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Milk and osteoporosis: A review

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Abstract

Bone mass gradually declines and the internal structure of bone tissue deteriorates in osteoporosis, a long-term skeletal illness that weakens and increases the risk of fractures (NOGG, 2017) [25]. Globally, more than 200 million individuals are affected by this condition (Upadhyaya *et al.*, 2020) [36], and nearly 50 million people in India suffer from osteoporosis or reduced bone mass. Milk and dairy products play a vital role in supporting bone health, as they contain essential nutrients such as calcium, phosphorus, magnesium, high-quality proteins, vitamins D and K2, and several bioactive components that help in bone formation and limit bone loss (Hess *et al.*, 2016; Nielsen, 2018) [10, 26]. Multiple studies have shown a significant inverse relationship between dairy intake and the risk of developing osteoporosis or fractures (Feskanich *et al.*, 2018; Malmir *et al.*, 2020) [8, 21].

Keywords: Milk, nutrients of milk, gut microbiota, osteoporosis

Introduction

Jean Lobstein first used the term "osteoporosis" to describe a condition that is thought to be age-related and is characterized by low bone mineral density, deterioration of bone micro-architecture, decreased bone mass, and increased bone fragility. According to the World Health Organization, osteoporosis is a systemic skeletal illness marked by low bone mass and micro-architectural degradation of bone tissue, which increases bone fragility and fracture risk. Osteoporosis is a dangerous bone condition that increases a person's risk of fractures by weakening their bones (NOGG, 2017) [25]. The condition is influenced by several factors including age, hormonal changes, inadequate nutrition, and lifestyle habits. With more than 200 million people affected worldwide, it represents a significant global health burden (Upadhyaya *et al.*, 2020) [36]. The number of hip fractures worldwide is expected to rise sharply, reaching an estimated 21.3 million cases by 2050 (Gullberg *et al.*, 1997) [9].

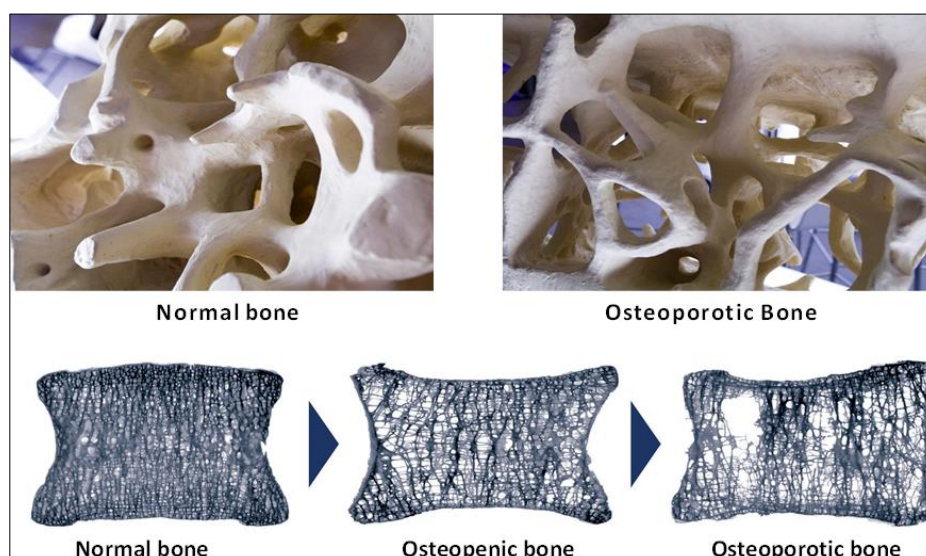


Fig 1: Process of osteoporosis from normal bone

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Normal bone is undergoing the process called “Remodeling” in which osteoblast and osteoclast both cells play an important role. Osteoblast is the cell which forms the bone whereas Osteoclast is the cells which remove/break the old bone cells. Balance between two cells is most important for bone remodeling. E.g. Osteoclast being more active than Osteoblast results in bone resorption; as a result, osteopenia or osteoporosis may occur (As given in Fig. 1). Osteopenic is a middle condition between normal and osteoporosis bone meaning that bone is porous but not easily breakable.

Types of Osteoporosis

There are two types of Osteoporosis. Viz. Primary Osteoporosis and Secondary Osteoporosis

1. Primary Osteoporosis

- Type 1 or Postmenopausal Osteoporosis
- Type 2 or Senile or Age related Osteoporosis

2. **Secondary Osteoporosis:** due to prolonged use of drugs like corticosteroids

Composition of Bone

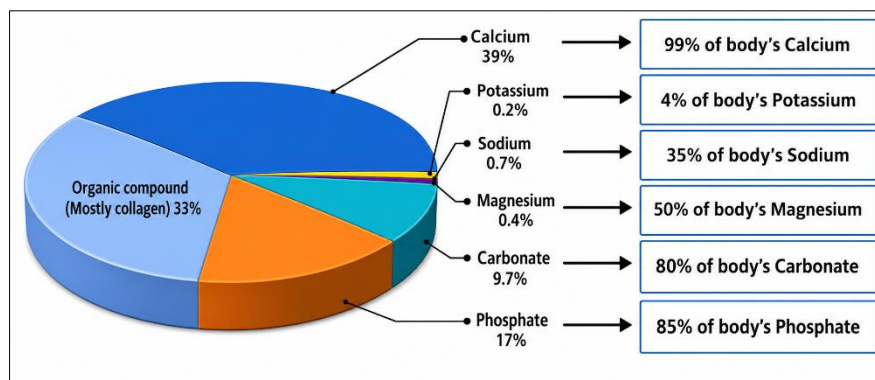


Fig 2: Composition of human bone

Risk Factors of Osteoporosis

There are various factors associated with the Osteoporosis which are listed as follows

- Early menopause
- Parental history of hip fracture or osteoporosis
- Medications associated with osteoporosis, such as longer-term daily use of glucocorticoids (steroids)
- Low calcium intake, Lower Exposure to Sunlight
- Being underweight (body mass index below 19)
- Sedentary lifestyle (little physical activity)
- Medical conditions associated with osteoporosis, such as rheumatoid arthritis, diabetes, breast cancer, or certain digestive diseases
- Smoking and/or excessive drinking of Alcohol

Osteoporosis Symptoms: The following is a list of some of the symptoms of osteoporosis

Tenderness or Pain in the Bones

- Over time, height loss and stooped posture
- Fracture with minimal or no trauma
- Persistent back, neck, or joint pain

Diagnosis of Osteoporosis

Since the Food and Drug Administration approved Dual-Energy X-ray Absorptiometry scanning for clinical use in 1988, it has maintained a niche for evaluating bone mineral density. The bone absorbs photons, and the amount of photons that are not absorbed is used to calculate bone mineral density; higher absorption corresponds to higher bone mineral density (Jain & Vokes, 2017) [17]. The results are presented as a "T-score," which shows the difference (standard deviation, SD) between the tested individual and the typical healthy population (IOF, 2023) (see table below).

Table 1: Results of dual-energy x-ray absorptiometry

Status	BMD (Bone Mineral Density)
Normal	T-score of -1 SD or above
Osteopenia	T-score lower than -1 SD and greater than -2.5 SD
Osteoporosis	T-score of -2.5 SD or lower
Severe osteoporosis	T-score of -2.5 SD or lower, with presence of at least one fragility fracture

Milk and Osteoporosis: Bones consist of minerals, collagen fibers, and organic matrix that provide strength and flexibility (Iyer, 2019) [16]. Major risk factors include age, gender, genetics, hormonal imbalance, low calcium intake, vitamin D deficiency, smoking, and physical inactivity (IOF, 2023). Nutrition is one of the most crucial factors determining bone health throughout life. Milk has various nutrients including major nutrients (Milk Fat, Milk protein and Lactose) and minor nutrients (Vitamins, Minerals etc.) which are directly or indirectly linked with osteoporosis. Preventing osteoporosis and promoting long-term skeletal health require an understanding of how these nutrients affect

bone physiology.

One of the most important minerals in milk for developing and preserving healthy bones is calcium (Hess *et al.*, 2016) [10]. It is absorbed in the intestine through vitamin D-dependent active transport and passive diffusion (Hess *et al.*, 2016) [10]. Approximately 60% of daily calcium should come from dairy foods (Infante and Tormo, 2000) [12]. Calcium absorption decreases with age due to reduced vitamin D activation (Hess *et al.*, 2016) [10]. Calcium intake varies across regions, with many developing nations showing low dietary calcium levels (Balk *et al.*, 2017) [3] (Refer the Fig. 3).

Global mean dietary calcium intake in adults (74 countries)

Rank	Country	Mean intake (mg/day)	Intake band
1	Nepal	175	< 400 mg/day
2	Uganda	238	< 400 mg/day
3	Colombia	297	< 400 mg/day
4	Thailand	313	< 400 mg/day
5	Gambia	335	< 400 mg/day
6	China	338	< 400 mg/day
7	Indonesia	342	< 400 mg/day
8	Vietnam	345	< 400 mg/day
9	Burkina Faso	358	< 400 mg/day
10	Ecuador	384	< 400 mg/day
11	Cape Verde	393	< 400 mg/day
12	Malaysia	399	< 400 mg/day
13	Argentina	427	400-499 mg/day
14	India	429	400-499 mg/day
15	Philippines	440	400-499 mg/day
16	Mali	444	400-499 mg/day
17	Bolivia	458	400-499 mg/day
18	Pakistan	462	400-499 mg/day
19	Tanzania	471	400-499 mg/day
20	South Africa	479	400-499 mg/day
21	South Korea	483	400-499 mg/day
22	Barbados	487	400-499 mg/day
23	Norway	488	400-499 mg/day
24	Guam	489	400-499 mg/day
25	Israel	492	400-499 mg/day
26	Egypt	495	400-499 mg/day
27	Myanmar	498	400-499 mg/day
28	Brazil	505	500-599 mg/day
29	Palestine	507	500-599 mg/day
30	Bangladesh	529	500-599 mg/day
31	Japan	533	500-599 mg/day
32	Taiwan	587	500-599 mg/day
33	Botswana	588	500-599 mg/day
34	Tonga	607	600-699 mg/day
35	Algeria	616	600-699 mg/day
36	Nigeria	636	600-699 mg/day
37	Ethiopia	664	600-699 mg/day
38	Morocco	672	600-699 mg/day
39	Hungary	673	600-699 mg/day
40	Costa Rica	673	600-699 mg/day
41	Kuwait	695	600-699 mg/day
42	Chile	702	700-799 mg/day
43	Belgium	728	700-799 mg/day
44	Cameroon	760	700-799 mg/day
45	Italy	765	700-799 mg/day
46	Austria	773	700-799 mg/day
47	Czech Republic	782	700-799 mg/day
48	Canada	787	700-799 mg/day
49	Russia	788	700-799 mg/day
50	Spain	789	700-799 mg/day
51	Singapore	794	700-799 mg/day
52	Australia	805	800-899 mg/day
53	Mexico	805	800-899 mg/day
54	New Zealand	807	800-899 mg/day
55	Poland	830	800-899 mg/day
56	Jamaica	837	800-899 mg/day
57	Serbia	838	800-899 mg/day
58	Jordan	856	800-899 mg/day
59	Iran	859	800-899 mg/day
60	Latvia	865	800-899 mg/day
61	France	877	800-899 mg/day
62	Portugal	923	900-999 mg/day
63	USA	934	900-999 mg/day
64	Greece	942	900-999 mg/day
65	Denmark	958	900-999 mg/day
66	Croatia	965	900-999 mg/day

67	Sweden	992	900-999 mg/day
68	UK	994	900-999 mg/day
69	Switzerland	1067	>= 1000 mg/day
70	Germany	1068	>= 1000 mg/day
71	Ireland	1080	>= 1000 mg/day
72	Finland	1097	>= 1000 mg/day
73	Netherlands	1102	>= 1000 mg/day
74	Iceland	1233	>= 1000 mg/day

Fig 3: Global dietary calcium intake in adults (Balk *et al.*, 2017) ^[3]

Intestinal calcium absorption efficiency is inversely related to calcium intake, so that a diet low in calcium leads to a compensatory increase in fractional absorption, due to activation of vitamin D. The calcium contents of Milk and Milk Products are as follows:

Table 2: Calcium content of milk and milk products (IOF, 2020)

Products	Portion	Calcium Content (mg)
Whole milk	200 mL	236
Semi-skimmed milk	200 mL	240
Skimmed milk	200 mL	244
Sheep milk	200 mL	380
Flavoured yoghurt	150 g	197
Natural yoghurt	150 g	207
Hard cheese (e.g., Parmesan, Cheddar)	30 g	240
Fresh cheese (e.g., Ricotta, cottage cheese)	200 g	138
Mozzarella	60 g	242

Table 3: RDA for calcium (IOF, 2021; NIH, 2021)

Age Group	RDA of Calcium
0-6 months*	200 mg
7-12 months*	260 mg
1-3 years	700 mg
4-8 years	1,000 mg
9-18 years	1,300 mg
19-50 years	1,000 mg
51-70 years	Male: 1,000 mg Female: 1,200 mg
≥70 years	1,200 mg

After calcium, phosphorus is the second fundamental component of bone tissue. 550-770 g of it are found in the human body (Butusov and Jernely, 2013) ^[6]. Three primary hormones control phosphorus homeostasis: osteocyte-secreted fibroblast growth factor 23 (FGF23), 1, 25(OH)₂ D₃, and parathyroid hormone (PTH) (Bergwitz & Jüppner). The dietary Ca/P ratio is necessary for optimal bone development. Bone's Ca/P ratio is thought to be about 2.2 (molar ratio) (Pastore *et al.*, 2012) ^[27]. Another mechanism regulating the increased bone resorption in response to a diet high in phosphorus is the bone matrix protein osteopontin (OPN) (Koyama *et al.*). The primary regulators of calcium homeostasis, 1, 25(OH)₂ D₃, are impacted by magnesium shortage, which has an effect on bones (Astor *et al.*, 2015) ^[2]. A lack of magnesium causes leukocytes and macrophages to become activated, which leads to the release of inflammatory cytokines and an overabundance of free radicals (Nielsen, 2018) ^[26]. Osteoclast development and activation are encouraged by interleukin (IL)-6. Another potent inducer of bone resorption that contributes to the increased bone loss seen in postmenopausal osteoporosis is

IL-1 (Wei *et al.*, 2005) ^[38]. The stimulation of the inducible Nitric Oxide synthesis (iNOS) pathway by various cytokines (e.g., IL-1) impairs osteoblast activity in vitro and promotes osteoblast apoptosis (Armour *et al.*, 2001) ^[1]. In addition to helping in the active transport of calcium across the intestinal lumen, vitamin D is essential for preserving calcium homeostasis (Hess *et al.*, 2016) ^[10]. A daily intake of 700-1000 IU of vitamin D lowers the incidence of fractures and falls by roughly 20% (Bischoff-Ferrari *et al.*, 2009) ^[4]. A 25-hydroxyvitamin D test is recommended for individuals with osteoporosis (Dawson-Hughes *et al.*, 2010) ^[7].

Table 4: RDA of vitamin D (NIH, 2021)

Age Group	RDA of Vitamin D
0-12 months*	10 µg (400 IU)
1-70 years	15 µg (600 IU)
>70 years	20 µg (800 IU)

By promoting the expression of cytokines such as osteoprotegerin (OPG), vitamin K2 promotes bone growth and inhibits bone resorption. Additionally, it enhances osteoblast development by preventing osteoblasts and osteoclasts from expressing receptor activator of nuclear factor kappa-B ligand (RANKL) (Kim *et al.*, 2013) ^[19]. Vitamin K2 downregulated basal and cytokine-induced NF-κB activation in humans. Osteoclast production requires the activation of the NF-κB signal transduction pathway. (Yamaguchi *et al.*, 2011) ^[39]. Dietary fat (CLA and omega-3 fatty acids) may influence bone formation and resorption by altering prostaglandin (PG) biosynthesis in bones. Prostaglandins (PG) have stimulatory effect at low concentration and inhibitory at high concentration (Li *et al.*). Dietary beef fat and a CLA supplement were able to maintain synthetic activity of osteoblastic cells and CLA was even able to reduce bone formation rate in rats given a diet high in omega-6 fatty acids (Watkins *et al.*, 2003) ^[37]. An increase in cytokines increases bone loss, and CLA appears to counter the effect of cytokines (Watkins *et al.*, 1997) ^[37]. Whey protein has been shown to increase the level of organic material in bone, especially collagen-specific amino acids such as proline and hydroxyproline. Whey protein reduces the formation of osteoclasts and activates the osteoblasts (Takada *et al.*, 1997) ^[34]. Active compound of milk basic protein (cystatin C) inhibits osteoclast activity by decreasing the secretion of collagen-digesting cathepsin (Matsuoka *et al.*, 2002) ^[35]. Higher protein intake increases blood levels of Insulin-like Growth Factor-1 (IGF-1), which promotes bone and muscle formation, and facilitates the transformation of vitamin D into its active form. (1, 25-dihydroxyvitamin D) (Bonjour *et al.*, 2013) ^[5].

Table 5: Studies related to bioactive peptides and bone formation

Bioactive peptide	Treatment	Outcome	Reference
NAVPITTL	Treatment of peptide to calvarial osteoblast cells at a dose of 30 ng/ml for 21 days.	Increased the expression of osteocalcin and collagen (type I).	Reddi <i>et al.</i> , 2016 ^[44]
VLPVPQK	Treatment of calvarial osteoblast cells with antioxidative peptide at a dose of 50-200 ng/ml for 7, 14, and 21 days.	Increases osteoblast cell viability and decreases inflammatory cytokines expression.	Mada <i>et al.</i> , 2017 ^[41]
Casein phosphopeptides (CPP)	Treatment of OVX rats with Ca-bound and Ca-free CPP for 17 weeks provided 62.5 and 100% of dietary phosphorus.	Increases bone mineral density (BMD) in OVX rats.	Tsuchita <i>et al.</i> , 1996 ^[46]
<i>Lactobacillus helveticus</i> fermented milk containing peptides IPP and VPP	Treatment of postmenopausal women with fermented milk containing 14.5 mg/100 g milk of IPP and VPP.	Fermented milk containing IPP and VPP reduces serum PTH level and increases serum calcium level.	Narva <i>et al.</i> , 2004 ^[43]
VLPVPQK	Treatment of OVX rats with peptide at a dose of 50 and 100 µg/kg/day for 8 weeks.	Increases bone mineral density (BMD) and improved trabecular microarchitecture of femur in OVX rats.	Mada <i>et al.</i> , 2018 ^[42]
NAVPITTL	Feeding of OVX rats with peptide at a dose of 100 µg/kg/day for 8 weeks.	Enhanced femur BMD and microarchitecture. Suppressed RANKL gene expression in OVX rats.	Reddi <i>et al.</i> , 2019 ^[45]

It is important to remember that lactose increases children's absorption of calcium (Hodges *et al.*, 2019)^[11]. The MCM6 gene's single polymorphism nucleotide in 13910CC and 22018GG is linked to lactose intolerance, which is genetically conditioned (Ratajczak *et al.*, 2021)^[28]. Lactose-tolerant individuals with genotypes LCT-13910 TT and LCT-13910 CT had higher bone mineral density than lactose-intolerant individuals with genotype LCT-13910 CC (Mnich *et al.*, 2018). Patients with lactose intolerance should eat fermented dairy products, lactose-free milk, and calcium-rich non-dairy products to avoid osteoporosis (Ratajczak *et al.*, 2021)^[28].

Gut Microbiota-Modulation of Bone Mineral Density

Production of biologically active compounds by Gut microbiota such as short-chain fatty acids and polyamines affects intestinal cells resulting in altered bone turnover and Bone Mineral Density. Galactooligosaccharides (GOS) and other human milk oligosaccharides (HMO) are essential for healthy gut microbial colonization. (2013)^[29] Sakurama *et al.* Short-chain fatty acids are produced by the fermentation of GOS by *Bifidobacterium* species. Lacto-N-biosidase, which is present in *Bifidobacterium* species, aids in the absorption of GOS (Sakurama *et al.*, 2013)^[29]. In healthy individuals, *Lactobacillus reuteri* raised serum levels of 25(OH) D, which impacts calcium absorption and may have an impact on the increasing activity of liver 25 hydroxylase (Jones *et al.*, 2013)^[18]. Additionally, there is breakdown of molecule-binding minerals (such as phytic acid and oxalates) and enhancement of calcium-binding protein expression (Scholz-Ahrens *et al.*, 2007)^[31]. The gut microbiome, which produces serotonin, decreases the activity of duodenal enterochromaffin cells (Yano *et al.*, 2015)^[40]. Serotonin inhibits the growth of osteoblasts by activating 5-HT1B receptors in preosteoblasts (Kode *et al.*, 2012)^[20].

Conclusion

For bone health throughout life, a healthy diet is essential. The building blocks for bone structure are found in dairy products. Because milk and dairy products provide high-availability protein, vitamin D, calcium, and phosphorus—all of which are crucial for preventing osteoporosis—elderly people shouldn't avoid them. Fermented dairy products (kefir, yoghurt) and lactose-free milk are the best options for patients with lactose sensitivity. Dairy products' beneficial effects on gut microbiota may boost calcium absorption, short-chain fatty acid synthesis, and serotonin production—all of which have a direct impact on bone metabolism.

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