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Fracture prevention in postmenopausal women

Olivier Bruyere MSc[1]
Research Fellow

John Edwards[2]
General Practitioner

Professor Jean-Yves L Reginster Mr MD PhD[3]
Professor of Epidemiology and Public Health
[1]*WHO Collaborating Center for Public Health Aspects of Osteoarticular Disease, Liege, Belgium*

[2]*Wolstanton Medical Centre, Newcastle-under-Lyme, UK*

[3]*Bone and Cartilage Metabolism Unit, University of Liege, Liege, Belgium*

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QUESTIONS

What are the effects of treatments to prevent fractures in postmenopausal women?

INTERVENTIONS

Prevention of fractures

Beneficial

Alendronate

Parathyroid hormone

Raloxifene

Risedronate

Likely to be beneficial

Calcitonin

Calcium plus vitamin D

Etidronate

Vitamin D analogue (calcitriol)

Unknown effectiveness

Environmental manipulation

Exercise

Hip protectors

Unlikely to be beneficial

Calcium alone

Vitamin D alone

Likely to be ineffective or harmful

Hormone replacement therapy

To be covered in future updates

Effects of dietary intervention

Effects of helmets

Effects of joint and limb pads

Prevention of pathological fractures

See glossary

Key Messages

Prevention of fractures

- **Alendronate** Two systematic reviews in postmenopausal women found that alendronate reduced vertebral and non-vertebral fractures compared with placebo at 1–4 years.
- **Parathyroid hormone** One RCT in women with prior vertebral fractures found that parathyroid hormone reduced the proportion of women with vertebral and non-vertebral fractures compared with placebo. One RCT found that parathyroid hormone plus oestrogen reduced vertebral fractures compared with oestrogen alone after 3 years.
- **Raloxifene** One large RCT in postmenopausal women with osteoporosis found that raloxifene reduced vertebral fractures compared with placebo, but no significant difference was found in non-vertebral fractures. We found no RCTs examining the effects of other selective oestrogen receptor modulators.
- **Risedronate** One systematic review in postmenopausal women

found that compared with control (placebo, calcium, or calcium plus vitamin D) risedronate reduced vertebral and non-vertebral fractures at 4 years.

- **Calcitonin** One systematic review in postmenopausal women found that calcitonin reduced vertebral fractures compared with placebo at 1–5 years after treatment, but found no significant difference between calcitonin and placebo in non-vertebral fractures.
- **Calcium plus vitamin D** One large RCT in women aged 69–106 years living in nursing homes found that calcium plus vitamin D3 reduced hip fractures and all non-vertebral fractures over 18 months to 3 years compared with placebo. One smaller RCT in women and men aged 65 years or older found that calcium plus vitamin D3 reduced non-vertebral fractures at 3 years compared with placebo, but found no significant difference in hip fractures. Another smaller RCT in postmenopausal women found no significant difference between calcium plus vitamin D3 and placebo in hip fractures after 2 years. The two smaller RCTs may have lacked power to detect clinically important differences.
- **Etidronate** One systematic review in postmenopausal women found that etidronate reduced vertebral fractures compared with control (placebo, calcium, or calcium plus vitamin D) over 2 years, but found no significant difference in non-vertebral fractures.
- **Vitamin D analogue (calcitriol)** One systematic review found limited evidence from two small RCTs in postmenopausal women that calcitriol reduced vertebral fractures over 3 years compared with placebo.
- **Environmental manipulation** We found no systematic review and no RCTs assessing environmental manipulation alone.
- **Exercise** Three RCTs found no significant difference in falls resulting in fracture at 8 months to 1 year between exercise (advice to walk briskly three times weekly, balance and strength exercises plus walking, or low-intensity exercise plus incontinence care) and control. One small RCT in postmenopausal women found no significant difference between a 2 year back strengthening exercise programme and usual care in vertebral fractures over 10 years.
- **Hip protectors** One systematic review in elderly community dwelling or nursing home residents found no significant difference in hip fractures at 6 months to 2 years between hip protectors and no protectors in RCTs where individuals were randomised. However, the review found that hip protectors reduced fractures

at 11–19 months in RCTs that used cluster analysis. The systematic review found no significant difference in pelvic fractures at 6 months to 2 years between hip protectors and no hip protectors in RCTs where individuals were randomised, but in RCTs with cluster analysis, the review found that hip protectors were associated with a reduction in pelvic fractures at 11–19 months. The review found no significant difference between hip protectors and no hip protectors in the rate of other fractures.

- **Calcium alone** One systematic review in postmenopausal women found no significant difference between calcium supplementation and placebo in vertebral or non-vertebral fractures at 1.5–4 years.
- **Vitamin D alone** One large RCT in postmenopausal women and two large RCTs in postmenopausal women and elderly men provided no evidence of a difference between vitamin D3 and placebo in hip, vertebral, and non-vertebral fractures after 2–5 years.
- **Hormone replacement therapy** We found insufficient evidence of benefit, but reliable evidence of harm. One systematic review in postmenopausal women found that hormone replacement therapy reduced vertebral fractures compared with control. However, another systematic review and two subsequent RCTs in postmenopausal women found no significant difference in vertebral fractures. Two systematic reviews and two subsequent RCTs provided insufficient evidence about the effects of hormone replacement therapy on non-vertebral fractures. One large RCT of oestrogen plus progestin versus placebo for primary prevention of coronary heart disease in healthy postmenopausal women was stopped because hormonal treatment increased risks of invasive breast cancer, coronary events, stroke, and pulmonary embolism.

DEFINITION

This topic covers interventions to prevent fractures in postmenopausal women. Fractures may be symptomatic or asymptomatic. A fracture is a break or disruption of bone or cartilage. Symptoms and signs may include immobility, pain, tenderness, numbness, bruising, joint deformity, joint swelling, limb deformity, and limb shortening.1 Diagnosis is usually based on a typical clinical picture combined with results from an appropriate imaging technique. Usually, in trials dealing with osteoporosis, menopause is considered to be present 12 months after the last menstruation.

INCIDENCE/PREVALENCE

The lifetime risk of fracture in white women is 20% for the spine, 15% for the wrist, and 18% for the hip.2 The incidence of postmenopausal fracture increases with age.3 One observational study found that age specific incidence rates for postmenopausal fracture of the hip increased exponentially beyond the age of 50 years.4

AETIOLOGY/RISK FACTORS

Fractures usually arise from trauma. General risk factors include those associated with increased risks of falling (such as ataxia, drug and alcohol intake, loose carpets), age, osteoporosis, bony metastases, and other bone disorders. Postmenopausal women are at increased risk of fracture because of hormone related bone loss. Risk factors for fractures in postmenopausal women include increasing age; low body mass index; time since menopause; alcohol consumption; smoking; some endocrine diseases, such as hyperparathyroidism or thyroid disease; and steroid use, among others.

PROGNOSIS

Fractures may result in pain, short or long term disability, haemorrhage, thromboembolic disease (see thromboembolism), shock, and death. Vertebral fractures are associated with pain, physical impairment, muscular atrophy, changes in body shape, loss of physical function, and lower quality of life.5 About 20% of women die in the first year after a hip fracture, representing an increase in mortality of 12–20% compared with women of similar age and no hip fracture. Half of elderly women who had been independent become partly dependent after hip fracture. A third become totally dependent.

AIMS OF INTERVENTION

To prevent fractures, with minimal adverse effects from treatment.

OUTCOMES

Incidence of hip, wrist, non-vertebral, and vertebral fractures (we have not reported intermediate outcomes such as bone mineral density data).

METHODS

Clinical Evidence search and appraisal January 2004. We also hand searched journals of bone diseases and carried out manual searches using the bibliographies of review articles published after 1985. Some of the RCTs identified provide results generalised to fracture per person per year overall fractures. These results provide an idea of the group effect of an intervention, but not of its effects on the incidence of fracture in an individual. Data on multiple fractures in one person

clearly differ from data on multiple people experiencing a single fracture. Regulatory authorities and scientific groups have recommended that the results of studies evaluating new interventions are expressed in terms of the proportion of people experiencing new fractures.6 This topic examines fracture prevention in postmenopausal women. However, we have included RCTs undertaken in people outside this group (men, premenopausal women) in some sections, as results from these trials may be generalisable to postmenopausal women.

QUESTION: What are the effects of treatments to prevent fractures in postmenopausal women?

OPTION: Bisphosphonates

Olivier Bruyere

Jean-Yves Reginster

Two systematic reviews in postmenopausal women found that alendronate reduced vertebral and non-vertebral fractures compared with placebo at 1–4 years. One systematic review in postmenopausal women found that etidronate reduced vertebral fractures compared with control (placebo, calcium, or calcium plus vitamin D) over 2 years, but found no significant difference in non-vertebral fractures. One systematic review in postmenopausal women found that risedronate reduced vertebral and non-vertebral fractures compared with control (placebo, calcium, or calcium plus vitamin D) at 4 years.

Benefits

Alendronate: We found two systematic reviews.7,8 The first systematic review (search date 1999, 11 RCTs, 12 855 postmenopausal women) included RCTs that randomised postmenopausal women to alendronate or placebo and had a follow up of at least 1 year.7 It found that alendronate (≥ 5 mg) significantly reduced vertebral fractures compared with placebo (8 RCTs, 9360 women; RR 0.52, 95% CI 0.43 to 0.65). It also found that alendronate (≥ 10 mg) significantly reduced non-vertebral fractures compared with placebo (6 RCTs, 3723 women; RR 0.51, 95% CI 0.38 to 0.69). The review did not state how fractures were diagnosed. The second systematic review (search date 1998, 7 RCTs, 10 287 postmenopausal women aged 39–85 years) found that, compared with placebo, alendronate significantly reduced vertebral fractures (fractures confirmed radiologically; 4 RCTs; RR 0.54, 95% CI 0.45 to 0.66) and non-vertebral fractures (6 RCTs; RR 0.81, 95% CI 0.72 to 0.92).8 It found that fewer people had hip fractures over 1–4 years, but the difference was not significant (3 RCTs; RR 0.64, 95% CI 0.40 to 1.01; results presented graphically).

Etidronate: We found one systematic review (search date 1998, 13 RCTs, 1010 postmenopausal women) comparing etidronate versus placebo, calcium, or calcium plus vitamin D.9 It found that etidronate (intermittent cyclic administration of 400 mg/day for 14–20 days followed by calcium and/or vitamin D) significantly reduced vertebral fractures over 2 years compared with control (9 RCTs; 32/538 [6%] *v* 54/538 [10%]; RR 0.60, 95% CI 0.41 to 0.88), but found no significant difference in non-vertebral fractures (7 RCTs; 48/433 [11%] *v* 49/434 [11%]; RR 0.98, 95% CI 0.68 to 1.42). The review did not describe clearly how fractures were diagnosed. **Risedronate:** We found one systematic review (search date 2001, 8 RCTs), which compared risedronate versus control (placebo, calcium, or calcium plus vitamin D).10 It found that risedronate (2.5 or 5 mg) significantly reduced vertebral and non-vertebral fractures compared with control at 4 years (vertebral fractures, 5 RCTs, 2604 postmenopausal women: RR 0.64, 95% CI 0.52 to 0.77; non-vertebral fractures, 7 RCTs, 12 958 postmenopausal women: RR 0.73, 95% CI 0.61 to 0.87). The review did not describe clearly how fractures were diagnosed.

Harms

Alendronate: Observational evidence suggests that oral alendronate is associated with oesophageal erosions and ulcerative oesophagitis. However, one RCT11 identified by the second review8 (in which people took alendronate with 180–240 mL water on rising in the morning and remained upright for at least 30 minutes after swallowing the tablet and until they had eaten something) found no significant difference in oesophagitis with alendronate compared with placebo. **Risedronate:** One systematic review (search date 2001) found no significant difference between risedronate (2.5 or 5 mg) and control in withdrawal due to any adverse effect or gastrointestinal effects, or in abdominal pain (withdrawal due to any adverse effect, 8 RCTs, 13 998 postmenopausal women: RR 0.94, 95% CI 0.84 to 1.06; withdrawal due to gastrointestinal effects, 4 RCTs, 12 313 women: RR 0.97, 95% CI 0.91 to 1.04; abdominal pain, 5 RCTs, 12 835 women: RR 0.93, 95% CI 0.83 to 1.05).10 One observational study found limited evidence suggesting that the gastrointestinal safety of risedronate seems to be in the same range as alendronate.12

Comment

Risedronate: The systematic review (search date 2001) noted that all of the included RCTs analysed data on an intention to treat basis, but that 5 RCTs had withdrawal rates greater than 25%. However, the authors noted that the magnitude of the treatment effect was unrelated to loss to follow up.10

OPTION: CALCIUM ALONE

Olivier Bruyere

Jean-Yves Reginster

One systematic review in postmenopausal women found no significant difference between calcium supplementation and placebo in vertebral or non-vertebral fractures at 1.5–4 years.

Benefits

Calcium versus placebo: We found one systematic review (search date 1998, 15 RCTs, 1806 postmenopausal women; see comment below).13 It found no significant difference between calcium (600–2000 mg) and placebo in vertebral or non-vertebral fractures at 1.5–4 years (vertebral fractures, 5 RCTs, 576 women: RR 0.79, 95% CI 0.54 to 1.09; non-vertebral fractures, 2 RCTs, 222 women: RR 0.86, 95% CI 0.43 to 1.72).13 It noted that the two RCTs reporting non-vertebral fractures had very few events, and that the pooled confidence intervals were wide (absolute numbers not reported).

Harms

The systematic review (search date 2001) did not report any data on harms.13

Comment

The systematic review (search date 2001) found that 13 of the 15 RCTs had withdrawal rates of 5–20% and two RCTs had losses greater than 20%.13

OPTION: VITAMIN D ALONE

Olivier Bruyere

Jean-Yves Reginster

One large RCT in postmenopausal women and two large RCTs in postmenopausal women and elderly men provided no evidence of a difference between vitamin D3 and placebo in hip, vertebral, and non-vertebral fractures after 2–5 years.

Benefits

Vitamin D3 versus placebo: We found one systematic review (search date 2000, 1 RCT)14 and two subsequent RCTs.15,16 The RCT identified by the review (2578 people [1916 women and 662 men], aged 70 years or older, living at home; see comment below) found no significant difference between vitamin D3 and placebo in hip fracture (confirmed by clinical assessment and x ray films; 58/1284 [4.5%] *v*

48/1280 [3.7%]; RR 1.20, 95% CI 0.83 to 1.75), or any non-vertebral fracture over 3 years (135/1284 [11%] *v* 122/1280 [10%]; RR 1.10, 95% CI 0.87 to 1.39).14 The first subsequent RCT (1144 people resident in nursing homes; mean age 85 years; 75% women) found no significant difference between vitamin D3 (10 µg/day) and placebo in hip fracture or any non-vertebral fracture (fractures confirmed by hospital discharge letter or x ray film) after 2 years' treatment (hip fracture: 50/569 [8.8%] with vitamin D *v* 47/575 [8.2%] with placebo; RR 1.09, 95% CI 0.73 to 1.63; non-vertebral fracture: 69/569 [12.1%] with vitamin D *v* 76/575 [13.2%] with placebo; RR 0.92, 95% CI 0.66 to 1.27).15 The second subsequent RCT (2686 people; 2037 men and 649 women; aged 65–85 years) reported separate results for men and women in the trial.16 In women, it found no significant difference between vitamin D3 and placebo in first fractures at any site after 5 years (42/326 [13%] with vitamin D3 *v* 58/323 [18%] with placebo; RR 0.68, 95% CI 0.46 to 1.01). In women, it also found no significant difference between vitamin D3 and placebo in first hip fractures after 5 years (10/326 [3%] with vitamin D3 *v* 10/323 [3%] with placebo; RR 0.98, 95% CI 0.41 to 2.36) or vertebral fractures (4/326 [1%] with vitamin D3 *v* 6/323 [2%] with placebo; RR 0.65, 95% CI 0.18 to 2.3).

Harms

Vitamin D3 or vitamin D analogue (calcitriol) versus placebo or calcium: One systematic review found that vitamin D or vitamin D analogues compared with placebo or calcium increased hypercalcaemia (5 RCTs, 1009 people; 22/498 [4.4%] with vitamin D or vitamin D analogues *v* 18/511 [3.5%] with placebo or calcium; RR 1.71, 95% CI 1.01 to 2.89).14

Comment

Although some RCTs included both men and women at risk of hip fracture, it is likely that the results are generalisable to postmenopausal women.14,15

OPTION: CALCIUM PLUS VITAMIN D

Olivier Bruyere

Jean-Yves Reginster

One large RCT in women aged 69–106 years living in nursing homes found that calcium plus vitamin D3 reduced hip fractures and all non-vertebral fractures over 18 months to 3 years compared with placebo. One smaller RCT in women and men aged 65 years or older found that calcium plus vitamin D3 reduced non-vertebral fractures at 3 years compared with placebo, but found no significant difference in hip fractures. Another smaller RCT in postmenopausal women found no

significant difference between calcium plus vitamin D3 and placebo in hip fractures after 2 years. The two smaller RCTs may have lacked power to detect clinically important differences.

Benefits

Calcium plus vitamin D3 versus placebo: We found one systematic review (search date 2000, 2 RCTs, 3715 people)14 and one subsequent RCT.17 The first RCT identified by the review (3270 mobile elderly women, aged 69–106 years, living in nursing homes) found that, compared with placebo, calcium plus vitamin D3 significantly reduced hip fractures (80/1387 [6%] with calcium plus vitamin D3 *v* 110/1403 [8%] with placebo; RR 0.74, 95% CI 0.60 to 0.91) and all non-vertebral fractures (160/1387 [11%] with calcium plus vitamin D3 *v* 215/1403 [15%] with placebo; RR 0.75, 95% CI 0.62 to 0.91) over 18 months. This difference remained significant after 3 years of treatment (hip fractures: 137/1176 [12%] with calcium plus vitamin D3 *v* 178/1127 [16%] with placebo; RR 0.74, 95% CI 0.60 to 0.91; all non-vertebral fractures: 255/1176 [22%] with calcium plus vitamin D3 *v* 308/1127 [27%] with placebo; RR 0.72, 95% CI 0.60 to 0.84). The review did not state how fractures were diagnosed.14 The second RCT identified by the review (246 women and 199 men, aged 65 years or older, living at home; see comment below) found no significant difference between calcium plus vitamin D3 and placebo in hip fractures over 3 years (0/187 [0%] *v* 1/202 [0.5%]; RR 0.36, 95% CI 0.01 to 8.78), but was underpowered to exclude a clinically important difference. It found that calcium plus vitamin D reduced overall non-vertebral fractures compared with placebo (11/187 [6%] with calcium plus vitamin D *v* 26/202 [13%] with placebo; RR 0.46, 95% CI 0.23 to 0.90). Fractures were diagnosed by self report, interview, and validation from case records.14 The subsequent RCT (583 women in institutional care, mean age 85 years, range 64–99 years) found no significant difference between calcium plus vitamin D3 and placebo in hip fracture at 2 years (27/393 [6.9%] with calcium plus vitamin D *v* 21/190 [11.1%] with placebo; RR 0.59, 95% CI 0.33 to 1.04).17

Harms

Vitamin D3 or vitamin D analogue (calcitriol) versus placebo or calcium: See harms of Vitamin D.

Comment

Although some RCTs included both men and women at risk of hip fracture, it is likely that the results are generalisable to postmenopausal women.14,15

OPTION: VITAMIN D ANALOGUES (calcitriol)

Olivier Bruyere

Jean-Yves Reginster

One systematic review found limited evidence from two small RCTs in postmenopausal women that calcitriol reduced vertebral fractures over 3 years compared with placebo.

Benefits

Vitamin D analogue (calcitriol) versus placebo: One systematic review14 identified two small RCTs (68 women aged ⩾ 54 years) comparing calcitriol (1,25-dihydroxy vitamin D) versus placebo. It found that calcitriol significantly reduced new vertebral fractures over 3 years compared with placebo (fractures confirmed radiologically; 8/34 [23%] with calcitriol *v* 17/34 [50%] with placebo; RR 0.49, 95% CI 0.25 to 0.95).

Harms

Vitamin D3 or vitamin D analogue (calcitriol) versus placebo or calcium: See harms of vitamin D.

Comment

None.

OPTION: CALCITONIN

Olivier Bruyere

Jean-Yves Reginster

One systematic review in postmenopausal women found that calcitonin reduced vertebral fractures compared with placebo at 1–5 years after treatment, but found no significant difference between calcitonin and placebo in non-vertebral fractures.

Benefits

We found one systematic review in postmenopausal women.18 The systematic review (search date 2000, 30 RCTs, 3993 postmenopausal women) included trials of at least 1 year's duration, which compared calcitonin versus placebo or calcium and/or vitamin D in postmenopausal women.18 It found that calcitonin significantly reduced vertebral fractures compared with placebo 1–5 years after treatment (4 RCTs, 1404 women; RR 0.46, 95% CI 0.25 to 0.87; see comment below). It found no significant difference between calcitonin and placebo in non-vertebral fractures (3 RCTs, 1481 women; RR 0.52, 95% CI 0.22 to 1.23).

Harms

The systematic review found that the relative risk for headache from one included RCT was 0.57 (95% CI 0.34 to 0.93) and that for climacteric symptoms from another included RCT was 0.20 (95% CI 0.05 to 0.77).18 It noted that, in general, included trials were poor in their reporting of adverse events.

Comment

The systematic review suggested caution in interpreting the magnitude of the effect of calcitonin in the pooled estimates.18 The pooled estimate for vertebral fractures was based on three small RCTs and a fourth larger RCT, with a large variability in results between them. Losses to follow up were 18.7%, 21%, 45%, and 59.3% in the four RCTs.18 Similar issues were raised in the pooled estimate for non-vertebral fractures.18 We found a second systematic review (search date 1996, 14 RCTs [7 RCTs in perimenopausal women with crush fractures or osteoporosis, 7 RCTs in men and women with osteoporosis or taking corticosteroids], 1309 people, exact proportions of women and men not specified; see comment below) compared calcitonin (salcatonin) versus placebo, no treatment, calcium, or calcium plus vitamin D.19 It included three RCTs identified by the first systematic review. It found that fewer people developed vertebral or non-vertebral fractures with calcitonin compared with no calcitonin, but the difference was not significant (vertebral fractures: 166/1190 [14%] people with calcitonin *v* 96/554 [17%] with no calcitonin; RR 0.80, 95% CI 0.64 to 1.01; non-vertebral fractures: RR 0.48, 95% CI 0.20 to 1.15; no further data reported). The review did not state how fractures were diagnosed. The second systematic review commented that its conclusions are limited because many of the RCTs identified did not report the occurrence of fractures, were not double blinded, and only two of the RCTs identified were of over 2 years' duration.19 The second systematic review gave no information on harms.19

OPTION: HORMONE REPLACEMENT THERAPY

Olivier Bruyere

Jean-Yves Reginster

We found insufficient evidence of benefit, but reliable evidence of harm. One systematic review in postmenopausal women found that hormone replacement therapy reduced vertebral fractures compared with control. However, another systematic review and two subsequent RCTs in postmenopausal women found no significant difference in vertebral fractures. Two systematic reviews and two subsequent RCTs provided insufficient evidence about the effects of hormone replacement therapy on non-vertebral fractures. One large RCT of oestrogen plus progestin versus placebo for primary prevention of coronary heart disease

in healthy postmenopausal women was stopped because hormonal treatment increased risks of invasive breast cancer, coronary events, stroke, and pulmonary embolism.

Benefits

Vertebral fractures: We found two systematic reviews 28,29 and two subsequent RCTs.30,31 The first systematic review (search date 2001, 22 RCTs, mean age 48–73 years) included RCTs of postmenopausal women who were healthy, or who also had coronary artery disease, a vertebral fracture, or established osteoporosis.28 It included RCTs that compared hormone replacement therapy (HRT) with placebo, calcium with or without vitamin D, or no treatment, with a follow up of at least 1 year. It found that HRT significantly reduced the incidence of vertebral fractures compared with control (13 RCTs; 42/3507 [1.2%] with HRT *v* 63/3216 [2%] with control; RR 0.67, 95% CI 0.45 to 0.98). The second systematic review (search date 1999, 57 RCTs, including 8 RCTs identified by the first review) included RCTs that evaluated fracture rates in postmenopausal women.29 It excluded three RCTs included in the first systematic review28 on methodological grounds.29 The HRT could be given in conjunction with a calcium and vitamin D supplement, provided that the comparison group received the same supplement, and that the follow up was for at least 1 year. It found no significant difference between HRT and control in the incidence of vertebral fractures (5 RCTs, 3385 women; RR 0.66, 95% CI 0.41 to 1.07). The first subsequent RCT (16 608 postmenopausal women, aged 50–79 years) found that HRT (oestrogen plus progestin) significantly reduced vertebral fractures compared with placebo (HR 0.66, 95% CI 0.44 to 0.98).30 However, after adjustment for multiple statistical testing as outlined in the monitoring plan, the difference between groups was no longer significant (HR 0.66, 95% CI 0.32 to 1.34). The second subsequent RCT (191 postmenopausal women) compared nylestriol–levonorgestrel versus placebo for 1 year.31 It found no vertebral fractures in either treatment group. However, this study is likely to have been underpowered to detect any clinically important differences between treatment groups. **Non-vertebral fractures:** We found two systematic reviews29,32 and two subsequent RCTs30,33 comparing HRT versus placebo, no treatment, calcium, or calcium plus vitamin D. The first review (search date 2000, 22 RCTs, 8774 women) found that HRT compared with placebo, no treatment, calcium, or calcium plus vitamin D significantly reduced the proportion of women with non-vertebral fractures after 1–10 years' follow up (258/4929 [5%] *v* 307/3845 [8%]; RR 0.73, 95% CI 0.56 to 0.94).32 This reduction remained significant in women taking HRT who had a mean age younger than 60 years (14 RCTs; RR 0.67, 95% CI 0.46 to 0.98; no further data provided). When RCTs in women with a mean age of 60 years or older were analysed, the review found no significant

difference in non-vertebral fractures between HRT and placebo (8 RCTs; RR 0.88, 95% CI 0.71 to 1.08; no further data provided).32 The second review (search date 1999) found no significant difference between HRT and control in non-vertebral fractures (6 RCTs, 5383 postmenopausal women; RR 0.87, 95% CI 0.71 to 1.08).29 The first subsequent RCT (2763 postmenopausal women, aged < 80 years) found no significant difference between HRT and placebo in hip fractures (fractures confirmed radiologically; 14/1380 [1.0%] with HRT *v* 13/1383 [0.9%] with placebo; RR 1.1, 95% CI 0.5 to 2.3) or wrist fractures (29/1380 [2.1%] with HRT *v* 29/1383 [2.0%] with placebo; RR 1.0, 95% CI 0.6 to 1.7), but it may have been too small to exclude a clinically important difference because the outcomes of interest were rare.33 In this RCT, prevention of fractures was a secondary outcome, the primary outcome was the secondary prevention of coronary heart disease.33 The second subsequent RCT (16 608 healthy postmenopausal women, aged 50–79 years) compared HRT (oestrogen plus progestin) versus placebo.30 The primary outcome assessed in the RCT was incidence of coronary heart disease in healthy postmenopausal women but it also assessed fracture rate. It found that HRT significantly reduced hip fractures after a mean 5.2 years' follow up compared with placebo (fractures confirmed radiologically; 44/8506 [0.52%] with HRT *v* 62/8102 [0.77%] with placebo; RR of hip fracture 0.66, 95% CI 0.45 to 0.98). However, after adjustment for multiple significance testing as specified in the monitoring plan, the difference was no longer significant (RR 0.66, 95% CI 0.33 to 1.33).

Harms

In one of the RCTs34 identified by the second review32 assessing non-vertebral fractures, 96/464 women (21%) withdrew from the trial, and more women withdrew from the HRT groups than from the non-HRT groups (72/232 [31%] from HRT group *v* 24/232 [10%] from non-HRT group; RR 3.0, 95% CI 2.0 to 4.6). The most common reasons cited for withdrawal were menstrual disorders and headache. The subsequent RCT comparing oestrogen plus progestin versus placebo as a primary prevention strategy for coronary heart disease in healthy postmenopausal women was stopped after 5.2 years' follow up because of increased risk of invasive breast cancer, coronary events, stroke, and pulmonary embolism among women receiving HRT compared with placebo (invasive breast cancer: 166/8506 [2.0%] with HRT *v* 124/8102 [1.5%] with placebo; RR 1.3, 95% CI 1.0 to 1.6; coronary events: 164/8506 [1.9%] with HRT *v* 122/8102 [1.5%] with placebo; RR 1.3, 95% CI 1.0 to 1.6; stroke: 127/8506 [1.5%] with HRT *v* 85/8102 [1.1%] with placebo; RR 1.4, 95% CI 1.1 to 1.9; pulmonary embolism: 70/8506 [0.8%] with HRT *v* 31/8102 [0.4%] with placebo; RR 2.1, 95% CI 1.4 to 3.3).30 See also HRT under secondary prevention of ischaemic cardiac events.

Comment

In the second RCT identified by the review assessing non-vertebral fractures,32 the use of multiple treatment groups without the correct statistical analyses limits the validity of the study results.34 In addition to the RCTs described, we found many observational studies with conflicting results.2,35,36,37,38,39,40,41 One non-systematic review of 11 observational studies found a reduced risk of hip fracture in women taking oestrogen compared with non-users.2 A prospective cohort study (9704 women, aged ⩾ 65 years) found a significant reduction in radiologically confirmed hip fractures with oral oestrogen only in women who started HRT within 5 years of menopause and who used it continuously thereafter.38 Other observational studies found similar fracture rates with HRT compared with no HRT.42 We found no observational studies that detected an increased risk of fracture with HRT. Several observational studies found that only 8–20% of women continued HRT for at least 3 years.43,44

OPTION: PARATHYROID HORMONE

Olivier Bruyere

Jean-Yves Reginster

One RCT in women with prior vertebral fractures found that parathyroid hormone reduced the proportion of women with vertebral and non-vertebral fractures compared with placebo. One RCT found that parathyroid hormone plus oestrogen reduced vertebral fractures compared with oestrogen alone after 3 years.

Benefits

Vertebral fractures: We found two RCTs. The first RCT (1637 women with prior vertebral fractures) found that both 20 µg and 40 µg of parathyroid hormone significantly reduced the proportion of women with vertebral fractures compared with placebo after a mean of 21 months (AR: 22/444 [5%] with 20 µg *v* 19/434 [4%] with 40 µg *v* 64/448 [14%] with placebo; RR for 20 µg *v* placebo 0.35, 95% CI 0.22 to 0.55; RR for 40 µg *v* placebo 0.31, 95% CI 0.19 to 0.50).45 The second RCT (34 women with osteoporosis taking hormone replacement therapy) found that parathyroid hormone plus oestrogen significantly reduced the proportion of women with vertebral fractures (diagnosed as a 15% reduction in vertebral height) compared with oestrogen alone after 3 years (2/17 [12%] with parathyroid hormone plus oestrogen *v* 7/17 [41%] with oestrogen alone; P = 0.04).46 **Non-vertebral fractures:** We found one RCT (1637 women with prior vertebral fractures), which found that both 20 µg and 40 µg of parathyroid hormone significantly reduced the proportion of women with new non-vertebral fractures compared with placebo after a mean of 21 months

(AR: 34/541[6%] with 20 µg *v* 32/552 [6%] with 40 µg *v* 53/544 [10%] with placebo; P = 0.04 for 20 µg *v* placebo; P = 0.02 for 40 µg *v* placebo).45

Harms

The first RCT found that parathyroid hormone 40 µg/day increased the proportion of women who experienced transitory nausea and headache compared with placebo (nausea: 18% with 40 µg/day parathyroid hormone *v* 8% with placebo; P < 0.001; headache: 13% with 40 µg/day parathyroid hormone *v* 8% with placebo; P = 0.01).45 Two women in the second RCT were reported to have withdrawn due to parathyroid hormone treatment. The first of these was due to increased back pain, the second due to the development of subcutaneous nodules at injection sites. There were no withdrawals in the oestrogen alone group.46

Comment

An intention to treat analysis was not conducted for vertebral fractures in the first RCT, as not all women had adequate radiographic evidence.45 Both RCTs used parathyroid hormone (1–34).45,46 Women in the second RCT were not blinded to treatment.46

OPTION: Selective oestrogen receptor modulators

Olivier Bruyere

Jean-Yves Reginster

One large RCT in postmenopausal women with osteoporosis found that raloxifene reduced vertebral fractures compared with placebo, but no significant difference was found in non-vertebral fractures. We found no RCTs examining the effects of other selective oestrogen receptor modulators.

Benefits

Vertebral fractures: We found one large RCT (7705 postmenopausal women with osteoporosis, aged 31–80 years), which found that 60 mg/day and 120 mg/day of raloxifene significantly reduced the proportion of women with vertebral fractures compared with placebo after 36 months (6.6% with 60 mg/day *v* 5.4% with 120 mg/day *v* 10.1% with placebo; RR for 60 mg/day *v* placebo 0.7, 95% CI 0.5 to 0.8; RR for raloxifene 120 mg/day *v* placebo 0.6, 95% CI 0.4 to 0.7).22 The proportion of women with fractures remained significantly lower after 4 years (RR for 60 mg/day *v* placebo 0.64, 95% CI 0.53 to 0.76; RR for raloxifene 120 mg/day *v* placebo 0.57, 95% CI 0.48 to 0.69).47 We found no RCTs examining the effects of other selective

oestrogen receptor modulators. **Non-vertebral fractures:** We found one RCT (7705 postmenopausal women with osteoporosis aged 31–80 years), which found no significant difference in the proportion of women with non-vertebral fractures between 60 mg/day and 120 mg/day of raloxifene and placebo after 36 months (8.5% with combined raloxifene results *v* 9.3% with placebo; RR 0.9, 95% CI 0.8 to 1.1).22 The difference remained non-significant after 4 years (10.7% with combined raloxifene results *v* 11.5% with placebo; RR 0.93, 95% CI 0.81 to 1.06 with raloxifene).47 We found no RCTs examining the effects of other selective oestrogen receptor modulators.

Harms

The RCT found that raloxifene significantly increased the risk of venous thromboembolic events compared with placebo (1.0% with 60 mg/day *v* 1.0% with 120 mg/day *v* 0.3% with placebo; RR for placebo *v* combined raloxifene 3.1, 95% CI 1.5 to 6.2).22

Comment

None.

OPTION: ENVIRONMENTAL MANIPULATION

John Edwards

We found no systematic review and no RCTs assessing environmental manipulation alone.

Benefits

We found no systematic review and no RCTs assessing fracture risk with environmental manipulation (see glossary) alone.

Harms

We found no systematic review and no RCTs assessing fracture risk with environmental manipulation (see glossary) alone.

Comment

We found one RCT (674 men and women, aged > 70 years) comparing health visitor care (aimed at assessing nutritional deficiencies, reducing smoking and alcohol intake, improving muscle tone and fitness, assessing medical conditions and use of medication, and improving home environment, such as lighting) versus control (not specified).20 It found no significant difference between health visitor care and control in new fractures over 4 years (16/350 [4.5%] with health visitor care *v* 14/324 [4.3%] with control; RR 1.06, 95% CI 0.52 to 2.13). The RCT did not state how fractures were diagnosed and gave no information on harms.20 Although the RCT included both men and

women at risk of hip fracture, it is likely that the results are generalisable to postmenopausal women.20 We found two further RCTs assessing different multifactorial interventions (including an environmental manipulation component — see comment for hip protectors).21,22

OPTION: EXERCISE

John Edwards

Three RCTs found no significant difference in falls resulting in fracture at 8 months to 1 year between exercise (advice to walk briskly three times weekly, balance and strength exercises plus walking, or low-intensity exercise plus incontinence care) and control. One small RCT in postmenopausal women found no significant difference between a 2 year back strengthening exercise programme and usual care in vertebral fractures over 10 years.

Benefits

We found one systematic review (search date 2003,23 3 RCTs comparing exercise alone versus control in preventing falls resulting in fracture) and one additional RCT (excluded from the systematic review, as it does not report on falls outcomes).24 The review did not perform a meta-analysis because of the heterogeneity of methods and interventions among trials.23 The first RCT identified by the review (165 postmenopausal women living in the community who had fractured an upper limb in the previous 2 years) compared advice to walk briskly for up to 40 minutes three times weekly versus advice to carry out upper limb exercises. It found no significant difference between groups in falls resulting in fracture after 1 year (2/81 [2%] with brisk walking *v* 3/84 [4%] with upper limb exercises; RR 0.69, 95% CI 0.12 to 4.03). The second RCT identified by the review (77 women and 22 men, aged > 65 years, living in the community; see comment below) compared a home based exercise programme (balance and strength exercises plus walking) versus no exercise programme for 14 weeks. It found no significant difference between groups in falls resulting in fracture over 44 weeks (1/45 [2%] with exercise *v* 0/48 [0%] with no exercise; RR 3.20, 95% CI 0.13 to 76.48). The third RCT (162 women and 78 men, aged > 75 years; see comment below) found no significant difference in falls resulting in fracture over 1 year with a home exercise programme (balance and strength exercises plus walking) compared with usual care (2/121 [2%] with home exercise *v* 7/119 [6%] with usual care; RR 0.28, 95% CI 0.06 to 1.33). The additional RCT excluded from the systematic review (65 postmenopausal women) compared a programme of back muscle strengthening exercises versus usual care for 2 years.24 It found no significant difference in vertebral fractures at 10 years between

strengthening exercises and usual care (fractures confirmed radiologically; 3/27 [11.1%] with exercise *v* 7/23 [30.4%] with usual care; P = 0.85).

Harms

One of the RCTs found that brisk walking significantly increased the number of falls compared with control (15.0/100 person years, 95% CI 1.4/100 person years to 29.0/100 person years — see methods).23 This result should be interpreted with caution, as reporting of falls is subject to recall bias.

Comment

Most of the RCTs identified by the review examined falls rather than fractures as the main outcome of interest.23 A fourth RCT identified by the review (190 incontinent men and women, all elderly, with multiple pathology and resident in nursing homes) compared exercise plus incontinence management versus usual care over 8 months.25 It found no significant difference between treatments in falls resulting in fracture at 8 months (4/92 [4%] with exercise and incontinence management *v* 1/98 [1%] with usual care; RR 4.26, 95% CI 0.49 to 37.42). The review did not state how fractures were diagnosed in the RCTs.23 We found two further RCTs assessing a multifactorial intervention (including an exercise component — see comment of hip protectors).21,22

OPTION: HIP PROTECTORS

John Edwards

One systematic review in elderly community dwelling or nursing home residents found no significant difference in hip fractures at 6 months to 2 years between hip protectors and no protectors in RCTs where individuals were randomised. However, the review found that hip protectors reduced fractures at 11–19 months in RCTs that used cluster analysis. The systematic review found no significant difference in pelvic fractures at 6 months to 2 years between hip protectors and no hip protectors in RCTs where individuals were randomised, but in RCTs with cluster analysis, the review found that hip protectors were associated with a reduction in pelvic fractures at 11–19 months. The review found no significant difference between hip protectors and no hip protectors in the rate of other fractures.

Benefits

Hip fractures: We found one systematic review (search date 2003, 13 RCTs, 6849 people, predominantly women; see comment below), which compared the effect of hip protectors versus no hip protectors on hip

fractures.26 The review did not pool all the RCTs in a meta-analysis because some of the RCTs used cluster randomisation and others randomised individuals. In the RCTs that randomised individuals, the review found no significant difference in fracture rate between hip protectors and no hip protectors at 6 months to 2 years (7 RCTs, 2392 people, > 75% women in 6 RCTs and proportion of women not reported in 1 RCT; AR 64/1306 [5%] with hip protectors *v* 64/1086 [6%] with no hip protectors; RR 0.94, 95% CI 0.67 to 1.31). Analysis subdivided by location (community dwelling or nursing/residential care) demonstrated no significant difference in fracture rate between intervention or control groups in either setting (community dwelling, 2 RCTs, 966 people: RR 1.11, 95% CI 0.65 to 1.90; nursing home/residential care, 5 RCTs, 1426 people: RR 0.83, 95% CI 0.54 to 1.29). Separate meta-analysis of the cluster randomised trials found that hip fractures were significantly reduced in the hip protector intervention clusters at 11–19 months (5 RCTs, 4316 people, ⩾ 70% women in 4 RCTs and proportion of women not stated in the other RCT; AR 47/1749 [3%] with hip protectors *v* 165/2567 [6%] with no hip protectors; RR 0.40, 95% CI 0.29 to 0.55). The review did not state how fractures were diagnosed.26 **Pelvic fractures:** The systematic review (search date 2003) identified 10 RCTs.26 The proportion of women, where reported, varied from 70% to 100% (one RCT did not report any details; see comment below). Meta-analysis of RCTs randomising individuals found no significant difference in pelvic fractures at 6 months to 2 years between hip protectors and control (6 RCTs, 16/1266 [1.3%] with hip protectors *v* 13/1055 [1.2%] with no hip protectors; RR 1.15, 95% CI 0.58 to 2.31). Meta-analysis of cluster randomised RCTs found a significant reduction in pelvic fractures at 11–19 months in the intervention clusters (4 RCTs, 3/1447 [0.2%] with hip protectors *v* 17/2125 [0.8%] with no hip protectors; RR 0.31, 95% CI 0.10 to 0.99). The other RCTs did not report pelvic fracture outcomes. **Other fractures:** We found one systematic review (search date 2003, 10 RCTs).26 In the RCTs identified by the review, the proportion of women varied from 70% to 100% (not reported in 1 RCT); see comment below. Meta-analysis of RCTs randomising individuals found no significant difference in non-hip, non-pelvic fractures between intervention and control groups (6 RCTs: 63/1266 [5%] with hip protectors *v* 56/1055 [5%] with no hip protectors; RR 1.06, 95% CI 0.75 to 1.50). Meta-analysis of the four cluster randomised RCTs showed no significant difference between treatments in non-hip, non-pelvic fractures in the intervention clusters (78/1447 [5%] with hip protectors *v* 119/2125 [6%] with no hip protectors; RR 0.93, 95% CI 0.70 to 1.24).

Harms

The systematic review (search date 2003) found that "no important

adverse effects of the hip protectors were reported".26

Comment

Much of the evidence is taken from RCTs that included both men and women at risk of hip fracture. However, it is likely that the results are generalisable to postmenopausal women.21,26 The systematic review (search date 2003) found that compliance with hip protectors was poor, particularly in the long term (rates ranged from 24–70% among 7 RCTs).26 Two additional RCTs were excluded from the review, as they examined multifaceted interventions that included hip protectors, rather than hip protectors alone.21,27 The first additional RCT was a cluster randomised trial (439 men and women resident in institutional care, aged ⩾ 65 years, 72% women).21 It compared a multifactorial intervention (including staff education, environmental manipulation (see glossary), exercise, walking aids, drug regimen reviews, and hip protectors for those considered at higher risk) versus usual care for 34 weeks. It found that the multifactorial intervention significantly reduced hip fractures over 34 weeks compared with usual care (3/188 [1.6%] with active intervention *v* 12/196 [6.1%] with usual care; RR 0.26, 95% CI 0.07 to 0.91). The RCT did not state how hip fractures were diagnosed. It was not clear which components of the intervention were responsible for reported effects. The second additional RCT was also cluster randomised (981 nursing home residents, mean age 85 years, 79% women).27 It compared environmental modification and modification of nursing care plus, optionally, staff training and feedback, information and education of residents, exercise, and hip protectors versus control (usual care). It found no significant difference in hip fractures at 1 year between intervention and control groups but it may have been too small to exclude a clinically important difference (17/509 [3%] with intervention *v* 15/472 [3%] with usual care; RR 1.05, 95% CI 0.53 to 2.08).27 The RCT did not state how hip fractures were diagnosed.

GLOSSARY

Environmental manipulation

This involves the restructuring of a person's environment to remove hazards and reduce the risk of falling or of a fall resulting in fracture.

Substantive changes since last issue

Updated 2005.02.01

Biphosphonates One systematic review added;10 categorisation unchanged.

Updated 2005.02.01

Calcium One systematic review added;13 categorisation unchanged.

Updated 2005.02.01

Hormone replacement therapy New RCT added;31 categorisation unchanged.

Updated 2005.02.01

Hip protectors Updated systematic review added;26 categorisation changed to Unknown effectiveness from Likely to be beneficial, in view of conflicting evidence from individually randomised and cluster randomised RCTs.

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