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ORIGINAL

Not only strenuous but also sustained moderate physical effort causes magnesium deficiency

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Key words
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Abstract. Serum magnesium (Mg) concentration (S-Mg), erythrocyte and mononuclear Mg content (E-Mg and M-Mg), were estimated in 35 apparently healthy male Israelis ($\bar{\chi}$ age 19.2, SD 0.4) following 12 months of moderate sustained physical training and again after an 80 km march of 18 h duration (energy expenditure; ≤ 40% of VO_{2max}) i.e. after strenuous effort attenuated in comparison to that studied earlier. Results: Following one year of sustained moderate training the mean S-Mg and M-Mg were significantly decreased compared with non-trainee controls ($p < 0.001$). After the 80 km march, the mean S-Mg rose slightly, but statistically significantly ($p < 0.001$), yet still remained below the mean of the controls ($p < 0.001$). The mean M-Mg decreased significantly after the march ($p < 0.01$). There was a decrease of M-Mg in 77% of the probands; in 46% thereof down to a non-detectable level. The mononuclear cell count decreased by 75%. Conclusion: Mg deficiency (MD) is a sequel not only of strenuous effort as reported earlier, but also of attenuated strenuous effort and of prolonged sustained moderate physical training. The significant fall of the mononuclear cell count in the probands indicates impairment of immune response due to MD. Untreated MD implies, in the long-term, a potentially serious health hazard. Therefore, it is important to try to prevent the occurrence of MD in professional athletes and other exposed individuals, and if present, to treat it early.

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Introduction

A decrease of serum magnesium concentration (S-Mg) immediately after intense sport activity, or mild exercise in a heat chamber, was reported by several authors [Bellar et al. 1975, Rama et al. 1993, Rose et al. 1970] and thought to be transient.

In our studies, we found that the hypomagnesemia seen immediately after the termination of very strenuous effort (a 120 km forced march) was followed by a rebound S-Mg increase at 24 h and a second decrease at 72 h, which was sustained over 3 months [Stendig-Lindberg et al. 1987]. After less severe effort (40 and 70 km forced marches) there was a gradual decrease of S-Mg reaching a maximum at 72 h [Stendig-Lindberg et al. 1989]. The decrease of S-Mg in two other studies was shown to persist throughout an observation time of up to 15 months [Stendig-Lindberg et al. 1991]. This showed that the daily food and water Mg intake was not sufficient to replenish the Mg deficit caused by exertion.

In addition, a 30% increase of serum triglycerides coincided with the peak decrease in S-Mg [Stendig-Lindberg et al. 1987]. On follow-up of this finding in other groups of young men in long-term studies, we confirmed our observation of increase of serum triglycerides and cholesterol and to a lesser degree of blood sugar, parallel to the persistent Mg deficiency (MD) following exertion [Stendig-Lindberg et al. 1989, 1991].

Our finding of the presence of (MD) as a sequel of strenuous effort was confirmed by Deuster et al. [1987] and others, reviewed by Stendig-Lindberg et al. [1995].

The present study was designed to observe the effect on the extracellular and intracellular Mg content of prolonged sustained, moderate physical training of attenuated strenuous effort (i.e. an 80-km march which allowed the

Table 1. Anthropometric data of the probands who participated in the 80-km forced march.

	n	$\bar{\chi}$	SD	Range	95% CI	Units
AGE	35	19.2	0.4	19 – 20	19.2 – 19.5	years
Height	35	176.8	6.7	166 – 192	174.5 – 179.1	cm
Weight	35	76.4	7.6	64.4 – 90.0	73.8 – 79.0	kg

probands to rest 10 min after every 50-min walk and was structured so as not to exceed the participants energy expenditure beyond 40% of their maximal aerobic capacity (VO_{2max}) compared with 40% – 75% VO_{2max} [Galun et al. 1987] in our previous studies [Stendig-Lindberg et al. 1987, 1989, 1991]. The intracellular Mg content was gauged by determining the erythrocyte and mononuclear cell Mg content (E-Mg, respectively M-Mg).

Participants and methods

Thirty-five apparently healthy trained male Israeli subjects, aged 19 – 20 years (Table 1) participated in the study, after giving informed consent. All probands underwent a medical examination to exclude the presence of concurrent disease, were free from medication, alcohol and drug abuse and serious past disease. The protocol for this study was reviewed and approved by the Institution's Ethical Committee of Investigations Involving Human Subjects (and is in accordance with the policy statements of the American College of Sports Medicine). All probands underwent an identical training regime during 12 months and consequently constituted a homogeneous group with respect to aerobic capacity (mean VO_{2max} 65.7 ± 0.6 ml×kg^{-1}×min^{-1}).

On termination of the 12-month physical training, all subjects completed an 80-km march, which started at 07.30 a.m. and terminated after 18 hours. All subjects maintained a similar marching pace of 5 – 6 km×h^{-1}, each carrying a 30 – 40 kg back pack according to body weight. The march consisted of 50-min walking followed by precisely 10-min rest. The predicted energy expenditure based on walking pace, load carried, slope of the path, and the nature of the terrain, was estimated to constitute approximately 40% of the subjects' VO_{2max} [Pandolf et al. 1977]. The maximal ambient temperature was 23° C and the relative humidity 70%. All subjects drank tap water ad libitum or were instructed to drink 900 ml during each hour of the march.

Magnesium intake

Since tap water Mg content is 28 mg/l in Tel-Aviv area and 30 mg/l in Jerusalem [Stendig-Lindberg et al. 1983], the recommended minimum water intake of 16.2 l during the march supplied 470 mg Mg water content. The extrapolated food Mg content was about 300 mg Mg during the march; a total of 770 mg Mg.

Laboratory estimation

Blood was drawn in the sitting position at 07.00 a.m. before the march, after overnight fast using short stasis, and again upon its termination after resting seated for 15 min.

The estimation of S-Mg, M-Mg and E-Mg was carried out according to the methods previously described [Elin and Hosseini 1985, Stendig-Lindberg et al. 1983, 1991]. The coefficient of variation (CV) for the intraassay variability for Mg determinations by atomic absorption spectrophotometry was 2.4%, for the estimates of M-Mg, 8.4% and for E-Mg, 1.7%. Hemoglobin, hematocrit, serum potassium, sodium and CPK, LDH, S-ALAT and S-ASAT enzyme activity were estimated in a standard manner. The mononuclear cell count was carried out in a blood cell counter. The CV for the intraassay variability for the mononuclear cell count was 8.7%.

Statistics

Dependent or independent Student's t-tests, Wilcoxon non-parametric test and Box-Cox test were used whenever appropriate to analyze the data. All data are presented as mean ± SD. The 95% confidence intervals (CI) were calculated. Significance was accepted at $p < 0.05$ level.

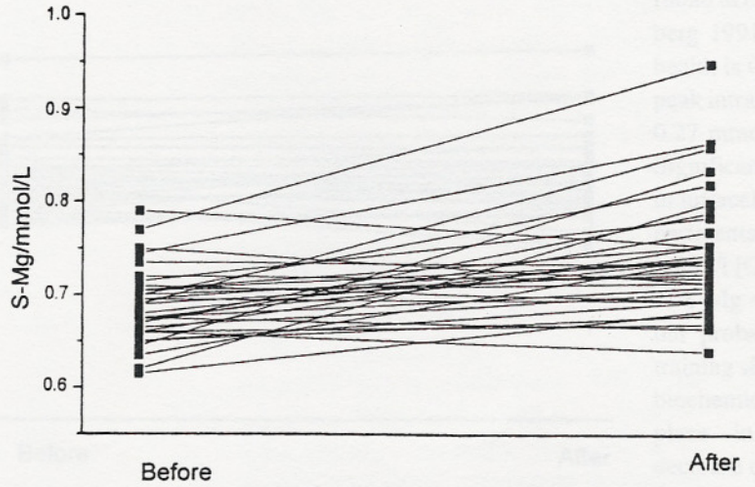

Figure 1. S-Mg before and after the 80-km forced march.

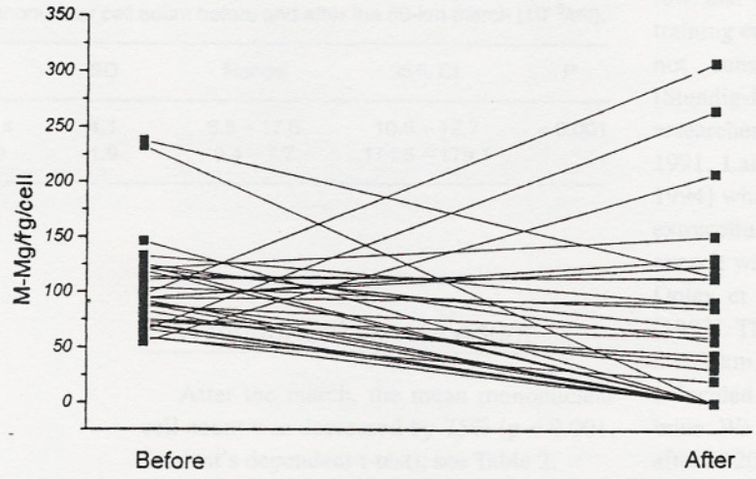

Figure 2. M-Mg before and after the 80-km forced march.

Results

S-Mg

After the 12-month training period and prior to the 80-km march, the mean S-Mg ($\bar{\chi}$ 0.689, SD 0.040, n = 33, range 0.62 – 0.84, 95% CI 0.67 – 0.70) was significantly lower than that of apparently healthy non-training Israeli controls ($\bar{\chi}$ 0.823, SD 0.057, n = 20, range 0.72 – 0.91, 95% CI 0.798 – 0.848, p = 0.001, independent Student's t-test) (Figure 1), and the mean lay below the lower border of the reference range of the controls [Stendig-Lindberg et al. 1991].

After the termination of the march, the mean S-Mg rose slightly, but significantly by 8% ($\bar{\chi}$ 0.746, SD 0.065, n = 33, range 0.64 – 0.95, 95% CI 0.72 – 0.77, p = 0.000; Student's dependent t-test), but remained still significantly lower than the mean S-Mg found in the apparently healthy Israeli non-trainees which served as a control ($p < 0.001$, independent Student's t-test). It lay also markedly below the lower border of the reference interval found in a steady-state (0.82 – 1.06 mmol/l) [Stendig-Lindberg 1991].

M-Mg

After the 12-month training period and prior to the 80-km march, the mean M-Mg was significantly lower than that of 20 apparently healthy non-training Israeli controls ($\bar{\chi}$ 164.8, S.D. 28.3, n = 20, range 125.0 – 221.4, 95%, CI 152.4 – 177.2; p = 0.000, independent Student's t-test).

After the march, there was a decrease of M-Mg in 24/31 (77%) participants; in 11/24 (46%) down to a non-detectable Mg level (Figure 2). Since the M-Mg did not show a normal distribution, the Wilcoxon non-parametric test was applied to compare M-Mg before and after the march. M-Mg after the march ($\bar{\chi}$ 70.5, S.D. 80.4, n = 31, median 56.6, range 0 – 308, CI 70.5 – 80.4) was significantly decreased compared with the baseline value ($\bar{\chi}$ 102.4, SD 42.7, median 94.0, n = 31, range 58.8 – 237.7, 95%, CI 86.7 – 118.0, p = 0.011).

E-Mg

There was no statistically significant difference between the baseline E-Mg and that seen on termination of effort (p = NS, Student's dependent t-test), Figure 3. In one single case there was a decrease to 0 value. This case was an outlier, as confirmed by a Box-Cox test and therefore was excluded from statistical analysis. The baseline E-Mg before the march ($\bar{\chi}$ 2.06, SD 0.20, n = 30, range 1.76 – 2.65, 95% CI 1.99 – 2.12) was virtually the same as that found after the march ($\bar{\chi}$ 2.07, SD 0.24, n = 30, range 1.67 – 2.70, 95% CI 1.98 – 2.16; NS).

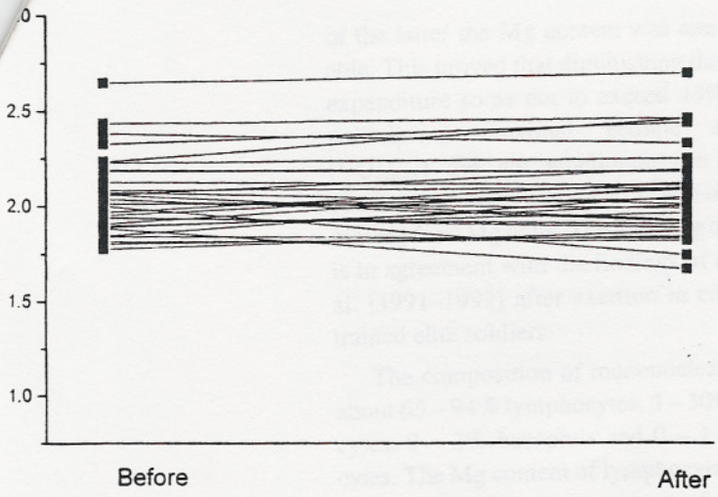

Figure 3. E-Mg before and after the 80-km forced march.

e 2. Mononuclear cell count before and after the 80-km march (10^{-6}/ml).

$\bar{\chi}$	SD	Range	95% CI	P
11.4	4.1	6.5 – 17.6	10.5 – 12.7	< 0.001
2.9	1.9	0.4 – 7.7	174.5 – 179.1	

The mononuclear cell count

After the march, the mean mononuclear cell count was decreased by 75% ($p = 0.001$, Student's dependent t-test), see Table 2.

Discussion

The mean S-Mg and M-Mg of the participants, who underwent 12 months of sustained moderate training, was significantly lower than that of apparently healthy non-training Israeli controls, which showed that even moderate training, sustained over a period of time gives rise to MD. This confirms the findings of Deuster and Singh [1993], who reported progressive lowering of extracellular Mg throughout the period of physical exertion.

It is important to point out that the mean S-Mg in apparently healthy population samples (as well as in experimental animals) is 0.80 – 0.90 mmol/l [Stendig-Lindberg et al. 1983]. The range in health is very narrow, about 0.2 mmol/l. In a steady state it was found to be 0.82 – 1.06 mmol/l [Stendig-Lindberg 1991]. The intraindividual variation in health is 0 – 0.02 mmol/l only. In disease the peak intraindividual variation was found to be 0.27 mmol/l [Stendig-Lindberg et al. 1983]. Significant changes in cell permeability and in intracellular metabolism were found in experimental animals once S-Mg fell below 0.70 mmol/l [Günter 1981]. Consequently, a mean of S-Mg of 0.689 mmol/l which was seen in our probands after 12 months of moderate training signifies that profound biological and biochemical intracellular changes were taking place – in spite of seemingly small numerical decrease of the mean S-Mg.

Immediately following the 80-km march, there was a small increase of the mean S-Mg (8%) which was nonetheless statistically significant although the mean remained still below that of apparently healthy Israeli non-training controls. The rise of mean S-Mg was not consistent with our earlier results [Stendig-Lindberg 1995] and those of other researchers [Deuster et al. 1987, Franck et al. 1991, Laires and Alves 1991, Resina et al. 1994] who reported a significant decrease in extracellular Mg after strenuous effort. However, it was in agreement with the reports of Dolev et al. [1991–1992] and Rama et al. [1993]. The latter attributed it, in his study of a 100-km march, to kidney failure because it coincided with a peak increase of serum creatinine. We interpreted the raised S-Mg at 24 h after a 120-km long march as due to exertional rhabdomyolysis [Stendig-Lindberg et al. 1987]. Two additional explanations can be offered:

- the integrity of the cell membrane is compromised in severe MD, which may lead to a leak of Mg out of the cell (together with potassium, and phosphate and to entry of sodium and calcium [Cronin et al. 1983, Stendig-Lindberg et al. 1977],
- adrenaline is excreted during exertion.

In Mg-deficient subjects, increase in adrenaline causes a rise of S-Mg [Durlach 1988a].

The mean M-Mg, which was already significantly decreased, as a result of the moderate effort of long duration, decreased further after the termination of the 80-km march. The decrease of M-Mg was observed in more than three thirds of the probands and in almost half

of the latter the Mg content was non-detectable. This proved that diminishing the energy expenditure so as not to exceed 40% of the participants maximal aerobic capacity (VO_{2max}) did not ameliorate the MD of strenuous effort in probands consuming about 300 mg food Mg daily. The lowering of M-Mg is in agreement with the findings of Dolev et al. [1991–1992] after exertion in endurance trained elite soldiers.

The composition of mononuclear cells is about 65 – 94% lymphocytes, 5 – 30% monocytes, 0 – 3% basophils and 0 – 1 granulocytes. The Mg content of lymphocytes, which comprise the largest constituent of mononuclear cells, decreases markedly during experimentally induced MD in the rat [Ryan and Ryan 1979]. The degree of lowering of Mg content in the lymphocytes is of the same magnitude as that measured in the skeletal and cardiac muscles [Durlach 1988b]. It can be postulated therefore that the dramatic decrease of M-Mg is indicative of a parallel lowering of myocardial Mg content. This, compounded with the long-term increase in blood lipids which we found to be a long-term sequel of the MD following strenuous effort, could serve as a predisposing factor for ischemic heart disease and possibly serve as an explanation of the sudden death encountered in athletes and others engaged in strenuous effort [Stendig-Lindberg 1992].

Northcote and Ballantyne [Northcote and Ballantyne 1983] revised the causes of sudden death among sportsmen. In 2% it was due to fatal arrythmia and in 73% to coronary disease. Mg maintains ionic balance across cell membrane which counteracts tendency to arrythmias, it regulates vascular smooth muscle tone and inhibits the entry of calcium into the cells, among others, the myocardial cells. Mg exerts, therefore, a cardioprotective effect. Consequently, the severe Mg deficit observed as a result of exertion should be viewed as a potentially serious health hazard, because in the long run it may predispose to either fatal ventricular fibrillation, coronary vasoconstriction or cardiac ischemia, any of which could trigger sudden death during peak effort.

In cases of sudden death during exertion, cardiac biopsy material from the myocardium has not to our knowledge been examined at autopsies for Mg content in order to compare it with the Mg content found on autopsies of non-training, matched for age and sex, apparently healthy victims of sudden death. Only such study could provide us with conclusive evidence, whether the cases of sudden death during exertion with no explanatory gross pathology found post mortem, may not be caused by a sustained, untreated MD of strenuous effort.

The mononuclear cell count after the march was highly significantly decreased by 75%, whereas an increase in white blood cells (WBC) is usually found after exertion. However, a decrease of WBC after a 24-h long 120-km march, which followed an initial increase, was reported and interpreted as partly due to a migration of leucocytes to damaged muscle fibres [Galun et al. 1987].

Experimentally induced MD in the laboratory animals shows an increase in circulating WBC, especially of lymphocytes and in particular T-lymphocytes and an increase in plasma levels of proinflammatory mediators such as prostaglandin (PGE_2) and histamine derived from mast cells and neuropeptides. The latter are interpreted by Weglicki et al. [1996] as the initiators of the focal perivascular inflammatory lesions invariably encountered in experimentally induced MD in all histopathological examinations in experimental animals in all tissues, and described in skeletal muscle in man.

In man, a significant rise in serum immunoglobulin fractions IgG, IgA and IgM and of CD3+ T-lymphocytes and CD19+ B-lymphocytes, parallel to the significant rise in the level of cortisol [Cordova and Alvarez-Mon 1996] was found in athletes after strenuous effort of brief duration, followed by a return to baseline 30 min later.

The significant lowering of mononuclear cell count in our probands suggests a failure of immune defenses, which are mobilized in the presence of neurogenic inflammatory response and immunopathological state due to the MD following strenuous effort [Weglicki et al. 1996].

No action has so far been taken to energetically prevent and/or treat the MD of strenuous effort. The present study shows that even moderate daily training causes in the long run MD in young apparently healthy men, whose daily food Mg content is about 300 mg. Pre-

vention and treatment of MD following strenuous effort and prolonged sustained moderate effort is urgently required in exposed populations to prevent the subsequent detriment to health and amongst others, the impairment of physical capacity due to the association of the extracellular Mg concentration (S-Mg) with the maximal voluntary muscle contraction force [Stendig-Lindberg et al. 1977, 1983].

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