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Therapeutic Role of Vitamin B12 in Patients with Chronic Tinnitus: A pilot Study.

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ABSTRACT

Background and Aim: True tinnitus had no audible acoustic origin and is a phantom auditoria experience originating from a cause or trigger in the cochlea, brainstem, or at highly centers. The Jastreboff neurophysiologic hypothesis, which emphasizes that tinnitus is a subcortical sensation and originates from the interpretation of weak neuronal activities in the peripherals, is the most widely recognized. This research seeks to understand the function of vitamin B12 in the management of chronic tinnitus.

Methods: A total of 100 individuals participated in this randomized, double-blinded pilot study, of whom 50 in Group A (patients) obtained intramuscular treatment of 1 ml Vitamin B12 (2500 mcg) once a week for a duration of six weeks, while the remaining 50 subjects in Group B (controls) obtained isotonic saline as a placebo. Pre- and post-treatment audiological and a Vitamin B12 testing were performed on the subjects.

Results: When standard dosages of vitamin B12 were set at 250 pg/ml, 43% of the overall tinnitus patients showed deficiencies. Upon receiving Vitamin B12 medication, individuals in Group A with Vitamin B12 insufficiency significantly improved their average tinnitus intensity index value and visual analogue scale (VAS), according to a paired t-test.

Conclusions: This study shows the substantial predominance of Vitamin B12 deficiency among-and the improved performance in tinnitus severity results and VAS in cobalamin-deficiency patients receiving intramuscular Vitamin B12 once a week for six weeks. It also establishes a connection between cobalamin deficiency and tinnitus, suggesting that B12 may be used therapeutically in cobalamins-deficient tinnitus subjects.

Keywords: Vitamin B12; Tinnitus Matching; Tinnitus; Audiometry; Neuropathy.

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INTRODUCTION

Since the dawn of civilization, tinnitus has presented as a problem for people, as documented in Egyptian papyri (6000 BC) [1].

The symptoms of tinnitus include ringing, roaring, or buzzing in the ears. These are all classified as tinnitus since they all come from the head in some manner [2].

Tinnitus may occasionally be caused by a supply of acoustic energy in the head and neck region, such as vascular abnormalities, myoclonic seizures, clicking jaws, pulmonary or cochlear otoacoustic emissions, etc., which may be detected by a second person regardless of the use of specific gear [3]. True tinnitus, on the other hand, is a phantom auditory impression with no audible acoustic source and originates from an origin or triggers in the cochlea, brainstem, or at higher centres. Tinnitus can be categorized as main or secondary [3]. Tinnitus that is idiopathic and can either be or not be connected to sensorineural deafness is known as main tinnitus [4].

Tinnitus with a recognized organic ailment or a specified causative agent (besides sensorineural deafness) is known as secondary tinnitus. It is a sign of numerous auditory and non-auditory system issues, including such simple cerumen impactions of the external auditory canals, middle ears conditions like otosclerosis or Eustachian tubes dysfunctions, cochlear malformations like Meniere's disorder, and auditory nerves pathology like vestibular schwannoma [5].

The Jastreboff neurophysiological hypothesis, which emphasizes that tinnitus is a subcortical experience and originates from the interpretation of weaker neuronal activities in the peripheral, is the most widely accepted, even though the precise reason of tinnitus remains unknown [6]. Tinnitus-related neuronal behaviours, which typically occurs close to the system's edge, is processed in subcortical auditory pathways before being recognized as sounds at a level of conscious awareness [7]. Similar to any neural activities produced by the external noises by the cochlea, the volume and frequency of tinnitus rely on the amplitude and patterns of electrical impulses coming at the temporal lobes' cortexes after subcortical signals recognition and feature matching have performed [8].

Due in large part to the fact that the source of tinnitus remains unknown, there has not yet been an effective therapy for the condition. Although the auditory system and nearby anatomical locations have been implicated in tinnitus creation, no tests can now accurately pinpoint these areas [9]. There is currently universal agreement that tinnitus is caused by abnormal neuronal activities, typically of an excitatory character, in the auditory system [10]. There have been many new medications that claim to help in tinnitus management. The vitamin B12 deficiency in tinnitus sufferers was discovered by Shemesh et al. in 1993, and its treatment was demonstrated to help these individuals [11].

The purpose of this investigation is to identify Vitamin B12's function in the management of tinnitus. Hypomethylations in central nervous system constitutes one of the strategies thought to be at work in vitamin B12 deficient neuropathy. An appropriate blood supply and healthy nerves tissues are required for cochlear functioning. Axonal degenerations, demyelinations, and consequent apoptotic neuronal death are all linked to B12 deficiency [12]. Lack of vitamin B12 might culminate in hearing impairment by demyelinating neurons in the auditory nerve. Moreover, lower intakes of vitamin B12 and folates are linked to the breakdown of the stria vascularis' microvasculature, which could cause hearing impairment, tinnitus, and diminished endocochlear potentiality [13]. The article's goal was to determine how common Vitamin B12 insufficiency is and what the treatment effects of Vitamin B12 injections on tinnitus are.

PATIENTS AND METHODS

Type of study: This was a pilot, double-blinded, randomized, placebo-controlled trial.

Study setting and duration: The study was conducted at Audio vestibular medicine unit ENT Department Al Ahrar teaching hospital from March 2022 to February 2023.

Patients: The survey included all adults aged between18 and 60 years old with chronic subjectively tinnitus who visited the ENT outpatient clinics. Tinnitus that lasts longer than six months, occurs frequently, and is so acute that a sufferer seeks therapy at a clinic is considered to have chronic tinnitus.

Inclusion criteria: Adult subjects between the ages of 18 and 60 who have sensorineural hearing loss that has lasted longer than six months with chronic subjectively tinnitus unbiased towards gender and having average intelligence.

Exclusion criteria: Individuals with pulsatile (objective) tinnitus or participants with any heart abnormalities that could cause an otological issue would be disqualified from the research. Individuals with any infectious otological condition as well as those experiencing any form of psychological illness will be disqualified from the trial. Individuals with otological conditions other than tinnitus and sensorineural deafness or those who have experienced recent acoustic trauma or ongoing noise exposures, individuals with

systemic conditions that may cause otological issues, such as anaemia, hypertension, diabetes mellitus, and hypothyroidism and those who have used any additional medications over the last four weeks that are associated with tinnitus, such as corticosteroids, cyclendalates, and vasodilators were excluded. Individuals with ear operations, tinnitus following a head trauma, or any kind of organic disease in the neck and head area were also eliminated.

Procedures:

A whole 100 individuals participated in this randomized, double-blind pilot trial, with 50 cases in Group A (patients) and 50 participants in Group B. (controls). Twenty participants from the group A were assigned randomly, and they underwent parenteral intramuscular treatment for six weeks, receiving 1 ml of vitamin B12 (2500 mcg) each week. Identical intramuscular administration of 1 ml of placebo isotonic saline in group B (50 participants) for 6 weeks. Both the sufferer and the physician were unaware of the treatment plan. The examiners wrote down the findings. The researcher evaluated the findings.

Following a thorough history and examination, patients with chronic subjective tinnitus lasting longer than six months having undergone audiometry, tinnitus matching (pitch and noise level), a Vitamin B12 test (pre and post medications) by chemiluminescence technique, and a self-reported using a tinnitus severity index survey [14]. Following receiving interventional treatment for six weeks, the individuals were followed for a total of one month. Participants underwent tinnitus screening, Vitamin B12 assays, tinnitus severity index assessment, pure tone audiometry, and a self-reported tinnitus survey once more.

Ethical considerations:

To participate in the trial, all patients were required to complete an informed consent form. The research was carried out in line with Heliniski's declaration.

Statistical analysis:

Statistical analysis was performed using MS Microsoft Excel version 13 and SPSS version 26.0 (IBM, Chicago, IL, USA). For categorical data, percentage was determined, while means and standard deviations were determined for continuous data. The student t-test was employed to determine the value of the variance for continuous data, and the chi-square analysis was performed to determine the relationship between categorical data. P <0.05 was regarded as statistically significant. The logistic regression used took into account the following variables: sex (males or females), age category (from18 to 29, from 30 to 49 and from 50 to 60 years old), tinnitus condition (existence and normal status of tinnitus), outcome reactions of therapy (yes/no), tinnitus period, Vitamin B12 amount (low/normal), and frequencies.

RESULTS

Personal traits of the study participants

The males to female's ratio equaled 2:3, and the average age of the tinnitus subjects was 37.26 years. Since adequate amount of vitamin B12 was set at 250 pg/ml, vitamin B12 deficiency was detected in 43% of participants. Its incidence is notably high. Tinnitus symptoms lasted an average of 1.25 ±1.2 years. 73 percent of instances of tinnitus were unilateral, with the right ear accounting for 33 percent of subjects and the left for 41 percent of total participants (Table 1).

Distribution of patients in Groups A and B

The incidence of vitamin B12 deficiency was 44.19% in patients' group and 55.81% among control individuals (Table 2).

Tinnitus severity scores of patient's pre- and post-therapy with Vitamin B_{12} injections

The average tinnitus severity scores significantly improved in Group A patients with Vitamin B12 deficiency following Vitamin B12 medication according to a paired t-test ($t = 2.53$, $P = 0.015$, $df = 17$). Yet, neither the severity index scoring of Group A participants without B12 deficiency nor those of Group B individuals undergoing a placebo significantly improved (Table 3).

In addition, the average visual analogue score (VAS) for Group A individuals with Vitamin B12 insufficiency was 3.23 ± 0.73 before treatment and 2.78 ± 0.36 after treatment. Upon treatment, the VAS revealed a substantial reduction in tinnitus loudness ($t = 2.02$, $P = 0.03$, $df = 17$). The outcomes of Vitamin B12 medication in vitamin deficiency people are positive and encouraging, according to the studies. Some groups did not significantly progress after treatment.

Audiological assessments of tinnitus in individuals with and without a Vitamin B12 deficiency

30 participants (about 30%) in Group A and four individuals (20%) in Group B both showed subjective improvements. There was no statistically relevant difference in the two groups' perceived tinnitus improvements. Tinnitus sufferers with Vitamin B12 deficiency had an average pitch of 5.8 ± 2.2 kHz, while those with typical Vitamin B12 doses had an average pitch of 5.5 ± 2.6 kHz (kHz). Individuals with Vitamin B12 deficiency had average tinnitus loudness scores of 4.1 ±

2.9 (db SL) while those with adequate B12 doses had 5.0 ± 2.8 (db SL) (Table 4).

Average hearing thresholds contrast between Groups A and B

There was no clear differentiation between the pitch and loudness scores for both groups, indicating that vitamin B12 doses have no effect on pitch and loudness. Furthermore, it was discovered that Group A and Group B's average hearing sensitivities were nearly identical (Table 5, P > 0.05). All subjects' routine hemograms were completed normally. Respondents experience maximal difficulties with tinnitus in a quiet area, falling asleep, and trouble ignoring tinnitus in the tinnitus severity scale.

Table (1): Personal traits of the study participants

		Variable	*n* = 100
Gender		Male	40 (40%)
		Female	60 (60%)
Age (in years)	**Mean±SD**		37.26 ±11.39
	Age group	18-29	30 (30%)
		30-49	50 (50%)
		50-60	20 (20%)
Vitamin B_{12} deficiency (n, %)		Yes	43 (43%)
		No	57 (57%)
Tinnitus duration (in years)			1.25±1.2
Tinnitus tolerance level		Unilateral	73 (73%)
		Bilateral	27 (27%)
Affected ear		Right	33 (33%)
		Left	41 (41%)
		Both ears	26 (26%)

Table (2): Distribution of patients in Groups A and B

Group	Without B_{12} deficiency (n=57)	With B_{12} deficiency (n=43)	Statistics
Group A (injection B_{12})	25 (43.86%)	19 (44.19%)	χ^2= 0.81, *P* = 0.22
Group B (injection NS)	32 (56.1%)	24 (55.81%)	

NS = Normal saline

Table (3): Tinnitus severity scores of patient's pre- and post-therapy with Vitamin B_{12} injections

Group	Mean tinnitus severity index score		Significance *t*, *P*
	Posttherapy	**Pretherapy**	
Group A (injection B_{12})			
Without B_{12} deficiency	36.12±10.1	37.05±11.0	*t*=0.21, *P*=0.74
With B_{12} deficiency	27.29±6.3	35.49±7.5	***t*=2.53, *P*=0.015***
Group B (injection NS)			
Without B_{12} deficiency	33.09±7.3	32.00±7.1	*t*=0.27, *P*=0.69
With B_{12} deficiency	31.29±8.1	31.79±8.6	*t*=0.10, *P*=0.80

NS = Normal saline, df = Degree of freedom, *Significant as *P* < 0.05 associated with paired *t*-test.

Table (4): Audiological assessments of tinnitus in individuals with and without a Vitamin B12 deficiency

Tinnitus parameters	Normal Vitamin B_{12}	Vitamin B_{12} deficiency	*t*, *P* and df
Tinnitus loudness (db SL)	5.0±2.8	4.1±2.9	0.94, 0.35,37
Tinnitus pitch (kHz)	5.5±2.6	5.8±2.2	0.25, 0.60,37

df = Degree of freedom, *P*-value using independent *t*-test.

Table (5): Average hearing thresholds contrast between Groups A and B

Group	Without B_{12} deficiency (db)	With B_{12} deficiency (db)
Group A (injection B_{12})	28.44±11.63	27.86±19.20
Group B (injection NS)	24.19±10.39	23.05±15.63
Significance (Group A vs. Group B)	*t*=1.12, *P*=0.15	*t*=0.72, *P*=0.15

NS = Normal saline, *independent t-test was used for calculating P-value.*

DISCUSSION

Tinnitus incidence in adults is regularly estimated by epidemiological research to be between 10% and 15% of the global population [15, 16]. In the Beaver Dam offspring research, which included more than 3000 adults aged 21 to 84 between 2005 and 2008, 10.6% of the participants indicated having tinnitus of at least moderate degree or difficulties maintaining sleep [17].

Tinnitus was shown to be higher commonly found in females (70.52%) and to be bilaterally distributed (89.5%) in individuals with auditory neuropathy spectrum. In people with lower frequencies hearing impairment, the reported pitch was higher with a flat design of loss, while the subjectively pitch was lower-pitched [18].

In the United States, the frequency of regular tinnitus rose with age, reaching a peak of 14.3% between 60 and 69 years old [19]. As people get older, tinnitus is more common [20].

Males are more likely than females to experience tinnitus [21]. Nonetheless, the current analysis indicated that women were more likely to have it than men (M: F = 2:3). About 25% of tinnitus patients claim that their condition has gotten worse over time [15].

Tinnitus is thought to affect 4.5 million people in India, despite the lack of precise statistics on the incidence of the condition. Extrapolating from the total population of 1,065,070,607, it is thought that 47,928,177 Indians might have tinnitus. These extrapolations of incidence for tinnitus are merely estimations depending on the population of India and the incidence ratios from the US (or a comparable nation) [22].

The findings from our research indicate that the population aged 18 to 60 years has a greater incidence of serum cobalamin insufficiency, with concentrations as higher as 43% when the threshold level was set at 250 pg/ml and 15% when the threshold was set at 150 pg/ml, both of which are statistically significant. Despite low serum cobalamin values, these individuals' hemograms didn't reveal anything unusual.

In 1993, **Shemesh *et al*.** [11] observed that tinnitus sufferers lacked sufficient Vitamin B12, and that these patients benefited from its administration. Individuals with tinnitus and noise-induced hearing problems had a 47% incidence of cobalamin insufficiency, compared to 27% of nontinnitus individuals with the same condition.

Based on the threshold used to define a cobalamin shortage in serum, the incidence of subnormal vitamin B12 levels in older people in an Indian study ranges from 3% to 40.5% [23].

In another study, 67% of males had lower vitamin B12 concentrations (considering 150 pmol/L as the criteria; 68% were rural, 51% lived in slums, and 81% were middle-class urban) [24]. Another finding revealed that 16% of the sample individuals had maladjusted plasma concentrations of vitamin B12 (lower than150 pmol/l) [23].

Once the cutoff was set at 250 pg/ml and 180 pg/ml, respectively, the incidence of cobalamins insufficiency in tinnitus sufferers in this research was extremely greater and comparable (43%) to the findings of **Shemesh *et al.*** [11] and at 15% comparable to **Shobha *et al.*** [25].

According to **Stouffer and Tyler** [15], tinnitus is bilaterally found in 52% of instances, unilateral in 37% of patients, located in the cranium rather than the ear in 10% of instances, and thought to be emanating from outside the head in 1% of instances.

According to **Berkiten *et al*.** [26], 43% and 57% of the participants, respectively, experienced bilateral and single-sided tinnitus. Yet, in this investigation, tinnitus more frequently manifested unilaterally in 73% of patients (right ear in 33% and left ear in 67% of instances), and in both ears in 26% of patients. Even though Group A's healthy cobalamin values had the greatest levels of tinnitus, the cobalamin-deficient group showed a considerable increase. There was no relationship between the loudness and pitch of tinnitus and serum cobalamin contents.

Tinnitus has been linked to issues with the cochlea, auditory nerves, and peripheral auditory tract in a number of different ideas.

Hypomethylation in the central nervous system is among the processes thought to be at work in vitamin B12 deficient neuropathy. S-adenosylmethionines (SAM) shortage inhibits methylation activities in the myelin sheath as a consequence of suppression of the B12-dependent enzymatic methionine synthases, which causes a decrease in the proportion of S-adenosylmethionines (SAM) to S-adenosylhomocysteines (SAH). Both methylcobalamin, an effective component of vitamin B_{12}, and the active component of folic acid are necessary for the methylation of homocysteines into methionines (5-methyltetrahydro-folates) [27].

Lack of vitamin B12 causes homocysteines, a neurotoxic and vascular toxin, to build up in the body. An appropriate blood supply and healthy nerve tissues are required for cochlear functionality. Axonal degenerations, demyelination, and consequent apoptosis neuronal death are all linked to B12 deficiency. Homocysteine has been linked to both vascular diseases and brain atrophy as risk factors [28].

As opposed to levels below 8.6 µmol/L, Homocysteine

values exceeding 11.9 mol/L were linked to an almost 3-fold greater risk of white matter injury [29].

A lack of vitamin B12 might resulted in hearing loss as well as tinnitus by demyelinating the neurons in the cochlear nerve [30]. Moreover, lower levels of vitamin B12 and folates are linked to the breakdown of the stria vascularis' microvasculature, which could cause deafness, tinnitus, and diminished endocochlear capability [30].

For the first time, **Martvnez-Vega *et al*.** [31] showed that the link between hyperhomocysteinemia brought on by a folate deficit and early deafness includes impaired cochlear homo-cysteines metabolisms and related oxidative stress.

High incidence of Helicobacter pylori and dietary practices including vegetarianism, insufficient consumption of dairy products and milk, as well as socioeconomic variables, may all contribute to the elevated incidence of vitamin B12 insufficiency. Symptoms of cobalamin insufficiency include hematological and neurological problems. The authors recommend serum cobalamin measurement in individuals who have ongoing tinnitus in light of the report's results, which indicate that cobalamin insufficiency could also emerge as tinnitus solely in the lack of other indications.

Tinnitus therapeutic interventions range from various drugs like antipsychotic drugs, vasodilators, herbal products, neurotonics, and cerebral cognitions enhancing drugs to tinnitus retraining medications, psychodynamic psychotherapy treatment [31], and lower-frequency recurrent transcranial magnetic stimulation. The etiology of tinnitus is as diverse as the range of tinnitus therapeutic interventions [32].

Conclusion

It is crucial to investigate the biology of tinnitus and discover treatments for this bothersome ailment in the ever-noisier environment of rapid living and bad eating practices. Given the high frequency of cobalamin insufficiency, the findings point to the importance of assessing serum Vitamin B12 amounts in individuals with chronic tinnitus. This pilot study clarifies the link between low B12 concentrations and tinnitus, and its supplementations have a therapeutic effect on the condition, albeit more research with bigger populations is needed to confirm and establish a clear connection.

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