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Effects of nandrolone decanoate on bone mass in established osteoporosis

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A double-blind, randomized, placebo-controlled study was conducted in 46 postmenopausal women with established osteoporosis in order to assess the long-term effects of nandrolone decanoate on the bone mineral density (BMD) of the lumbar vertebrae and of the distal third of the radius and on the biochemical markers of bone turnover. The patients received intramuscular injections of placebo or 50 mg nandrolone decanoate every 3 weeks for 18 months. Thirty-two of the initial 46 patients completed 1 year of study and 25 completed the whole study period of 18 months. Overall, vertebral BMD increased by 2.9% in the nandrolone decanoate group and fell by 2.3% in the placebo group. Radial BMD showed a slight but transient improvement, with a subsequent return to basal levels in the nandrolone decanoate group, whereas there was a progressive decrease in the placebo group. Patients treated with nandrolone decanoate also complained less of bone pain. Urinary hydroxyproline decreased significantly in treated patients, whereas osteocalcin tended to increase, but the change was not significant. HDL cholesterol concentrations decreased only slightly and haemoglobin increased significantly in the nandrolone decanoate group. Two patients treated with nandrolone decanoate withdrew from the study because of hirsutism and hoarseness. The results indicate that nandrolone decanoate exerts positive effects on vertebral BMD and on bone pain in patients with established postmenopausal osteoporosis.

Key words: Osteoporosis, Nandrolone decanoate, Bone mineral density, Bone turnover, Bone pain

Introduction

Osteoporosis represents one of the major and most common disorders in people over 65 years old. Since the population in the Western world is ageing and the incidence of osteoporotic fractures increases with age [1,2], osteoporosis will become one of the most important issues of geriatric health care, with major social and economic consequences. It is, therefore, urgent to identify effective preventive and therapeutic measures for osteoporosis.

Antiresorptive agents, such as oestrogens or calcitonin, which are currently used

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for the prevention of osteoporosis, reduce bone resorption, but, because of the coupling phenomenon, they eventually also reduce bone formation. Therefore, the initial beneficial effect on bone is not maintained in the long-term [3].

Albright was the first to propose that reduced bone formation played a crucial role in the development of osteoporosis [4] and was also able to demonstrate that testosterone had positive effects on calcium balance in osteoporotic patients [5]. However, the virilizing side-effects of the hormone made it unsuitable for the treatment of postmenopausal women with osteoporosis. Subsequently, steroid compounds with maintained anabolic activity and minimal androgenic activity have been developed to avoid the virilizing effects. Among these, nandrolone decanoate shows a favourable ratio of anabolic to androgenic activity [6].

Several studies have examined the effects of anabolic steroids on bone mass in osteoporotic patients [7–14], finding an increase of the bone mineral density, with evidence of increased bone formation or reduced bone resorption, and a reduction of the incidence of new vertebral fractures.

The purpose of the present double-blind, placebo-controlled study was to examine the long-term effects of nandrolone decanoate on the bone mineral density (BMD) and on the biochemical markers of bone resorption and bone formation in postmenopausal patients with established osteoporosis.

Patients and methods

The study comprised 46 postmenopausal women, aged 46–68 years, with at least one vertebral compression fracture. All patients gave their informed consent to the study. Exclusion criteria included concurrent treatment or diseases known to influence bone or mineral metabolism. Some patients had received calcitonin or calcium in the past, but no specific therapy had been given in the last 6 months. No patient had ever received bisphosphonates.

The women were randomized to receive either 50 mg nandrolone decanoate (DecaDurabolin (R), Organon International, The Netherlands) intramuscularly every 3 weeks ($n = 25$), or a placebo injection every 3 weeks ($n = 21$), for 18 months. All patients received 1000 mg of a daily oral supplementation of calcium.

BMD and biochemical parameters were measured at the start of the trial and at 3-month intervals. X-ray films of the spine were taken before and after 12 and 18 months of treatment.

Radial BMD was measured by Single-Photon Absorptiometry using a Gambro densitometer with a 241-Americium radioactive source. The site of measurement, the distal third of the radius, contains predominantly (>90%) cortical bone. The values obtained were not corrected for the thickness of the subcutaneous fat. In our laboratory the coefficient of variation (CV) in vivo in normal volunteers is 2.9%. Vertebral BMD was measured on L2–L4 by Dual-Photon Absorptiometry by means of a Norland densitometer equipped with a 153-Gadolinium source (Norland Corp., Ft. Atkinson, WI). In our laboratory the CV in vivo is 2.7%.

Plasma osteocalcin (OC) levels were determined by a commercial RIA kit (INCSTAR, Stillwater, MN), with an intra-assay CV of 6% and inter-assay CV of 8%. Calcitonin, somatomedin C and parathyroid hormone (PTH) were measured with

commercial kits purchased from Nichols (Nichols Inst., S.Juan Capistrano, CA). Intra- and inter-assay CV are, respectively, 6% and 9%, 7% and 10% and 6% and 8%. The PTH assay is based on an antiserum which recognizes the sequence 44–68 of the molecule. Urinary hydroxyproline in second-voided morning urine samples were determined by a modification of the colorimetric method of Neuman and Logan [15] and expressed in terms of glomerular filtration rate, to allow for changes in urinary creatinine due to increased muscle mass during nandrolone decanoate therapy. Other biochemical parameters were measured with routine laboratory techniques.

Bone pain was assessed by means of a visual analogue scale (VAS). Vertebral fractures were evaluated by inspection of lateral X-ray films of the thoracic and lumbar spine. No morphometric technique was used in the evaluation of spinal fractures.

Basal values of the densitometric and biochemical parameters were compared by means of one-way analysis of variance, while changes during therapy were examined with analysis of variance for repeated measures. Differences in the time trends between groups were tested by means of orthogonal polynomials, while within-group comparisons with the baseline value were made by means of general linear contrasts (Systat ver. 4.0, Systat INC, Evanston, IL). Scores obtained by VAS were compared by the Mann-Whitney test.

Results

Thirty-two of the initial 46 patients completed 1 year of study and 25 completed the whole 18-month study period. The early and late drop-outs were evenly distributed over both groups. Two patients withdrew from the nandrolone decanoate group because of side effects (hirsutism and hoarseness) after 15 months of treatment. One patient in the placebo group died. Three patients dropped out for intercurrent illness (2 in the nandrolone decanoate group and 1 in the placebo group).

TABLE I

CLINICAL AND BIOCHEMICAL CHARACTERISTICS OF PATIENTS WHO COMPLETED THE 18-MONTH STUDY

Data given as Mean ± S.D.

	Nandrolone decanoate ($n = 13$)	Placebo ($n = 12$)
Age (years)	56.3 ± 4.4	57.9 ± 7.4
Years since menopause	10.6 ± 6.1	15.3 ± 9.1
Weight (kg)	64.3 ± 11	57.5 ± 5.3
Height (cm)	160 ± 6	158 ± 7
Radial BMD (g/cm^2)	0.64 ± 0.10	0.66 ± 0.09
Lumbar BMD (g/cm^2)	0.70 ± 0.10	0.72 ± 0.11
Osteocalcin (ng/ml)	5.4 ± 1.9	5.3 ± 2.2
Alkaline phosphatase (units/l)	164 ± 37	170 ± 50
Hydroxyproline/creatinine (mg/mg)	0.18 ± 0.07	0.15 ± 0.02

Fifteen patients dropped out for personal reasons (8 in the nandrolone decanoate group and 7 in the placebo group).

The patients that completed the study are described in Table I. No significant differences were found between the 2 groups for any variable.

Compared with patients in the placebo group, patients treated with nandrolone decanoate had a significant increase (4%) of the BMD of the distal radius (Fig. 1) after 6–12 months ($P < 0.05$), and then returned to baseline levels. The placebo group showed a progressive decrease of radial BMD, with an average loss of 4.2% after 18 months. The difference in the time trends of the two groups was significant ($P < 0.01$).

Lumbar BMD (Fig. 2) increased gradually in patients treated with nandrolone decanoate in the first 9 months of observation and remained stable and significantly higher than the basal values ($P < 0.02$) thereafter. The placebo group showed a gradual decrease in the first half of the study which levelled off in the last 9 months of follow-up ($P < 0.02$ vs. base). Overall, vertebral BMD increased by 2.9% in the nandrolone decanoate group and fell by 2.3% in the placebo group. The difference between groups was significant ($P < 0.01$).

Plasma osteocalcin (Fig. 3) and alkaline phosphatase levels tended to increase in the nandrolone decanoate group and to decrease in the placebo group. However, these changes from baseline did not reach statistical significance. Throughout the study, the urinary excretion of hydroxyproline remained constant in the placebo group and decreased significantly ($P < 0.02$) in the nandrolone decanoate group

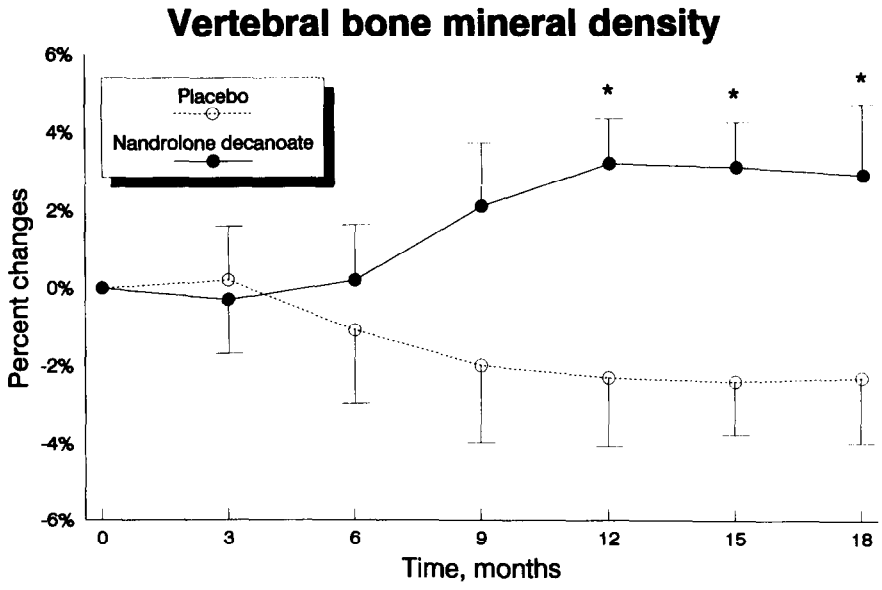

Fig. 1. Changes in vertebral bone mineral density (Mean ± S.E.M.). *$P < 0.05$ for comparison with the basal values of the respective group.

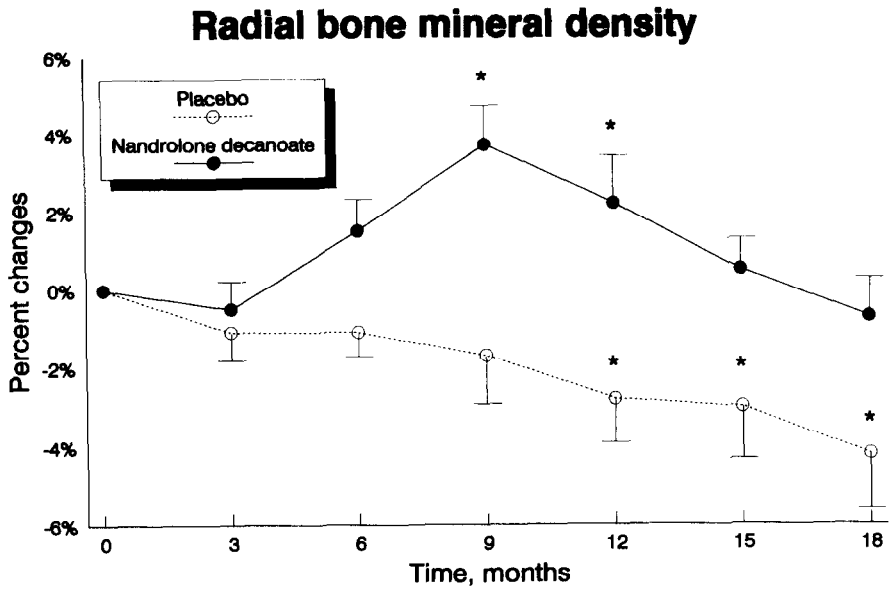

Fig. 2. Changes in the bone mineral density of the distal radius (Mean ± S.E.M.). $^*P < 0.05$ for comparison with the basal values of the respective group.

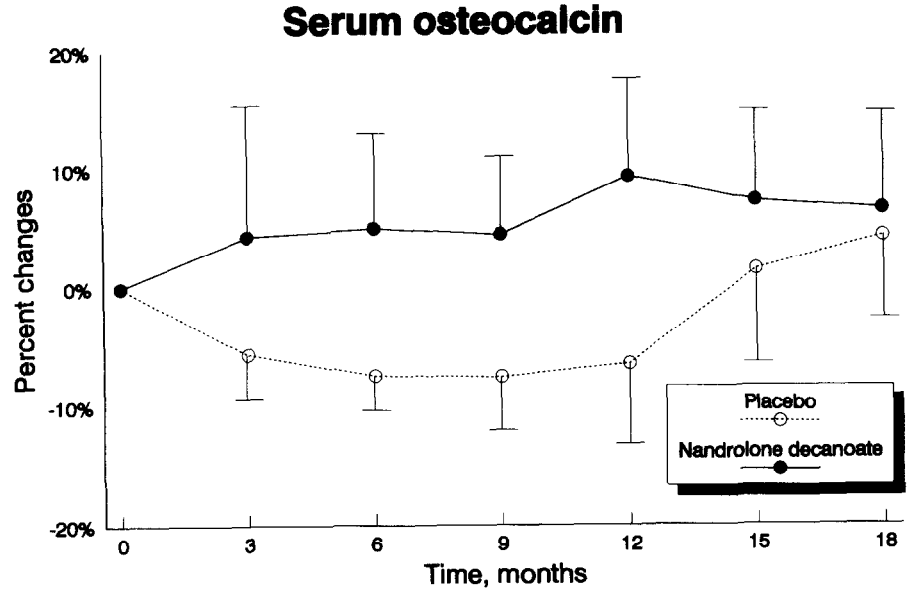

Fig. 3. Changes in serum osteocalcin (Mean ± S.E.M.). $^*P < 0.05$ for comparison with the basal values of the respective group.

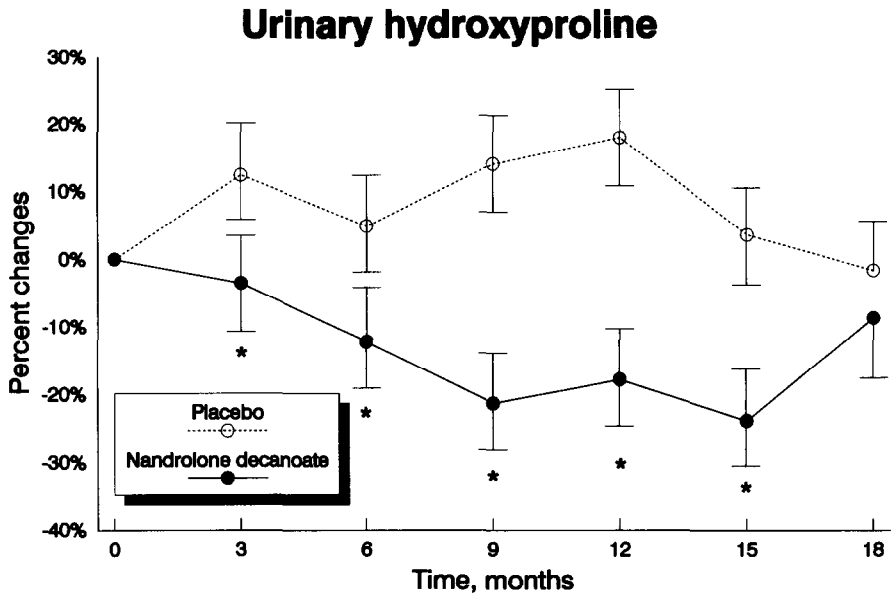

Fig. 4. Changes in urinary hydroxyproline (Mean ± S.E.M.). *$P < 0.05$ for comparison with the basal values of the respective group.

(Fig. 4). A significant increase in haemoglobin concentration and a significant reduction in HDL cholesterol were also seen in the nandrolone decanoate group. There were no significant changes in the serum levels of total cholesterol, triglycerides, creatinine, SGOT, SGPT, γ-GT, calcium, phosphate, PTH, calcitonin or somatomedin C in either group.

From a clinical point of view, patients in the nandrolone decanoate group complained less of bone pain than patients in the placebo group ($P < 0.05$), in agreement with the results of a previous study [13]. The VAS scores are given in Table II. One

TABLE II

VAS SCORES DURING THE STUDY PERIOD IN PATIENTS TREATED WITH NANDROLONE DECANOATE OR WITH PLACEBO

Data expressed as Mean ± S.D.

	Months						
	0	3	6	9	12	15	18
Nandrolone decanoate	4.1 ± 1.6	3.1 ± 1.0	2.9 ± 1.0	2.4 ± 1.1	2.5 ± 1.2	2.2 ± 1.2	2.3 ± 1.2
Placebo	4.0 ± 1.4	3.7 ± 1.1	3.5 ± 1.1	3.3 ± 1.1*	3.6 ± 1.3*	3.2 ± 1.1*	3.4 ± 1.4*

*$P < 0.05$.

new vertebral fracture occurred in the placebo group, whereas no fracture was observed in the nandrolone decanoate group.

Side effects, including increased facial hair, weight gain, increased blood pressure and hoarseness, were observed in a total of 7 patients receiving nandrolone decanoate. More than one side-effect occurred in some women and their incidence increased with the cumulative dose administered to the patients. Increased facial hair was the most common untoward effect, and was observed in 4 out of the 25 patients of the initial cohort (16%), leading to withdrawal from the trial of one of these women. The other drop-out related to treatment with nandrolone decanoate was due to voice changes. Other side-effects were mild and well tolerated: weight gain increased slightly (less than 2 kg) in 3 subjects, and blood pressure increased by 5–15 mmHg in 2 women.

Discussion

The results of this study show that nandrolone decanoate exerts positive effects on bone mass, increasing the vertebral BMD and preserving the radial BMD in patients with established postmenopausal osteoporosis. Lumbar BMD increased progressively during the first year of therapy and remained stable in the second year, with a mean increment of about 3%, compared with a 2% decrease in the placebo group. Comparable or even higher increases are reported by other investigators [12–14]. Radial BMD showed only a transient increase. This result may, in part, be due to a slight overestimation of the data, which were not corrected for changes in the subcutaneous fat layer of the forearm [14]. However, if not actually increased, the BMD of the radius was at least maintained at its previous levels. This finding is compatible with the results of other studies [9,14], in which the fat-corrected radial BMD was also not influenced by the nandrolone decanoate therapy, but the bone mineral content (BMC) was increased. It was suggested that, because of an increase of BMC and a stable BMD, the width of the bone increases. However, in other studies [10,11] an increment of the radial BMD was found, that was confirmed even after fat correction [14]. Though the reasons are unclear, it is likely that the technical performance of different densitometers plays a major role.

The mechanism of these effect of nandrolone decanoate seems related mainly to inhibition of bone resorption, as suggested by the significant reduction of hydroxyproline, a finding reported by others [9,13,14]. This view is consistent with the effect of treatment on lumbar BMD: in fact, the plateau of BMD increase in the second year is typical of the action of an inhibitor of bone resorption [3]. Therefore, we are confident that a reduction of bone resorption actually occurred in the nandrolone decanoate group.

The effects on bone formation are less certain. Though a tendency to increased values of osteocalcin and alkaline phosphatase was present in the nandrolone decanoate group, we could not find significant differences between treated and placebo patients. In some reports there is indirect evidence that anabolic steroids, including stanozolol [8] and nandrolone decanoate [9–12] increase bone formation, but this has not been confirmed by others. In vitro data suggest the possibility of a direct action on osteoblast-like cells [16]. Since our sample was small, a positive

effect of nandrolone decanoate on biochemical markers of bone formation may have been missed. Therefore our data are insufficient to draw definite conclusions on the effects of nandrolone decanoate on bone forming activity.

From a clinical point of view, it is important to emphasize that patients in the nandrolone decanoate group complained less of bone pain than patients in the placebo group, in agreement with the results of a previous study [13]. This favourable subjective response may have enhanced compliance despite the occurrence of side effects.

With regard to side effects in the nandrolone decanoate group, the most common complaint was increased facial hair, which appeared in 4 out of the initial 25 patients after several months of therapy. The incidence (16%) is similar to that reported in other studies [10–12]. Weight gain, increased blood pressure, and hoarseness were less common disturbances. Usually these side effects appeared after several months of treatment suggesting that the cumulative dose may be important in their appearance. Other authors have found that side-effects of nandrolone decanoate are dose-related and patient-dependent [10–12]. It is to be emphasized that the side effects were mild and well tolerated by the patients, and this is confirmed by the fact that only 2 patients withdrew from the study because of treatment-related side effects (one for hirsutism and one for voice changes).

Other biological effects of nandrolone decanoate treatment were an increase of haemoglobin levels (as a result of the stimulatory action of nandrolone decanoate on erythropoiesis [6]) and a slight decrease (6%) of HDL cholesterol levels. Lipoprotein changes are often [17], though not always [14] found during treatment with anabolic steroids. The long-term significance of these changes is unknown, but since their magnitude is small, it is unlikely to be of great concern for patients' health.

In conclusion, we have found that nandrolone decanoate has positive effects on bone mass and on bone pain in established postmenopausal osteoporosis. Side-effects are mild and well tolerated and appear to depend on the cumulative dose. Though nandrolone decanoate appears to be relatively safe, other studies with different dose and time schedules, or the combination with other treatments, may be of value to determine the optimal place of this drug in the therapy of osteoporosis.

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