REVIEW ARTICLE

Relationship between Dietary Acid Load and Bone Health in Post-menopausal Women: A Systematic Review

Leila Moghari[1], MSc;
Armin Ebrahimzadeh[2], MSc;
Zahra Shamekhi[3], PhD;
Nasrin Sharifi[1], PhD

[1]Research Center for Biochemistry and Nutrition in Metabolic Diseases, Kashan University of Medical Sciences, Kashan, Iran
[2]Nutrition Research Center, School of Nutrition and Food Sciences, Shiraz University of Medical Sciences, Shiraz, Iran
[3]Sepidan Bagherololoom Higher Education College, Shiraz University of Medical Sciences, Shiraz, Iran

Correspondence:
Nasrin Sharifi, PhD;
Research Center for Biochemistry and Nutrition in Metabolic Diseases, Basic Science Research Institute, Kashan University of Medical Sciences, Postal Code: 87159-73474, Kashan, Iran
Tel: +98 9133058234
Fax: +98 31 55620608
Email: sharifi-na@kaums.ac.ir
Received: 02 July 2024
Revised: 03 August 2024
Accepted: 08 September 2024

Abstract

Background: There is a lack of summarized reports of the relationship between dietary acid load (DAL) and bone health in post-menopausal women. Therefore, we aimed to design a systematic review and summarize eligible studies evaluating this association.

Methods: The present study was a systematic review. From the literature search on PubMed, Google Scholar, Scopus, and Medline until March 2020, six studies comprising 2 cross-sectionals, 2 cohorts, and 2 randomized control trials were selected and included in this study.

Results: Four studies revealed a significant correlation between DAL and osteoporosis in post-menopausal women. In two reviewed studies, a significant association was seen between DAL and BMD, but in this association was not obtained in n another study. In addition, out of two randomized clinical studies (RCTs), one showed positive changes in bone markers when PRAL was decreased; however, no change was obtained in another RCT.

Conclusion: The present study showed that post-menopausal women, especially those with a fracture history, may have a greater susceptibility to osteoporosis because of the detrimental effect of dietary acidity. In addition, DAL rather than protein might be the main risk factor for bone loss in this population. It should be noted that insufficient calcium intake may exacerbate bone loss following a high protein–high acid ash diet in these women.

Please cite this article as: Moghari L, Ebrahimzadeh A, Shamekhi Z, Sharifi N. Relationship between Dietary Acid Load and Bone Health in Post- menopausal Women: A Systematic Review. J Health Sci Surveillance Sys. 2024;12(4):361-369.

Keywords: Bone density, Dietary acid load, Post menopause, Systematic review

Introduction

Osteoporosis fracture is one of the most common chronic metabolic bone diseases in the world among the elderly. Bone destruction begins between the ages of 35-45 in both sexes.[1] Women are more vulnerable to developing osteoporosis compared with men.

In addition, the prevalence of osteoporosis in women is higher than in men due to lower estrogen levels after menopause.[2, 3] It is estimated that by 2025, osteoporosis fracture will have increased by 50%, and most of this increase will be in the elderly population, which is not only due to aging but also due to unhealthy diet and lifestyle.[4] Nutritional status is one of the factors affecting bone health.

Western diet has a high dietary acid load (DAL), leading to metabolic acidosis.[5] Cereal grains, salted foods, meats, fish, hard cheeses, and legumes are acid-based foods, while vegetables and fruits are alkaline-based foods.[6] Non-volatile acids are made from the metabolism of foods with high DAL. These nonvolatile acids are removed by the kidney so that acid-base homeostasis is maintained. Metabolic acidosis occurs if the production of the acids is greater

than the renal excretion capacity, or if the kidneys cannot excrete excess acid due to renal dysfunction.[7] According to the theory of acid ash, which was proposed nearly 50 years ago, bone is the main buffer system for neutralizing excess acid in the body due to carbonate and phosphate salts. Thus, alkaline salts delivered from the bone lead to osteoporosis.[6, 8]

The potential of diet to make acid in the body is defined as dietary acid load (DAL). DAL can be estimated using the information on nutrient intake from several formulas, but the two most important of them are NEAP (based on protein and potassium intake) and PRAL (based on the dietary phosphorus, protein, magnesium, and potassium).[9, 10] NEAP (net endogenous acid production) and PRAL (potential renal acid load) have been used in many studies to evaluate the relationship between DAL and BMD, while the outcomes are conflicting and mixed.

The question raised here is whether high DAL can lead to osteoporosis and bone loss. Many studies have shown that high DAL is related to increased urinary calcium excretion, decreased bone mineral content, and calcium loss.[11-20] However, some studies did not show any significant relationship between DAL with bone health.[21-28] Therefore, in the present systematic review, we aimed to assess the available evidence on the relationship of DAL with the risk of fractures and bone mineral density (BMD) by limiting the study population to post-menopausal women and considering PRAL or NEAP for estimating DAL.

Methods

Search Strategy

At first, we systematically searched the electronic databases such as Scopus, PubMed/Medline, and Google Scholar up to March 2020 for the studies on BMD and DAL in post-menopausal women. Furthermore, we used the reference lists of related articles to find more eligible papers. Our search terms were (dietary OR diet-related OR diet-induced OR diet OR diet-dependent) AND (acid-ash OR acid-base OR acid-base imbalance OR Acid-base equilibrium OR alkaline-ash OR acid load), AND (metabolic bone disorder OR osteopenia OR osteoporosis OR densitometry OR bone mineral density). For some unavailable studies, we sent emails to the authors to request the full text.

Outcome Measures

The outcome measures included diagnostic double-energy x-ray absorptiometry (DXA),[29] Quantitative computed tomography (QCT),[30] Quantitative ultrasound (QUS)[31] fracture risk,[32] calcium absorption,[33] and bone markers.[34]

All selected studies in our research used two validated methods to estimate DAL. First, potential renal acid load (PRAL) was calculated using the formula described by Remer and Manz:[9]

PRAL (mEq/d) = [0.0366 × phosphorus (mg/d)] + [0.4888 × protein intake (g/d)] - [0.0205 × potassium (mg/d)] – [0.0125 × calcium (mg/d)]-[0.0263 × magnesium (mg/d)]

Second, net endogenous acid production (NEAP) was estimated using the formula explained by Frassetto et al.:[10]

NEAP (mEq/d) = [54.5 × protein intake (g/d)/ potassium intake (mEq/d)]-10.2

Inclusion and Exclusion Criteria

The inclusion criteria for selecting studies were: 1) studies with the observational and clinical trial design, 2) postmenopausal women, 3) the indices of DAL estimated based on the evaluation of dietary intake (i.e. PRAL and NEAP), 4) the BMD and fracture risk as the primary or secondary outcomes, 5) as to clinical trials, only the studies that had a control group and had examined the effects of the different levels of DAL on BMD and bone markers among post-menopausal women, and 5) The studies published in English. The study types such as review, case reports, thesis, editorial, or commentary were excluded. In addition, any studies performed on cells and animal models were excluded. Bibliographic references of articles were inspected to search for extra studies. The two researchers independently determined which studies were eligible for review.

Data Items

Items considered in each report included country, year of publication, study design, age, sample size, target population, the methods and tools of DAL estimation, outcomes related to bone health, the assessment methods of BMD, intervention, and the study duration.

Data Extraction

Extraction of information from the included studies was performed independently by two authors and any differences in information extraction were discussed and resolved by them. Itemized tables were utilized to record pertinent information from each report.

Results

As shown in Figure 1, we found 165 articles. In the next stage, we excluded duplicates (n=28). Then, abstracts and titles were inspected, and 62 articles were excluded as they did not meet the criteria. The full text of the 75 remaining articles was assessed; 69 publications were removed (the reasons are shown in Figure 1).

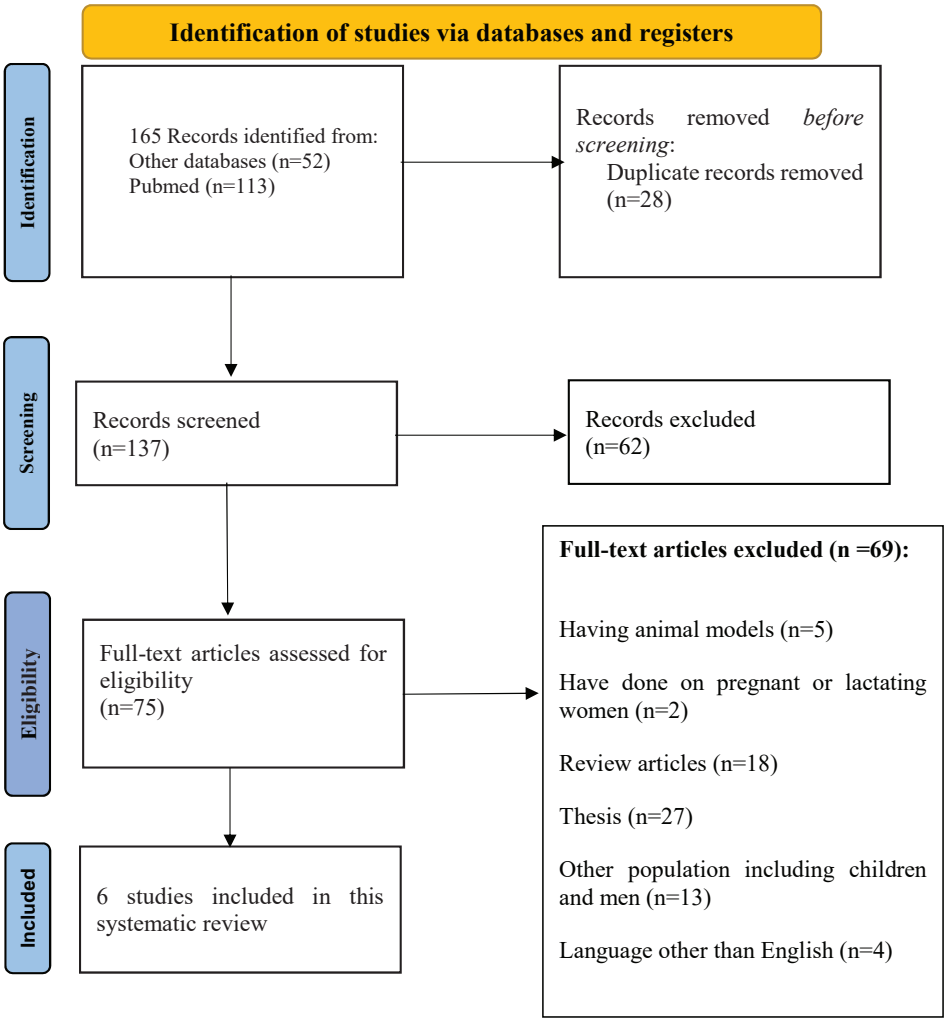

Figure 1: Literature search and review flowchart for study selection

Ultimately, six papers met the inclusion criteria and were included in the current systematic review. BMD was the study outcome in three included studies,[29-31] and the fracture risk and calcium absorption were the outcome variables in two studies.[32, 33] In two reviewed studies, a significant association was seen between DAL and BMD,[29-31] but in one study this association was not obtained.[30] In addition, out of two randomized clinical studies (RCTs), one showed positive changes in bone markers when PRAL was decreased;[34] however, no change was obtained in another RCT.[33]

Characteristics of the Reviewed Studies

Characteristics of the included studies are presented in Tables 1 and 2. Four studies had a cross-sectional and cohort design (Table 1), and two were RCTs (Table 2).

The Association between DAL and BMD

There was a statistically significant inverse relationship between DAL and bone mass in two included cross-sectional surveys.[29-31] The cohort study, included in our review, showed no significant correlation between DAL and bone mass.[30] In the study by Wynn et al. in 2009, 256 older ambulatory women, aged >70 years were divided into 2 subgroups: 120 with a fracture history and the other participants without it (n=145).[31] The result showed that the lower values of NEAP in the very old women were significantly associated with the higher broadband ultrasound attenuation (BUA) measured by bone ultrasound at the hill. However, such an association was not seen in women without fractures. In addition, there was an association between a higher potassium intake and a lower NEAP with a higher BUA.[31]

In the study of Shariati-Bafghi et al., 151 postmenopausal women aged 55 to 85 years were enrolled and dual-energy x-ray absorptiometry (DEXA) was employed to measure the lumbar spine and femoral neck BMDs. The participants' food intakes were obtained via a food frequency questionnaire (FFQ) with 168 items. Based on the formulas of Remer (PRAL) and Frassetto (NEAP), DAL was determined, and the subjects were divided into three groups. After adjustment of confounding variables, a significant inverse relationship was found between DAL and BMD in postmenopausal women, even with adequate calcium intake (>800 mg/day).[29]

Table 1: Features of the included observational studies

Author (year)	Country	Study design	Mean age	Sample size/ Population	Groups	DAL assessment method/ tool	Outcome/ Outcome assessment tool	Results
Wynn et al. (2008)[31]	Switzerland	Cross-sectional	80.4 y	401 PM women	2 subgroups: Women with a fracture history (n=256) and without a fracture history (n=145)	NEAP/FFQ	Achilles BMD/ QUS	Lower NEAP and higher potassium intake were associated with higher BUA.
Dargent-Molina et al. (2008)[32]	France	Prospective cohort	56.1 y	36,217 PM women	4 grouped according to the quartile of both calcium and protein intake	PRAL/ dietary questionnaire of 208 items	fracture risk	High acid ash- high protein diets were related to an increased fracture risk when the dietary calcium was low (<400 mg/1000 kcal)
Pedone et al. (2010)[30]	Italy	Cohort	74.8 y	497 PM women from IN CHIANTI study	3 groups according to the tertile of BMD	PRAL/EPIC questionnaire	Tibial BMD/ PQCT	No relationship between DAL and BMD in elderly women with a well-balanced diet.
Shariati-Bafghi et al. (2015)[29]	Iran	Cross-sectional	54 y	151 PM women	Tertiles of RNAE	NEAP,PRAL /FFQ	Lumbar spine and femoral neck BMD/ DEXA	The inverse relationship between DAL and BMD in PM women which was independent of the dietary calcium intake

BMD: Bone mineral density; BUA: Broadband ultrasound attenuation; DAL: Dietary acid load; DEXA: Dual x-ray absorptiometry; FFQ: Food frequency questionnaire; NEAP: Net endogenous acid production; PM: Post-menopausal; PRAL: Potential renal acid load; QUS: Quantitative ultrasound; RNAE: Renal net acid excretion; PQCT: Peripheral quantitative computed tomography

Table 2: Features of the included randomized clinical trial

Author (year)	Country	Study design	Total sample size	Study population	Age years	BMI (kg/m²)	Intervention and study group	Duration (weeks)	Outcomes	Results
Cao et al. (2011)[33]	USA	Randomized crossover design	16	Healthy, nonsmoking PM women	40–75	26.8 6	2 groups: Low PRAL and low protein (LPLP) High PRAL and high protein (HPHP)	15	Ca absorption IGF-I and PTH Serum Ca, Cr, CTX, OC, OPG, and RANKL	HPHP group: ↑ Ca absorption ↑ IGF-I and ↓PTH, No change in other biomarkers of bone metabolism
Gunn et al. (2015)[34]	New Zealand	Randomized controlled trial	143 Group A=50 Group B=50 Group C=43	Healthy PM women	50 - 70	25.3	Group A and B: consuming ≥9 servings of F&V/ day + bone resorption-inhibiting properties in Group B. Group c: control group	12	CTX P1NP urinary pH	Group B: ↓ (P1NP), and ↓ (CTX) in women with osteopenia Groups A and B: ↓ PRAL, ↑ urine pH ↓urinary calcium excretion. In all groups: ↑Urinary potassium.

BMI: Body mass index; Ca: Calcium; Cr: Creatinine; CTX: C-terminal telopeptide of type I collagen; F&V: Fruits and vegetables; IGF-1: Insulin-like Growth Factor-1; PM: Post-menopausal; P1NP: Procollagen type 1 N propeptide; PTH: Parathyroid hormone; OC: Osteocalcin; OPG: Osteoprotegerin; RANKL: Receptor activator of nuclear factor kappa-B ligand

In another study by Pedone et al. (2009), participants were divided into three groups based on baseline kidney function and body weight.[30] After 6 years of follow-up, the results revealed that there was no relationship between DAL and BMD in elderly women.

The Association of DAL with Fracture Risk

The prospective cohort study by Dargent-Molina examined the association of DAL with fracture risk in post-menopausal women. In that study, 2,408 women reported fractures during an eight-year follow-up period.[32] The study researchers concluded that there was no association between fracture risk and DAL or total intake of protein. However, in women with a low dietary calcium intake (<400 mg/1000 kcal), the increase in protein intake was related to a significantly increased the risk of fracture. Moreover, increased animal protein intake has been observed to increase the fracture risk.

The Relationship between DAL and Plasma Biomarkers of Bone Metabolism

In the two reviewed RCTs, the association between DAL and serum or plasma biomarkers of bone health was examined. However, only in one of them, the relevant association was reported.[34]

In a cross-over study by Cao et al.,[33] 16 postmenopausal women consumed two different types of dietary patterns; one was a low protein and low PRAL (LPLP) and the other was a high protein and high PRAL (HPHP) diet. Participants followed these diets for 7 weeks, with a 1-week washout period. Theresults showed that the HPHP diet significantly increased the Ca absorption and the levels of serum insulin-like Growth Factor-1 (IGF-1), and significantly decreased serum intact parathyroid hormone (PTH) concentrations in comparison to the LPLP diet. The researchers in this study concluded that a high-protein diet did not adversely affect bone health in post-menopausal women. In another included RCT conducted by Gunn et al.,[34] 100 healthy postmenopausal women (50 to 70 years old) were divided into two groups (groups A and B) to consume more than 9 servings of fruits and vegetables per day for three months. Group A was asked to eat a generic range of herbs/vegetables/fruit, whereas Group B was encouraged to take specific herbs/fruit/vegetables that had a bone resorption-inhibiting properties. Group C was a negative non-randomized control that consumed the usual diet. The study results showed that procollagen type I N propeptide (P1NP), a biomarker of bone formation, decreased significantly only in the group B. In addition, the C-terminal telopeptide of type I collagen (CTX), a biomarker of bone resorption, was significantly decreased in women with osteopenia compared with those with normal BMD in the group B. DAL and calcium loss in urine were decreased in both trial groups. Overall, the investigators of the mentioned study concluded that the increased intake of selected herbs, fruits, and vegetables might have positively effected bone turnover markers and calcium homeostasis.

Discussion

The present systematic review was conducted to summarize the results of studies reporting the relationship between DAL (estimated by NEAP and PRAL) and bone health in post-menopausal women. Six studies that had different experimental methods and outcome measurements were eligible for this systematic review.

Even though most included studies in the present systematic review revealed an inverse relationship between DAL and bone health, it is still too early to conclude about the effects of DAL on bone health and metabolism in post-menopausal women. Further prospective studies and clinical trials would be needed to prove such an association. In a recent systematic review that included healthy adults, although a significant weak negative relationship was reported between NEAP and BMD, there was not any association of PRAL with the BMD. Moreover, a high DAL was not associated to the risk of fractures.[35] A meta-analysis study conducted by Fenton et al. examined the effects of changes in net acid excretion (NAE), through diet manipulation, on osteoporosis and calcium balance. Their study result did not support the association between DAL and bone loss.[26] This inconsistency between the present study results and the two mentioned systematic reviews may be due to different inclusion criteria. We included studies that only investigated the association of DAL with bone health in postmenopausal women, while the mentioned systematic reviews included studies with male and female participants in different ages. Of note, bone loss in the elderly has been shown to occur more rapidly than bone loss in younger adults. On the other hand, with increasing age, the function of the kidneys decreases; this leads to a lower level of blood pH. As a result, the elderly is more prone to acidosis. Thus, any association between DAL and interested outcomes can be more likely identified in this population. In line with the present study, the results of studies, which only included the elderly, support the acid-ash hypothesis which suggests that high DAL can increase the risk of bone loss.[36-39]

In Pedone et al.'s study, no association was found between DAL and BMD in elderly women with a well-balanced diet. Due to a healthy lifestyle and high-quality diet, none of the participating groups was on either side of the diet spectrum. As a result, no inverse relationship was found between DAL and BMD in the mentioned study. Moreover, the 6-year span between

the onset and final BMD evaluation is too short to determine the effect of diet on BMD.[30]

In Wynn et al.'s study, researchers indicated that a lower amount of NEAP was related to a higher BUA, which was independent of confounders such as age, BMI, and osteoporosis.[31] However, this association was not seen in women without fractures, indicating that postmenopausal women with fractures were more sensitive than post-menopausal women without fractures. A similar result of Gunn et al.'s study indicates that women with osteopenia were more sensitive to DAL than those with normal BMD.[34]

The study by Dargent-Molina et al. found no significant association of protein intake with fracture risk in the general population; however, there was an elevated fracture risk in women who had a diet of high protein intake in the presence of low calcium intake.[32] The adverse effect of protein on DAL was shown under a low intake of calcium. When calcium intake is low, the intestinal absorption of calcium is not sufficient to compensate for increasing excreted calcium in the urine. The interaction between the intake of calcium and protein has been suggested by a few other studies on the effect of protein intake on bone metabolism. For example, in a large cohort of middle-aged Norwegian study, women with a low intake of calcium (<623 mg per day) and high non-dairy protein intake were twice as likely to have fractures as women with a high calcium and low non-dairy protein intake.[40] Similar relations were also found between the intake of animal protein and the risk of hip fracture which was increased 2.8 times with the calcium intake of less than 800 mg/day in either men or women.[41]

Here, we can mention the importance of protein in dairy products because they are good sources of calcium which can compensate for urinary calcium losses. These sources of animal protein have high biological value (HBV) and provide adequate calcium for the body. However, in Shariati-Bafghi et al.'s study, the inverse association between DAL and BMD in postmenopausal women was independent of their dietary calcium intake.[29] A possible reason for this finding may be that calcium sources were not reported in the mentioned study.

Another finding of Dargent-Molina et al.'s[32] study was a negative association between vegetable proteins and PRAL, and a positive association of animal proteins with PRAL, which is similar to the previous studies demonstrating the beneficial alkaline effect on bone health.[42-46] The results of a systematic review showed that in postmenopausal women, there was a positive association of vegetable and fruit intake with bone health.[44] According to a study on middle-aged women and men, eating less than five portions of vegetables and fruits a day increases the risk of hip fractures.[46] In other words, a diet that contains a higher amount of vegetal proteins can be considered less acidic. Vegetal proteins produce more alkali in the body compared to animal proteins.[47] In addition, fruits and vegetables contain phytochemicals that can help increase bone density.[48-50]

The study by Cao et al. demonstrated an increased fractional absorption of dietary Ca via receiving a diet with a high amount of protein and high PRAL (HPHP), compared to a diet with low protein and low PRAL (LPLP).[33] Then, the subsequent increased Ca absorption is compensated by an increased urinary Ca excretion. This result was also shown by other reports.[51-56] This suggests that DAL, rather than protein, contributes to an increase in urinary calcium excretion.[33, 53] Of note, the high DAL may not be only due to the high protein in the diet. There are some foods that have a low amount of protein and a high DAL, such as many grain products (brown rice, cornflakes, white bread, oat flakes, and white pasta(. On the other hand, the DAL of dairy products, such as milk and yogurt, is low, despite being high in protein.

In Gunn et al.'s study, reducing DAL by eating 9 servings of fruits/herbs/vegetables, in post-menopausal women, decreased urinary calcium excretion and increased the pH of urine.[34] However, the reduction in bone markers was only shown in a group who consumed fruits/herbs/vegetables that had a protective effect on bone resorption (Scarborough Fair Diet which included the herbs sage, dill, parsley, garlic, rosemary and thyme, and vegetables and fruits such as green beans, tomatoes, broccoli, cucumber, lettuce, oranges, and prunes). This result also demonstrated that the reduction of PRAL by consuming of fruits/herbs/vegetables without resorption-inhibiting properties was not adequate to decline bone markers.[34, 57]

The present systematic review had some limitations. Most of the included studies used food frequency questionnaire to assess nutrient intake and calculate DAL indices. Since the FFQ relies on the participants' memories, it is susceptible to measurement errors. Moreover, different methods were used for BMD assessment in the included studies. Finally, few small RCTs with a short duration had been available to be included in our systematic review. Therefore, it seems that further well-designed cohort studies and RCTs are recommended to shed light on the association of DAL with bone health in post-menopausal women.

Conclusion

Postmenopausal women, especially those with a fracture history, may have a greater susceptibility for osteoporosis because of the detrimental effect of dietary acidity. In addition, DAL rather than protein might be the main

risk factor of bone loss in this population. It should be noted that insufficient calcium intake may exacerbate bone loss following a high protein and high-acid ash diet in these women.

Authors' Contribution

LM and NS designed, supervised, and drafted the research. LM, AE, ZS, and NS were involved in the study design, searching databases, extracting data, and drafting the manuscript. All authors reviewed and confirmed the final draft of the manuscript.

Acknowledgment

The authors thank the Vice-Chancellor for Research and Technology of Kashan University of Medical Sciences and the Research Center for Biochemistry and Nutrition in Metabolic Diseases, Kashan University of Medical Sciences, Kashan, and Iran.

Funding

This research received no specific grant from any funding agency.

Conflict of Interest: None declared.

References

1 Shepherd AJ. An overview of osteoporosis. Altern Ther Health Med. 2004; 10(2):26-33. PMID: 15055091.

2 Ji MX, Yu Q. Primary osteoporosis in postmenopausal women. Chronic Dis Transl Med. 2015; 1(1):9-13. doi: 10.1016/j.cdtm.2015.02.006. PMID: 29062981; PMCID: PMC5643776.

3 Alswat KA. Gender Disparities in Osteoporosis. J Clin Med Res. 2017; 9(5):382-387. doi: 10.14740/jocmr2970w. PMID: 28392857; PMCID: PMC5380170.

4 Jia T, Byberg L, Lindholm B, Larsson T, Lind L, Michaëlsson K, et al. Dietary acid load, kidney function, osteoporosis, and risk of fractures in elderly men and women. Osteoporos Int. 2015; 26(2):563-70. doi: 10.1007/s00198-014-2888-x. PMID: 25224295.

5 López M, Moreno G, Lugo G, Marcano G. Dietary acid load in children with chronic kidney disease. Eur J Clin Nutr. 2020;74(Suppl 1):57-62. doi: 10.1038/s41430-020-0687-3. PMID: 32873958.

6 Frassetto L, Banerjee T, Powe N, Sebastian A. Acid balance, dietary acid load, and bone effects—a controversial subject. Nutrients. 2018; 10(4):517. doi: 10.3390/nu10040517. PMID: 29690515; PMCID: PMC5946302

7 Scialla JJ, Anderson CA. Dietary acid load: a novel nutritional target in chronic kidney disease? Adv Chronic Kidney Dis. 2013; 20(2):141-9. doi: 10.1053/j.ackd.2012.11.001. PMID: 23439373; PMCID: PMC3604792.

8 Wachman A, Bernstein D. Diet and osteoporosis. Lancet. 1968; 1(7549):958-9. doi: 10.1016/s0140-6736(68)90908-2. PMID: 4172759.

9 Remer T, Dimitriou T, Manz F. Dietary potential renal acid load and renal net acid excretion in healthy, free-living children and adolescents. Am J Clin Nutr. 2003; 77(5):1255-60. doi: 10.1093/ajcn/77.5.1255. PMID: 12716680. 10.

10 Frassetto LA, Todd KM, Morris Jr RC, Sebastian A. Estimation of net endogenous noncarbonic acid production in humans from diet potassium and protein contents. Am J Clin Nutr. 1998; 68(3):576-83. doi: 10.1093/ajcn/68.3.576. PMID: 9734733.

11 Sellmeyer DE, Stone KL, Sebastian A, Cummings SR. A high ratio of dietary animal to vegetable protein increases the rate of bone loss and the risk of fracture in postmenopausal women. Study of Osteoporotic Fractures Research Group. Am J Clin Nutr. 2001; 73(1):118-22. doi: 10.1093/ajcn/73.1.118. PMID: 11124760.

12 Wynn E, Krieg MA, Aeschlimann JM, Burckhardt P. Alkaline mineral water lowers bone resorption even in calcium sufficiency: alkaline mineral water and bone metabolism. Bone. 2009; 44(1):120-4. doi: 10.1016/j.bone.2008.09.007. PMID: 18926940.

13 Shi L, Libuda L, Schönau E, Frassetto L, Remer T. Long term higher urinary calcium excretion within the normal physiologic range predicts impaired bone status of the proximal radius in healthy children with higher potential renal acid load. Bone. 2012; 50(5):1026-31. doi: 10.1016/j.bone.2012.01.026. PMID: 22342797.

14 Sebastian A, Harris ST, Ottaway JH, Todd KM, Morris RC, Jr. Improved mineral balance and skeletal metabolism in postmenopausal women treated with potassium bicarbonate. N Engl J Med. 1994; 330(25):1776-81. doi: 10.1056/NEJM199406233302502. PMID: 8190153.

15 Jehle S, Hulter HN, Krapf R. Effect of potassium citrate on bone density, microarchitecture, and fracture risk in healthy older adults without osteoporosis: a randomized controlled trial. J Clin Endocrinol Metab. 2013; 98(1):207-17. doi: 10.1210/jc.2012-3099. PMID: 23162100.

16 Buclin T, Cosma M, Appenzeller M, Jacquet AF, Décosterd LA, Biollaz J, et al. Diet acids and alkalis influence calcium retention in bone. Osteoporos Int. 2001;12(6):493-9. doi: 10.1007/s001980170095. PMID: 11446566.

17 Barzel US. The effect of excessive acid feeding on bone. Calcif Tissue Res. 1969;4(2):94-100. doi: 10.1007/BF02279111. PMID: 5363276.

18 Arnett TR, Dempster DW. Effect of pH on bone resorption by rat osteoclasts in vitro. Endocrinology. 1986; 119(1):119-24. doi: 10.1210/endo-119-1-119. PMID: 3720660.

19 Bushinsky DA, Frick KK. The effects of acid on bone. Curr Opin Nephrol Hypertens. 2000; 9(4):369-79. doi: 10.1097/00041552-200007000-00008. PMID: 10926173.

20 Bushinsky DA, Smith SB, Gavrilov KL, Gavrilov LF, Li J, Levi-Setti R. Chronic acidosis-induced alteration in bone bicarbonate and phosphate. Am J Physiol Renal Physiol. 2003; 285(3):F532-9. doi: 10.1152/ajprenal.00128.2003. PMID: 12759230.

21 Oh MS. Irrelevance of Bone Buffering to Acid-Base Homeostasis in Chronic Metabolic Acidosis. Nephron. 1991;59(1):7-10. doi: 10.1159/000186509. PMID: 1944749.

22 Uribarri J, Douyon H, Oh MS. A re-evaluation of the urinary parameters of acid production and excretion in patients with chronic renal acidosis. Kidney Int. 1995; 47(2):624-7. doi: 10.1038/ki.1995.79. PMID: 7723250.

23 Oh MS. New perspectives on acid-base balance. Semin Dial. 2000; 13(4):212-9. doi: 10.1046/j.1525-139x.2000.00061.x. PMID: 10923347.

24 Macdonald HM, Black AJ, Aucott L, Duthie G, Duthie S, Sandison R, et al. Effect of potassium citrate supplementation or increased fruit and vegetable intake on bone metabolism in healthy postmenopausal women: a randomized controlled trial. Am J Clin Nutr. 2008; 88(2):465-74. doi: 10.1093/ajcn/88.2.465. PMID: 18689384.

25 Frassetto LA, Hardcastle AC, Sebastian A, Aucott L, Fraser WD, Reid DM, et al. No evidence that the skeletal non-response to potassium alkali supplements in healthy postmenopausal women depends on blood pressure or sodium chloride intake. Eur J Clin Nutr. 2012; 66(12):1315-22. doi: 10.1038/ejcn.2012.151. PMID: 23093337.

26 Fenton TR, Lyon AW, Eliasziw M, Tough SC, Hanley DA. Meta-analysis of the effect of the acid-ash hypothesis of osteoporosis on calcium balance. J Bone Miner Res. 2009; 24(11):1835-40. doi: 10.1359/jbmr.090515. PMID: 19419322.

27 Fenton TR, Eliasziw M, Tough SC, Lyon AW, Brown JP, Hanley DA. Low urine pH and acid excretion do not predict bone fractures or the loss of bone mineral density: a prospective cohort study. BMC Musculoskelet Disord. 2010; 11:88. doi: 10.1186/1471-2474-11-88. PMID: 20459740; PMCID: PMC2890599.

28 Mardon J, Habauzit V, Trzeciakiewicz A, Davicco MJ, Lebecque P, Mercier S, et al. Long-term intake of a high-protein diet with or without potassium citrate modulates acid-base metabolism, but not bone status, in male rats. J Nutr. 2008; 138(4):718-24. doi: 10.1093/jn/138.4.718. PMID: 18356326.

29 Shariati-Bafghi SE, Nosrat-Mirshekarlou E, Karamati M, Rashidkhani B. Higher dietary acidity is associated with lower bone mineral density in postmenopausal iranian women, independent of dietary calcium intake. Int J Vitam Nutr Res. 2014;84(3-4):206-17. doi: 10.1024/0300-9831/a000207. PMID: 26098484.

30 Pedone C, Napoli N, Pozzilli P, Lauretani F, Bandinelli S, Ferrucci L, et al. Quality of diet and potential renal acid load as risk factors for reduced bone density in elderly women. Bone. 2010; 46(4):1063-7. doi: 10.1016/j.bone.2009.11.031. PMID: 20005315; PMCID: PMC2881463.

31 Wynn E, Lanham-New SA, Krieg MA, Whittamore DR, Burckhardt P. Low estimates of dietary acid load are positively associated with bone ultrasound in women older than 75 years of age with a lifetime fracture. J Nutr. 2008; 138(7):1349-54. doi: 10.1093/jn/138.7.1349. PMID: 18567759.

32 Dargent-Molina P, Sabia S, Touvier M, Kesse E, Bréart G, Clavel-Chapelon F, et al. Proteins, dietary acid load, and calcium and risk of postmenopausal fractures in the E3N French women prospective study. J Bone Miner Res. 2008; 23(12):1915-22. doi: 10.1359/jbmr.080712. PMID: 18665794; PMCID: PMC2929535.

33 Cao JJ, Johnson LK, Hunt JR. A diet high in meat protein and potential renal acid load increases fractional calcium absorption and urinary calcium excretion without affecting markers of bone resorption or formation in postmenopausal women. J Nutr. 2011; 141(3):391-7. doi: 10.3945/jn.110.129361. PMID: 21248199.

34 Gunn CA, Weber JL, McGill AT, Kruger MC. Increased intake of selected vegetables, herbs and fruit may reduce bone turnover in post-menopausal women. Nutrients. 2015; 7(4):2499-517. doi: 10.3390/nu7042499. PMID: 25856221; PMCID: PMC4425157.

35 Gholami F, Naghshi S, Samadi M, Rasaei N, Mirzaei K. Dietary Acid Load and Bone Health: A Systematic Review and Meta-Analysis of Observational Studies. Front Nutr. 2022; 9:869132. doi: 10.3389/fnut.2022.869132. PMID: 35600825; PMCID: PMC9120865.

36 New SA, MacDonald HM, Campbell MK, Martin JC, Garton MJ, Robins SP, et al. Lower estimates of net endogenous noncarbonic acid production are positively associated with indexes of bone health in premenopausal and perimenopausal women. Am J Clin Nutr. 2004; 79(1):131-8. doi: 10.1093/ajcn/79.1.131. PMID: 14684409.

37 de Jonge EAL, Koromani F, Hofman A, Uitterlinden AG, Franco OH, Rivadeneira F, et al. Dietary acid load, trabecular bone integrity, and mineral density in an ageing population: the Rotterdam study. Osteoporos Int. 2017; 28(8):2357-2365. doi: 10.1007/s00198-017-4037-9. PMID: 28405729; PMCID: PMC5524850.

38 Macdonald HM, New SA, Fraser WD, Campbell MK, Reid DM. Low dietary potassium intakes and high dietary estimates of net endogenous acid production are associated with low bone mineral density in premenopausal women and increased markers of bone resorption in postmenopausal women. Am J Clin Nutr. 2005; 81(4):923-33. doi: 10.1093/ajcn/81.4.923. PMID: 15817873.

39 Mangano KM, Walsh SJ, Kenny AM, Insogna KL,

Kerstetter JE. Dietary acid load is associated with lower bone mineral density in men with low intake of dietary calcium. J Bone Miner Res. 2014; 29(2):500-6. doi: 10.1002/jbmr.2053. PMID: 23873776; PMCID: PMC3946957.

40 Meyer HE, Pedersen JI, Løken EB, Tverdal A. Dietary factors and the incidence of hip fracture in middle-aged Norwegians. A prospective study. Am J Epidemiol. 1997 Jan 15;145(2):117-23. doi: 10.1093/oxfordjournals.aje.a009082. PMID: 9006308.

41 Sahni S, Cupples LA, Mclean RR, Tucker KL, Broe KE, Kiel DP, et al. Protective effect of high protein and calcium intake on the risk of hip fracture in the Framingham offspring cohort. Bone Miner Res. 2010 Dec;25(12):2770-6. doi: 10.1002/jbmr.194. Epub 2010 Jul 26. Erratum in: J Bone Miner Res. 2011; 26(2):439. PMID: 20662074; PMCID: PMC3179277.

42 New SA, Robins SP, Campbell MK, Martin JC, Garton MJ, Bolton-Smith C, et al. Dietary influences on bone mass and bone metabolism: further evidence of a positive link between fruit and vegetable consumption and bone health? Am J Clin Nutr. 2000; 71(1):142-51. doi: 10.1093/ajcn/71.1.142. PMID: 10617959.

43 Macdonald HM, New SA, Golden MH, Campbell MK, Reid DM. Nutritional associations with bone loss during the menopausal transition: evidence of a beneficial effect of calcium, alcohol, and fruit and vegetable nutrients and of a detrimental effect of fatty acids. Am J Clin Nutr. 2004; 79(1):155-65. doi: 10.1093/ajcn/79.1.155. PMID: 14684412.

44 Hamidi M, Boucher BA, Cheung AM, Beyene J, Shah PS. Fruit and vegetable intake and bone health in women aged 45 years and over: a systematic review. Osteoporos Int. 2011; 22(6):1681-93. doi: 10.1007/s00198-010-1510-0. PMID: 21165601.

45 Byberg L, Bellavia A, Orsini N, Wolk A, Michaëlsson K. Fruit and vegetable intake and risk of hip fracture: a cohort study of Swedish men and women. Bone Miner Res. 2015; 30(6):976-84. doi: 10.1002/jbmr.2384. PMID: 25294687.

46 Tucker KL, Hannan MT, Chen H, Cupples LA, Wilson PW, Kiel DP. Potassium, magnesium, and fruit and vegetable intakes are associated with greater bone mineral density in elderly men and women. Am J Clin Nutr. 1999; 69(4):727-36. doi: 10.1093/ajcn/69.4.727. PMID: 10197575.

47 Schneider DL, Barrett-Connor EL. Urinary N-telopeptide levels discriminate normal, osteopenic, and osteoporotic bone mineral density. Arch Intern Med. 1997; 157(11):1241-5. PMID: 9183236.

48 Remer T, Manz F. Potential renal acid load of foods and its influence on urine pH. Arch Intern Med. 1997; 157(11):1241-5. PMID: 9183236.

49 Mühlbauer RC, Lozano A, Reinli A. Onion and a mixture of vegetables, salads, and herbs affect bone resorption in the rat by a mechanism independent of their base excess. J Bone Miner Res. 2002; 17(7):1230-6. doi: 10.1359/jbmr.2002.17.7.1230. PMID: 12096836.

50 Mühlbauer RC, Lozano A, Reinli A, Wetli H. Various selected vegetables, fruits, mushrooms and red wine residue inhibit bone resorption in rats. J Nutr. 2003; 133(11):3592-7. doi: 10.1093/jn/133.11.3592. PMID: 14608079.

51 Kerstetter JE, O'Brien KO, Caseria DM, Wall DE, Insogna KL. The impact of dietary protein on calcium absorption and kinetic measures of bone turnover in women. J Clin Endocrinol Metab. 2005; 90(1):26-31. doi: 10.1210/jc.2004-0179. PMID: 15546911.

52 Kerstetter JE, O'Brien KO, Insogna KL. Dietary protein affects intestinal calcium absorption. Am J Clin Nutr. 1998; 68(4):859-65. doi: 10.1093/ajcn/68.4.859. PMID: 9771863.

53 Hunt JR, Johnson LK, Fariba Roughead Z. Dietary protein and calcium interact to influence calcium retention: a controlled feeding study. Am J Clin Nutr. 2009; 89(5):1357-65. doi: 10.3945/ajcn.2008.27238. PMID: 19279077.

54 Mahalko JR, Sandstead HH, Johnson L, Milne DB. Effect of a moderate increase in dietary protein on the retention and excretion of Ca, Cu, Fe, Mg, P, and Zn by adult males. Am J Clin Nutr. 1983; 37(1):8-14. doi: 10.1093/ajcn/37.1.8. PMID: 6849284.

55 Hegsted M, Linkswiler HM. Long-term effects of level of protein intake on calcium metabolism in young adult women. J Nutr. 1981; 111(2):244-51. doi: 10.1093/jn/111.2.244. PMID: 7463168.

56 Zemel M. Calcium utilization: effect of varying level and source of dietary protein. Am J Clin Nutr. 1988; 48(3 Suppl):880-3. doi: 10.1093/ajcn/48.3.880. PMID: 3414594.

57 Gunn CA, Weber JL, Kruger MC. Midlife women, bone health, vegetables, herbs and fruit study. The Scarborough Fair study protocol. BMC Public Health. 2013; 13:23. doi: 10.1186/1471-2458-13-23. PMID: 23305630; PMCID: PMC3552690.