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Review

Osteoporosis: Is milk a kindness or a curse?

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ABSTRACT

Cow's milk is often severely criticized as a cause of multiple health problems, including an increased risk of fractures. A close look at the scientific literature shows a striking contradiction. On the one hand, experimental studies of surrogate markers (e.g., bone turnover markers and bone mineral density [BMD]) usually indicate benefits from drinking cow's milk. On the other, the findings from epidemiological studies are conflicting and disconcerting. In all age groups, including children and postmenopausal women, consuming cow's milk, powdered milk supplements, or whey protein is associated with a slower bone turnover and unchanged or higher BMD values. These benefits are particularly marked in populations where calcium deficiency is prevalent, for instance in Asian countries. No interventional studies have addressed the fracture risk potentially associated with drinking cow's milk. The only available data come from epidemiological observational studies, whose results are conflicting, with a lower fracture risk in some cases and no difference or a higher risk in others. Several hypotheses have been offered to explain these findings, such as a deleterious effect of D-galactose, lactose intolerance, and acid overload. Epidemiological studies face many obstacles when seeking to detect effects of a single food, particularly the multiplicity of interactions among foods. Furthermore, reliable dietary intake data must be collected over prolonged periods, often long before the occurrence of a fracture, and defective recall may therefore introduce a major yet often unrecognized bias, particularly in populations where calcium deficiency is uncommon. To date, there is no conclusive evidence that we should modify our currently high level of consumption of cow's milk.

1. Introduction: cow's milk in the dock

For many years, cow's milk has been vociferously accused of harming human health. This hostility is fed by a conspiracy theory suggesting that the dairy industry will go to any lengths to sell its produce and has bribed medical experts, scientific societies, and public health authorities into encouraging the consumption of milk. Milk, a complex food that has been consumed by humans in large amounts for millennia, is thus accused of causing numerous diseases that range from prostate and ovarian cancer to obesity, diabetes, multiple sclerosis, and otitis media. A study in women reported in 2014 found that cow's milk consumption was associated with excess mortality, osteoporosis, and fractures [1]. Processed dairy products and milk from other animals have largely escaped the animosity directed at cow's milk.

The arguments used to militate against cow's milk are drawn from eclectic sources ranging from philosophy and ethics to speciesism and science. Some can be immediately discarded as irrational, although popular and seductive, for instance, the notion that cow's milk is intended for calves and not for humans, that humans started drinking milk only a few thousand years ago, that humans are the only mammals that continue to drink milk after being weaned, and that Scandinavians have both the highest milk consumption and the highest incidence of hip fractures. These arguments are popularized in books, mainstream magazines, and the audio media.

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Here, we report a literature review that focused on potential effects of cow's milk on bone health in humans. Milk from other mammals is not discussed; hereafter, "milk" is designated as "cow's milk". Data on bone turnover and BMD are considered first, before a review of studies of the incidence of osteoporotic fractures.

2. Studies of bone turnover and BMD vs. studies of fractures: disturbing discrepancies

Humans have been consuming large amounts of milk for several thousands of years. The nutritional properties of milk are remarkable. Milk is an abundant source of calcium, whose bioavailability is high compared to other dietary sources, and the calcium/phosphate ratio in cow's milk is optimal for ensuring bone mineralization. The mean calcium content in whole and skim milk is 1150 mg/L, providing a ready means of meeting the daily requirement of 900–1200 mg. Milk is a well-balanced food, with powdered milk being composed of equal parts of protein, fat, and lactose.

A careful analysis of the scientific literature on milk and bone health uncovers a striking discrepancy: experimental and observational studies of surrogate markers (e.g., bone turnover markers and BMD) usually showed that milk consumption was associated with a slower pace of bone remodeling and a higher bone mass (Table 1). In contrast, studies that focused on osteoporotic fractures produced conflicting results, with some showing a protective effect of milk consumption and others no effect or an increase in the fracture risk (Table 2).

3. Milk consumption slows bone remodeling and protects bone mass in all age groups

In children and adolescents, who normally have a fast pace of bone turnover to meet the needs of skeletal growth, a high milk intake suppresses the secretion of parathyroid hormone (PTH) [2] and decreases the levels of bone resorption markers, while enhancing bone growth, whereas a high intake of meat does not share these effects [3]. In healthy postmenopausal women, milk supplementation also lowers the levels of bone turnover markers [4–6]. The effect of milk or any other source of calcium in slowing bone turnover is particularly marked in populations where the dietary calcium intake is low, such as elderly individuals in Asian countries [2,7–10].

In many countries, the consumption of milk as an abundant source of calcium and protein is encouraged during adolescence to optimize peak bone mass. In many observational studies, milk intake was associated with greater bone accretion as assessed based on BMD, both in Asia [11] and in the West [12,13], and with significantly higher levels of insulin-like growth factor (IGF) and growth hormone [12]. BMD correlates positively with milk protein intake, perhaps due to the ability of protein to increase the intestinal absorption of calcium [14]. Protein from low-fat milk is more beneficial to femoral neck bone mass compared to protein from red meat or processed foods [15].

In postmenopausal women, BMD correlates positively with milk intake during childhood and adolescence [16–21]. In older individuals, a diet high in low-fat milk was associated with bone mass preservation [15]. As with children and adolescents, the effect of milk intake in individuals older than 50 years is greatest in populations whose diet is low in calcium, for instance in Asia [7,8,22] and Poland [21].

Interventional studies of milk intake are methodologically more robust than case-control studies. They are few in number, however, and focused on postmenopausal women, in whom milk intake prevented bone loss at specific sites [22–26].

Metabolic syndrome may be associated with stronger protective effects of milk calcium in postmenopausal women aged 65 ± 5 years [27]. One possible explanation involves the production of incretins related to metabolic syndrome, as incretins have anabolic effects on bone.

4. Whey: a side-product with pivotal effects?

The benefits of milk are chiefly mediated by calcium and proteins, such as casein. Other components may also have favorable effects on bone, however. Several studies, many conducted in Asia, looked at the effects of whey protein on bone. Whey is the liquid left after curdled milk is strained. In mice, whey proteins diminished bone turnover [28], increased BMD and mechanical strength of the femur [29] and possibly promoted fracture healing [30]. Whey protein intake increased lumbar spine BMD in postmenopausal women [26] and lean mass in older women [27]. In mice, in vitro and in vivo studies demonstrated that bovine angiogenin purified from milk basic protein (MBP), a constituent of whey, strongly inhibited osteoclast activity [31]. Bovine angiogenin impaired F-actin ring formation and diminished the levels of mRNA for TRAP and cathepsin K, which are crucial to the bone-resorption effect of osteoclasts. Further work is warranted to evaluate these effects.

5. Milk and fractures: a jumble

Findings from epidemiological studies are not always consistent with those of surrogate endpoints such as bone turnover markers and BMD. Several obstacles exist to the demonstration of effects in epidemiological studies. One is the large number of interactions among nutrients in populations that are not always calcium-deficient. Another is the challenge raised by measuring food intakes, particularly retrospectively, which introduces multiple sources of bias. The occurrence of a fracture is a reliable endpoint that is fairly easy to collect in epidemiological studies, as there is usually a medical intervention and sometimes a hospital admission, at least for appendicular fractures. However, the occurrence of a fracture is difficult to interpret, as it is related not only to the characteristics of the bone tissue, but also to the existence of risk factors for falls. Interventional trials of milk intake with fracture occurrence as the primary endpoint (as done for osteoporosis drugs) would be extremely difficult to conduct, and none has been reported to date. A few case-control studies have been published. Most of the data, however, come from vast observational cohort studies that can detect statistical associations but are unable to demonstrate causality. Only a double-blind randomized controlled design can prove a causal link between milk intake and fracture risk. A randomized trial with no placebo evaluated the effects of milk powder supplementation for 2 years in postmenopausal Chinese women [7,32]. Fractures occurred in 3 of the 90 control women compared to 1 of the 95 supplemented women. This difference was not statistically significant. However, the trial was designed to assess changes in BMD and bone turnover; it was not powered to detect a difference in the fracture risk.

In children, milk intake was associated with a decreased risk of childhood fractures in some studies [33–35] but not in others [36,37]. A low milk intake during childhood was associated with a 2-fold increase in osteoporotic fractures in adulthood [20]. MEDOS is a case-control study of women in Mediterranean countries aged 50 years or over [38]. Higher milk intake was associated with a lower risk of hip fracture. However, this association may have been related to confounders, as women with a low milk intake more often had risk factors for fractures such as younger age at menopause, less physical activity, and heavier smoking. In individuals older than 68 years in the Framingham cohort, drinking more

Table 1
Studies evaluating links between cow's milk intake and bone turnover markers.

Authors (reference)	Study design	Study products	Population Age, mean ± SD (years)	Daily calcium intake, mg, mean ± SD	PTH	BAP	P1NP	OC	NTXu	Deoxypyri-dinoline	CTXs
Du et al. [2]	Randomized controlled trial 2 years	330 mL of calcium-supplemented milk ± vitamin D vs. controls	G[1]: calcium-supplemented milk, 238 girls G[2]: calcium- and vitamin D-supplemented milk, 260 girls G[3]: controls, 259 girls 10–12 years	457.5 ± 197.3	G[1]: 6.68 ± 3.03 G[2]: 5.64 ± 3.34 G[3]: 8.19 ± 6.30						
Aoe et al. [26]	Randomized controlled trial 6 months	Milk basic protein	27 postmenopausal women 50.5 ± 3.0	≈ 500				5.73 ± 0.59	47.3 ± 8.3*		
Bonjour et al. [5]	Randomized crossover trial 6 weeks	250 mL of low-fat milk 300 mg calcium	30 postmenopausal women 59.3 ± 3.3	600	– 3.2 pg/mL**		– 5.5 ng/mL**	– 2.8 ng/mL***			– 624 pg/mL***
Budek et al. [3]	Randomized controlled trial 7 days	1.5 liter of milk vs. 250 g meat/d	24 boys 8 years			– 3.9%^{NS}		– 30.9%*			–18.7%*
Cadogan et al. [12]	Randomized controlled trial 18 months	450 mL milk vs. 150 mL milk	80 girls 12.2 ± 0.3	746	– 8.9% ^{NS}	– 29.7%^{NS}		– 26.8%^{NS}	– 16.6%^{NS}	– 7.6%^{NS}	
Ma et al. [6]	Metaanalysis of randomized controlled trials 11 trials	Milk, fortified "milk"	2397 males and females					– 5.90 ng/ml*** 95%CI: 7.23–4.57	– 5.41 nmol/L* 95%CI: – 10.35–0.47		

NS: non significant; PTH: parathyroid hormone; BAP: bone alkaline phosphatase; P1NP: procollagen type 1 N propeptide; OC: osteocalcin; NTXu: urinary type 1 collagen cross-linked N telopeptide; CTX: collagen type 1 cross-linked C telopeptide.

* $P < 0.05$.
** $P < 0.01$.
*** $P < 0.001$.

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Table 2
Studies evaluating links between cow's milk intake and fracture incidence.

Authors (reference)	Study design Study duration	Pays	Sample size Age	Calcium and vitamin D supplements considered	Overall efficacy of calcium	Overall efficacy of vitamin D	Association with milk
Kanis et al. [53]	Metaanalysis EVOS/EPOS, CaMos, DOES, Rotterdam study, Sheffield study, Gothenburg II cohort	19 European countries	39,563 males and females 21–103 years	No	No	–	No fracture risk increase with < 1 glass of milk/day vs. remainder of the population Except > 80 years (abolished by adjusting for BMD)
Feskanish et al. [44]	Prospective Nurses' Health Study 12 years	US	77,761 female nurses 34–59 years	Yes	No	No	No decrease in the risk of hip or forearm fracture dependent on milk intake during childhood or adulthood
Feskanich et al. [46]	Prospective Nurses' Health Study 18 years	US	72,337 postmenopausal women	Yes	No	Yes	No decrease in the incidence of hip fracture Protective effect of vitamin D supplements
Mickaëlsson et al. [47]	Prospective Swedish Mammography Screening Cohort	Sweden	60,689 females 40–74 years	Yes	No	No	No decrease in the incidence of hip fracture or of other osteoporotic fractures
Kalkwarf et al. [20]	Cross-sectional study NHANES III	US	3251 Caucasian females ≥ 50 years	Yes	–	–	Low milk intake in childhood associated with lower BMD and 2-fold higher fracture incidence after 50 years of age
Bischoff-Ferrari et al. [48]	Metaanalysis 7 prospective trials 3–26 years	US Europe Canada Australia Japan	195,102 females and 75,149 males 47–71 years	Yes, depending on the study	–	–	No association between milk intake and hip fracture risk Trend toward a protective effect in males
Mickaëlsson et al. [1]	Prospective Swedish Mammography Cohort Cohort of Swedish Men 20 years	Sweden	61,433 females 39–74 years 45,339 males 45–79 years	Yes	No	No	In females, increased risk of osteoporotic fractures, including hip fractures
Feskanish et al. [51]	Prospective Nurses' Health Study Males > 50 years 22 years	US	96,000 Caucasian postmenopausal women Men > 50 years	Yes	Yes	Yes	Milk intake between 13 and 18 years of age Each additional glass of milk per day associated with a 9% higher fracture risk in males with low intakes of calcium and vitamin D Abolished after adjustment for height or when sufficient intake of calcium and vitamin D
Sahni et al. [39]	Prospective Framingham Original Cohort	US	830 males and females 68–96 years	Yes	–	–	Drinking > 1 glass of milk/day associated with a 40% lower risk of hip fracture

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than one glass of milk each day was associated with a 40% lower risk of fracture compared to little or no milk consumption, whereas other dairy products had no effect [39]. In contrast, in the Framingham Offspring Study, in individuals aged 55 ± 10 years, milk consumption was associated with higher BMD values at the hip but not with a lower risk of fractures [40].

Several studies in adults found no significant association between milk intake and fracture risk [41–49]. They were conducted in populations whose usual diet supplied sufficient calcium. The closer the usual calcium intake is to the estimated average requirement (700 mg/day for calcium), the more difficult it is to detect a statistically significant effect of supplements. High milk intake was associated with an increased fracture risk in vast epidemiological cohort studies. This finding created a considerable stir, both in the scientific community and in the general public. It also raises many questions, however, as observational studies of nutritional factors are exposed to many sources of bias.

The first suggestion that milk might be harmful came from a case-control study in males and females older than 65 years [50]. A higher intake of dairy products (milk and cheese) starting at 13 years of age was associated with a higher risk of hip fracture. As acknowledged by the authors, many sources of bias were present. The statistical analysis was not adjusted for health status or falls. The cases were older and in poorer health than the controls. The study participants, who were older than 65 years, were asked about their dietary intakes early in life. The risk of recall bias was therefore high, particularly as 27% of participants were unable to answer questions and had their data provided by proxies. Finally, the large amount of missing data led to the exclusion of nearly half the participants from the statistical analysis.

A prospective cohort study evaluated whether milk intake between 13 and 18 years of age was associated with the risk of hip fracture later in life [51]. In men, each additional glass of milk per day was associated with a 9% higher risk of hip fracture. The association was stronger in men with low intakes of calcium and vitamin D. It was no longer significant after adjustment for height. These findings indicate that the fracture risk was higher in taller individuals who had high intakes of milk calcium and, above all, protein during peak bone mass acquisition at adolescence. Each additional glass of milk per day was associated with a significantly taller height, the difference being 0.47 cm in males and 0.38 cm in females. Other studies have established that taller height is associated with a greater risk of hip fracture due solely to mechanical factors, i.e., the greater height from which falls occur and the greater length of the femoral neck.

In Sweden, two vast cohorts were studied, one composed of women (39–74 years at enrolment, Swedish Mammography Cohort) and the other of men (45–79 years at enrolment, Cohort of Swedish Men) [1]. The risk of any fracture and the risk of hip fracture were both higher in women consuming at least three glasses of milk each day compared to those consuming less than one glass. Milk intake was not associated with fracture risk in men. There would not seem to be any explanation for a gender difference in the effect of milk, and the existence of a causal effect is therefore unlikely [52]. The risk difference between males and females may be ascribable to residual or unknown confounding factors or to structural differences between the two cohorts, particularly as no tests for interaction were performed.

The earliest metaanalysis included six prospective cohorts [53]. Consuming less than one glass of milk per day was associated with a small increase in the risk of osteoporotic fractures, confined to the group older 80 years, with both sexes combined. However, adjusting for BMD abolished this association. Milk consumption was taken as a marker for calcium intake, although total calcium intake was not estimated. Milk intake showed a weak correlation with BMD. As recognized by the authors, this weak correlation did not constitute proof that milk intake correlated with fracture risk. Demonstrating such as link would have required the inclusion of over 500,000 individuals; the sample size was 39,563.

6. Which mechanisms might underlie harmful effects?

Many mechanisms have been suggested to explain the possible harmful effects of milk components on bone. In subsamples of the two above-mentioned Swedish cohorts, milk intake was positively associated with urine levels of 8-iso-PGF2α, a marker for oxidative stress, and with serum levels of interleukin 6, a marker for inflammation [1]. Another study by the same group demonstrated a negative association between urinary 8-iso-PGF2α and BMD [54]. In the same study, the intake of fermented dairy products (yogurt, sour milk, and cheese) was associated with a lower fracture risk. One glass of fresh milk contains about 5 g of D-galactose, which may have adverse effects on bone mass and cardiovascular risk. Low BMD is a feature of the genetic metabolic disorder galactosemia [55]. A possible role for D-galactose was not tested in the Swedish cohorts, and apart from galactosemia, there is no evidence of deleterious effects on bone in humans.

Lactose intolerance, whether proven or perceived, is often claimed to require eliminating milk from the diet. Among Caucasians, about 10% have lactose intolerance. The intestinal absorption of many nutrients found in milk, including calcium, is enhanced by the presence of enzymes that convert lactose to D-glucose and D-galactose. Persistence of the ability to digest lactose in adulthood is ascribable to a lactase gene mutation that is common in populations originating in northern Europe, where dairy cattle have been raised since the Neolithic agricultural revolution. According to one claim, milk protein ingestion results in acid overload which, in turn, causes an increase in the urinary excretion of calcium. Although urinary calcium does increase with milk intake, the underlying mechanism is increased intestinal absorption of calcium due to the presence of milk proteins [14]. Allergy to cow's milk protein resolves gradually after 2 years of age. In prepubertal children with documented cow's milk allergy and a long history of a cow's milk-free diet showed low values of the osteoprotegerin/RANKL ratio, suggesting a high level of bone resorption [56].

7. Sources of bias in available studies

One possible source of bias is the reverse causality bias, in which individuals with known risk factors for osteoporosis increase their milk intake [57]. Recall bias may act in two different directions: some individuals may have only limited recollections of their diet during childhood and adolescence and, on the other hand, individuals with a history of events such as a fracture or diagnosis of osteoporosis may be more likely to remember whether they consumed foods known to affect bone, such as milk [58]. Although milk intake by a given individual often remains relatively stable throughout life [44], recall bias may affect the many studies that relied on recollections about diet in the past or distant past [16,17,19,20,45]. Furthermore, some of these studies failed to consider current milk intake [16,17]. When interpreting findings from epidemiological studies, risk factors must be clearly differentiated from risk markers. The anti-milk lobby points out that countries with the highest dietary calcium intakes (chiefly as dairy products) are also those with the highest hip fracture incidences. However, the high frequency of fractures among Scandinavians is chiefly ascribable to genetic factors and not to the high milk intake inherent in the local culture. Furthermore, a higher milk intake is often a marker for a healthier lifestyle [17,44]. Thus, individuals who drink milk smoke less, drink less alcohol, exercise more, and more often take calcium supplements. They also take fewer medications, such as diuretics, suggesting a better health status [17].

Whether factors independent from the intake of dairy products influence the risk of death or health events in individuals who consume milk and in those who consume fermented dairy products is unknown. The available studies did not differentiate raw milk and pasteurized milk, which differ in content, structure, nutritional characteristics, and associations with various health conditions. Raw milk may contain beneficial bacteria such as *Lactobacillus acidophilus*, as well as high concentrations of vitamins (A, B, C, D, E, and K), various enzymes, and linoleic acids. Pasteurization diminishes the risk of contamination by pathogenic organisms but also kills *L. acidophilus*, which produces vitamin K, enhances the absorption of several nutrients, and regulates gut function. Pasteurization also breaks down the enzymes and other proteins found in milk and lowers the vitamin content. Finally, none of the studies considered the fat content of milk. Milk fat contains liposoluble vitamins (A, D, E, and K), whose deficiency is associated with a lower bone mass and higher risk of osteoporosis [59].

8. Conclusion

The controversy about cow's milk and fractures is occurring within a climate of mistrust directed at science, technologies, and the industries that use them. Léon Guéguen, a former researcher at the French national agronomy institute (INRA), aptly summarized the situation: "A growing number of people claim that the human body cannot handle a high-calcium intake, because milk has been available for only a few thousand years and cow's milk is not designed for humans, which are the only animals that continue to drink milk after being weaned. These arguments collapse when one considers that most of our current diet is composed of foods that were unknown by our prehistoric ancestors and that no other animal ever learned to domesticate and milk cows!" In the current state of scientific knowledge, no indisputable evidence exists to support the removal from our diet of a widely consumed food such as cow's milk, particularly as many individuals have dietary calcium intakes below the recommended level, particularly in populations at high risk for osteoporotic fractures.

Disclosure of interest

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