Postmenopausal Bone loss: Prevention and Replacement.

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Clinical trial on efficacy of a combination of elcatonin (carbocalcitonin) and conjugated oestrogens in normal early postmenopausal woman.

Summary

Combination therapy of Carbocalcitonin (Elcatonin) and oral conjugated oestrogens (Premarin) not only prevents postmenopausal bone loss but leads to an increase in bone mass in normal early postmenopausal women.

Introduction

Osteoporosis is a skeletal disorder predominantly affecting postmenopausal women.

The physiologically balanced coupling mechanism of bone formation and bone resorption ensures the skeleton's integrity and renewal.

Peak bone mass is reached in the fourth decade of life. In the early postmenopausal years there is an accelerated bone loss. By the age of 79 years a woman loses 50% of her bone mass while a man loses only 25% by the age of 90 (1). It is estimated that by the age of 65 some 40% of women would have experienced at least one osteoporotic fracture (2). This is due to a decline in bone organic matrix, the primary pathological event leading to osteoporosis (3).

Oral oestrogen administration has been shown to arrest postmenopausal bone loss (4,5). However, it has been suggested that oestrogen treatment on its own will only reduce the risk of osteoporotic fractures by 50% (6). This is probably because therapy is started too late or bone mass at the start of the menopause in certain individuals lies within the low normal range.

Calcitonin, like oestrogen, when used alone has also been shown to prevent postmenopausal bone loss (7,8).

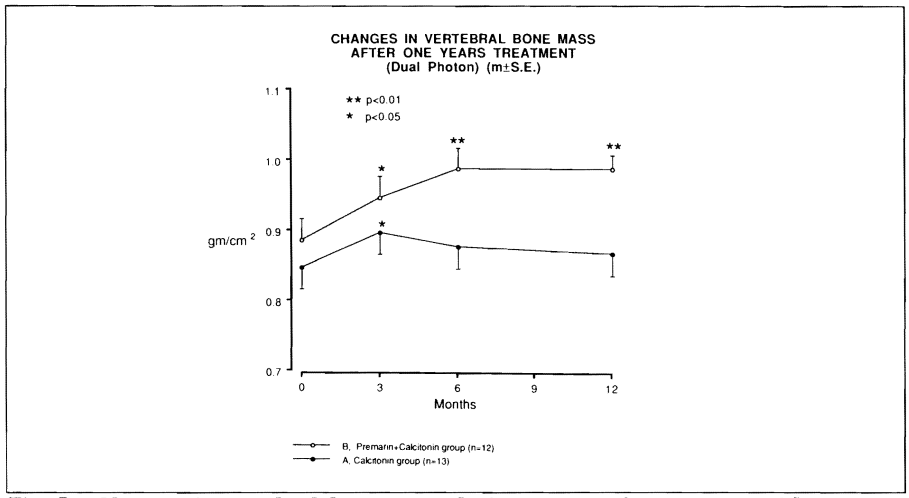

Fig. I. Changes in vertebral bone mass during one year's treatment with Premarin and Calcitonin compared to changes with Calcitonin only. The significance levels shown indicate comparisons with base line levels.

Many treatment strategies have been developed in the management of postmenopausal bone loss aimed at maintaining bone mass. To date only limited work has been aimed at increasing bone mass.

Aims

The aims of the study was to investigate the effect of combination therapy on early postmenopausal bone loss. A combination of Elcatonin (Carbocalcitonin) and Premarin was compared to Premarin alone, and to Elcatonin (Carbocalcitonin) alone and all groups were then compared to a control group.

RATIONALE OF TREATMENT

Positive Bone Former (oestrogens) — Osteoblastic Activity → Increase in Bone Mass

Anti-Resorber (Calcitonin) — Osteoblastic Activity

Elcatonin

Calcitonin is an endogenous 32 - amino acid polypeptide hormone which binds to specific receptors on osteoclasts inhibiting bone resorption.

Elcatonin (ISF) is a recently developed synthetic analogue of eel calcitonin with a greater stability to pH and temperature than other Calcitonins. Weight for weight Elcatonin is more biologically active than other calcitonins. Weight for weight Elcatonin is as biologically active as salmon and natural eel calcitonin.

Patients and Methods

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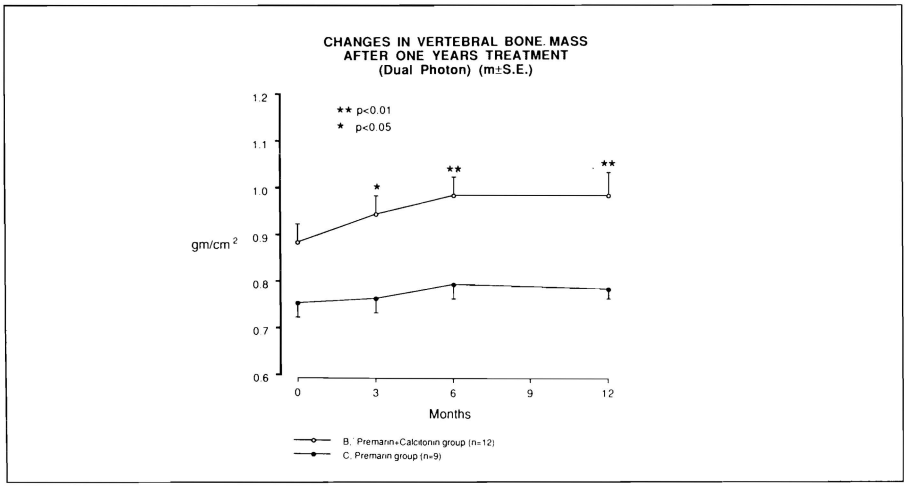

Fig. II. Changes in vertebral bone mass during one year's treatment with Premarin and Calcitonin compared to changes with Premarin only. The significance levels shown indicate comparisons with base line levels.

The patients were randomly assigned to one of the following treatment groups:

Group A 40 MRCU of Elcatonin (1 ampoule) i.m. twice a week
Group B 40 MRCU of Elcatonin (1 ampoule) i.m. twice a week associated with conjugated oestrogens 1.25mg daily orally, plus medroxyprogesterone acetate 10mg daily orally for 10 days monthly.
Group C Conjugated oestrogens 1.25mg daily orally plus medroxyprogesterone acetate 10mg daily orally for 10 days monthly.
Group D no treatment

All the patients were normal women who were at least 6 months and not more than 10 years postmenopausal. Table 1 gives the patient data.

Patients were recruited if they had clinical evidence of the menopause supported by a high plasma level of Follicle- stimulating Hormone (FSH value > 40 IU/l).

Patients were excluded from entering the study if they had any of the following:

- Therapy with sex steroids during the year preceding the admission to the study
- severe hepatic, renal, cardiac or gastroenterologic disease
- inflammatory or degenerative osteomuscular diseases (Paget's disease, osteomalacia, rheumatoid arthritis)
- alcoholism
- metabolic disorders (e.g. diabetes mellitus) unless under stable medical control (none in fact were involved)
- neoplastic disease
- treatment with drugs affecting bone metabolism in the 4 weeks preceding the inclusion in the study

Patients were assessed at baseline and after 3, 6 and 12 months on the study. The following information was obtained before randomisation to treatment:

- Age
- Years since the onset menopause
- Follicle - stimulating hormone (FSH) serum levels
- Bone density of lumbar spine (L2
- L4) by Dual Beam Photon Absorptiometry (Norland)
- Clinical examination

On the 3rd, 6th and 12th month, a repeat assessment of the lumbar spine was carried out using Dual Beam Photon Absorptiometry (Norland).

This method was used to assess the bone density of L2 to L4. All cases were assessed in a blind fashion by one of us (WA). The error in the method at the lumbar spine was calculated as being 1.5%.

In this report we present the results of 44 patients who completed 1 year of follow up. (75 were originally admitted to the study and randomised to one of the treatment groups).

The high rate of drop-outs (30%) is due to the long treatment duration and to the difficulties in getting full compliance from patients, especially since this involved a considerable amount of travelling. To our knowledge no patients have dropped out because of side effects, although some women on Calcitonin alone complained of flushes in the initial months of the study.

Statistical Methods

After testing for normality, statistical analysis was carried out using a paired Student's t-test. Across group comparisons at 0, 3, 6 and 12 months were carried out using a one-way analysis of variance.

Results

The results of the study are shown in Figures 1, 2 and 3.

The *Premarin and Elcatonin* group showed a significant mean increase in vertebral bone mass of 11.24% at the end of one year's therapy.

The *Premarin only* group showed a non-significant mean increase of 3.9% as did the *Elcatonin* only group (2.3%) at the end of one year's therapy.

The *control group* showed a significant mean bone loss of 4.8% after being followed up for one year.

There was no statistical significance in bone mass between the groups at the start of the study.

Table (2) gives a comparison of the results on the different regimens at the end of one year's therapy.

Conclusion and Discussion

The data for the patients who completed 12 months of treatment,

(A) Confirms that vertebral bone mass is lost rapidly in the initial postmenopausal years (1).

(B) Confirms that this loss can be prevented by either Oestrogens alone (4,5) or Calcitonin alone (7,8).

(C) Indicates that Oestrogens (Premarin) and Carbocalcitonin (Elcatonin) combined in adequate doses, *not only prevents early postmenopausal bone loss but results in a significant gain.* In our study the mean gain was of 11.2% after

one year. The indications are that most of this gain occurs in the first 6 months of therapy with levelling off then occurring.

Although the clinical significance of such a gain in bone mass in the combined group in early postmenopausal women still needs to be assessed it would be logical to suggest the following regimen for women who are at a high risk of developing postmenopausal osteoporotic fractures:-

(A) Combined therapy of Premarin/ Gestogens + Elcatonin for the first year of treatment.

(B) Maintenance of the bone mass after that with eight Premarin/ Gestogen combinations alone or Elcatonin alone, depending on the overall clinical picture of the woman concerned.

This therapeutic regimen is currently being analysed in a separate study.

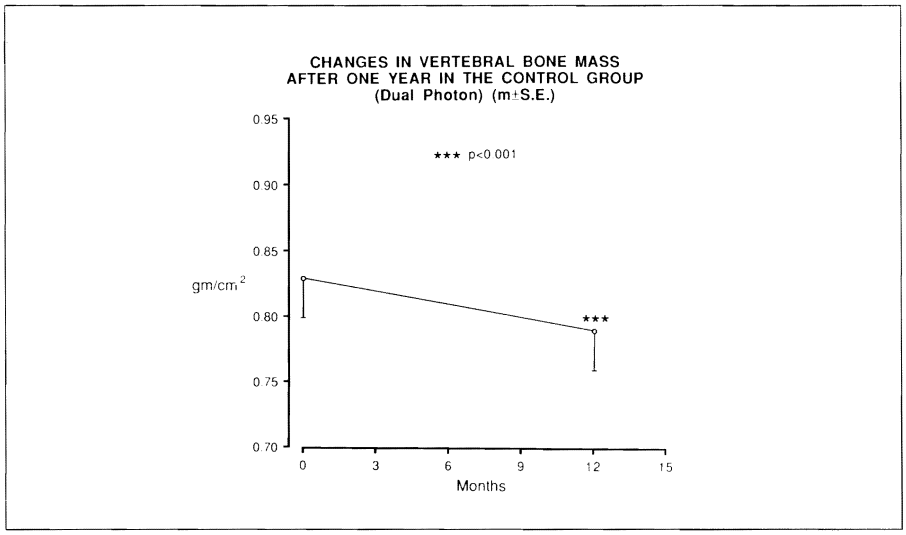

Fig. III. Changes in vertebral bone mass after one year in a group of postmenopausal woman who were on no treatment.

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