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The impact of probiotic supplementation on bone health in postmenopausal women: literature review

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Abstract: Intestinal dysbiosis affects numerous health conditions in human body. At the same time its impact on the bone remodelling process has been discovered quite recently. Studies are in agreement that the gut microbiota might directly or indirectly affect on bone metabolism through the functions of the immune system, hormone levels or calcium absorption. Having said that regulation of the intestinal microbiota will play a significant role in the bone metabolism it may represent a potential therapeutic measure in those at the risk of osteoporosis.
The purpose of the following review was to assess the impact of probiotics, as major gut microbiota regulators, on the parameters of bone health. In particular as it refers to the bone mineral density, bone turnover markers as well as calcium and vitamin D in the blood serum. Special attention was placed on postmenopausal women, due to their increased risk of osteoporosis and fragility fractures. The analysis of the available literature suggests potential anti-osteoporotic effect of some selected probiotic bacteria strains. Therapy with the use of probiotics might be complementary in the prophylactics and treatment of osteoporosis due to its good tolerance and well documented effectiveness in majority of the studies. Despite the promising results, there is still a great need for further clinical studies which would allow to determine the optimal dosage, duration of the supplementation as well as the efficiency confirmation of particular probiotic strains.

Keywords: probiotics, Lactobacillus, BMD, osteoporosis, BTM, bone turnover markers, calcium, vitamin D.

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Introduction

The progressive aging process of the society leads to an increase in a number of patients with metabolic bone diseases. Due to its prevalence, health consequences and healthcare costs — osteoporosis is considered to be one of the most significant among them. Osteoporosis is defined

as a bone disease, characterised by an impaired bone strength resulting in an increased fracture risk. Bone strength is mainly associated with a mineral density along with the bone quality [1]. The main challenge in the osteoporosis diagnostic process is fracture risk assessment in order to identify those that ought to be treated. Both international and polish recommendations allow for the differentiation of preventive and therapeutic measures depending on the low energy fracture risk assessed via FRAX fracture risk calculator (Fracture Risk Assessment Tool). Implementing healthy lifestyle is crucial in terms of prevention and treatment of osteoporosis. For those with a low fracture risk (FRAX ≤5%) prophylactics are focused on inducing proper diet and regular physical activity followed by the elimination of modifiable risk factors (i.e. smoking tobacco) [2, 3]. Optimising the calcium intake (to 1200 m/day) and covering potential vitamin D deficits (30–50 ng/ml in the serum) is crucial to maintain bone health. Diet should also provide adequate supply of protein (1.2 g/kg of body mass/day), potassium (>3500 mg/d), magnesium (>300 mg/d) and phosphorus (700 mg/d) [4]. For those with a moderate fracture risk (FRAX from 5 to <10%), general practitioners should consider introducing pharmacotherapy additionally to the above mentioned measures [2, 3].

In 2019 in Poland, a total of 1,985,000 people had been diagnosed with osteoporosis, of which 80% were women [5]. According to the National Health Fund the stats have been increasing in the past years, reaching 2.4 mln patients in 2024. At the same time, number of those qualified for pharmacological treatment in 2024 was established at 197.4 K which shows that merely 9% of those in need, had received adequate treatment [6]. The reasons for limitations in implementing recommended osteoporosis treatments are multifactorial. Those include challenges in accessing specialist therapies (only some drugs are being refunded, major refund limitations to novel drugs, high costs for the patient). Studies conducted among postmenopausal women, on reasons to discontinue pharmacotherapy, revealed that a great deal of patients are interested in alternative therapies such as vitamin combinations, OTC (over the counter) supplements or they fear the side effects of anti-osteoporotic drugs [7]. Considering the above it is justified to search new ways to treat and prevent osteoporosis, especially among those at low risk. Having said that, the authors decided to conduct the following research on the matter. It is our belief that it will allow to properly assess the impact of supplementation, with different probiotic strains on changes in bone mineral density (BMD), bone turnover markers (BTM) as well as calcium and vitamin D concentration in the blood serum.

Search strategy

In order to conduct the research, between the June 1st till the 6th of July 2025, authors selected targeted publications through the MEDLINE (Pubmed) database as well as Google Scholar. The search was carried with the use of specific keywords such as "probiotics"/"Lactobacillus"/"Bifidobacterium" AND "osteoporosis" which allowed to identify 313 studies. The search was not limited by any additional filters. As a next step the authors successively analysed every paper in order to exclude those not fitting the topic of the following review (i.e. being based on animal studies), manuscripts available only in other languages (i.e. Chinese) or those with limited access to the full text version of the article (abstracts were not included in the review). Papers fitted the criteria by: being carried out on humans, assessing the relation between probiotic consumption and parameters impacting bone quality, being available in English or Polish.

Data extraction

For every study included in the following review authors highlighted information concerning country, size of the study sample, and group specifics covering the differentiation between study and control groups. The latter covering the age span and the crucial inclusion criteria. Additional analysis were referred to the type and timing of the intervention. All the following data, along with the most important parameters assessing the bone health, have been presented via a graphical form.

Gut microbiota and bone metabolism

There are approximately 100 trillion microorganisms forming gut microbiota, which have an impact on a number of health issues in an adult organism. One of them being the regulation of the bone metabolism, through the gut-bone axis [8]. An imbalance state of the gut microbiota known as dysbiosis, has been considered a cause for many health issues. But at the same time its relation to bone remodelling disorders has been discovered quite recently [9]. Scientists confirmed that dysbiosis, by its effect on the metabolism, immune and the endocrine systems, has an impact on the incidence and progress of osteoporosis and general bone loss [9, 10]. Gut microbiota might directly or indirectly affect the bone metabolism through some functions of the immune system, hormone levels or calcium absorption [11]. Studies show that microbiota might impact the intestinal metabolite diffusion into the bloodstream. This refers to the short-chain fatty acids (SCFAs), which are recognised as efficient regulators of the bone tissue metabolism, and therefore play an important role in maintaining the bone homeostasis [10]. Additionally, microbiota controls both innate and adaptive immune response. It has a significant role in the modulation of lymphocytes B, via the surface receptors and cytokines, and also promotes the recruitment of proinflammatory monocytes as osteoclasts precursors [12]. Finally, the increased intestinal permeability (aka 'leaky gut') allows the inflammatory mediators to enter the bloodstream, causing inflammation and excessive osteoclast activation [13]. Having said that, gut microbiota plays an important role in the bone metabolism and constitutes a great therapeutic potential for those at risk or with a confirmed osteoporosis.

Probiotics and gut microbiota

The composition of the gut microbiota may vary depending on a number of factors (such as age, latitude, ethnicity and comorbidities) [14]. Studies including animal [15] and twin [16] models showed that gut microbiota might be affected by both genetics as well as a number of environmental factors (lifestyle, diet, hygiene, antibiotic therapies) [17–19]. In order to restore the microbiota homeostasis, and hence improve one's health, the probiotic therapy appears as a vital option. Generally probiotics are perceived as live microorganisms, which when applied in appropriate quantities, may have a beneficial impact on a human health [20].

Waldbaum *et al.* confirmed there are significant differences in gut microbiota between osteoporotic and non-osteoporotic patients [21]. As key microbiota modulators, probiotics have a positive effect on bone metabolism, by increasing the amount of beneficial intestinal bacteria, restoring the microbiological balance and modulating the immune response. Studies with animal models showed that Lactobacillus rhamnosus GG promotes anti-inflammatory cytokine secretion (TGF-β, IL-10) and inhibits some pro-inflammatory cytokines (TNF-α, IL-17). This is likely to result with a relieving of the inflammation process associated with the lack of oestrogen and

decreased osteoclast activity [22]. Furthermore, probiotics increase the production of short-chain fatty acids (i.e. butyric acid) which in response inhibit the osteoclast differentiation [23] and stimulate the gut oestrogen production [24]. They are also supporting the integrity of the intestinal barrier (by modulating the expression and function of tight junction protein), preventing the endotoxin translocation, reduce the inflammation and its negative impact on bone health [23].

Impact on bone mineral density

Bone mineral density is a basic diagnostic tool used to assess the risk of osteoporosis and fragility fractures. Therefore is appears to be a natural choice as the most important parameter allowing to assess the impact of probiotics on condition of the skeletal system. The literature is generally in agreement about the positive impact of probiotic therapy on bone mineral density. This includes postmenopausal women using Lactobacillus paracasei and plantarum [25–31]. Since the only significant drop in BMD reported after 12 months was observed in the control group, it is likely that the above mentioned strains might be of assistance when it comes to preventive strategies for bone loss in postmenopausal women [25]. Similar conclusions have been drawn from the study by Jansson *et al.* and Morato-Mortinez *et al.* where the authors used the same type of probiotics [26, 27]. The first paper had the largest study sample of all analysed studies (n = 249). Authors reported a significant decrease in BMD spine, but only in the control group ($p = 0.031$) and the difference was not observed in the BMD hip [26]. Morato-Martinez *et al.* study, which included women with osteopenia, also proved the efficiency of the probiotic supplementation. Study emphasized that not only the bone mass had been maintained at a steady level throughout the study period, but also it has significantly increased in 24 months. This allowed for the number of women with osteopenia to be reduced by 6% in the study group. The positive impact of probiotic therapy in osteopenic women has also been confirmed in relation to the supplementation of red clover extract enriched with probiotic lactic acid. Authors reported a significant decrease in T-score spine ($p = 0.045$) and T-score hip ($p = 0.0061$) after 12 months, but only in the control group [28]. Similar results have been maintained regarding BMD hip (but not BMD spine), favouring study group over placebo, with a Lactobacillus fermentum [29] and Bacillus subtilis [30]. Nillson *et al.* used high-resolution peripheral quantitative computed tomography in order to assess bone quality in women with osteopenia. The authors reported a reduction in volumetric bone mineral density (vBMD) loss in those under probiotic therapy. At the same time no effect of probiotics on the bone microarchitecture, has been observed [31].

Contrary with the above, there are other studies that ought to be highlighted, which show no positive impact of probiotics on BMD [32–35]. Zhao *et al.* analysed the effect of Bifidobacterium animalis on BMD among osteoporotic women. The study had a short observation period (3 months) which may have had an impact on the obtained results [32]. Studies, carried out among women with osteopenia under proper supplementation, for 6 months, did not show any significant differences between study group and control (both in BMD spine and hip) [33]. Also in healthy postmenopausal women, probiotic supplementation lasting 12 weeks, did not provide any meaningful results [34]. The only long lasting study (24 months), where no positive BMD-related impact was reported, was associated with the Limosilactobacillus reuteri [35]. To sum up, the results of the analysed studies suggest potential positive effects of probiotic supplementation in reference to the prevention of BMD loss in healthy postmenopausal women, as well as osteopenic patients. It should be however emphasized that in order to achieve proper efficiency, the probiotic supplementation should last at least 12 months. Detailed characteristics of the analysed studies are presented in Table 1.

Table 1. Assessment of the effect of probiotic supplementation on bone mineral density.

Ref.	Country	Participants (n)		Mean age (years)	Inclusion criteria	Supplementation	Duration	Tests	Outcome
25	Poland	SG	84	56.3	Postmenopausal women (2–5 years last menstrual) T-score ≥−1.5	L. paracasei LPC100 (DSM 33793): 1.5×10^9 CFU L. plantarum LP140 (DSM 33804): 3.5×10^9 CFU 5×10^9 CFU / capsule /day	12 months	LS DXA	Significant (p = 0.041) T-score decrease only in the CG (mean values 0.06 to −0.28) after 12 months. In SG reduction did not reach significance (0.19 vs. −0.08, p = 0.125). No differences between groups (p = 0.089).
		CG	83	57.0					
26	Sweden	SG	126	59.1	Postmenopausal women (≥2 years and ≤12 years last menstrual) T-score >−2.5	L. paracasei 8700: 2 (DSM 13434) L. plantarum Heal 9 (DSM 15312) L. plantarum Heal 19 (DSM 15313) 1×10^{10} CFU/capsule/day Each strain equally represented in total dose	12 months	LS, TH, FN DXA	Significant (p <0.001) LS BMD reduction after 12 months reported in CG (−0.72%) while no change was observed in the SG (−0.01%). Significant reduction in LS BMD in SG compared with CG (mean difference 0.71%, p = 0.031). Significant (p <0.001) reduction in BMD FN and TN after 12 months both in SG and CG.
		CG	123	58.1					
27	Spain	SG	33	56	Menopausal women T-score −1.0 to −2.5	Diary product enriched with L. plantarum 3547: 1×10^{10} CFU/day And also: calcium, vitamin D, vitamin K, vitamin C, zinc, magnesium, L-leucine	24 weeks	DXA, BC	Significant BM increase in the SG compared to the CG (change −0.01 vs. 0.01kg; p <0.05) after 24 weeks. No difference in BMD in SG. In CG BMD declined significantly from baseline (change −0.01 kg/cm^2; p <0.05). In SG percentage of osteopenia decreased significantly (p <0.05) after 24 weeks (from 30% to 24%), while in CG increased.
		CG	32						
28	Denmark	SG	38	60.8	Postmenopausal women (>1 years last menstrual) T-score −1.0 to −2.5	RCE (red clover extract) with probiotic lactic acid 2 × 95 mL = 60 mg isoflavones/day	12 months	LS, FN DXA	Greater significant decrease in T-score LS (−0.2 vs. −0.8; p = 0.045) and FN (−0.19 vs. −0.06 p = 0.0061) in CG compared to SG
		CG	40	62.8					

Table 1. Cont.

Ref.	Country	Participants (n)		Mean age (years)	Inclusion criteria	Supplementation	Duration	Tests	Outcome
29	Korea	SG	27	58.4	Postmenopausal women (>1 year last menstrual) T-score >–2.5	L. fermentum SRK414: 4.0×10^9 CFU/capsule 2 capsule/day	6 months	LS, TH, FN DXA	PP: Significant (p = 0.030) increase in BMD at the FN in the SG (0.691 vs. 0.716) after 6 months, contrary to CG (p = 0.95). ITT: Significant (p = 0.043) increase in BMD at the FN in the SG (0.688 vs. 0.717) after 6 months, contrary to CG (p = 0.95). PP + ITT: No significant differences in DXA LS and TH both in SG and CG after 6 months.
		CG	26	59.5					
30	Japan	SG	31	57.5	Postmenopausal women (>2 years last menstrual) T-score > –2.5	Bacillus subtilis C-3102: 3.4×10^9 CFU/3 capsules/day	24 months	LS, TH DXA	Significant increase (p = 0.043) in TH BMD in SG (mean change from baseline 2.53%) compared to CG (mean change from baseline 0.83%) after 24 months. LS BMD was not significantly (p = 0.112) different between the both groups.
		CG	30	57.8					
31	Sweden	SG	32	76.4	T- score <–1.0 to > –2.5	L. reuteri 6475: 5×10^9 CFU/capsule 2 capsule/day 1×10^{10} CFU/day	12 months	distal tibia HR-pQCT	ITT: Change in vBMD after 12 months was –0.83% in SG and –1.85% in CG. Mean difference between groups was 1.02%, significant (p = 0.047). No significant differences (p >0.05) in bone microarchitectural indices between groups. PP: Mean change in vBMD after 12 months was –0.93% in SG and –1.86% in CG. Difference between group was significant (0.93%; p = 0.013). Significant reduction in trabecular bone volume fraction in SG (–0.49%) compared to CG (–1.29%), with a mean difference 0.80% (p = 0.02). No significant differences in Ct.Th, cortical vBMD between groups.
		CG	36	76.3					

Table 1. Cont.

Ref.	Country	Participants (n)		Mean age (years)	Inclusion criteria	Supplementation	Duration	Tests	Outcome
32	China	SG	20	62.8	Postmenopausal women T-score <−2.5 >−1.0	B. animalis subsp.lactis: 1.5×10^{10} CFU/day	3 months	LS, TH, FN DXA	No significant (p >0.05) difference in the LS, FN, TH BMD between groups or time points.
		CG	20	61.6					
33	Iran	SG	20	58.9	Postmenopausal women T-score −1.0 to −2.5	L. casei: 1.3×10^{10} CFU B. longum: 5×10^{10} CFU L. acidophilus: 1.5×10^{10} CFU L. rhamnosus: 3.5×10^{9} CFU L. bulgaricus 2.5×10^{8} CFU B. breve 1×10^{10} CFU S. thermophilus 1.5×10^{8} CFU	6 months	LS, TH DXA	No significant (p >0.05) changes in LS and TH BMD after 6 months both in SG and CG.
		CG	21	57.3					
34	Poland	SG	30	45–70	Postmenopausal women (≥1 year last menstrual)	L. acidophilus UALa-01™: 1×10^{9} CFU/capsule/day	12 weeks	LS, FN DXA	No significant (p >0.05) changes in BMD either in CG (LS: 1.20 vs. 1.18; FN: 1.05 vs. 1.05 g/cm^2) or SG (1.14 vs. 1.14; FN: 0.98 vs. 0.98 g/cm^2) from baseline to endline.
		CG	25						
35	Sweden	SG	160	55	Postmenopausal women (1–4 years last menstrual) T-score >−2.5	Limosilactobacillus reuteri ATCC (PTA 6475) High dose — 5×10^{9} CFU / capsule (n = 80 of SG) Low dose — 5×10^{8} CFU / capsule (n = 80 of SG 2 capsule HR-pQCT / day	24 months	LS, TH, DXA + BC distal tibia	Total vBMD, LS and TH BMD, Ct.Th, and cortical vBMD decreased (p <0.001) in all groups (high, low dose, placebo) at 1 and 2 years. Relative change in LS BMD (high dose: −1.95%; low dose: −2.36%) and TH BMD (high dose: −2.43%; low dose: −2.39%) compared to CG (−2.18%) after 2 years. No group-to-group differences in percent change in vBMD high dose (least squares mean −0.08%) and low dose (least square mean −0.22%) compared to CG.
		CG	79	55					

Legend: n — number of participants; SG — study group; CG — control group; L — Lactobacillus; B — Bifidobacterium; S — Streptococcus; CFU — colony-forming units; DXA — Dual-energy X-ray Absorptiometry; HR-pQCT — high-resolution peripheral quantitative computed tomography; BC — body composition; BMD — bone mineral density; vBMD — total volumetric BMD; Ct.Th — cortical thickness; BM — bone mass; BMC — bone mineral content; LS — lumbar spine; FN — femoral neck, TH — total hip; PP — per protocol; ITT — intention to treat.

Impact on bone turnover markers

Bone turnover markers are a biochemical indicators of the osteogenesis and osteolysis activities, which characterise the rate of the bone tissue remodelling. Analysing BTM allows the assessment of bone metabolism through the changes in the concentration of resorption markers (i.e. CTX, TRAP, NTx), or bone formation ones (i.e. OC, BALP, P1NP) in response to various medical interventions [36], including probiotic therapy. The literature on the matter highlights the positive impact of BTM concentrations in those under probiotic supplementation. Although, the results are varied. A great deal of studies emphasizes a significant decrease in the bone resorption markers (such as CTX, TRAP and NTx) in women after probiotic therapy when compared with a placebo group [27, 28, 30, 33, 37]. Analysis of the TRAP concentration showed its increase solely in women from placebo group, contrary to subjects supplemented with Lactobacillus acidophilus — proving the preventive effect of probiotic therapy [34]. In contrast to the above results, it has been established that a shorter supplementation period (3–6 months) does not provide significant changes in CTX concentration in the blood [29, 32]. When Lactobacillus reuteri was considered, even for a longer period of time (12–24 months), there were no major changes in NTx and CTX concentrations [31, 35].

The analysis of the osteoblast bone turnover markers shows a major concentration increase in P1NP after 24 months of probiotic therapy, contrary to the control group [27, 28]. Supplementing Lactobacillus fermentum kept the osteocalcin concentration at a steady level, even after the therapy discontinuation, unlike in the control group where the drop was significant [29]. Contrary to the above results, no bone forming BTM concentration changes have been observed when the probiotics were used for shorter periods of time [32, 34]. Bifidobacterium animalis therapy lasting for 3 months, did not present any significant changes in P1NP nor OC in the blood serum [32]. Accordingly, probiotic therapy lasting for 12 weeks did not affect BALP or P1NP in women [34, 37]. The probiotic therapy also has not proven effective, in terms of BALP, in the studies which divided women into healthy and osteopenia patients [30, 31, 33].

In one of the papers, the authors analysed the parathormone (PTH) concentration, chosen due to its major role in the regulation of bone turnover regulation. As the authors stated, probiotic therapy in postmenopausal women effectively reduced PTH concentration, after the intervention was over contrary to the placebo group [32]. Therefore the study supports the idea of combining conventional pharmacotherapy with adjacent probiotics in order to improve bone metabolism. Significant reduction in PTH was noticed also in a therapy lasting 6 months in a group of healthy women. Detailed analysis covering the assessment of BTM concentration is presented in Table 2.

Impact on vitamin D and calcium levels

In light of the recent reports on the positive impact of gut microbiota on the regulation of calcium and vitamin D absorption in the human body [11], the authors decided to include the concentration analysis of the above parameters, after probiotic therapy, in the following paper. The studies analysing the impact of probiotics on vitamin D level are promising, both in case of healthy subjects and those with osteoporosis. Zhao *et al.* confirmed the positive impact of Bifidobacterium animalis supplementation in women with osteoporosis. Authors reported a significant increase in vitamin D level in blood serum ($p = 0.032$), which highlights the complementary potential

Table 2. Assessment of the effect of probiotic supplementation on bone turnover markers.

Ref.	Country	Participants (n)		Mean age (years)	Inclusion criteria	Supplementation	Duration	Biochemical analysis	Outcome
27	Spain	SG	33	56	Menopausal women T-score –1.0 to –2.5	Diary product enriched with L. plantarum 3547: 1×10^{10} CFU/day And also: calcium, vitamin D, vitamin K, vitamin C, zinc, magnesium, L-leucine	24 weeks	Blood samples: P1NP, CTX	Significant ($p < 0.05$) improvement in P1NP (change 13.19 ng/mL) and CTX (change –0.05 ng/mL) was observed after 24 weeks in SG. No significant ($p > 0.05$) change in P1NP and CTX after 24 weeks in CG.
		CG	21						
28	Denmark	SG	38	60.8	Postmenopausal women (>1 year last menstrual) T-score –1.0 to –2.5	RCE (red clover extract) with probiotic lactic acid 2 × 95 mL = 60 mg isoflavones/day	12 months	Blood samples: CTX, OC	Significant reduction ($p = 0.045$) in CTX in SG (–0.04 vs. 0.03 ng/mL) compared with CG. No significant differences in OC between groups.
		CG	40	62.8					
29	Korea	SG	27	58.4	Postmenopausal women (>1 year last menstrual) T-score >–2.5	L. fermentum SRK414: 4.0×10^9 CFU/capsule 2 capsule/day	6 months	Blood samples: CTX, OC	PP + ITT: Significant ($p = 0.028$) OC decrease (21.50 vs. 18.01 ng/mL) in CG after 6 months. PP+ITT: No significant ($p = 0.615$) change in CTX after 6 months in CG. PP: Neither OC ($p = 0.497$) nor CTX ($p = 0.587$) showed any significant change over the 6-months in SG. ITT: Neither OC ($p = 0.318$) nor CTX ($p = 0.644$) showed any significant change over the 6-months in SG.
		CG	26	59.5					

Table 2. Cont.

Ref.	Country	Participants (n)		Mean age (years)	Inclusion criteria	Supplementation	Duration	Biochemical analysis	Outcome
30	Japan	SG	31	57.5	Postmenopausal women (>2 years last menstrual) T-score >−2.5	Bacillus subtilis C-3102: 3.4×10^9 CFU/3 capsules/day	24 months	Blood samples: TRAP-5b, BALP, PTH* Urinary samples: NTx	A trend-level interaction effect of group-by-time was observed for TRACP-5b ($p = 0.082$) and NTx ($p = 0.033$). No significant interaction effect for BALP ($p = 0.522$) and also iPTH ($p = 0.513$). In the SG there was a decrease (mean change−4.8%) in TRACP-5b compared CG (mean change 4.5%) after 12 weeks ($p = 0.054$). CG showed significantly increase (mean change: 23.3%) uNTx compared to SG (mean change: 1.6%) after 12 weeks ($p = 0.015$). No significant difference in TRAP-5b ($p = 0.183$) and uNTx ($p = 0.857$) after 24 months.
		CG	30	57.8					
31	Sweden	SG	32	76.4	T- score <−1.0 to >−2.5	L. reuteri 6475: 5×10^9 CFU/capsule 2 capsule/day 1×10^{10} CFU/day	12 months	Blood samples: NTx, BALP	No differences in NTx and BALP between the SG and CG after 12 weeks (mean difference between groups: NTx: −4.95%; BALP: 10.3%).
		CG	36	76.3					
32	China	SG	20	62.8	Postmenopausal women T-score <−2.5 >−1.0	B. animalis subsp. lactis: 1.5×10^{10} CFU/day	3 months	Bood samples: OC, P1NP, CTX, PTH*	PTH were significantly ($p = 0.039$) lower in SG (36.49 pg/L) compared to CG (45.05 pg/L). Significant PTH reduction after 3 months only in SG (44.16 vs. 36.49 pg/L). Significant OC reduction only in SG after 3 months (20.25 vs.16.82 ng/mL; $p = 0.012$). No significant difference in P1NP and CTX between groups or time points.
		CG	20	61.6					

Table 2. Cont.

Ref.	Country	Participants (n)		Mean age (years)	Inclusion criteria	Supplementation	Duration	Biochemical analysis	Outcome
33	Iran	SG	20	58.9	Postmenopausal women T-score –1.0 to –2.5	L. casei: 1.3×10^{10} CFU B. longum: 5×10^{10} CFU L. acidophilus: 1.5×10^{10} CFU L. rhamnosus: 3.5×10^{9} CFU L. bulgaricus: 2.5×10^{8} CFU B. breve: 1×10^{10} CFU S. thermophilus: 1.5×10^{8} CFU	6 months	Blood samples: BALP, OC, CTX, PTH*	Significant (p = 0.033) reduction in BALP in SG after 6 months compared (19.65 vs. 16.53 U/L) to CG. CTX level was significantly lower in the SG (0.41 vs. 0.35 ng/ml) compared to the CG (0.45 vs. 0.42 ng/ml) at the end of the study (p = 0.046). OC were not significantly different after 6 months. Significant decrease in PTH in SG (31.92 vs. 29.05 pg/ml) compared to CG (p = 0.012).
		CG	21	57.3					
34	Poland	SG	30	45–70	Postmenopausal women (≥1 year last menstrual)	L. acidophilus UALa-01™: 1×10^{9} CFU/capsule/day	12 weeks	Blood samples: CTX and TRAP-5b, BALP, P1NP	Significant decrease in CTX (6.224 vs. 5.11 pg/ml; p = 0.01) and a significant increase in TRAP-5b (18.00 vs. 21.13 ng/ml; p = 0.04) in CG after 12 weeks compared to the baseline period. No significant (p >0.05) differences in bone resorption, and bone formation biomarkers within the SG between the preintervention and postintervention.
		CG	25						
35	Sweden	SG	160	55	Postmenopausal women (1–4 years last menstrual) T-score >–2.5	Limosilactobacillus reuteri ATCC (PTA 6475) High dose — 5×10^{9} CFU/capsule (n = 80 of SG) Low dose — 5×10^{8} CFU/capsule (n = 80 of SG) 2 capsule/day	24 months	Blood samples: P1NP, CTX	Significantly higher percent change in PINP was observed at 1 year for the high-dose group compared with CG (relative change 13.48%; p = 0.008) and at 2 years for both the high (change 14.41%; p = 0.03) and low-dose (change 14.24%; p = 0.03) groups compared with CG. No significant (p >0.05) change in CTX compared to SG and CG after 24 months
		CG	79	55					

Table 2. Cont.

Ref.	Country	Participants (n)		Mean age (years)	Inclusion criteria	Supplementation	Duration	Biochemical analysis	Outcome
37	Thailand	SG	20	62	Postmenopausal women (≥1 year last menstrual) T-score –1 to –2.5	L. reuteri GL-104: 1.5×10^{12} CFU L. paracasei MP-137: 0.6×10^{12} CFU L. rhamnosus: MP108: 0.6×10^{12} CFU L. rhamnosus F-1: 0.3×10^{12} CFU L. rhamnosus BV77: 0.6×10^{12} CFU B. animalis ssp.lactis CP-9: 2.4×10^{12} CFU B. longum ssp. longum OLP-01: 1×10^{12} CFU Bacillus coagulans: 1×10^{12} CFU + inulin 270 mg (prebiotic)	12 weeks	Blood samples: CTX, P1NP	Significant decrease in CTX (0 = 0.026) at 12 weeks compared with baseline in SG. No significant (p = 0.18) change in CTX in the CG after 12 weeks compared baseline. No significant change in P1NP in CG (p = 0.86) and SG (p = 0.64) after 12 weeks compared baseline. Changes in the CTX was significantly (p <0.001) different between SG (mean difference –0.06) and CG (mean difference 0.04). No significant (p = 0.06) changes in mean difference of P1NP between SG and CG.
		CG	20	64					

Legend: n — number of participants; SG — study group; CG — control group; L — Lactobacillus; B — Bifidobacterium; S — Streptococcus; CFU — colony-forming units; CTX — serum C-terminal telopeptide; P1NP — N-terminal propeptide of type 1 procollagen; TRAP-5b — tartrate-resistant acid phosphatase; OC — osteocalcin; PTH — parathyroid hormone; NTx — type I collagen cross-linked N-telopeptide; BALP — bone-specific alkaline phosphatase; PP — per protocol; ITT — intention to treat; *PTH concentration was analyzed as an indicator of bone turnover, not as a bone turnover marker.

of probiotics in combination with conventional pharmacotherapy (calcium, calcitriol) [32]. Numerous studies confirm that probiotic therapy might be beneficial for women with osteopenia identified as vitamin D deficient [25, 27]. In the study of individuals taking Lactobacillus plantarum authors reported a significant increase of vitamin D by 4.49 ng/mL after 24 months therapy [27]. Other studies showed a major drop in vitamin D level in the control group after a 12 month intervention. It is worth mentioning that the percentage of individuals with vitamin D deficiency was lower in the study group (22.6%) than the placebo group (28.9%) [25]. The positive effect of probiotic therapy, have been noticed in women and additionally in men, in a study with the use of Lactobacillus reuteri. Supplementation in the study was related to a significant increase in vitamin D concentration after 12 months of therapy (67.9 vs. 82.6 nmol/l). Even after taking the variety of seasons into consideration, the results were statistically significant [38]. The only paper with the contrary results, the authors were able to identify, was related to a study where the probiotic therapy lasted 6 months ($p = 0.72$). This supports the conclusion on limited efficiency of probiotics when the therapy lasts shorter than 12 months.

The results for the analysis of probiotic therapy and calcium concentration have been inconclusive. Majority of the analysed studies did not report any significant changes in calcium concentration in groups of healthy postmenopausal [25, 34], osteopenic [27, 33] or osteoporotic women [32]. It should be however emphasized that it does not necessary mean there is effect on the skeletal system in the matter. Rather that the mechanism of the process might be far more complex than anticipated. Calcium level is regulated strictly homeostatically, therefore possible changes might not be visible directly in the blood serum, but rather be affected by other factors (i.e. parathormone level, BTM) [39]. Detailed characteristics on the analysis of probiotic use on vitamin D and calcium levels are presented in Table 3.

Conclusions

The following review presents the potential anti-osteoporotic effects of probiotic therapy by its impact on the bone metabolism. Due to its good tolerance and well documented efficiency in majority of the studies, probiotic therapy might be adjacent in the prevention and treatment of osteoporosis. It should be emphasized however that the effects may vary depending on the study group, study period and probiotic strain. Having said that, despite promising results, it is crucial to conduct studies that would allow to identify proper dosing, therapy period and particular probiotic strains — to find the most effective course of action. At the same time, it should be remembered that there are no studies assessing the effect of probiotic therapy on the risk of fractures.

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Authors contribution

M.W. — research project preparation, data collection, data interpretation, literature review, manuscript preparation; J.A. — literature review, manuscript preparation; M.B. — literature review; W.K. — literature review.

Table 3. Assessment of the effect of probiotic supplementation on vitamin D and calcium status.

Ref.	Country	Participants (n)		Mean age (years)	Inclusion criteria	Supplementation	Duration	Outcome
25	Poland	SG	84	56.3	Postmenopausal women (2–5 years last menstrual) T-score ≥−1.5	L. paracasei LPC100 (DSM 33793): 1.5×10^9 CFU L. plantarum LP140 (DSM 33804): 3.5×10^9 CFU 5×10^9 CFU/capsule/day	12 months	Significant decrease in VD_3 concentration only in CG ($p = 0.014$) with no significant difference between groups. Percentage of women with VD_3 deficiency (<30 ng/mL) was lower in SG (22.6%) than in CG (28.9%), but the difference was not significant. Ca concentrations showed no differences after the intervention within or between groups.
		CG	83	57.0				
27	Spain	SG	33	56	Menopausal women T-score –1.0 to –2.5	Diary product enriched with L. plantarum 3547: 1×10^{10} CFU/day And also: calcium, vitamin D, vitamin K, vitamin C, zinc, magnesium, L-leucine	24 weeks	Significant ($p < 0.05$) increase in serum VD_3 in the SG after 24 weeks (change 4.49 ng/mL) in comparison to CG (change 1.93 ng/mL). No significant change in Ca status both in SG (change 0.03 mg/mL) and CG (–0.03 mg/mL) after 24 weeks.
		CG	21					
32	China	SG	20	62.8	Postmenopausal women T-score <−2.5 >−1.0	B. animalis subsp. lactis: 1.5×10^{10} CFU/day	3 months	Significant differences were shown in VD_3 and Ca after 3 months between SG and CG ($p < 0.05$). Ca status increased after 3 months in CG (2.27 vs. 2.38 mmol/L) not in SG (2.27 vs. 2.27 mmol/L). Significant ($p = 0.032$) increase in VD_3 status only in SG (21.44 vs. 26.22 ng/L) after 3 months.
		CG	20	61.6				
33	Iran	SG	20	58.9	Postmenopausal women T-score –1.0 to –2.5	L. casei: 1.3×10^{10} CFU B. longum: 5×10^{10} CFU L. acidophilus: 1.5×10^{10} CFU L. rhamnosus: 3.5×10^9 CFU L. bulgaricus: 2.5×10^8 CFU B. breve: 1×10^{10} CFU S. thermophilus: 1.5×10^8 CFU	6 months	No significant ($p = 0.72$) differences in VD_3 between SG and CG after the 6 months. Nonsignificant but marginal effect of probiotic supplementation on increasing serum Ca in SG (9.40 vs. 10.15 mg/dl) compared to CG ($p = 0.067$).
		CG	21	57.3				

Table 3. Cont.

Ref.	Country	Participants (n)		Mean age (years)	Inclusion criteria	Supplementation	Duration	Outcome
34	Poland	SG	30	45–70	Postmenopausal women (≥1 year last menstrual)	L. acidophilus UALa-01™: 1×10^9 CFU/capsule/day	12 weeks	No significant ($p > 0.05$) differences in Ca status between CG (1.90 vs. 2.04 mmol/L) and SG (2.10 vs. 1.88 mmol/L) after supplementation.
		CG	25					
38	Canada	SG	66	50.5	Adult men and women	L. reuteri NCIMB 30242: 2.9×10^9 CFU/capsule 2 capsules/day	12 weeks	Significant ($p = 0.003$) increase in VD_3 over the intervention period in SG (67.9 vs. 82.6 nmol/l). Significant VD_3 increase in SG observed after adjustment for seasonality of the intervention period as a confounder ($p < 0.001$). No significant differences between groups over the intervention period in Ca status.
		CG	61	47.6				

Legend: n — number of participants; SG — study group; CG — control group; L — Lactobacillus; B — Bifidobacterium; S —Streptococcus; CFU — colony-forming units; VD_3 — vitamin D; Ca — calcium.

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