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NEWSLETTER

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AUCKLAND Bonedensity
Managing Bone Health

CALCIUM AND VITAMIN D—EVIDENCE AND UNCERTAINTY

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Calcium and Vitamin D

Calcium and vitamin D are often linked together as though there were a single entity. Of course, they are not, and optimising levels of each is important for optimising bone health.

CALCIUM

The average dietary intake of calcium amongst postmenopausal women in Auckland is 700–900 mg/day. Many studies have demonstrated that providing a daily supplement of about 1000 mg of calcium will substantially reduce the rate of postmenopausal bone loss but will not eliminate it completely, since calcium is not a substitute for oestrogen. Long term compliance with calcium supplements is poor, both in trials and in clinical practice, probably because the tablets are bulky, hard to swallow, and commonly cause gastrointestinal side-effects. Possibly as a result of this, the decreases in fracture numbers associated with calcium use have been disappointing. Meta-analyses show a 10% decrease in total numbers of fractures[1], but paradoxically suggest that hip fractures might be increased[2]. Thus, the net benefit from the use of calcium supplements has been disappointing.

Against this must be balanced the recent evidence that calcium supplements increase the risk of myocardial infarction. This was first reported in a pre-planned secondary analysis of the Auckland Calcium Study[3] and has now been confirmed in an unpublished meta-analysis of all studies of calcium supplementation, comprising almost 50,000 patient years of data (Bolland et al, submitted). In the meta-analysis there is a 30% increase in myocardial infarction risk associated with a randomisation to calcium supplements. This results in the number needed to treat to cause one myocardial infarction being lower than that needed to prevent one fracture, suggesting that the benefit to risk ratio is negative.

The mechanism by which calcium supplements increase vascular risk is uncertain, but it may be related to the substantial increase in serum calcium which occurs following the ingestion of a calcium supplement. This is in marked distinction to the minimal change in serum calcium after ingestion of a dairy product containing the same amount of calcium. There is now an abundance of epidemiological data suggesting that high-normal serum calcium levels are associated with an increased risk of atherosclerosis.

As a result of these findings, I no longer advocate the use of calcium supplements but encourage patients to aim for a total calcium intake of 1g/day through the use of calcium-rich foods, primarily dairy products. For those unable to tolerate dairy products, the use of calcium supplements may be reasonable, but I suggest the use of carbonate or phosphate preparations (which are less soluble and therefore more slowly absorbed) and that these are taken after meals, again to slow their absorption. The key message from these findings, however, is that we cannot look to calcium supplements as a cheap, safe, 'natural' way of preventing fractures, and that we should have a lower threshold for using agents of known efficacy and safety for preventing fractures in those at significant risk. In practice, this means a wider use of bisphosphonates.

VITAMIN D

Vitamin D is not a vitamin, in that it is not an essential constituent of the diet, but a pro-hormone synthesised in the skin as a result of sunlight exposure. Thus, individuals that are at risk of vitamin D deficiency are those who do not expose their skin to the sun, have very dark skin that impedes vitamin D synthesis, or that are obese, in whom adipose tissue uptake of this fat-soluble compound results in lower circulating levels. Adequate levels of vitamin D are necessary for normal intestinal calcium absorption, and low levels result in increased parathyroid hormone secretion leading to higher bone resorption. This allows maintenance of serum calcium levels at the expense of progressive loss of bone density.

AUCKLAND BONE DENSITY NEWSLETTER

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Vitamin D status is assessed by measurement of serum 25-hydroxyvitamin D (25D). Normal levels used to be given as >30nmol/L, but now labs are quoting reference ranges that are thought to be optimal rather than normal. Thus, some labs use a reference range of >75nmol/L, though the evidence base for this is of dubious merit. It is clear that levels <25nmol/L can be associated with musculoskeletal pain and osteomalacia, and that bone resorption is increased in individuals with levels <50nmol/L. Some cross-sectional studies have demonstrated an *association* between levels >75nmol/L and healthier outcomes with respect to bone, heart, obesity, diabetes, cancer and infectious diseases. However, association is not causation and many of these findings could be accounted for by healthier individuals spending more time outdoors and having lower body weight. Clinical trials are awaited which could demonstrate the advantage of maintaining 25D levels above 75nmol/L. A recent but as yet unpublished study has suggested that levels >150nmol/l may be associated with adverse outcomes, whereas in the past such levels have generally been regarded as safe.

Until these uncertainties are resolved, there is a consensus that 25D levels should be maintained at >50nmol/L, but many believe that pushing 25D to >75nmol/L is of uncertain benefit. Satisfactory vitamin D status can be achieved with the use of Calciferol 1.25mg/month, and it is reasonable to routinely use this intervention in the frail elderly without measurement of 25D, in light of the high prevalence of vitamin D deficiency in this group, the known safety and efficacy of this intervention, and the cost ($50.00) of the blood test. The new preparation of alendronate, Fosamax Plus, contains 0.14 mg Calciferol in each weekly tablet, (0.56mg/month) which should be adequate to maintain 25D levels in most osteoporotic patients, without additional supplementation.

References

1. Tang BMP, et al. *Lancet.* 2007;370:657-666.
2. Reid IR, et al. *Osteoporosis. Int.* 2008;19:1119-1123.
3. Bolland MJ, et al. *BMJ.* 2008;10.1136/bmj.39440.525752.BE

Depo-Provera and Bone Density

Injectable depot medroxyprogesterone acetate (DMPA, Depo-Provera) acts as a contraceptive by suppressing pituitary gonadotrophin production and thereby ovulation. As a consequence, it induces oestrogen deficiency, although not to as great a degree as occurs after the menopause. As a further consequence, DMPA induces bone loss of modest degree. Collectively, the many studies in this area have demonstrated that spine and hip bone density are lowered by about 5-10% as a result of DMPA use. The effect may be somewhat greater in women in whom treatment is initiated in adolescence. This loss of bone density is substantially reversible upon cessation of DMPA, so long as menses return (an indication of restoration of normal endogenous oestrogen levels). DMPA-induced bone loss is preventable by the use of oestrogen at similar doses to those prescribed to postmenopausal women. Women who use DMPA up until the time of menopause do not manifest faster bone loss at the time of menopause, although bone loss will not naturally be reversed.

DMPA is a highly effective and well tolerated contraceptive. The detrimental skeletal effects are mild to modest and for the vast majority of women do not warrant discontinuation of DMPA treatment. However in a minority of women, particularly those with low bone mass and/or multiple clinical risk factors for osteoporosis prior to initiation of DMPA, consideration should be given to use of an alternative means of contraception that does not influence the skeleton. It is reasonable to consider BMD measurement in women who are starting DMPA therapy, particularly adolescents and young women with other clinical risk factors. However, routine monitoring of BMD in all DMPA-treated women is not required.