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Calcium and osteoporosis

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SUMMARY. Calcium and osteoporosis. Osteoporosis is a crippling disease that emerges as an important public health problem both in developed and developing countries including Brazil. The clinical condition is characterized mainly by loss of bone mineral mass in later life as the net result of complex physiological and environmental interacting factors during lifetime. Calcium intake appears as an obvious nutritional factor in the prevention of osteoporosis but its contribution is still not well established particularly when populations with different habitual levels of calcium intake are compared. In this section, we examine the role of calcium intake as affecting bone mineral density at different stages of development and with aging, with special attention to the possible stress on bone mass due to pregnancy and lactation. Nutritional studies demonstrate that, in general, adequate calcium intake during lifetime contributes to decrease the risk of osteoporosis. However, the long term effects on bone health of sub-adequate, but not very low, habitual calcium intakes during highly demanding physiological periods such as adolescence, pregnancy and lactation, are still largely unknown. Sub-adequate calcium intakes are probably common in Brazil.

INTRODUCTION

Osteoporosis is the clinical condition characterized by a reduction in both bone mineral and bone matrix, decreasing bone density with a consequent higher risk of fractures following trauma. This condition is emerging as an important public health problem, both in developed and developing countries, due to the worldwide trend in increased life expectancy leading to a larger number of elderly persons. Osteoporosis affects millions of individuals around the world, but even with reduced bone density incidence of fractures vary for different populations possibly due to the complex etiology of this condition (1,2). Data from Brazil are scarce and it mainly relates to incidence of fractures (3). Considering that on a global basis osteoporosis affects about 10 % of the population older than 60 years (4) it may be estimated that in Brazil at least 1.5 million persons are affected.

Bone density in the adult and aged organism depends both on the peak of bone density achieved through adolescence and early adulthood and on the subsequent bone loss associated with aging. In general, women reach a lower peak bone density and loose bone faster with age than men and therefore have higher life-time risk of fractures than men (5). Complex physiological and environmental interacting factors need to be considered as affecting peak bone density, maintenance of peak bone mass through the reproductive years in the adult, and bone loss with aging. Genetic factors seem to have the higher contribution, accounting for up to 80 % of population variance of peak bone density (5) and about 25 % of bone density in the elderly (1). Most of the genetic differences in bone density seem to be explained by allelic variations of the vitamin D receptor gene (6). Although calcium nutrition seems to contribute with less than 20% to these variances, the importance of adequate calcium intake and calcium status on the prevention of osteoporosis is at present under intense investigation as a readily implementable and relatively inexpensive environmental preventive factor.

We will examine in this section, the role of calcium intake in the prevention of osteoporosis as it affects bone mineral density at different stages of development and aging, with special attention to pregnancy and lactation.

CALCIUM INTAKE AND PEAK BONE DENSITY

Interest in the role of calcium intake on adolescent bone mineralization as a preventive factor of osteoporosis is based on the hypothesis that a greater peak bone mass reached in young adulthood will be a determinant of a greater bone mass at menopause and a greater sustained bone density during aging.

The acquisition of bone mass and density is a result of age, sex, other genetic factors, pubertal status, physical exercise and calcium intake. Bone density increases dramatically during puberty in response to gonadal steroids. During the adolescent growth spurt, about 45% of the adult's skeletal volume is formed, with the bone mineral content increasing at a rate of about 8.5% per year (5). Increase in bone mass, particularly in cancellous bone, is strongly influenced by hormonal changes in adolescence (7), which is explained by the strong relationship between osteoblast activity and gonadal steroid stimulation (5,8). In situations of puberty delay due to gonadal hormone deficiency, normal peak bone density is not reached (7).

Several recent studies have focused on the role of adequate calcium intake on bone mineral acquisition during adolescence. An investigation examining 487 calcium balance studies in children aged <18 years (9) suggested that together with rates of skeletal modeling and turnover, calcium intake is a main determinant of calcium balance during growth. This investigation also suggested that the threshold for achieving positive adequate balances for skeletal growth may require calcium intakes at levels exceeding present recommended allowances. Moreover, based on estimations from cross-sectional studies relating bone density and calcium intakes, it was concluded that adolescents with average intakes below 1000 mg/d for boys and 850 mg/d for girls, will probably not reach optimal peak bone mass (10). Some recent studies of calcium supplementation during several months of pre-adolescents with average calcium intake of 950 mg/d resulted, in fact, in significant increase of bone mineral density (11,12) consistent with the critical role of calcium intake on bone mineralization during this period.

Low calcium intake in children and adolescents appears to limit acquisition of bone mass and bone maturation. Reduced bone

development and bone density have been observed in African children and adolescents possibly related to low calcium intakes (13). Studies in South African children, 9-12 years of age, with calcium intakes lower than 400 mg/d, showed that many of them had biochemical signs of hyperparathyroidism and delayed bone maturation as indicated by low serum calcium and raised activity of plasma alkaline phosphatase, which normalized after calcium supplementation (14). A study of 900 children in Brazil, 7-17 years of age, comparing bone maturation and biochemical bone indices in privileged and underprivileged (15), showed that plasma alkaline phosphatase and inorganic phosphorous were abnormal in the underprivileged group. Moreover, these children also showed delayed bone maturation as indicated by difference between chronological and bone age. Although differences in calcium intakes between these groups may be expected, calcium intake was not evaluated in this study. In fact, habitual calcium intakes in the Brazilian population, including children and adolescents, are largely unknown (3).

Calcium intake seems to play a critical role for achievement of skeletal maturity since marginal intake in children and adolescents is a limiting factor of peak bone mass and calcium supplementation can increase bone mass, even in individuals with dietary intakes close to present recommendations . What it is still not known is whether an increased bone density in children and adolescents, obtained by a temporary calcium supplementation, will persist during adulthood as an intrinsic part of peak bone mass, thus reducing the risk of osteoporosis, and if this effect will be different in individuals with habitually low or close to adequate dietary calcium intakes.

CALCIUM INTAKE AND BONE STATUS WITH PREGNANCY AND LACTATION

Pregnancy and lactation may potentially affect the maintenance of peak bone mass during adulthood due to the substantial amounts of calcium that need to be transferred from the mother to the fetus or to the infant. A full-term pregnancy demands about 30 g of calcium for transfer to the fetus while milk production for exclusive breastfeeding during 6 months may demand 47-63 g of calcium (16). If maternal bone mineral was the only source of calcium in these states, the maternal skeleton would lose about 3% and 4-6% of calcium after pregnancy and lactation, respectively. Moreover, both physiological states are characterized by hormonal alterations that may influence bone turnover and bone density (16,17). Levels of circulating maternal estrogen are greatly increased during pregnancy due to the massive placental production; progesterone, prolactin and PTHrP are also increased while PTH levels remain normal or even decreased. Lactation is a hypoestrogenic state with elevated prolactin levels and normal or increased PTH levels. Due to the different hormonal environments, the physiological adjustments to maintain calcium homeostasis are different in these states, with increased efficiency of intestinal calcium absorption occurring in pregnancy, but not in lactation, and renal calcium conservation occurring only in lactation. Although relationship with dietary intake remains largely unknown, the calcium demands of the fetus and infant may outstrip the calcium available from intestinal absorption and renal economy, particularly in women with limited calcium intake, resulting in increased mobilization of maternal bone calcium and increased risk of osteoporosis.

Studies in women with calcium intakes close or higher than present recommendations during pregnancy have obtained biochemical indication of both increased bone resorption and bone formation in this period (18,19), suggesting that increased maternal bone turnover is a physiological mechanism to ensure adequate maternal calcium availability for fetal demands. However, this mechanism will not necessarily result in maternal bone loss. Prospective studies examining changes in bone density during pregnancy in healthy women did not produce consistent results on bone loss with pregnancy since either small detectable decrease in trabecular bone (20,21) or no change in bone mass (22,23) have been observed. There are no reported studies on bone changes during pregnancy in women with low or marginal calcium intakes.

Mobilization of maternal bone calcium may be more variable during lactation than during pregnancy because the degree of calcium demand relates to the amount of breast milk produced and to the duration of breastfeeding. Moreover, the overall demand is generally higher in lactation. Several longitudinal studies have clearly confirmed that there is significant bone loss with established and extended lactation in well nourished women (20, 24-27). These findings are supported by biochemical evidence of increased bone turnover during lactation compared to control women (18,19,28). An interesting fact emerging from some studies (20,26,27) is that bone loss during lactation is followed by recovery of bone mineral mass with re-establishment of menses, particularly after weaning, consistent with increased efficiency of intestinal calcium absorption in those situations (29). The bone mass recovery does not seem to be affected by a subsequent pregnancy following an extended lactation period (30). In fact, multiple pregnancies followed by lactation may have a protective role (31) or no effect (32) on bone density and risk of fractures in later life. Moreover, bone recovery seems to be largely independent of variations in calcium intake in well nourished women (27,28).

Studies in lactating women in The Gambia with very low calcium intakes (< 300 mg/d) (33,34) demonstrated that maternal bone minerals make a substantial contribution to calcium requirements during lactation in these women, by adaptive physiological mechanisms such as high efficiency of intestinal calcium absorption and very low urinary calcium excretion, that do not seem to respond to calcium supplementation. A significant decrease in midshaft radious bone mineral content after 13 weeks of lactation was observed in these women, with recovery after 52 weeks while still breast-feeding, and no effect of calcium supplementation on these changes. It is interesting to note that bone density of Gambian women was not different from that of British women. In fact, osteoporosis is not a clinical problem in The Gambia and it is still unclear if this is due to environmental an/or to genetic factors (33).

There is no information on bone changes after pregnancy and lactation in women with sub-adequate although not very low calcium intakes, a situation that is probably very common worldwide and in many urban areas in Brazil. We have been studying calcium homeostasis during pregnancy and lactation of Brazilian women with habitual calcium intakes of about 600 mg/d, half the RDA for these periods (35-37). We observed renal calcium conservation and increase in markers of both bone mobilization (urinary hydroxyproline and D-pyridinoline) and bone formation (plasma activity of bone-alkaline phosphatase) during pregnancy and lactation in these women compared to never-pregnant women with similar calcium intakes but the consequences on maternal bone mass are unknown. Hydroxyproline excretion in the 3rd trimester of pregnancy was lower in multiparas compared to primiparas (35) but it is unclear if this relates to preservation of maternal bone in multiparas or to differences in composition of gained tissue not related to bone. Responses of biochemical indices to a 7-day calcium supplementation trials with 1000 mg Ca/d given as lactogluconate, measured in 3rd trimester pregnant women, fully lactating women two months postpartum, and never-pregnant women, all with dietary calcium intakes <600 mg/d were, in general, more similar between pregnant and controls than between pregnant and lactating women (36,37). After the supplementation trial, urinary calcium excretion increased in a similar extent in pregnants and controls but did not change in the lactating women. Bone formation, based on bone-alkaline phosphatase activity, was favored in all three groups, but to a smaller extent in the lactating women. Bone degra-

dation, based on hydroxyproline excretion, was reduced mainly in pregnant primiparas and slightly in the lactating women but did not change in the other women. These results may suggest that the increased bone turnover in both pregnancy and lactation in women with sub-adequate calcium intake is sensitive to short term increase in calcium intake although to a lower extent in lactation. It remains to be shown if a sustained increase of calcium intake during pregnancy and lactation with habitual sub-adequate but not very low dietary calcium, will modify the rates of bone loss and recovery associated with these states, and have long-term beneficial effects on maternal bone.

CALCIUM INTAKE AND BONE LOSS DURING AGING

Bone loss during aging is strongly dependent on physiological factors, initially related to decline in gonadal steroids, affecting mainly trabecular bone, and at later stages related to mild secondary hyperparathyroidism and decrease in osteoblastic bone formation, affecting also cortical bone. Bone loss begins in the pre-menopausal period in women and by the fifth decade in men. During the first decade after menopause, women may lose 25-30% of trabecular bone and 10-15% of cortical bone (5).

The effect of calcium supplementation on bone mass during aging have been examined by several clinical studies, particularly in women. Although some inconsistencies arise from these studies, it appears that both the habitual dietary calcium intake and the stage in life of the woman (pre, early or late menopause) are important factors affecting the rate of bone loss and bone response to calcium supplementation. A longitudinal study of postmenopausal women found that women with dietary intakes < 400 mg/d lost spinal bone density at a greater rate than did those with intakes >770 mg/d (38). Calcium supplementation was beneficial in reducing bone loss in postmenopausal women with calcium intake <400 mg/d, particularly in those at later stages, but not in women with habitually higher calcium intake (39). Studies like these call attention on the critical role of adequate calcium nutrition in reducing the rate of bone loss during aging, particularly in women with habitually low calcium intakes. Although sub-adequate calcium intakes have been observed in adults and older individuals in Brazil (3) the possible association with bone health remains to be established.

CONCLUSIONS

Although calcium intake is only one of many complex factors affecting bone mineral density during lifetime, nutritional studies have demonstrated that adequate calcium intake makes an important preventive contribution to decrease the risk of osteoporosis, with specific role at different stages of development and during aging. However, evidence is still insufficient to evaluate the long term effects on bone health of sub-adequate but not very low habitual calcium intakes during highly demanding physiological periods such as growth spurt, pregnancy and lactation. These sub-adequate intakes are probably common in Brazil.

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