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# Phase 2 study examining magnesium-dependent tinnitus

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## Abstract

**Background:** Recent studies in noise-induced and idiopathic sensorineural hearing loss have suggested that magnesium supplementation may lessen both hearing loss and the severity of tinnitus in patients. Further epidemiological evidence indicates that all age groups of Americans fall short of the recommended daily allowance for magnesium by 100 mg daily. **Purpose:** The purpose of this study was to examine any potential benefit in lessening the severity of tinnitus in patients taking supplemental magnesium. **Research Design:** The study was a single-arm, open-label, before-and-after study of oral magnesium (532 mg per day) in 26 patients for 3 months. Tinnitus severity was evaluated and recorded daily by the patient using the Tinnitus Distress Rating (TDR) scale of 0 (no tinnitus) to 10 (worst possible tinnitus). The Tinnitus Handicap Inventory (THI) was administered before and at the end of the study, and scores were converted to the grades of the 5-item Tinnitus Severity Scale (TSS). The purpose of this phase 2 study was to investigate whether the treatment was effective at all, and, as such, a placebo control was not performed. All data were collected at Mayo Clinic in Scottsdale, Arizona, between March 6 and December 10, 2008. **Study Sample:** Patients with moderate to very severe tinnitus (TDR score of 3 through 8). Intervention: Daily magnesium supplementation, 532 mg; patient completion of the THI; and daily self-report of TDR. **Data Collection and Analysis:** The main outcome measures were mean TDR scale scores and THI scores as converted to TSS grades. The primary analysis was done on the basis of intention to treat. **Results:** Twenty-six patients were enrolled; 19 completed the study. The extent of handicap, as measured by THI/TSS, for subjects with slight or greater impairment was significantly decreased (P=.03). Patients who ranked slight or greater on the THI/TSS before intervention showed a significant decrease in the severity of their tinnitus at post-testing (P=.008). **Conclusion:** The results suggest that magnesium may have a beneficial effect on perception of tinnitus-related handicap when scored with the THI.

**Keywords:** clinical trial, hearing, magnesium, phase II, tinnitus.

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## INTRODUCTION

Descriptions of tinnitus date back to the time of ancient Egypt, yet science has failed to unravel the mysterious underlying mechanisms that produce these subjective auditory perceptions of sound. These perceptions may be manifestations of damage resulting from noise exposure, ototoxicity, or other abnormal conditions of the auditory system. However, many individuals have idiopathic tinnitus for which no specific cause can be determined. Although often presenting in conjunction with hearing loss, the magnitude of hearing loss does not necessarily correspond with the severity of tinnitus. In addition, some individuals reporting tinnitus experience concomitant hyperacusis. This relationship suggests these processes may be linked by underlying imbalances at the level of the hair cell. The possible influence of magnesium and its antagonist, calcium, has been discussed in the literature as a contributing factor in the mitigation of noise-induced hearing loss, ototoxicity, and the hyperexcitability of the auditory system (Cevette et al., 2003). Permanent and temporary changes in auditory function have been linked to nutritional deficiencies of magnesium. Magnesium deficiency has resulted in increased susceptibility to noise-induced hearing loss (Ising et al., 1982; Joachims et al., 1983; Joachims et al., 1987; Scheibe et al., 2000), ototoxicity (Vormann and Gunther, 1993), and hyperexcitability (Kruse et al., 1932; Cevette et al., 1989; Bac et al., 1994) of the auditory system.

The recommended daily allowance (RDA) for magnesium in adults is 4.5 mg/kg (Saris et al., 2000); however, all age groups of Americans fall short of the RDA for magnesium by 100 mg daily (Standing Committee on the Scientific Evaluation of Dietary Reference Intakes, 1997). This lack of appropriate magnesium intake may have negative consequences. For example, the putative magnesium mechanism within the auditory system involves a metabolic cellular cascade of events. Specifically, magnesium deficiency leads to increased permeability of the calcium channel in the hair cells with a consequent over-influx of calcium, an increased release of glutamate via exocytosis, and overstimulation of *N*-methyl-D-aspartate receptors on the auditory nerve fibers. Recent studies of both noise-induced hearing loss and idiopathic sensorineural hearing loss have suggested that magnesium supplementation may lessen the severity of tinnitus in patients. Magnesium improved hearing recovery and lessened tinnitus in patients with idiopathic sudden hearing loss (Gordin et al., 2002). More recently, Nageris et al. (2004) showed in a well-controlled study that magnesium was a relatively safe and convenient adjunct to corticosteroid treatment for enhancing the improvements of hearing in acute-onset sensorineural hearing loss at a dose of 4 g. The protective effect of magnesium in noise-induced hearing loss has been previously reported (Ising et al., 1982; Scheibe et al., 2000).

Despite these encouraging findings, no controlled study has examined the effect of magnesium supplementation for patients with moderate to severe tinnitus. Additionally, no study to date has examined self-reported tinnitus severity before and after magnesium supplementation. The purpose of this study was to examine any potential lessening of the severity of tinnitus in patients receiving magnesium supplementation.

## METHODS

Between March 6 and December 10, 2008, patients aged 18 years or older who were seen for an audiological evaluation at Mayo Clinic in Scottsdale, Arizona, and who had a Tinnitus Distress Rating (TDR) scale score from 3 through 8 (Figure 1) were eligible for the study. The TDR was adapted from an existing pain scale, with the subject rating him- or herself between 0 (no tinnitus) to 10 (worst possible tinnitus). The Tinnitus Handicap Inventory (THI) and Tinnitus Severity Scale (TSS) (Table 1), developed by McCombe et al. (2001), were used to grade the severity of each subject's tinnitus before enrollment in the study and at the end of the study (Figure 2). The THI scores were converted to the grades of the TSS for the purpose of categorizing the numeric values of the THI into a reliable 5-item grading scheme.

Individuals with decreased kidney function within the preceding 3 months (creatinine level >2.2 mg/dL for women and >2.6 mg/dL for men) were excluded from the study (these criterion values are twice the normal creatinine levels according to the Mayo Clinic Arizona laboratory). A review by the Division of Cardiovascular Diseases indicated that daily magnesium supplementation at the level of 532 mg was benign for heart patients whose kidney function was normal. A review by the Mayo Pharmacy indicated that there were no major drug interactions with magnesium at the levels of the current protocol.

Participants were given a daily magnesium supplement, 532 mg (Mg Plus Protein, 133-mg tablets; Miller Pharmacal Group, Carol Stream, Illinois). After beginning magnesium supplementation, the participants rated themselves daily for 3 months using the TDR. Differences in TDR scores before and after supplementation were compared to determine any effect of supplementation on a participant's self-rated tinnitus. In addition, all participants completed another THI after 3 months of magnesium supplementation.

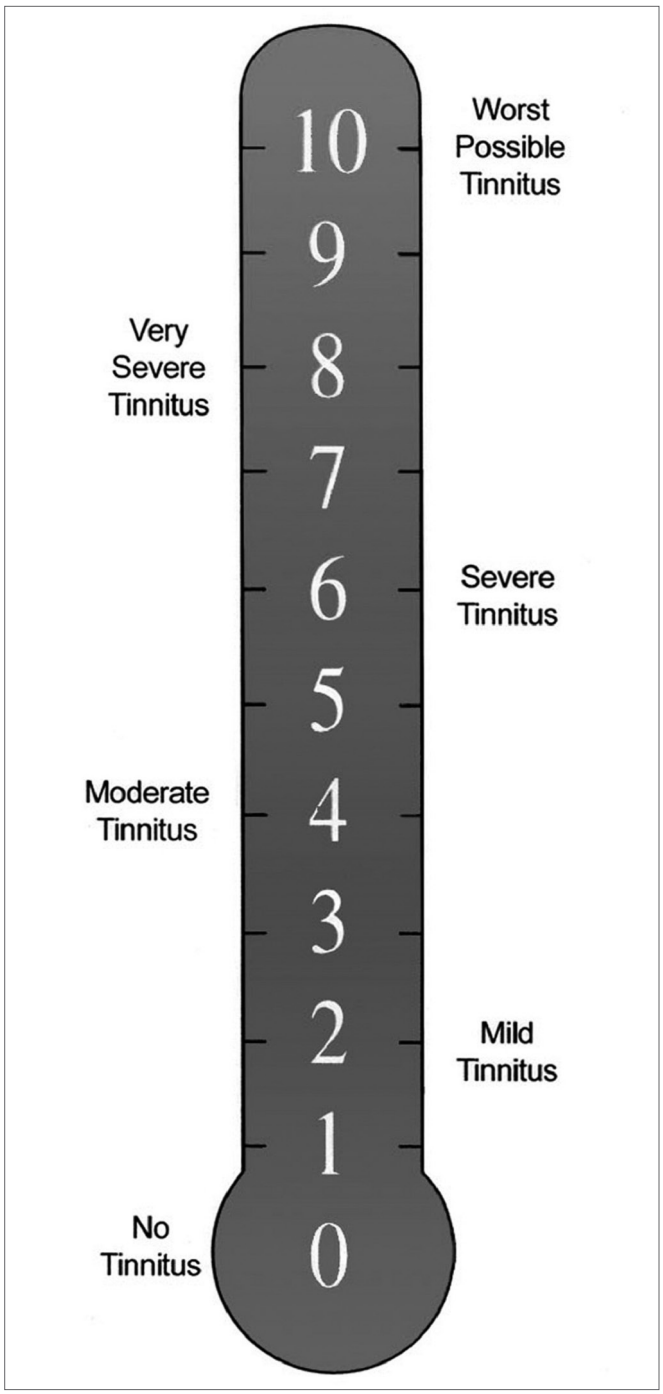


**Figure 1.** Tinnitus Distress Rating scale.

The present study received Mayo Clinic Institutional Review Board approval. The data collected for each participant included informed consent, sex, date of birth, hearing threshold at 8 frequencies (250, 500, 1,000, 2,000, 3,000, 4,000, 6,000, and 8,000 Hz), weekly diaries of daily TDR ratings of tinnitus, THI questionnaires at baseline and the end of the study, dates of first and last dose of magnesium, number of tablets used, reason for discontinuation, and adverse events. The adverse event data included the date of onset and whether the adverse event led to premature discontinuation of the intervention.

**Table 1.** Tinnitus Severity Scale[a].

| Score[b] | Grade | Description |
|---|---|---|
| 0-16 | Slight | Only heard in a quiet environment, very easily masked. No interference with sleep or daily activities. |
| 18-36 | Mild | Easily masked by environmental sounds and easily forgotten with activities. May occasionally interfere with sleep but not daily activities. |
| 38-56 | Moderate | May be noticed, even in the presence of background or environmental noise, although daily activities may still be performed. Less noticeable when concentrating. Not infrequently interferes with sleep and quiet activities. |
| 58-76 | Severe | Almost always heard, rarely, if ever, masked. Leads to disturbed sleep pattern and can interfere with ability to carry out normal daily activities. Quiet activities affected adversely. Hearing loss is likely to be present, but its presence is not essential. |
| 78-100 | Catastrophic | All tinnitus symptoms at level of severe or worse. Should be documented evidence of medical consultation. Hearing loss is likely to be present, but its presence is not essential. Associated psychological problems are likely to be found in hospital or general practitioner records. |

[a] Data categorized and developed by McCombe et al. (2001).
[b] Scores derived from the Tinnitus Handicap Inventory.

The primary outcome measures were comparisons of TDR scale scores and THI scores as converted to TSS grades at baseline and the end of the study. Patients were included in the primary analysis on the basis of intention to treat. The THI was measured at the time of discontinuation if a patient discontinued the study before 3 months. The mean hearing thresholds and mean TDR scores before and after treatment were assessed using a paired *t* test. The effect of magnesium on THI scores/TSS grades was evaluated using a McNemar test. Differences were considered statistically significant if $P < .05$.

## RESULTS

The study comprised 26 eligible and consenting participants. Of these, 2 patients (8%) discontinued the study because of adverse events and subsequently had no follow-up data. Adverse events reported were constipation, syncope, and nausea. Five patients (19%) discontinued for other reasons (lost to follow-up). Thus, 19 patients had complete follow-up data to analyze. The 7 patients who lacked follow-up were used for the

**Tinnitus Handicap Inventory (THI)**
**A 25-item self-report questionnaire that takes approximately 10 minutes to complete.**
**Scoring takes 5-10 minutes with a score of 4 for Yes, 2 for Sometimes, and 0 for No.**

| | | Points | | |
|---|---|---|---|---|
| | | 4 | 0 | 2 |
| 1. | Because of your Tinnitus is it difficult for you to concentrate? | Yes | No | Sometimes |
| 2. | Does the loudness of your Tinnitus make it difficult for you to hear people? | Yes | No | Sometimes |
| 3. | Does your Tinnitus make you angry? | Yes | No | Sometimes |
| 4. | Does your Tinnitus make you confused? | Yes | No | Sometimes |
| 5. | Because of your Tinnitus are you desperate? | Yes | No | Sometimes |
| 6. | Do you complain a great deal about your Tinnitus? | Yes | No | Sometimes |
| 7. | Because of your tinnitus do you have trouble falling asleep at night? | Yes | No | Sometimes |
| 8. | Do you feel as though you cannot escape from your Tinnitus? | Yes | No | Sometimes |
| 9. | Does your Tinnitus interfere with your ability to enjoy social activities (such as going out to dinner, to the cinema)? | Yes | No | Sometimes |
| 10. | Because of your Tinnitus do you feel frustrated? | Yes | No | Sometimes |
| 11. | Because of your Tinnitus do you feel that you have a terrible disease? | Yes | No | Sometimes |
| 12. | Does your Tinnitus make it difficult to enjoy life? | Yes | No | Sometimes |
| 13. | Does your Tinnitus interfere with your job or household responsibilities? | Yes | No | Sometimes |
| 14. | Because of your Tinnitus do you find that you are often irritable? | Yes | No | Sometimes |
| 15. | Because of your Tinnitus is it difficult for you to read? | Yes | No | Sometimes |
| 16. | Does your Tinnitus make you upset? | Yes | No | Sometimes |
| 17. | Do you feel that your Tinnitus has placed stress on your relationships with members of your family and friends? | Yes | No | Sometimes |
| 18. | Do you find it difficult to focus your attention away from your Tinnitus and on to other things? | Yes | No | Sometimes |
| 19. | Do you feel that you have no control over your Tinnitus? | Yes | No | Sometimes |
| 20. | Because of your Tinnitus do you often feel tired? | Yes | No | Sometimes |
| 21. | Because of your Tinnitus do you feel depressed? | Yes | No | Sometimes |
| 22. | Does your Tinnitus make you feel anxious? | Yes | No | Sometimes |
| 23. | Do you feel you can no longer cope with your Tinnitus? | Yes | No | Sometimes |
| 24. | Does your Tinnitus get worse when you are under stress? | Yes | No | Sometimes |
| 25. | Does your Tinnitus make you feel insecure? | Yes | No | Sometimes |

**Figure 2.** The Tinnitus Handicap Inventory is a 25-item self-report questionnaire that the patient can complete in about 10 minutes. Answers receive a score of 4 for Yes, 2 for Sometimes, and 0 for No. The Tinnitus Severity Scale (Table 1) is then used to apply a grade to the score.

intention-to-treat analysis. The mean (SD) follow-up time was 2.74 (0.24) months (range, 2.50-3.42 months). The mean age was 62 years (range, 30-76 years). Ten of 26 participants (37%) were women. There was no significant change in hearing thresholds from 250 Hz through 8,000 Hz for either ear during the duration of the study (Table 2). There was a significant decrease in the severity of tinnitus for subjects on the basis of their THI responses ($P=.03$). Those patients whose THI scores translated to "slight" or greater grade on the TSS before the intervention showed a significant decrease in the severity of their tinnitus ($P=.008$) (Table 3). Table 4 illustrates a significant decrease in participants' rating of tinnitus on the TDR at 1 month ($P=.049$), 2 months ($P=.04$), and 3 months of supplementation ($P=.045$). Figure 3 graphically represents the change in TDR in 26 patients from baseline to 3 months after treatment with magnesium. Before magnesium supplementation, 22 of 26 patients (85%) had more than slight impairment on THI/TSS. After supplementation, by intention-to-treat analysis, 14 of 26 patients (54%) continued to have more than slight impairment; by analysis of patients who completed the study, only 7 of 19 patients (37%) had more than slight impairment.

**Table 2.** Hearing Threshold and Tinnitus Handicap Inventory Resultsa

| | Mean (SD) Hearing Threshold, dB | | | | |
|---|---|---|---|---|---|
| Frequency, Hz | Baseline | Post-Mg | Difference | 95% CI | *P* Value |
| Right ear | | | | | |
| 250 | 23.65 (18.52) | 24.04 (18.11) | -0.38 (6.92) | -3.18 to 2.41 | .78 |
| 500 | 25.19 (19.05) | 25.58 (20.22) | -0.38 (4.22) | -2.09 to 1.32 | .65 |
| 1,000 | 25.38 (21.63) | 26.35 (22.16) | -0.96 (4.48) | -2.77 to 0.85 | .28 |
| 2,000 | 30.19 (23.39) | 30.00 (21.07) | 0.19 (5.00) | -1.83 to 2.21 | .85 |
| 3,000 | 41.15 (23.97) | 41.15 (23.85) | 0.00 (3.46) | -1.40 to 1.40 | >.99 |
| 4,000 | 48.46 (24.69) | 49.04 (24.78) | -0.58 (3.26) | -1.90 to 0.74 | .38 |
| 6,000 | 53.27 (23.79) | 53.27 (22.71) | 0.00 (4.00) | -1.62 to 1.62 | >.99 |
| 8,000 | 57.50 (23.16) | 58.65 (23.39) | -1.15 (5.53) | -3.39 to 1.08 | .30 |
| Left ear | | | | | |
| 250 | 21.92 (18.92) | 20.96 (18.55) | 0.96 (6.48) | -1.66 to 3.58 | .46 |
| 500 | 24.81 (18.95) | 24.81 (17.63) | 0.00 (4.24) | -1.71 to 1.71 | >.99 |
| 1,000 | 25.00 (17.78) | 24.81 (17.92) | 0.19 (4.58) | -1.66 to 2.04 | .83 |
| 2,000 | 30.38 (19.49) | 31.54 (19.74) | -1.15 (6.83) | -3.91 to 1.60 | .40 |
| 3,000 | 46.92 (22.54) | 47.12 (23.63) | -0.19 (7.93) | -3.40 to 3.01 | .90 |
| 4,000 | 54.04 (22.98) | 55.00 (23.62) | -0.96 (6.17) | -3.45 to 1.53 | .43 |
| 6,000 | 56.73 (25.22) | 56.92 (24.98) | -0.19 (4.35) | -1.95 to 1.57 | .82 |
| 8,000 | 57.88 (26.99) | 59.42 (24.47) | -1.54 (5.96) | -3.95 to 0.87 | .20 |
| Tinnitus Handicap Inventory score | 34.77 (21.74) | 28.69 (24.88) | 6.08 (13.89) | 0.47 to 11.69 | .03 |

Abbreviations: CI, confidence interval; Post-mg, after magnesium supplementation; SD, standard deviation.
[a] n=26.

**Table 3.** Differences in Tinnitus Severity Scale Gradea.

| | Baseline/Post-Mg | | | | Baseline | Post-Mg | | | |
|---|---|---|---|---|---|---|---|---|---|
| Grade | Y/Y | N/Y | Y/N | N/N | No. (%) | No. (%) | D | 95% CI | *P* Value |
| >Slight[b] | 14 | 0 | 8 | 4 | 22 (85) | 14 (54) | 0.31 | -0.52 to -0.09 | .008 |

Abbreviations: CI, confidence interval; Post-Mg, after magnesium supplementation.
[a] N=26.
[b] As defined in Table 1.

**Table 4.** Tinnitus Distress Rating Scalea

| Self-report | Mean (SD) | Difference From Baseline (SD) | 95% CI | *P* Value vs Baseline |
|---|---|---|---|---|
| Baseline | 6.23 (1.82) | … | … | … |
| 1 mo | 5.93 (1.69) | 0.30 (0.74) | 0.00 to 0.60 | .049 |
| 2 mo | 5.85 (1.70) | 0.38 (0.91) | 0.02 to 0.75 | .04 |
| 3 mo[b] | 5.79 (1.83) | 0.44 (1.07) | 0.01 to 0.87 | .045 |

Abbreviations: CI, confidence interval; SD, standard deviation; TDR, Tinnitus Distress Rating.
[a] Based on intention-to-treat analysis. N=26.
[b] Five of 26 patients (19% [95% CI, 7%-39%]) had a decrease in TDR by at least 1 point from baseline; 1 of 26 (4% [95% CI, 0%-20%]) had an increase in TDR by 1 point.

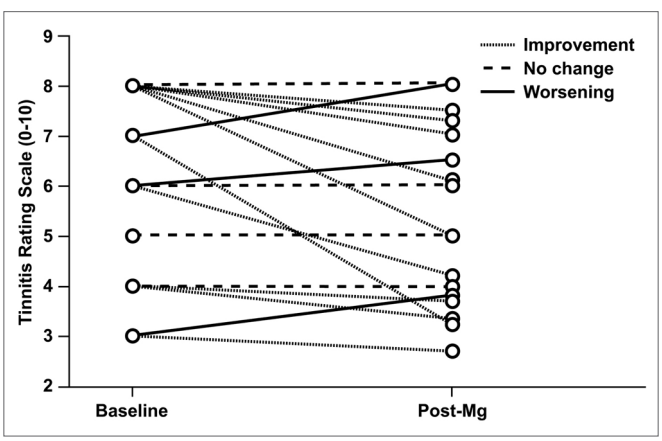


**Figure 3.** Change in tinnitus rating in 26 patients from baseline to 3 months after treatment with magnesium.

## DISCUSSION

The results of the present study indicated that self-reported measures of tinnitus severity using the THI/TSS and the TDR improved significantly with magnesium supplementation over a 3-month period of intervention. In fact, significant improvement in the TDR occurred as early as 1 month into the study, suggesting that benefit of magnesium supplementation occurred early in treatment and was sustained throughout the 3 months of the study. As illustrated in Figure 3, there was a greater reduction in tinnitus severity (based on THI/TSS results) for subjects who completed the full 3 months of supplementation compared with those who dropped out of the study before completion. For the subjects lost to follow-up, we assumed for the purposes of this analysis that there was no benefit from treatment. These participants were included because if noncompleters doing poorly enough to drop out were not analyzed, then selection bias would be likely. Therefore, subjects with no follow-up were treated as though they had no improvement and were included in the analysis. However, the noncompleters had a significant improvement on the THI/TSS, suggesting a benefit of magnesium in the reduction of severity of tinnitus. Based on the results of the present study, the authors have initiated a Phase 3 study using a placebo and double-blinding to control for factors unrelated to the magnesium supplementation.

## SUMMARY

The present study indicated that subjects showed significant improvement in their self-rating of tinnitus with a magnesium supplement of 532 mg daily for 3 months. Further investigations should control for the placebo effect.

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