Hormone replacement therapy prevents bone loss in patients with inflammatory bowel disease

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Abstract

Patients with inflammatory bowel disease have an increased prevalence of osteoporosis, and suffer high rates of spinal bone loss. Hormone replacement therapy (HRT) is effective in the treatment and prevention of osteoporosis but has not been studied in patients with inflammatory bowel disease. A two year prospective study of HRT in inflammatory bowel disease was performed in 47 postmenopausal women aged 44 to 67 years with ulcerative colitis (25) or Crohn's disease (22). Patients had radial and spinal bone density measured annually by single photon absorptiometry and quantitative computed tomography respectively. The mean (95% confidence intervals) annual change in radial bone density was +1.42%/yr (+0.58 to +2.26; $p < 0.005$) and for spinal bone +2.60%/yr (+1.06 to +4.15; $p < 0.005$). There was no significant correlation between rates of change of bone density at the two sites, or between the rates of change and the initial bone density either in the radius or spine. Twelve patients were given prednisolone during the study, and their rates of change for spinal bone density were lower, but values were not statistically significantly different from those who did not receive corticosteroids. Changes in bone density for patients with ulcerative colitis and Crohn's disease were not significantly different. The change in bone density did not correlate with the patients' age or number of years after the menopause. It is concluded that HRT is effective in prevention of bone loss in postmenopausal women with inflammatory bowel disease.

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Osteoporosis is more common in patients with inflammatory bowel disease (IBD) compared with the normal population, and causes significant morbidity when fractures occur.¹⁻⁴ One study identified that 25% of women had a bone mineral density more than 2 standard deviations below normals.² Increased rates of spinal bone loss have been reported in some patients and the average spinal bone loss was 3%/yr.⁵

Hormone replacement therapy (HRT) is effective in the prevention and treatment of postmenopausal bone loss.⁶⁻¹⁵ HRT also reduces the risk of fracture, but there have been no studies of its effect in patients with inflammatory bowel disease.¹⁶⁻²²

We have studied postmenopausal women with inflammatory bowel disease given HRT for two years and followed up changes in their bone density by annual measurements. Patients were given a 'standard dose' of oral oestrogen, which

has been shown to prevent bone loss in normal women.^{23, 24}

Methods

PATIENT DETAILS

Postmenopausal women with IBD were recruited from a gastrointestinal outpatient clinic. Patients were not included if HRT was contraindicated for medical reasons, such as the presence of an oestrogen dependent tumour or thromboembolic disease. Forty seven postmenopausal women aged 44 to 67 years were studied. The mean age when first measured was 54 years. Ten had had a hysterectomy and their postmenopausal state was confirmed biochemically by measurement of serum gonadotrophins; the age of these patients at their menopause could not be estimated. The average age of menopause in those who had not had a hysterectomy was 48 years (range 42 to 59) and they were 5 years (mean; range 1 to 18) postmenopausal at the time of the study.

Twenty five had ulcerative colitis (4 total, 3 subtotal, 16 distal, and 2 proctitis) while 22 had Crohn's disease (19 small bowel, 1 ileocolonic and 2 colonic). Fourteen with Crohn's disease had had small bowel resections. The average duration of their disease was 12 years (range 1 to 32). Eight patients were current smokers.

All patients were advised to achieve a daily intake of at least 700 mg of calcium; five patients were unable to take sufficient dairy products to sustain this and were given oral calcium supplements. Vitamin D was not prescribed. None were receiving thyroxine, anti-convulsants, thiazide diuretics, sodium fluoride, calcitonin, or bisphosphonates.

The risks and benefits of HRT were first explained with the aims of the study. All patients were given 0.625 mg daily of oral conjugated oestrogen (Premarin, Wyeth). Thirty seven who had not had a hysterectomy were given cyclic progestogen with 150 micrograms of norgestrel for 12 days each month in addition to 0.625 mg of conjugated oestrogen (Prempak C 0.625, Wyeth). This dose of oestrogen has previously been shown to be the minimum required to prevent bone loss in normal menopausal women.^{23, 24}

Over the subsequent two years, details of corticosteroid use and surgery were recorded although biochemical parameters were not monitored. There were no adverse effects from the oestrogen therapy apart from breast tenderness in some patients that resolved without treatment. Those receiving cyclic progestogen had regular withdrawal bleeds.

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TABLE 1 Changes in cortical bone of the radius (BMC/BW; bone mineral content/bone width, g/cm²) and spinal trabecular bone (BMD; bone mineral density, g/l) in forty seven postmenopausal women with inflammatory bowel disease treated with hormone replacement therapy for two years.

	First measurement (n=47)		Third measurement (n=47)	
	Mean	Range	Mean	Range
Age	54	44 to 67	56	46 to 69
BMC/BW (g/cm ²)	0.64	0.39 to 0.84	0.65	0.37 to 0.85
BMC/BW (Z-score)	-0.19	-2.71 to 3.17	0.17	-3.17 to 3.33
BMD (g/l)	125	72 to 190	130	79 to 201
BMD (Z-score)	-0.79	-2.71 to 0.97	-0.44	-2.58 to 1.38
Change in radial BMC/BW (n=47)	Mean	95% CI	Range	p
BMC/BW (g/cm ²)	+0.015	+0.004 to +0.025	-0.06 to +0.09	<0.01
% Of initial BMC/BW per year of follow up	+1.42	+0.58 to +2.26	-3.92 to +8.69	<0.002
Change in Z-score	+0.37	+0.16 to +0.58	-1.67 to +1.66	<0.001
Change in spinal BMD (n=47)	Mean	95% CI	Range	p
BMD (g/l)	+4.8	1.07 to +8.46	-28 to +28	<0.02
% Of initial BMD per year of follow up	+2.60	+1.06 to +4.15	-9.5 to +16.2	<0.002
Change in Z-score	+0.34	+0.22 to +0.47	-0.71 to +1.10	<0.0001

BONE DENSITY MEASUREMENT

Bone mineral density was measured at two sites – the left radius and the lumbar spine as described previously.^{2,25-28}

Radial bone mineral content was measured at the junction of the distal third and proximal two thirds of the left radius, a site where bone is predominantly cortical, with a single photon absorptiometer based on the design of Cameron and Sorenson.²⁹ Results were expressed as the ratio of bone mineral content to bone width (BMC/BW) in g/cm². The long term in vitro and in vivo precision (coefficient of variation) of the technique were estimated from repeated measurements (n=41) over five years. In vitro precision for an aluminium/perspex phantom was 2.1% while the in vivo precision was 2.7%.²⁸

Spinal trabecular bone mineral density (BMD) was measured in the anterior part of the first three lumbar vertebrae by quantitative computed tomography (Philips Tomoscan 350 CT scanner) using a modification of the method of Cann and Genant.^{30,31} The bone density was calculated using a calibration phantom containing known concentrations of K₂HPO₄ solution

and expressed in grams per litre. The precision of this technique in our hands is 2.8%.^{2,25-28}

Bone density was measured initially and then annually for two years. The same instruments and techniques were used for all the measurements.

DATA ANALYSIS

Each value of bone mineral content/bone width was converted to a Z-score relative to age and sex dependent norms ((patient value – mean)/standard deviation) using the reference data of Ringe.³² Each value for bone mineral density was converted to a Z-score (Z-bone mineral density) using the reference data of Cann and Genant.³¹

Each patient had three measurements of bone mineral density and rates of bone loss were estimated by linear regression for each subject. The annual percentage changes in bone mineral content/bone width and bone mineral density were calculated by (slope/intercept) × 100. Statistical analysis was performed using correlation coefficients, *t* tests, and Mann-Whitney U test. Statistical significance was taken as *p* < 0.05.

Results

Table I summarises the results.

The mean percentage change for bone mineral content/bone width (95% confidence intervals) was +1.42%/yr (+0.58 to +2.26) and for bone mineral density was +2.60%/yr (+1.06 to +4.15) (Table I). Figure 1 shows the cumulative absolute changes in radial BMC/BW and spinal BMD after ranking each patient by age.

The increase in both forearm and spinal bone mineral density achieved statistical significance in absolute units, percentage per annum, and also in the Z-score. Figures 2 and 3 show the percentage changes in bone mineral density.

There was no significant correlation between the baseline values of BMC/BW or BMD and the subsequent changes in bone mineral or between the rates of change of spinal and radial bone mineral density. There was no significant correlation between the improvements in bone mineral density and the patient's age or the number of years postmenopause.

Twelve patients (seven Crohn's disease) received a mean daily dose of 3.9 mg of prednisolone (range 0.5 to 10 mg) during the two years. The rate of change of spinal trabecular bone (bone mineral density) was lower in those given corticosteroids, but this was not statistically significant (Table II, Fig 2). The correlations between steroid dose and the changes in bone mineral density were not statistically significant.

Three patients had surgery during the second year of the study; two with total ulcerative colitis had a colectomy, and one patient had a terminal ileal resection. All were given prednisolone before surgery.

There was no significant difference in the response to HRT between patients with ulcerative colitis and Crohn's disease, smokers and non-smokers, and those who had had a hysterectomy and those who had not. There was no significant change in the patient's height, weight, or body mass index during the study.

Figure 1: Changes in bone mineral in individual women plotted as the cumulative absolute changes in BMC/BW (bone mineral content/bone width; g/cm²) in the radius and BMD (bone mineral density; g/l) in the lumbar spine after ranking patients by age – that is, a 'Cusum plot'. The radius is representative of cortical and the spinal vertebrae of trabecular bone.

Figure 2: The age of patients at the beginning of the two year study plotted against the subsequent percentage change per annum in spinal trabecular BMD (bone mineral density). UC=ulcerative colitis.

Figure 3: The age of the patients at the beginning of the two year study plotted against the subsequent percentage change per annum in radial cortical BMC/BW (bone mineral content/bone width). UC=ulcerative colitis.

Discussion

This is the first study of hormone replacement therapy in patients with inflammatory bowel disease. It shows that oral treatment with a standard dose of oestrogen not only prevents bone loss but after two years produced a significant improvement in bone density. The improvement occurred even in women more than 10 years postmenopausal and in both ulcerative colitis and Crohn's disease. The percentage improvement in spinal bone mineral density is similar to that reported in normal

women receiving this dose of oestrogen.^{23 24} There are no other comparable studies in the prevention of secondary osteoporosis.

Our study did not include a control group. There is already a large amount of data on normal women, which shows that HRT prevents bone loss after the menopause.⁶⁻¹⁵ In addition, without treatment patients with inflammatory bowel disease lose bone at normal or increased rates.^{2 4 5 28} We therefore felt it was inappropriate to withhold HRT from some of our patients so that this study was open and prospective, and depend on our previous studies of untreated patients with inflammatory bowel disease for comparison. Our patients treated with HRT, however, show significant improvements in their own right.

A dose response to oestrogens has been shown with increasing doses having greater effects on bone density.^{12 14 23 24} In this study, a standard bone sparing dose of oral oestrogen was used. Despite HRT some patients showed a reduction in bone density (Figs 2 and 3). In some this may be a result of an imprecision of the techniques of bone density measurement. Even in normal women on 0.625 mg oestrogen, although overall bone density increases, some still show a reduction.^{23 24 32-35} Absorption of the HRT was satisfactory as regular periods returned in those who had not had hysterectomy, menopausal symptoms resolved, and compliance with the treatment was good. Subjects may vary in their response to oestrogens and some may need a higher dose. Future studies should perhaps investigate the effect of increased doses of oestrogen and the value of transdermal administration.^{36 37} In some patients the use of prednisolone (or the exacerbation of the inflammatory bowel disease) may have resulted in net bone loss.

Although treatment with prednisolone was associated with reduced improvement in spinal trabecular bone, this was not statistically significant and there was no correlation with the dose. This study is comparatively insensitive, however, for an assessment of the effect of prednisolone because of the one year interval between measurements, the small number of patients given corticosteroids, and the variable dose and duration of treatment. While corticosteroids have an adverse effect on bone mass, this may be partly counterbalanced by improvement in the inflammatory bowel disease. Our findings of an apparently greater adverse effect on trabecular rather than cortical bone is in keeping with other publications on the effect of prednisolone.³⁸ A recent study has shown that HRT can be effective in preventing bone loss in patients receiving concurrent glucocorticosteroids.³⁹

Measurement of bone density is helpful in assessing the risk of osteoporosis in patients and in monitoring response to treatment.^{40 41} For clinicians without access to bone densitometry, these results are helpful in showing that the improvement with HRT was similar in both Crohn's disease and ulcerative colitis; in addition, the response to oestrogens was not related to the patients age or the number of postmenopausal years.

In view of the increased prevalence of osteoporosis and high rates of bone loss in some

TABLE II Changes in per cent per annum and Z-scores of those who did (n=12) and did not receive prednisolone (n=35) during the two year study while treated with hormone replacement therapy (mean; 95% confidence intervals). BMC/BW=radial bone mineral content/bone width (g/cm²), and BMD=spinal bone mineral density (g/l)

	No prednisolone (n=35)	Received prednisolone (n=12)	
	% per annum mean (95% CI)	% per annum mean (95% CI)	P
BMC/BW	+1.42 (+0.56 to +2.29)	+1.41 (-1.01 to +3.84)	0.87
BMD	+3.54 (+1.86 to +5.21)	-0.11 (-3.66 to +3.43)	0.06
	Change in Z-score mean (95% CI)	Change in Z-score mean (95% CI)	P
BMC/BW	+0.36 (+0.13 to +0.60)	+0.39 (-0.12 to +0.89)	0.98
BMD	+0.40 (+0.27 to +0.52)	+0.18 (-0.14 to +0.51)	0.22

patients we feel that all postmenopausal women with inflammatory bowel disease should be considered for HRT, particularly in those with extensive disease or those requiring longterm corticosteroid treatment.^{2,4,5,28}

Corticosteroids have a deleterious effect on bone density that can be reduced by concurrent treatment with HRT.^{39,42} Bone mineral measurement allows one of the important complications of corticosteroids to be monitored. The state of a patient's bones and the effect of corticosteroids can be balanced when considering surgery or continued medical treatment. Not all patients on corticosteroids at the same time as HRT lose bone.

We have shown that not only can bone loss be prevented in inflammatory bowel disease with hormone replacement therapy but significant improvements can be achieved.

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