Reversal of postmenopausal vertebral bone loss by oestrogen and progestogen: a double blind placebo controlled study

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Abstract

Because of uncertainty about the place of hormones in the treatment of postmenopausal bone loss vertebral and forearm bone loss was measured by absorptiometry in early postmenopausal women before and after continuous or sequential treatment with combined oestrogen and progestogen in a double blind placebo controlled trial. Treatment with hormones significantly reversed the vertebral bone loss. The net gain in vertebral bone density amounted to 6.4% a year with continuous supplementation and 5.4% a year with sequential supplementation; the net gain in forearm bone density was lower (3.6% with continuous and 3.7% with sequential supplementation).

Before a policy of supplementation with hormones can be recommended to all postmenopausal women with the aim of reducing the incidence of vertebral crush fractures further studies with different doses and combinations of hormones, administered over several years, are needed.

Introduction

Epidemiological evidence suggests a relation between subnormal vertebral bone mass and vertebral crush fractures¹ and hip fractures.² If this is so reduction or reversal of postmenopausal bone loss might reduce the incidence of osteoporotic crush fractures. We have previously shown that systematic physical exercise reverses postmenopausal vertebral bone loss.³ Supplementation with oestrogen or progestogen alone^{4,5} or in combination^{6,7} can increase the mineral content of the peripheral skeleton in postmenopausal women. Recent work suggested that prophylaxis with oestrogen is effective against the loss of bone from all parts of the skeleton.⁸ Lack of precise measurement has limited how much is known about the effects of hormones on vertebral bone mass. Using high precision dual photon absorptiometry, we studied whether oral oestrogen and progestogen combined, given continuously or sequentially, would reduce the rate of "physiological" loss of bone from the axial skeleton of postmenopausal women.

Patients and methods

All 5800 women in Frederiksborg county born during 1930-3 were invited to enter a longitudinal study of vertebral bone loss and its possible prevention. Volunteers were required to be in the early menopause (last

vaginal bleeding more than six months and less than 24 months earlier). The criteria for exclusion were: previous or current breast cancer, endometrial cancer, thromboembolic disease, parenchymatous liver disease, chronic pancreatitis, intestinal malabsorption, diabetes mellitus, obesity, and diseases with high or low turnover of bone and treatment with oestrogen, progestogen, corticosteroids, fluoride, vitamin D, or drugs known to provoke induction of liver enzymes.

Altogether 176 women fulfilling these criteria agreed to enter the study (mean (SD) menopausal age at entrance 14.6 (6.1) months). Four volunteers were subsequently excluded: one was too large for the equipment, one had chronic pyelonephritis and possible bone disease, and two had normal serum oestrogen concentrations and were therefore not truly menopausal. During the six months before the start of the treatment (with either the hormonal supplement or the placebo) 21 women defaulted because they could not accept the possibility of treatment with placebo. The remaining 151 volunteers had no signs of vertebral fractures or severe osteoarthritis in radiographs. Lumbar spine and forearm (dominant arm) bone mineral contents were measured by dual photon and single photon absorptiometry, respectively, at recruitment and after six, 12, and 18 months. On the day before treatment was started at six months all the women had an endometrial biopsy. No specimens showed histological signs of malignancy. The volunteers were then allocated by block randomisation (block size 15) into three groups (table I). Each woman was given tablets in calendar phials for the next twelve 28 day cycles. One group took oestrogen and progestogen

TABLE I—Mean (SE) at randomisation of menopausal age and bone mineral density in the three groups

Treatment	No of patients	Menopausal age (weeks)	Bone mineral density at randomisation (g/cm ²)	
			Lumbar spine	Forearm
Continuous oestrogen and progestogen	50	91.1 (3.8)	0.92 (0.02)	0.39 (0.01)
Sequential oestrogen and progestogen	50	94.6 (4.0)	0.94 (0.02)	0.39 (0.01)
Placebo	51	92.7 (3.9)	0.94 (0.02)	0.39 (0.01)

continuously (one tablet daily containing 2 mg oestradiol and 1 mg norethisterone acetate); another group took oestrogen and progestogen sequentially (first 12 days one tablet daily containing 2 mg oestradiol; next 10 days one tablet daily containing 2 mg oestradiol and 1 mg norethisterone acetate; last six days one tablet daily containing 1 mg oestradiol); and the third group took placebo tablets. The tablets given to all 151 women were of identical colour and size. Extra calcium was not supplied.

An abbreviated version of the protocol was enclosed with the initial invitation to participate in the study. All women gave informed consent to the study, which was double blind and carried out in accordance with the Helsinki II declaration. The investigation was approved by the local ethical committee.

ASSESSMENT OF BONE MINERAL CONTENT

Bone mineral content was measured in the lumbar spine and forearm to see whether the hormones acted similarly at both sites and whether it was possible to predict lumbar bone mineral density from the forearm bone mineral density, which is easier to estimate. The lumbar bone mineral content was measured by scanning dual photon absorptiometry over the second, third, and fourth lumbar vertebrae, gadolinium-153 (44 and 100 keV) being used as the radioactive source. Lumbar bone mineral content was expressed in terms of bone mineral density (units/cm², approximating

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g/cm²).⁹ The transverse processes were excluded from analyses to increase the proportion of trabecular bone in the measured areas and obtain better precision.

We used a non-commercial absorptiometer; its short term precision (coefficient of variation of repeated measurements on different days within weeks) averaged 0.3% for bone powder standards and 1% for normal, non-obese subjects without osteoporosis. Forearm bone mineral content in terms of density was measured immediately after lumbar bone mineral density with a commercial single photon absorptiometer, iodine-125 being used as the radioactive source. The measurements started at a 10 mm distance between the radius and the ulna. Six scans proximal to this site were used.

Results

EFFECTS OF PROPHYLAXIS

Altogether 130 women (86%) completed the study. Side effects were few

Discussion

Our study shows that continuous or sequential administration of oestrogen and progestogen for one year significantly reverses postmenopausal vertebral bone loss. The same is true for loss of bone from the distal forearm. Our finding that the action of the hormones was more pronounced in the spine than the forearm is consistent with the greater metabolic activity of trabecular bone compared with cortical bone. (The trabecular:cortical bone ratio is about 7:3 in the lumbar spine and about 1:9 in the forearm at the measured sites.) Caution should, however, be exercised when bone mineral densities in terms of mass per unit area are compared. Mass per unit area does not express a true density and is not a true index of porosity. An assessment of the third dimension is lacking and cannot at present be obtained by single plane scanning. Furthermore, although mass per unit area may remain constant in longitudinal studies, it is theoretically subject to alteration.

TABLE II—Reasons for women dropping out of study at start and end of run in period (0 and 6 months) and at 12 and 18 months

	Continuous oestrogen and progestogen				Sequential oestrogen and progestogen				Placebo			
	0	6	12	18	0	6	12	18	0	6	12	18
Breast swelling			2									
Vaginal bleeding			2					1				
Weight gain							1					
Confusion											1	
Breast cancer				1			1					
Leiomyosarcoma of the uterus							1					
Paraesthesia			1									
Private reasons (transport problems etc)			1	3			2				3	1
Technical errors*:												
Lumbar measurements	4	2			7	3	1		4	4		4
Forearm measurements	1				1		3		2	1		1
Participating women	50	50	44	40	50	50	45	44	51	51	47	46

*Most were due to erroneous use of a contaminated radioactive source for three weeks.

and generally of moderate importance (table II). Two breast cancers and one leiomyosarcoma of the uterus were seen in the groups treated with hormones. Symptoms of these became apparent three months after treatment, suggesting that the diseases had been present before treatment. The lumbar bone mineral density increases with crush fractures and reductions of vertebral height,¹⁰ but these were not seen during the 18 months of investigation.

Lumbar bone mineral density fell by an average of 1.6% a year during the run in period, which was almost identical with the mean change in lumbar bone mineral density of -1.5% a year seen in the placebo group during the study period. Postmenopausal lumbar vertebral bone loss was significantly reversed to gain of bone by continuous and sequential oestrogen and progestogen treatment for one year. Bone gain was seen after six months' treatment and increased further after 12 months' treatment. The mean net gain in bone density over that in the placebo group was 6.4% (confidence interval 4.8 to 8.0%) with continuous administration and 5.4% (3.6 to 7.2%) a year with sequential administration. The difference between the gain of bone in the two groups treated with hormones was not significant.

Although there was a significant net gain in bone density in the forearm, it was less pronounced (3.6% (confidence interval 1.9 to 5.3%) and 3.7% (2.3 to 5.1%) with continuous and sequential administration, respectively). The change in forearm bone mineral density in both groups receiving hormones averaged -2.7% a year during the run in period. The bone mineral density in women in the placebo group fell by 2.6% a year during the study period.

PREDICTION OF LUMBAR BONE MINERAL DENSITY FROM FOREARM MEASUREMENTS

The correlation coefficient between forearm bone mineral density and lumbar bone mineral density for the cohort was 0.52 at entrance to the study and 0.53 at the end of the run in period (just before treatment). The residual standard deviation was high (0.11). The prediction error for patients was rather larger, which suggests that forearm bone mineral density should not be used as an alternative to lumbar bone mineral density when vertebral bone density has to be assessed.

Mean (SE) lumbar bone mineral density and forearm bone mineral density expressed as percentage of initial value.

*p<0.01, **p<0.001, compared with placebo group.

The long term (within a year) precision of applied dual photon absorptiometry might reach 5% when normal early postmenopausal women are studied.⁹ With this precision controlled trials require numbers of subjects similar to those in our study to detect a change in bone mineral density of 5%. Detection of a change of 5% in one year in one patient without a control would require a method with a long term precision below 2%. With the sensitivity of current methods it is hardly possible to identify a subject rapidly losing bone by two measurements 12 months apart.¹¹ Seemingly, however, all women lose vertebral bone at a fairly high rate during the first years after the menopause.¹² Oophorectomy seems to be followed by a rapid rate of bone loss. In one study five to 10 years after oophorectomy the bone mineral content of the third lumbar vertebra was reduced by 20%, a larger decrease than that in the peripheral skeleton (7%).¹³ For this reason a longitudinal study of postmenopausal bone loss should include women of roughly the same menopausal age rather than the same chronological age.

It has been suggested that for clinical investigations measurement of lumbar bone mass might not be necessary and that forearm measurements might suffice. We have shown previously in patients with spinal osteoporosis and crush fractures that lumbar spine bone mass cannot be predicted from forearm measurements.¹⁴ The data reported here are consistent with those findings.

This study shows that prophylactic treatment with hormones can for some time abolish one of several risk factors for osteoporotic fractures—namely, bone loss. Although epidemiological evidence would encourage prophylactic treatment with hormones on a wider scale,¹² considerable scepticism is appropriate. Bone density and bone mass are not the only determinants of crush fractures—for example, many patients with crush fractures have normal vertebral bone mass.¹⁴ Vertebral bone elasticity might also be a factor. The compressive strength of vertebral bodies decrease with age, possibly independently of bone mass.¹⁵ A prerequisite for the more widespread use of hormonal prophylaxis against osteoporosis should be longitudinal studies, of longer duration, of the effects and side effects of different combinations and doses of hormones.

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ONE HUNDRED YEARS AGO

HIS Imperial Highness the Crown Prince of Germany having expressed his wish that I (Sir Morell Mackenzie, MD) should now place on record my opinion of his case, the opportunity is afforded of correcting some of the statements which from time to time have been inaccurately attributed to me.

The general idea is that I am of opinion that the disease from which His Imperial Highness is suffering is not cancer!; the view on the other hand, which I have consistently maintained is, that there never has been any proof of the existence of cancer.

To enter more into detail: When I arrived in Berlin, last May, I stated to my colleagues that, in my opinion the appearances seen in the throat were of a negative character, that is to say, that the disease might be either benign or malignant, and that its nature could only be determined by microscopical examination. A portion of the diseased tissue having been taken away by me from the throat of His Imperial Highness, it was submitted to Professor Virchow, who could not detect in it anything of a malignant nature. Repeated examinations by Professor Virchow of other portions removed by me yielded similar results.

In the month of July, whilst His Imperial Highness was staying in the Isle of Wight, I pointed out to more than one of his august relatives that the danger that I most dreaded was the occurrence of perichondritis at a future date, and three months later this fear was proved to be well grounded. At the end of October and early part of November entirely fresh symptoms appeared, and at that time the local disease presented an appearance which was consistent with the diagnosis of cancer. It was then impossible to obtain any fresh microscopical evidence in the matter, and I considered it safer accordingly to treat the case as one of a malignant nature; at the same time, however, I drew up and submitted to my colleagues a *protocol*, in which I stated that although the disease at that moment looked like cancer, I could

not agree that the malady was proved to be malignant until a further microscopical examination had been made. The document in which I set forth my views was forwarded to Berlin to be placed in the State Archives. Although the unfavourable symptoms then present were explicable on the ground of the existence of cancer, yet it was clear to the majority of the physicians at that time in attendance that perichondritis had supervened.

In the middle of December, however, the unfavourable signs had passed away, and there were no longer any clinical symptoms of cancer. Microscopical evidence on the subject was, however, still wanting. This was furnished at the end of January, when a slough was expectorated from the very spot which had presented such a highly suspicious appearance in November. This slough was most carefully and repeatedly examined by Professor Virchow, and the result (which is now published) again shows that cancer could not be detected.

To recapitulate: In my opinion the clinical symptoms have always been entirely compatible with non-malignant disease, and the microscopical signs have been in harmony with this view. I need only add that although in nearly every case of laryngeal disease it is possible at the first inspection to form an accurate opinion as to the nature of the disease presenting itself, yet, in a few rare instances, the progress of the complaint alone permits its character to be determined. Unfortunately, the case of His Imperial Highness is among the latter number, and at this moment medical science does not permit me to affirm that any other disease is present than chronic interstitial inflammation of the larynx combined with perichondritis.

San Remo, February 12th, 1888. (*British Medical Journal* 1888;i:370)

¹ In this statement the words "cancer," "cancerous," and "malignant," are used synonymously.