Chapter 11

A two year controlled Therapeutic trial of Peroral Magnesium in Osteoporosis

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Introduction

Osteoporosis is an important health hazard for menopausal females (Avioli, 1983).

Calcium medication the most widely used treatment method, has recently been questioned by Riis et al. (1987) and by Stevenson et al. (1988). Estrogen therapy, which prevents bone loss and osteoporotic fractures in postmenopausal women (Lindsay et al, 1976, Christiansen et al 1980, Savvas et al, 1988) is not without risk (Bennet, 1987). Also the treatment with sodium flouride (Mammelle, 1988) has been questioned by Riggs et al (1990). Other treatments used were calcitonin (Hesch, et al, 1989) sodium etidronate, (Watts et al, 1990) vitamin D and its metabolities (Reichel et al, 1983) and boron, the effect of which is enhanced in the presence of adequate magnesium (Mg) (Nielsen, 1990). The effect of Mg on skeletal metabolism has been recently revised by wallach (1990).

Observations over time suggested that a long term Mg substitution administered to Mg deficient postmenopausal women, resulted in a global clinical improvement, in patients with postmenopausal osteoporosis.

In order to validate this patient-relayed information and to be able to assess the possible value of Mg treatment, we examined its effect on trabecular bone density (BD) in postmenopausal osteoporotic women with documented BD loss, in a controlled prospective two-year open study therapeutic trial.

Material and Methods

Thirty-one patients, (a mean age of 57.6±10.6 years) suffering from musculoskeletal pain of non-inflammatory and non-malignant origin, consecutively admittd to Back Rehabilitation Unit of Tel-Aviv Sourasky Medical Center and whose initial trabecular bone density BD (BDI) was<1.19g/cm^3, were included in the study. The BD was measured at the ultra-distal radius with Compton Bone Densitometry (Leichter et al, 1987, Simkin and Ajalon, 1990) at the Jerusalem Osteoporosis Center. None suffered from kidney disease, hypotension, A-V block or myasthenia gravis, which contraindicate Mg treatment. All patients gave informed consent.

All patients complained of chronic back pain. The majority of the patients complained of bony pain. X-ray evidence of osteoporosis, using the criteria of Smith and Rizek (1966), was found in 17 cases (55%) and compression fractures in 4 (13%).

Twenty three sympton-free age matched post menopausal women (mean age 61.2±6.2 years) served as controls. They came to assess their BD during the time of the trial, on two consecutive years, and although they were found to have osteoporosis (BD < 1.19g/cm^3), they refused treatment.

Blood was sampled after a brief stasis at 8:00-10:00 am after an overnight fast. Serum Mg (S-Mg) and 24 hour urinary Mg (U-Mg) concentrations were examined twice each time at an interval of one week, and estimated in duplicate on a Perkin Elmer atomic absorption spectrophotometer No. 305 A (Stendig-Lindberg et al, 1984) and every 3 months during the first year and every 6 months during the second. Twenty-four urinary sodium, potassium, calcium (U-Ca), phosphate (U-P) and urinary creatinine (U-Cr) were measured as well.

All the treated patients received Magnesium Magma USP tablets: ("Mazor", Israel) containing 125 mg Mg per tablet in an open study design therapeutic trial.

In case of diarrhoea, the treament was discontinued for 8 days, and then resumed with 125 mg Mg only. The dose was titrated upwards, according to individual tolerance levels, to reach a maximum of 750 mg Mg. This dose was given for six months, followed by a maintenance dose of 250 mg Mg for another 18 months.

In order to check complaince, the patients had to fill a compliance chart during the first three months, and to bring all the empty medicine containers to the clinic throughout the course of treatment so that the amounts taken could be controlled.

Results

There were no patient drop-outs during the first year of therapy, but 10 (32%) only returned for checkup at the end of two years.

There were no side-effects due to treatment. No new fractures occurred after its

commencement. In addition, the majority of patients voiced subjective improvement and experienced a decrease in pain beginning 6-12 months after treatment commenced. The subjective sense of improvement may have caused the increasing drop-out rate during the second year of the trial.

There was a statistically significant increase of BD in 22/31 responders after 12 months of treatment ($p<0.001$, Student's paired t-test), and after 24 months ($p<0.02$).

In the 22 responder cases (71%), the trabecular BD increased by the end of the trial by 1-8%. In another 5/31 treated cases (16%) it remained unchanged, Thus in 27 patients (87%), there was either an improvement or an arrest of the disease attributable to the treatment. Four (13%) patients showed a 2-6% decrease in BD despite treatment; all four had endocrine disease, one was thyroidectomized and three were hyperparathyroid.

In the 23 age matched, untreated osteoporotic controls, the decrease of BD values after one year was highly statistically significant ($p<0.001$, Student's paired t-test). After one year, there was a 1-3% decrease of BD values in 17 controls (74%), no change in five (22%) and a 1% increase in one (4%).

The degree of change between the initial BD (BDI) and BD values of one year later (BDII) in the treated patients differed highly significantly from that in the controls ($p<0.001$, Independent Student's t-test).

No correlation was found between the BD values and any of the laboratory constituents.

A significant increase was found for S-Mg following treatment ($p<0.01$).

Discussion

Twenty two of thirty one (71%) patients responded by a significant rise of BD on reexamination after 12 and after 24 months of treatment, whereas the BD of age matched osteoporotic controls decreased significantly after one year.

Another 5/31 (16%) treated cases showed no change on BD following treatment, but, since in postmenopausal untreated cases, a lowering is known to occur, as seen in our controls, our interpretation was that absence of change signified an arrest of bone loss.

Consequently, in 27/31 (87%) Mg treated postmenopausal osteoporotics there was a rise of BD or arrest of bone loss.

The four non-responders suffered from endocrine diseases in addition to involutional osteoporosis. One was thyroidectomized and three were hyperparathyroid; both are diseases known to cause secondary osteoporosis (Riggs and Melton, 1986). The lack of response to treatment may have been due in one case to the presence of osteocalcitionin deficiency (Riggs and Melton, 1988) Combined with the intracellular Mg deficiency known to occur in hypothyroidism. In the hyperparathyroid patients the tendency to

hypercalciuria and magnesuria interfere with adequate conservation of Mg. Consequently, these patients may require a more intensive, prolonged Mg repletion not envisaged in the present study.

No new fractures occured in the treated patients and no ill side effects of Mg treatment were reported.

The result suggest that Mg therapy in postmenopausal osteoporosis is most promising. Recently, Driessens et al, (1990), tried Mg lactate in different types of osteoporosis and reported decreased back pain and increased mobility, while Abraham and Grewak, (1990) gave Mg in the form of a dietary program, combined with hormonal therapy and claimed a significant increase in the density of calcaneous bone measured by a single photon absorptiometry.

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

References

Abraham, G.E. & Grewal, H. (1990): A total dietary program emphasising magnesium instead of calcium. Effect on te mineral density of calcenous bone in postmenopausal women on hormone therapy. J. Reprod. Med. 35, 503-507.

Avioli, L.V. (1983): The osteoporotic syndrome: detection, prevention and treatment. New York: Grune and Stratton.

Bennet, R.W. (1987): Osteoporosis. U.S. Pharmacist. 12, 56-72.

Christiansen, C., Christiansen, M.S., McNair, P., Hagen, C., Stacklund, K.E.& Transbol, I. (1980): Prevention of early postmenopausal bone loss in controlled 2-year study in 315 normal females. Eur. J. Clin. Invest. 10, 273-279.

Hesch, R.D., Busch, U., Proskop, M., Delling, G. & Rittinghaus, E.F. (1989): Increase of vertebral density by combination therapy with pulsatile 1-38 hPTH and sequential addition of calcitonin nasal spray in osteoporotic patients. Calcif. Tissue Int. 44, 176-180.

Leichter, I., Bivas, A., Giveon, A., Margulies, J.Y. & Weinreb, A. (1987): Therelative significance of trabecular and cortical bone density as a diagnostic index for osteoporosis. Phys. Med. Biol. 32, 1167-1174.

Leichter, I., Simkin, A., Margulies, J.Y., Bivas, A., Steinberg, R., Giladi, M. & Milgram C. (1989): Gain in mass density of bone following strenuous physical activity. J. Orthop. Res. 7, 86-90.

Lindsay, R., Hart, D.M., Aitken, J.M., MacDonald, E.B., Anderson, J.B. & Clarke, A.C. (1976): Long-term prevention of postmenopausal osteoporosis by estrogens: evidence for an increased bone mass after delayed onset of estrogen treatment. Lancet. 1, 1038-1040.

Mamelle, N. (1989): Risks and benefits of treatment with sodium flouride of osteoporosis with vertebral collapse. Rev. Prat. 39, 237-238.

Nielsen, F.H. (1990): Studies on the relationship between boron and magnesium which possibly affects the formation and maintenance of bones. Magnesium Trace Elem. 9, 61-69.

Reichel, H., Koeffler, P. & Norman, A. (1983): The role of the vitamin D endocrine system in health and disease. N. Engl. J. Med. 320, 980-991.

Riggs, B.L., Hodgson, S.F., O'Falloh, W.M., Chao, E.Y.S., Wahner, H.W., Muhs, J.M., Cedel, S.L. & Melton L.J. (1990): Effect of fluoride treatment on the fracture rate in postmenopausal women with osteoporosis. New. Engl. J. Med. 322, 802-809.

Riggs, B.L. & Melton, J.L. III. (1986): Involutional osteoporosis. N. Engl. J. Med. 314, 1676-1676.

Riggs, B.L. & Melton J.L. III, eds. (1988): Osteoporosis: etiology. Diagnosis and management. New York: Raven Press, pp. 155-177.

Savvas, M., Studd, J.W.W., Fogelman, I., Dooley, M. & Montgomery, B. (187): Skeletal effects of oral oestrogen compared with subcutaneous oestrogen and testosterone in postmenopausal women. BMJ. 297, 331-334.

Riis, B., Thomsen, K. & Christiansen, C. (1987): Does calcium supplementation prevent postmenopausal bone loss? N. Engl. J. Med. 316, 173-177.

Simking, A. & Ayalon, J. (1990): Bone loading, the new way to prevent and combat the thinning bones of osteoporosis. London: Privon, 132.

Smith, R.W. & Rizek, J. (1966): Epidemiologic studies of osteoporosis in women in Puerto Rico and southeastern Michigan with special reference to age, race, national origin and other related or associated findings. Clin. Orthop. 45, 31-47.

Stendig-Lindberg, G., Rudy, N., Penciner, J.G. & Wacker, W.E.C. (1983): Comparison of dilutents for serum magnesium estimation by AA Spectophotometry. Magnesium Exp and Clin. Res. 3, 50-56.

Stevenson J, Whitehead, M.D., Padwick, M. Et al. (1988): Dietary intake of calcium and postmenopausal bone loss, BMJ, 297, 15-17.

Wallach, S. (1990): Effects of magnesium on skeletal metabolism. Magnesium Trace Elem. 9, 1-14.

Watts, N.B., Harris, S.T. & Genant, H.K. et al. (1990): Intermittent cyclical etidronate treatment of postmenopausal osteoporosis. New Engl. Med. 323, 73-79.