Effect of nandrolone decanoate and 1-α-hydroxy-calciferol upon magnesium plasma levels in postmenopausal osteoporotic women

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Zusammenfassung

Das erste Ziel dieser Studie war, die Mg-Werte im Serum zwischen osteoporotischen und nicht-osteoporotischen Frauen in der Menopause zu vergleichen und das zweite, die Auswirkung von zwei knochenaktivierenden Medikamenten (Nandrolone und Calciferol) auf die Mg-Werte bei osteoporotischen und nicht-osteoporotischen Frauen darzustellen. Das Krankengut betrug 40 nicht-osteoporotische und 77 osteoporotische Frauen. Zunächst wurden die Mg-Werte in beiden Patientengruppen gemessen und miteinander verglichen. Anschließend wurden die 77 osteoporotischen Frauen in eine prospektive randomisierte Studie eingeschlossen und mit 50 mg Nandrolone bzw. mit 1µg 1-α-hydroxy-calciferol behandelt. Die Ergebnisse zeigten: 1. Daß in Altersgruppen von 51 bis 70 Jahre die Mg-Werte signifikant niedriger bei osteoporotischen als bei nicht-osteoporotischen Frauen sind. 2. Daß Frauen, behandelt mit 1-α-hydroxy-calciferol erhöhte Mg-Werte gegenüber den mit Nandrolone behandelten Frauen aufweisen. Aus dieser Studie kam heraus, daß der Magnesiumspiegel sowohl zur Diagnostik der Osteoporose als auch zur Auswertung des Langzeiteffekts bei der Behandlung osteoporotischer Frauen mit knochenaktivierenden Medikamenten dient.

Summary

The aims of this study were to evaluate the differences in serum magnesium levels between postmenopausal osteoporotic and non-osteoporotic women in specific age groups, as well as to ascertain the influence of two bone active drugs upon serum Mg levels in postmenopausal osteoporotic women. We measured serum Mg levels in 40 non-osteoporotic and 77 osteoporotic women. The osteoporotic women were included in a two-year double-blind prospective clinical study and treated either with 50 mg nandrolone decanoate, or with 1µg 1-α-hydroxy-calciferol. Our results showed that, postmenopausal osteoporotic women aged 51 - 70 had significant lower serum Mg levels than age matched non-osteoporotic postmenopausal women. 1-α-vitamin D_3 increased significantly serum Mg during the 2nd year of therapy in osteoporotic patients aged 51 - 70. It is concluded that, serum Mg could serve as an index for the establishment of postmenopausal osteoporotic patients, as well as for the monitoring of the therapeutic response to bone active drugs in patients below 70 years old.

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Introduction

Magnesium makes up 0.5 - 1 % of bone ash and influences both mineral and matrix metabolism in bone by a combination of effects on hormones and other factors that regulate skeletal and mineral metabolism and by direct effects on bone itself [1]. Postmenopausal osteoporosis has been reported to be associated with decreased bone magnesium content expressed both per unit weight of fat-free dry bone and per unit volume of bone tissue [2, 3]. The fact that lower than normal bone magnesium concentrations were found in osteoporotic women during the active phase of their disease indicates low total body magnesium stores in active osteoporosis. Over the last years a growing interest for the role of serum magnesium in bone metabolism and its effect in the pathogenesis and diagnosis of osteoporosis has been reported. There are indications that osteoporotic patients have low serum magnesium levels [4], but there is no knowledge for the effect of bone active drugs upon serum magnesium.

In the present study, serum magnesium levels between osteoporotic and non-osteoporotic postmenopausal women were compared and the effect of two bone active drugs (nandrolone decanoate and 1-α-vitamin D_3) upon serum magnesium levels of patients with established postmenopausal osteoporosis was investigated.

Methods

One hundred seventeen postmenopausal women were included in a double blind controlled prospective trial. Seventy-seven women suffered from established postmenopausal osteoporosis proved by low bone mineral density of the distal radius and one at least nontraumatic vertebral collapse. These women had not received bone active drugs in the past and had no other diseases affecting bone metabolism. The other forty age-matched postmenopausal women were selected from the general population and served as control group after they excluded of any evidence of primary or secondary osteoporosis. The osteoporotic women were randomly separated in two main groups of thirty-nine and thirty-eight individuals respectively and were treated for a period of two years. Patients' characteristics were comparable (Table 1). The first group (group A) received 50 mg of nandrolone decanoate intramuscularly (Decadurabolin R, Organon) every three weeks and a placebo tablet daily. The second group (group B) received orally 1µg 1-α-hydroxy-calciferol (One-Alpha, Leo) daily and a placebo intramuscular injection every three weeks.

All treated patients underwent clinical examination, history taking and serum/urine biochemical measurements every three months. Serum magnesium was measured with atomic absorption spectrophotometry (902/903 GBC). This

Effect of nandrolone decanoate and 1-α-hydroxy-calciferol upon magnesium plasma levels in postmenopausal osteoporotic women

Tab. 1: Patients characteristics.

Parameter	*Group A*	*Group B*
Age (years)	67.5 ± 9.1	66.3 ± 8.5
Weight (kg)	60.6 ± 10.2	62.2 ± 9.8
Height (cm)	151.0 ± 8.0	150.0 ± 7.0
Height sitting (cm)	79.0 ± 8.0	78.0 ± 5.0
Quelet index	266.0 ± 41.0	277.0 ± 36.0
Blood pressure (systolic)	148.0 ± 19.0	136.0 ± 17.0
Blood pressure (diastolic)	82.0 ± 10.0	76.0 ± 9.0
Heart rate	75.0 ± 8.0	73.0 ± 10.0

Data are presented as mean ± S.D., Group A: Nandrolone decanoate treated patients, Group B: 1-a Vitamin D_3 treated patients.

Tab. 2: Serum magnesium levels at baseline.

	n	*mean ± SD*	*Statistical significance*
Patients aged 51–70 years	46	2.20 ± 0.37	<0.05
Control group aged 51–70 years	24	2.38 ± 0.40	
Patients aged 71–80 years	31	2.33 ± 0.42	NS
Control group aged 71–80 years	16	2.36 ± 0.30	

Tab. 3: Alterations of serum magnesium levels in nandrolone decanoate treated patients (group A).

GROUP A					
Month of therapy	n	mean ± SD (baseline)	mean ± SD (at month of therapy)	% change	Statistical significance
Patients aged 51–70					
3	19	2.18 ± 0.40	2.27 ± 0.22	4.12	NS
6	19	2.18 ± 0.40	2.41 ± 0.48	10.58	NS
9	16	2.17 ± 0.44	2.42 ± 0.26	11.31	0.05
12	14	2.26 ± 0.40	2.40 ± 0.27	6.19	NS
15	14	2.26 ± 0.40	2.47 ± 0.41	9.22	NS
18	13	2.24 ± 0.41	2.39 ± 0.24	6.47	NS
21	11	2.21 ± 0.40	2.46 ± 0.37	11.04	0.05
24	11	2.21 ± 0.40	2.47 ± 0.39	11.76	0.05
Patients aged 71–80					
3	19	2.30 ± 0.31	2.41 ± 0.42	4.65	NS
6	17	2.31 ± 0.33	2.44 ± 0.26	5.75	NS
9	15	2.25 ± 0.30	2.47 ± 0.47	9.90	NS
12	13	2.26 ± 0.32	2.43 ± 0.52	7.20	NS
15	13	2.26 ± 0.32	2.42 ± 0.29	7.07	NS
18	12	2.25 ± 0.32	2.34 ± 0.26	4.14	NS
21	9	2.38 ± 0.23	2.28 ± 0.26	– 4.40	NS
24	9	2.38 ± 0.23	2.30 ± 0.22	– 3.36	NS

technique is the most popular for the detection and measure of trace elements such as sodium, potassium, magnesium, zinc, copper and many other [5]. It is based in the fact that, the amount of energy absorbed from the atoms of the sample element is characteristic of their chemical constitution ("spectrum sign"). So, considering the pattern of absorption in different wavelenghts we can specify the identity of the trace element [6]. Serum magnesium was expressed in mg/dl with normal values between 1.80 - 2.41.

The statistical method Student's *t*-test was used to compare baseline data for serum magnesium from postmenopausal osteoporotic patients with those from normal controls and a paired *t*-test to compare values of serum magnesium at baseline with those every three months at a two-year therapy. For the statistical analysis the two main groups of women were divided in two subgroups according to the patients' age (51 - 70 and 71 - 80 years). This division was performed because, postmenopausal osteoporosis (patients up to 65 - 70 years) is a nonidentical entity in comparison to senile osteoporosis (patients older than 65 - 70 years), having different pathogenetic mechanisms.

Results

Fifty-six women completed one year of therapy, while thirty-eight women completed the two years.

Patients aged 51 - 70

Serum magnesium levels at baseline are presented at table 2, while the alterations of serum magnesium levels in the two groups are shown in tables 3 and 4 respectively. Figure 1 shows the percentage change of serum magnesium in both groups during the two-year therapy. At the beginning of the study all osteoporotic patients were found to have significant lower serum magnesium levels ($p<0.05$) in comparison to the non-osteoporotic control group. In nandrolone decanoate treated patients, serum magnesium was increased moderately until the 9th month of the therapy. This rise was marginally significant ($p=0.05$) compared to the baseline value. A sudden reduction of serum magnesium was found at 12th month and then a moderate rise during the second year of therapy, which was marginally significant at 21st and 24th month ($p=0.05$). In vitamin D_3 treated group, no significant difference of serum magnesium during the first nine months of therapy was found. From 12th month to the end of the study serum magnesium increased and remained to values that were always significant higher than the baseline ($p<0.05$).

Patients aged 71 - 80

Serum magnesium levels at baseline are presented at table 2, while the alterations of serum magnesium levels in the two groups are shown in tables 3 and 4 respectively. Figure 2 shows the percentage change of serum magnesium in both groups during the two-year therapy. At the beginning of the study no significant

Effect of nandrolone decanoate and 1-α-hydroxy-calciferol upon magnesium plasma levels in postmenopausal osteoporotic women

difference in serum magnesium levels between osteoporotic and non-osteoporotic women was found. Nandrolone decanoate treated patients had serum magnesium levels during the study non-significantly higher than these at initial time (except at 21st and 24th month which were lower). In vitamin D_3 treated group, serum magnesium dropped and remained to values always lower than these at the beginning of the study.

Discussion

Osteoporosis is a condition of bone fragility resulting from micro-architectural deterioration and decreased bone mass. Postmenopausal osteoporosis (type I) is characterized by negative bone balance and consequently bone loss due to estrogens deficiency. Controversially, senile osteoporosis (type II) results mainly from calcium deficiency due to impaired intestinal absorption [7]. Although calcium is the main mineral involving in the physiology of bone, other minerals such as potassium, sodium and magnesium have been reported to affect the pathogenesis of osteoporosis [8, 9].

Magnesium makes up 0.5 - 1 % of bone ash and is therefore not a trace element in the skeleton. It influences both mineral and matrix metabolism in bone by a combination of effects on hormones and other factors that regulate skeletal and mineral metabolism, and by direct effects on bone itself. Dietary magnesium has a direct influence on skeletal magnesium content and age an inverse influence [1]. Although the precice role of magnesium deficiency in human skeletal conditions requires more investigation, it seems that is causes decreased osteoblastic and osteoclastic activity with osteopenia and increased fragility, despite enhanced mineralisation and the development of large bone salt crystals [10, 11]. In conditions of experimental magnesium deficiency, the antiosteoclastic effect predominates, and an increased cortical thickness rather than osteopenia may be seen. Also, periosteal hyperplasia may occur in some experimental models. This latter response may be an indirect effect of impaired secretion and/or skeletal responsiveness to parathyroid hormone.

Tab. 4: Alterations of serum magnesium levels in 1-α OH vitamin D_3 treated patients (group B).

GROUP B					
Month of therapy	n	mean ± SD (baseline)	mean ± SD (at month of therapy)	% change	Statistical significance
Patients aged 51 – 70					
3	25	2.23 ± 0.34	2.21 ± 0.32	– 1.29	NS
6	23	2.22 ± 0.36	2.25 ± 0.43	1.05	NS
9	23	2.22 ± 0.36	2.28 ± 0.40	2.47	NS
12	22	2.21 ± 0.35	2.43 ± 0.25	10.23	< 0.02
15	21	2.18 ± 0.34	2.52 ± 0.22	15.49	< 0.003
18	19	2.17 ± 0.36	2.37 ± 0.27	8.78	< 0.03
21	12	2.15 ± 0.39	2.33 ± 0.28	8.56	< 0.04
24	12	2.15 ± 0.39	2.34 ± 0.30	8.83	< 0.04
Patients aged 71 – 80					
3	12	2.34 ± 0.54	2.16 ± 0.65	– 7.91	NS
6	11	2.22 ± 0.36	2.23 ± 0.22	0.12	NS
9	11	2.22 ± 0.36	2.22 ± 0.34	– 0.08	NS
12	8	2.31 ± 0.39	2.21 ± 0.37	– 4.00	NS
15	8	2.31 ± 0.39	2.21 ± 0.21	– 4.33	NS
18	8	2.31 ± 0.39	2.20 ± 0.23	– 4.71	NS
21	6	2.43 ± 0.27	2.19 ± 0.20	– 10.00	NS
24	6	2.43 ± 0.27	2.21 ± 0.23	– 9.05	NS

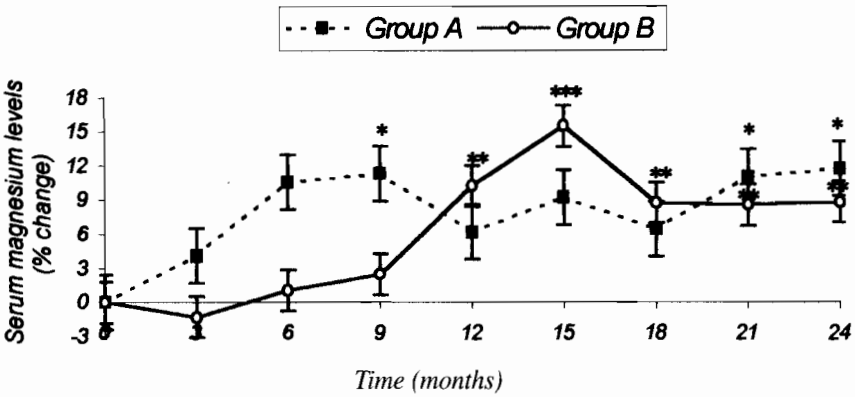

Fig. 1: Percentage change of serum magnesium levels (mean ± SD) in patients aged 51 – 70 years (* p = 0.05, ** p<0.05, *** p<0.005).
Group A: Nandrolone decanoate treated patients, Group B: 1-α-OH vitamin D_3 treated patients.

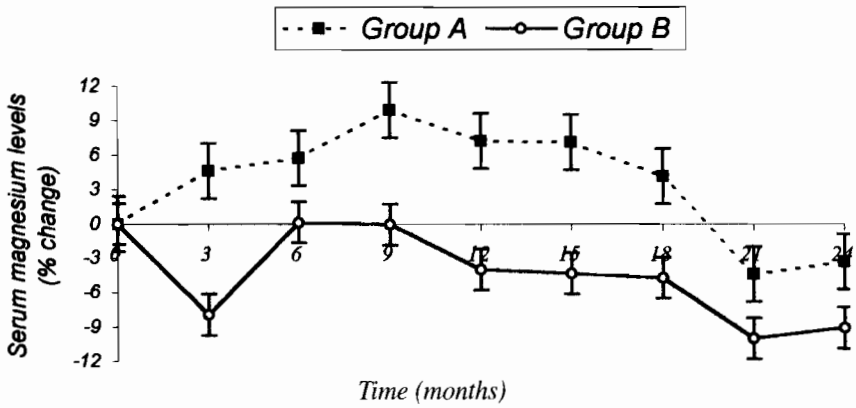

Fig. 2: Percentage change of serum magnesium levels (mean ± SD) in patients aged 71 – 80 years.
Group A: Nandrolone decanoate treated patients, Group B: 1-α-OH vitamin D_3 treated patients.

Effect of nandrolone decanoate and 1-α-hydroxy-calciferol upon magnesium plasma levels in postmenopausal osteoporotic women

Some studies [1, 12] have theorized that magnesium depletion in humans can be a proximate cause of primary osteoporosis because of the ubiquity of low magnesium levels in osteoporotic iliac crest biopsies in their experience. Other investigators [13] have hypothesized that the ability of magnesium deficiency to induce osteoporosis is due to impairement of a skeletal ATPase responsible for transporting K^+ into the skeletal interstitium in exchange for H^+ extrusion. The resulting decrease in the pH of the skeletal interstitium presumably can cause a slow but relentless dissolution of bone independently of other direct effects of magnesium deficiency on bone or indirect effects on PTH secretion and action. The most critical issue at present is whether magnesium depletion plays a causal role in osteoporosis in humans.

Serum magnesium levels are not completely close to bone magnesium levels, which could be the ideal place for measurement, but impossible in clinical practice. For practical reasons measurement of serum magnesium is attractive and there are indications that it can be served as an index of bone metabolism [4]. In the present study, we investigated the implication of age in serum magnesium levels of osteoporotic and normal women. All untreated osteoporotic patients aged 51 - 70 years were found to have significant lower serum magnesium levels compared to that of the normal individuals. Controversially, no significant difference upon serum magnesium between osteoporotic and non-osteoporotic women ages more than 70 years was found. Our findings are partially in agreement with other studies [4], as in the present study significant low magnesium levels were not found in elderly osteoporotic patients. Our results showed that the measurement of serum magnesium has some diagnostic value in the localization of osteoporotic women after menopause.

Another critical question is whether alterations of serum magnesium levels can be served as an index of positive response in the treatment for osteoporosis. There is a little knowledge in the literature in this field [14, 15]. In the present clinical trial we investigated the effect of a two year therapy of osteoporotic women with nandrolone decanoate and 1-α-vitamin D_3 upon serum magnesium levels. Nandrolone decanoate increased non-significantly serum magnesium levels in osteoporotic women aged 51 - 70 (marginally significant at 9^{th}, 21^{st} and 24^{th} month). On the other hand 1-α-vitamin D_3 increased significantly serum magnesium during the second year of therapy in osteoporotic patients aged 51 - 70. Both drugs had no effect in osteoporotic women aged 71 - 80.

In conclusion, the findings of the present study support the measurement of serum magnesium levels for the establishment of postmenopausal osteoporosis, as well as for the monitoring of therapeutic response, although this factor is not well documented in the literature. Further large controlled studies are needed to define the role of magnesium depletion as a risk factor for osteoporosis.

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