The articles in this series are independently researched and compiled by PSA commissioned authors and peer reviewed.

Vitamin supplements in the elderly

Dr Luke Bereznicki and Professor Gregory Peterson

Learning objectives:

After reading this article, the reader should be able to:

- Describe some of the nutritional challenges in the elderly;
- Summarise the current evidence surrounding the use of B-group vitamins, calcium and vitamin D; and
- Discuss how this evidence will influence your practice.

The elderly present several nutritional challenges: they are the largest group of nutritionally vulnerable people in Australia.

Introduction

It has been estimated that Australians spend approximately $4 billion annually on complementary and alternative medicine (CAM; includes purchases of products and visits to practitioners), just under half of which is spent on CAM products.[1] Spending on CAM products equates to roughly half of all non-subsidised health care products in Australia.[1,2] While the elderly appear less likely to use CAM products and visit CAM practitioners than their younger counterparts, 58% and 35% of Australians over 65 years of age admitted to using a CAM product or visiting a CAM practitioner within the past 12 months, respectively, in a recent nationwide survey.[1] The most frequently used CAM product type in Australian representative surveys is clinical nutrition, accounting for 40–50% of CAM product usage.[1,3] In this article we will review recent evidence relating to the use of vitamin supplements in the elderly, particularly B-group vitamins, calcium and vitamin D.

Nutrition in the elderly

The elderly present several nutritional challenges: they are the largest group of nutritionally vulnerable people in Australia (with those in residential aged care at greatest risk); there is a simultaneous reduction in energy requirements and increasing requirements for a number of nutrients (e.g. protein, riboflavin, pyridoxine, calcium, vitamin D and vitamin B_{12}) with advancing age; and these issues are compounded by a reduction in appetite.[4] It may therefore be difficult for the elderly to meet minimum nutritional requirements from their diets alone, and fortified foods and/or vitamin supplements may be required. The recently published Nutrient Reference Values (NRVs) for Australia and New Zealand now present differing recommended nutrient intakes for various age groups.[5]

Suboptimal nutrition

Suboptimal nutrition is defined as a state in which nutritional intake is sufficient to prevent the classical symptoms and signs of deficiency, yet insufficient to significantly reduce the risk of developmental or degenerative diseases. In some cases, high-level scientific evidence exists to support supplementation to reduce the rate of clinical events. For example, the use of folate supplementation in pregnancy to prevent neural tube defects,[6] and calcium and vitamin D supplementation in elderly women with osteoporosis.[7] There has also been strong awareness that nutritional intakes beyond the recommended daily intake may have a role in the prevention of some chronic diseases which are often associated with advanced age, such as cardiovascular disease, stroke, macular degeneration, dementia and cancer.

B-group vitamins

In the 1960s it was proposed that homocysteine was a cause of arterial and venous thrombotic disease. This theory was based on the observation that children with extremely elevated homocysteine levels due to inborn metabolic errors suffered from premature atherothrombotic disease.[8] Similarly, it was observed that patients with Alzheimer's disease had higher plasma levels of homocysteine (regardless of the presence of cerebrovascular disease) than age-matched controls.[9] An inverse relationship has been demonstrated between B-group vitamins (e.g. folic acid and vitamin B_{12}) and plasma homocysteine levels.[10] Elevated homocysteine levels have been linked directly to an increased risk of cardiovascular disease, stroke and dementia in observational studies.[11,12] Homocysteine is a sulfur-containing amino acid derived from methionine, and in experimental settings promotes oxidative stress, endothelial damage and dysfunction, inflammation, thrombosis and cell proliferation.[13] Folic acid and vitamin B_{12} are required for the methylation of the homocysteine molecule.[14] In combination with vitamin B_6 they effectively lower serum homocysteine levels through regeneration of methionine.[14]

a. Cardiovascular disease

While plasma homocysteine levels can be easily reduced by supplementation with B-group vitamins (vitamin B_6, vitamin B_{12} and folic acid), randomised controlled trials (RCTs) do not provide clear evidence that B-group vitamins are beneficial in cardiovascular disease risk reduction. A large number of RCTs conducted in North America and Europe, mostly in patients with pre-existing vascular disease, have failed to show a benefit of B-group vitamins on cardiovascular risk.[15-18] In fact, in two studies where folic acid was given in combination with other B-group vitamins (vitamin B_6 and vitamin B_{12}) in high doses, there was a suggestion that the combination actually increased cardiovascular risk.[16,17] The vitamin dosages in these studies were 0.8–2.5mg folic acid, 40–50mg vitamin B_6 and 0.4–1mg vitamin B_{12}. The comparable RDIs for these vitamins are 0.4mg, 1.3–1.7mg and 0.002mg, respectively for adults.[5] Finally, a 2006 meta-analysis of RCTs confirmed that folate supplementation did not reduce the risk of cardiovascular disease or mortality in patients with pre-existing vascular or renal disease.[19] Based on this evidence, B-group vitamins cannot currently be recommended for the prevention of cardiovascular disease.

b. Stroke

While the HOPE-2 study did not show a reduction in its primary outcome (a composite of death from cardiovascular disease, myocardial infarction and stroke), it did find a reduction in the risk of stroke (a secondary outcome).[16] This result was not found in another RCT designed specifically to investigate the effects of homocysteine lowering in patients with a history of stroke.[15] A recent meta-analysis, however, found that folic acid supplementation (at a dosage of 0.8–15mg/day) did reduce the risk of stroke, although the finding was of borderline statistical significance.[20] A greater beneficial effect from folate supplementation was seen in trials of longer duration (>36 months), in those with a greater decrease in plasma homocysteine, in patients who lived in countries with no mandatory grain fortification (which, as you would expect, tends to nullify the benefit of supplementation) and in patients with no prior history of stroke. It is also important to recognise that the patients without a history of stroke in this analysis had significant baseline cardiovascular disease (34% to 55% had significant cardiovascular disease). Based on this information, it is difficult to justify the use of folate supplementation; B-group vitamin supplementation does not appear to be beneficial in patients who have a history of stroke (although this may be because trials need to be longer in duration) and B-group vitamin supplementation may further increase the risk of cardiovascular disease in those at risk of both cardiovascular disease and stroke. Based on the current evidence, we can not be certain that the benefits of B-group vitamin supplementation at the doses studied to reduce the risk of stroke outweigh the risk of other adverse cardiovascular outcomes, particularly in countries (such as the USA and Australia) where food sources are fortified with folate.

c. Dementia

The combination of elevated homocysteine levels and low levels of vitamin B_6, vitamin B_{12} and folate has been correlated with decreased performance on cognitive tests, and may contribute to the pathophysiology of Alzheimer's disease by contributing to the formation of amyloid plaques (microvascular disease) and neurofibrillary tangles (oxidative stress).[21-23] A meta-analysis of 14 small RCTs in 2007 concluded that the evidence did not support the use of vitamin B_6, vitamin B_{12} or folic acid alone, or in combination, on cognitive function testing in people with either normal or impaired cognitive function.[12] The meta-analysis was limited by the inclusion of few studies of significant enough size or duration to assess a change in cognitive function. The FACIT RCT enrolled people whose folate status was suboptimal; participants had elevated plasma homocysteine in the absence of disorders or diseases that could account for the raised level (e.g. vitamin B_{12} deficiency or renal disease), and were otherwise healthy.[24] In this population, the supplementation of 0.8mg folic acid per day for three years led to expected significant increases in folate status and a reduction in plasma homocysteine.[25] These changes were accompanied by significant improvements in memory, information processing speed and sensorimotor speed.[25] Other trials assessing the effect of B-group vitamin supplementation on cognitive function have failed to provide any evidence of benefit. The most recent RCT in this area investigated the effects of high-dose B-group vitamin supplementation in North American patients with mild to moderate Alzheimer's disease.[26] In this

study, patients received 5mg folate, 25mg vitamin B_6 and 1mg of vitamin B_{12} per day. Despite resulting in a significant reduction in homocysteine levels, vitamin B supplementation failed to result in significant changes in cognitive function. A chance finding was that significantly more patients receiving B-group vitamins suffered from depression, despite no difference in the use of antidepressants between the groups. These results support the conclusion that B-group vitamins are not effective in slowing cognitive decline in individuals with normal folate and vitamin B_{12} levels in societies with folate-enriched foods.[23]

Fracture risk reduction was greater in women who received calcium and vitamin D supplements, were adherent to therapy, were institutionalised, had a low dietary intake of calcium.

Calcium and vitamin D

Calcium and vitamin D have been shown to reduce the risk of fracture in institutionalised elderly women who are deficient in calcium and vitamin D.[27] Similarly, none of the anti-resorptive therapies (e.g. bisphosphonates and strontium) have been shown to be effective without co-administration of calcium and vitamin D.[28] The role of calcium and vitamin D preventive therapy for fracture in women living in the community is less clear. In a sub-study of the Women's Health Initiative, 36,282 healthy women aged between 50 and 79 years were randomised to receive either 1000mg elemental calcium with 400 IU of vitamin D3 or placebo.[29] Over a follow-up period of seven years, the rate of hip fractures did not differ significantly between the two groups, although hip bone density improved in the group receiving calcium and vitamin D. However, in women adherent to calcium and vitamin D (defined as taking >80% of study medication doses) the risk of hip fracture was significantly reduced compared to those taking placebo. Other than a slightly increased risk of renal stone formation, no significant risks or additional benefits were associated with calcium and vitamin D supplementation. A RCT in a group of Western Australian women aged over 70 years who received either 1200mg of calcium per day or placebo for five years also found that in the overall study population, calcium supplementation did not significantly reduce fracture risk.[30] However, when women who were adherent (>80% of study medication doses) to calcium supplementation were considered (~60% of the overall study population), calcium supplementation was effective in reducing fracture rates. Finally, a recent meta-analysis confirmed that calcium alone and in combination with vitamin D successfully reduced the risk of fractures of all types in women over the age of 50 years.[31] Fracture risk reduction was greater in women who received calcium and vitamin D supplements, were adherent to therapy, were institutionalised, had a low dietary intake of calcium (<700 mg/day), received supplemental calcium doses of >1200mg per day and supplemental vitamin D doses >800 IU per day. The degree of fracture risk reduction also increased with age. It is clear that good adherence to calcium is critical in achieving a fracture risk reduction – no significant benefit from calcium supplementation was seen in non-adherent patients (<80% of doses taken).

In spite of the beneficial effect of regular calcium supplementation in elderly women, the safety of calcium supplementation was recently called into question by the results of a RCT from New Zealand.[32] This study involved 1,471 postmenopausal women (mean age 74 years) who were randomised to receive 1000mg calcium or placebo for five years. These women did not receive vitamin D, but women with low vitamin D status were excluded from the trial. In this study, women who received calcium were twice as likely to suffer a myocardial infarction than their counterparts. The results of this study suggest that in elderly women without a previous osteoporotic fracture, the risk of myocardial infarction might outweigh the benefits of calcium supplementation. The Women's Health Initiative study did not show evidence of an increased risk of myocardial infarction,[29] but the younger age of participants and poor adherence to study medications in that study may have contributed to this result.[28] Until this concern has been addressed with additional data and further analysis of additional trials, the safety of calcium supplementation alone in elderly women is under question.

The reduction in fracture risk associated with vitamin D is often attributed to its effect on bone mineral density, but it may also directly increase muscle strength, thereby reducing fracture risk by preventing falls. A systematic review concluded in 2004 that vitamin D reduced the risk of falls in both the institutionalised and ambulatory elderly.[33] This review was limited in that it included studies using various metabolites of vitamin D, which are not necessarily as safe for dietary supplementation as ergocalciferol (D_2) or cholecalciferol (D_3). Another review was less positive, and suggested the lack of effectiveness might be due to variations in the calcium status of patients.[34] A recent RCT recruited 302

community-dwelling elderly Western Australian women aged between 70 and 90 years and randomised them to receive either vitamin D (ergocalciferol 1000IU/day) and calcium supplementation (1000mg/day) or calcium supplementation alone. These women had a history of falling in the previous year and low vitamin D status. Vitamin D reduced the risk of having at least one fall over one year. The risk of falling was reduced mostly in winter and spring, but not in summer or autumn. Other studies have found that the risk of fractures is higher in the colder months when serum vitamin D levels are lower due to a lower skin exposure to the sun.[35,36] Vitamin D_3 (cholecalciferol) is more potent than ergocalciferol on a unit to unit basis,[37] and may be more beneficial in reducing falls.

Conclusion

In conclusion, pharmacists need to be continually aware of the evidence for vitamin therapy in the elderly, particularly with regard to recommendations for high-dose vitamin therapy in otherwise healthy patients. Experimental and observational (non-RCT) data often do not translate into therapeutic benefits, and often well designed studies raise a number of additional safety concerns. This was well documented with a recent systematic review of high-dose antioxidants finding that, contrary to previous observational data, not only that high-dose beta-carotene, vitamin A and vitamin E did not reduce the risk of mortality, but that they may actually increase mortality risk.[38] This theme is followed in some of the examples discussed here: high-dose B-group vitamins do not seem effective in the prevention of cardiovascular disease and may even accelerate progression of cardiovascular disease in certain patients. The benefits of B-group vitamin supplementation for cardiovascular disease, stroke and dementia are also limited in the presence of adequate dietary folate intake. Calcium supplementation has also recently come under question in healthy elderly women due to a possible increased risk of myocardial infarction. There seems to be little likelihood for causing harm when patients are either deficient in certain vitamins, and are supplemented at doses at or below the recommended daily intake.

Some authors have suggested that all adults would benefit from taking a basic multivitamin on the basis that most people do not consume an optimal amount of vitamins by diet alone.[39] The various nutritional challenges in the elderly population[4] also seem to support this concept. At present there appear to be few indications for high-dose or mega-dosing of vitamins in the elderly. Even in fracture and fall prevention in the elderly, it is patients who are deficient in calcium or vitamin D who tend to benefit most from supplementation; patients with a dietary intake nearer to normal seem to face a reduction in benefit and an increase in the risk of adverse effects from high-dose supplementation of calcium.

Dr Luke Bereznicki is Lecturer in Pharmacy Practice and Professor Gregory Peterson is Professor in Pharmacy at the Tasmanian School of Pharmacy, Unit for Medication Outcomes Research and Education.

References

1. Xue CC, Zhang AL, Lin V et al. Complementary and alternative medicine use in Australia: A national population-based survey. J Altern Complement Med 2007;13:643-50.
2. Australian Institute of Health and Welfare. Health expenditure 2003-04. Canberra 2005
3. MacLennan AH, Myers SP, Taylor AW. The continuing use of complementary and alternative medicine in South Australia: Costs and beliefs in 2004. MJA. 2006;184:27-31.
4. Nowson C. Nutritional challenges in the elderly. Nutrition & Dietetics. 2007;64 (Suppl. 4):S150-S155.
5. National Health and Research Council. Nutrient reference values for Australia and New Zealand including recommended daily intakes. Canberra: Commonwealth Department of Health and Ageing; 2006.
6. MRC Vitamin Study Research Group. Prevention of neural tube defects: Results of the medical research council vitamin study. Lancet. 1991;338:131-7.
7. Dawson-Hughes B, Harris SS, Krall EA et al. Effect of calcium and vitamin d supplementation on bone density in men and women 65 years of age or older. NEJM. 1997;337:670-6.
8. Clarke R, Daly L, Robinson K et al. Hyperhomocysteinemia: An independent risk factor for vascular disease. N Engl J Med. 1991;324:1149-55.
9. Clarke R, Smith AD, Jobst KA et al. Folate, vitamin B12, and serum total homocysteine levels in confirmed Alzheimer disease. Arch Neurol. 1998;55:1449-55.
10. Selhub J, Jacques PF, Wilson PW et al. Vitamin status and intake as primary determinants of homocysteinemia in an elderly population. JAMA. 1993;270:2693-8.
11. Homocysteine Studies Collaboration. Homocysteine and risk of ischemic heart disease and stroke: A meta-analysis. JAMA. 2002;288:2015-22.
12. Balk EM, Raman G, Tatsioni A et al. Vitamin B6, B12, and folic acid supplementation and cognitive function: A systematic review of randomized trials. Arch Intern Med. 2007;167:21-30.
13. Welch GN, Loscalzo J. Homocysteine and atherothrombosis. N Engl J Med. 1998;338:1042-50.
14. Braun L, Cohen M. Herbs & natural supplements: An evidence-based guide. 2nd ed. Sydney: Elsevier; 2007.
15. Toole JF, Malinow MR, Chambless LE et al. Lowering homocysteine in patients with ischemic stroke to prevent recurrent stroke, myocardial infarction, and death: The vitamin intervention for stroke prevention (VISP) randomized controlled trial. JAMA. 2004;291:565-75.
16. Lonn E, Yusuf S, Arnold MJ et al. Homocysteine lowering with folic acid and B vitamins in vascular disease. N Engl J Med. 2006;354:1567-77.
17. Bonaa KH, Njolstad I, Ueland PM et al. Homocysteine lowering and cardiovascular events after acute myocardial infarction. N Engl J Med. 2006;354:1578-88.
18. Albert CM, Cook NR, Gaziano JM et al. Effect of folic acid and B vitamins on risk of cardiovascular events and total mortality among women at high risk for cardiovascular disease: A randomized trial. JAMA. 2008;299:2027-36.
19. Bazzano LA, Reynolds K, Holder KN et al. Effect of folic acid supplementation on risk of cardiovascular diseases: A meta-analysis of randomized controlled trials. JAMA. 2006;296:2720-26.
20. Wang X, Qin X, Demirtas H et al. Efficacy of folic acid supplementation in stroke prevention: A meta-analysis. Lancet. 2007;369:1876-82.
21. Riggs KM, Spiro A, 3rd, Tucker K et al. Relations of vitamin B-12, vitamin B-6, folate, and homocysteine to cognitive performance in the normative aging study. Am J Clin Nutr. 1996;63:306-14.
22. Wang HX, Wahlin A, Basun H et al. Vitamin B(12) and folate in relation to the development of Alzheimer's disease. Neurology. 2001;56:1188-94.
23. Clarke RJ, Bennett DA. B vitamins for prevention of cognitive decline: Insufficient evidence to justify treatment. JAMA. 2008;300:1819-21.
24. Morris MC, Tangney CC. Is dietary intake of folate too low? Lancet. 2007;369:166-67.
25. Durga J, van Boxtel MP, Schouten EG et al. Effect of 3-year folic acid supplementation on cognitive function in older adults in the FACIT trial: A randomised, double blind, controlled trial. Lancet. 2007;369:208-16.
26. Aisen PS, Schneider LS, Sano M, et al. High-dose B vitamin supplementation and cognitive decline in Alzheimer disease: A randomized controlled trial. JAMA. 2008;300:1774-83.
27. Chapuy MC, Arlot ME, Duboeuf F et al. Vitamin D3 and calcium to prevent hip fractures in the elderly women. NEJM. 1992;327:1637-42.
28. Jones G, Winzenberg T. Cardiovascular risks of calcium supplements in women. BMJ. 2008;336:226-7.
29. Jackson RD, LaCroix AZ, Gass M et al. Calcium plus vitamin D supplementation and the risk of fractures. N Engl J Med. 2006;354:669-83.
30. Prince RL, Devine A, Dhaliwal SS et al. Effects of calcium supplementation on clinical fracture and bone structure: Results of a 5-year, double-blind, placebo-controlled trial in elderly women. Arch Intern Med. 2006;166:869-75.
31. Tang BM, Eslick GD, Nowson C et al. Use of calcium or calcium in combination with vitamin D supplementation to prevent fractures and bone loss in people aged 50 years and older: A meta-analysis. Lancet. 2007;370:657-66.
32. Bolland MJ, Barber PA, Doughty RN et al. Vascular events in healthy older women receiving calcium supplementation: Randomised controlled trial. BMJ. 2008;336:262-66.
33. Bischoff-Ferrari HA, Dawson-Hughes B, Willett WC et al. Effect of vitamin D on falls: A meta-analysis. JAMA. 2004;291:1999-2006.
34. Latham NK, Anderson CS, Reid IR. Effects of vitamin D supplementation on strength, physical performance, and falls in older persons: A systematic review. J Am Geriatr Soc. 2003;51:1219-26.
35. Lau EM, Gillespie BG, Valenti L et al. The seasonality of hip fracture and its relationship with weather conditions in New South Wales. Aust J Public Health. 1995;19:76-80.
36. Mirchandani S, Aharonoff GB, Hiebert R et al. The effects of weather and seasonality on hip fracture incidence in older adults. Orthopedics. 2005;28:149-55.
37. Armas LA, Hollis BW, Heaney RP. Vitamin D2 is much less effective than vitamin D3 in humans. J Clin Endocrinol Metab. 2004;89:5387-91.
38. Bjelakovic G, Nikolova D, Gluud LL et al. Mortality in randomized trials of antioxidant supplements for primary and secondary prevention: Systematic review and meta-analysis. JAMA. 2007;297:842-57.
39. Fletcher RH, Fairfield KM. Vitamins for chronic disease prevention in adults: Clinical applications. JAMA. 2002;287:3127-29.

CPD questions on pages 1018.