Pathogenesis of vertebral crush fractures in women

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Summary
In a series of 214 women with vertebral crush fractures, 119 (55.6%) were found to have either an underlying secondary cause of osteoporosis or an early menopause before the age of 45 or both. A secondary cause of osteoporosis was present in 65 women (30.4%), the most common of which was corticosteroid therapy (13.6%) followed by previous or present hyperthyroidism (7.5%). Seventy-eight women (36.4%) had undergone menopause before the age of 45, occurring naturally in 55 (25.7%) and after surgery in 23 women (10.7%). We conclude that secondary osteoporosis and early menopause are major causes of vertebral crush fractures in women. We suggest that wider use of hormone replacement therapy following early menopause and prompt recognition and treatment of secondary causes of osteoporosis may reduce the risk of vertebral crush factures in women.

Introduction
The amount of bone in the skeleton and therefore the risk of fracture is determined by the peak bone mass, the age at which bone loss starts and the rate at which it progresses[1]. Peak bone mass is influenced by race, gender, heredity, hormonal factors, physical activity and dietary calcium intake during childhood and adolescence[1,2]. Bone loss starts at about the age of 35 in both sexes, though there is a rapid increase in the rate of bone loss at the menopause[1]. Other causes of bone loss include low body weight, smoking, alcohol consumption, physical inactivity and malabsorption of calcium[2]. There are also a number of secondary causes of osteoporosis, such as corticosteroid therapy, neoplastic disease and thyrotoxicosis, which may accelerate the development of the condition[2].

The identification of secondary causes of osteoporosis in patients presenting with osteoporotic fractures is important, as treatment of the underlying disease may reduce the rate of bone loss. Previous studies suggest that up to 55% of men with vertebral crush fractures have secondary osteoporosis[3-5]. There is relatively little published on the prevalence of secondary osteoporosis in women with vertebral crush fractures, but it is thought to be about 20-35%[1,2]. It is also uncertain how often a history of early menopause is present in women with osteoporosis. We have therefore examined the prevalence of secondary causes of osteoporosis and early menopause in a group of women with vertebral crush fractures.

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Patients and methods
Over a 4-year period 214 women (mean age 66.5, range 33-89) were seen at the Bone Clinic at Newcastle General Hospital with radiological evidence of vertebral crush fractures. After taking a full history and performing clinical examination, the following investigations were performed: full blood count (FBC); erythrocyte sedimentation rate (ESR); serum biochemical profile (SBP); free thyroxine; thyroid stimulating hormone; and serum and urine electrophoresis (SUE). Other tests such as bone marrow examination and isotope bone scan were performed as clinically indicated.

History concentrated on risk factors for osteoporosis such as early menopause; alcohol consumption; hypopituitarism; corticosteroid excess; hyperthyroidism; hyperparathyroidism; immobilization; myeloma; neoplastic disease; gastric surgery and anticonvulsant treatment[1,2]. Alcohol consumption was considered to be significant if the patient consumed more than 30 g of ethanol per day for at least 10 years, and had a raised γ-glutamyl transferase or mean cell volume, without evidence of folate or vitamin B_{12} deficiency. Corticosteroid and anticonvulsant treatment was considered significant if the patient had taken oral medication for at least 6 months.

Only immobilization of greater than two months duration was considered significant, whilst neoplastic disease was regarded of aetiological importance if there was evidence of skeletal metastases. Women with any of the above conditions were defined as having an underlying secondary cause of osteoporosis. If none of these conditions were present, the women were considered to have primary osteoporosis. Cessation of the menses before the age of 45 years was defined as an early menopause, as this is approximately two standard deviations below the mean age of menopause of 50 years in English women[6].

Results
The baseline characteristics of the women in this study are shown in Table 1. Of the 214 women with vertebral crush fractures, 65 (30.4%) were considered to have an underlying secondary cause of osteoporosis (Table 2). The commonest of these were oral

Table 1. Baseline characteristics of study population

	Mean	*SD*	*Median*	*Range*
Age	66.5	10.6	67	33-89
Height (cm)	153.0	6.7	153	137-168
Weight (kg)	57.0	10.0	56	27-90
Age at menopause	44.9	6.4	46	17-59

SD=Standard deviation

Table 2. Prevalence of secondary causes of osteoporosis in 214 women with vertebral crush fractures. The other causes category includes Paget's disease, immobilization and hyperprolactinaemia

	Number	*%*
Steroid therapy	22	10.3
Hyperthyroidism	10	4.7
Gastric surgery	4	1.9
Anticonvulsants	3	1.4
Malabsorption	3	1.4
Excess alcohol	3	1.4
Neoplastic disease	2	0.9
Hyperparathyroidism	2	0.9
Other causes	3	1.4
Multiple secondary causes	13	6.1
Total	65	30.4

corticosteroid therapy (22 women, 10.3%) and previous or present hyperthyroidism (10 women, 4.7%). Multiple secondary causes were present in another 13 women (6.1%).

In the 29 women (13.6%) on oral corticosteroid therapy, seven also had other potential causes of osteoporosis. The main reasons for corticosteroid treatment were rheumatic disorders (13 women) and chest disease (12 women).

Hyperthyroidism was implicated as a cause of osteoporosis in 16 women (7.5%), of whom six had other causes. Five women were hyperthyroid on presentation, whilst 11 gave a past history of hyperthyroidism. In two cases, hyperthyroidism was due to the exogenous administration of excess thyroxine.

Neoplastic disease was felt to be the cause of vertebral deformation in four women (1.9%), two of whom were found to have myeloma on bone marrow examination, after detection of a paraprotein band on serum and urine electrophoresis. Two women had skeletal metastases, one from carcinoma of the lung and the other from an unknown primary site. The diagnosis of malignancy was considered after an abnormal chest X-ray in the first case and elevation of the alkaline phosphatase in the second.

A history of early menopause was obtained in 78 (36.4%) women, occurring naturally in 55 and after surgery in 23 cases (Table 3). Of the surgical menopause cases, 20 followed bilateral oophorectomy (with hysterectomy in all but one), and three occurred after hysterectomy with conservation of one or both ovaries, though climacteric symptoms developed shortly after surgery. Whilst some of the women received hormone replacement therapy after an early menopause, none had taken it for longer than a year. The early menopause and secondary osteoporosis groups were not mutually exclusive however, such that in total 119 women (55.6%) had an apparent cause for their osteoporosis (Table 3).

When we analysed the women according to age, there were 88 women at or below the age of 65 and 126 women over 65 years. There was no significant difference between these two groups as regards the prevalence of secondary osteoporosis (31.8 and 29.8%, respectively). However, after excluding premenopausal women, significantly more women in the younger group had undergone an early menopause (43.2% versus 31.7%), $\chi^2=5.43$ with Yates' continuity correction, $P<0.02$).

Discussion

Our study demonstrates that secondary causes of osteoporosis and history of early menopause are found in over 50% of women presenting with vertebral crush fractures. Previous reviews suggest that the prevalence of secondary osteoporosis in such women is 20-35%, though the source of this information is not given[1,2]. We found a prevalence of secondary osteoporosis of 30.4%, despite our fairly conservative criteria for considering secondary causes as significant. Particular difficulties arise with quantifying alcohol consumption, cigarette smoking, immobilization and corticosteroid use, because of the lack of a clear threshold level beyond which bone loss occurs and problems with recall.

The commonest causes of secondary osteoporosis in our series of women with vertebral crush fractures were corticosteroid therapy and hyperthyroidism, though gastric surgery, anticonvulsant treatment, malabsorption, excess alcohol consumption, neoplastic disease and hyperparathyroidism were each implicated in at least two cases. The diagnosis of hyperthyroidism, excess alcohol consumption, neoplastic disease and hyperparathyroidism was not always apparent from the initial history and examination. We therefore suggest that the following investigations should be performed in all women with vertebral crush fractures: chest X-ray, FBC, ESR, SBP, thyroid function tests and SUE.

We also found a history of early menopause in 36.4% of our patients with vertebral crush fractures. Late menarche and secondary amenorrhoea are also well recognized risk factors for osteoporosis in women[1,2], but we chose to enquire only about the timing of the menopause, because it would be a more recent event and the data would be more likely to be accurate. Furthermore, previous work has shown a good concordance between recall and medical records for information regarding the menopause[7].

In a series of 180 patients with either low bone density or vertebral crush fractures, Johnson found that only 9.4% of the women gave a history of premature menopause, though this was defined as

Table 3. Menopausal status of study population

	Menopause >Age 45	*Early natural menopause*	*Early surgical menopause*	*Premenopausal*	*Total (%)*
Primary osteoporosis	87	35	19	8	149 (69.6)
Secondary osteoporosis	39	20	4	2	65 (30.4)
Total	126	55	23	10	214
(%)	(58.9)	(25.7)	(10.7)	(4.7)	(100.0)

cessation of the menses before the age of 40[8]. We defined early menopause as cessation of the menses before age 45, based on data showing that the mean age of menopause in English women is about 50, with a standard deviation of approximately 3 years[6]. A recent review of the published literature suggests that the mean age of menopause in Caucasian women ranges from 47.5 to 49.8 years, whilst the median value varies from 49.6 to 50.8 years[9]. Even if we analyse our data using Johnson's definition of premature menopause, 27 women (12.6%) would be considered to have had an early menopause, and 84 (39.3%) would be classified as having secondary osteoporosis or an early menopause.

Risk factor analysis has been used in attempts to differentiate women with vertebral fractures or low bone density from controls[10-16]. In none of these studies were the authors satisfied that clinical data could predict fracture risk with sufficient sensitivity or specificity, though many important secondary causes of osteoporosis were excluded from the data collection and analysis. Whilst risk factor analysis is of limited value in the identification of osteoporotic individuals, we have shown that secondary causes of osteoporosis and early menopause are common in women with vertebral fractures. We suggest that prompt recognition and treatment of secondary causes of osteoporosis and wider use of hormone replacement therapy following early menopause may reduce the risk of osteoporotic fractures in women.

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