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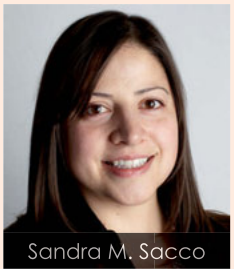
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Flaxseed to maintain bone health during aging:
what do the human studies tell us?

KEYWORDS: aging, alpha-linolenic acid, bone, flaxseed, lignans, osteoporosis

Abstract: Flaxseed consumption is associated with health benefits, mainly due to its alpha-linolenic acid (ALA) and lignan content. While there is no direct evidence that whole ground flaxseed modulates bone metabolism, epidemiological studies suggest that higher intakes of ALA, may support bone health in aging men and women. Further investigation is needed to determine whether and how flaxseed and its components affect skeletal health during aging, and if baseline bone health modulates the response. It is also important to consider that flaxseed is a rich source of many healthful components - ALA, lignans, fibre, protein, micronutrients – that support overall health and have a role in prevention of other chronic diseases.

INTRODUCTION

Osteoporosis is a disease characterized by low bone mass and microarchitectural deterioration of bone tissue, leading to an increased risk of fragility fractures (1). Once a fragility fracture occurs, quality of life often declines substantively due to chronic pain and a loss of independence. The once simplest of tasks may no longer be possible, i.e. personal care including dressing and bathing; preparing meals; holding or lifting a small child (1). In addition to its large personal toll, osteoporosis places a substantial burden on the economy. More than 200 million people worldwide are affected with osteoporosis and in developed countries, the lifetime risk for sustaining a fracture is similar to that for coronary heart disease (2). Among Canadians, osteoporotic fractures are more common than heart attack, stroke and breast cancer combined (1). The postmenopausal period is a particularly vulnerable time as the loss of oestrogen production by the ovaries heightens the risk of fragility fracture. Men typically experience an accelerated incidence of fragility fracture later in life, during their mid to late seventies (3).
Human data demonstrate that specific nutrients, especially calcium and vitamin D, support the development and maintenance of bone mass throughout the lifespan (4-6). n-3 polyunsaturated fatty acids (n3 PUFA) and phytoestrogens may also support bone health (7-10). Flaxseed is one example of a food that is rich in n3 PUFA, specifically alpha-linolenic acid (ALA), as well as phytoestrogens such as the lignan, secoisolariciresinol diglycoside (SDG). The global demand for flaxseed is rising largely due to its reported health benefits (11): improved glycemic control (12) and blood lipids (13); and reduced risk of developing breast cancer (14). The present paper discusses flaxseed and bone health, focusing on findings from human research including epidemiological and clinical trials that investigated whether and how flaxseed and its components may support bone health during aging.

FLAXSEED

Flaxseed contains exceptionally high amounts of n3 PUFA, mainly ALA (19-25 percent by weight) (15-17), and lignans (0.165-0.375 percent by weight) (18-21). ALA mainly undergoes beta-oxidation for production of energy. However, it may also decrease the n6 PUFA production of pro-inflammatory compounds as a result of their competition for the same series of enzymes that are shared for n3 and n6 PUFA conversion (22). SDG and other flax lignans (i.e. matairesinol, pinoresinol, lariciresinol) are metabolized by the action of colonic microflora into the mammalian lignans enterodiol and enterolactone (23) that may regulate oestrogen signalling (24).

INCORPORATING FLAXSEED INTO THE DIET

Flaxseed is an attractive food to consume because it contains appreciable levels of essential nutrients (including n3 PUFA) and other healthful components such as fibre, lignans and plant sterols. It is also relatively easy to incorporate whole ground flaxseed or milled flaxseed into foods or to add it directly to the diet. Commonly consumed food products that

may contain flaxseed include breads, cereals, cereal bars, and pasta. In addition, eggs may contain ALA if chickens were fed a diet rich in flaxseed (25). Other foods such as milk and yogurt can be enriched with flaxseed oil during production to obtain appreciable levels of ALA (Table 1). Reported ALA levels in selected products containing flaxseed or flaxseed oil range from 0.16-0.80 g (Table 1) while lignan levels have been reported to reach up to 3770 ug per serving of flaxseed-enriched bread (20).

	ALA Content
Nutrient Reference Values	
EFSA Dietary Reference Value (Adequate Intake)	0.5%§
IOM Dietary Reference Intake (Adequate Intake)	1.1-1.6 g
Foods Containing ALA	
Flaxseed Oil (1 tablespoon)	7.30 g
Canola Oil (1 tablespoon)	1.30 g
Soybean Oil (1 tablespoon)	0.92 g
Corn Oil (1 tablespoon)	0.81 g
Flaxseed Bread (1 slice, Dempster's® Whole Grains™ Flax)	0.80 g
Cereal (55 g, Nature's Path Pumpkin Flax Plus® Granola)	0.45 g
Cereal Bar (1 bar, Kashi® Chewy Granola Bars Honey Almond Flax)	0.30 g
Pasta (56 g, DeBoles Gluten Free Rice Angel Hair Plus Golden Flax)	0.32 g
Milk (250 mL, Natrel Omega-3 1% Milk)	0.30 g
Yogurt (100 g, Astro® BioBest® Omega 3 Yogurt)	0.30 g
Eggs (1 egg, Land O Lakes® All Natural Brown Eggs)	0.16 g

Table 1. Alpha linolenic acid (ALA) nutrient reference values* and content of foods per serving‡.
* Based on adult males and famales (36, 41).
‡ ALA content as reported by the USDA nutrient database for oils (17), and as reported in product Nutrition Facts tables.
§ Percentage of total dietary energy intake (41).
EFSA = European Food Safety Authority, IOM = Institute of Medicine, USDA = US Department of Agriculture.

EPIDEMIOLOGIC DATA

To date, no studies have examined if long-term consumption of whole flaxseed, flaxseed oil or flaxseed lignans is associated with BMC or BMD or risk of fragility fracture. This may be due to the fact that the components of flaxseed of greatest research interest (i.e. ALA, lignans) are also found in foods that are common in the diet of multiple European and North American populations (26-28). Thus, total intakes of ALA (i.e. oils, fish, grains, beans, seeds, vegetables) and lignans (grains, beans, seeds, vegetables, fruits) from all dietary sources and supplementation with ALA or lignan supplements as well as markers of total intakes (i.e. ALA content in red blood cells, urinary lignan excretion) have been commonly studied in relation to various health outcomes (7-10, 29-34). A few studies have examined if n3 PUFA, lignans, or their metabolites are associated with BMC, BMD and/or risk of fragility fracture (7-10, 29-31). More studies have been conducted in postmenopausal women than premenopausal women and men.

With regards to ALA, Orchard et al (2010) examined the relationship between dietary intake of fatty acids and fracture risk in postmenopausal women from the Women's Health Initiative (29). A food frequency questionnaire was completed at baseline and total fractures and fractures at the hip were measured after an average follow-up of 7.8 years. No association between ALA or total n3 PUFA intakes and fracture were observed (29). The authors later noted that plant foods high in ALA have become common ingredients in many food products, making it more difficult for ALA intake to be measured by questionnaires and nutrient databases (8). In addition, n3 PUFA supplementation use was not recorded (29). Thus, in a subsequent study, Orchard et al (2013) measured n3 PUFA levels in red blood cells, a biomarker of total n3 PUFA exposure (35), to examine the association between n3 PUFA levels in red blood cells and risk of hip fracture (8). The study was a nested case-control study within the Women's Health Initiative. Interestingly, higher ALA and total n3 PUFA contents in red blood cells were associated with a 56 percent and 45 percent lower risk of hip fracture, respectively (8). In addition, women that had red blood cells with the highest ratio of n6/n3 had twice the risk of hip fracture compared to women that had red blood cells with the lowest n6/n3 ratio (8). Thus, higher red blood cell n3 PUFA content, which is a marker of n3 PUFA dietary intake, may be predictive of a lower risk of fragility fracture at the hip in postmenopausal women.

In the Framingham Osteoporosis Study, older men and women completed a semi-quantitative food frequency questionnaire that identified fatty acid consumption including the n3-, n6- and total PUFA (9). Subjects were followed over 18 years during which the incidence of hip fracture was recorded. The results from this study demonstrated that the highest quartile of ALA intake was associated with a 56 percent lower risk for hip fracture than those in the lowest quartile. Interestingly, average ALA intake was calculated to be approximately 1.03-1.05 g/day, lower than the daily reference intake of ALA of adult women (1.1 g/day) and men (1.6 g/day) as set out by the Institute of Medicine (IOM) (36). The estimated average ALA intake in the highest quartile was 1.39 g/day (9). A similar study by the same authors observed no relationship between ALA consumption and hip BMD (30). These data support the idea that ALA protects the microstructure of bone. Using data collected within the Rancho Bernardo Study, Weiss et al (2005) reported that a lower ratio of linoleic acid to ALA and was associated with a higher BMD at the hip in older men as well as postmenopausal women who were or were not using hormone therapy (10). Both users and non-users of hormone therapy were included in this study since preliminary analyses demonstrated a significant interaction between hormone therapy and PUFA on BMD (10). This study demonstrated that the observed link between the ratio of n6/n3 PUFA and hip BMD was independent of hormone therapy use. In contrast, a higher n6 to n3 PUFA ratio was associated with a lower BMD at the lumbar spine in women not using hormone therapy. Thus, the interaction between n6 and n3 PUFA intake and hormone therapy use was site-specific.

With regards to lignans, a cross-sectional study was

conducted to determine the relationship between urinary mammalian lignan excretion and BMD in postmenopausal women that were classified as healthy, osteopenic or osteoporotic (7). Urinary enterolactone and enterodiol levels and BMD at the lumbar vertebrae, femur neck and Ward's triangle were measured. Women with osteoporosis had lower urinary excretion of enterolactone (7). In addition, greater urinary excretion of enterodiol was associated with a higher BMD at the lumbar vertebrae, femur neck and Ward's triangle. These results suggest that lignans may be linked to healthier bone mass in postmenopausal osteopenic/ osteoporotic women. Contrary to these findings, others have observed that a greater urinary excretion of the mammalian lignan enterolactone is not associated with BMD at the radius and that it is positively associated with cortical bone loss in healthy Danish postmenopausal women (31). The contradictory findings from both studies may be due to population differences. The positive association between urinary lignan excretion and BMD was observed in osteoporotic and osteopenic women (7), while the positive association between urinary lignan excretion and bone loss was observed in healthy postmenopausal women (31). Clinical trials are required to compare the effects of lignan intake and bone parameters in healthy women versus women with osteopenia or osteoporosis to clarify this relationship.
In summary, epidemiological evidence points towards a positive relationship between ALA or the ratio of linoleic acid to ALA and bone health in the aging population. The link between lignans and bone health is less clear and has been less studied. Further study of this association is warranted using established biomarkers of fatty acid (i.e. PUFA levels in red blood cells) and lignan (i.e. urinary lignans) intake and bone health.

CLINICAL DATA FROM RANDOMIZED CONTROLLED TRIALS

In contrast to existing epidemiologic data that have investigated whether flaxseed components or their metabolites are associated with bone health, clinical trials have mainly examined the skeletal effects of feeding whole flaxseed. In a randomized control trial that investigated the effects of whole ground flaxseed on bone health, healthy postmenopausal women (normal BMD) received either 40g of ground flaxseed or a wheat-based placebo daily for 3 months (37). There were no benefits to markers of bone formation (i.e. bone-specific alkaline phosphatase) or bone resorption (i.e. tartrate-resistant acid phosphatase, deoxypyridinoline, helical peptide) with flaxseed consumption. Similar observations were reported in another study of healthy postmenopausal women who consumed 25g of ground flaxseed or soy flour or wheat flour (placebo) that were incorporated into muffins (38). At the end of the 16-week study, no difference in the bone resorption marker urinary deoxypyridinoline was observed among groups (38). While a change in total urinary lignan excretion was inversely correlated to the change in serum bone alkaline phosphatase, suggesting that higher lignan intake may be linked to lower bone formation, similar levels in bone-specific alkaline phosphatase was observed among groups. A longer intervention (1 year) randomized healthy postmenopausal women to 40 g of either flaxseed or wheat germ placebo per day for 12 months, half of which was incorporated within 2 slices of bread and half of which was ground and added to foods such as cereal, juice and yogurt (39). Flaxseed did not protect against the loss of BMD at the lumbar vertebrae or femur neck. Taken together, these clinical studies (37-39) demonstrate that flaxseed does not provide a clear benefit to bone health.
The findings from the randomized control trials differ from the findings of epidemiological studies that observed positive associations between ALA and markers of bone health. It is possible that flaxseed exerts its effects on bone metabolism during periods of rapid bone loss such as that seen during osteopenia or osteoporosis. It is also possible that lifelong intakes of ALA influence bone metabolism more than shorter-term interventions in individuals who likely consumed relatively low levels on a regular basis. Further study is required to confirm these hypotheses. There is also the consideration that intervention with higher levels of ALA or lignans may be needed to achieve a change in bone metabolism. Considering that 25-40g of flaxseed were consumed in the randomized controlled studies, the ALA intake may have easily ranged from 5.1 g to 9.1g per day, exceeding the IOM Dietary Reference Intake of 1.1g and 1.6g per day for adult women and men, respectively (36). These levels are much higher than the ALA intakes (1.03/1.39 g per day) that were reported in the epidemiological studies discussed earlier (8-10, 30). The reasons for discrepancies in the results observed between the clinical and epidemiological studies are unclear. It is possible that a higher intake in ALA in the epidemiological studies is also a marker for a healthier dietary or lifestyle pattern.
One randomized control trial has investigated the effects of flaxseed lignans on total and lumbar spine bone mineral content (BMC) and BMD in older adults that underwent cardiovascular training (40). In this study, older adult men and postmenopausal women were treated with a lignan complex (1350 mg) providing 543 mg SDG daily for 6 weeks while completing 30-60 minutes of walking, 6 days per week. No effects on lumbar and total BMC and BMD were observed (40).

CONCLUSIONS AND FUTURE DIRECTIONS

While there is no direct evidence that whole ground flaxseed modulates bone metabolism - either favourably or adversely - data from human studies suggest that higher intakes of ALA, abundant in flaxseed, may support bone health in aging men and women. Prospective studies are needed to establish potential benefits of flaxseed consumption to bone health. Future studies are also needed to determine long term benefits to bone health, particularly in men and women who have existing low bone mass (osteopenia) or osteoporosis. While data regarding flaxseed and bone health are not definitive, it is important to consider that flaxseed is a rich source of many healthful components - ALA, lignans, fibre, protein, micronutrients - that support overall health and have a role in prevention of other chronic diseases.

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REFERENCES AND NOTES

1. Osteoporosis Canada: http://www.osteoporosis.ca/osteoporosis-and-you/what-is-osteoporosis/ (last checked on Feb. 18 2014).
2. Kanis J.A., on behalf of the World Health Organization Scientific Group. Assessment of osteoporosis at the primary health care level., WHO Collaborating Centre for Metabolic Bone Diseases, University of Sheffield (2007).
3. Khosla S., Amin S., Orwolle E., Endocr Rev, **29(4)**, 441-464 (2008).
4. Braegger C., Campoy C., et al., J Pediatr Gastroenterol Nutr, **56(6)**, 692-701 (2013).
5. Reid I.R., Mason B., et al., Am J Med, **119(9)**, 777-785 (2006).
6. Chung M., Lee J., Terasawa T., et al., Ann Intern Med, **155(12)**,827-838 (2011).
7. Kim M.K., Chung B.C., et al., Clin Endocrinol (Oxf), **56(3)**, 321-328 (2002).
8. Orchard T.S., Ing S.W., et al., J Bone Miner Res, **28(3)**, 505-515 (2013).
9. Farina E.K., Kiel D.P., et al., J Nutr, **141(6)**, 1146-1153 (2011).
10. Weiss L.A., Barrett-Connor E., von Muhlen D., Am J Clin Nutr, **81(4)**, 934-938 (2005).
11. Manitoba Agriculture, Food and Rural Development: http://www.gov.mb.ca/agriculture/market-prices-and-statistics/crop-statistics/pubs/crop_flax_sector.pdf (last checked on Feb. 18 2014).
12. Hutchins A.M., Brown B.D., et al., Nutr Res, **33(5)**, 367-375 (2013).
13. Pan A., Yu D., Demark-Wahnefried W., et al., Am J Clin Nutr, **90(2)**, 288-297 (2009).
14. Lowcock E.C., Cotterchio M., Boucher B.A., Cancer Causes Control, **24(4)**, 813-816 (2013).
15. Flaxseed in Human Nutrition, Edited by Thompson L.U. and Cunnane S.C., Ed. AOAC Press, Champaign, Illinois, USA (2003).
16. Sacco S.M., Jiang J.M., et al., Menopause, **16(3)**, 545-554 (2009).
17. USDA Nutrient Database: http://www.nal.usda.gov/fnic/foodcomp/search/ (last checked on Feb. 18 2014).
18. Milder I.E., Arts I.C., van de Putte B., et al., Br J Nutr, **93(3)**, 393-402 (2005).
19. Penalvo J.L., Haajanen K.M., Botting N., et al., J Agric Food Chem, **53(24)**, 9342-9347 (2005).
20. Thompson L.U., Boucher B.A., Liu Z., et al., Nutr Cancer, **54(2)**, 184-201 (2006).
21. Smeds A.I., Eklund P.C., et al., J Agric Food Chem, **55(4)**, 1337-1346 (2007).
22. Calder P.C., Biochimie, **91(6)**, 791-795 (2009).
23. Thompson L.U., Robb P., Serraino M., et al., Nutr Cancer, **16(1)**, 43-52 (1991).
24. Penttinen P., Jaehrling J., et al., Endocrinology, **148(10)**, 4875-4886 (2007).
25. Antruejo A., Azcona J.O., et al., Br Poult Sci, **52(6)**, 750-760 (2011).
26. Singh S.R., Levine M.A., Can J Clin Pharmacol, **13(2)**, e240-e250 (2006).
27. Mazur W.M., Wähälä K., et al., Br J Nutr, **79(1)**, 37-45 (1998).
28. Mazur W., Baillieres Clin Endocrinol Metab, **12(4)**, 729-742 (1998).
29. Orchard T.S., Cauley J.A., et al., Am J Clin Nutr, **92(6)**, 1452-1460 (2010).
30. Farina E.K., Kiel D.P., et al., Am J Clin Nutr, **93(5)**,1142-1151 (2011).
31. Kardinaal A.F., Morton M.S., Brüggemann-Rotgans I.E., van Beresteijn E.C., Eur J Clin Nutr, 52(11),850-855 (1998).
32. de Goede J., Verschuren W.M., Boer J.M., Kromhout D., Geleijnse J.M., PLoS One, **6(3)**, e17967 (2011).
33. Xie J., Tworoger S.S., et al., Breast Cancer Res Treat, **139(3)**, 801-809 (2013).
34. Anderson L.N., Cotterchio M., Boucher B.A., Kreiger N., Int J Cancer, **132(7)**, 1683-1692 (2013).
35. Sun Q., Ma J., Campos H., Hankinson S.E., Hu F.B., Am J Clin Nutr, **86(1)**, 74-81 (2007).
36. Dietary reference intakes for energy, carbohydrate, fiber, fat, fatty acids, cholesterol, protein, and amino acids (macronutrients): http://www.nal.usda.gov/fnic/DRI/DRI_Energy/energy_full_report.pdf (last checked on Feb. 18 2014).
37. Lucas E.A., Wild R.D., et al., J Clin Endocrinol Metab, **87(4)**, 1527-1532 (2002).
38. Brooks J.D., Ward W.E., et al., Am J Clin Nutr, **79(2)**, 318-325 (2004).
39. Dodin S., Lemay A., et al., J Clin Endocrinol Metab, **90(3)**, 1390-1397 (2005).
40. Cornish S.M., Chilibeck P.D., et al., Appl Physiol Nutr Metab, **34(2)**, 89-98 (2009).
41. Scientific Opinion on Dietary Reference Values for fats, including saturated fatty acids, polyunsaturated fatty acids, monounsaturated fatty acids, *trans* fatty acids, and cholesterol: http://www.efsa.europa.eu/en/efsajournal/doc/1461.pdf (last checked on Apr. 4 2014).