99.52 (11.66)	100.2 (9.07)	99.21 (11.15)

*Values are means (SD).
SD: standard deviation, HL: hearing loss, dB: decibel, Hz: Hertz.

While tinnitus is often bilateral, it can also occur on only one side. Stouffer and Tyler,[9] reported that tinnitus was bilateral in 52% of cases, one-sided in 37% of cases, and localised in the cranium instead of the ear in 10% of cases; in 1% of cases, sounds were perceived as coming from outside the head. In our study, 43% of the patients and 57% of the patients had bilateral and single-sided tinnitus respectively.

The mechanism of tinnitus has not been fully elucidated. Tinnitus is considered to be based on anatomical and/or functional changes in the auditory system.[10,11] Vitamin B12 deficiency is a risk factor in cerebral, coronary, and peripheral vascular diseases.[12] On the basis of electro-physiological studies, Hall[3] observed that sensorineural motor axonopathy is seen in vitamin B12 deficiency, and Zegers *et al*.,[13] observed an increase in central transmission time in B12 deficiency.

The most common cause of tinnitus is probably hearing loss. Because the cochlea is a highly vascularised entity, vitamin B12 deficiency can reduce blood flow in the cochlea and may result in hearing loss, especially in older people.[5,14] Additionally, vitamin B12 deficiency may adversely affect the myelinisation of the cochlear nerve[15]. Shemesh *et al*.,[4] found B12 deficiency in 47% of the patients with tinnitus and hearing loss, showed that B12 replacement treatment was useful, and suggested routine control of vitamin B12 levels in patients with chronic tinnitus.

Bilateral symmetrical hearing loss occurs in patients with tinnitus, especially at 8000–20000 Hz. Hearing loss increases slightly toward higher frequencies.[8] Savastona,[16] reported sensoroneural hearing loss in 85.6% of patients, 65% of whom had hearing loss at high frequencies. Our study showed an increase in hearing loss in patients with tinnitus up to 20,000 Hz. Hearing loss was higher in the ear with tinnitus. Greater hearing loss on the right side was associated with right-sided tinnitus, whereas greater hearing loss in the left ear was associated with left-sided tinnitus.

Huston *et al*.;[5] suggested that B12 deficiency may be a risk factor in age-related hearing loss based on a study of 55 females between 60 and 71 years of age. Berner *et al*.,[17] concluded that there was no relationship between hearing loss and vitamin B12 in a study conducted in subjects aged 67-88. Similarly, in our study, no relationship was observed between age and vitamin B12 deficiency ($p>0.05$). In our study, the age at which tinnitus was found most frequently was between 30 and 49 years, followed by 50-66 and 17-29 years. The

prevalence of tinnitus was therefore not related to age. Additionally, no relationship was established between vitamin B12 deficiency and tinnitus severity ($p>0.05$). Demeester *et al*.,[18] reported that gender had a significant effect and tinnitus is more common in males than in females. However, tinnitus was more common in females than in males (38% males, 62% females) in our study.

There are many measures to estimate the impact of tinnitus. Many studies have been performed of treatment for tinnitus, and most of these reports have evaluated tinnitus subjectively, generally by using different questions on a VAS. The VAS is a reliable method that is commonly used in studies to assess the results of therapy. Our patients received questionnaires that assessed how troublesome their tinnitus was and evaluated its influence on their daily activities and ability to function. We compared the results of the VAS before and after treatment, which helped to establish an objective assessment of the results of therapy.

The treatment of tinnitus depends on its cause. The first step in treatment is therefore to establish the aetiology. However, because the aetiology is unknown in most cases, symptomatic treatment is typically applied. The preferred agents for treatment include betahistine hydrochloride, ginkgo biloba extract, local anaesthetics, trimetazidin, vitamins, nimodipin, misoprostol, siklandelate, antidepressants, zinc, melatonin, and baclofen.[12,19,20] Many other products have been tried, along with many medical treatment modalities. Rosenberg *et al*.,[12] concluded that melatonin treatment was effective, especially in patients with intense tinnitus. Quaranta *et al*.,[21] stated that an increase in serum vitamin B12 levels after vitamin B12 treatment produced a protective effect with a temporary threshold shift, especially at 3000 Hz, and that high plasma cyanocobalamin levels can reduce the risk of hearing loss as a result of noise. Our study did not show any effect of vitamin B12 replacement treatment on patient complaints of tinnitus and hearing levels in pure tone audiometry. Statistically significant improvement was only observed at 250 Hz ($p<0.001$); no change was observed at other frequencies (Figures 1, 2).

Conclusion

The effect of vitamin B12 therapy remains controversial. In our study, no significant relationship was found between non-pulsatile tinnitus and vitamin B12 and vitamin B12 replacement treatment was not found to be effective in these patients with tinnitus. The widely-varying aetiology of tinnitus indicates that more studies are needed to find causes of and effective treatments for tinnitus.

References

1. Hoffman HJ, Red GW. Epidemiology of tinnitus. In: Snow Jr JB, ed. *Tinnitus Theory and Management*. BC Decker Inc, London, 2004:16-41.
2. Coles RR. Epidemiology of tinnitus: prevalence. *J Laryngol Otol Suppl*. 1984;9:7-15.
3. Hall CA. Function of vitamin B12 in the central nervous system as revealed by congenital defects. *Am J Hematol*. 1990;34(2):121-127.
4. Shemesh Z, Attias J, Ornan M, Shapira N, Shahar A. Vitamin B12 deficiency in patients with chronic-tinnitus and noise-induced hearing loss. *Am J Otolaryngol*. 1993;14(2): 94-99.
5. Houston DK, Johnson MA, Nozza RJ, Gunter EW, Shea KJ, Cutler GM, Edmonds JT. Age-related hearing loss, vitamin B-12, and folate in elderly women. *Am J Clin Nutr*. 1999;69(3):564-571.
6. Agamanolis DP, Chester EM, Victor M, Kark JA, Hines JD, Harris JW Neuropathology of experimental vitamin B12 deficiency in monkeys. *Neurology*. 1976; 26(10):905-914.
7. Krumholz A, Weiss HD, Goldstein PJ, Harris KC. Evoked responses in vitamin B12 deficiency. *Ann Neurol*. 1981; 9(4):407-419.
8. Yildirim G, Berkiten G, Kuzdere M, Ugras H. High frequency audiometry in patients presenting with tinnitus. *Int Adv Otol*. 2010;6:(3) 401-407.
9. Stouffer JL, Tyler RS. Characterization of tinnitus by tinnitus patients. *J Speech Hear Disord*. 1990;55(3):439-453.
10. Tonndorf J. Acute cochlear disorders: the combination of hearing loss, recruitment, poor speech discrimination, and tinnitus. *Ann Otol Rhinol Laryngol*. 1980;89(4 Pt 1):353-358.
11. Møller AR. Pathophysiology of tinnitus. *Ann Otol Rhinol Laryngol*. 1984;93(1 Pt 1):39-44. Review
12. Rosenberg SI, Silverstein H, Rowan PT, Olds MJ. Effect of melatonin on tinnitus. *Laryngoscope*. 1998;108(3):305-310.
13. Zegers de Beyl D, Delecluse F, Verbanck P, Borenstein S, Capel P, Brunko E. Somatosensory conduction in vitamin B12 deficiency. *Electroencephalogr Clin Neurophysiol*. 1988;69(4):313-318.
14. Ubbink JB, Vermaak WJ, van der Merwe A, Becker PJ. Vitamin B-12, vitamin B-6, and folate nutritional status in men with hyperhomocysteinemia. *Am J Clin Nutr*. 1993; 57(1):47-53.
15. Savage DG, Lindenbaum J. Folate-cobalamin interactions. In: LB Bailey, ed. *Folate in Health and Disease*. Marcel Dekker, New York, 1995:237-285.

16. Savastano M. Tinnitus with or without hearing loss: are its characteristics different? *Eur Arch Otorhinolaryngol*. 2008;265(11):1295-1300.
17. Berner B, Odum L, Parving A. Age-related hearing impairment and B vitamin status. *Acta Otolaryngol*. 2000;120(5): 633-637.
18. Demeester K, van Wieringen A, Hendrickx JJ, Topsakal V, Fransen E, Van Laer L, De Ridder D, Van Camp G, Van de Heyning P. Prevalence of tinnitus and audiometric shape. *B-ENT*. 2007;3 Suppl 7:37-49.
19. Murai K, Tyler RS, Harker LA, Stouffer JL. Review of pharmacologic treatment of tinnitus. *Am J Otol*. 1992;13(5): 454-464.
20. Dobie RA, Sakai CS, Sullivan MD, Katon WJ, Russo J. Antidepressant treatment of tinnitus patients: report of a randomized clinical trial and clinical prediction of benefit. *Am J Otol*. 1993;14(1):18-23.
21. 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(3):162-165.

Guler Berkiten
Okmeydanı Training and Research Hospital
Şişli, Istanbul, Turkey
Tel: +905057278724
Fax: +902122332661
E-mail: gulerberkiten@gmail.com