North Central London
Joint Formulary Committee

Calcium + vitamin D supplementation for the prevention of osteoporotic fragility fractures

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Document control

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Contents

Summary

1) Assess lifestyle factors, dietary calcium intake and vitamin D level in all adults at risk of fragility fractures.
2) All patients prescribed anti-osteoporotic therapy (e.g. bisphosphonate) or oral glucocorticoid steroids should be considered for calcium + vitamin D supplementation unless their dietary calcium intake is adequate and vitamin D level is > 50 nmol/L. Patients should also be offered lifestyle advice.
3) Residential home residents are often vitamin D deficient, so vitamin D supplementation can be considered (outside the scope of this guideline). Calcium + vitamin D should not be routinely prescribed, particularly in those with a history of vascular disease or in those at risk of hypercalcaemia.
4) In those that do not fall into these groups, calcium + vitamin D supplementation is not routinely recommended. Patients should be offered lifestyle advice.

1. Target audience

Rheumatologists, endocrinologists, general practitioners (GPs), physicians involved in care of the elderly, orthopaedic surgeons, gynaecologists, specialist nurses involved in the care of patients with osteoporosis and pharmacists.

2. Purpose

To provide advice on the appropriate use of calcium + vitamin D supplements for the prevention of osteoporotic fragility fractures in adults (men and women).

This guideline does not include advice on:

- paediatrics
- vitamin D monotherapy (adults with vitamin D deficiency, chronic kidney disease)
- the use of bisphosphonates for osteoporosis (e.g. drug choice, dose or duration of treatment)

3. Introduction

Calcium and vitamin D are important nutrients for bone health. The Government's advisors on nutrition have set levels of dietary calcium intake or Reference Nutrient Intake (RNI) of 700mg/day [1]. If a patient has been diagnosed with osteoporosis, calcium intake may be increased to approximately 1200mg/day for adults taken as part of the diet or given as a supplement. It is recommended that the daily intake from all sources should not exceed more than 2000-2500mg of calcium a day, as higher levels may have a detrimental effect on health. The calcium intake calculator recommended by the International Osteoporosis Foundation is available at http://www.iofbonehealth.org/calcium-calculator (requires a modern browser).

Vitamin D controls the absorption of calcium from the intestines and its use in bone mineralization. NCL recommendations for vitamin D supplementation for patients requiring anti-osteoporotic medication are available at http://ncl-jfc.org.uk/prescribing-guidelines.html.

Osteoporosis is a skeletal disorder characterised by compromised bone strength predisposing to an increased risk of fracture; bone strength reflects both bone mineral density and bone quality. Clinicians should provide fracture risk assessments in line with national guidance (e.g. NICE Osteoporosis: assessing the risk of fragility fracture).

The goal for osteoporosis treatment is to reduce the number of fragility fractures. This guideline sets out recommendations for the place of calcium + vitamin D supplements in achieving this goal. Osteoporotic fragility fracture is defined as a low-trauma fracture (a fracture sustained as the result of a force equivalent to the force of a fall from ≤ the height of an ordinary chair) secondary to osteoporosis.

4. Recommendations

Appendix 1 provides a summary of the appropriate use of calcium + vitamin D supplements.

4.1. Consider calcium + vitamin D supplementation

4.1.1. Prescribed anti-osteoporotic medication (e.g. bisphosphonates, denosumab)

- All patients who receive anti-osteoporotic medication should have an adequate calcium intake (1200mg/day) and be vitamin D replete (serum vitamin D >50 nmol/L).
  - Unless a clinician is confident that the patient meets these criteria, calcium + vitamin D supplementation should be considered.
- Patients who are vitamin D deplete (serum vitamin D ≤50 nmol/L) should be treated in line with local guidelines (outside the scope of this guideline).
- Patients considered for a bisphosphonate treatment break ('bisphosphonate holiday') should maintain adequate calcium intake and remain vitamin D replete
- Lifestyle advice should be offered to all patients to reduce the individual's underlying risk of fragility fracture, see Table 1 [3,4]:

Table 1: Recommendations associated with modifiable risk factors for osteoporotic fragility fractures

Risk category	Affected group	Recommendation
Alcohol	People who consume >3 units per day of alcohol	Reduced alcohol intake to nationally recommended levels (<14 units per week in men and women)
Smoking	All smokers	Smoking cessation
Weight	People with low BMI (<20 kg/m^2)	Achieve and maintain a BMI level of 20-25 kg/m^2
Exercise	People who infrequently take part in weight-bearing exercise	30 minutes of weight-bearing exercise on most days of the week (e.g. elliptical training machines, low-impact aerobics, stair-step machines or stair climbing, fast walking on a treadmill or outside)

4.1.2. Long term oral glucocorticoids

- All patients with a prolonged oral glucocorticoid course[a] corticosteroids should undergo a risk assessment for consideration of specific anti-osteoporotic medication (e.g. alendronic acid)[6]. NOGG in their risk assessment tool (FRAX) use a prednisolone level of 2.5 mg daily for ≥ 3 months however a lower level may be appropriate for patients with coexistent morbidities and previous fracture history.
  - Follow advice in section 4.1.1 for patients who require treatment with anti-osteoporotic medication.
- Patients who do not require anti-osteoporotic medication should be offered calcium + vitamin D supplementation unless the clinician is happy that the patient has adequate calcium intake (1200mg/day) and is vitamin D replete (serum vitamin D >50 nmol/L).
- Patients who are vitamin D deplete (serum vitamin D ≤50 nmol/L) should be treated in line with local guidelines (outside the scope of this guideline).
- Lifestyle advice should be offered to all patients to reduce the individual's underlying risk of fragility fracture, see Table 1.

[a] Studies that account for confounding have not found a connection between inhaled glucocorticoids and fracture risk [5]

4.1.3. Long-term residential and nursing care (men and women)

- Patients in residential and nursing care settings are likely to be vitamin D deplete.
  - Patients who are vitamin D deplete (serum vitamin D ≤50 nmol/L) should be treated in line with local guidelines (outside the scope of this guideline).
- There is no evidence to suggest calcium + vitamin D supplementation is beneficial for people in residential / nursing home who are vitamin D replete, therefore calcium + vitamin D supplementation is not recommended.
- If calcium + vitamin D supplementation is prescribed, calcium monitoring should be considered for patients with:
  - history of hypercalcaemia
  - taking concurrent digoxin (increased risk of cardiac toxicity)
  - taking concurrent thiazides (reduced calcium clearance)
  - high tendency for renal calculus formation ie. personal history
  - endocrine disorders

4.2. Do not prescribe calcium + vitamin D supplementation

- Patients who do not meet the criteria for supplementation in Section 4.1 should be offered lifestyle advice only (see Table 1) and *should not* be offered supplementation with calcium + vitamin D.

Rationale for recommendation in Section 4.2

Two recent systematic literature reviews and meta-analyses do not support the use of calcium and vitamin D in otherwise healthy individuals. One study concluded that additional calcium ± vitamin D supplements produced a clinically insignificant increase in bone mineral density and the second study concluded supplements had no effect on hip or forearm fracture and only a small impact on vertebral fracture [7,8]. Furthermore, studies included in the second meta-analysis with the lowest risk of bias showed no effect on fracture [8]. It can therefore be concluded that the small and inconsistent benefit of calcium and vitamin D supplementation in otherwise healthy individuals, does not justify the cost or potential for harm (e.g. renal calculus, gastrointestinal disturbances and possible cardiovascular disease).

5. Cardiovascular risks associated with calcium + vitamin D supplementation

The effect of calcium supplementation on risk of cardiovascular disease (CVD) is controversial. Randomised controlled trials of calcium ± vitamin D supplementation with CVD events ascertained as a primary endpoint are lacking. Two large meta-analyses found conflicting results primarily due to differing approaches to data from the Women's Health Initiative trial, see Appendix 2. On balance, it is important to assess dietary calcium intake in all patients, and be aware of patients with significant cardiovascular history, who should preferably be having dietary calcium rather than calcium supplementation.

6. Choice of therapy

There are a number of supplements available, both on prescription and over the counter preparations. In general, patients eligible for supplementation should receive 1.0 to 1.2g/day calcium and 800iU/day vitamin D. Patients should be encouraged to split the dose of the supplement to ensure maximal calcium absorption from the GI tract. Patients who take concurrent oral bisphosphonates should either be told to take the morning supplement 30 minutes after the bisphosphonate, or miss the morning supplement on the day of the bisphosphonate. When prescribing supplements, clinicians should elicit patients preferences regarding the form, tablet size and flavour of the various preparation to facilitate compliance.

Table 2 provides first-choice calcium + vitamin D supplements. Table 3 provides alternative calcium + vitamin D supplements.

- Supplements provide 1.2g calcium + 800iU vitamin D unless otherwise specified.
- Evacal D3 is suitable for vegetarians.
- Cacit D3, TheiCal-D3 and Calceos contain a lower calcium dose therefore may be useful for patients reporting calcium related adverse effects (i.e. nausea, constipation, diarrhoea, epigastric pain).

Table 2: First choice calcium + vitamin D supplements

Form	Brand name	Flavour	Recommended dose
Tablet	Accrete D3	NA (large tablets swallowed whole)	1 twice-daily
Chewable tablets	Evacal D3[†]	Tutti frutti	1 twice-daily
Dissolve	Cacit D3[††]	Lemon	1 twice-daily

Table 3: Alterative calcium and vitamin D supplements (not an exhaustive list)

Form	Brand name	Flavour	Recommended dose
Tablet	Adcal-D3 Caplets	NA (mid-sized tablets swallowed whole)	2 twice-daily
Chewable tablets	TheiCal-D3[††]	Orange	1 once-daily
Chewable tablets	Calceos*	Lemon	1 twice-daily
Dissolve	Adcal-D3	Lemon	1 twice-daily
Dissolve	Calfovit D3	Lemon	1 once-daily

[†] Suitable for vegetarians. [††]1g/day calcium and 880iu/day vitamin D. *Provides 1g/day calcium and 800iU/day vitamin D. Choice based on prices correct October 2016.

7. Associated documents and resources

NCL Osteoporosis Service Guidelines on Management of Vitamin D Deficiency in Adults with Low Bone Mineral Density. Version 1 (21/05/2015): http://ncl-jfc.org.uk/prescribing-guidelines.html

PrescQIPP Bulletin 110. Bisphosphonate treatment break (December 2016)

8. References

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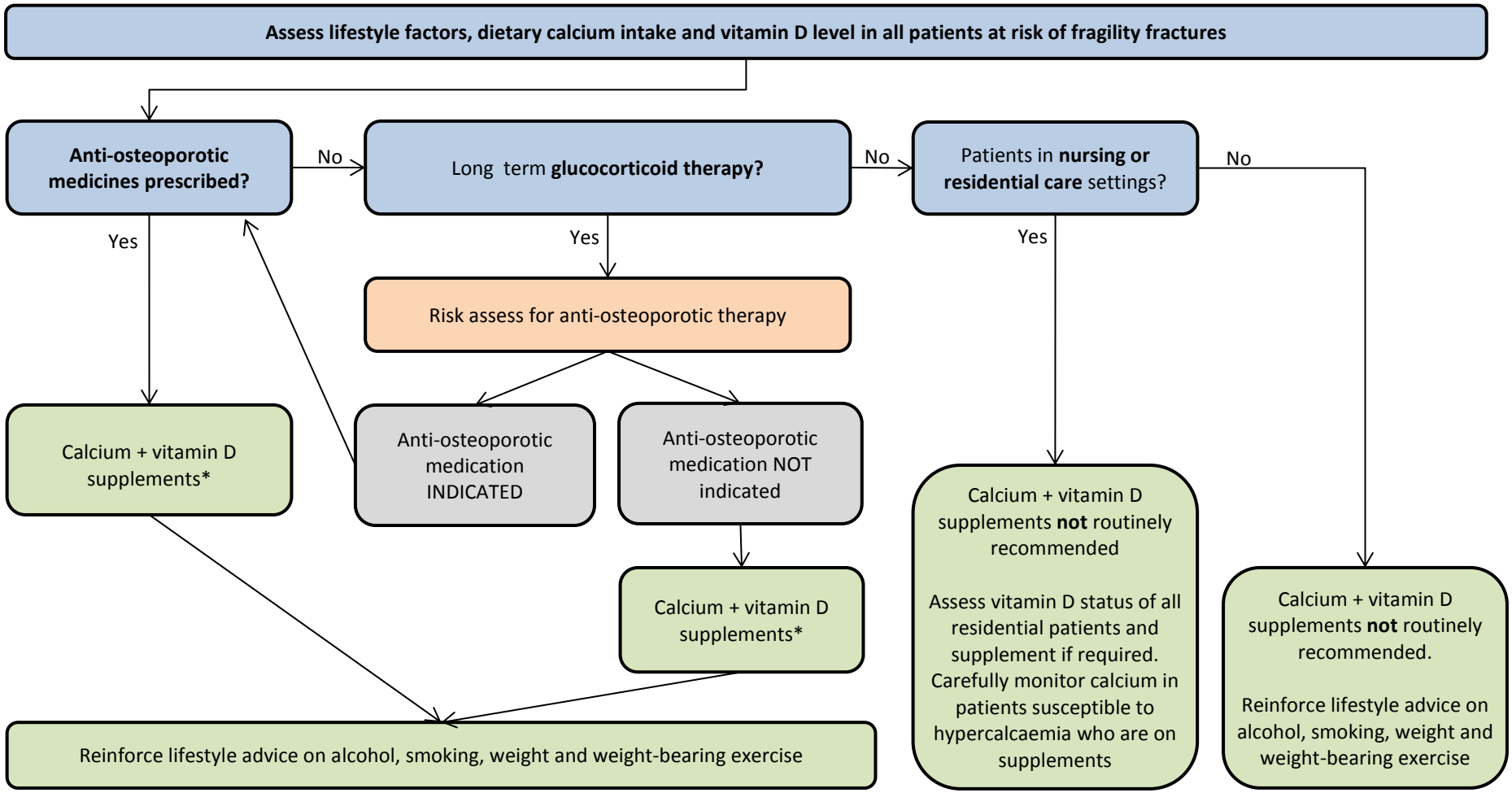
Appendix 1: Flow diagram for the use of combined calcium + vitamin D supplements in adults at risk of fragility fractures



FRAX tool available at https://www.shef.ac.uk/FRAX/tool.aspx?country=1
Q-Fracture tool available at http://www.qfracture.org/index.php

*Supplements are not required if the patient has an adequate calcium intake (1200mg/day) and is vitamin D replete (serum vitamin D >50 nmol/L). Care ought to be taken with patients who have a high risk for or previous history of vascular disease.

Appendix 2: Cardiovascular risks associated with calcium + vitamin D supplementation – summary of the evidence

Women's Health Initiative trial 2006, NEJM [10–12]

In this trial, 36,282 postmenopausal women aged 50 to 69 years were randomised to calcium + vitamin D (1000mg + 400iU/day) or placebo. Personal supplementation of up to 1000mg additional calcium and 600 units vitamin D was allowed in both arms. At baseline 54% were taking personal calcium supplementation; 29% were taking >500mg/day and the mean calcium intake (supplements, diet, medication) was 1150mg per day. After seven years, calcium + vitamin D supplementation had no significant effect on the incidence of myocardial infarction (confirmed in 411 and 390 women assigned to calcium/vitamin D and placebo, respectively; hazard ratio [HR] 1.05 [95% CI: 0.91 to 1.20]) or stroke (362 versus 377 strokes, HR 0.95 [95% CI: 0.82-1.10]).

Bolland et al meta-analysis 2011, BMJ [13]

Preparatory work for this meta-analysis required a post-hoc subgroup analysis from the Women's Health Initiative trial, using only patients without personal calcium supplementation at baseline (46% of the total population). The post-hoc analysis was considered justified because allowing participants free access to the intervention being studied in both treatment arms, had the potential to obscure both adverse and beneficial effects. It was therefore hypothesised that the high baseline use of personal calcium supplementation might obscure an adverse effect of calcium + vitamin D on cardiovascular risk. Results from the post-hoc analysis found calcium + vitamin D supplementation had a borderline effect on the incidence of myocardial infarction (confirmed in 209 and 168 women assigned to calcium/vitamin D and placebo respectively; hazard ratio [HR] 1.22 [95% CI: 1.00 to 1.50]) but no significant effect on stroke (196 versus 163 strokes, HR 1.17 [95% CI: 0.95-1.44]). The post-hoc analysis did not identify a correlation between the treatment effect (hazard ratio) and the daily dose of personal supplement intake, although the trial was not powered to do so.

The post-hoc data from the Women's Health Initiative trial was combined with *patient-level data* from two other RCTs comparing calcium + vitamin D with placebo in postmenopausal women and older men. The hazard ratios for myocardial infarction and stroke were 1.21 (95% CI: 1.01 to 1.44) and 1.20 (95% CI: 1.00 to 1.43) which suggests an increased risk for both events.

Results were similar when combining the new data with *patient-level data* from six other RCTs comparing calcium ± vitamin D with placebo; hazard ratios for myocardial infarction and stroke were 1.26 (95% CI: 1.07 to 1.47) and 1.19 (95% CI: 1.02 to 1.39) respectively. A *trial-level* meta-analysis of nine RCTs also yielded very similar results.

The Bolland study used post-hoc data from the Women's Health Initiative trial and concluded calcium ± vitamin D supplements modestly increased the risk of cardiovascular events, especially myocardial infarction. The methodological acceptability of using the post-hoc analysis has been criticised by some; a decision on whether this post-hoc analysis is acceptable is of fundamental importance as the subgroup has a greater weighting than all other studies included in the meta-analyses.

Lewis et al meta-analysis 2014, Journal of Bone and Mineral Research [14]

In this meta-analysis, the risk of developing coronary heart disease (myocardial infarction, angina pectoris, acute coronary syndrome and chronic coronary heart disease) in postmenopausal women was evaluated. The meta-analysis included *trial-level data* from 5 RCTs (including all patients in the Women's Health Initiative trial) and found no difference in the risk of coronary heart disease between women taking calcium supplements and placebo (risk ratio: 1.02 [95% CI: 0.96 to 1.09]). The meta-analysis is dominated by the Women's Health Initiative trial. This has been criticised, since there was no correction for baseline calcium supplementation that could have impacted on the results.