

## 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.

## INTRODUCTION

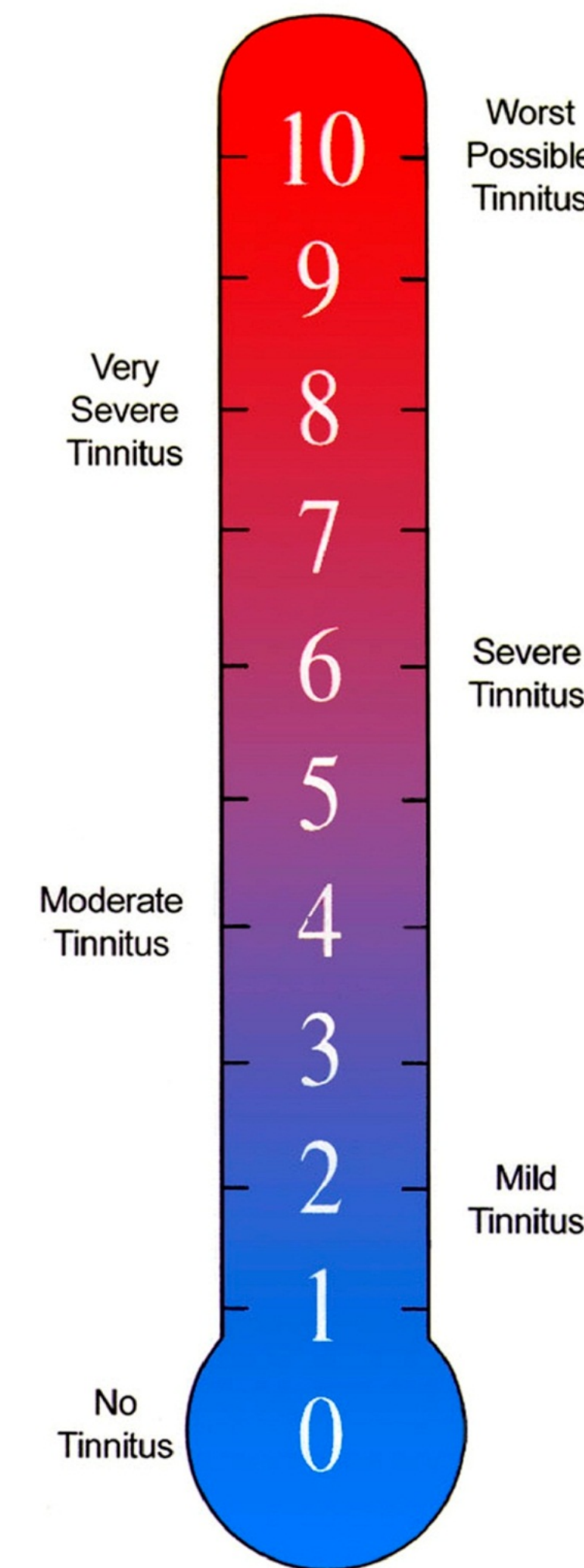
The last several decades have revealed clinical and experimental data regarding the importance of magnesium (Mg) in hearing. Increased susceptibility to noise damage, ototoxicity, and auditory hyperexcitability are linked to states of Mg deficiency (Cevette et al. 2003). Recent studies in noise-induced 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 Americans fall short of the recommended daily allowance for magnesium by 100 mg daily for all age groups. The purpose of this study was to examine any potential benefit in lessening the severity of tinnitus in patients supplemented with magnesium (532 mg daily). Magnesium improved hearing recovery and lessened tinnitus in cases of idiopathic sudden hearing loss (Gordin et al. 2002). More recently, Nageris, Ulanovski, and Attias (2004) showed in a well-controlled study that magnesium was a relatively safe and convenient adjunct to steroid treatment for enhancing the improvements of hearing in acute-onset sensorineural hearing loss. The protective effect of magnesium in noise induced hearing loss has been previously reported (Ising et al. 1982; Scheib et al. 2000). Additionally, permanent and temporary changes in auditory function have been linked to nutritional deficiencies of magnesium (Mg). Mg deficiency has resulted in increased susceptibility to noise-induced hearing loss (Ising et al. 1982; Joachim et al. 1983; Joachim et al. 1987; Scheib et al. 2000), ototoxicity (Vormann and Günther, 1993), and hyperexcitability (Kruse et al. 1932; Cevette et al 1989; Bac et al, 1994) of the auditory system.

## METHODS

26 patients with a Tinnitus Distress Rating (TDR) from 3 to 8 (Figure 1) were given a supplement (Mg plus protein, Miller Pharmacal Group, 133 mg/tablet) of magnesium daily (4 tablets to total 532 mg) for three months. Differences of TDR scores before and after supplementation were compared to determine any effect of supplementation on a patient's self-rated tinnitus. Also, all subjects completed a Tinnitus Handicap Inventory (THI) before and following 3 months of supplementation with magnesium (Figure 2). Subjects 18 years and older who were seen for an audiological evaluation and who had tinnitus with a rating from 3 through 8 were eligible for the study. Patients with decreased kidney function within three months (creatinine greater than 2.2 mg/dL for females and 2.6 mg/dL for males) were excluded from the study (these values are two times normal creatinine levels for the Mayo Clinic Arizona laboratory.) A review by Cardiovascular Diseases indicated that magnesium at the level of 532 mg was benign for heart patients and absent decreased kidney function. A review by the Mayo Pharmacy indicated that there were no major drug interactions with magnesium at the levels of the current protocol. The data included exclusion criteria, consent, sex, date of birth, hearing threshold at 8 frequencies, weekly diaries, tinnitus scale questionnaires at baseline and end of study, dates of first and last dose, number of tablets used, reason for discontinuation, and adverse events. The adverse event data included the date of onset and whether serious problems led to premature discontinuation of the intervention. The primary outcome measures were the TDR and THI scores. The mean tinnitus level at the end of treatment was compared to the mean at baseline and the statistical significance was calculated by using the paired *t* test. Patients were included in the primary analysis on the basis of intention to treat. The tinnitus rating was measured at time of discontinuation if a patient discontinued prior to three months.

## RESULTS

Comparisons for hearing threshold and the TDR before and after treatment with magnesium were assessed using a paired *t*-test. The effect of magnesium on the Tinnitus Handicap Inventory (THI) rating scales was evaluated using a McNemar test. Differences were considered statistically significant if *p* < 0.05. There were 26 patients who were eligible and consented. 2 of 26 (8%) patients discontinued due to adverse events and subsequently had no follow-up data. 5 of 26 (19%) discontinued for other reasons (lost to follow-up). There were 19 patients had follow-up data to analyze. The 7 patients that lacked follow-up were used for the intention to treat analysis. 3 adverse events were reported in 2 patients. Adverse events reported were constipation, syncope, and nausea. The follow-up time (months); mean (SD), [range] was 2.74 (0.24) [2.50 – 3.42]. The mean age was 62 years with a range of 30-76 years. 10 of 26 (37%) were female. There was no significant change in hearing thresholds from 250 Hz through 8000Hz for either ear during the duration of the study (Table 1). There was a significant decrease in the severity of tinnitus for subjects using the THI (*p* = 0.03) As can be seen in Table 2, the THI scores were converted to the categories of the TSS. Those patients who ranked slight or greater on the THI Severity Scale prior to intervention showed a significant decrease in the severity of their tinnitus at post-testing (*p* = 0.008) (Table 3). Table 4 shows that there was a significant decrease in the subject's rating of tinnitus on the TDR at the 1 month (*p* = 0.049), 2 month (*p* = 0.04), and 3 month intervals (*p* = 0.045). Figure 3 shows the change in TDR in 26 patients from baseline to 3 months after treatment with magnesium. Figure 4 shows percentage of patients with more than slight impairment on THI before treatment with magnesium (Pre-Mg, n=26), after treatment with magnesium using intention to treat (Post-Mg1, n=26), and after treatment with Mg for those who completed treatment (Post-Mg2, n=19).



**Figure 2: 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 |

**Table 1: Hearing Threshold and THI Results**

|   | Baseline Mean (SD) | Post-Mg Mean (SD) | Difference Mean (SD) | P    | 95% CI        |
|---|--------------------|-------------------|----------------------|------|---------------|
| <b>Hearing Threshold (dB): Right Ear (N=26)</b> |                    |                   |                      |      |               |
| 250 Hz  | 23.65 (18.52)      | 24.04 (18.11)     | -0.38 (6.92)         | 0.78 | -3.18 to 2.41 |
| 500 Hz  | 25.19 (19.05)      | 25.58 (20.22)     | -0.38 (4.22)         | 0.65 | -2.09 to 1.32 |
| 1000 Hz   | 25.38 (21.63)      | 26.35 (22.16)     | -0.96 (4.48)         | 0.28 | -2.77 to 0.85 |
| 2000 Hz   | 30.19 (23.39)      | 30.00 (21.07)     | 0.19 (5.00)          | 0.85 | -1.83 to 2.21 |
| 3000 Hz   | 41.15 (23.97)      | 41.15 (23.85)     | 0.00 (3.46)          | 1.00 | -1.40 to 1.40 |
| 4000 Hz   | 48.46 (24.69)      | 49.04 (24.78)     | -0.58 (3.26)         | 0.38 | -1.90 to 0.74 |
| 6000 Hz   | 53.27 (23.79)      | 53.27 (22.71)     | 0.00 (4.00)          | 1.00 | -1.62 to 1.62 |
| 8000 Hz   | 57.50 (23.16)      | 58.65 (23.39)     | -1.15 (5.53)         | 0.30 | -3.39 to 1.08 |
| <b>Hearing Threshold (dB): Left Ear (N=26)</b>  |                    |                   |                      |      |               |
| 250 Hz  | 21.92 (18.92)      | 20.96 (18.55)     | 0.96 (6.48)          | 0.46 | -1.66 to 3.58 |
| 500 Hz  | 24.81 (18.95)      | 24.81 (17.63)     | 0.00 (4.24)          | 1.00 | -1.71 to 1.71 |
| 1000 Hz   | 25.00 (17.78)      | 24.81 (17.92)     | 0.19 (4.58)          | 0.83 | -1.66 to 2.04 |
| 2000 Hz   | 30.38 (19.49)      | 31.54 (19.74)     | -1.15 (6.83)         | 0.40 | -3.91 to 1.60 |
| 3000 Hz   | 46.92 (22.54)      | 47.12 (23.63)     | -0.19 (7.93)         | 0.90 | -3.40 to 3.01 |
| 4000 Hz   | 54.04 (22.98)      | 55.00 (23.62)     | -0.96 (6.17)         | 0.43 | -3.45 to 1.53 |
| 6000 Hz   | 56.73 (25.22)      | 56.92 (24.98)     | -0.19 (4.35)         | 0.82 | -1.95 to 1.57 |
| 8000 Hz   | 57.88 (26.99)      | 59.42 (24.47)     | -1.54 (5.96)         | 0.20 | -3.95 to 0.87 |
| <b>Tinnitus Handicap Inventory (N=26)</b>       |                    |                   |                      |      |               |
|   | 34.77 (21.74)      | 28.69 (24.88)     | 6.08 (13.89)         | 0.03 | 0.47 to 11.69 |

**Table 2: Tinnitus Severity Scale (TSS)**

Data categorized and developed by McCombe, Bagtley, Coles, McKenna, McKinney and Windle-Taylor, 2001, 391.

| Score  | 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. Associate psychological problems are likely to be found in hospital or general practitioner records. |

**Table 3: Differences in Tinnitus Handicap Inventory Severity Scale**

|         | Baseline/Post-Mg |     | Baseline |     | Post-Mg    |            | P    | 95% CI         |
|---------|------------------|-----|----------|-----|------------|------------|------|----------------|
|         | Y/Y              | N/Y | Y/N      | N/N | No. (%)    | No. (%)    |      |                |
| >Slight | 14               | 0   | 8        | 4   | 22/26 (85) | 14/26 (54) | 0.31 | -0.52 to -0.09 |

**Table 4: Tinnitus Distress Rating (TDR) Scale (N=26)**

|          | vs. Baseline |                      |       |              |
|----------|--------------|----------------------|-------|--------------|
|          | Mean (SD)    | Difference Mean (SD) | P     | 95% CI       |
| Baseline | 6.23 (1.82)  | -                    | -     | -            |
| 1 month  | 5.93 (1.69)  | 0.30 (0.74)          | 0.049 | 0.00 to 0.60 |
| 2 month  | 5.85 (1.70)  | 0.38 (0.91)          | 0.04  | 0.02 to 0.75 |
| 3 month* | 5.79 (1.83)  | 0.44 (1.07)          | 0.045 | 0.01 to 0.87 |

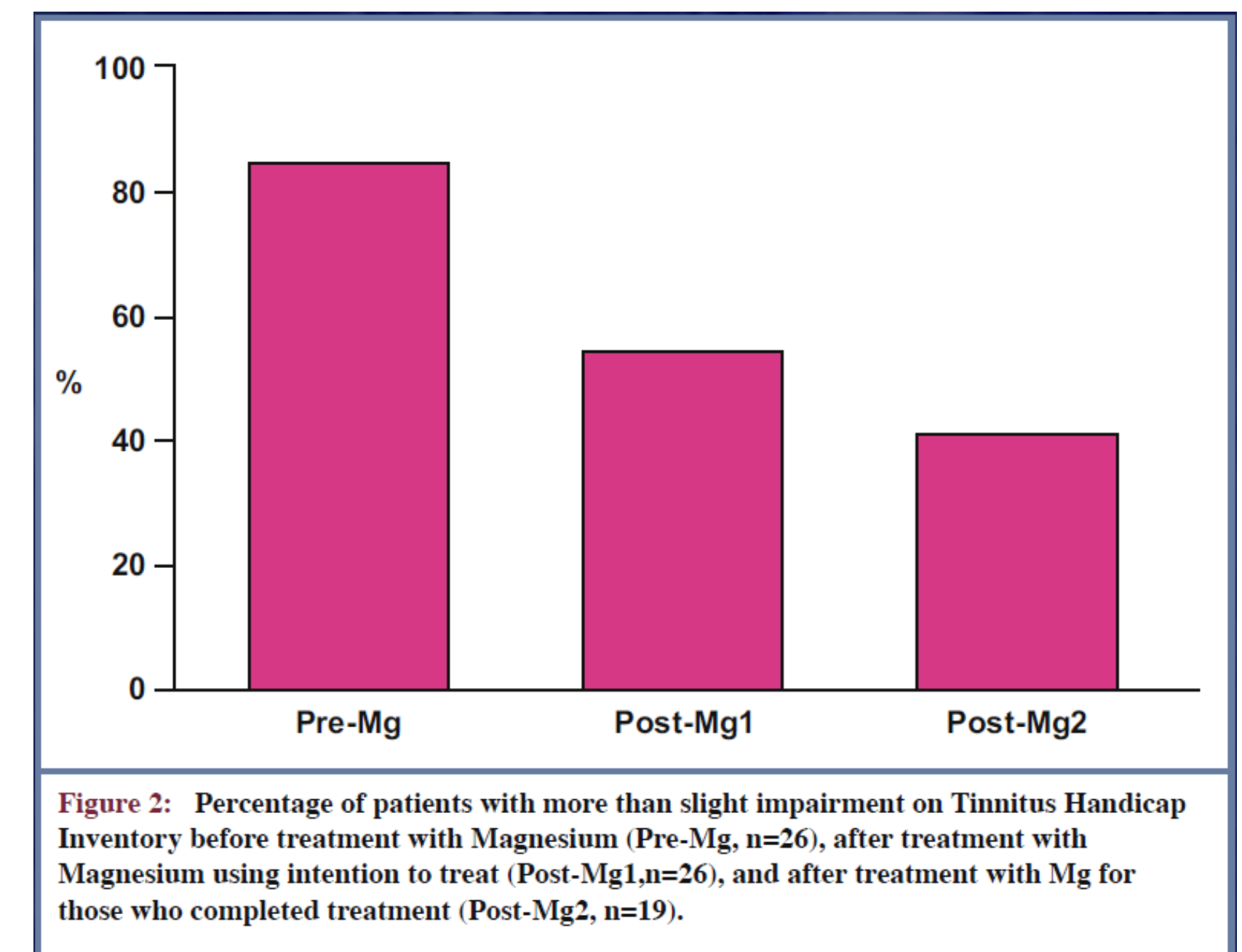
\*5/26 (19%), 95% CI = 7% to 39% of patients had a decrease in TDR by at least 1 point from baseline. 1/26 (4%), 95% (CI = 0% to 20%) patients had an increase in TDR by 1 point.

## DISCUSSION

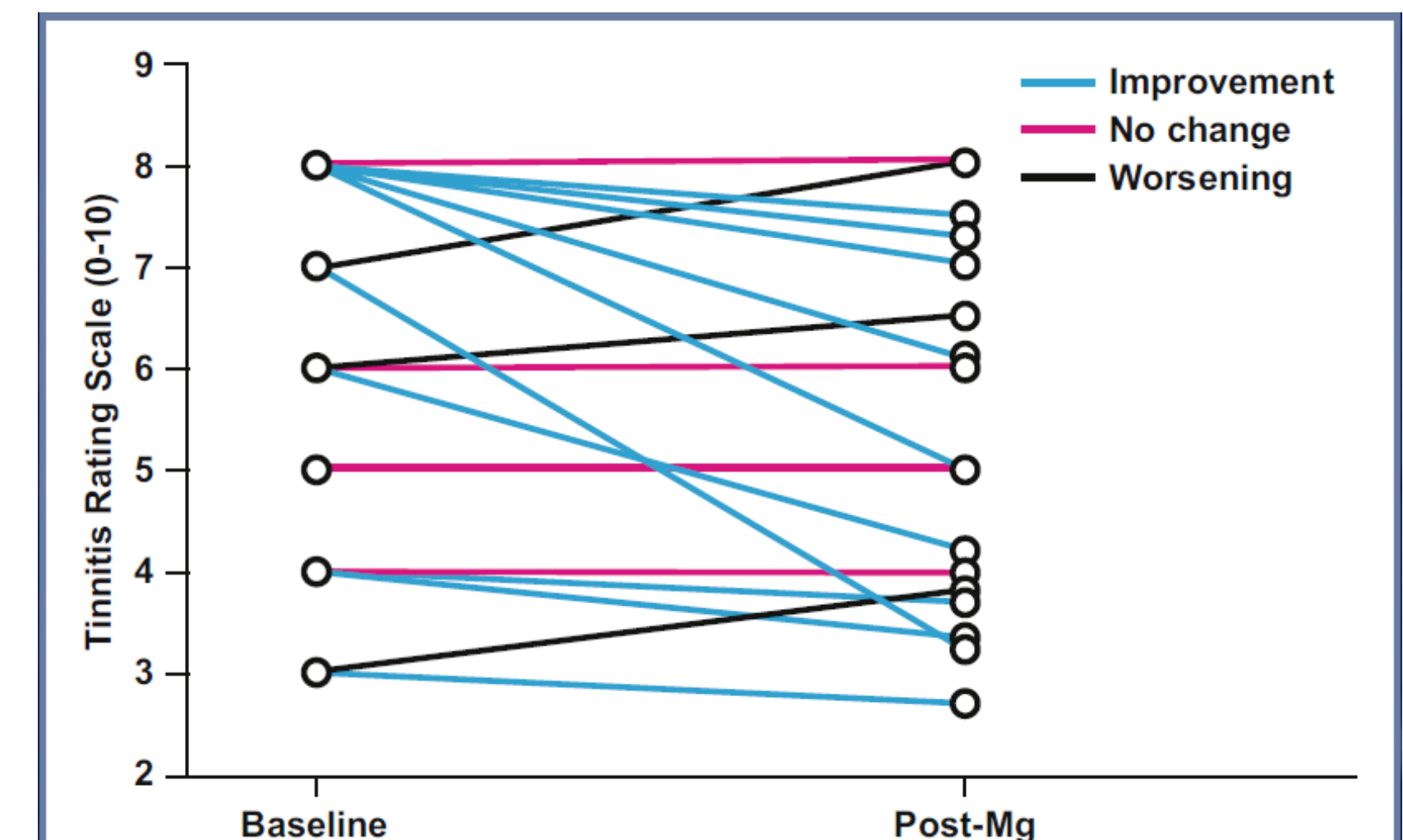
The results of the present study indicated that self-report measures of tinnitus severity, the THI and the TDR, improved significantly with magnesium supplementation over a 3-month period of intervention. As noted in Figure 4 there was a greater reduction in tinnitus severity (THI) for subjects who completed the full 3 months of supplementation compared to those who dropped out of the study before completion. It should be noted, however, that for those subjects lost to follow-up, it was assumed that there was no benefit from treatment. It was determined that an introduction of selection bias would occur if only completers were analyzed and not include those non-completers doing poorly enough to drop out. Therefore, subjects with no follow-up were treated as though they had no improvement and were included in the analysis. Even in the group of non-completers there is a significant improvement on the THI suggesting a benefit of magnesium in the reduction of severity of tinnitus. The current design, however, cannot distinguish the effect of treatment from a placebo effect or regression to the mean. Based upon the results of the present study an investigation using a placebo and double-blinding would be important to control for factors that may have influenced the results unrelated to the magnesium supplementation itself. It is important to note that there was significant improvement in the TDR as early as one month suggesting that benefit of Mg supplementation was observed early in treatment and was sustained throughout the 3 months of the study.

## CONCLUSION

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. Currently, a phase III randomized control trial is in progress.



**Figure 2: Percentage of patients with more than slight impairment on Tinnitus Handicap Inventory before treatment with Magnesium (Pre-Mg, n=26), after treatment with Magnesium using intention to treat (Post-Mg1, n=26), and after treatment with Mg for those who completed treatment (Post-Mg2, n=19).**



**Figure 3: Change in Tinnitus Rating scale in 26 patients from baseline to 3 months after treatment with magnesium.**