Dairy Products, Vitamin D, and Bone Health

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Introduction

Osteoporosis is estimated to affect over 200 million people worldwide [1]. In the United States alone, around ten million Americans older than 50 years are estimated to have osteoporosis, of whom approximately 1.5 million suffer from fractures related to osteoporosis [2]. Given the increase in life expectancy and consequent burden of osteoporosis among older adults, dietary modification offers a feasible approach for osteoporosis prevention and related fractures.

The complex combination of essential nutrients in dairy products includes fatty acids (essential and nonessential), calcium, potassium, high-quality protein, and magnesium, and in some countries dairy is also fortified with vitamin D. Thus, dairy products provide a unique package of nutrients that are thought to be beneficial for bone health. Consequently, dairy foods are part of nutritional recommendations in many countries worldwide. The American guidelines recommend an intake of three servings [one serving of milk = 1 cup (250 ml)] of fat-free or low-fat milk and milk products per day for adults [3]. Dairy products contribute to adequate macro- and micronutrient intakes in developed countries. They contribute to around 52–65% of the dietary reference intake of calcium [4–6], but they only represent 9–12% of the total energy consumption [7]. The bioavailability of dietary calcium is >50% of the total intake in the diet. Furthermore, dairy foods also contribute 10% of magnesium, almost all of the vitamin D, 24% of vitamin B12, 15% of zinc, and

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21% of riboflavin in the typical American diet [8]. Previous research has shown a decreasing trend of dairy consumption with age. Total dairy intake by age groups among Americans is reported to be 1.7 cup equivalents per day among those aged 19–50 years, 1.5 cup equivalents per day among those aged 51–70 years, and 1.3 cup equivalents per day among those aged 71 years and above, where 1 cup equivalent of dairy contains 81 kcal, 8.5 g protein, 0.87 g saturated fat, 298 mg calcium, 20 mg magnesium, 99 retinol activity equivalent (RAE) vitamin A, 1.55 μg vitamin D, 237 mg potassium, and 181 mg sodium [9]. The main determinants for this decreasing trend are sex, substitution of milk with other beverages, overall dietary quality, and parental influence [10]. Furthermore, not all dairy products have equivalent nutrient compositions, and it is likely that dairy products other than milk such as yogurt, cheese, and cream have a significant impact on bone health. For example, in addition to providing bone-beneficial nutrients, yogurt and certain softer fermented cheeses contain probiotics, which may provide a useful therapeutic to prevent and/or treat bone loss [11]. On the other hand, cream has lower amounts of bone-beneficial nutrients and higher levels of saturated fats and therefore may even have deleterious effects on bone health [12]. However, previous research has been largely focused on milk intake.

Previous studies determining the role of dairy food intake upon bone health were largely focused on examining the association of milk intake with dual-energy X-ray absorptiometry (DXA)-derived areal bone mineral density (aBMD) in young, premenopausal women. Majority of the studies were cross-sectional in design, and limited studies examined the bone effects of yogurt, cream, and cheese. Nonetheless, our previous study of dairy food intake and hip and spine aBMD in the Framingham Study [12] along with our review paper [13] on this topic concluded that there is strong evidence for a positive association between milk and aBMD and that evidence for yogurt intake with aBMD looks promising. However, data on cheese and cream is very limited. A recent review by Rizzoli et al. [14] summarized information from several studies suggesting that dairy food intake was associated with lower levels of bone turnover markers [such as parathyroid hormone levels (PTH), C-telopeptide of type I collagen (CTX), osteocalcin (OC), procollagen type I N-propeptide (PINP), tartrate-resistant acid phosphatase isoform 5b (TRAP 5b)] and higher levels of bone mineral content (BMC)/BMD. Fermented dairy products, such as cheese and yogurt, might contain bacterial species with a potential beneficial effect on the gut microbiome. This might in turn have beneficial effects on human health [14]. Consequently, due to the dissimilar nutrient profiles and level of fermentation, not all dairy products may have a similar effect on bone health. Therefore, more research is needed to investigate how other dairy foods, such as yogurt, cream, and cheese, are associated with bone health. Furthermore, there is limited data on specific dairy foods and hip fractures in older adults.

The synergistic or additive roles of the various bone-beneficial nutrients such as protein, phosphorus, calcium, vitamin D, and magnesium in dairy need further clarification, since a single nutrient cannot account for the proposed beneficial effect of dairy intake. For example, vitamin D status can enhance calcium absorption, which is beneficial for building bones [15]. Yet, it is unclear if the effect of vitamin D on calcium absorption is substantial enough to translate into beneficial effects on BMD. This interaction may be particularly important for older adults who tend to be deficient in vitamin D (<20 ng/mL in blood) as recommended intakes are difficult to achieve without fortified foods (such as dairy) or supplements and a declining ability to make vitamin D in the skin with advancing age. Consequently, research into the role of dairy foods upon bone health continues to be an active area of research. The objective of this book chapter is to highlight findings from latest studies on this topic to summarize recent research examining individual dairy products, their role in bone health, and interaction of dairy products with vitamin D intake and status. We further highlight the emerging research in this area relating dairy food intake with novel measures of bone, derived using quantitative computed tomography (QCT) and high-resolution peripheral QCT (HR-pQCT).

Interaction with Vitamin D

The Institute of Medicine reported that serum 25-hydroxy vitamin D (25-OH D) concentrations of less than 12 ng/mL (30 nmol/L) are associated with deficiency, inadequate levels are considered between 12 and < 20 ng/mL (50 nmol/L), and levels ≥20 ng/mL are generally considered adequate. There is emerging evidence that 25-OH D levels greater than 50 ng/mL (125 nmol/L), achieved through high-dose vitamin D supplementation, could have adverse effects, such as weight loss, arrhythmias, vascular and tissue calcification, or kidney damage [16]. Sunlight contributes around 2/3 to our vitamin D status; therefore, dietary vitamin D alone is insufficient to meet the body's requirements for vitamin D. Hence, some countries (e.g., Canada and the United States) have decided to fortify their dairy products and other foods (e.g., cereal) with vitamin D [17, 18].

The aging skin has a decreasing capability of producing vitamin D [19]. Consequently, older adults may be more prone to vitamin D deficiency, and fortification with vitamin D could be a useful strategy for improving circulating 25-OH D concentrations [20]. Endocrine Society Clinical Practice Guideline recommends that adults 50–70 years and those over the age of 70 years require at least 600 and 800 IU/day, respectively, of vitamin D to maximize bone health and muscle health [21]. Total calcium concentration in the serum is highly regulated. If the serum calcium levels drop, parathyroid hormone (PTH) is secreted, which stimulates the kidney to produce calcitriol, the active form of vitamin D. Vitamin D then acts in an endocrine manner in the intestines to absorb calcium available from the diet and supplements and in the bones to activate bone resorption. This process is called calcium homeostasis. The role of calcium is mainly skeletal strength and dynamic storage, to maintain intra- and extracellular calcium concentrations. Therefore, vitamin D has a major physiologic role in maintaining the intra- and extracellular calcium concentrations and skeletal homeostasis [22]. This suggests that both calcium and vitamin D levels are important for bone health [23, 24] and may have interactive effects upon bone health. Consequently, several previous studies have reported on the benefit of vitamin D on BMD [6, 21, 25–27]. A recent study showed that there was no threshold of calcium absorption (range 32–38% of intake) with increased vitamin D intakes [28]. However, recent data evaluating the effect of vitamin D on BMD have been inconsistent. A meta-analysis [26] and a randomized controlled trial (RCT) [29] concluded that there was no evidence of an overall benefit of vitamin D supplementation on BMD, yet there was a small but relevant effect on calcium absorption. It thus remains unclear whether the effect of vitamin D on calcium absorption is substantial enough to translate into beneficial effects on BMD, especially in older women who tend to be deficient in calcium and were not represented in the recent clinical trial [29].

A recent prospective cohort study [$n = 628$, mean age = 75 years (range, 67–93)] determined the association of dairy foods (defined as intake of milk, yogurt, cheese, cream, milk + yogurt, and milk + yogurt + cheese) with aBMD and bone loss (femoral neck, trochanter, and lumbar spine) over 4 years in older adults [25]. This study further assessed whether these associations were modified by vitamin D supplement use in this cohort of older men and women from the Framingham Original Cohort. Dietary assessment in this study was conducted at baseline (in 1988–1989) using Willett semiquantitative food frequency questionnaire. Baseline BMD was measured at the hip (femoral neck and trochanter) and at the spine using Lunar DP3 dual-photon absorptiometer. Follow-up BMD was measured after 4 years using DXA. Four-year percentage change in BMD was calculated as [(follow-up BMD – baseline BMD)/baseline BMD] × 100. This study reported that a higher intake of dairy foods (milk, fluid dairy, and milk + yogurt + cheese) was associated with a higher spine BMD among vitamin D supplement users, but not among nonusers. Among vitamin D supplement users, there was a 0.006 g/cm^2 difference in spine BMD for an increase of one serving of milk per week. Similarly, among vitamin D supplement user, but not among nonusers, higher milk + yogurt + cheese intakes were protective against bone loss at the trochanter. There was a 0.23% increase in trochanter BMD over 4 years for every serving increase of milk + yogurt + cheese per week among vitamin D supplement users. This suggests that vitamin D supplementation may provide bone-protective benefits with higher dairy intakes. However, a higher dairy food consumption did not seem to be protective in non-vitamin D supplement users. This might suggest that a sufficient vitamin D intake is important for dairy to provide bone benefits. However, vitamin D intake does not account for the vitamin D formed in the skin by sun exposure. Therefore, future studies should confirm these findings by using serum vitamin D concentrations.

Studies on Novel Bone Measures

Previous studies examining dairy foods with bone health were largely focused on DXA-derived aBMD, a surrogate for bone strength. Recently, novel measures for bone health have become available such as quantitative computed tomography (QCT) and high-resolution peripheral QCT (HR-pQCT). These measures provide three-dimensional images and volumetric BMD measures to address bone strength, quality, and microarchitecture, which are key determinants of bone health [30, 31].

These new measures provide information on cortical, trabecular, and whole bone volumetric BMD (vBMD) not confounded by individual differences in bone size. Hence, these novel measures enable us to address the associations of dairy intake with bone strength.

There is limited evidence on the impact of calcium intake and dairy protein upon bone strength and microarchitecture. One of the earlier studies in this area reported on cross-sectional associations between calcium intake and non-weight-bearing radius and weight-bearing tibia in 218 healthy women (*n* = 92 premenopausal women, mean age, 33 years; *n* = 126 postmenopausal women, mean age, 67 years) [32]. This study reported that high calcium intake seemed to benefit radial shaft but not the tibia. In premenopausal women, the bone strength index (density-weighted section modulus, mm^3) was 7.8% (95% CI 0–16.3%) higher among those with dietary calcium of over 1200 mg/day than those with intakes less than 800 mg/day. In postmenopausal women, cross-sectional area (mm^2) was 5.2% (95% CI 0–10.7%) greater among those with dietary calcium of over 1200 mg/day than those with intakes less than 800 mg/day. However, calcium intake was not associated with tibial bone characteristics. Two recent studies have reported on dairy protein intake and bone health. One cross-sectional study of 746 Caucasian women (aged 65 years) from Geneva determined the association of dietary protein intake (total intake and intake from dairy, nondairy animal, and plant sources) with peripheral skeleton-predicted failure load and stiffness and bone microstructure at the distal radius and tibia [33]. This study reported a beneficial effect of animal and dairy protein intakes on bone strength and microstructure. Dietary protein, particularly from dairy products, was positively associated with bone failure load and stiffness of the peripheral skeleton; with every gram per day increase in dairy protein intake, the failure load increased by 0.009 N at the distal radius and 0.461 N at the distal tibia (*p*-values 0.025 and 0.048, respectively). With every gram per day increase in dairy protein intake, the stiffness increased by 0.011 N/mm at the distal radius and by 0.013 N/mm at the distal tibia (*p*-values 0.032 and 0.045, respectively). Similarly, another cross-sectional study of 1016 men, aged ~83 years from the Osteoporosis Fractures in Men (MrOS) Study, determined the association of protein intake by source (from dairy, nondairy animal, plant) with bone strength and bone microarchitecture (HR-pQCT) scans of the distal radius and distal or diaphyseal tibia among older men [34]. This study reported that higher dairy protein intake was associated with higher estimated failure load at the distal radius and distal tibia [radius effect size = 0.17 (95% CI 0.07, 0.27), tibia effect size = 0.13 (95% CI 0.03, 0.23) for 1 SD change in dairy protein intake], while higher nondairy animal protein was associated with higher failure load at only the distal radius [radius effect size = 0.07 (95% CI 0.00, 0.13)]. Plant protein intake was not associated with failure load at any site. Thus, the association between protein intake and bone strength varied by source of protein.

In spite of these studies reporting beneficial role of dietary calcium and dairy protein on bone health, only a few studies have directly assessed the association between dairy food intake and bone measures from QCT or HR-pQCT. A study of 564 older women (aged 80–92 years) evaluated the association of dairy food intake (sum of milk, yogurt, and cheese intake) with peripheral QCT (pQCT) bone measures at the distal tibia. The participants were from the Calcium Intake Fracture Outcome Study (CAIFOS, a 5-year RCT), which enrolled 1500 women aged 70–85 years in 1998. Once the RCT was completed, these participants were followed up for a further 5 years in the CAIFOS Aged Extension Study (CARES) cohort [35]. In this study a dairy intake of ≥2.2 servings/day was associated with higher total and trabecular vBMD (least square adjusted means for total vBMD was 410.1 ± 81.6 mg/cm^3 and for trabecular vBMD was 223.8 ± 59.1 mg/cm^3) as compared to women with an intake of ≤1.5 servings/day (least square adjusted means for total vBMD was 387.7 ± 81.3 mg/cm^3 and for trabecular vBMD was 367.7 ± 81.1 mg/cm^3). These associations became nonsignificant when the models were adjusted for dairy protein and calcium intake. However, the effect of dairy intake upon bone measures from these novel techniques is understudied in men.

A recent study examined the association of dairy food intake (defined as intake of milk, cheese, yogurt, cream, milk + yogurt, and milk + yogurt + cheese) with QCT-derived bone measures of the spine in 2626 men and women from the Framingham Study Offspring and Third Generation (Gen3) cohorts [36]. This study further determined whether these associations were modified by 25-OH D concentrations. In this cross-sectional study, information on dietary intake was collected by Willett semiquantitative food frequency questionnaire in 1998–2001 (Offspring cohort) and in 2002–2005 (Gen3 cohort). QCT assessment was performed in 2002–2005, and the study examined spine measures at the L3 level in the spine. The mean age was 50 years (SD 10.6; range 32–80) for men and 55 years (SD of 9.2; range 36–81) for women. Sixty-four percent of men and 70% of women reached the recommendation of three servings of dairy per day. Thirty-three percent of men and 48% of women did not have adequate blood levels of 25-OH D (20 ng/mL), and 68% of men and 51% women did not achieve recommended dietary allowance (RDA) of calcium intake for their age and sex. A higher milk, milk + yogurt, and milk + yogurt + cheese intake was positively associated with trabecular and integral (entire vertebral body, both cortical and trabecular) volumetric BMD (vBMD, g/cm^3) and vertebral compressive strength (N), estimated using engineering beam theory [37], but not with cross-sectional area (cm^2) in men at the L3 level in the spine. Among men, there was a 0.0002 g/cm^3 and 0.0003 g/cm^3 difference in trabecular and integral vBMD, respectively, for an increase of one serving of milk per week. Similarly, there was a 9.9 N difference in vertebral strength for an increase of one serving of milk per week. No association was seen for yogurt, cheese, and cream with integral and trabecular vBMD or vertebral compressive strength. Only cheese was positively associated with cross-sectional area in men. In women, no association was seen overall, except a higher cream intake was associated with the cross-sectional area. This could be due to high calcium intake (mean calcium intake, ~1200 mg/day) in women in this study. These sex-specific differences in spine indices should be further explored in the context of dairy intake in future studies. In the same study, significant interactions were observed for serum 25-OH D and milk, milk + yogurt, and milk + yogurt + cheese in men for trabecular vBMD (p range, 0.02–0.007), integral vBMD (p

range 0.001–0.004), and vertebral compressive strength (p = 0.003 each). No interaction was observed for 25-OH D and dairy intake in women (p range 0.14–0.97). Consequently, the analyses in men were stratified by 25-OH D. Due to small sample size in the low 25-OH D group, investigators could not use predefined clinical cutoffs for 25-OH D (<20 ng/mL and ≥ 20 ng/mL). Instead, they used cutoffs based on tertiles [lowest tertile (≤24.2 ng/mL) vs. higher two tertiles (>24.2 ng/mL)]. Upon stratification by 25-OH D levels, the authors reported that in men with low 25-OH D, a higher dairy intake showed larger magnitude of association for some but not all bone health measures compared with men with a higher 25-OH D level. However, even among men with 25-OH D > 24.2 ng/mL, dairy continued to have positive associations for milk, milk + yogurt, and milk + yogurt +cheese and vBMD and vertebral compressive strength. These associations also appeared to be stronger in older men aged 50 years and older. In summary, this study concluded that men with higher intakes of milk, milk + yogurt, and milk + yogurt + cheese had higher trabecular and integral vBMD and vertebral compressive strength, but not cross-sectional area. Dairy intake seemed to be most beneficial for older men, and dairy continued to have positive associations across all 25-OH D levels.

Conclusion

Dairy intake is an essential source of bone-beneficial nutrients such as calcium, protein, vitamin D (in fortified dairy), magnesium, and potassium in the Western diet. This provides a specific opportunity for dairy foods to improve bone health specifically in older adults. Evidence for a positive association between milk and bone health is strong. However, evidence for other dairy products is limited. Both calcium and vitamin D levels are important for bone health, and these nutrients may have interactive effects upon bone. However, it remains unclear whether the effect of vitamin D on calcium absorption is substantial enough to translate into beneficial effects on BMD, especially in older adults. Furthermore, majority of nutrition studies used areal BMD from DXA, and there is limited information on dairy's effect upon bone strength, quality, and microarchitecture. Therefore, future studies on dairy foods should focus on specific dairy foods beyond milk intake and novel measures of bone beyond aBMD, and future studies should take vitamin D status into consideration. Given that more than 80% of Americans do not meet the recommended dairy intake of three servings per day and older adults are prone to vitamin D deficiency, this area of research could have important public health implications.

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