The Effects of Probiotic Supplementation on the Bone Health of Postmenopausal Women

Erin Myhre

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The Effects of Probiotic Supplementation on the Bone Health of Postmenopausal Women

Abstract
Background: Osteopenia is a very common problem in postmenopausal women, with significant risk of fracture and progression to osteoporosis, yet despite the variety of treatment options, hormone-related bone loss is difficult to treat effectively while minimizing side effects. The composition of the gut microbiota is strongly associated with bone health, and probiotics are a promising adjunct therapy to the standard of care for osteopenia.

Methods: An exhaustive search of the literature was performed using the search terms probiotics, synbiotics, osteoporosis, bone mineral density, low bone mass, age-related bone changes, postmenopausal, fracture healing, fracture, and spontaneous fracture. Studies were assessed for quality using GRADE.

Results: The initial search generated 75 articles excluding duplicates. Two randomized clinical trials met eligibility criteria, with a study duration of at least 6 months and enrolled osteopenic postmenopausal women. One study found that supplementation of a mixed probiotic supplement seemed to induce a more positive profile of osteometabolic biomarkers, and the other study combined probiotics and isoflavones which significantly diminished bone loss over 12 months.

Conclusion: Probiotics are a promising option for the treatment of osteopenia, especially in combination with plant-derived isoflavones. Further studies will likely provide more support for probiotic administration in postmenopausal women, but in the meantime it would be safe and probably beneficial for clinicians to recommend probiotics to patients as an osteoprotective effort.

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Master of Science in Physician Assistant Studies

Keywords
probiotics, osteoporosis, osteopenia, postmenopausal, bone density, gut microbiome, isoflavones, bone loss

Subject Categories
Medicine and Health Sciences

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The Effects of Probiotic Supplementation on the Bone Health of Postmenopausal Women

Erin Myhre

A Clinical Graduate Project Submitted to the Faculty of the School of Physician Assistant Studies Pacific University Hillsboro, OR For the Master of Science Degree, August 10, 2019

Clinical Graduate Project Coordinator: Annjanette Sommers, PA-C, MS
Biography

[redacted]
Abstract

Background: Osteopenia is a very common problem in postmenopausal women, with significant risk of fracture and progression to osteoporosis, yet despite the variety of treatment options, hormone-related bone loss is difficult to treat effectively while minimizing side effects. The composition of the gut microbiota is strongly associated with bone health, and probiotics are a promising adjunct therapy to the standard of care for osteopenia.

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Keywords: Probiotics, postmenopausal, bone loss, osteopenia, and isoflavones
Acknowledgements

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List of Abbreviations
DXA - dual energy X-ray absorptiometry
BMD - bone mineral density
RANKL - receptor activator of nuclear factor Kappa-β (RANK) ligand
ER - estrogen receptor
GM - gut microbiota
PICP - procollagen type I C-terminal propeptide
PINP - procollagen type I N-terminal propeptide
OC - osteocalcin
BALP - bone-specific alkaline phosphatase
CTX - C-terminal telopeptide of type I collagen
NTX - N-terminal telopeptide of type I collagen
DPD - deoxypyridinoline
OPG - osteoprotegerin
BMI - body mass index
BP - blood pressure
BMC - bone mineral content
RCT - randomized controlled trial
The Effects of Probiotic Supplementation on the Bone Health of Postmenopausal Women

BACKGROUND

The cessation of estrogen production that causes menopause often leads to a variety of health concerns in peri- and postmenopausal women, including cardiovascular disease, urogenital atrophy and sexual dysfunction, and osteopenia, or low bone mass. Bone density may be measured using dual energy x-ray absorptiometry (DXA), and is reported as a T-score, or the number of standard deviations from the mean. Osteopenia is defined as a T-score between -1 and -2.5 and increases the risk of a fragility fracture and progression to osteoporosis (T-score equal to or below -2.5). Despite the variety of treatment options, hormone-related bone loss is difficult to treat effectively while minimizing side effects.

Current Recommendations for Osteoporosis Treatment and Prevention

The standard of care is vitamin D and calcium supplementation, weight-bearing activity, and reduction of fall risk factors. Estrogen therapy is also effective in maintaining or improving bone mineral density (BMD) but associated with increased risk of reproductive cancer. Pharmacologic agents such as bisphosphonates, calcitonin, and denosumab (a RANKL inhibitor) are not recommended for long-term use, often require regular appointments for infusion, and carry their own risk of adverse drug reactions. Isoflavones, a type of phytoestrogen (plant-derived), are gaining interest as a possibly safer alternative to estrogen therapy. Isoflavones selectively bind estrogen-
receptor-β (ERβ), as opposed to exogenous estrogen which binds both ERβ and ERα, the latter of which is associated with estrogen-sensitive cancers.⁴,⁵ Therefore, isoflavones have the potential to provide the benefits of estrogen supplementation without incurring the cancer risks.⁶

**Bone and the Gut Microbiota**

The human gastrointestinal system is home to trillions of bacteria, whose total cell count far exceeds that of their human host.⁷,⁸ These microbes are beneficial in a number of ways, and recent research has begun to demonstrate their association with bone health. The gut microbiota (GM) supports the immune system, specifically the gut-associated lymphoid tissue, and disruptions in the GM composition is thought to be a potential factor in the development of inflammatory diseases.⁸,⁹ McCabe et al⁷ list 3 main contributions of the GM to bone health: the modulation of immunologic activity, the digestion and absorption of nutrients such as calcium and phosphate, and the secretion of various small molecules. When the GM becomes dysfunctional, it can affect physiologic processes all over the body.

Probiotics, defined by the International Scientific Association for Probiotics and Prebiotics™ (ISAPP) as “live microorganisms that, when administered in adequate amounts, confer a health benefit on the host,”¹⁰ have been shown in several animal studies to have a positive effect on bone physiology, and human trials are promising. Li et al¹⁰ found that the lack of a GM altogether in mice who were raised in germ-free conditions actually prevented leuprolide-induced estrogen deficiency-related bone loss, demonstrating that the osteopenia associated with cessation of estrogen
production is dependent on the GM. The same study\textsuperscript{10} also showed that mice with a conventional GM experienced bone loss as expected when treated with leuprolide, but mice supplemented with probiotics were protected from this bone loss. Ohlsson et al\textsuperscript{11} and Britton et al\textsuperscript{12} induced estrogen deficiency by performing ovariectomies in mice, and both studies found that treatment with probiotics protected estrogen-deficient mice from bone loss.

**Markers of Bone Turnover**

To assess overall bone turnover, there are a number of measurable bone biomarkers present during bone formation or bone resorption. All are circulating in the serum unless otherwise specified. Bone formation markers include propeptides of type 1 collagen (PICP and PINP), byproducts of collagen synthesis; osteocalcin (OC), a protein produced by osteoblasts which constitutes 15\% of the bony matrix; and alkaline phosphatase (ALP), an enzyme present in the plasma membrane of osteoblasts which is also produced in bone-specific isoform (BALP). Bone resorption markers include telopeptides of type 1 collagen (CTX and NTX), collagen degradation products; deoxypyridinoline (DPD), a breakdown product of mature cross-linked collagen that is measured in the urine; and receptor activator of nuclear factor Kappa-\(\beta\) (RANK) ligand (RANKL). RANKL is a protein produced by osteoblasts and activated by B and T lymphocytes, and promotes osteoclastic activity.\textsuperscript{13} Osteoprotegerin (OPG) is also produced by osteoblasts and binds to RANKL as a decoy receptor, inhibiting osteoclastogenesis and thus inhibiting bone resorption.\textsuperscript{14} Systemic inflammation has also been found to increase bone resorption, and inhibition of inflammatory markers such as
TNF-α, interleukin-1, and other cytokines is associated with a decrease in bone resorption markers. See table 1 for a summary of these biomarkers.

METHODS

An exhaustive search of the literature was performed using Cochrane Library, CINAHL via EBSCOhost, MEDLINE-PubMed, and ScienceDirect via Elsevier. Search terms included probiotics, synbiotics, osteoporosis, bone mineral density, low bone mass, age-related bone changes, postmenopausal, fracture healing, fracture, and spontaneous fracture. Other sources included the bibliographies of articles found in the database searches, and suggested similar articles from NCBI PubMed. Studies meeting inclusion criteria were performed on postmenopausal women, were available in English, used a control group, and measured endpoints that included at least one of the following: bone mineral density, fracture healing time, spontaneous fracture, bone turnover biomarkers, or inflammatory markers.

A search of clinicaltrials.gov revealed two clinical trials seeking to assess the effects of probiotics on the BMD of osteopenic postmenopausal women, one currently recruiting and the other recently completed with no results available at the time this paper was written.

Articles were assessed for quality using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE).
RESULTS

After the initial search which generated 75 articles excluding duplicates, 2 articles\textsuperscript{5,18} met eligibility criteria. Both were randomized, double-blind, controlled trials conducted on osteopenic postmenopausal women, with a study duration of at least 6 months (see table 2). Two other studies\textsuperscript{19,20} were considered but ultimately excluded because their focus was acute calcium metabolism and not long term bone turnover, and their study sizes and durations were very limited.

Jafarnejad et al

This study\textsuperscript{18} sought to determine the effects of a daily probiotic supplement as well as calcium and vitamin D, and measured these effects via changes in BMD and various osteometabolic and immunologic biomarkers. Study subjects were 50 osteopenic but otherwise healthy postmenopausal women between the ages of 50-75 years. Exclusion criteria included osteoporosis (defined as T-score below -2.5), recent treatment with pharmacologic agents that modified bone metabolism such as bisphosphonates or parathyroid hormone, tobacco use, BMI over 40, and chronic diseases of the bone, kidneys, liver, gastrointestinal tract, pancreas, or lungs.\textsuperscript{18}

A total of 50 participants were randomized into 2 groups, and all participants and researchers were blinded throughout the study. The intervention group was given Gerilact capsules daily, a probiotic supplement containing \textit{Lactobacillus casei}, \textit{Lactobacillus rhamnosus}, \textit{Lactobacillus}
acidophilus, Lactobacillus bulgaricus, Bifidobacterium longum, Bifidobacterium breve, and Streptococcus thermophilus. The control group was given placebo capsules that matched the probiotic capsules in appearance. Both groups also received 500 mg of calcium and 200 IU vitamin D daily, and instructed to avoid any foods that contained probiotics (such as yogurt) and other supplements containing calcium or vitamin D.¹⁸

Baseline characteristics measured at the beginning of the study included BMD of the L1-L4 vertebrae and total hip, weight, height, BMI, age, and time since menopause. None of these variables were significantly different between the 2 groups. Biomarkers were measured to get baseline levels, and these markers included BALP, OC, CTX, vitamin D, RANKL, OPG, TNF-α, IL-1β, and DPD. Other baseline labs included serum calcium, magnesium, phosphorus, creatinine, albumin, and alkaline phosphatase, and urine calcium, magnesium, phosphorus, and creatinine. Participants provided information about their typical diet and physical activity level at the beginning of the study, and these were reassessed several times throughout the study to ensure consistency.¹⁸

By the end of the study, 9 women had dropped out due to GI issues (in the intervention group), medication changes, and personal reasons, leaving 21 in the control group and 20 in the intervention group for final analysis. Changes in bone mineral density were minimal and not significant. In the intervention group, baseline BMD was 0.919 in L1-L4 and 0.837 in the hip, and after 6 months BMD was 0.920 in L1-L4 and 0.822 in the hip. In the control group, baseline BMD was 0.912 in L1-L4 and 0.808 in the hip, and
after 6 months BMD was 0.914 in L1-L4 and 0.792 in the hip. Two bone biomarkers showed statistically significant changes: bone-specific ALP increased 0.82 U/L in the control group and decreased 3.12 U/L in the treatment group, and CTX decreased 0.03 in the control group and 0.06 in the treatment group. Inflammatory marker TNF-α increased 0.49 pg/ml in the control group and decreased 0.51 pg/ml in the treatment group\(^{18}\) (see table 3).

Limitations in this study included small sample size and short duration, which limited the possible results and their significance. In addition, all biomarkers were measured in the serum, as this was less invasive, but authors stated that bone biopsy would have provided more accurate samples.\(^{18}\)

**Lambert et al**

This randomized double-blind study\(^{5}\) was a 12-month reproduction of a previous 3-month study in postmenopausal women also carried out by Lambert et al. It sought to observe the effects on bone of taking isoflavones, along with probiotics to improve bioavailability, for a longer duration than their initial 3-month study. The authors tracked an extensive number of variables, including bone mineral density in 3 locations, T-score, bone turnover markers, and estrogen metabolites. Participants were postmenopausal osteopenic women between the ages of 60-85 years, with a BMI between 20-40kg/m\(^2\). Exclusion criteria included T-score \(\geq 1\) or \(\leq 3\), pharmacologic osteoporosis therapy within 3 months including hormone therapy, history of treatment with estrogen receptor (ER) agonists or
antagonists, history of cancer or substance abuse, BP >160/110, or severe cardiovascular, renal, neurologic, or psychiatric disease. All participants were verified to be estrogen deficient, measured throughout the study with serum estrogen ranging from 0.03-0.04 ng/ml.\textsuperscript{5}

Participants were randomized into 2 groups, both of whom received daily supplementation of 1040 mg calcium, 487 mg magnesium, and 25 ug vitamin D. Both groups had similar baseline characteristics with no statistically significant or notable differences except for trochanter BMC, which was higher in the control group. All participants and researchers were blinded throughout the duration of the study. The intervention group was given packets of a liquid supplement containing red clover extract (a natural source of isoflavones) and unspecified probiotic lactic acid bacteria to increase bioavailability of the isoflavones,\textsuperscript{21} to be taken twice daily, and the placebo group was given packets filled with a similarly-flavored and colored liquid. The trial was completed over 12 months, and 78 out of 85 women finished the study with a high compliance rate. All women who completed the study were included in the data analysis, and the authors added 25\% to the final N value “to account for dropouts and losses,” bringing the new total to 85.\textsuperscript{5}

The only bone biomarker that showed a statistically significant reduction in the intervention group compared to the control at the end of 12 months was plasma CTX, which increased 0.03 ng/ml in the control but decreased 0.04 ng/ml in the intervention group (P value <0.05). Bone mineral density was measured in the lumbar spine, femoral neck, and
trochanter at baseline, 6 months, and 12 months. All 3 areas showed statistically significantly less change in BMD in the intervention group compared to the placebo group. In addition, lumbar and femoral neck T-scores and trochanter BMC decreased statistically significantly less in the intervention group (see table 4).

Lambert et al\(^5\) stated that evidence would be strengthened by a study duration of at least 2 years because it would allow for more complete cycles of bone turnover, and the use of peripheral quantitative computed tomography in order to assess the bone qualities more thoroughly. A limitation of the study was the fact that all participants were normotensive and of a normal weight, and given that hypertension and high BMI are common in many elderly women, these would be important variables to include in further study.\(^5\)

**DISCUSSION**

Probiotic supplementation, especially in combination with isoflavones, appears to be a potentially beneficial adjunct therapy for promoting bone health. However, this is still an area of research with many questions, as human studies are lacking in number. Jafarnejad et al\(^1^8\) found that participants who took a daily capsule containing 7 probiotics, as well as calcium and vitamin D supplementation, showed lower serum levels of inflammatory markers, decreased CTX, and increased ALP after 6 months, all changes that supported decreased bone resorption. Bone density changes
between treatment and placebo group were statistically insignificant. In addition to small study size and short duration, this study was limited by the fact that it excluded participants with a history of tobacco use and chronic conditions of the bone, kidneys, liver, gut, pancreas, or lungs. These factors apply to a large portion of the American adult population, and the study would be more widely relevant if it included common comorbidities such as diabetes, chronic obstructive pulmonary disease, and fatty liver disease. Lambert et al\textsuperscript{5} appeared to allow a few more common comorbidities in their study sample, however all participants happened to be normotensive and non-obese. This study found that daily supplementation of isoflavones combined with a probiotic, along with calcium, magnesium, and vitamin D, was associated with increased bone mineral density in the intervention group compared to placebo. Biomarker CTX increased in the control but decreased in the intervention group, a statistically significant difference that correlates with less bone resorption in the intervention group. Authors also acknowledge their relatively short study length (12 months) and asserted that the results would be stronger if the study were long enough to encompass more complete bone turnover cycles.

Another limitation for both of these studies is their use of surrogate outcomes (bone biomarkers). While some of these biomarkers have been well-studied in regards to their association to bone turnover, the most useful outcomes to measure would be those that are patient-important, such as bone density or fracture rate.
There are a few additional human studies regarding the effects of probiotics on other bone-related processes. A randomized trial by Lei et al.\textsuperscript{22} followed 417 elderly patients with distal radius fracture, and found that those who received daily probiotics had their healing time shortened by 2 months. A crossover study by Narva et al.\textsuperscript{19} found that postmenopausal women who drank milk fermented with \textit{Lactobacillus rhamnosus} showed increased calcium absorption, while Cheung et al.\textsuperscript{20} saw that acute calcium absorption in osteopenic women was minimally affected by consumption of fermented calcium-fortified soy milk.

**Probiotic safety**

Probiotics are microorganisms that naturally exist in and on the body, and are also found in fermented foods such as yogurt or fresh unpasteurized sauerkraut.\textsuperscript{9} The gut microbiome is increasingly shown to be associated with many physiologic processes, including bone turnover, digestion homeostasis, immune system function, and mental health, and probiotic supplementation is becoming more popular as a way to boost the overall health of an individual by fixing a dysregulated microbial population. Since probiotics have been safely consumed in food for many years, they were initially categorized by the FDA as Generally Recognized As Safe (GRAS). As they gained momentum as a potential therapeutic intervention for various health problems, the lack of large standardized studies became more of an issue.\textsuperscript{23} Hundreds of small studies found probiotics to have few adverse effects, save for rare cases of sepsis and gut ischemia primarily in critically ill or otherwise
immunocompromised patients, and the many years of safe consumption is also reassuring.

Studies on probiotics most commonly utilize various species or strains of *Lactobacillus*, as it is most well known, but other genera such as *Bifidobacterium, Bacillus*, and *Streptococcus thermophilus* have also been studied to a lesser extent and found to have unique qualities and benefits. Some of the characteristics that could classify an organism as a probiotic include the ability to tolerate and survive in the gut without invoking an immune response, phenotypic and genotypic stability, and no intrinsic pathogenic qualities as well as activity against known pathogens.\(^{24}\)

*Saccharomyces boulardii*, a strain of *S. cerevisiae*, is a yeast that is occasionally used as a probiotic and has been shown to reduce gut inflammation and prevent *Clostridium difficile* infection,\(^ {25,26}\) though it may carry a risk of fungemia even in immunocompetent people.\(^ {27}\)

Given the current body of research on probiotics regarding their benefits and safety, they are probably safe and beneficial for most adults, though more research is still needed in order to consider probiotics an effective biotherapeutic option. For clinicians interested in recommending probiotics to patients, the website [http://usprobioticguide.com/](http://usprobioticguide.com/) compiles the current clinical evidence from PubMed and EMBASE, updated yearly, as a reference for indications, safety, and dosage.

**Mixed evidence for isoflavones**

Isoflavones (genistein, daidzein, and glycitein) are phytochemicals with both mild estrogenic and antiestrogenic properties, which has made
them the center of much research over the last several decades, both for their potential benefits and for their possible risk of potentiating ER+ reproductive cancer. A few small studies showed that isoflavones might stimulate estrogen-sensitive breast tissue or growth of ER+ cancer cells. But several large studies that followed thousands of breast cancer survivors with moderate or high isoflavone intake found that they actually had reduced recurrence and risk of death, and negative outcomes seemed to be associated with concurrent tamoxifen administration.

A 2017 review by Zaheer and Humayoun also found that soy products (the best natural source of isoflavones) are associated with decreased incidence and severity of cancer and chronic disease including age-related bone loss, and have a good safety profile. However, while most current research seems to generally agree on the relative safety of isoflavones, there is conflicting evidence about their therapeutic benefits, especially in regards to bone metabolism. Brink et al observed unchanged bone mineral density and levels of bone biomarkers in a RCT that provided isoflavone rich diets to postmenopausal women for 1 year. Tai et al carried out a RCT of 431 postmenopausal women consuming high amounts of isoflavones or placebo, and found no statistically significant differences in BMD or bone biomarkers after 2 years. The Linus Pauling Institute at Oregon State University, which studies micronutrients and their effects on health and aging, compiled some 25 clinical trials, reviews, and meta-analyses about isoflavones and bone integrity, and found significant conflict. None found any detrimental effect of isoflavones to bone, but the high variability of study
results precludes a stand-out recommendation since benefits are not well-supported by current evidence.  

**Recommendations for future probiotic research**

Further study is needed to establish more definitive evidence for probiotics, both on their own and with isoflavones, and their effect on bone metabolism. Ideally, future studies would rely on definitive clinical measurements such as bone density, rather than surrogate outcomes like bone and inflammatory biomarkers. It would also be useful to know if probiotic administration has similar effects in patients with common comorbidities such as hypertension, obesity, diabetes, lung disease, and systemic inflammatory conditions. A search on clinicaltrials.gov yielded 2 current clinical trials on the topic of probiotics in postmenopausal women, a 249-participant trial recently completed in Sweden\(^1\) and an ongoing Emory University 40-participant trial.\(^2\) These studies should shed more light on the relationship between probiotics and bone metabolism, and hopefully include women with some of the previously mentioned comorbidities.

**CONCLUSION**

Osteopenia is a very common problem in postmenopausal women, with significant risk of fracture and progression to osteoporosis, yet there is still no stand-out treatment option that is highly effective and tolerable. Probiotics are a promising option for the treatment of osteopenia, especially in combination with plant-derived isoflavones. They appear to have a
regulatory effect on bone turnover and have a low side-effect profile. Further studies will likely provide more support for probiotic administration in postmenopausal women, but in the meantime it would be safe and probably beneficial for clinicians to recommend probiotics to patients as an osteoprotective effort.
References


## Table 1. Summary of bone biomarkers, Shetty et al

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Description</th>
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<tbody>
<tr>
<td><strong>Markers of bone formation</strong></td>
<td></td>
</tr>
<tr>
<td>Procollagen type I C-terminal and N-terminal propeptides (PICP and PINP, respectively)</td>
<td>Byproducts of collagen synthesis, primarily from proliferating osteoblasts. PINP is better marker, as PICP clearance is affected by thyroid or pituitary dysfunction.</td>
</tr>
<tr>
<td>Osteocalcin (OC)</td>
<td>Constitutes 15% of bony matrix, produced by osteoblasts, odontoblasts, and chondrocytes. Levels influenced by vitamin K, renal function, and circadian rhythm.</td>
</tr>
<tr>
<td>Alkaline phosphatase (ALP), bone-specific isoform (BALP)</td>
<td>Enzyme in osteoblast plasma membrane. Promotes mineralization by degrading pyrophosphate, which inhibits mineralization.</td>
</tr>
<tr>
<td><strong>Markers of bone resorption</strong></td>
<td></td>
</tr>
<tr>
<td>C-terminal and N-terminal crosslinked telopeptides of type 1 collagen (CTX and NTX, respectively)</td>
<td>Type I collagen degradation products, produced by enzymatic activity of cathepsin K. Levels influenced by circadian rhythm, and liver and renal failure.</td>
</tr>
<tr>
<td>Deoxypyridinoline (DPD)</td>
<td>Type I collagen degradation products, only produced with breakdown of mature crosslinked collagen. Specific to bone and dentin.</td>
</tr>
<tr>
<td>Receptor activator of nuclear factor Kappa-β ligand (RANKL)</td>
<td>Produced by osteoblasts, activated by B and T lymphocytes. Binds osteoclasts and promotes differentiation and activity.</td>
</tr>
<tr>
<td>Osteoprotegerin (OPG)</td>
<td>Produced by osteoblasts. Binds RANKL as decoy receptor to inhibit osteoclastogenesis.</td>
</tr>
</tbody>
</table>
Table 2. Quality assessment of reviewed articles, GRADE

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Study Design</th>
<th>Downgrade Criteria</th>
<th>Upgrade Criteria</th>
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<tr>
<td></td>
<td></td>
<td>Limitations</td>
<td>Indirectness</td>
<td>Inconsistency</td>
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<tr>
<td>Jafarnejad et al&lt;sup&gt;a&lt;/sup&gt;</td>
<td>RCT</td>
<td>Serious&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Not serious</td>
<td>Not serious</td>
</tr>
<tr>
<td>Lambert et al&lt;sup&gt;10&lt;/sup&gt;</td>
<td>RCT</td>
<td>Serious&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Not serious</td>
<td>Not serious</td>
</tr>
</tbody>
</table>

<sup>a</sup> Short study duration and reliance of surrogate biomarkers (rather than DEXA)

<sup>b</sup> Small sample size
Table 3. Changes from baseline in bone mineral density and statistically significant biomarkers in 6 month, Jafarnejad et al

<table>
<thead>
<tr>
<th>Variable</th>
<th>Probiotic group</th>
<th>Control group</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>6 months</td>
<td>Baseline</td>
</tr>
<tr>
<td>Spine BMD (g/cm²)</td>
<td>0.919 ± .08</td>
<td>0.920 ± .07</td>
<td>0.912 ± .06</td>
</tr>
<tr>
<td>Hip BMD (g/cm²)</td>
<td>0.837 ± .07</td>
<td>0.822 ± .08</td>
<td>0.808 ± .1</td>
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<tr>
<td>BALP (U/L)</td>
<td>19.65 ± 1.66</td>
<td>16.53 ± 0.90</td>
<td>17.81 ± 1.35</td>
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<tr>
<td>CTX (ng/mL)</td>
<td>0.41 ± 0.02</td>
<td>0.35 ± 0.02</td>
<td>0.45 ± 0.02</td>
</tr>
<tr>
<td>TNF-α (pg/mL)</td>
<td>4.24 ± 0.5</td>
<td>3.73 ± 0.43</td>
<td>3.83 ± 0.47</td>
</tr>
</tbody>
</table>

Table 4. Changes from baseline in bone mineral density and statistically significant biomarkers in 12 months, Lambert et al

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control change from baseline (95% CI)</th>
<th>Intervention change from baseline (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spine BMD (g/cm²)</td>
<td>-0.022 (-0.032, -0.012)</td>
<td>-0.0085 (-0.017, 0.00006)</td>
<td>0.043</td>
</tr>
<tr>
<td>Spine T-score</td>
<td>-0.2 (-0.29, -0.11)</td>
<td>-0.08 (-0.16, 0.0001)</td>
<td>0.045</td>
</tr>
<tr>
<td>FN BMD (g/cm²)</td>
<td>-0.022 (-0.03, -0.015)</td>
<td>-0.008 (-0.015, 0.00003)</td>
<td>0.0059</td>
</tr>
<tr>
<td>FN T-score</td>
<td>-0.19 (-0.25, -0.12)</td>
<td>-0.06 (-0.13, -0.0001)</td>
<td>0.0061</td>
</tr>
<tr>
<td>Trochanter BMD (g/cm²)</td>
<td>-0.017 (-0.025, -0.008)</td>
<td>-0.004 (-0.01, 0.004)</td>
<td>0.03</td>
</tr>
<tr>
<td>Trochanter BMC (g)</td>
<td>0.54g (-0.79, -0.3)</td>
<td>-0.23 (-0.39, -0.07)</td>
<td>0.034</td>
</tr>
<tr>
<td>CTX (ng/mL)</td>
<td>0.03 (-0.02, 0.07)</td>
<td>-0.04 (-0.09, 0.01)</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>