'CALCIUM AND BONE HEALTH'
POSITION PAPER FOR THE AUSTRALIAN AND NEW ZEALAND BONE AND MINERAL SOCIETY (ANZBMS), OSTEOPOROSIS AUSTRALIA AND THE ENDOCRINE SOCIETY OF AUSTRALIA.

PREPARED BY THE WORKING GROUP OF THE AUSTRALIAN AND NEW ZEALAND BONE AND MINERAL SOCIETY AND OSTEOPOROSIS AUSTRALIA.

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Consensus process: *A working group commissioned by the ANZBMS and Osteoporosis Australia (OA) developed this position statement. Drafts were developed and circulated within the working group with expertise in bone health and osteoporosis. A consensus draft was then circulated to other experts in the area before a subsequent draft was posted on the ANZBMS website for widespread comment and feedback. Suggested revisions were incorporated with consensus from the working party. The scientific affairs committees of the ANZBMS and OA reviewed the final manuscript. This edited version of the full position statement has been reviewed by all members of the Working group and senior representatives of Osteoporosis Australia and ANZBMS.*

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KEY POINTS

- The available data suggest that supplementation with calcium plus vitamin D prevents fractures in the frail elderly, particularly in women in residential care.
- Inadequate vitamin D status exacerbates the deleterious effects of a low calcium intake.
- Early puberty is likely to be an ideal time to ensure adequate calcium intake in order to maximise bone health in the growing skeleton.
- The requirement for calcium during pregnancy and lactation is not increased above that required in the non-pregnant state, except for teenagers.
- Foods high in calcium provide protein and other micronutrients that may be important for general health, particularly in the frail elderly [1].
- Long-term adherence to calcium supplementation is poor, possibly related to individuals suffering from digestive problems or constipation, and the cost of products to the individual.
- Improved bone health can result from the additive effect of calcium intake and weight-bearing physical activity.

SUMMARY

- Randomised controlled trials demonstrate that individuals with baseline intakes of 500-900 mg/day show beneficial changes in bone density when those intakes are increased by a further 500-1,000 mg/day.
- The effect of calcium supplementation on bone health is modest, as shown by increases in bone density and reductions in excessive bone turnover. The relative risk reduction for osteoporotic fracture is likely not to be more than 10 to 20 per cent although reductions of over 30 per cent have been reported in compliant adults.
- Although inadequate calcium intake is likely to be deleterious to bone, calcium intakes significantly above the recommended level are unlikely to achieve additional bone health benefit. Thus, strategies to increase calcium intake should be focused on people with the lowest calcium intakes.
- Low salt diets can decrease urinary calcium loss and may lead to improvements in bone health but requires further study.

INTRODUCTION

Osteoporosis is a disorder in which the amount of bone present in the skeleton is reduced although the mineral content and osteoid surface of such bone is generally normal. Patients with osteomalacia on the other hand, have a reduced mineral content and excessive amounts of uncalcified osteoid can be seen on histological examination. In patients with hip fracture and severe chronic vitamin D deficiency (serum 25OH vitamin D levels less than 12.5 nmol/L), osteomalacia and osteoporosis often coexist[3, 4]. The reduced bone mass seen in osteoporosis may result from increased resorption and/or reduced formation of new tissue. Calcium deficiency reduces bone mass by increasing bone resorption to preserve the ionised calcium in the extracellular fluid. Secondary hyperparathyroidism and increased bone resorption occur in both calcium and vitamin D deficiencies.

Bone is composed of type 1 collagen hardened by crystals of hydroxyapatite. The physiology of calcium metabolism is primarily directed towards maintaining the concentration of ionised calcium in the extracellular fluid. This is protected and maintained by a feedback loop through calcium receptors in the parathyroid glands. Parathyroid hormone increases the renal tubular reabsorption of calcium, promotes intestinal calcium absorption by stimulating the renal production of 1,25-dihydroxyvitamin D and, if necessary, resorbs bone. The integrity of the system depends critically on the vitamin D status.

The body's calcium reserve is stored in the skeleton and is affected by the dietary calcium intake and absorption on the one hand and losses of calcium through the skin, kidney and bowel on the other[5]. Intestinal calcium absorption has an active saturable component and a diffusion component. At low calcium intakes calcium is mainly absorbed by active transport but at higher intakes an increasing proportion of calcium is absorbed by simple diffusion. As calcium intake increases, net absorbed calcium also increases, steeply at first but then, as the active transport becomes saturated, more slowly until only about 5-10 percent of the calcium is absorbed[5].

From birth to puberty the skeleton increases in mass about 7-fold and a further 3-fold during adolescence[6]. Bone mass then remains relatively stable during early adulthood. For about the first 5 years after the menopause women lose bone at a rate of about 2-3% and then continue to lose at about 1% per annum to the end of life[7]. During this time there is a decline in intestinal calcium absorption and an increase in urinary calcium excretion[8]. Men also start to lose bone at about the age of 50 but rather more slowly than women. The rate of bone loss in older men and women is about the same and calcium absorption decreases with age.

CALCIUM AND THE GROWING SKELETON

Clinical, longitudinal, retrospective and cross-sectional studies in children show inconsistent findings with respect to the effect of calcium intake[9]. A number of caveats need to be considered when evaluating studies of calcium status during childhood and adolescence. Factors affecting calcium balance are likely to change with stages of development. Calcium kinetics studies have demonstrated that net calcium retention is greatest when the growth spurt is at its peak in early pubertal children, compared with pre-pubertal or late pubertal girls[10]. In a 3-year calcium supplementation study a positive effect on bone mineral density (BMD) was observed in pre-pubertal twin pairs but not pubertal or post-pubertal twin pairs[11]. When

baseline habitual calcium consumption is low, larger increments in BMD occur with increased dietary calcium[12] and sustained beneficial effects of higher intakes are more likely to occur in individuals with previously low habitual calcium intakes[13]. Although a prospective observational study has estimated that 26% of adult calcium is laid down during the two years of peak skeletal growth, in this study the calcium intake explained less than one per cent of the variance in maximal bone growth[14]. Others have estimated 2 to 5 per cent of the variance in adolescent bone gain and later peak bone mass is associated with calcium intake during adolescence[15]. While there is some data linking calcium intake to skeletal accrual of calcium, the effect size appears to be small and a positive association is not a consistent finding[15, 16].

Most[11, 13, 17-24] but not all[17] randomised controlled trials with children and adolescents using either dairy supplemented foods or calcium supplementation demonstrate some beneficial results. In early pubertal groups, an increased rate of gain of bone mineral content (BMC) and BMD among supplemented calcium compared to controls has been reported for total BMC (14% vs 8%, $p<0.001$) and BMD at the lumbar spine (23% vs 13%, $p<0.001$) but not at the femoral neck[25, 26]. Increasing calcium intake from a mean baseline of 730 mg/day to 1600 mg/day significantly increased lumbar spine and total hip BMD over an 18 month period in post-menarcheal but not pre-menarcheal twin pairs[18]. Nevertheless, a recent meta-analysis demonstrates that although the point estimates for the 19 RCT are positive in favour of benefit, the confidence intervals usually cross zero[27]. The authors conclude that there was no effect of calcium supplementation on BMD in children at the femoral neck or lumbar spine. There was a small effect on total body BMC and upper limb BMD while the small increase (1.7 percentage point greater increase in the supplemented group) in upper limb BMD was the only site where a sustained benefit could be demonstrated following cessation of the calcium supplementation. More studies are required in children with low calcium intakes and in peripubertal children.

An association between fragility fractures in older age and calcium status in childhood is difficult to establish because of inherent difficulties in assessing habitual calcium intakes as well as potential confounding differences in other associated lifestyle factors. Nevertheless, an association between childhood fracture and calcium intake has been reported. Peri-pubertal boys and girls who had sustained a fracture had lower calcium intakes compared with those with no fracture history[28].

The recommended daily intake of calcium for children and adolescents in Australia and New Zealand is 1,000-1,300 mg/day and the estimated average requirement (EAR)[α] is 800-1,050 mg/day[8]. In those with very low calcium intakes, either by choice or because of intolerance to dairy products, dietary modification or calcium supplementation is advisable.

REPRODUCTIVE YEARS INCLUDING PREGNANCY AND LACTATION

Pregnancy and lactation are characterised by physiological adaptive processes that provide the calcium necessary for foetal growth and breast milk production, independent of maternal calcium intake[29]. Calcium absorption and urinary calcium excretion are higher during pregnancy than before conception or after delivery[29]. The

[α] The new recommended dietary intake (RDI) meets the needs of 98% of the population and the estimated average requirement (EAR) meets the needs of 50% of the population.

increases are evident in early to mid pregnancy and precede the increased demand for calcium by the foetus for skeletal growth. Bone resorption and bone formation markers increase early in gestation and increase further during pregnancy. The patterns of change in calcium and bone metabolism during pregnancy and lactation are consistent with the mobilisation of calcium from the maternal skeleton to meet the high requirement for foetal growth toward the end of gestation and for breast milk production during lactation, with subsequent restoration in the later stages of lactation and after weaning. The skeletal effects of pregnancy may be modified by the maternal skeletal maturity. In adolescents, pregnancy seems to increase bone resorption to a lesser extent than in adults and to decrease bone formation compared with pregnant women who are over 21 years[30].

Lactation associated decreases in bone mineral are reversible and by 3 months post weaning there is little to distinguish mothers who have breast-fed from those who have not, including those who have breast-fed for an extended period. Furthermore, parity and lactation do not appear to be associated with increased fracture risk[31]. Calcium concentration in breast milk is not influenced by maternal calcium intake during the breast-feeding period and lactational performance does not appear to be impaired in women consuming a low calcium intake[32]. However, calcium supplementation in pregnancy does suppress maternal bone turnover[33] and may be associated with skeletal benefits in the newborn, particularly among women with low dietary calcium intakes[34,35].

The RDI of calcium in Australia and New Zealand is 1,000 mg/day and the EAR is 840 mg/day. The RDI and EAR for teenage pregnant or lactating females is 1,300 and 1050 mg/day, respectively[8].

ADULTS

There is some evidence that calcium supplementation in men and young women before the menopause is beneficial but most research has focused on postmenopausal women. There is little evidence regarding the effect of calcium on the bone health of men aged less than 50 years.

Randomised controlled trials assessing bone density generally show a beneficial effect, typically between 1 and 2% (absolute difference over 2-3 years) in calcium-treated men and women[36-39,40,41]. This results in a sustained reduction in bone loss of 50-60%[36-39]. Increases in bone density have been demonstrated at the radius, spine, proximal femur as well as total body BMC[36, 42]. Benefits in late postmenopausal women are more consistent across studies than in peri-menopausal women perhaps due to greater variation in the rate of bone loss among peri-menopausal women. Beneficial effects in perimenopausal women have been reported in some[43] but not all studies[37]. By contrast a calcium intervention trial that divided into women aged above and below 60 years reveals no difference in BMD change with calcium treatment[36]. As with children and adolescents, the effects among women appear greater in those with lower baseline dietary calcium intakes[36, 42].

The beneficial effect of calcium supplementation is most marked in the first year of treatment[44] and is attributed to a suppression of circulating parathyroid hormone concentrations. The decreased activation of bone remodelling foci and filling of the

bone remodelling space is particularly evident in trabecular bone. This mechanism probably explains the transient increase in BMD over the first year of therapy even among women with high calcium intakes[43]. The more sustained and cumulative benefit in cortical bone may reflect the slower turnover of this type of bone but probably also implies a sustained positive effect on bone balance. It may be that this is observable in total body scans due to their greater precision and high proportion of cortical bone (80%), though it might also imply that calcium supplementation and the fall in parathyroid hormone that results from it, have a qualitatively different effect on cortical bone.

Randomised controlled trials with fracture endpoint in older adults have suggested some reduction in fracture risk in subjects receiving calcium even though between-group differences in absolute bone density are modest[44-46]. Selective reporting of positive fracture results may occur when a significant difference was found but fracture was not the primary endpoint. The commonly reported moderate to low compliance in studies using daily calcium supplements is likely to limit the effectiveness as a public health intervention[2, 47]. Although the per protocol analysis of a 5-year Australian study in 1,500 older women suggests that calcium supplementation (1,200 mg/day) reduces the risk of clinical fracture by 34%, no significant effect was reported in the intention-to-treat analysis[2]. Comparable results have been reported from a similar New Zealand study[48]. Compliance was similarly low in these two studies and the RECORD study (80% or more of study tablets taken: 50 to 58%)[2, 48,49]. The RECORD study, a factorial-design trial of 5,292 people aged 70 years and over (85% women) with a history of low-trauma fracture[49] reported no difference in fracture risk between the groups, suggesting that calcium (1g/day); vitamin D (800 IU/day) - either alone or in combination, is likely to be inadequate therapy for established osteoporosis. It has been argued that these results differ from most earlier calcium intervention trials because of low compliance however, the per-protocol analysis did not suggest a benefit associated with supplementation. Recent data suggests that hip fracture risk may not be reduced with calcium supplementation, and an increased risk is possible[48,50].

Randomised controlled trials of calcium plus vitamin D.
In the landmark study in this area, Chapuy and colleagues[51] randomised more than 3000 institutionalised elderly women, aged 69-106 years, to placebo or 1.2 g of elemental calcium plus 800IU vitamin D daily. Baseline concentrations of serum 25-hydroxyvitamin D were low (mean values 13 -16 μg/L) and were normalized by the intervention. At the end of 3 years of treatment, the probabilities of non-vertebral fractures and hip fractures were reduced by 24% and 29%, respectively ($P<0.001$), in those receiving active therapy. Some studies[52-55] but not all[49, 51], have duplicated these results. Variation in the baseline vitamin D status between groups would at least partially explain the heterogeneity in the responses to calcium and vitamin D interventions. It appears nursing home residents in whom baseline serum vitamin D levels are likely to be quite low, benefit to the greatest extent from such interventions.

Whether the calcium supplement or the vitamin D supplement produced the therapeutic benefit, or the combination produced the therapeutic benefit is unclear. The balance of evidence remains in favour of there being significant fracture prevention from a combined intervention with calcium and vitamin D in elderly men and women. Results from the Women's Health Initiative Study did not clarify the

issue[56]. This large trial of over 36,000 postmenopausal women given 1,000 mg calcium and 400 IU vitamin D_3 daily for seven years reported no reduction in hip fracture risk despite a small but significant improvement in hip bone density. Several confounders including low compliance, the high proportion of participants on hormone therapy and the study design that permitted the personal use of calcium/vitamin D supplements and bisphosphonates challenge the validity of the findings. Among those who were adherent (ie took >80% of their study medication) calcium and vitamin D supplementation resulted in a 29 percent reduction in hip fracture (hazard ratio, 0.71; 95 percent confidence interval, 0.52 to 0.97). This is despite the comparatively young age of participants for a hip fracture endpoint (mean age at baseline 62 years).

FOOD SOURCES AND INTERACTION WITH OTHER DIETARY COMPONENTS

Calcium is predominantly found in dairy foods but smaller amounts are found in bony fish, legumes, some nuts and in calcium-fortified soy beverages or breakfast cereals. Low fat options are a preferable choice for many individuals and can also be a good source of calcium.

Some dietary constituents can impair calcium bioavailability by forming insoluble calcium complexes[57]. These substances include phytates (found in cereals, bran, soybean and seeds) and oxalates (found in spinach, rhubarb and walnuts). Some vegetarian diets may therefore adversely affect calcium balance, particularly if the calcium content is low due to the avoidance of dairy products [58]. However, lacto-ovo vegetarians appear to have similar calcium intakes to omnivores who avoid any milk-based products[59, 60] and similar urinary calcium excretion[61, 62].

Sodium is an important determinant of urinary calcium excretion. A high salt intake has been associated with lower bone mass in some but not all studies[63]. The varying ratios of calcium to sodium in the diet may explain inconsistent findings between studies although higher calcium intakes levels (1,800 mg/day) or lower daily sodium excretion levels (less than 2,000 mg/day) is associated with a slowing or cessation of bone loss[63].

The effect of protein intake on bone density is uncertain, and evidence exists for beneficial effects of both low and high protein intakes[64]. While an adequate protein intake is important for supporting bone growth in children and maintaining bone mass in older adults, higher intakes of protein, particularly animal protein may be associated with increasing urinary calcium losses[65,66]. However the benefit of additional calcium from dairy products outweighs the possible deleterious effects of extra protein[67]. High calcium foods such as dairy products contain a range of other essential nutrients with calcium-fortified soy products acting as a substitute in those unable or unwilling to ingest dairy products. However there is little evidence that the small amounts of various mineral and vitamin additives present in some marketed calcium supplements improve the effectiveness of the calcium supplement.

Adequate vitamin D status is essential for calcium uptake in the gut and bone development and remodelling[68]. The prevalence of vitamin D insufficiency in Australia is now being recognised[4] and adequate vitamin D status should be established particularly in older patients requiring supplementation with calcium. The addition of vitamin D in doses less than 400 IU per day is unlikely to have a

significant effect on bone health in a younger person and those aged over 70 years require amounts more than 600 IU to affect bone status[4].

The RDI for calcium is 1000mg/day, and the EAR 840mg/day in women aged 19 -50 years and men aged 19 -70 years[8]. This increases to 1300mg/day for RDI and 1100mg/day for EAR for women over 50 years and men over 70 years. There is no additional allowance for pregnancy and lactation except for the teenage pregnant or lactating female. However, it is difficult for most older women and men to meet a dietary intake of 1300mg per day, as many in this group eat only small amounts of foods and are generally on low energy intakes. On a 'usual Australian diet' 60% of dietary calcium is derived from dairy products. People who avoid dairy products need to ensure substitute food products are calcium-fortified. To achieve a daily intake of 1,000mg -1,300 mg calcium at least 3 serves of dairy per day is recommended with at least one of those being calcium fortified. For those who do not wish to consume dairy products calcium fortified soy products eg soy milk provide similar amounts of calcium. The skeletal benefit of increasing calcium intakes may be greatest in those with lower baseline calcium intakes although this is not a consistent finding between studies[2].

INTERACTION WITH EXERCISE

There appears to be an additive interaction between weight-bearing physical activity and calcium intake across the various age groups. Calcium intake has been shown to modify the bone response to activity in young children[69]. Greater gains in bone mass at loaded sites (weight-bearing) have also been demonstrated in pre- and early-pubertal girls when moderate exercise is combined with increased dietary calcium[70]. In older women, a cross-sectional study of 1,363 Australian women has reported a 5 per cent higher total hip BMD among those in the highest compared to the lowest tertile for both physical activity and calcium intake[71]. Resistance and /or impact exercise can result in an osteotrophic effect but increased BMD will only occur when sufficient calcium is available[72]. It is thought that the exercise produces region-specific effects whereas the higher calcium intake produces a more generalized effect additive to the benefits of exercise[70].

TYPES OF CALCIUM SUPPLEMENTATION

Although calcium intake can be increased by dietary means, long-term adherence to high calcium diets is poor[73]. Calcium supplements are a useful way of helping individuals who are unable to consume sufficient calcium from dietary sources. The ability to adapt to low calcium diets and intestinal calcium absorption deteriorates with age. An extra 500-1,000 mg elemental calcium per day will usually suffice for most people. When checking the true calcium content of foods and supplements, it is the elemental calcium that matters. Calcium carbonate contains 40% elemental calcium by weight compared with 21% in calcium citrate. Although calcium citrate is more soluble and its bioavailability may be approximately 25% greater than that of calcium carbonate[74] it is generally more expensive[75]. Since calcium carbonate requires an acid environment to dissolve and calcium citrate does not, the latter supplement is preferable for people with achlorhydria and those on medications that inhibit gastric acid secretion[76].

There is some evidence that taking calcium supplements in the evening may be advantageous by suppressing the nocturnal rise in bone resorption although it has also

been suggested that divided dose regimens may lead to a greater total calcium absorption (1/3rd dose morning, 2/3rd dose evening)[77].

Calcium supplements are usually given with bisphosphonates and SERMs as therapy for established osteoporosis. The landmark clinical trials demonstrating the efficacy of these therapies used calcium, with or without vitamin D, in both the placebo and active treatment arms [78,79,80,81]. The efficacy of bisphosphonate and SERM therapy in fracture prevention in the absence of a calcium supplement is unknown. It is critical that calcium and oral bisphosphonates are taken several hours apart as calcium binds with these medications and prevents their absorption.

Calcium supplements are generally well tolerated and do not have major effects on the absorption of other micronutrients[1]. Occasional adverse effects include constipation, bloating and flatulence. The generation of CO_2 by gastric acid action on calcium carbonate may explain the high prevalence of gastrointestinal side effects and be a factor in the poor adherence to this form of calcium supplementation. Changing preparations (eg. from calcium carbonate to calcium citrate) may alleviate these adverse effects. Calcium supplementation is contraindicated in the presence of hypercalcemia or marked hypercalciuria. Renal impairment is associated with calcium malabsorption and this aspect of care in patients with renal disease requires specialist advice. The common practice of using calcium supplementation for phosphate binding in patients with renal impairment may contribute to the increased risk of cardiovascular disease in this population[82].

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