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Original article

Milk intake increases bone mineral content through inhibiting bone resorption: Meta-analysis of randomized controlled trials

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SUMMARY

Background and aims: To clarify the effects of milk intake on bone mineral density (BMD) , bone mineral content (BMC) and bone metabolism markers.
Methods: We identified randomized controlled trials related to urinary N-telopeptide cross-links of type I collagen (NTx), serum osteocalcin, BMD and BMC listed on MEDLINE (January 1966–November 2010), Science Citation Index and PUBMED (updated till November 2010), China National Knowledge Infrastructure (1979–November 2010) etc.
Results: Eleven studies with a total of 2397 subjects were selected for meta-analysis. The osteocalcin in subjects who consumed milk decreased by 5.9 (95% confidence interval (CI) 7.23, 4.57) ng/ml in comparison to that in control treatment. Milk intake vs control treatment significantly decreased urine NTx by 5.41 (95% CI 10.35, 0.47) nmol/mmol. Moreover, the total body BMC in subjects who consumed milk increased significantly by 40.32 (95% CI 17.58, 63.05) g in comparison to that in control treatment. Milk intake vs control treatment increased total body BMD by 0.01 (95% CI -0.02, 0.03) g/cm^2 with borderline significance.
Conclusions: Milk intervention significantly attenuates bone loss through inhibiting bone metabolism.

Introduction

Osteoporosis is an increasing public health problem worldwide. The fractures caused by the bone density reduction and bone microstructure alteration result in a lower life quality. Calcium supplementation, protein supplementation, exercise, and hormone replacement therapy and so on have long been demonstrated to be the main strategies to prevent osteoporosis. Clinical trials have shown that calcium supplementation combined with Vitamin D can increase bone mineral density (BMD) and prevent bone loss in elderly women.[1] However, the association between dietary protein and osteoporosis are controversial. A prospective study indicated that higher consumption of animal protein had an increased risk of forearm fracture.[2] While a systematic review on 31 cross-sectional surveys showed a small positive effect of protein intake on lumbar spine BMD.[3]

Historically, milk has been widely consumed because of its excellent nutritional value.[4] Milk that contains several factors such as bioactive peptides, calcium, growth factors related to bone metabolism might affect both bone formation and bone resorption.[4] In particular, milk is a good source of bioavailable calcium compared with other food sources. During the latest several decades, RCTs on bone health suggested that milk intervention might increase BMD and bone mineral content (BMC). In the large, third National Health and Nutrition Examination Survey (NHANES III), they found that among women aged 20–49 year, BMC was 5.6% lower in those who consumed <1 serving of milk/d (low intake) than that in those who consumed >1 serving/d (high milk) during childhood ($p < 0.01$).[5] Cadogan et al. reported that the intervention group consuming, on average, 300 ml milk a day throughout the intervention trial had greater increases of BMD ($p = 0.017$) and BMC ($p = 0.009$) compared with the control group.[6] Liu et al. found that 45 g milk powder supplementation could increase serum osteocalcin (a biochemical marker for bone formation, $p < 0.05$) and decrease urinary hydroxyproline (a biochemical marker for bone

Abbreviations: RCTs, randomized controlled trials; BMD, bone mineral density; BMC, bone mineral content; NTx, N-telopeptide cross links of type I collagen; MBP, milk basic protein.

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resorption, $p < 0.05$) in Chinese women.[7] Aoe et al. found that 40 mg of milk basic protein (MBP) supplementation was able to significantly suppressed the urinary excretion of cross-linked N-teleopeptides of type-I collagen (NTx, a biochemical marker for bone resorption) in healthy adult women.[8] However, the effects of milk intake on BMD, BMC, and bone metabolism appear inconsistent in RCTs. Moreover, it's difficult to clarify whether the beneficial effects are from milk or from calcium because that calcium fortified milk was widely used in the studies on bone health and milk. Thus, a statistical method of combining these diverse data is needed to evaluate the usefulness of milk therapy. Meta-analysis combines or integrates the results of several studies to provide an increased statistical power for the quantitative identification of trends.[9]

To clarify the effects of milk intake on bone health, we identified all RCTs related to the effects of milk on bone mass and bone turnover markers and analyzed the effects of milk or calcium fortified milk on bone metabolism quantitatively.

Materials and methods

MEDLINE (January 1966–November 2011), the Cochrane Controlled Trials Register, EMBASE (1985–November 2011), Science Citation Index and PUBMED (updated till November 2011), China National Knowledge Infrastructure (1979–November 2011), VIP Database for Chinese Technical Periodicals (1989–November 2011), and Wanfang database (1982–November 2011) were used to search articles (in English and Chinese) that described RCTs investigating the effect of milk on bone metabolism.

In the RCTs, BMD and BMC were generally measured to assess the bone mass, and serum osteocalcin was generally used as a bone formation marker, urine NTx was generally used as bone resorption marker.[6,10,11] Hence, titles, abstracts, and subject headings in the databases were searched with the use of the following Boolean phrases: ("bone" or "osteoporosis" or "bone mass" or "BMD" or "BMC" or "osteocalcin" or "NTX") and ("milk" or "fortified milk"). We carried out a broad search for all studies with the Boolean phrases "diet" and ("osteoporosis" or "bone metabolism"). We also examined all references of related reviews and papers identified by the search. Additionally, we tried to contact the authors for the obtaining of unpublished data. Studies were selected for analysis if they met all of the following criteria: 1) subjects ingested milk products for at least 1 week; 2) the RCTs included a parallel control group; 3) Total body BMD, total body BMC, NTx or osteocalcin was used as an index of bone turnover. Studies were excluded if they are lack of indices of interest, lack of a control group, insufficient original data or baseline values. If the study sample was found to overlap with that in another article or if two articles described aspects of the same study, only the publication with the largest sample was used. If the study reported some comparisons, we included all comparisons in the meta-analysis.

Two researchers (De Fu Ma and Wei Zheng) extracted data independently. A data collection form was designed, and data were entered into the form twice to reduce input errors. The items entered in the form included participant characteristics, treatment duration, interventional design, and values of relevant indices (Total body BMD, total body BMC, NTx and osteocalcin) before and after milk or control treatments. Jadad Scores were used to measure the quality of the RCTs.[12] A numerical score between 0 and 5 was assigned as a rough measure of study design and reporting quality, 0 being the weakest and 5 the strongest. One point was assigned if the trial was either randomized or double-blind or in the case of an accurate description of the drop-out patients. Moreover, further points were given if randomization and blinding procedures were appropriate, whereas, instead, points were subtracted in the case of inappropriate descriptions of the same procedures. An overall score more than 3 indicated a good quality study. Two researchers rated study quality independently. There was 90% agreement on Jadad Scores. If the researchers disagreed, a final score was reached by discussion.

In this meta-analysis, we obtained the mean differences from the post-randomization baseline to after-treatment values for each trial and calculated the pooled standard deviation of the mean differences according to the standard method of Cochrane handbook.[13] Weighted mean difference was calculated by subtracting the mean difference of the control group from that of the treatment group. The inverse variance method was used to pool the weighted mean difference with STATA software (version 9.2; Stata Corp., College Station, TX, USA).[14] To assess the heterogeneity (apparent diversity in weighted mean differences across studies), we conducted a test based on χ^2 distribution ($p < 0.05$ is considered significant). Random-effects model was used as the method of combination for all the analyses showing significant heterogeneity .The funnel plot was performed to detect publication bias.

In addition, we performed subgroup analyses for osteocalcin by 4 variables one at a time: form of intervention, treatment length, race, and intervention subjects to identify impact factors that can influence the effects of milk intake according to the characters of the data.

Results

The trial flow chart was illustrated in Fig. 1. Our literature search identified 39 RCTs including 2 of them obtained from the reference lists. We also tried to contact the authors for unpublished data, but unfortunately none was obtained. 28 studies were excluded because of lack of indices of interest, lack of a control group, insufficient original data or baseline values. Thus, 11 studies (8 in English, 3 in Chinese) with a total of 2397 subjects were included in this meta-analysis.[4,6,10,11,15–22] The characteristics of the trials included were shown in Table 1. One study had quality score of four, 7 studies had quality score of three, and 3 studies had quality score

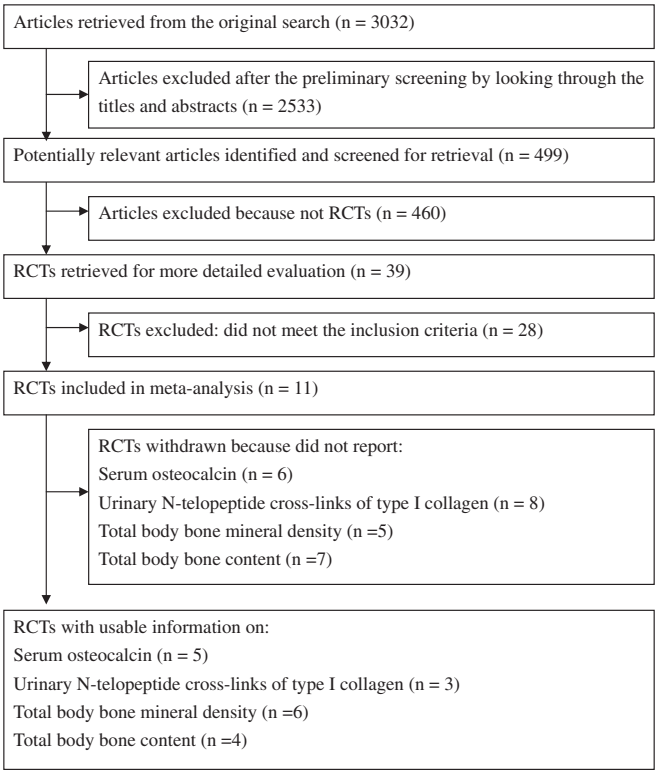

Fig. 1. Results of search for eligible studies.