REVIEW

OPEN

Bone health: biology and nutrition

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Purpose of review
Recent findings in the influence of dietary patterns, dairy products, beverages and microbiota composition and function on bone health are reviewed and discussed.

Recent findings
Evidence is accumulating on the increased risk of fracture in individuals following a vegan diet. Meta-analysis of randomized controlled trials indicates a favourable, though of low amplitude, effect of dairy products on bone mass accrual during childhood and adolescence. Though mostly based on results from observational studies, it seems that dairy product consumption, particularly fermented dairy products, is associated with a lower risk of hip fracture. Regular green tea drinkers may have a lower fracture risk than tea abstainers. Magnesium intake is beneficial for bone health. Prune supplements prevents bone loss in untreated postmenopausal women. This seems to be associated with modification of gut microbiota.

Summary
This information should help the medical practitioners facing questions from their patients on how to protect bone health through nutrition.

Keywords
dairies, dietary intakes, fracture, gut microbiota, minerals, osteoporosis, protein

INTRODUCTION

Following peak bone mass attainment, bone mass decreases with age, with an accelerated bone loss occurring after menopause, and the risk of osteoporotic fractures increases [1]. The lifetime risk of sustaining an osteoporotic fracture is around 50% for women and 20% for men by the age of 50 years. Changes in bone metabolism, bone mineral density (BMD), bone geometry, microstructure, bone matrix mineralization and material level properties, all determinants of bone strength, hence resistance to fracture, are potentially influenced by nutritional factors [2]. Indeed, there is a large body of evidence linking nutritional intake to bone growth and bone loss later in life, both of which influence fracture risk (Fig. 1). With this respect, not only the variety of foods supply and their ingestion is of importance, but also the appetite, particularly in the oldest old. Food-seeking behaviour is controlled by several hormonal pathways. A new concept is the triggering of food-seeking behaviour in men by skin ultraviolet exposure [3].

The aim of this article is to review and discuss recent publications issued over the last 18 months reporting studies assessing the role of nutrients, foods and dietary patterns on bone metabolism and fracture risk.

DIETARY PATTERNS

Dietary patterns are defined as the quantity, proportion and combination of various foods, nutrients and drinks in diets, and their habitual frequency of consumption. Fracture risk has been shown to be influenced by various dietary patterns. For instance, eating disorders like anorexia nervosa characterized by low calorie intakes are associated with an increased risk of falls, of all types of fracture and specifically of hip fracture [4].

For many generations over millennials, human individuals have been accustomed to consume proteins from both animal and plant origin. For instance, dairy products intake was detected as early

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KEY POINTS

- Adherence to a vegan diet is associated with higher fracture risk.
- Adherence to a Mediterranean diet is associated with higher total hip BMD.
- Dairy products during childhood and adolescence slightly increase bone mass accrual as assessed in randomized controlled trials.
- Green tea consumption is beneficial for bone health.
- Prune consumption blunts postmenopausal bone loss, and is associated with gut microbiota modification.

as 8000 years BC as shown by the presence of dairy proteins in dental calculus on teeth from skeletons found in East Africa [5]. Over a few last decades, a move towards less animal protein intakes has spread out. Though there is no universal agreement on definitions of these low animal protein dietary patterns, commonly accepted patterns are vegetarians (lacto-ovo-vegetarians), that is plant-based diets but including eggs and dairies, and vegans, that is 100% plant-based diets. Strict adherence to a vegan diet leads to a variety of deficiency [6], including low calcium intake and low vitamin D levels. Vegetarian and vegan patterns have been associated with lower bone mineral density and increased fracture risk as indicated in a 2019 published meta-analysis [7]. More recently, among 26 318 women enrolled in the UK Women's Cohort study, 822 hip fractures occurred [8▪]. Hip fracture risk was 1.33-fold higher [95% confidence interval (95% CI): 1.03–1.71] in vegetarians as compared with regular meat eaters. Occasional meat eaters or pescatarians had similar risk as compared with regular meat-eaters. In the conclusion, the authors state that whether this finding obtained in women applies also to men and non-Europeans populations is not known. In a much larger cohort of UK men and women (7638 vegetarians vs. 258 765 regular meat eaters), hazard ratio for hip fracture was 1.50 (95% CI: 1.18–1.91) [9].

Combining data from EPIC-Oxford and Oxford Vegetarian Study, that is two large cohorts of 65 000 and 11 000 individuals, respectively, hazard ratio for the risk of all fractures was 1.11 (95% CI: 1.02–1.21) in vegetarians as compared with meat-eaters and hazard ratio for risk of hip fracture 1.34 (95% CI: 1.12–1.61) [10] (Table 1). In vegans hazard ratio was 1.50 (95% CI: 1.26–1.78) and 2.64 (95% CI: 1.90–3.67) for all and hip fractures, respectively. There was an interaction with BMI, since hip fracture risk was 3.17 (95% CI: 2.13–4.71) in vegans with BMI less than 22.5 kg/m^2, whilst it was not increased if BMI was higher than 22.5 kg/m^2 [10]. In their meta-

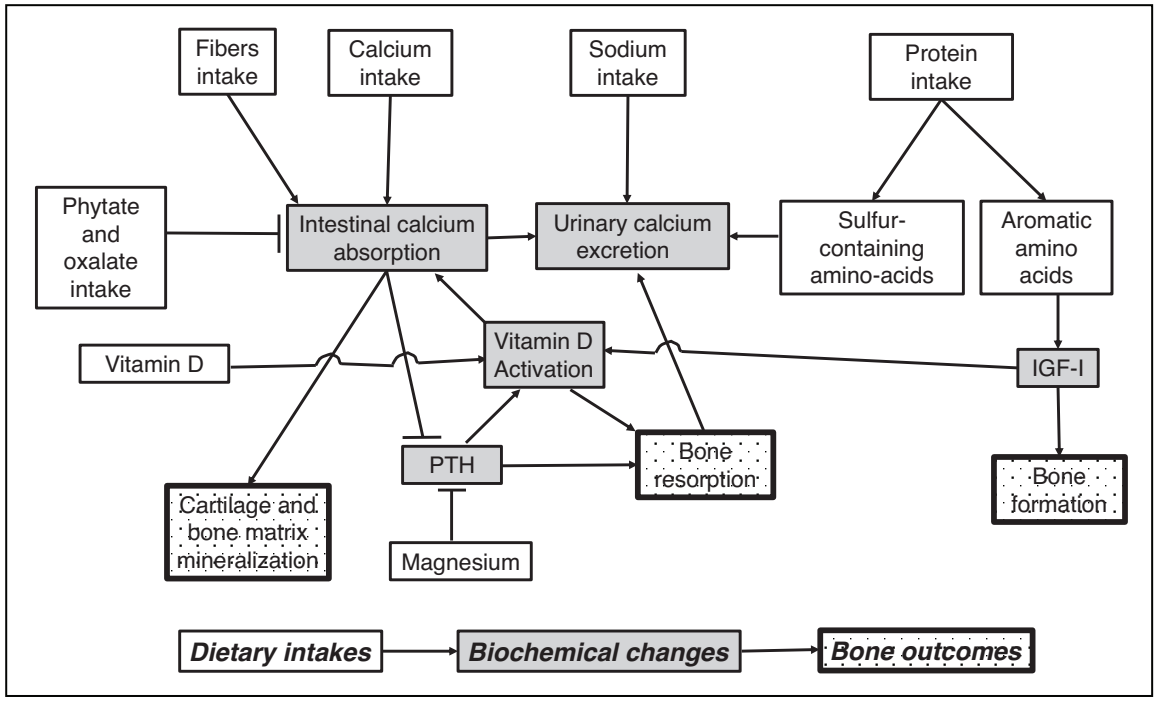

FIGURE 1. Nutrient intake, main physiological responses and bone health variables. Nutrients are in white, biochemical changes in response to nutrients intake are in gray and bone-related outcomes are in stipple. Arrows indicate stimulation and flat arrowheads indicate inhibition. Adapted with permission from the publisher from [2].

Table 1. Risk of fracture in vegetarians and vegans compared to regular meat eaters

Ref.	Participants	Fracture risk	
		All fractures	Hip fracture
Iguacel *et al.* [7]	Four combined studies Vegans ($n=5690$) vs. regular meat eaters ($n=37\,173$)	RR: 1.44 (1.05–1.98) RR: 1.25 (0.92–1.71)	NA NA
	5 combined studies Vegetarians ($n=23\,645$) vs. regular meat eaters ($n=42\,658$)		
Key *et al.* [10]	EPIC-Oxford ($n=65\,000$) + Oxford Vegetarian study ($n=11\,000$) men and women	HR: 1.50 (1.26–1.78); 1.43[a]	HR: 2.64 (1.90–3.67); 2.31[a]
	Vegans vs. regular meat eaters	HR: 1.11 (1.02–1.21); 1.09[a]	HR: 1.34 (1.12–1.61); 1.25[a]
	Vegetarians vs. regular meat eaters		
Webster *et al.* [8▪]	UK Women's Cohort study ($n=26\,318$, 822 hip fractures)	NA	[b]HR: 1.33 (1.03–1.71)
	Vegetarians ($n=4393$) vs. regular meat eaters ($n=13\,984$)		
Webster *et al.* [9]	Middle-aged UK men and women		
	Vegetarians ($n=7638$) vs. regular meat eaters ($n=258\,765$)	NA	[b]HR: 1.50 (1.18–1.91)

HR, hazard ratio (95% CI); NA, not available; RR, relative risk (95% CI).
[a]Adjusted for BMI.
[b]Multivariable-adjusted HR.

analysis, Iguacel *et al.* [7] reported a similar increase in fracture risk in vegan populations of European and of Asian origin.

Regarding the influence of protein of animal or plant origin on BMD, a cross-sectional study was conducted in 1570 individuals, among them 57% were women, and with a median age of 71 years [11]. There was a positive association between total and animal protein intake with higher BMD. In contrast, the association between plant protein and BMD was negative. The data agree with a previous study [12].

In the Adventist Health Study 2, the 2.99 (95% CI: 1.54–5.82) hazard ratio for hip fracture recorded in the vegan women compared to nonvegetarians went down to 0.84 (95% CI: 0.42–1.66) in those receiving both calcium and vitamin D supplements [13].

A 6-week intervention trial in healthy men investigated whether the partial replacement of red and processed meat by nonsoya vegetables would modify bone turnover [14]. Increasing the proportion of nonsoya vegetables and decreasing that of meat did not change the circulating levels of bone specific alkaline phosphatase nor of tartrate-resistant acid phosphatase, indicating the absence of any deleterious effect of this plant derived diet on bone turnover. However, 2 years earlier, the same research group has reported that plant proteins as compared with animal protein accelerated bone turnover in a 12-week intervention carried out in 107 women and 29 men, as shown by higher serum CTX and P1NP levels [15]. Whether the duration of the dietary intervention, the sex of the individuals or the biochemical marker of bone turnover evaluated can explain this difference remains to be determined.

Compared with omnivores, peripheral skeleton trabecular and cortical microstructure were altered in vegan people [16]. The differences were attenuated in the subgroup reporting regular resistance training. Altogether, these results suggest that the higher fracture risk associated with a vegan diet as compared with omnivores can be mitigated by calcium-vitamin D supplements and possibly regular resistance training.

In contrast, a balanced diet like a Mediterranean diet appears to be beneficial for bone health. Indeed, a meta-analysis of observational studies including 13 209 participants [17] showed that a greater adherence to a Mediterranean diet was associated with a positive linear relationship with total hip and trochanter BMD. This observation is in agreement with a previous meta-analysis having demonstrated a lower hip fracture risk in people adherent to a Mediterranean diet [18]. The influence of a Mediterranean diet

on osteoporosis and sarcopenia has been recently reviewed [19].

DAIRY PRODUCTS

Nutrients like calcium, phosphorus and protein are major nutritional determinants of bone mass accrual [20]. These nutrients are combined in dairy products. Indeed, 1 l of standardized cow milk provides 1200 mg/l calcium, 1150 mg/l phosphorus, 32–35 g/l protein, that is casein and whey proteins, which also contain a series of cellular growth factors, together with calories, trace elements and vitamins [21]. The question of the effect of dairy products supplementation on bone mass accrual was specifically addressed in a meta-analysis including the results of randomized controlled trials conducted in children and adolescents [22▪]. Though of small amplitude, differences in BMD and BMC changes at the level of whole body, lumbar spine, femoral neck and total hip were significantly higher in subjects with dairy products supplementation. In the latter, height was also significantly higher. A recent randomized controlled trial has tested the effect on lumbar spine BMD as primary outcome of three dairy servings per day and of more than four servings per day over a 12-month intervention period in 94 post pubertal adolescents' intake [23]. The small number per group limited the power to detect a difference. However, it appears that increasing dairy intakes to four servings per day during the bone consolidation period had a beneficial effect in girls but not in boys, with a low calcium intake.

The effects of milk supplementation on bone health in adults were evaluated in a meta-analysis of 20 randomized controlled trials [24]. Compared to controls, milk supplementation resulted in a small but significant higher lumbar spine and total hip BMD, together with lower levels of CTX and P1NP. Serum PTH was reduced in the intervention groups, and IGF-I increased.

Several meta-analyses with different inclusion criteria explaining marked differences in the number of observational studies included have shown a lower hip fracture risk in dairy products consumers, as reviewed in [2,21]. This was true for milk, yoghurts and cheese. Analysing specifically the role of fermented dairy products, yoghurt consumers had a 24% lower risk of hip fracture. Symbiotic yoghurts enriched in inulin (a prebiotic used to render the matrix denser) and in the probiotic *Lactobabacillus rhamnosus* increased intestinal absorption in healthy young women [25]. Considering the delay in calcium tracer recovery, this higher intestinal calcium absorption likely took place in the large intestine.

Dairy products could also contribute to protect bone health together with physical activity during pregnancy. Indeed, in a randomized controlled trial, 12–17 week gestation women received either high dairy diet and a walking programme, or usual care [26]. The intervention group, hence that with increased protein and calcium intakes, displayed lower serum CTX by the end of pregnancy and in the cord blood.

A possible cause of intolerance to cow milk is the presence of A1 beta-casein, produced by some cow breeds, particularly those of European origin, instead of A2 beta-casein, found in Asian or African cattle [27]. Both beta-casein proteins, which represent 30% of total protein content in cow milk, differ by only one nucleotide changing the codon in position 67 of the 209 amino acid protein, with a histidine instead of a proline. A1 but not A2 beta-casein digestion produces beta-casomorphin-7, which activates μ-opioid receptors located along the gastro-intestinal tract, and may account for an increase in gastro-intestinal transit time and occasional abdominal pain upon milk consumption. In a 2022 review of this issue, the conclusions are that A2 beta-casein exerts beneficial effects on the gastro-intestinal tract as compared with A1 beta-casein, but there is no evidence that the latter is harmful for human health [28].

BEVERAGES

Numerous studies have suggested that sugar-sweetened beverages consumption, particularly carbonated beverages, is inversely correlated to BMD in both children and adults with even some trend to a higher fracture risk [29]. One of the explanations is that sugar-sweetened beverages are replacing milk, which is considered to be beneficial for bone health [30]. In a longitudinal cohort study performed between the age of 14 and 20 years, consistently higher consumption of sugar-sweetened beverages during adolescence and early adulthood was associated with increased fat mass, but not with BMC nor lean mass differences at the age of 20 years [31]. It is thus proposed that reducing sugar-sweetened beverages in adolescence may help to prevent fat mass accumulation in young adulthood.

Tea, particularly green tea, which is largely consumed worldwide, contains flavonoids and polyphenols with oestrogen-like activity. In a Korean nationwide survey in postmenopausal women, odds ratio for osteoporosis was 1.91 (95% CI: 1.13–3.23) and 1.82 (95% CI: 1.09–3.05) in nonconsumers and consumers of less one cup a day of green tea, respectively, compared to at least one cup a day [32]. Whether all kinds of tea have protective effects

was tested in a Taiwan biobank database [33]. Men older than 60 years had a lower risk of developing osteoporosis if they were drinking nonfermented, that is green tea, than fermented tea, that is black tea. In a large Taiwanese database of 42 742 individuals aged 45–74 years, followed-up for a median time of 8.5 years, multivariate adjusted hazard ratio for hip fracture was 0.69 (95% CI: 0.55–0.86) in the high tea consumption group as compared to no tea drinking [34]. A reduction of hip fracture risk can also be detected in a non-Asian region like UK, with a 36% (95% CI: 19–49) lower risk in women with a BMI less than 18.5 kg/m^2 [35]. In the whole UK cohort, irrespective of BMI, hip fracture risk was lower by 4% (95% CI: 0–8) in consumers of both tea and coffee.

The interaction between hip fracture risk and coffee consumption was assessed in a meta-analysis of 13 studies comprising 391 956 individuals [36]. As compared with no coffee drinking, 1, 2–3 and 4 cups/day appeared to be rather protective with relative risk (RR) of 0.92 (95% CI: 0.87–0.97), 0.89 (95% CI: 0.83–1.95) and 0.91 (95% CI: 0.85–0.98), respectively, whilst high coffee consumption could be rather deleterious (RR: 1.10; 95% CI: 0.76–1.59). The significance of the association between fracture risk and coffee intake decreased with larger cohort size, higher study quality and more adjustments [36]. In contrast, in another meta-analysis including 22 cohort and case–control studies, there was no association between fracture risk and coffee consumption [37]. However, in a subgroup including cohort studies only, fracture risk was lower in men with higher coffee drinking (RR: 0.85; 95% CI: 0.76–0.94) whilst there was no difference in women (RR: 1.0; 95% CI: 0.95–1.06). In the same subgroup, consumption of all kinds of caffeinated beverages was accompanied by a higher relative risk of fracture [1.16 (95% CI: 1.09–1.24)] [37]. Whether these discrepancies are related to different cohorts included in either analysis or to the presence of protective polyphenols in coffee but not in other caffeinated beverages is not known.

High alcohol consumption is considered as detrimental to human health. There is some evidence that the risk of osteoporotic fracture numerically increases with higher intake of alcohol, without reaching statistical significance, as shown in a recent meta-analysis [38]. Since BMD was even higher in light drinkers as compared with abstainers, the effect on bone health of alcohol at low doses remains to be further investigated.

Magnesium influence on BMC, BMD and fracture risk has been examined in a systematic review and meta-analysis [39▪]. Higher magnesium intake was associated with an increase in total hip and femoral neck BMD, but no relationship with fracture risk could be detected. In the recommendations for higher calcium and magnesium intakes through drinking water in the frame of a balanced diet for osteoporosis prevention, the safety of these cations for the cardiovascular system has been questioned. It appears that drinking water with high concentration of calcium and magnesium, particularly magnesium, may lower the risk of stroke in postmenopausal women [40].

GUT MICROBIOTA

A significant role of gut microbiota composition and function in bone and mineral homeostasis is more and more recognized [41]. In a 3-month intervention pilot trial in subjects receiving 600 mg/day of calcium and 0.25 μg/day of calcitriol, the administration of *Bifidobacterium lactis* led to a decrease in PTH [42]. The study duration was too short to detect any effect on BMD.

A 12-month placebo-controlled randomized trial investigated the effects of a potent phytoestrogen, 8-prenylnaringenin supplied as a standardized hop extract, on BMD and gut microbiota composition and function in osteopenic postmenopausal women [43]. This supplementation increased whole body BMD by 1.8% versus baseline. A higher abundance of *Turicibacter* and *Shigella* was observed but there was no difference between groups in alpha-diversity nor in short chain fatty acids production in gut microbiota.

As assessed by the urinary Ca41/Ca in healthy postmenopausal women, net bone calcium balance was evaluated in response to 17.5, 35 and 70 g/day of freeze-dried blueberry (corresponding to 0.75, 1.5 and 3 cups/day of fresh blueberries) in a twice 6-week cross over study [44]. Compared to no treatment, the small and medium doses caused a 6 and 4% increase in net calcium balance, respectively. Blueberry polyphenols may influence gut microbiota diversity.

Prunes (i.e. dried plumbs) are sources of polyphenols. A 12-month 3-arm randomized controlled trial tested the effects of 50 and 100 g/day versus controls on BMD in 255 healthy postmenopausal women [45]. The total hip BMD 1.1% decrease in the controls was blunted by prunes ingestion. In the prune consumers group, microbiota was modified with an increase in *Lachnospiraceae*, together with higher hippuric acids production and lower activated monocytes [46].

How a Mediterranean diet, thus a diet rich in fibres, improves intestinal barrier integrity, has been investigated in a cohort of 260 women [47]. Three months after the beginning of the diet, there was a

marked increase in the short chain fatty acids propionate and butyrate production associated with an improvement in the intestinal barrier integrity.

Urolithin A is a gut microbiota postbiotic derived from pomegranate. In a 4-month placebo-controlled randomized trial in middle-aged healthy adults, oral urolithin A supplementation improved muscle strength (around 12%) and exercise performance [48▪], possibly in relation to a lower inflammation state as indicated by reduced circulating levels of C-reactive protein. The trial duration was too short to assess BMD changes. However, several preclinical studies have demonstrated an inhibition of osteoclastogenesis and a decrease in experimental bone loss, raising some hope on the effect of urolithin A on bone health [49,50].

CONCLUSION

The aim of this review was to address the most recent publications over the last 18 months in the field of nutrition influencing bone health. The present article alludes to salient aspects in the authors' opinion. With the time and also space limit constraints, the topic could obviously not be extensively and deeply covered.

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Conflicts of interest

There are no conflicts of interest.

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- ▪ of special interest
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