Calcium and Vitamin D in Osteoporosis: Supplementation or Treatment?

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Replacement, Substitution, and Supplementation vs Pharmacological Actions

Calcium (Ca) and Vitamin D contribute to the prevention of osteoporotic fractures [1–3]. The optimal doses to be recommended are still debated, but fundamental considerations can still be helpful, such as the difference between substitution and treatment and its clinical consequences. «Substitution,» at least in the field of endocrinology and metabolism corresponds to the «replacement» of a deficient substance. For instance hormone replacement therapy (HRT) in estrogen deficiency is a substitution or «replacement» therapy. The administration of vitamin D in situations of vitamin D deficiency, as in institutionalized elderly people, is also a substitution or «replacement therapy.» «Supplementation» on the other hand, a term used in the field of nutrition, signifies the administration of an additional amount of a natural nutrient, mineral, or vitamin to an individual with supposedly or apparently insufficient intake. This includes the prescription of Ca when intake is insufficient, or that of vitamin D in elderly people with limited or no sun exposure, where vitamin D status is insufficient. «Treatment» on the other hand, is first a pharmacological term as long as it concerns the administration of drugs. Treatment implies the intention to achieve a specific biological effect. This not only applies to drugs, but also can be applied to natural substances, such as Ca and vitamin D. Ca can be given with the specific intention to reduce plasma parathyroid hormone (PTH), and vitamin D for correcting low Ca absorption, thereby lowering PTH, which in turn will decrease bone turnover and improve bone mineral density (BMD). In these cases the difference between substitution and treatment depends on the indications and the doses used.

Calcium as Supplement

Low Ca intake leads to a negative Ca balance and accelerates bone loss in postmenopause and in elderly people. Insufficient intake is frequent, and for this reason Ca supplementation is recommended, in the presence of osteoporosis and for its prevention. It decreases bone loss, and even has some antifracture effect [3]. This supplementation is meant to increase Ca intake to an optimal level, which was defined by the NIH among others [4]. The NIH considered as optimal 1000 mg for men and premenopausal women, and 1500 mg for elderly people of both sexes. It could be debated that this relatively high amount is still substitution, as it meets a natural need. Since the Ca intake in animals, related to body weight, is much higher than in humans, and the Ca intake of prehistoric humans [5] was higher and closer to the animal world than that of actual diets, an intake of 1500 mg can still be considered as physiological. By raising the Ca intake to this optimal level, growth and maintenance of bone and bone turnover are meant to be stabilized within physiological limits.

The effect of Ca can be shown by the immediate inhibition of bone resorption after ingestion of physiological amounts: a normal breakfast or ingestion of only 200 mg Ca decreases PTH and bone resorption markers by 20–65% for several hours [6–8]. This transient effect is therefore a physiological phenomenon, not to be confused with the more persistent inhibition bone resorption obtained with higher doses.

Calcium as a Drug

Ca can also be used as a drug, i.e., a substance which causes a specific biological effect. Its effectiveness is probably underestimated because it was rarely compared with placebo, but when it was done, it was revealed to have its own long-term effect on BMD [9, 10]. Although less effective than antiresorptive drugs, 1 g of Ca lowers PTH [11] and bone resorption [8] in the hours following the ingestion. This effect is more pronounced than that observed after smaller, physiological doses. In the longterm, 1 g of Ca lowers bone resorption markers by about 20%. This latter effect can be seen in the control groups of therapeutic trials for the prevention and the treatment of osteoporosis, which were treated with Ca alone [12]. With a dose of 1600 mg, which is at
the limit of a physiological supplementation, a slight and partially transient effect on BMD was obtained [10, 13]. When higher doses were given to normal peri- and postmenopausal women, such as 2 g above nutritional intake, BMD increased slightly [14] due to the decrease of PTH and of bone turnover, and therefore increased mineralization of resorption spaces, but this effect was mostly transient. Therefore, with doses of 2 g and above, which can not be considered as supplementation, no further benefit can be expected other than the eventual advantage of an almost totally suppressed PTH secretion, a fact that remains to be proven (Fig. 1).

Different parameters can be used for defining the limits between supplementation and a pharmacological treatment. The first ones to mention are the limits of the physiological needs, which lie between about 500 and 1500 mg/day. Any prescription of 2 g, or of 1000 mg over a normal nutritional intake or more, will exert a pharmacological effect, with a sustained and nonphysiological suppression of bone resorption. Other parameters are the levels of PTH and bone resorption markers, which can be lowered to normal levels (supplementation) or suppressed to subnormal levels (treatment) by oral Ca. This has been illustrated by several studies. When 1200 mg of Ca are given to postmenopausal women with a low intake of about 500 mg, almost all decrease their markers of bone resorption to levels below the normal mean [15]. This suppressive effect on bone metabolism seems to confirm the assumption that an intake of 1700 mg is more than a substitution. It probably has an additional effect, compared with supplementation. As shown in another study, supplementation with 1062 mg in the form of milk increased lumbar BMD and lowered resorption markers slightly, but not significantly, which corresponds to a physiological state. The control group, which had a low Ca intake of 699 mg/day, increased resorption markers over time, which indicates a deficient state. A third group received 1673 mg Ca in the form of carbonate. With this pharmacological dose, there was a significant increase in BMD and reduction in resorption markers, suggesting a pharmacological or therapeutic effect rather than a physiological one [16].

Not only the amount of Ca given, but also the form in which it is given, contributes to the distinction between a physiological and a pharmacological effect. When Ca is taken in a biological combination, such as in the form of bone powder, it increases ionized Ca slowly and with no immediate change in urinary Ca output, even when given at high doses; but when the same amount is given as Ca gluconate, i.e., as a drug, ionized plasma Ca and urinary Ca output rise immediately [17]. Or when 1 g of Ca is given in the form of milk, it causes an increase of plasma Ca and urinary Ca output, and a decrease of PTH, which are less marked than when the same dose is given as Ca carbonate [8].

**Vitamin D as Supplement**

For many years vitamin D and its metabolites were used in declared deficiencies, such as rickets, osteomalacia, and renal osteopathy. When subclinical hypovitaminosis D was discovered as a frequent phenomenon, first in elderly and institutionalized subjects, then also in healthy, free living elderly [18], and even middle-aged persons [20], vitamin D supplementation was introduced for the prevention of osteoporosis. Indeed, vitamin D— together with calcium—decreased bone loss, increased BMD, improved ultrasonic bone measurements, and lowered hip fracture incidence in the elderly. This beneficial effect illustrates the contribution of latent vitamin D deficiency to the pathogenesis of osteoporosis, and justifies the use of vitamin D as a supplement, especially in the elderly.

The state of latent deficiency or «insufficiency» is mainly defined by elevated PTH levels, which rise above the normal limit when the levels of 25OHD drops below 12–15 nmol/l in one study [20] and below 20 nmol/l in another [19]. The latter value corresponds to the fifth percentile of the healthy population [21]. In this situation, supplementation with vitamin D helps to normalize the PTH level. But with increasing levels of 25OHD, the PTH further decreases within the normal range, and for this reason a plasma level of 25OHD of 30 nmol/l was considered as the lowest limit, which most specialists agreed on. Then a “minimized” PTH level was found only at plasma concentrations of 25OHD as high as 50–80 nmol/l [22]. However, a meta-analysis of numerous studies showed that with increasing plasma 25OHD, the PTH level still decreased further until it reached a nadir at a 25OHD level of above 100 nmol/l [23]. Therefore, the lower normal limit of 25OHD became debatable. In a Swiss survey, this level of 100 nmol/l corresponds to the 97.5th percentile of 3276 healthy adults [2]. Therefore, if a maximally suppressed PTH is the optimal goal, the whole Swiss population.