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REVIEW

Calcium revisited: part II calcium supplements and their effects

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Calcium supplements were tested in pregnancy and lactation, in childhood and adolescence, in pre- and postmenopausal women and in elderly persons with various effects on bone density and fracture incidence. They must be properly chosen and adequately used. In this case, the reported minor negative side-effects do not restrict their use. All these aspects are reviewed here.

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Introduction

Calcium supplements are widely used, mainly in combination with vitamin D. This review discusses the use and effects of calcium supplements without Vitamin D or estrogen. Results of published, large, crossover or follow-up studies and randomized controlled trials (RCTs) are mentioned when significant.

Calcium supplements substitute or enrich nutritional calcium. They are generally as well absorbed as calcium from milk and milk products.[1] An oral calcium load lowers immediately the blood parathyroid hormone level and the resorption markers for several hours.[2,3] A daily dose lowers bone turnover for up to 5 years.[4] As high bone turnover is a fracture risk factor for itself, it can be expected that calcium supplements improve bone mineral density (BMD) on the long-term and lower the fracture risk.

The Choice of Supplement

Several calcium salts are on the market. The most commonly used as supplements or food fortificants exhibit similar absorption rates when tested in pure chemical form.[5] Most studies have used calcium carbonate, citrate, citrate–malate and lactate-gluconate. Differences in bioavailability are small and of no practical significance, because the liberation of calcium from its binding substances or ions by the gastric acidity results in comparable amounts of free calcium available for absorption.[6] The role of the gastric pH is evident. Proton pump inhibitors lower calcium absorption,[7] and their long-term intake is associated with an increased fracture risk.[8]

However, some differences were reported. For example, calcium citrate appears to be better absorbed compared with calcium carbonate when taken with food[9] or more bioavailable.[3,10,11] Calcium citrate–malate was also better absorbed in adolescents compared with calcium carbonate.[12] A recent extensive review confers superior qualities to calcium citrate–malate and concludes that it is especially beneficial for individuals with hypochlorhydria or achlorhydria (induced or not by medications).[13] Calcium malate is absorbed at 35–36% and calcium carbonate at 26–27%.[14,15] The absorption of calcium citrate–malate was reported to be 50% higher than that of tricalcium phosphate.[16] However, as each intake of 500 mg calcium decreases phosphorus absorption by 166 mg (confidence limits (CL) 144–188 mg),[17] it might be preferable to prescribe tricalcium phosphate to elderly and malnourished patients, whose risk of phosphate deficiency is high. Indeed, the especially positive anti-fracture effect observed in the study of Chapuy *et al.*[18] might be explained by the fact that this particular calcium preparation was chosen as supplement. Some differences in absorption and in the effect on bone metabolism between the various supplements—for example, the superiority of calcium citrate over carbonate—remain unexplained.[11]

The inconsistency of the results on the absorption and bioavailability of the different calcium salts can be explained by differences in methodology. The increase in urinary calcium excretion during 4–5 h after the ingestion is not a reliable criterium for absorption, because it evaluates the speed but not the total amount of absorption. Tracer methods are more precise, and measurements of the effect on markers and parathyroid hormone are more relevant, because they measure bioavailability.[11]

Conclusion: instead of considering the relatively small differences in absorption rates, the choice of a supplement should rather depend on the palatability and the acceptance by the patient, which enhances the long-term compliance. In some meta-analysis on the effect of supplements, the type of calcium salts was even ignored.[19]

When to Take Supplements

Calcium supplements should be taken with or after meals for various reasons: the absorption rate increased by 10–30%;[20]

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glucose and glucose polymers stimulate calcium absorption;[21] in achlorhydria, and probably in the numerous patients taking proton pump inhibitors drugs, calcium carbonate is much better absorbed with meals than in the fasting state.[22] Finally, in the fasting state calcium supplements not only are often not tolerated, but they also lead to a transient increase in the blood calcium level, which might be responsible for the eventual increase in cardiovascular diseases (CVDs) and of renal stones (see later).

The most effective regimen seemed to divide the doses, which increases absorption. The combination of a small dose of 500 mg taken together with a meal or shortly after, not only prevents the post-prandial rise of serum calcium but also that of urinary calcium, and this lowers the already weak risk of renal stone formation.

Evening calcium supplementation resulted in marked suppression of the nocturnal increase in resorption markers (Dpd and NTx) and of PTH. In contrast, morning calcium supplementation had no significant effect on the circadian rhythm of these markers.[23] However, it was also shown that the effect on serum calcium and PTH was similar whether calcium was taken in the morning or in the evening.[19,24]

Conclusion: the moment of the intake seems not to be crucial, it just has to coincide with a meal.

Effects of Calcium Supplements by Age

The effect of calcium given alone on BMD is relatively small. With advancing age, adequate calcium intake becomes more important and calcium supplementation more effective, especially in populations with a low nutritional calcium intake.

Infants

The literature on calcium supplementation in infants concerns mainly the nutritional intake of the pregnant mother (see below).

Childhood and adolescence

Peak bone mass is influenced by nutrition, which includes calcium intake, but this influence is small. It is, however, modifiable, which makes it clinically relevant. In case of inadequate nutritional calcium intake, supplements can be used.

The majority of RCTs assessing the effects of calcium supplementation in healthy children are industry funded and support calcium supplementation.[25]

An early review of RCTs concluded that calcium supplementation was associated with higher bone mass in healthy children who are consuming amounts of dietary calcium in accordance with the US recommendations showed.[26] A review of 2005 again associated calcium supplementation with an increase in bone mineralization in children and adolescents. However, the effect did not necessarily last, as catch-up mineralization later in puberty occurred when the intake was consistent with the average US intake.[27]

A study of adolescent boys with calcium carbonate supplementation suggests that the intervention effect was mediated through an effect on growth.[28]

A meta-analysis of 19 RCTs of calcium supplementation (including food sources) was less optimistic. It showed no effect on the femoral neck or lumbar spine BMD, except a small effect on total body bone mineral content (BMC) and on BMC of the upper limb, and only the latter effect persisted after supplementation ceased. The effect was approximately equivalent to a 1.7% greater increase in the supplemented groups, which is too small to reduce the fracture risk in children.[29]

So far, positive short-term effects have been shown in boys and girls, particularly in weight-bearing appendicular bone, but these effects seemed to be small, once even called 'marginal'.[30] Whether the positive results are maintained after interruption of the supplement intake was questioned already in early reviews.[31]

Withdrawal of supplements

After calcium supplementation withdrawal, bone mass differences between treatment and control groups disappeared.[32,33] In an 18-month study in adolescent girls the effects were no longer evident after 2 years follow-up, although the supplementation with 792 mg calcium per day was associated with greater gains in BMC and BMD.[34] Even in areas of low calcium intake, the increase in BMD after a supplementation of 18 months was not sustained after supplement withdrawal.

Other studies showed some small persistent effects. In girls who received 1 g supplement over 7 years from childhood into early adulthood, significant differences remained by early adulthood but only at metacarpals and at the forearm of tall girls.[35] Eventually, the taller girls were relatively deficient without supplements. In another study, the positive effect on total body BMD was still significant 3.5 years after the end of supplementation in adolescent girls.[36] In prepubertal $\pm$7.4-year-old boys, foods enriched with 0.85 g calcium per day for 1 year increased areal BMD (aBMD) at some sites, and the effect was maintained 1 year after treatment discontinuation.[37] In this context, Tanner scores are crucial, as the hormonal effect on bone development is stronger compared with nutritional influences. For instance, in one study, the positive effect of calcium supplementation could only be observed in adolescent girls with a Tanner score above median.[38]

The increment of BMC was not significantly more pronounced when supplements were given to children with a low habitual calcium intake than to calcium-sufficient children,[29] but in one study it was doubled by the supplements (11% versus 5%).[39] This goes along with the trivial observation that any substitution is probably more efficient in deficient than in sufficient subjects.

Conclusion: calcium supplementation has a small beneficial effect on BMD and BMC in childhood and adolescence. After withdrawal of supplements, the benefice disappears.

Role of physical exercise

The effect of exercise on bone mineral acquisition is enhanced in the presence of adequate calcium intake, according to several studies.[40,41] Calcium supplementation without physical activity had no effect in a study in prepubertal children.[42] In physically active children with a normal calcium intake, supplementation has probably no effect.[43] Exercise enhances the calcium effect in adults too.

Effect on fracture risk in children

Calcium supplementation probably decreases the fracture risk in children. The results of the longest controlled trial point in this direction.[35] Because the number of children included in the

RCTs is relatively small compared with the incidence of fractures, the question remains open.

Extraosseous effects

Calcium supplementation was found to decrease fat mass gain in children with a low calcium intake.[44] However, according to a large meta-analysis, there was no statistically significant association between calcium supplements and weight, height, body fat or lean mass.[45] In adolescents with a low calcium intake, calcium supplementation reduced diastolic blood pressure significantly.[46]

Pregnancy

Effect on the pregnant women. A review of 2010 showed that calcium supplementation had no other benefits than to approximately halve the risk of pre-eclampsia, to reduce the risk of preterm birth and to reduce the rare occurrence of the composite outcome 'death or serious morbidity'.[47] A recent study too reported no bone effect.[48] In addition, a follow-up study showed no sustained reduction in the risk of high blood pressure in pregnancy or 4–7 years later, neither in the pregnant women nor in their children; however, calcium supplementation may lower blood pressure in children of pregnant women with hypertension.[49] Calcium supplement during pregnancy and lactation also reduces the levels of circulating lead in the mother and by that reduces lead exposure of the fetus and the infant.[50]

Effect on the offspring. Despite positive results of early studies, supplementation during pregnancy had no influence on fetal growth or neonatal anthropometric characteristics, even in women with a low calcium intake.[51]

There are, however, extraosseous effects reported. Children of supplemented pregnant women had significantly less dental caries at the age of 12 years[52] and had improved parameters of cardiovascular risk (CVR), although the size at birth and at the age of 9 years was not influenced.[53] A meta-analysis concluded that calcium supplementation during pregnancy reduces the risk of hypertension in the offspring. This was, however, not evident in children below 1 year of age.[54] Again, these observations were not confirmed by other studies. In a large follow-up study, maternal calcium intake during the first and second trimesters was not associated with the systolic blood pressure in the offspring at the age of 3 years.[55] A more recent study was also negative.[56]

Conclusion: Supplementation with calcium during pregnancy has no measurable effect on the bone development of the children and has a very questionable beneficial effect on CVRs of the mother.

Lactation. Lactation, especially multiple periods of breast feeding or long-term lactation, has been associated with bone loss.[57] Although BMD normally returns to baseline during the 6–12 months post weaning,[58] calcium supplementation was tested. The loss of bone during lactation could not be influenced, it only enhanced slightly the regain in bone density after weaning.[59] A review of five studies in lactating women concluded that increased calcium consumption is profitable for their bones;[60] the post-weaning period was not taken into account. The risk of bone loss might exist in adolescent mothers. For this reason, calcium supplementation was beneficial in this group.[61] In addition, calcium supplementation in lactating women decreased slightly the blood level of lead in women with an initially high level.[62]

Conclusion: The effect of calcium supplementation on BMD during lactation is uncertain.

Pre- and perimenopausal women

Age-related bone loss is determined by genetic factors, hormones, underlying diseases and lifestyle behaviors. For this reason, the effect of calcium supplements during the pre-and perimenopausal depends on the presence or the absence of these factors. Personal knowledge about osteoporosis and BMD testing enhances lifestyle modifications and increases the use of calcium supplements in premenopausal women.[63] Women who had the information of low BMD showed a greater increase in femoral neck BMD with calcium supplements compared with women with normal BMD.[64]

The amount of calcium supplements and that of dietary calcium has an important role. In early postmenopausal women, a 500 mg per day calcium supplementation for 2 years was ineffective in preventing the bone loss, independently from the basal calcium intake.[65] When 1 g was compared with 2 g and placebo in perimenopausal women (46–55 years) for 2 years, 2 g was more effective on the bone loss compared with 1 g,[66] but the effect being significant only during the first year. In early postmenopausal women ($\pm$54.5 years), calcium supplementation with 500 mg per day for 2 years had no effect on bone loss. Later, at age $\pm$59.9 years it lowered the bone loss, but only when the dietary calcium intake was low ($<$400 mg per day).[12]

Conclusion: Peri- and early postmenopausal bone loss is mainly linked to the loss of estrogen. In the early postmenopause, calcium supplementation has no effect. Later the effect of a small calcium supplementation in preventing bone loss is modest or even not significant in women with a sufficient nutritional intake. Supplements are effective when nutritional intake is very low.

Postmenopausal and elderly women

RCTs have shown that calcium supplementation decreases postmenopausal bone loss. Calcium 1 g given to postmenopausal women ($\pm$58 years) over 2 years went along with a smaller bone loss, by about 40% at the lumbar spine and the appendicular skeleton.[67] In women $\pm$66.6 years, 1 g calcium added to a nutritional intake of 760 mg was associated with a decrease in the loss of bone over 4 years,[68] and in a study of the same age group 1 year of calcium supplementation with 1600 mg was associated with differences in BMD of 2% at the spine compared with placebo.[69] However, the difference was not significant after 4 years, which could be the result of declining adherence.

When the nutritional intake is low, the dose of supplementation becomes crucial. In Japanese women with a low calcium intake (mean 493 mg per day), supplementation over 2 years with 500 mg (but not 250 mg) decreased the lumbar spine bone loss.[70] A higher dose of 1 g was given over 5 years to elderly women ($\pm$74 years) in the Auckland calcium study and had beneficial influence on BMD.[4] The strongest effect was observed in the per-protocol analysis because of low compliance, with differences of 2.3% (spine) and 2.8% (hip) compared with the placebo group. However, a 5-year follow-up after the treatment showed no remaining effect on BMD.[71]

The first meta-analysis including 12 studies showed that calcium supplements have a preventive influence on the rate of bone loss in postmenopausal women, which was greatest when the baseline calcium intake was low.[72] A later meta-analysis of 15 trials specified that the significant differences in the changes from baseline were 1.5–2% for total body, lumbar spine, hip and distal radius BMD.[73] The apparent effect was stronger after the first 2 years than after 3 and 4 years. A recent review of 32 trials showed that a medium dose of 1000 mg during 2 years was associated with a decreased loss of BMD by 0.8% at all sites, which would be a modest effect. It demonstrated also an advantage of an intake of >1350 mg per day over lower intakes.[19] Again, the effect seems to be lost after 4 years.

Despite this cumulated evidence, cross-sectional studies, such as the NHANES 2005–2006, concluded that a high calcium intake, 'commonly achieved by calcium supplements, did not provide any benefit for hip or lumbar BMD'. However, a high calcium intake was beneficial for hip BMD in men, and the NHANES anyway did not analyze specifically calcium supplements.[74] In any case, it has to be recognized that any effect of supplementation is probably transient, as 2 years after interruption of the substitution, the benefice on BMD is lost.[75]

Conclusion: calcium supplementation in postmenopausal and elderly women is associated with a smaller loss in BMD. This positive effect is particularly true for the first 2 years of supplementation and was greater with a higher compliance and a low dietary calcium intake.

Fractures

The earliest studies demonstrating an anti-fracture effect were published in the nineties. In the first study, the incidence of symptomatic fractures was 5.3% after 4 years of calcium supplementation with 1 g, whereas it was 17.5% in the placebo group.[76] In the second study, the vertebral fracture reduction was almost 50% with 1.2 g calcium over 4.3 years in women with prevalent fractures.[77] An early meta-analysis of four RCTs found an important decrease in the hip fracture incidence with ± 1 g of calcium.[78]

A later meta-analysis of RCTs showed an average decrease in the fracture risk with calcium supplements by 10% and by more when the dietary calcium intake was low, the supplementation high (that is, >1.2 g), the patients old or institutionalized and the compliance higher than 80%.[79] Compliance was examined in a 5-year RCT, where the effect of 1.2 g calcium became evident only when the compliant patients were examined separately.[80] This is in agreement with the observation that the anti-fracture effect disappears after treatment withdrawal.[81]

Surprisingly, in the 5-year Auckland RCT, calcium supplementation was associated with an increased risk of hip fracture (hazard ratio 3.55).[4] Two meta-analyses of three, respectively, four studies confirmed this.[82,83] It can be explained by the inhibitory effect of calcium on Phosphate absorption (see above).[17] That the first study with calcium and Vitamin D in old persons decreased hip fracture incidence so efficiently was eventually also because of the fact that calcium was given as tricalcium phosphate, as already mentioned.[18]

Recently, a subgroup of the Auckland study was reevaluated 5 years after the treatment with calcium supplements over 5 years. There was no negative effect on hip fracture incidence any more, but a significant reduction in forearm (hazard ratio 0.62) and vertebral fractures (hazard ratio 0.52).[71]

Studies, where calcium was administered together with Vitamin D, showed a reduction in the fracture incidence but are not discussed in this review. In a large meta-analysis, Vitamin D alone showed no effect for the prevention of hip fracture, whereas adding calcium was effective.[84]

Conclusion: calcium supplementation seems to be associated with a small fracture risk reduction, particularly in the elderly with a good compliance.

Bone Evaluation in Men

There is one RCT involving only men. A total of 323 healthy men (± 57 years) were given 600 or 1200 mg per day calcium or placebo for 2 years. The BMD increased significantly at all sites (1–1.5%) only in the group receiving calcium 1200 mg per day. There were all the expected effects on bone metabolism, dosage related and sustained.[85] The anti-fracture efficacy was also demonstrated in pooled data or meta-analysis including men and women.[79,86]

Conclusion: The effects of calcium supplements on bone remodeling parameters and BMD seem to be comparable in men with those found in postmenopausal women.

Adverse and Side Effects

Cardiovascular diseases

Calcium supplements eventually may increase the CVR: a controversy started when an increased incidence of CVD was found with calcium supplements.[87] This was partially confirmed by a large follow-up study in subjects <65 years.[88] Total calcium intake was not associated with CVR, but taking calcium supplements increased the risk for myocardial infarction. The methodology of the first study was criticized: the CVR at onset was not equally distributed between both groups, and the participants were asked long after the study if they recalled a CVD event during the study. However, once verified by various registers, the difference in CVD was not significant any more. The authors defended their hypothesis by a meta-analysis of 15 RCTs with calcium supplements, where information on CVD were requested retrospectively. Data obtained in 63% of participants showed an increased risk of myocardial infarction (relative risk 1.27), but only if the dietary calcium intake was >805 mg per day.[89] The authors further analyzed the data of the large Women's Health Initiative (WHI) study where 36 282 women were randomized to receive for 7 years calcium 1 g per day and vitamin D 400 IU per day or placebo. Their hypothesis was confirmed only in women who already were on calcium supplements before.[90] This was partially confirmed by a huge 12-year follow-up study of the National Institute of Health (NIH). In men, but not in women, calcium supplements of 1 g were associated with an increased risk of CVD death.[91]

Arguments against the increase in the CVR. Another group analyzed the WHI study too and found no difference in CVD with or without calcium supplements. Women taking supplements >5 years, without vitamin D, had even less CVD.[92] This was in agreement with an earlier analysis of the WHI study, which also showed no increased CVR.[93] Even in the study defending the CVR induced by calcium supplements it was shown that in women taking personal calcium supplements at randomization,

calcium-Vitamin D supplements did not alter the CVR.[90] In fact, several large studies found no increased or even a decreased CVR in subjects >65 years taking calcium supplements,[94] also when CVD was a primary end point of the study. calcium supplements may even have reduced the risk of hospitalization and mortality in patients ±75 years with preexisting CVD atherosclerotic CVD, as well as the risk of heart failure deaths.[95]

Eventual explanations. This inconsistency may be partially explained by the differences in age of the subjects and in the dose but also in the risk of biased results when CVDs were established *post hoc* in studies designed for osteoporosis and not for CVD. The Swedish cohort of >60 000 women of ±50 years found a U-shaped association between both dietary and total calcium intake and CVD; an intake of <600 or of >1400 mg per day was associated with an increased CVR.[96] That calcium deficiency goes along with various diseases has already been discussed,[97] but the eventual association between high total calcium intake and increased health hazards deserves further confirmation. A biological explanation for the eventually increased CVR is lacking. Evaluation of vascular calcification, a strong predictor of CVD, may be a surrogate marker of the deleterious effect of calcium supplementation. In a sub-study of the WHI, coronary artery calcium was measured by cardiac CT at baseline and after 7 years in women of 50–59 years and showed no negative effect of calcium supplements and intake.[98] Equally negative were the 4-year results of Cardiac CT in the Framingham Offspring Study (±60 year).[99] In another study, neither changes in abdominal aortic calcification, nor in coronary artery calcification (men) was associated with dietary and supplementation calcium intake.[100] Carotid artery intimal medial thickness or carotid atherosclerosis also lacked association with calcium supplementation in elderly women. In contrast, women in the highest tertile of total calcium intake had reduced carotid atherosclerosis.[101]

Therefore, if calcium supplements influence CVR, it is not because of vascular calcifications. It is, however, possible, that the eventual CVR is indirectly caused by the daily transient increase in the plasma calcium level. Nutritional calcium was never associated with an increased CVR. In general, calcium from food is absorbed slower compared with calcium from supplements taken on the empty stomach, and for this reason does not increase the plasma level by the same amount. Many patients take their supplements in a fasting state, and no study recorded the way of administration.

Conclusion: calcium supplements have probably no negative side-effects on CVD, especially when taken with food. The negative data on vascular calcification are reassuring.

Mortality

In the WHI study, calcium supplements had no effect on total mortality.[92] In the Swedish mammography cohort, women with a calcium dietary intake of >1400 mg per day, who were taking additionally calcium supplements, had a higher mortality rate compared with women with a similar intake of dietary calcium without supplements.[96] On the other side, as already discussed, mortality was also higher among women with a calcium intake below 600 mg per day, with or without calcium supplements. In the Iowa Women's Health study, over 38 000 women (±61.6 years) were followed for 22 years. Mortality decreased with the use of calcium supplements.[102] A patient-level (mainly elderly women) meta-analysis of 8 RCTs showed that vitamin D given with calcium reduced the risk of death, whereas vitamin D alone had no effect on mortality. The meta-analysis at trial level (24 RCTs) showed similar results.[103]

Conclusion: The use of calcium supplements is not associated with increased mortality. In any case, when calcium supplementation is given with vitamin D, the overall mortality risk decreases.

Kidney stones

According to the IOM report, calcium supplements increase the risk for renal stones. However, this risk is small. In a prospective cohort study a 12-year follow-up in 91 731 women (Nurses' Health Study I), calcium supplements showed a 20% increase in the risk, but most of the women did not take the supplements with a meal. The same study showed that calcium-rich food had a protective effect, in a dose-dependent manner.[104] Indeed, a high intake of dietary calcium appears to decrease the risk for kidney stones,[105] even in patients with a history of calcium oxalate stone formation, because calcium lowers the absorption of oxalate. Calcium supplements have even been proposed as treatment of urinary stone disease.[106] A recent systematic review (eight RCTs, two cohorts, >8000 patients) did not find any significant increase in the risk of nephrolithiasis induced by calcium supplements.[107]

This might be different for calcium plus Vitamin supplements. Daily supplementation with calcium-Vitamin D for ±7 years was associated with an increase in the number of self-reported urinary tract stones.[108] According to the USPSTF, 1 in 373 women who take low-dose vitamin D plus calcium supplements for 7 years will develop kidney stones.[109]

Conclusion: The advice to be cautious in patients with a history of urolithiasis seems pragmatic. Patients should always be advised to take supplements with meals to minimize their risk of urolithiasis.[110]

Prostate cancer

The analysis of 12 prospective studies suggested that dairy products and calcium intakes were both associated with the risk of prostate cancer (P (trend) = 0.029 and 0.014, respectively). It was, however, not clear whether calcium intake itself was an independent risk factor for prostate cancer.[111] An analysis of the entire EPIC study cohort found that only calcium from dairy products was positively associated with this risk (P (trend) = 0.02) but not calcium from other foods.[112] However, a large prospective study refuted this supposed risk. In 10 011 men with 815 prostate cancer cases, neither increasing intake of dairy products nor that of calcium from dairy products, nor calcium supplements, was associated with prostate cancer.[113]

Finally, a meta-analysis of 45 observational studies did not support an association between dairy product use and an increased risk of prostate cancer.[114] When systematic PSA screening was available the search for nutritional risk factors for prostate cancer among nearly 10 000 participants in the Prostate Cancer Prevention Trial (United States and Canada, 1994–2003) revealed that dietary calcium was positively associated (P (trend) = 0.165) with low-grade but inversely (P (trend) = 0.034) with high-grade cancer.[115] There was even a preventive effect of high calcium intake against high-grade cancers in a recent case-control study among US veterans.[116] A preventive effect was

also reported by a recent review (relative risk 0.54, 95% CI 0.30–0.96), although there were only few events.[117]

Conclusion: The majority of studies did not confirm an increased prostate cancer risk induced by calcium supplements or nutritional calcium intake.

Colorectal and other cancers

There were a few trials reporting an effect of calcium supplementation on Cancer risk, which motivated numerous reviews without significant outcomes. In 2009, the FDA reviewed the literature and found no credible evidence to support health claims for calcium and for a reduced risk of breast and prostate cancers.[118] In 2010, a Cochrane analysis reported that two RCTs suggested an eventual contribution of calcium supplementation to a moderate prevention of colorectal adenomatous polyps. However, it emphasized that this does not justify the recommendation of calcium supplements for the prevention of colorectal cancer.[119] Finally, a recent meta-analysis of published studies on the anticancer effect of calcium supplements showed that the risk of total cancer was not altered, neither that of colorectal cancer, breast cancer or cancer-related mortality, but that the risk of prostate cancer was reduced, as already reported. The meta-analysis of patient-level data showed even an increased incidence of colorectal cancer with calcium supplements, which the authors explained by an eventual difference in screening.[117]

Milk alkali syndrome

The milk alkali syndrome is not anymore a rarity; it became more frequent because of the wide-spread use of supplements of calcium carbonate, which combines calcium and alkali. However, although some reports claim that 9–12% of patients hospitalized with hypercalcemia have the milk alkali syndrome,[120] it appears that this concerns mainly patients with renal failure[121] or heart transplant recipients and might be specific for a country where unconsidered overuse of nutritional supplements is a topic of concern.

Effect of Calcium Supplements as Adjuvant of the Medical Treatment of Osteoporosis

Three quarters of women initiating treatment of osteoporosis are supplemented with calcium and/or Vitamin D (France).[122] Because calcium is usually added to the medical treatment of osteoporosis and to the control groups of controlled trials too, it is not certain what would be the effect of the drugs used for treatment without calcium.

Nutritional Cofactors

The absorption and efficacy of calcium supplements depend partially on the concomitant nutritional intake. The influence of nutrients on the absorption and the necessity to guarantee an adequate protein intake are discussed in part I of this review.[97] Some nutrients decrease calcium absorption—for example, fibers, phytic acid, oxalate—whereas others enhance the absorption and increase its bone effect, such as proteins. Calcium supplements should not be given without correcting a low protein intake. A high sodium intake, which increases urinary calcium excretion, should be compensated by a potassium rich diet, before calcium supplements are given.[123] Calcium intake has to be optimized in subjects with a high caffeine intake, because it results in bone loss in individuals with a low total calcium or milk intake.[124,125] The consumption of carbonated soft drinks with a high phosphate content was associated with reduced bone mass and increased fracture risk in children, but this is due to a 'displacement' effect rather than to phosphorus itself, because it goes along with a low intake of milk and dairies.[126] The same observation applies to caffeine consumption, which goes along with poor calcium intake and for itself does not affect bone,[127] except when the intake is particularly high.

Conflict of Interest

The authors declare no conflict of interest.

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