

Trabecular bone density in a two year controlled trial of peroral magnesium in osteoporosis

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Summary: Since magnesium regulates calcium transport, and magnesium replacement in magnesium-deficient postmenopausal patients resulted in unexpected improvement in documented osteoporosis, we investigated the effect of magnesium treatment on trabecular bone density in postmenopausal osteoporosis. Thirty-one postmenopausal patients (mean age \pm SD = 57.6 \pm 10.6 years), consecutively admitted to the Back Rehabilitation Unit with musculoskeletal pain of non-malignant origin and bone density values of ≤ 1.19 g/cm³ (measured by Compton Bone Densitometer), received two to six tablets daily of 125 mg each of magnesium hydroxide (Magnesium Magma USP[®]; 'Mazor', Israel) for 6 months and two tablets for another 18 months in a 2 year, open, controlled therapeutic trial. Twenty-three symptom-free postmenopausal women (mean \pm SD = 61.2 \pm 6.2 years) whose bone density was concurrently assessed at the same laboratory and who were found to have osteoporosis but refused treatment, served as controls. No new fractures occurred. Twenty-two patients (71 per cent) responded by a 1-8 per cent rise of bone density. The mean bone density of all treated patients increased significantly after 1 year ($P < 0.02$) and remained unchanged after 2 years ($P > 0.05$). The mean bone density of the responders increased significantly both after one year ($P < 0.001$) and after 2 years ($P < 0.02$), while in untreated controls, the mean bone density decreased significantly ($P < 0.001$). The disparity between the initial mean bone density and bone density after one year in all osteoporotic patients and in the responders differed significantly from that of the controls (both $P < 0.001$). In 5/31 treated patients (16 per cent), bone density remained unchanged, suggesting an arrest of bone loss. Thus, in a total of 27/31 patients (87 per cent) there was either an increase of bone density or arrest of bone loss. In 4/31 (13 per cent), bone density decreased significantly ($P < 0.01$); all four patients had endocrine diseases which affect magnesium metabolism. Magnesium therapy, which had no ill effects, prevented fractures and resulted in significant increase of bone density in 71 per cent and arrest of bone loss in another 16 per cent of the patients holds great promise in postmenopausal osteoporosis treatment.

Key words: Bone density, magnesium, postmenopausal osteoporosis.

Introduction

Osteoporosis is one of the most important age-associated health hazards for menopausal females¹. Oestrogen therapy prevents bone loss in postmenopausal women, and is a well established prophylactic measure in reducing the frequency of osteoporotic fractures²⁻⁵, although it is not risk-free⁶. Calcium supplements, the most widespread alternative to oestrogen treatment,

have been questioned by Riis *et al.*⁷ and by Stevenson *et al.*⁸. Alternative treatments have been tried with sodium fluoride⁹, but the results have been challenged by Riggs *et al.*¹⁰, with calcitonin¹¹, sodium etidronate¹², vitamin D and its metabolites¹³, and boron¹⁴. The effect of the latter is enhanced in the presence of adequate magnesium¹⁴.

Magnesium has been reported to stabilize amorphous calcium phosphate¹⁵. Magnesium

deficiency, induced in animal experiments, has been shown to reduce bone formation, osteoclastic bone resorption and osteoid mineralization rates^{16,17}.

In humans, the mean serum magnesium concentration, which among premenopausal women has been found to be positively correlated with bone mineral content¹⁸, has been reported by some authors to be significantly decreased in well documented osteoporosis¹⁹.

Clinical observation by one of us (G.S.-L.) revealed that long term magnesium supplementation given to magnesium-deficient postmenopausal women resulted in a global subjective improvement in cases of postmenopausal osteoporosis. In order to validate this patient-relayed information and to gauge the possible value of magnesium treatment, we assessed its effect on trabecular bone density in postmenopausal osteoporotic women with well documented bone density loss in a prospective, two year, open, controlled therapeutic trial.

Subjects and methods

Subjects

Thirty-one female postmenopausal patients (mean age \pm SD = 57.6 \pm 10.6 years) entered the study. They were consecutively admitted to the Back Rehabilitation Unit of Ichilov Hospital with musculoskeletal pain of non-malignant origin and an initial bone density value below the reference range (≤ 1.19 g/cm³), measured at the ultra-distal radius with Compton bone densitometry²⁰. All patients were free of diseases which preclude magnesium treatment (kidney disease, hypotension, A-V block or myasthenia gravis). None of the patients received any medication for osteoporosis throughout the trial. All subjects gave informed consent after the nature of the study was fully explained.

X-ray evidence of osteoporosis, assessed by the criteria of Smith and Rizek²¹, was found in 17 cases (55 per cent) and compression fractures in four (13 per cent). The low incidence of bone fractures suggests that the patients, in spite of their low bone density, had developed osteoporosis relatively recently.

All patients complained of chronic back pain, and the majority also complained of bone pain. In 30/31 patients (97 per cent), osteoarthritis of cervical, dorsal and/or lumbar spine was found

in addition to osteoporosis. In 17 patients (55 per cent), spinal deformities, i.e. cervical hyperlordosis, scoliosis, kyphosis, gibbus, etc., were also present.

Twenty-three symptom-free postmenopausal women, matched for age (mean age \pm SD = 61.2 \pm 6.2 years) served as controls. They all came for assessment of bone density on two consecutive years during the period of the study, due to the increased public awareness of osteoporosis risk. Their bone density values, assessed by the same technique as used in the patients, were below the reference range, i.e. ≤ 1.19 g/cm³. Although they were told that they had osteoporosis, they refused any treatment.

Trabecular bone density measurements

The absolute mass density of trabecular bone tissue at the ultra-distal radius of the forearm was measured at the Jerusalem Osteoporosis Centre using a Compton bone densitometer (CBD) which determines the bone density to an accuracy of about 1 per cent²⁰ and a precision of 1 per cent (calculated as the coefficient of variation [CV; SD/mean \times 100] of short term consecutive measurements). The CBD is based on Compton gamma ray scattering from the bone; since the fraction of Compton scattered photons from the tissue is directly related to its mass density, this method yields an overall volumetric analysis of bone density in grams per unit volume (g/cm³) of bone^{20,22}. The results are unaffected by the dimensions of bone cross-section, because the measurement is confined to a small specific volume within the bone. A scanning device along two axes enables the measurement to be confined to regions consisting of pure trabecular bone tissue, which, due to its high metabolic turnover, responds at a very early stage to any metabolic changes. Our choice of use of the CBD for bone density assessment in this study was dictated, among other factors, by our preference for the relatively safe ultra-distal radius exposure to gamma rays, rather than an exposure of the axial skeleton. The bone density measurement by CBD at the ultra-distal radius showed a comparable degree of sensitivity to bone loss to that demonstrated by the assessment of bone mineral changes in the lumbar spine, measured by dual-X-ray absorptiometry^{23,24}. The bone density estimation was carried out in parallel with clinical assessment and laboratory screening.

Laboratory assays

Blood was sampled at 8:00–10:00 a.m. after an overnight fast. Brief stasis was used during venepuncture. Serum magnesium and 24 h urinary magnesium concentrations were measured twice at an interval of one week, and estimated in duplicate by atomic absorption spectrophotometry on a Perkin Elmer absorption spectrophotometer No. 305 A²⁵. These measurements were made prior to the trial, every 3 months during the first year, and every 6 months during the second. Serum and 24 h urinary sodium, potassium, calcium, phosphate, creatinine and serum alkaline phosphatase activity were measured as well.

Design of the therapeutic trial

All the treated patients received Mg(OH)₂ tablets (Magnesium magma USP tablets; 'Mazor', Israel) containing 125 mg magnesium per tablet in an open, age-matched, controlled study.

The treatment started with two Mg(OH)₂ tablets (250 mg magnesium) to be chewed on an empty stomach at bedtime. In case of diarrhoea, the treatment was discontinued for 8 d, and then resumed with only one tablet (125 mg magnesium). The dosage was increased according to individual tolerance levels, to reach a maximum of two tablets three times daily (750 mg magnesium)). The maximum dose was given for 6 months, followed by a maintenance dose of two tablets once daily (250 mg magnesium) for another 18 months.

The patients were asked to complete a compliance chart during the first three months, and were told to bring all the empty medicine containers to the clinic throughout the course of treatment so that the amounts taken could be controlled. The estimated daily food magnesium content of the patients was 200–300 mg²⁶.

Statistical analyses

Means, standard deviations and 95 per cent confidence intervals (CI) for the means were calculated. Paired Student's *t* tests, independent *t* tests and Pearson correlation coefficient matrix were used for statistical analyses.

Results

No patients withdrew from the trial during the first year, but only 10/31 (32 per cent) returned for examination at the end of two years. There

were no reported side effects of the treatment. No new fractures occurred in the treated patients. The mean trabecular bone density in treated patients showed a significant increase after the first year of treatment ($P < 0.02$) and no change after the second year ($P > 0.05$; paired Student's *t* test, Table 1).

Table 1. Trabecular bone density (BD) of patients and controls

Patients	Mean	SD	n	Range	95 per cent CI for the mean	P value
BDI	1.09	0.04	31	1.02–1.18	1.08–1.10	
BDII	1.11	0.04	31	1.02–1.20	1.10–1.12	< 0.02
BDIII	1.11	0.03	10	1.07–1.15	1.09–1.13	> 0.05

Reference interval for trabecular bone density: ≤ 1.19 g/cm³. BDI = initial measurement, BDII = after one year, BDIII = after two years. *P* = probability of statistical difference tested by Student's paired *t* tests.

On further analysis, we found that 22/31 of the treated cases (71 per cent) responded by a rise of bone density (Table 2). The initial mean trabecular bone density (BDI) of the responders was significantly increased, both after 12 months (BDII) and after 24 months (BDIII) ($P < 0.001$ and $P < 0.02$, respectively; paired Student's *t* test). In 18/22 of the responders (82 per cent), the increase was 2–8 per cent, (clearly exceeding the margin of error for the CBD measurement), and in the remaining 4/22 cases (10 per cent) it was 1 per cent.

In another 5/31 cases (16 per cent), the bone density measurements remained unchanged ($P > 0.05$). These cases were referred to as 'stationary' (Table 2), since in untreated cases the bone density should have decreased, as seen in our controls. Consequently, in 27/31 of the treated patients (87 per cent), there was either an improvement or an arrest of the disease.

Four of 31 patients (13 per cent) showed a 2–6 per cent decrease in bone density and a significant decrease of mean bone density ($P < 0.01$, paired Student's *t* test; Table 2) despite treatment. All four had endocrine disorders: one had had a thyroidectomy and three were hyperparathyroid. These four cases were referred to as 'non-responders' (Table 2).

In the 23 age-matched, untreated, osteoporotic controls, the mean bone density on re-examination one year after the initial measurement was highly significantly decreased ($P < 0.001$, paired Student's *t* test; Table 2). In 17/23 controls (74 per cent) there was a 1–3 per cent decrease of

bone density values, in 5/23 (22 per cent) there was no change, and in 1/23 (4 per cent) there was a 1 per cent increase.

Table 2. Trabecular bone density (BD) among the patient subgroups and controls

	Mean	SD	n	Range	95% CI for the mean	P value
Responders						
BDI	1.08	0.04	22	1.02–1.18	1.063–1.097	<0.001
BDII	1.11	0.04	22	1.02–1.20	1.093–1.127	
BDIII	1.12	0.02	6	1.10–1.15	1.104–1.136	
Stationary						
BDI	1.12	0.03	5	1.07–1.15	1.094–1.146	NS
BDII	1.11	0.03	5	1.07–1.15	1.084–1.136	
BDIII	1.09	0.03	3	1.07–1.12	1.056–1.124	
Non-responders						
BDI	1.10	0.04	4	1.07–1.15	1.061–1.139	0.01
BDII	1.07	0.04	4	1.02–1.12	1.031–1.109	
BDIII	1.08	-	1	-	-	
Controls						
BDI	1.15	0.03	23	1.08–1.19	1.138–1.162	<0.001
BDII	1.14	0.03	23	1.07–1.19	1.128–1.152	

Reference value for trabecular bone density: $\leq 1.19 \text{ g/cm}^3$. BDI = initial measurement, BDII = after one year, BDIII = after two years. NS = non significant. P = probability of statistical difference tested by Student's paired *t* test.

The disparity between BDI and BDII values of the treated patients, as well as of the responder group, differed highly significantly from that of the untreated controls ($P < 0.001$, independent Student's *t* test; Table 3).

No significant correlation was found between the bone density values and any of the other laboratory measurements.

The means, SD, n, reference values, and 95 per cent CI for the mean of initial and final laboratory values of the patients are given in Table 4.

Hypercalciuria (urine calcium $> 6.3 \text{ mmol/24 h}$) was initially found in 12 treated patients (39 per cent), hypomagnesaemia ($< 0.75 \text{ mmol/litre}$) in 11 (35 per cent), and reduced urine magnesium ($< 4.0 \text{ mmol/24 h}$) in 11 (35 per cent). Sideropenia was found in two cases (6 per cent). Serum alkaline phosphatase activity and serum phosphate concentration were each decreased in one case (3 per cent).

On final laboratory estimation, the only significant change was the increase found for serum magnesium and urine magnesium ($P < 0.01$;

paired Student's *t* test; Table 3). Hypercalciuria was still present in four patients, hypomagnesaemia in three, and one patient still had a low urine magnesium.

Discussion

Among other things, magnesium regulates active calcium transport. Consequently, there has been a growing interest in its possible role in bone metabolism²⁷. Magnesium may play a decisive role in the regulation of bone metabolism, even though the mechanism is not currently fully understood. A recent study²⁸ showed that magnesium deprivation in the rat lowered circulating calcitonin levels, and the experimental animals concurrently showed disorganized bone remodelling. This finding gains significance in the light of a comparative study of drug effects on fracture prevention in postmenopausal women which showed that calcitonin significantly reduces osteoporotic fracture risk²⁹. Magnesium affects the binding of the bone-specific proteins, e.g., osteocalcin protein to hydroxyapatite³⁰. Other possible ways in which magnesium may affect bone remodelling are: (1) its ability to safeguard the integrity of the bone protein matrix, since it is involved in protein and amino acid synthesis; (2) its possible effect on the regulation of osteoclast function through changes of intracellular calcium ion concentration³¹; (3) its regulatory effect

Table 3. Mean differences between BDI and BDII in all treated patients compared with controls and in responders compared with controls

(a) Comparison of mean differences between BDI and BDII in patients and controls				
	Mean	SD	n	P value
All treated patients	+0.013	0.029	31	< 0.001***
Controls	-0.010	0.009	23	
(b) Comparison of mean differences between BDI and BDII in responders and controls				
	Mean	SD	n	P value
Responders	+0.026	0.021	22	< 0.001***
Controls	-0.010	0.009	23	

***Independent Student's *t* test.

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Table 4. Laboratory constituents before beginning of trial and on completion; n = 26 patients

	Before the trial				After the trial				
	Mean	SD	Range	95% CI for the mean	Mean	SD	Range	95% CI for the mean	Reference values
Serum Mg (mmol/litre)	0.773	0.107	0.493-0.946	0.753-0.793	0.881**	0.115	0.699-1.131	0.837-0.925	0.75-0.94
Serum Ca (mmol/litre)	2.33	0.52	2.25-2.75	2.12-2.53	2.42	0.58	2.25-2.58	2.20-2.64	2.20-2.60
Serum phosphate (mmol/litre)	1.16	0.17	0.77-1.55	1.09-1.23	1.18	0.20	0.81-1.78	1.10-1.26	0.81-1.60
Serum creatinine (μ mol/litre)	77.8	12.4	53.0-106.1	73.03-82.57	71.6	17.7	42.2-97.2	64.6-78.4	< 120
Serum alkaline phosphatase (IU/litre)	65.4	17.4	45.0-120.0	58.71-72.08	64.1	17.4	32.0-97.0	57.41-70.78	30-85
24 h urine Mg (mmol)	3.66	1.63	0.52-7.86	3.03-4.29	5.43**	1.97	1.81-9.46	4.67-6.18	4.0-6.2
24 h urine Ca (mmol)	4.33	2.18	1.79-10.60	3.49-5.17	4.33	2.42	1.00-8.70	3.40-5.26	2.5-6.2
24 h urine phosphate (mmol)	26.64	10.11	4.84-50.05	22.75-30.53	27.80	11.04	14.30-59.09	23.56-32.04	29.1-42.0
24 h urine creatinine (mmol)	11.29	2.28	6.19-14.67	10.41-12.16	10.13	3.99	5.39-24.75	8.60-11.66	9.3-16.1

** $P < 0.01$; the remaining variables did not differ significantly on comparison of values 1 and 2 (paired Student's t test).

on calcium transport^{27,32,33}; and (4) its effect on osteoblast function^{33,34}.

The identification of the distribution of the $\text{Ca}^{2+}/\text{Mg}^{2+}$ -ATPase in the osteoblasts of growing bone cells of chick tibias³², as well as the localization of a $\text{Ca}^{2+}/\text{Mg}^{2+}$ -ATPase calcium pump (which is similar to that found in human erythrocytes) in human osteoblast-like cells, suggests a role for this enzyme in intracellular calcium homeostasis in the osteoblast³³. A calmodulin-sensitive $\text{Ca}^{2+}/\text{Mg}^{2+}$ -ATPase, demonstrated in the plasma membrane and thought to affect the ionic control of osteoblastic function, was shown to have an absolute requirement for magnesium ions³⁴. The latter accelerate the phosphorylation by ATP of the plasma membrane calcium pump, apparently by a direct action³⁵.

The choice of $\text{Mg}(\text{OH})_2$ in tablet form as the magnesium vehicle to be used in the trial was based on long term clinical experience of its use in the treatment of magnesium deficiency³⁷⁻³⁹. Although not the ideal vehicle, since it is an antacid, it is widely available and safe when used in a strictly controlled manner.

Anticipated lowering of bone density with age, without treatment, is about 2-3 per cent annually⁴⁰. This agrees with our findings in the

treated controls, as well as with an earlier CBD study which showed that untreated postmenopausal women had a 10 per cent mean decrease of bone density over a period of 10 years²².

The CBD measurement in the distal radius is advantageous because the common extraskelatal calcification of the lumbar spine and aorta, which distorts the results of measurements in the axial skeleton, is absent. The capability of measuring precisely the absolute density of trabecular bone tissue²⁰ is another advantage of the bone density assessment technique using CBD. It allows the performance of clinical studies to diagnose the early effect of age and metabolic skeletal disorders on bone status²², to estimate atraumatic fracture risk²⁴, and to pinpoint the effect of therapeutic intervention on bone remodelling at early and advanced age⁴¹.

In our study, the mean bone density of the 31 treated patients increased significantly after the first year and remained stationary after the second, whereas mean density in the 23 untreated controls, who were measured concurrently at the same centre, using the same technique and the same time interval, was highly significantly decreased after one year. Furthermore, the disparity between BDI and BDII values of the treated

patients differed highly significantly from that of the age-matched osteoporotic controls. We conclude therefore that the increase in bone density was due to the treatment.

The absence of a further increase of mean bone density after the second year in the treated patients ($n = 31$) may have been due to (1) the decrease of magnesium dosage after 6 months of the trial, (2) the small number of patients who persisted throughout the second year ($n = 10$), or (3) the fact that one of the four non-responders was among those 10 patients.

On close analysis we found in 22/31 of the treated patients (71 per cent), the responders; a highly significant increase of bone density after both 12 and 24 months.

In another 5/31 treated patients (16 per cent), the absence of a significant change between mean BDI, BDII, and BDIII suggests an arrest of the disease, since in the absence of treatment a decrease would have been anticipated.

Thus in 27/31 of the treated patients (87 per cent) there was an improvement, or an arrest of the disease, which could be ascribed to the treatment, leaving four patients (13 per cent) who did not respond.

The four non-responders (Table 2) all had endocrine disorders in addition to involutional osteoporosis. One case had had a thyroidectomy and three were hyperparathyroid; both conditions are known to cause secondary osteoporosis⁴². It is possible that the lack of response to treatment may have been due in the former case to the presence of osteocalcin deficiency⁴², combined with the intracellular magnesium deficiency known to occur in hypothyroidism⁴³, while in hyperparathyroidism, the tendency to hypercalciuria and magnesuria inherent in this condition could cause inadequate conservation of magnesium. Consequently, these patients may have required a more intensive and prolonged magnesium repletion than that provided in our study³⁹.

No side effects were observed due to treatment. No new fractures occurred after treatment began. In addition, the majority of patients voiced subjective improvement and experienced a decrease in pain, beginning 6–12 months after the start of treatment. The subjective sense of improvement may have been the cause for the increasing drop-out rate during the second year of the trial. There was also a parallel and significant increase in serum and 24 hour urinary magnesium concen-

tration in the treated patients, most of whom were initially magnesium-deficient.

The overall impression is that the results are most encouraging, suggesting that magnesium therapy in postmenopausal osteoporosis holds great promise.

Driessens *et al.*⁴⁴ gave magnesium lactate in different types of osteoporosis and reported decreased back pain and increased mobility, while Abraham and Grewal⁴⁵ gave magnesium in the form of a dietary programme, combined with hormonal therapy, and claimed a significant increase in the density of calcaneous bone as measured by single photon absorptiometry.

Further studies are needed to establish the optimal magnesium vehicle, dosage, and duration of treatment.

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Densité osseuse trabéculaire au cours d'un essai contrôlée de deux ans de traitement par le magnésium *per os* dans l'ostéoporose

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Résumé: Puisque le magnésium (Mg) régule le transport du calcium et qu'une supplémentation magnésique chez des femmes post-ménopausiques Mg- déficientes amène une amélioration inattendue dans d'authentiques ostéoporoses, nous avons étudié l'effet d'une magnésothérapie sur la densité osseuse trabéculaire (BD) dans des ostéoporoses post-ménopausiques. 31 patientes en post-ménopause (âge moyen \pm ISD: 57.6 ± 10.6 ans) ont été admises à l'unité de Réhabilitation du Dos, avec des douleurs musculosquelettiques d'origine non cancéreuse et des valeurs de BD ≤ 1.19 g/cm³ (mesurées par le Densitomètre Osseux de Compton). Elles ont reçu 2 à 6 comprimés de 125 mg d'hydroxyde de Mg (Magnesium Magma USP, Mazor, Israël) pendant 6 mois, 2 comprimés pendant les 18 mois consécutifs: soit un essai, 'en ouvert', de 2 ans de magnésothérapie contrôlée. 23 femmes en post-ménopause (âge moyen \pm ISD: 61.2 ± 6.2 ans), qui faisaient à cette même période évaluer leur BD dans le même laboratoire et présentaient aussi une ostéoporose mais qui avaient refusé le traitement, ont servi de témoins. Aucune fracture nouvelle n'a été observée. 22 (soit 71 per cent) des patientes ont répondu au traitement par une augmentation de 1 à 8 per cent du BD. Le BD moyen des 'répondeurs' a augmenté significativement tant après 1 an (BD II) ($P < 0.001$) qu'après 2 ans (BD III) ($P < 0.02$). La disparité entre la BD moyenne initiale et la BD II des 'répondeurs' et celle des témoins a différé significativement ($P < 0.0001$). Chez 5 des 31 patientes (16 pour cent), la BD est demeurée inchangée suggérant un arrêt de la perte osseuse. Ainsi sur un total de 27/31 malades (87 pour cent) il y a eu soit une augmentation de la BD ou un arrêt de la perte osseuse. Chez 4 des 31 malades (13 pour cent), la BD a diminué significativement; tous ces 4 malades présentaient des endocrinopathies qui affectent le métabolisme du Mg. Ainsi la magnésothérapie, qui n'a exercé aucun effet secondaire, a été capable de prévenir les fractures et elle a entraîné une augmentation significative de la BD dans 71 pour cent des cas et un arrêt de la perte osseuse dans 16 autres pour cent des cas. Elle semble donc représenter une thérapeutique prometteuse dans le traitement de l'ostéoporose post-ménopausique.

Mots clés: Densité osseuse, magnésium, ostéoporose post-ménopausique.

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