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Calcium in the prevention of postmenopausal osteoporosis: EMAS clinical guide

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ABSTRACT

Introduction: Postmenopausal osteoporosis is a highly prevalent disease. Prevention through lifestyle measures includes an adequate calcium intake. Despite the guidance provided by scientific societies and governmental bodies worldwide, many issues remain unresolved.
Aims: To provide evidence regarding the impact of calcium intake on the prevention of postmenopausal osteoporosis and critically appraise current guidelines.
Materials and methods: Literature review and consensus of expert opinion.
Results and conclusion: The recommended daily intake of calcium varies between 700 and 1200 mg of elemental calcium, depending on the endorsing source. Although calcium can be derived either from the diet or supplements, the former source is preferred. Intake below the recommended amount may increase fragility fracture risk; however, there is no consistent evidence that calcium supplementation at, or above, recommended levels reduces risk. The addition of vitamin D may minimally reduce fractures, mainly among institutionalised people. Excessive intake of calcium, defined as higher than 2000 mg/day, can be potentially harmful. Some studies demonstrated harm even at lower dosages. An increased risk for cardiovascular events, urolithiasis and even fractures has been found in association with excessive calcium intake, but this issue remains unresolved. In conclusion, an adequate intake of calcium is recommended for general bone health. Excessive calcium intake seems of no benefit, and could possibly be harmful.

1. Introduction

Osteoporosis is a chronic disease with a growing prevalence due to the increase in life expectancy [1]. It is far more common in women than in men, and its prevalence increases markedly after the menopause. Approximately 30% of all postmenopausal women have osteoporosis in the United States and Europe, and at least 40% of these women will suffer one or more fragility fractures [2]. As with other chronic diseases affecting modern societies, such as cardiovascular disease and cancer, risk reduction is a preferred strategy.

There are several options for the reduction of osteoporosis risk. Lifestyle is pivotal, as the use of anti-osteoporotic drugs, at least in

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Europe, has been limited by governmental agencies for treatment only [3]. Physical activity and nutrition are two crucial lifestyle measures aimed at reducing osteoporosis risk [4]. Nutrition, including an adequate calcium intake, has been shown to be an excellent approach for the maintenance of a healthy bone status at all life stages, starting from early infancy [5].

The aim of the present clinical guide is to aid health professionals, when advising women regarding calcium intake for the prevention of postmenopausal osteoporosis. The recommendations have been graded to provide evidence-based guidance. Systematic reviews, meta-analyses and randomized controlled trials (RCTs) have been given priority. PubMed was searched from January 2007 through to June 2017 to obtain the most up-to-date evidence.

These recommendations do not apply to women already receiving anti-osteoporotic drugs, since their efficacy has been proved in clinical trials in which the participants were supplemented with calcium and vitamin D.

2. The rationale for calcium supplementation

Calcium plays a key role in human physiology. As a second messenger, calcium has a central role in mediating a wide array of functions, including muscle contraction, and metabolic pathways [6]. Moreover, it is a basic constituent of hydroxyapatite crystals, the mineral component providing stiffness to the collagen network of mature bone. Insufficient calcium accrual, leading to a sub-optimal bone mass peak and low bone mineralisation, is an important factor favouring osteoporosis and fracture [7].

The rationale for recommending an adequate calcium supply is simple; calcium is crucial for bone mineralisation, hence its intake has to be sufficient.

2.1. Biochemical mechanisms of calcium metabolism

There are still unresolved questions regarding the biochemical mechanisms involved in calcium metabolism. Current evidence suggests that the intestine absorbs a low percentage only, which does not generally exceed 35%, of the calcium present in food. Two mechanisms are operative: passive diffusion, which acts only when the luminal concentration of calcium is sufficiently high; and active absorption, a saturable transport pathway involving vitamin D receptors that operates when calcium concentrations are low [8,9]. Parathyroid hormone (PTH) acts as a sensor that, in the event of a decrease in calcium levels, stimulates the production of calcitriol, the active metabolite of vitamin D.

2.2. Adolescence and menopause

While maintaining an adequate calcium intake is important throughout life, it is even more so during childhood and adolescence and after the menopause. Bone density increases during the growth periods of the teenage years reaching a peak soon after the cessation of linear skeletal growth. While bone mass is genetically determined, some clinical studies have suggested a key modulatory role for physical activity and nutrition. A Swiss study detected a synergistic interaction between physical activity and high protein intake on parameters related to bone structure and strength development in a population of children followed-up for 8 years up to mid-adolescence [10] (Evidence level IIa).

The bone density peak is sustained for some years and thereafter begins to decline, the process being stimulated during the mid-40s, when menopause transition commences. After the menopause, an accelerated period of bone loss occurs, which lasts for 6–10 years. Thereafter, bone loss continues until the end of life.

3. The daily intake of calcium

For clinical practice, it is important to know how much calcium needs to be ingested. The answer to this question is presently unknown, because intestinal absorption is subject to many variables, including age, gender, gonadal function, ethnic group, other dietary components and even the pattern of calcium intake (i.e. variation of ingested amounts throughout the day).

Recommended dietary intake levels vary throughout life, being higher during the time of bone formation and in older people. Most health agencies recommend higher requirements in those specific life periods, which may increase up to 1000–1300 mg/calcium per day, as detailed below. As the main source of dietary calcium is derived from dairy products, people with low intake (i.e. vegans or those with lactose intolerance) should have their intake re-assessed. The prevalence of lactose intolerance has been estimated at around 25% among US adults [11]. Furthermore, coeliac disease and previous bariatric surgery may impair absorption.

The importance of vitamin D was shown in a study of 9961 US adults that found that 25-hydroxyvitamin D status seems to be the dominant predictor of bone mineral density (BMD) relative to calcium intake [12].

Recommendations on calcium intake vary worldwide. For example, those from the US National Institutes of Health are based on recommended dietary allowances (RDA); i.e. the average daily intake sufficient to meet the requirements of 97–98% of healthy individuals [11]. RDA for women are 1300 mg between 9 and 18 years of age, 1000 mg between19 and 50 years and 1200 mg thereafter. The National Osteoporosis Society (NOS) in the UK uses the term reference nutrient intake. In the case of calcium, it is set at a daily requirement of 700 mg. This lower daily calcium intake is considered sufficient to meet the daily requirements of 97.5% of the adult population. This amount is increased to 1000 and 800 mg in peripubertal and adolescent boys and girls, respectively [13]. The NOS recommendation is consistent with balance data from metabolic studies in which individuals had their intake and output of calcium (stool, sweat, urine) measured. The authors concluded that neutral calcium balance, defined as calcium output equal to input, was achieved at an intake of 741 mg/day [14]. The NOS also defines 400 mg/day as a lower reference nutrient intake (LRNI), i.e. the lowest amount of calcium required to maintain a healthy skeleton [13].

3.1. Calcium intake at the population level

Data exist on the average calcium intake at the population level. One US study analysing data from NHANES (2003–2006) [15] showed that less than one third of women aged 9 to71 had an adequate intake of calcium (or the level assumed to ensure nutritional adequacy) from their diet alone; the proportion improved among supplement users but, still, less than 50% achieved age-specific recommendations. In this population, two thirds of women aged over 51 years took calcium supplements.

Information from Europe shows differences between countries. The Mediterranean diet, for example, often contains inadequate amounts of calcium. One Spanish study using dietary questionnaires found that the mean daily calcium intake of a group of 2009 adults from the general population was 698 mg [16]. However, low rates of fragility fracture are found in that country [1]. In contrast, intake averaged 1250 mg/day in a cohort of Finnish women [17].

4. Calcium for the prevention of postmenopausal osteoporosis

Daily calcium intake should be estimated before deciding on a management strategy and this can be undertaken using online calculators [see for example 18]. Alternatively, a basic dietary anamnesis may offer information on the amounts of consumed dairy products and

nuts (foods with the highest calcium content). Commonly, though, clinicians simply apply the “better over than under” principle, and recommend calcium supplementation in all cases, obviating the need for any dietary assessment.

When calcium supplementation is required, the question arises of whether this should be through diet or supplements.

4.1. Diet

The advantages of dietary interventions are that they are largely free of adverse effects (food intolerance excepted) and cost-effective for both consumers [19,20] and the public health system in countries where supplements are funded. They may also be preferred by women who favour “natural” interventions and whose taste preferences align with such diets.

Moreover, it is likely that a more regular distribution of calcium intake, free of the peaks associated with supplements, could decrease potential harms, as described below, although this issue has not been sufficiently investigated. Dietary change, in turn, requires behavioural modification, which may be difficult. Nevertheless, the use of dietary intervention seems supported (Grade B recommendation).

4.2. Supplements

Calcium supplements are often available in salt formulations, the most popular being calcium carbonate and calcium citrate [21]. Calcium carbonate is cheap, but is poorly tolerated by some women, who complain of constipation, abdominal cramps and bloating. Moreover, calcium carbonate, but not calcium citrate, should be taken with meals because gastric acid is required for optimal absorption [21,22].

One advantage of supplements is that the administration of a defined amount of calcium, which is generally reported on the label as elemental calcium, is secured. However, there are three main concerns regarding the use of supplements: systemic calcium peaks, poor adherence and inappropriate supplementation.

High levels of calcium are accompanied by a concurrent reduction in PTH secretion, and changes in bone metabolism markers have been shown hours following the administration of oral preparations of different calcium salts [23–25]. This phenomenon persists long after treatment initiation [26]. The possibility that repeated calcium peaks have deleterious health effects has some experimental support [27]. To reduce this effect, a maximum of 500 mg of elemental calcium is recommended per dose. In this regard, it is unclear how changes induced by a diet rich in calcium compares to that of pharmacological supplementation.

Adherence is another difficulty related to pharmacological supplements. Compliance to treatment seems to be poor, even when supplements are given to women already diagnosed with osteoporosis. In a cross-sectional study of women receiving calcium and vitamin D supplements due to osteoporosis, only 50% had good self-reported adherence to treatment. Women in the poor adherence group had more problems with tolerance and more concurrent pathologies; often calcium adds to the list of concomitant medications in already polymedicated patients [28].

Finally, a problem of inappropriate prescription exists, often as a result of the “better over than under” principle mentioned above. A Spanish cross-sectional study found that at least one criterion for inappropriate prescription was met by 85.8% of the 11,035 participating adults; among the most relevant criteria, 53.8% of subjects were given calcium in quantities higher than 500 mg per dose, and 29% had an excessive consumption, defined as over 2000 mg per day [29].

5. Clinical impact of calcium supplements

5.1. Impact on bone

Clinical studies have produced inconsistent results regarding the role of calcium for the reduction of fracture risk. A meta-analysis of 15 RCTs comparing calcium supplementation with the usual diet, with a total of 1806 participants, found only a very modest effect on BMD and no discernible effect on the incidence of fracture [30] (Evidence level 1a). A more recent systematic review and meta-analysis came to similar conclusions [31].

Another recent meta-analysis of 170,991 women, pooling data from 7 prospective cohort studies, concluded that there was no relationship between total calcium intake and the risk of hip fracture (Evidence level 1a); the additional inclusion of 5 clinical trials with a total of 5666 women could not reject the possibility that high calcium consumption might actually have a negative effect on health [32].

An observational study in Sweden related to 61,433 women attending the national mammography programme and followed-up for 19 years found that in women ingesting less than 741 mg/day of calcium the crude rate of a first fracture of any type was 17.2/1000 persons/year, whereas this rate decreased to 14.0/1000 persons/year among those taking 882–996 mg/day. No further reduction was observed in women with higher calcium intakes and, of importance,the risk increased in those higher calcium consumers when considering hip fracture separately [33]. The authors recognised that the threshold for calcium intake might have been exaggerated, because diet questionnaires tend to overestimate calcium consumption.

Interventional studies based on vitamin D added to calcium also render conflicting results. Two meta-analyses found some degree of fracture protection. The US Preventive Services Task Force (2011) found a modest 12% risk reduction of any type of fracture, but this was limited to institutionalised individuals [34]. More recently, the National Osteoporosis Foundation (NOF) (2016) found a 15% reduction in total fractures and a 30% reduction in hip fractures in both community-dwelling and institutionalised adults [35]. In contrast, a recent analysis of the Women's Health Initiative Calcium and Vitamin D trial (WHI CaD) could not find any effect of the supplements on height loss, a clinical indicator of vertebral fracture [36]. Furthermore, a recent expert consensus meeting of the European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (ESCEO) and the International Osteoporosis Foundation (IOF) concluded that supplementation with calcium alone for fracture reduction is not supported by current evidence [37].

In summary, the benefits of calcium supplementation have been shown only when it is combined with vitamin D. Even then, fracture reduction seems modest and does not warrant a population-level intervention (Evidence level Ib) [37]. The possibility that the effect might be mediated by specific genetic factors has been recently suggested, but the issue needs further investigation [38].

5.2. Potential risks

Clinical decision-making requires a detailed knowledge of potential adverse effects, particularly if, as described above, the benefit is unclear or, in the best of cases, only modest. Two issues have raised concern: the possible risk of renal stones and cardiovascular disease.

5.2.1. Renal stones

The logical basis for a hypothetical increase in the incidence of renal stones as a consequence of calcium supplementation is straightforward. The rise in serum calcium concentration is expected to increase calciuria, which in turn would increase the risk for nephrolithiasis. However, this supposition has not had clinical confirmation and observational studies have not sustained this relationship [39,40]. The WHI CaD trial, however, detected a 17% increase in clinical urolithiasis

in the group supplemented with 1000 mg of calcium versus the group receiving placebo (Evidence level IIa) [41]. Adequate hydration, though, may help reduce this risk [42].

5.2.2. Cardiovascular disease

The initial suggestion that calcium supplementation might increase cardiovascular risk came from the Auckland Calcium Study, a 5-year RCT in which older women allocated to calcium supplements suffered an increased rate of cardiovascular events [43].

The debate has become intense since 2010, with the publication of a meta-analysis of 15 RCTs of calcium supplementation (500 mg/day or more), each with at least 100 participants of a mean age more than 40 years and study duration of more than 1 year [44]. This meta-analysis found that calcium supplements were associated with a higher risk of myocardial infarction [hazard ratio (HR) 1.31, 95% CI 1.02–1.67].

Following criticisms of this paper, Bolland et al. reported a subsequent meta-analysis that pooled RCTs of calcium only and data from the WHI CaD. Again, they found that calcium or calcium plus vitamin D increased the risk of myocardial infarction [relative risk (RR) 1.24, 95% CI 1.07–1.45] and the composite outcome of myocardial infarction or stroke [1.15 (1.03–1.27)] [45].

Furthermore, a similar conclusion was obtained in two longitudinal cohort Scandinavian studies. The 19-year follow-up database of the national mammography programme of Sweden, which evaluated total calcium intake, i.e. dietary and supplemental calcium, concluded that high intakes of calcium in women were associated with higher death rates from all causes [HR 1.40 (95% CI 1.17-1.67)] and from cardiovascular disease (1.49, 1.09-2.02)), but not from stroke [46]. In Finland, the Kuopio Osteoporosis Risk Factor and Prevention Study found that the use of calcium or calcium plus vitamin D supplementation increased the risk for coronary heart disease [multivariate adjusted HR 1.26 (95% CI 1.01-1.57)] in 10,555 women aged 52–62 years [47]. Another 5-year follow-up study in Gothenburg, Sweden, found that elderly women taking calcium supplements doubled their dementia risk [48].

The debate has not been settled, as methodological concerns have been raised. For instance, the second meta-analysis by Bolland et al. [45] has been criticized because women who were already taking calcium supplements upon enrolment in the WHI CaD were excluded. The authors argued that the reason for this exclusion criterion was that 54% of the participants were already taking non-prescribed calcium supplements upon randomisation and 47% were taking non-prescribed vitamin D supplements. Inclusion of those participants would have violated the objectives of the trial by rendering it a comparison of higher-dose and lower-dose calcium and vitamin D.

The biological plausibility of these findings is another issue. It has been claimed that calcium supplements increase circulating calcium levels, an effect that is maintained long term. Calcium levels are associated with some biomarkers of atherosclerotic burden, including thickness of the carotid intima-media [49]. In addition to contributing to the calcification of atheroma plaques, other mechanisms have been suggested, including acute deleterious effects on blood pressure and blood coagulation [50] and an increased risk of atrial fibrillation [51]. The significance of these findings, nonetheless, is unknown at present.

Two subsequent meta-analyses of observational and clinical studies could not ascertain an association with cardiovascular risk [52,53]. Because of these discrepancies, the NOF undertook another analysis, which included studies of both dietary and supplemental calcium [54]. Again, a dose-response relationship could not be found between dietary or total calcium intake and the risk of cardiovascular disease (Evidence level 1a). Because of the importance of the issue, a statement was issued by the NOF and the American Society for Preventive Cardiology in 2016, indicating that calcium intake, either from diet or from supplements, has no apparent effect on the risk of cardiovascular or cerebrovascular disease [55]. The limitation of the evidence, however, is recognised, because cardiovascular disease has been only a secondary outcome in all trials.

6. Summary

- An adequate intake of calcium as a mainstay in the prevention of postmenopausal osteoporosis remains a universal recommendation in guidelines.
- It is important to get an assessment, even approximate, of the individual's intake of calcium. Supplementation may be recommended, where levels are or seem to be insufficient.
- Women should be warned that calcium intakes above the recommended levels may be useless, or may even entail some harm, though this remains uncertain.
- Dietary interventions may be advantageous, but this also lacks strong evidence and is not universally agreed.
- Women who do not wish to take supplements and who have problems in maintaining a diet sufficiently rich in calcium should be reassured that this is unlikely to affect adversely their fracture risk. Other measures, like physical activity and vitamin D supplements may help to maintain bone health.

Contributors

Antonio Cano prepared the initial draft, which was circulated to all other named authors – EMAS board members – for comment and approval; production was coordinated by Irene Lambrinoudaki and Margaret Rees.

Conflict of interest

1. Antonio Cano, none declared
2. Peter Chedraui, none declared
3. Dimitrios G. Goulis, none declared
4. Patrice Lopes, none declared
5. Gita Mishra, none declared
6. Alfred Mueck, in the past year has received funding of research by various pharmaceutical companies who produce and/or sell products for the use of hormone therapy in peri- and postmenopausal women and lecture fees from various pharmaceutical companies speaking on hormone therapy or other issues of menopause.
7. Levent M. Senturk, none declared
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