META-ANALYSIS OF THE CORRELATION BETWEEN PROBIOTICS AND BONE MINERAL DENSITY

Xuefeng Feng, Xin Long, Zucai Pang*
Department of Orthopedics, Shunde Hospital of Guangzhou University of Chinese Medicine, Foshan, Guangdong 528333, China

ABSTRACT

Introduction: *To explore the effect of probiotics on bone density.*

Materials and methods: *English literature on the effect of probiotics on bone mineral density was searched by computer in cnki, cqvip.com, wanfang database, Chinese biomedical literature database, Pubmed, Embase, Web of Science, and Cochrane library from December 1, 2011 to January 1, 2019. Two researchers independently screened the literature and extracted the data. After literature quality evaluation was conducted according to the Newcastle-Ottawa scale, RevMan5.3 software was used for Meta-analysis.*

Results: *A total of 85 papers were initially retrieved, and after screening 7 papers were adopted in this analysis, all of which were in English. The 7 selected literatures were of relatively high quality, and all the scores of the Newcastle-Ottawa scale were ≥6. The results of Meta-analysis showed that compared with the control group, the bone density of the experimental group was significantly increased after drinking probiotics [SMD=5.25, 95% CI (1.49, 9.00)]; in the experimental group, there was no significant change in bone density of lumbar vertebra [SMD=0.03, 95% CI (-0.27, 0.33)]; compared with the control group, the femoral neck bone mineral density (BMD) of the experimental group after drinking probiotics had a significant increase trend [SMD=0.50, 95% CI (-0.46, 1.45)]. The funnel plot shows a gap in the lower-left corner.*

Conclusions: *Probiotics may increase BMD and reduce the risk of BMD reduction.*

Keywords: *Probiotics, bone mineral density, meta-analysis.*

DOI: 10.19193/0393-6384_2022_3_296

Received *March 15, 2021;* ***Accepted*** *January 20, 2022*

Introduction

Osteoporosis is a disorder of bone metabolism, which is caused by low bone mass and degeneration of bone tissue, resulting in increased bone mass[1]. Due to osteoporosis, bone density and microstructure of bone tissue are reduced, leading to an increased risk of fracture[2]. The incidence of osteoporosis-related hip fractures is on the rise worldwide, and the elderly are more affected by fractures. The total disability-adjusted life expectancy worldwide is reported to be 5.8 million years in the worldwide. Fifty-one percent of these are due to fractures, which occur mainly in European and American populations[3]. Therefore, osteoporotic fractures are considered to be an important factor of mortality and morbidity in developed countries. In addition, it is also found that the most common osteoporosis is related to postmenopausal diseases in women aged 50 and over[4, 5]. Probiotics, as a type of microorganisms that are beneficial to the health of the body, are widely used in the prevention and treatment of gastrointestinal diseases, obesity and metabolic disorders related diseases, and depression. Studies have found that probiotics can interfere with the composition of intestinal flora, regulate

the immune system, inhibit the production of pro-inflammatory factors, thus reducing bone absorption and achieving the purpose of preventing and treating osteoporosis[6].

Many studies have also shown that moderate consumption of probiotics can promote bone density and reduce the risk of osteoporosis[7-9]. In order to objectively evaluate the effect of probiotics on bone mineral density, we systematically evaluated the existing relevant studies, and the summary report is as follows.

Materials and methods

Inclusion criteria for literature

- Case-control literature published at home and abroad;
- English literature;
- The exposure factor is probiotics, and the types of probiotics are not limited;
- Outcome evaluation indicators should include the number of patients in the experimental group and the control group, mean bone density and standard deviation, OR value, 95% CI, etc.

Exclusion criteria for literature

- Repeatedly published literature;
- Repeated publications;
- Reports with incorrect results, incomplete data and unavailable full text;
- Non-English literature;
- Research reviews.

Literature search and screening

Related literature was searched by computer in cnki, cqvip.com, wanfang database, Chinese biomedical literature database, Pubmed, Embase, Web of Science, and Cochrane library from December 1, 2011 to January 1, 2019. English key words include probiotics bone mineral density, BMD, bone density, bone mass, osteoporosis, fracture etc.

Use the above keywords to perform a combined search and trace the references of the retrieved documents. wo researchers independently screened the literature and extracted the data according to the inclusion and exclusion criteria. If there is any difference, the two parties shall decide whether to include it after discussion.

Data extraction and literature quality evaluation

Information such as the year of publication, type of research design and object of study were extracted from the included literature. The Newcastle-Ottawa scale was used to evaluate the quality of the literature included in the study. 1.5 Statistical analysis. Revman5.3 software was used for analysis.

First, homogeneity test was conducted on all included studies. If there was homogeneity among all studies (I2≤50%), meta-analysis of fixed-effect model was used; if there was no homogeneity among all studies (I2>50%), meta-analysis of random-effect model was used.

SMD is used as the comprehensive effect parameter for the risk of bone density reduction. the difference was statistically significant if the upper and lower limits of 95% CI were all greater than or less than 1, and the difference was not statistically significant if the 95% CI contains 1. Funnel plots were used to assess publication bias in included studies.

Results

The results of literature retrieval and quality evaluation

Initially, a total of 85 documents were retrieved. After screening, 7 documents[11-17] were included in this analysis, all in English. The document screening process is shown in Figure 1.

The basic characteristics of the included literature are shown in Table 1.

The quality of the included 7 articles are both high, and the scores on the Newcastle-Ottawa scale are all ≥6 points. Seen Table 2 for details.

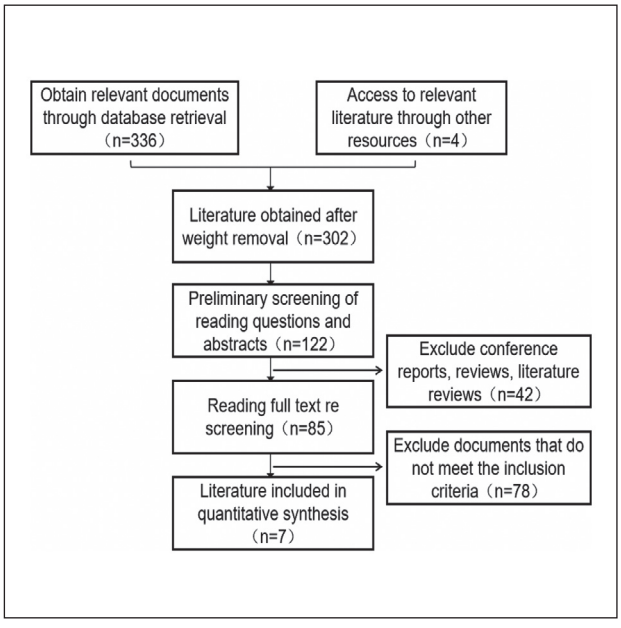

Figure 1: The process of document screening.

Author	Time	Sample size		Volumetric bone density (mg/cm^{-3})		Bone density (mg/cm^{-3})		Bone density (T score) - lumbar spine		Bone density (T score) - hip joint		Bone density (T score) - femoral neck		Sample source
		Experimental	Control	Experimental	Control	Experimental	Control	Experimental	Control	Experimental	Control	Experimental	Control	
Nilsson[11]	2018	45	45	25.5±3.5	25.3±3.3			-0.90 ±0.95	-1.00 ±0.95	-1.14 ±0.65	-1.24 ±0.53	-1.68 ±0.59	-1.69 ±0.62	Swedish
Ohlsson[12]	2014	10	10			344±8	298±7							Germany
Parvaneh[13]	2015	8	8			1060± 20	590±70							Malaysia
Hou[14]	2017	21	22			716± 93	529±78							China
Lambert[15]	2017	40	38					-1.97 ±0.16	-1.96 ±0.18			-1.55 ±0.09	-1.64±0.09	Danish
Mccabe[16]	2013	10	10			193±7	166±6							The United States
Collins[17]	2016	10	10			905±32	857±17							The United States

Table 1: The basic characteristics of the included literature.

Author	Issuing time	Choose (score)	Comparability (score)	Exposure/ outcome (score)	Total score
Ohlsson	2014	4	2	2	8
Parvaneh	2015	3	2	2	7
Hou	2017	3	2	1	6
Lambert	2017	4	1	2	7
Nilsson	2018	4	1	1	6
MCCABE	2013	4	2	2	8
Collins	2016	4	1	2	7

Table 2: Scores of the Newcastle-Ottawa scale of included literature.

Meta-analysis results

Seven articles have analyzed the relationship between probiotics and bone mineral density, two of which have studied the relationship between probiotics and bone mineral density in different parts. Five references[12-14, 16, 17] studied the relationship between probiotics and total BMD, but there was no homogeneity among the five studies (I2=84%), so the random-effect model was used for meta-analysis.

Compared with the control group, the bone mineral density of the experimental group was significantly increased after drinking probiotics [SMD=3.89, 95% CI (2.22, 5.56)]. As shown in Figure 2.

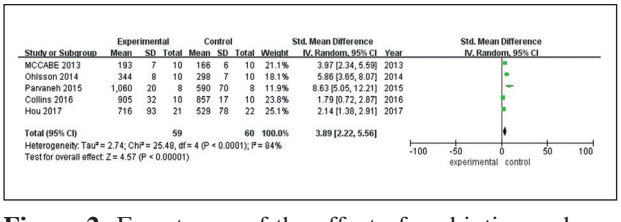

Figure 2: Forest map of the effect of probiotics on bone density.

Two literatures[11, 15] studied the relationship between probiotics and lumbar spine bone mineral density. The two studies have homogeneity (I2=0), so a fixed-effects model Meta-analysis was used.

Compared with the control group, the experimental group had no significant changes in lumbar bone mineral density after drinking probiotics [SMD = 0.03, 95% CI (-0.27, 0.33)]. As shown in Figure 3.

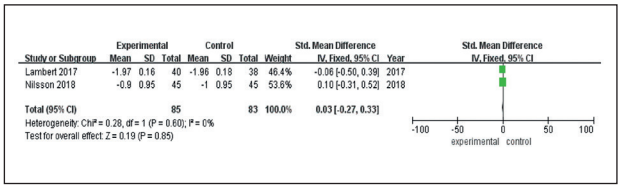

Figure 3: Forest diagram of the effect of probiotics on lumbar bone density.

Two literatures[11, 15] studied the relationship between probiotics and femoral neck bone mineral density. There is no homogeneity between the two studies (I2 =89%), so random-effects model Meta-analysis was used. Compared with the control group, the femoral neck bone mineral density of the experimental group increased significantly after drinking probiotics [SMD = 0.50, 95% CI (-0.46, 1.45)]. As shown in Figure 4.

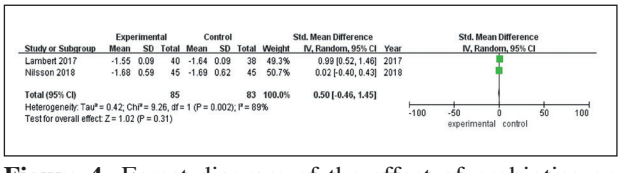

Figure 4: Forest diagram of the effect of probiotics on femoral neck bone density.

The analysis results of sensitivity and publication bias

Among the 7 included articles, the 2 with larger sample size was eliminated, and the funnel chart showed a gap in the lower-left corner (Figure 5).

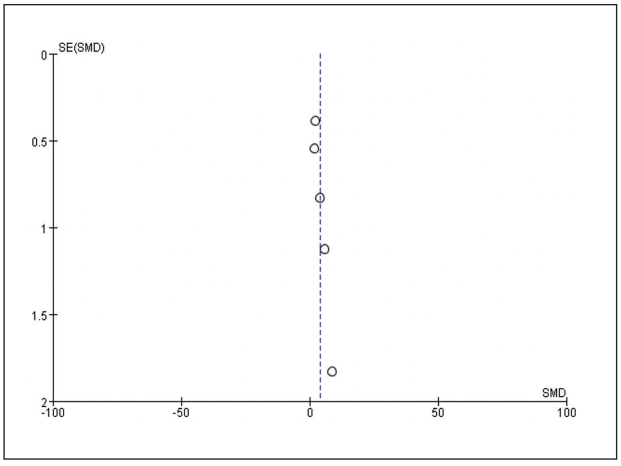

Figure 5: Funnel plot of the effect of probiotics on bone density.

Discussion

Studies have found that the cause of osteoporosis is the decrease of bone mass, which results in the increase of brittle bone and easy to cause brittle fracture. These causes lead to osteoporotic fractures with high incidence, low healing rate and high recurrence rate, etc.[18]. Fracture healing mainly involves bone regeneration, while the process of bone growth is the process of absorbing old bone and new bone-forming through the coordination of osteoblasts and osteoclasts. In this process, blood Ca provides raw materials for bone repairment. One possible treatment for osteoporosis is to consume probiotics[19, 20].

Probiotics are living microorganisms[21], sometimes from fermented foods[22], when given in sufficient amounts, it will have a beneficial physiological effect on the host[23, 24]. Some scholars have also studied the effects of probiotics such as Lactobacillus casei, Lactobacillus Plantarum, Lactobacillus paracasei and Bifidobacterium longum on osteoporosis, and gave the same conclusion[25]. In addition, a large number of cell and animal experiments have confirmed the ability of probiotics to prevent and improve diabetes and metabolic syndrome[26]. Besides, studies at home and abroad have dynamically shown that probiotics (represented by lactobacillus and bifidobacterium) can affect lipid metabolism and related inflammatory factors, affect the leptin level of patients, promote bone formation, and maintain normal bone density[27].

Ohlsson et al.[12] found that feeding probiotics to ovariectomy mice could increase cortical bone mass and bone density, and reduce levels of bone resorption markers CTX-I and urinary calcium. In the study of osteoporosis patients, it was found that the control group and the osteoporosis group had significant differences in the number of lactobacillus and bifidobacterium. The reduction of lactobacillus and bifidobacterium leads to a decrease in bone density. The results of meta-analysis showed that the bone density of the experimental group increased significantly after drinking probiotics. Compared with the control group, the lumbar spine bone density of the experimental group did not change significantly after drinking probiotics, but the femoral neck bone density showed a significant trend of increase, suggesting that taking probiotics will increase bone density and reduce the risk of bone density reduction, which is consistent with the research results in literature[11-13]. The results of this study suggest that probiotics can increase the overall bone density, but have a small effect on the bone density of the lumbar spine, and increase the bone density of the femoral neck. Therefore, medical staff should pay attention to the situation of patients with osteoporosis taking probiotics and use them rationally.

The shortcomings of this study include:

• Only searched English literature, lack of research on literature in other languages;

• The included literature is mainly case-control studies, and others such as cohort studies are not sufficient;

• There is no excessive subgroup analysis, and the results are not sufficiently convincing and representative; In the future, a large sample of observational studies based on the types of probiotics with the strict control of confounding factors should be carried out in my country to better explore the effects of different probiotics on bone density.

References

1) Sidhu K, Ali B, Burt LA, Boyd SK, Khan A. Spectrum of microarchitectural bone disease in inborn errors of metabolism: a cross-sectional, observational study. Orphanet J Rare Dis 2020; 15(1).

2) Wang Z, Wang D, Liu Y, Liu D, Ren Y, Liu Z, Yu B, Hao M, Xie J. Mesenchymal stem cell in mice uterine and its therapeutic effect on osteoporosis. Rejuven Res 2021; 24(2): 139-150.

3) Johnell O, Kanis JA. An estimate of the worldwide prevalence and disability associated with osteoporotic fractures. Osteopor Int 2006; 17(12): 1726-1733.

4) Rahmani P, Morin S: Prevention of osteoporosis-related fractures among postmenopausal women and older men. Can Med Assoc J 2009; 181(11): 815-820.
5) Islam S, Liu Q, Chines A, Helzner E. Trend in incidence of osteoporosis-related fractures among 40-to 69-year-old women: analysis of a large insurance claims database, 2000-2005. Menop J North Am Menop Soc 2009; 16(1): 77-83.
6) Zhong Y, Zheng C, Zheng JH, Xu SC: The relationship between intestinal flora changes and osteoporosis in rats with inflammatory bowel disease and the improvement effect of probiotics. Eur Rev Med Pharmacol Sci 2020; 24(10): 5697-5702.
7) Collins FL, Rios-Arce ND, Schepper JD, Parameswaran N, McCabe LR. The Potential of Probiotics as a Therapy for Osteoporosis. Microbiology Spectrum 2017; 5(4): 54.
8) Paccou J. Nutritional facets of osteoporosis management: Can probiotics help? Joint Bone Spine 2020; 87(2): 115-117.
9) Ilesanmi-Oyelere BL, Kruger MC. The Role of Milk Components, Pro-, Pre-, and Synbiotic Foods in Calcium Absorption and Bone Health Maintenance. Front Nutr 2020; 7: 182.
10) Ofek Shlomi N, Rao S, Patole S. Efficacy of interventions to improve hand hygiene compliance in neonatal units: a systematic review and meta-analysis. Eur J Clin Microb Infect Dis Office Public Eur Soc Clin Microb 2015; 34(5): 887-897.
11) Nilsson AG, Sundh D, Backhed F, Lorentzon M. Lactobacillus reuteri reduces bone loss in older women with low bone mineral density: a randomized, placebo-controlled, double-blind, clinical trial. J Int Med 2018; 284(3): 307-317.
12) Ohlsson C, Engdahl C, Fak F, Andersson A, Windahl SH, Farman HH, Moverare-Skrtic S, Islander U, Sjogren K. Probiotics Protect Mice from Ovariectomy-Induced Cortical Bone Loss. Plus One 2014; 9(3).
13) Parvaneh K, Ebrahimi M, Sabran MR, Karimi G, Hwei ANM, Abdul-Majeed S, Ahmad Z, Ibrahim Z, Jamaluddin R. Probiotics (Bifidobacterium longum) Increase Bone Mass Density and Upregulate Sparc and Bmp-2 Genes in Rats with Bone Loss Resulting from Ovariectomy. Biomed Res Int 2015; 2015.
14) Hou KJ, Lin CJ, Chen C, Wu BT, Zhu D, Zhong WJ, Wang XH, Xie X, Chen QM. Association of probiotics and bone mineral density in Chinese patients with type 2 diabetes. Biomed Res India 2017; 28(1): 129-133.
15) Lambert MNT, Thybo CB, Lykkeboe S, Rasmussen LM, Frette X, Christensen LP, Jeppesen PB. Combined bioavailable isoflavones and probiotics improve bone status and estrogen metabolism in postmenopausal osteopenic women: a randomized controlled trial. Am J Clin Nutr 2017; 106(3): 909-920.
16) McCabe LR, Irwin R, Schaefer L, Britton RA. Probiotic use decreases intestinal inflammation and increases bone density in healthy male but not female mice. J Cell Phys 2013; 228(8): 1793-1798.
17) Collins FL, Irwin R, Bierhalter H, Schepper J, Britton RA, Parameswaran N, McCabe LR. Lactobacillus reuteri 6475 Increases Bone Density in Intact Females Only under an Inflammatory Setting. Plus One 2016; 11(4).
18) Kweh BT, Lee HQ, Tan T, Rutgers J, Marion T, Tew KS, Bhalla V, Menon S, Oner FC, Fisher C, Tee JW. The role of spinal orthoses in osteoporotic vertebral fractures of the elderly population (age 60 years or older): systematic review. Global Spine J 2021; 11(6): 975-987.
19) Chiang SS, Pan TM. Antiosteoporotic Effects of Lactobacillus-Fermented Soy Skim Milk on Bone Mineral Density and the Microstructure of Femoral Bone in Ovariectomized Mice. J Agric Food Chem 2011; 59(14): 7734-7742.
20) Rodrigues FC, Castro ASB, Rodrigues VC, Fernandes SA, Fontes EAF, de Oliveira TT, Martino HSD, Ferreira C. Yacon Flour and Bifidobacterium longum Modulate Bone Health in Rats. J Med Food 2012; 15(7):664-670.
21) Howarth GS, Wang HR. Role of Endogenous Microbiota, Probiotics and Their Biological Products in Human Health. Nutrients 2013; 5(1): 58-81.
22) Chilton SN, Burton JP, Reid G. Inclusion of Fermented Foods in Food Guides around the World. Nutrients 2015; 7(1): 390-404.
23) Reid G, Sanders ME, Gaskins HR, Gibson GR, Mercenier A, Rastall R, Roberfroid M, Rowland I, Cherbut C, Klaenhammer TR. New scientific paradigms for probiotics and prebiotics. J Clin Gastroenterol 2003; 37(2): 105-118.
24) Kim JG, Lee E, Kim SH, Whang KY, Oh S, Imm JY. Effects of a Lactobacillus casei 393 fermented milk product on bone metabolism in ovariectomised rats. Int Dairy J 2009; 19(11): 690-695.
25) Saulnier DMA, Gibson GR, Kolida S. In vitro effects of selected synbiotics on the human faecal microbiota composition. Fems Microb Ecol 2008; 66(3): 516-527.
26) Kassian N, Feizi A, Aminorroaya A, Amini M. Probiotic and synbiotic supplementation could improve metabolic syndrome in prediabetic adults: A randomized controlled trial. Diabetes Metab Synd Clin Res Rev 2019; 13(5): 2991-2996.
27) Legette LL, Lee WH, Martin BR, Story JA, Arabshahi A, Barnes S, Weaver CM. Genistein, a phytoestrogen, improves total cholesterol, and Synergy, a prebiotic, improves calcium utilization, but there were no synergistic effects. Menop J North Am Menop Soc 2011; 18(8): 923-931.

Acknowledgments:
This work was supported by the Guangdong Provincial Basic and Research Fund Project (No. 2019A1515110630) and Foshan Science and Technology Bureau Project (No. 1920001000314) and the construction project of Foshan City's "14th Five-Year Plan" key specialty and special disease for Chinese medicine.

Corresponding Author:
Zucai Pang
Department of Orthopedics, Shunde Hospital of Guangzhou University of Chinese Medicine, Foshan, Guangdong 528333, China
Email: 1808860178@qq.com
(China)