MANAGING FRACTURE RISK IN THE ELDERLY AND IN OBESE WOMEN

Calcium and vitamin D supplementation in the elderly

KEY MESSAGES

- Adequate vitamin D status 25(OH)D levels (> 50nmol/l) and calcium intake (1g/day) should be ensured in high-risk elderly patients
- High-risk elderly patients can be defined as: housebound or institutionalised, receiving treatment for osteoporosis and frequent fallers
- Screening for vitamin D deficiency/insufficiency may also be considered for other high-risk groups
- An adequate calcium intake (1g/day) should be achieved through dietary means where possible, but calcium supplementation should not be avoided on the basis of ‘a perceived/fear of increase in cardiovascular risk’
- 800IU/day vitamin D is adequate in most individuals requiring supplementation, but higher doses may be required in some groups (e.g. the obese)
- Recent analyses in the Cochrane Database of Systematic Review support vitamin D and calcium supplementation to the levels described above as being safe and efficacious

There is reasonable evidence that vitamin D insufficiency is harmful to bone, causing secondary hyperparathyroidism with adverse effects, increased bone turnover and bone loss, particularly of cortical bone.

Calcium is stored mainly in the bone, which acts as a reservoir and releases and absorbs calcium. It constitutes the main component of bone on which bone strength is built. On average, in a typical adult, approximately 1g elemental calcium (Ca++) is ingested daily of which 200mg/day is absorbed and the remainder excreted. Approximately 1kg calcium is stored in bone and about 500mg/day is released by resorption or deposited during bone formation. Vitamin D is obtained mainly as a result of endogenous synthesis in the skin; dietary vitamin D is more difficult to source, and is obtained mainly from fatty fish or fortified food.

Prolonged deficiency of calcium and/or vitamin D is harmful to the skeleton and Professor John Pettifor (South Africa) was the first to show that rickets developed in children as a consequence of primary calcium deficiency. The question of whether lesser degrees of vitamin D and calcium insufficiency are harmful to the skeleton is still unanswered. There is reasonable evidence that vitamin D insufficiency is harmful to bone, causing secondary hyperparathyroidism with adverse effects, increased bone turnover and bone loss, particularly of cortical bone. It is known from many studies around the world that vitamin D insufficiency is common in older people; as is evident from a recently published study from Belgium (Figure 1).1
Cochrane reviews have shown a modest reduction in risk of both hip and non-vertebral fractures in postmenopausal women and older men given vitamin D and calcium supplementation. Interpretation of nutritional studies of vitamin D or calcium supplementation on skeletal health must take into consideration the classic sigmoid response curve for most nutrients, i.e. nutrient uptake is determined by baseline clinical levels of the nutrient being studied. The heated public debate around calcium and cardiovascular risk has led to numerous meta-analyses which should be evaluated very carefully.

Professor Compston noted that the thorough studies typified by the Cochrane review are very useful. A very recent Cochrane review of the benefits of vitamin D and vitamin D analogues for preventing fractures in postmenopausal women and older men is very pertinent. The results of the analyses concerning vitamin D and calcium versus placebo or no treatment are the most pertinent findings of this review for clinical practice.

Cochrane reviews have shown a modest reduction in risk of both hip and non-vertebral fractures in postmenopausal women and older men given vitamin D and calcium supplementation and the benefit was significant. There was weaker evidence of benefit in prevention of all fractures with vitamin D and calcium supplementation, but this benefit was not statistically significant. The safety data were reassuring, with no increase in myocardial infarction (MI) and only a small increase in renal side effects (not statistically significant).

This safety data have been further supported by another Cochrane review of vitamin D supplementation involving more than 95,000 patients, mainly older women, receiving vitamin D supplementation for more than four years. These data showed an overall decrease in mortality following vitamin D supplementation; but only with vitamin D3 supplementation was a statistically significant decline in mortality observed in a separate analysis of the different therapeutic modalities. Overall reduction in mortality was shown not to be affected if calcium supplements were also given and results were similar regardless of whether vitamin D was supplemented at a dose of less than 800 or more than 800IU/day.

One of the ways vitamin D may influence fracture incidence is by reducing falls. A reduction in the rate of falls following vitamin D supplementation in frail older patients has been shown in a
The WHI study showed no difference in MI, coronary death or stroke in women receiving calcium supplementation

Calcium supplementation and potential cardiovascular risk

Turning to the controversy concerning calcium supplementation and a possible, related increase in cardiovascular events, Professor Compston described the sequence of events that led to the publicity about a potential risk of heart disease from calcium supplementation and resulting concern among clinicians and their patients.

The concern initially arose from a study undertaken in New Zealand\(^7\) where the effect of calcium supplementation on bone health and fractures was investigated in healthy older women taking these supplements. The primary endpoint of this study was fractures and fracture prevention with a pre-planned secondary outcome of cardiovascular events; the latter parameter may therefore have been less carefully adjudicated as a result of this protocol design, Professor Compston noted. Nonetheless, the study showed a significant increase in myocardial infarction (MI) in the women receiving supplementation as compared to the placebo group. This finding was supported a year later by a further meta-analysis, undertaken by the same group of researchers, of calcium supplementation with or without vitamin D supplementation, which also showed increased cardiovascular risk, particularly for MI.\(^3\) This meta-analysis did not show an increase in the composite risk of death/stroke in the supplemented groups. Overall, this meta-analysis has been severely criticised, as it removed a large cohort of women from the Women’s Health Initiative (WHI) study who had received calcium supplementation prior to being admitted into the study, thereby distorting the statistical representativeness of this study.

The design of the WHI study, in contrast to the New Zealand study, included cardiovascular events as a primary outcome thereby ensuring a more careful adjudication of these events. The WHI study showed no difference in MI, coronary death or stroke in women receiving calcium supplementation.

A further, very recent meta-analysis of calcium supplementation with or without vitamin D supplementation in postmenopausal women has also shown no increase in cardiovascular risk in the supplemented women.\(^9\) So while the data are inconsistent, the issue has been greatly tempered by the results from the fuller analysis of the total cohort of women in the WHI and these safety data are very reassuring, Professor Compston explained.

A possible mechanism whereby calcium supplementation may raise cardiovascular risk is deposition of calcium in the arteries. Coronary artery calcium scores have not, however, shown any relationship to calcium supplementation in a number of studies.

International recommendations for vitamin D and calcium intake

With regard to international recommendations on the intake of vitamin D and calcium, the Institute of Medicine’s recommendations for the daily intake of these minerals for older people are widely accepted (Figure 2). The Endocrine Society’s recommendations for vitamin D supplementation of vitamin D-deficient and vitamin D-insufficient postmenopausal women and older men, while using non-standard and more encompassing definitions of these terms, are also useful. The Society recommends 800IU/ day in order to prevent falls and fractures with the additional provision of increasing the dosage to 1500-2000IU/ day if needed based on the patient’s risk of fractures and experience of falls, in order to reach protective serum 25(OH)D levels of 75nmol/l.
In obese individuals and elderly people, higher levels of serum vitamin D may be needed to have a similar effect to increase calcium absorption rates. The lower response to vitamin D supplementation has been shown particularly for obese individuals, indicating that these individuals may require higher levels of supplementation in order to achieve overall fracture prevention.\(^{10}\)

In conclusion, Professor Compston emphasised four practical recommendations for clinical practice:

- The clinical focus is to achieve adequate vitamin D and calcium status in housebound and institutionalised people, in people receiving therapy for osteoporosis and in those experiencing frequent falls.
- Screening for vitamin D insufficiency and vitamin D deficiency should be considered for other high-risk groups
- Adequate calcium intake of 1g/day should be achieved through dietary intake wherever possible, but supplementation should be given where this is not possible
- 800IU/day vitamin D is adequate for most individuals, with the vitamin D status of obese and elderly patients requiring further evaluation for consideration of higher doses.

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### Vitamin D

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<tr>
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<th>EAR IU/d</th>
<th>RDA IU/d</th>
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<tr>
<td>Men 51–70 yr</td>
<td>400</td>
<td>600</td>
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<tr>
<td>Women 51–70 yr</td>
<td>400</td>
<td>600</td>
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<tr>
<td>Men + women ≥ 70 yr</td>
<td>400</td>
<td>800</td>
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### Calcium

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<th>EAR mg/d</th>
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<tr>
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<td>Men + women ≥ 70 yr</td>
<td>1000</td>
<td>1200</td>
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EAR – estimated average requirement
RDA – recommended dietary allowance
http://www.ncbi.nlm.nih.gov/books/NBK56072

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Figur 2. Calcium and vitamin D intake recommendations for older people: IOM 2010
OsTeOpOrOsis: elDerly anD Obese paTienTs

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**OBESITY AND OSTEOPOROSIS**

**KEY MESSAGES**

- Fractures in obese postmenopausal women make a significant contribution to the overall fracture burden.
- As obesity increases among postmenopausal women, this phenotype will be increasingly evident in clinicians’ practice and will require specific attention.
- Obese postmenopausal women with fractures frequently have normal bone mineral density (BMD) T-scores.
- The DXA and WHO classification of BMD is based on: Normal BMD = T-score of –1; osteopenic = T-score between –1 and –2.5; and osteoporotic = T-score of < –2.5.
- If weight loss is envisaged/advised in obese postmenopausal women, this strategy should be combined with exercise in order to reduce the adverse effect of weight loss on BMD.
- Further studies are required to establish the anti-fracture efficacy of bone protective therapy in obese individuals.

Obese postmenopausal women presenting with fractures frequently have normal bone mineral density (BMD) scans with a T-score of greater than –1 and sometimes even higher to levels of +1.11

The question being explored, both clinically and scientifically, is whether these fractures are osteoporotic in nature and if so, should these women be placed on therapy to protect against further fractures.

A major study contributing to the clinical understanding of osteoporosis in obesity is the Global Longitudinal study of Osteoporosis in Women (GLOW), which included more than 60 000 non-institutionalised women (mean age 69 years) attending clinics in North America, Australia and Europe and who were then followed up by self-administered questionnaires for five years.12 This cohort was used specifically to investigate fracture prevalence and fracture incidence in relation to BMI over two years of follow-up (Table 1).13

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<th>Table 1. Fracture prevalence and incidence according to BMI: GLOW13</th>
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<td><strong>Prevalent fracture at baseline</strong> n (%)</td>
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<tr>
<td>Obese BMI ≥ 30kg/m²</td>
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<tr>
<td>Non-obese BMI 18.5-30kg/m²</td>
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<tr>
<td>Underweight ≤ 18.5kg/m²</td>
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<td>Total</td>
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Fractures in obese women accounted for 23% and 22% of all prevalent and incident fractures, respectively.
It is important to note from this study that the prevalence of fractures in obese and non-obese women was similar, with the underweight women still showing a higher prevalence; but contributing smaller numbers as this group are a vanishing minority among postmenopausal women. Fractures are site-specific according to BMI with obese women being somewhat protected from spine and hip fractures, but being at a higher risk for ankle and leg fractures (Figure 3). This finding has also been shown in other studies of postmenopausal women.14, 15

Figure 3. Site of prevalent fracture in obese and non-obese women: GLOW

Further investigations using the GLOW data looked at BMI as a continuous variable and showed for the first time a new relationship between BMI and fractures. The resulting ‘bathtub’ curve of pelvic fractures versus BMI shows, for example, that obese women (BMI: 35 and above) experienced an increased risk of pelvic fracture above the normo-BMI women (25-30), although this upward trend with rising BMI did not reach the highest level of risk seen among underweight women (Figure 4).16

Figure 4. Relationship between BMI and pelvic fracture
In the evaluation of co-morbidities in this study, obese women were more likely to report co-existing asthma, emphysema and osteoarthritis and generally showed more frailty relative to non-obese women, with fractures occurring at a greater frequency and at a younger age.

The anomaly of obese women with fractures having a normal BMD should perhaps be interpreted in terms of the weight-bearing load of the skeleton, i.e., a skeleton with normal BMD having to bear a greater weight-load may be at equal risk of fracturing as an osteoporotic/osteopenic skeleton carrying normal weight, Professor Compston suggested.

It is important to ascertain whether obese women who experience non-vertebral fracture have a lower BMD than obese women who do not fracture as this can help to guide risk assessment and the need for treatment. A study of femoral hip and lumbar spine BMD in obese women with fractures has shown that these women have lower normal to osteopenic BMD levels at these sites compared to the generally normal levels of obese women who do not fracture (Figure 5).17

Pathogenesis of fractures related to obesity

There are two main causes of fracture events in obese postmenopausal women:

1. Trauma due to an increased risk of falls, a greater impact of the fall and a reduced ability to protect the body from the fall contributing to a greater morbidity.

2. Reduced BMD with potential causes being vitamin D deficiency, which is more common in women with visceral fat, secondary hyperparathyroidism, action of adipokines released from visceral fatty tissue and general immobility induced by obesity.

A new interest in the role of intramuscular fat has arisen from studies that have shown that higher levels of intramuscular fat are related to a higher risk of falls in obese women; also that higher levels of this fat contribute to a drop in muscle mass (sarcopenia) and this relates also to a higher risk of hip fractures.18

Should obese women with fractures and normal BMD receive anti-osteoporosis medication such as alendronate?

Evidence from pivotal clinical trials is scanty as obese women with normal BMD are generally not included in these trials. The GLOW study has shown that the treatment rates for obese women with incident fractures are much lower than treatment of non-obese and underweight women, reflecting the current lack of clarity with regard to this issue.13

There is some evidence that obese women do respond to bisphosphonate therapy. In a study of bisphosphonate treatment, women with a lower BMI had a significant reduction in fracture rates, but as BMI increased this benefit became smaller and was lost at very high BMIs (>40kg/m²).19

This is perhaps due to the fact that higher doses of these bone-active medications are required in obese women in order to achieve a positive protective response, Professor Compston pointed out.
Weight loss in obese, older women reduces BMD and may not be beneficial to bone health.20 However, there is evidence that exercise, when combined with diet and subsequent weight loss, can protect bone density from decline.20 Advising weight loss in older obese women is not without risk and they should be motivated to increase their exercise levels as much as practical, Professor Compston concluded.

References
6. Sanders KM, Stuart AL, Williamson EJ. Annual high-dose oral vitamin D and falls and fractures in older women: a randomised controlled trial. JAMA 2010; 303(18): 1815-1822.