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Oral Magnesium Intake Reduces Permanent Hearing Loss Induced by Noise Exposure

JOSEPH ATTIAS, DSc, GIORA WEISZ, MD, SHLOMO ALMOG, PhD, AMNON SHAHAR, MD, MICHAEL WIENER, MD, ZWI JOACHIMS, MD, ABRAHAM NETZER, MD, HARTMUT ISING, PhD, EKKEHARD REBENTISCH, MD, AND THEODOR GUENTHER, MD

Introduction: Following animal experiments where correlations were observed between serum magnesium level and noise-induced permanent hearing threshold shifts (NIPTS), we tested the prophylactic effect of magnesium in human subjects exposed to hazardous noise.
Methods: Subjects were 300 young, healthy, and normal-hearing recruits who underwent 2 months of basic military training. This training necessarily included repeated exposures to high levels of impulse noises while using ear plugs. During this placebo-controlled, double-blind study, each subject received daily an additional drink containing either 6.7 mmol (167 mg) magnesium aspartate or a similar quantity of placebo (Na-aspartate).
Results: NIPTS was significantly more frequent and more severe in the placebo group than in the magnesium group, especially in bilateral damages. NIPTS was negatively correlated to the magnesium content of blood red cells but especially to the magnesium mononuclear cells. Long-term additional intake of a small dose of oral magnesium was not accompanied by any notable side effect.
Conclusion: This study may introduce a significant natural agent for the reduction of hearing damages in noise-exposed population.

Noise-induced permanent threshold shift (NIPTS) is considered one of the most frequent occupational health hazards in both industrial and military environments. For the 90th percentile of the exposed population, the risk for presumed NIPTS increases exponentially for noise levels beyond 85 dB(A) and over prolonged periods.[1] More than 9 million Americans are exposed to daily average occupational noise levels above 85 dB(A).[2] NIPTS manifests irreversible subtle changes in the sensory cells and other structures in the organ of corti in the cochlea. Streocilia of the hair cells, and primarily of the outer hair cells, become fused and/or disappear, they and supporting cells disintegrate, and ultimately even the nerve fibers that innervated the hair cells disappear.[3] Individual susceptibility to noise seems to play an important factor determining the eventual NIPTS.[4] With this respect, biochemical mechanisms including the preexposure levels of magnesium were suggested as affecting the susceptibility to NIPTS.[5]

Magnesium is an essential factor in regulating cellular membrane permeability, neuromuscular excitability, and energy production and consumption.[6] Mechanoelectric trans-

From the Institute of Noise Hazards Research and Evoked Potentials Laboratory, I.D.F. Medical Corps, and the Ear Nose and Throat Department, Rambam Medical Center, Haifa, Israel; the Institute for Water, Soil and Air Hygiene, Federal Health Office, and the Institute of Molecular Biology and Biochemistry, Free University, Berlin, Germany.

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Address reprint requests to Joseph Attias, DSc, Institute for Noise Hazards Research and Evoked Potentials Laboratory, I.D.F., Chaim-Sheba Medical Center/Bldg 87, 52621, Israel.

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mission itself consumes energy.[7] Any condition that increases this energy consumption or reduces the energy supply, increases the risk that the function of the hair cells may be limited temporarily or permanently.[8] In noise exposure, where a high energy consumption of the hair cells is required, magnesium deficiency may increase the potential for NIPTS.

The association of increased NIPTS with low levels of perilymph and serum magnesium (SMg) concentrations has been demonstrated by experiments with animals. In rodents fed with a high-dietary magnesium intake and subjected to high-impulse noise, NIPTS was reduced.[9,10] In a retrospective study in humans, subjective thresholds across the frequencies 3 kHz, 4 kHz, and 5 kHz were negatively correlated to serum Mg.[11] This finding was the first indication that magnesium status in humans may be one of the factors determining variations in sensitivity to noise-induced hearing loss. The purpose of the present study was to consider whether increasing long-term intake of magnesium has any prophylactic value in reducing NIPTS in humans exposed to repeated impulsive noise.

METHODS

Subjects

This field research was performed during 2 months of military basic training, in the form of a placebo-controlled, double-blind study. Four-hundred male recruits, aged 17.7 to 18.5 years, were informed about the aims and methods of the study and gave their written consent to participate. The military basic training necessarily included an exposure to impulse noises that may be harmful to the exposed subjects even with the use of ear protectors. The study was approved by the local Helsinki committee and was performed between February and April 1990.

All the recruits underwent a detailed clinical and audiological examination as well as an extensive battery of laboratory tests before the study commenced. Requirements for participation were normal blood biochemical measures, normal kidney function, normal electrocardiogram, and intact auditory thresholds (<20 dB hearing threshold level [HL] in the frequency range of 1 to 8 kHz). Three hundred subjects who met these entrance conditions were divided randomly into two groups (placebo and magnesium) of 150 subjects. The weight range was 49 to 116 kg, with an average of 70 ± 12.2 kg. The demographic, personal, and medical parameters analyzed revealed no differences between the placebo and treatment groups. Living and eating conditions were similar for all subjects as was the military training.

Threshold Measurements and Blood Samples

Threshold measurements and blood samples were collected from all the subjects before and after the study. Air and bone conduction thresholds were determined in mobile sound-proof compartments (Industrial Acoustic Company, Bronx, NY) using Siemens audiometers (SD 25) and calibrated earphones (TDH-49) all conforming to International Standards Organization (ISO) specifications.[12] The audiological examinations were performed by certified and experienced audiologists. As mentioned earlier, preexposure audiometric values were normal in all participating subjects. To avoid contamination with temporary threshold shifts, the postexposure measurements were performed 7 to 10 days after the last exposure.

From each subject 12 mL blood samples were drawn for magnesium estimation in serum, erythrocytes (EMg), and mononuclear cells (monocytes and lymphocytes) (MMg). The blood samples were taken between 8 AM and 11 AM. Using the method of Elin and Hosseini,[13] blood mononuclear cells were separated with a discontinuous Ficoll-Hypaque gradient, washed, centrifuged at 400g for 3 minutes, and lysed by sonication in 10 mmol/L NaCl. Differential counts (Cell-Dyn 400, Sequoia Turenr Corp, Mountain View, CA) were performed on cytocentrifuge smears of final suspensions to document the percent of mononuclear cells. The validity of the cells was checked by trypan-blue index. Magnesium levels in serum, red cells, and mononuclear cells were determined with a Perkin-Elmer (2380, Perkin-Elmer Corp, Norwalk, CT) atomic absorption spectrophotometer. Standard errors were less then 4% for all assays with the exception of MMg, with a standard error of 7.1%.

Exposure to Noise

The subjects underwent training 6 days a week for 8 weeks and were exposed to shooting range noises with an M16 rifle. On average, each subject fired 420 shots. The average peak level of each shot was 164 dB(A) with less than a 1-millisecond duration. The impulse noise had the main energy in a spectrum between 2 to 5 kHz. Ear plugs were worn for hearing protection, reducing the peak noise level on average by 25 dB(A).

Administering the Magnesium and the Placebo

Close medical supervision was maintained throughout the training period. Each subject re-

ceived daily, during the afternoon meal, an additional 200-mL drink of lemonade containing either 6.7 mmol magnesium-aspartate or a placebo (sodium-aspartate) (Artersan Pharma GmbH). All the subjects received a uniform diet. The magnesium content of the diet was constant and averaged to 387 ± 23 mg magnesium per person per day. Possible side effects such as gastrointestinal complaints and other symptoms such as tinnitus, dizziness, and weakness were monitored by a weekly questionnaire and medical interview.

Statistical Analysis

Only data from subjects who completed the full military training were included. The statistical analysis was performed by a certified statistician using a repeated-measures multivariate analysis of variance, paired and unpaired Student's *t*-tests, chi-square and Mantel-Haenszel chi-square and Pearson correlations. Throughout this study, we used the term postexposure permanent threshold shift (PTS) for indicating the actual threshold measured following the exposure and NIPTS for the difference in hearing thresholds before and after exposure. The differences between the treated groups were assessed in terms of postexposure PTS prevalence and of NIPTS severity.

RESULTS

Auditory Thresholds

Forty five subjects were eliminated from data analysis for various reasons, including absence and poor blood sampling. Table 1 summarizes the incidence of the postexposure PTS for the two groups. For each subject tested, postexposure PTS was defined as a threshold greater than 25 dB HL for at least one frequency in the range of 2 to 8 kHz. The differences in the incidence of PTS between the groups were statistically significant. Moreover, the incidence of bilateral PTS was remarkably (χ^2 = 8.1, $P < .001$) higher in placebo (11.5%) then in the magnesium (1.2%) groups.

TABLE 1. Incidence of Postexposure Permanent Threshold Shift in the Two Test Groups

	Left Ear		Right Ear	
	No PTS	PTS	No PTS	PTS
Mg group	111 (88.8%)	14 (11.2%)	111 (88.8%)	14 (11.2%)
Placebo group	102 (78.5%)	28 (21.5%)	93 (71.5%)	37 (28.5%)

NOTE. Group differences were statistically significant (left ear – χ^2 = 4.95, $P < .05$; right ear – χ^2 = 11.9, $P < .001$).

Figure 1 details the prevalence of the resultant NIPTS as a function of its severity and group. In both groups the maximum NIPTS resulted in 4 to 6 kHz and an NIPTS greater than 21 dB in 3 to 4 kHz was observed in 11% of the subjects. The placebo group demonstrated more frequent and worse NIPTS than the magnesium group. This was evident for the frequency range of 4 to 8 kHz in the right ear and 3 to 4 khz for the left ear. Changes in auditory threshold differences up to 10 dB HL are considered within normal limits. Moreover, differences between preexposure and postexposure thresholds greater than 21 dB HL for all frequencies together occurred more than twice as often in the placebo than in the magnesium group. Thus, according to a variety of audiological measures, placebo groups demonstrated an NIPTS that was more severe and had higher prevalence than the magnesium group.

The group averages and standard deviations for the three magnesium measures before and after the treatment period are presented in Table 2. Before exposure, the magnesium values of the two groups were similar.

After the training, which included noise exposure and magnesium (or placebo) administration, SMg increased similarly in both groups by nearly 11% without a statistically significant difference. EMg increased in both groups following training; however, the elevation in the magnesium group (12%) was sig-

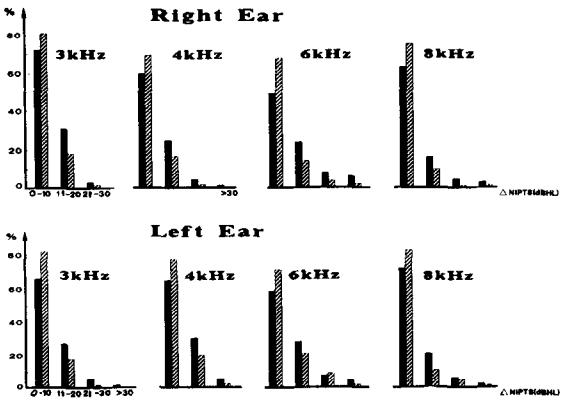

Fig 1. Prevalence of NIPTS in placebo (■, n = 130) and Mg (▨, n = 125) as function of severity.

TABLE 2. Means Values ± Standard Deviations of Magnesium Concentrations in the Blood Serum, Erythrocytes, and Mononuclears for Both Test Groups Before and After the Exposure Period

	SMg (mEq/L)	EMg (mEq/L)	MMg (fEq/Cell)
Magnesium			
Before	1.72 ± 0.14	3.8 ± 0.44	5.01 ± 2.62
After	1.84 ± 0.32	4.25 ± 0.67	5.35 ± 1.81
Placebo			
Before	1.70 ± 0.14	3.78 ± 0.39	5.13 ± 2.84
After	1.82 ± 0.14	4.07 ± 0.51	4.5 ± 1.64

nificantly (Student's t-test = 1.84, $P < .03$) greater than in the placebo group (8%). In contrast, there was a mean decrease in MMg in the placebo group (−0.63 fEq/cell) as compared with preexperiment values, whereas the Mg group tended to increase MMg by an average of 0.34 fEq/cell. The postexposure values of MMg in both groups differed significantly (Student's t-test = 3.2, $P < .001$).

Magnesium and Auditory Thresholds

In order to determine a possible correlation between magnesium in mononuclear blood cells and NIPTS, a magnesium threshold that might significantly differentiate subjects with and without NIPTS was explored. Regardless of the treatment group, an MMg level of 6.1 fEq/cell significantly differentiated between the affected and unaffected subjects. In the placebo group, the percent of subjects above this vulnerable magnesium threshold was 19%, whereas in the magnesium group it was 33.7% ($\chi^2 = 4.5$, $P < .03$).

Table 3 shows the blood MMg levels in subjects with and without postexposure PTS for frequencies between 2 and 8 kHz. For each tested frequency, lower magnesium levels were measured in subjects with PTS compared with those without PTS. This trend was statistically evident for all frequency thresholds in the right ear and for PTS at 3 kHz and 4 kHz in the left ear.

Pearson correlation coefficients between NIPTS and intracellular magnesium-parameters were performed. The results have shown negative low but significant coefficients between the EMg level and NIPTS at 6 kHz in the left ($r = -.17$, $P < .02$, $n = 177$) and right ear separately ($r = -.2$, $P < .006$) as well as with NIPTS at 8 kHz in the right ear ($r = .15$, $P < .04$). Significant correlates were also observed between NIPTS at 8 kHz in the right ear with EMg ($r = -.15$, $P < .04$) and with MMg separately ($r = -.15$, $P < .04$, $n = 165$). These correlations indicate that as the level of MMg or EMg decreases the severity of NIPTS increases.

Figure 2 summarizes the relation between the incidence of the subjects with postexposure PTS and their blood MMg levels. The Mantel-Haenszel chi-square test for linear trend showed a significant relation (right ear $\chi^2 = 17.5$, $P < .001$; left ear $\chi^2 = 8.7$, $P < .01$) indicating that as the magnesium level decreases, the incidence of PTS increases.

Side Effects

During the study, no subject reported any serious side effect that would have made it necessary to cease administration of the additional intake of magnesium. The mean relative frequency of possible associating symptoms as reported by the groups are listed in Table 4.

TABLE 3. Means and Standard Deviations of Mononuclear Cell Magnesium Content (fEq/cell) in Subjects With and Without Postexposure Permanent Threshold Shift

Frequency (kHz)	Left Ear		Right Ear	
	PTS	Normals	PTS	Normals
2	4.9 ± 1.7	4.9 ± 1.8	4.3 ± 1.6	5.0 ± 1.8*
3	4.5 ± 1.9	5.1 ± 1.7*	4.5 ± 2.1	5.1 ± 1.6*
4	4.6 ± 2.0	5.0 ± 1.6*	4.4 ± 1.9	5.2 ± 1.7†
6	5.0 ± 2.2	4.9 ± 1.7	4.6 ± 1.8	5.0 ± 1.7*
8	4.8 ± 2.2	4.9 ± 1.6	4.3 ± 1.9	5.1 ± 1.6*

* $P < .04$.

† $P < .005$ by unpaired Student's t-tests for group comparisons.

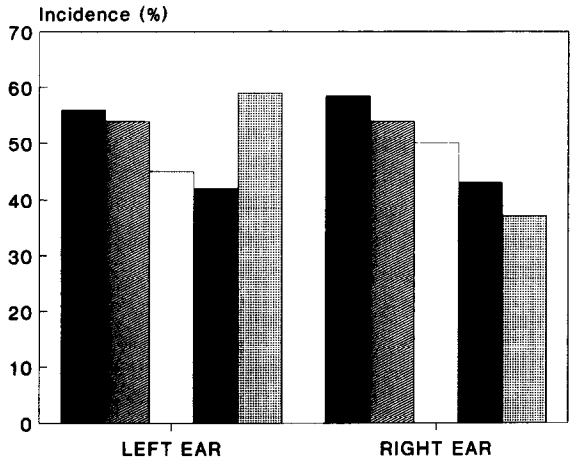

Fig 2. Incidence of postexposure PTS (greater than 25 dB HL) according to magnesium mononuclear blood levels (fEq/cell) ■, <3.6; ▧, 3.5-4.2; □, 4.2-5.03; □, 5.03-6.44; ▩, >6.44.

The incidence of gastrointestinal symptoms (nausea, stomachache, vomiting, and diarrhea) was calculated. Although there was a slightly higher incidence in the subjective reporting of gastrointestinal symptoms in the magnesium group (43%) compared with the placebo group (34%), the difference was not statistically significant. Similarly, in spite of the small increase in the combined incidence of tinnitus, dizziness, and headache in the placebo group (44%) compared with the magnesium group (33%), the difference was not statistically significant.

There were no differences with respect to weight change and ear plug use during the study for the two groups.

DISCUSSION

The additional intake of 6.7 mmol of magnesium daily did not result in differences of serum magnesium between the two groups. However, the intracellular magnesium parameters differed significantly. This result seems to be a paradox at first glance. It can be explained, however, by taking into account the variation in time of these parameters. The oral intake causes an increase of SMg for a few hours. In this period of time, intracellular magnesium at different sites will increase as well as the magnesium flux through the blood-brain barrier.[14] Although SMg is reduced to normal values via renal excretion[15] within several hours, a magnesium depletion from intracellular sites and through the blood-brain barrier is much slower. In this study, at the time of blood sampling, the transient increase of SMg was equalized already, whereas the intracellular parameters showed the long-term effect of the applied magnesium supplementation.

TABLE 4. Relative Incidence of Symptoms in the Placebo and Magnesium Groups

Symptom	Placebo Group (%)	Mg Group (%)
Tinnitus	10	7
Headache	20	14
Dizziness	14	12
Nausea	8	11
Stomachache	9	17
Vomiting	6	3
Diarrhea	11	12
Weakness	15	16

The extracellular level of magnesium is an important factor in maintaining a normal cell membrane permeability. Free extracellular magnesium influences the calcium channels and is a factor in preserving membrane polarization.[16,17] The slow influx of Ca^{2+} is reduced by an increase in free extracellular magnesium, and deactivation of voltage-dependent calcium channels is determined by the magnesium gradient at the membrane.[18]

The relation between blood cell Mg levels and NIPTS can be explained by the following mechanisms. In reduced Mg levels, its concentration at the hair cell membrane decreases, leading to an overall increase in membrane permeability. This causes an increase in intracellular Ca^{2+} and Na^{+}, and K^{+} decreases by passive flow diffusion. The decreased electrolyte gradients induce greater transport activity with respect to these ions and with it, an increase in energy turnover.[19] A lasting increase in free intracellular Ca^{2+} can lead to the cell's energic depletion and, through activation of Ca-dependent enzymes, lead to the death of the cell. In addition, the influx of Ca-ions caused by the mechanical deflection of streocilia is of fundamental importance to the hearing process.[20] If magnesium is deficient, the Ca-content of the hair cells can increase as a result of the greater membrane permeability.

Furthermore, if extracellular free magne-

sium decreases, there is a greater secretion of catecholamines and prostaglandins, subsequently leading to a reduction of the blood flow because of vasoconstriction in the inner ear and with it, a higher risk of energetic depletion in the hair cells.[21,22] Increased magnesium intake can also improve inner ear microcirculation. The muscle tone of the vessels diminishes with higher concentrations of intracellular free magnesium, and their reactivity to vasoactive substances decreases.[23] It has, in fact, been observed that blood flow in the vessels supplying the cochlea is reduced to 70% after noise exposure.[24] These basic mechanisms of the action of magnesium were found in experimentally magnesium-deficient animals. These basic mechanisms are also probably operating in men within the normal range of SMg, because in pilots exposed to noise, NIPTS was negatively correlated to SMg.[11] However, from the measured parameters of magnesium metabolism in the present study, it cannot be defined which of the above-reported mechanisms may be involved in the development of NIPTS and what may be the mechanism of the beneficial effect of magnesium supplementation.

In the above-discussed mechanisms, the concentration of free Mg^{2+} in the serum and perilymph during noise exposure would be a decisive parameter. However, only total serum magnesium, EMg, and MMg were measured once before and once after the training in both groups. Free magnesium in serum and consequently in perilymph may be transiently reduced during the noise exposure by a β-adrenergic (stress)-induced increase in free fatty acids that bind free magnesium. This was not measured in the present study. In other studies using healthy men, magnesium supplementation of 2- × 5-mmol magnesium-aspartate-hydrochloride for 10 days had a protective effect against the release of stress hormones (cortisol) during an exhaustive step test without a significant alteration in Smg and Emg.[25] Therefore, that mechanism of beneficial effect of oral magnesium supplementation cannot be explained so far. To date, external hearing protection devices are used to preventing NIPTS. However, selecting, fitting, and wearing procedures are as important as the protectors themselves, needing cooperation and motivation. Moreover, in high-impulse noise exposures, the occluded ear receives sound energy through a variety of transmission paths. Therefore, at a high level of noise exposure, and especially in subjects with high susceptibility, NIPTS can not be excluded despite the use of hearing protectors.

This study has shown that oral magnesium administration may serve as a natural prophylactic agent for preventing NIPTS in subjects exposed to noise. This is especially useful where the use of mechanical hearing protector devices is limited or not applicable.

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