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LIFESTYLE MANAGEMENT OF BONE HEALTH

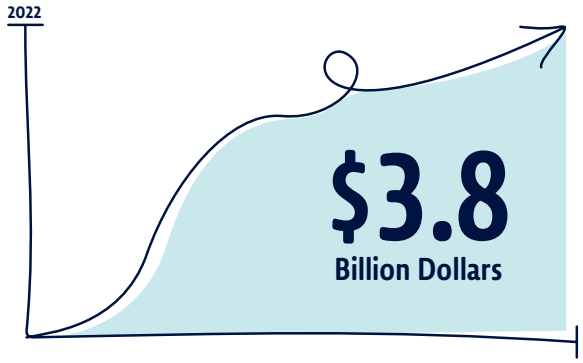
Professor Belinda Beck

THE IMPORTANCE OF BONE HEALTH

Osteoporosis (meaning 'porous bones') is a condition of very low bone mass that predisposes individuals to fracture from relatively low trauma, such as a fall from standing height, a sudden lift, or a forceful jolt. As the skeleton is hidden, the occurrence of a minimal trauma fracture is often the first sign of osteoporosis. Osteopenia refers to low bone mass that is not as severe as osteoporosis. A diagnosis of osteoporosis increases the risk of fracture 2- to 3-fold[1]. However, as many more people have osteopenia than osteoporosis, and a multitude of factors beyond bone mass contribute to the risk of fracture, most minimal trauma fractures (>50% of women and >70% of men) actually occur in individuals who are osteopenic[2].

In Australia, almost two thirds of adults over the age of 50 have osteoporosis or osteopenia, which equates to almost 5 million individuals, a number that is predicted to rise to over 6 million by 2022. In that time, the annual financial cost of osteoporosis and osteopenia to Australians is expected to reach $3.84 billion[3].

COST OF OSTEOPOROSIS



The personal cost of osteoporotic fractures, including chronic pain, deformity, loss of height, disability, loss of independence and premature death, however, is a more dramatically tangible consequence for millions of Australians.

RISK FACTORS

Risk factors for osteoporotic fracture include increasing age, female sex, family history of low bone mass, physical inactivity, insufficient serum vitamin D, low intake of calcium, low body weight, smoking, excessive alcohol consumption, prolonged corticosteroid use and reduced circulating oestrogen[4]. The occurrence of a fracture greatly increases the risk of subsequent fractures.

GENETICS

Genes play a dominant role in determining the size and strength of our skeleton[5], however, lifestyle practices, including diet and exercise, are highly influential. Indeed, for many, it is likely that osteoporosis can be prevented by making appropriate behavioural choices across the full course of the lifespan. The most potent preventative strategies include consistently engaging in regular bone and muscle stimulating exercise, and obtaining adequate calcium and vitamin D[4] throughout life. It has been estimated that merely eliminating calcium and vitamin D deficiencies in Australia would reduce the direct costs of osteoporosis by over $400 million a year[6].

LIFESTYLE FACTORS TO IMPROVE BONE HEALTH

EXERCISE

Exercise is a vital stimulus for bone, however, only certain forms of physical activity are notably effective[7]. Weight bearing loading (performed while standing up) that includes rapid impact and strenuous muscle contractions is key. Swimming, cycling and other seated exercises are beneficial for improving muscle strength, which may maintain function, but are unlikely to increase bone mass. Sarcopenia (low muscle mass and strength) often accompanies osteoporosis, so resistance training is apposite exercise for the musculoskeletal system as a whole.

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The strong association of falls with fracture highlights the importance of balance and mobility training in addition to bone and muscle strengthening, particularly in the later years.

IT HAS BEEN ESTIMATED THAT INCREASING PEAK BONE MASS BY 10% COULD DELAY THE DEVELOPMENT OF OSTEOPOROSIS BY 13 YEARS[8].

The engagement in regular high intensity jumping and muscle stimulating exercise is vitally important for children and adolescents to maximise bone development and optimise peak bone mass (largely attained by age 20). Doing so is an important preventative strategy for low trauma fracture later in life, as it has been estimated that increasing peak bone mass by 10% could delay the development of osteoporosis by 13 years[8]. Exercise appears to exert the strongest stimulus in early-to-mid-puberty[9] so school-based, bone-targeted exercise programs are strongly recommended. Calcium supplementation may enhance the positive effect of exercise during growth[10].

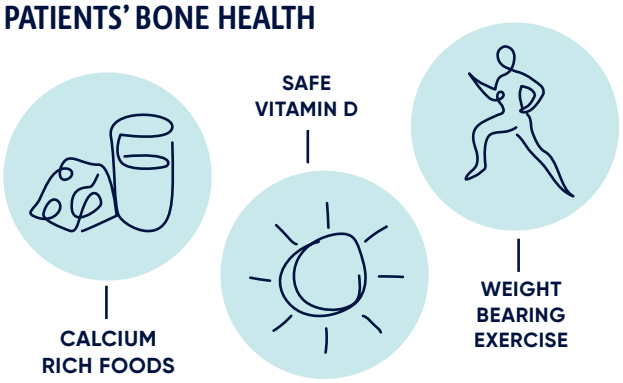
Exercise programs including high impact and unusual loading patterns in combination with high intensity resistance training is recommended for young to middle aged adults to consolidate and maintain bone mass acquired in youth[11,12]. Ongoing engagement in high intensity weight bearing exercise throughout life, incorporating a variety of sports that require unusual patterns of loading (basketball, field hockey, soccer, volleyball, netball) is highly recommended during the adult years[7]. An increased focus on resistance and balance training in middle age will prevent entering older age with strength and stability deficits that will predispose to falls and fracture.

Until recently, exercise appeared to effect only relatively small improvements in bone mass in aging adults with osteopenia and osteoporosis[13,14]. In reality, this lack of efficacy appears to have been a function of overly conservative exercise prescription. Recent work has shown great efficacy of high intensity resistance and impact training (HiRIT) for bone mass even in individuals with advanced osteoporosis, along with marked improvements in back and lower extremity strength and functional performance[15,16]. The caveat to recommendations of HiRIT for individuals with poor bone mass is the requirement for close supervision by exercise specialists to ensure correct technique and appropriately graduated progressions in order to prevent injury. Improvements in bone from HiRIT appear to be greatest at the lumbar spine[16,17] however, thickening of cortical bone has been observed at the femoral neck[16], the common site of osteoporotic hip fractures. Such morphological adaptations are likely to translate to considerable improvements in bone strength and resistance to hip fracture.

Individuals who have already suffered an osteoporotic fracture have a high risk of refracture. In such cases, exercise prescription should emphasise fall prevention along with a very closely supervised and somewhat more conservative HiRIT program. There is evidence that function[18,19], falls prevention[20-22] and quality of life[23] benefits can be achieved from considerably less intense exercise programs, including in long term care facilities[24]; all of which are highly meaningful outcomes irrespective of bone efficacy.

A minimum of six months duration and twice per week frequency are likely to be necessary for the benefits of exercise to be realised and detectable[12,15], however very simple exercise routines (50 multidirectional hops) may require more frequent (daily) application[26].

3 SIMPLE ACTIONS TO SUPPORT PATIENTS' BONE HEALTH



DIET

A diet including all five food groups is important for bone health. As calcium is the major building-block of bone tissue it is a vital nutrient for skeletal health[27]. Vitamin D must be considered a partner nutrient of calcium as it is required for the absorption of calcium from the gut. A third nutritional priority for bone is protein. While young and middle-aged adults in Western societies typically consume adequate protein to sustain all body systems and functions, protein is particularly important during growth in childhood and can be less available in inadequate diets of old age which will contribute to losses in musculoskeletal mass. Fruits and vegetables contain an array of vitamins, minerals, antioxidants and alkaline salts - many of which may have a beneficial effect on bone. It is commonly held that excessive caffeine, salt and alcohol are detrimental to bone health.

CALCIUM

Inadequate dietary calcium increases the risk of bone loss and fracture[28]. The Australian Dietary Guidelines (ADG) recommend dietary intakes (RDI) for calcium during childhood from 500 mg/day during infancy, to 1300 mg/day around puberty[29], the latter reflecting the dramatic rate of bone growth during the teenage years – equating to roughly 40% of adult bone mass[30].

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During adulthood the calcium RDI drops to 1000 mg/day until age 50 for women and 70 for men when it returns to 1300 mg[29]. The Australian Health Survey (AHS)[31] determined that 73% of females and 51% of males did not meet their calcium requirements from food, a trend which began in early childhood. Over the age of 50, men and women consumed an average of only ~700 mg/day[31].

AUSTRALIAN DIETARY GUIDELINES RECOMMENDED CALCIUM INTAKES

Infants	500 mg/day
Adolescents	1300 mg/day
Adults	1000 mg/day
Women (50+) & Men (70+)	1300 mg/day

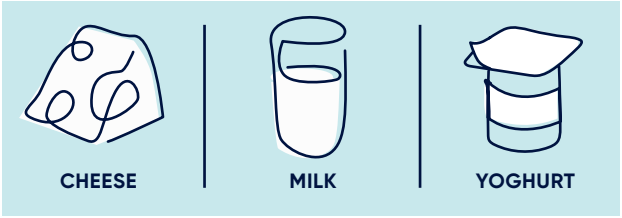
It is recommended that at least three servings of dairy are consumed to achieve 1000-1300 mg of calcium per day[4]. Key findings of the AHS Consumption of Food Groups analysis[32] indicated that Australians over the age of 2 years consumed an average of only 1.5 serves of dairy per day, with only 10% meeting the recommended number of serves (7.2% of females and 12% of males). In fact, less than 1% of men and women aged 71 years achieved the dairy and/or alternatives consumption recommendation on a usual basis and half consumed less than a third in 2011-12[32].

ONLY 10% OF AUSTRALIANS OVER 2 YEARS MEET THE RECOMMENDED NUMBER OF SERVES FROM THE DAIRY FOOD GROUP[32].

Owing to a degree of uncertainty regarding a potentially increased risk of myocardial infarction from calcium supplementation[33-35], there is a general consensus that calcium requirements should be obtained from the diet where possible. Milk and milk-based foods such as cheese and yoghurt are the greatest contributors to calcium in the Australian diet[36]. Lactose intolerant individuals can often tolerate cheese as most are low in lactose, and yoghurt, as lactose is broken down by the bacteria. Other food sources of calcium include sardines and salmon with edible bones, green leafy vegetables such as kale, broccoli, bok choy, tofu set with calcium, figs, apricots, almonds, and sesame products such as tahini. Plant-based beverages such as soy and almond drinks can provide a source of calcium, particularly if fortified. To be considered suitable dairy milk substitutes, they should contain similar levels of calcium to milk (100mg calcium per 100ml)[31]. Where preferences or intolerances prevent sufficient dietary calcium consumption, supplementation is recommended to a maximum of 500-600 mg/day[4], as the body cannot absorb larger boluses of calcium.

The upper limit for calcium absorption is 2500 mg/day. For greatest efficacy, calcium supplements should be administered with vitamin D[35, 37, 38]. Excessive caffeine, alcohol and diets high in oxalates (spinach and rhubarb) and phytates (cereal husks and dried beans) reduce calcium absorption.

MAJOR SOURCES OF CALCIUM



VITAMIN D

A serum level of >50 nmol/L vitamin D (25-hydroxyvitamin D) is generally recommended to support good bone health[4], however, a large epidemiological study in 2012 showed around 31% of Australians were deficient[39]. The most effective source is exposure to sunshine[40] as vitamin D3 is produced in the skin in response to UVB light. In view of the high risk of skin carcinogenesis in fair-skinned populations, comprehensive guidelines for safe sun exposure that will provide the recommended serum concentration of 25(OH) D according to time of year, geographical location and skin type have been developed and are available from a number of sources[41-43]. For those who nevertheless receive minimal sun exposure, the Institute of Medicine (IOM) recommended vitamin D intake is 400-600 IU daily for all ages and sexes[44, 45], however, the Endocrine Practice Guidelines Committee (EPGC) recommends 600-1000 IU up to age 18 and then 1500-2000 IU for older adults[45]. The relative difficultly of obtaining adequate vitamin D from the diet (oily fish, beef liver, butter, eggs, mushrooms) and the equivocation in respect to optimum supplementation suggests appropriately conservative sun exposure is the most effective strategy to obtain sufficient levels of 25(OH) D. It is important to note that individuals with dark skin and the elderly produce less vitamin D for the same degree of sun exposure. While meta-analyses suggest minimal BMD or fracture benefit from vitamin D supplementation in isolation[46, 47], there is some evidence that combined calcium/vitamin D supplementation may be efficacious in compliant patients[48, 49], more is not necessarily better[46], and deficient patients are likely to respond most[47].

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PROTEIN

Protein is required to develop and maintain bone and muscle mass and strength[50]. Higher protein intake is associated with higher BMD[51-53], lower risk of hip fracture[54, 55], and improved recovery in hospitalised hip fracture patients[56]. Animal sources of dietary protein include lean red meat, poultry and fish, eggs and dairy products. Vegetable sources of protein include legumes such as lentils and kidney beans, soya products such as tofu, as well as grains, nuts and seeds. Most Australians are replete in macronutrients, including protein, however 14% of men and 4% of women over the age of 71 did not meet their protein requirements in 2011-12[31]. As dairy foods provide a source of both protein and calcium they may provide a simple dietary option to address shortfalls in both nutritional requirements.

PROTEIN IS REQUIRED TO DEVELOP AND MAINTAIN BONE AND MUSCLE MASS AND STRENGTH [50].

OTHER NUTRIENTS

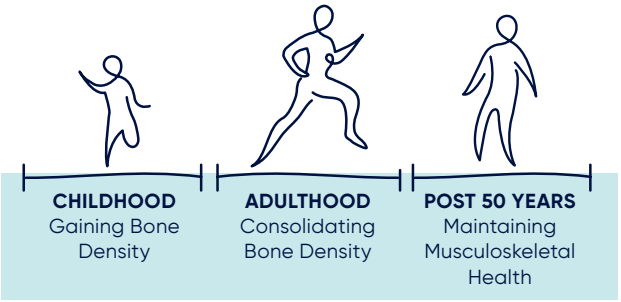
There is evidence to suggest higher fruit and vegetable consumption is associated with beneficial effects on bone density in elderly men and women[57]. The influence of non-D vitamins and minerals on bone health is not well-understood owing to a lack of high-quality evidence, however, potassium, phosphorous, magnesium, carbohydrate, vitamin A (moderate amounts), riboflavin, vitamin B12, vitamin K and zinc may be important for bone health[58]. Dairy foods provide a natural source of those nutrients[59]. Plant-based 'milks' such as those made from soy and almonds, do not have the same combination of nutrients for bone and muscle strength.

THE ROLE OF HEALTH PROFESSIONALS

Traditionally there has been no single medical specialty dedicated to the management of osteoporosis. Typically, patients consult a GP and are referred to either an endocrinologist or a rheumatologist for specialist care. Orthopaedic surgeons play a role following fracture if surgery is required, but are not typically involved in prevention or rehabilitation. While all consulting clinicians are likely to make generalised recommendations about healthy lifestyle practices, the primary therapeutic strategy for GPs and specialists is osteoporosis medication. Recent evidence suggests a bone-targeted exercise program combined can be a potent therapeutic stimulus to improve bone mass and reduce falls in individuals with low to very low bone mass[16, 60].

The relative fragility of osteoporotic patients and the high intensity nature of bone-stimulating exercise requires close supervision by appropriately qualified specialists, such as accredited exercise physiologists or physiotherapists. The identification of dietary sources of calcium, vitamin D and protein, along with other important micronutrients will be aided by consultation with a suitably trained dietitian.

BONE HEALTH OVER TIME



PROFESSOR BELINDA BECK

Belinda Beck is a Professor in the Griffith University School of Allied Health Sciences (Gold Coast, QLD) and the Menzies Health Institute Queensland. She heads the Griffith University Bone Densitometry Research Laboratory and co-founded The Bone Clinic, an innovative translational research facility and clinical practice providing evidence-based exercise for patients at risk of osteoporotic fracture. She graduated from The University of Queensland (BHMS[Ed]) and the University of Oregon (MSc and PhD) and completed a postdoctoral research fellowship in the Stanford University School of Medicine (CA, USA). Her work, primarily related to the effects of mechanical loading on bone, has involved both animal and human models, from basic to clinical research. Her particular focuses have been exercise interventions across the lifespan for the prevention of osteoporotic fracture, and the management of bone stress injuries in athletes and military recruits.

REFERENCES

1. Marshall, D, Johnell, O, and Wedel, H. Meta-analysis of how well measures of bone mineral density predict occurrence of osteoporotic fractures. BMJ, 1996. 312(7041): 1254-1259.
2. Sanders, KM, Nicholson, GC, Watts, JJ, Pasco, JA, Henry, MJ, Kotowicz, MA, and Seeman, E. Half the burden of fragility fractures in the community occur in women without osteoporosis. When is fracture prevention cost-effective? Bone, 2006. 38(5): 694-700.
3. Watts, J, Abimanyi-Ochom, J, and Sanders, KM. Osteoporosis costing all Australians A new burden of disease analysis – 2012 to 2022. 2013: Sydney.
4. Ebeling PR, Daly RM, Kerr DA, and MG, K, Building Healthy Bones Throughout Life; an evidence-informed strategy to prevent Osteoporosis in Australia Med J Aust Open, 2013. 2(Supplement 1): 1-49.
5. Flicker, L, Hopper, JL, Rodgers, L, Kaymakci, B, Green, RM, and Wark, JD, Bone density determinants in elderly women: a twin study. J Bone Miner Res, 1995. 10(11): 1607-13.
6. The Burden of Brittle Bones. Epidemiology, Costs & Burden of Osteoporosis in Australia. Report prepared for Osteoporosis Australia by the Department of Medicine, University of Melbourne, 2007: 1-27.
7. Beck, BR, Daly, RM, Singh, MA, and Taaffe, DR. Exercise and Sports Science Australia (ESSA) position statement on exercise prescription for the prevention and management of osteoporosis. J Sci Med Sport, 2017. 20(5): 438-445.
8. Hernandez, CJ, Beaupre, GS, and Carter, DR. A theoretical analysis of the relative influences of peak BMD, age-related bone loss and menopause on the development of osteoporosis. Osteoporos Int, 2003. 14(10): 843-7.
9. Beck, BR. Exercise for Bone in Childhood-Hitting the Sweet Spot. Pediatr Exerc Sci, 2017. 29(4): 440-449.
10. Specker, B and Binkley, T. Randomized trial of physical activity and calcium supplementation on bone mineral content in 3- to 5-year-old children. J Bone Miner Res, 2003. 18(5): 885-92.
11. Martyn-St James, M and Carroll, S. Effects of different impact exercise modalities on bone mineral density in premenopausal women: a meta-analysis. J Bone Miner Metab, 2010. 28(3): 251-67.
12. Kelley, GA, Kelley, KS, and Kohrt, WM. Exercise and bone mineral density in premenopausal women: a meta-analysis of randomized controlled trials. Int J Endocrinol, 2013. 2013: 741639.
13. Howe Tracey, E, Shea, B, Dawson Lesley, J, Downie, F, Murray, A, Ross, C, Harbour Robin, T, Caldwell Lynn, M, and Creed, G. Exercise for preventing and treating osteoporosis in postmenopausal women. Cochrane Database of Systematic Reviews, 2011. DOI: 10.1002/14651858.CD000333.pub2.
14. Kelley, GA, Kelley, KS, and Kohrt, WM. Effects of ground and joint reaction force exercise on lumbar spine and femoral neck bone mineral density in postmenopausal women: a meta-analysis of randomized controlled trials. BMC Musculoskelet Disord, 2012. 13: 177.
15. Watson, SL, Weeks, BK, Weis, LJ, Horan, SA, and Beck, BR. Heavy resistance training is safe and improves bone, function, and stature in postmenopausal women with low to very low bone mass: novel early findings from the LIFTMOR trial. Osteoporos Int, 2015. 26(12): 2889-94.
16. Watson, SL, Weeks, BK, Weis, LJ, Harding, AT, Horan, SA, and Beck, BR. High-Intensity Resistance and Impact Training Improves Bone Mineral Density and Physical Function in Postmenopausal Women With Osteopenia and Osteoporosis: The LIFTMOR Randomized Controlled Trial. J Bone Miner Res, 2018. 33(2): 211-220.
17. Martyn-St James, M and Carroll, S. High-intensity resistance training and postmenopausal bone loss: a meta-analysis. Osteoporos Int, 2006. 17(8): 1225-40.
18. Marks, R. Physical activity and hip fracture disability: a review. J Aging Res, 2011. 2011: 741918.
19. Varahra, A, Rodrigues, IB, MacDermid, JC, Bryant, D, and Birmingham, T. Exercise to improve functional outcomes in persons with osteoporosis: a systematic review and meta-analysis. Osteoporos Int, 2018. 29(2): 265-286.
20. Hauer, K, Rost, B, Rutschle, K, Opitz, H, Specht, N, Bartsch, P, Oster, P, and Schlierf, G. Exercise training for rehabilitation and secondary prevention of falls in geriatric patients with a history of injurious falls. J Am Geriatr Soc, 2001. 49(1): 10-20.
21. Tiedemann, A, Sherrington, C, Close, JC, and Lord, SR. Exercise and Sports Science Australia position statement on exercise and falls prevention in older people. J Sci Med Sport, 2011. 14(6): 489-95.
22. Sherrington, C, Tiedemann, A, Fairhall, N, Close, JC, and Lord, SR. Exercise to prevent falls in older adults: an updated meta-analysis and best practice recommendations. N S W Public Health Bull, 2011. 22(3-4): 78-83.
23. Li, WC, Chen, YC, Yang, RS, and Tsauo, JY. Effects of exercise programmes on quality of life in osteoporotic and osteopenic postmenopausal women: a systematic review and meta-analysis. Clin Rehabil, 2009. 23(10): 888-96.
24. Silva, RB, Eslick, GD, and Duque, G. Exercise for falls and fracture prevention in long term care facilities: a systematic review and meta-analysis. J Am Med Dir Assoc, 2013. 14(9): 685-9 e2.
25. Kemmler, W and von Stengel, S. Dose-response effect of exercise frequency on bone mineral density in post-menopausal, osteopenic women. Scand J Med Sci Sports, 2014. 24(3): 526-34.
26. Bailey, CA and Brooke-Wavell, K. Optimum frequency of exercise for bone health: randomised controlled trial of a high-impact unilateral intervention. Bone, 2010. 46(4): 1043-9.
27. Weaver, CM, Gordon, CM, Janz, KF, Kalkwarf, HJ, Lappe, JM, Lewis, R, O'Karma, M, Wallace, TC, and Zemel, BS. The National Osteoporosis Foundation's position statement on peak bone mass development and lifestyle factors: a systematic review and implementation recommendations. Osteoporos Int, 2016. 27(4): 1281-1386.
28. Ebeling, PR, Daly, RM, Kerr, DA, and Kimlin, MG. Building healthy bones throughout life: an evidence-informed strategy to prevent osteoporosis in Australia. Med J Aust, 2013. 199(7 Suppl): S1.
29. NHMRC. Australian Dietary Guidelines, Australian Government. 2013: Canberra.
30. Heaney, RP, Abrams, S, Dawson-Hughes, B, Looker, A, Marcus, R, Matkovic, V, and Weaver, C, Peak bone mass. Osteoporos Int, 2000. 11(12): 985-1009.
31. Australian Bureau of Statistics. Australian Health Survey: Usual Nutrient Intakes, 2011-12 2015.
32. Australian Bureau of Statistics. Australian Health Survey: Consumption of Food Groups from the Australian Dietary Guidelines, 2011-12 2016.
33. Bolland, MJ, Avenell, A, Baron, JA, Grey, A, MacLennan, GS, Gamble, GD, and Reid, IR. Effect of calcium supplements on risk of myocardial infarction and cardiovascular events: meta-analysis. BMJ, 2010. 341: c3691.
34. Bolland, MJ, Grey, A, Avenell, A, Gamble, GD, and Reid, IR. Calcium supplements with or without vitamin D and risk of cardiovascular events: reanalysis of the Women's Health Initiative limited access dataset and meta-analysis. BMJ, 2011. 342: d2040.
35. Lewis, JR, Zhu, K, Thompson, PL, and Prince, RL. The effects of 3 years of calcium supplementation on common carotid artery intimal medial thickness and carotid atherosclerosis in older women: an ancillary study of the CAIFOS randomized controlled trial. J Bone Miner Res, 2014. 29(3): 534-41.
36. Australian Bureau of Statistics. Australian Health Survey: Nutrition First Results - Foods and Nutrients, 2011-12. 2014.
37. Tang, BM, Eslick, GD, Nowson, C, Smith, C, and Bensoussan, A. 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(9588): 657-66.
38. Lewis, JR, Zhu, K, and Prince, RL, Adverse events from calcium supplementation: relationship to errors in myocardial infarction self-reporting in randomized controlled trials of calcium supplementation. J Bone Miner Res, 2012. 27(3): 719-22.
39. Daly, RM, Gagnon, C, Lu, ZX, Magliano, DJ, Dunstan, DW, Sikaris, KA, Zimmet, PZ, Ebeling, PR, and Shaw, JE. Prevalence of vitamin D deficiency and its determinants in Australian adults aged 25 years and older: a national, population-based study. Clin Endocrinol (Oxf), 2012. 77(1): 26-35.
40. Kimlin, MG, Lucas, RM, Harrison, SL, van der Mei, I, Armstrong, BK, Whiteman, DC, Kricker, A, Nowak, M, Brodie, AM, and Sun, J. The contributions of solar ultraviolet radiation exposure and other determinants to serum 25-hydroxyvitamin D concentrations in Australian adults: the AusD Study. Am J Epidemiol, 2014. 179(7): 864-74.
41. Nowson, CA, McGrath, JJ, Ebeling, PR, Haikerwal, A, Daly, RM, Sanders, KM, Seibel, MJ, Mason, RS. Working Group of, A, New Zealand, B, Mineral Society, ESoA, and Osteoporosis, A, Vitamin D and health in adults in Australia and New Zealand: a position statement. Med J Aust, 2012. 196(11): 686-7.
42. Victorian Cancer Council. How much sun is enough? Getting the balance right: vitamin D and sun protection, in SunSmart website. http://www.sunsmart.com.au/uv-sun-protection/how-much-sun-is-enough
43. Health, G. Sunshine calendar. Available from: https://grassrootshealth.net/document/sunshine-calendar/.
44. Institute of Medicine. Dietary reference intakes for calcium and vitamin D. 2011, The National Academies Press: Washington DC.
45. Holick, MF, Binkley, NC, Bischoff-Ferrari, HA, Gordon, CM, Hanley, DA, Heaney, RP, Murad, MH, Weaver, CM, and Endocrine, S, Evaluation. treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab, 2011. 96(7): 1911-30.
46. Reid, IR, Bolland, MJ, and Grey, A. Effects of vitamin D supplements on bone mineral density: a systematic review and meta-analysis. Lancet, 2014. 383(9912): 146-55.
47. Bischoff-Ferrari, HA, Willett, WC, Orav, EJ, Lips, P, Meunier, PJ, Lyons, RA, Flicker, L, Wark, J, Jackson, RD, Cauley, JA, Meyer, HE, Pfeifer, M, Sanders, KM, Stahelin, HB, Theiler, R, and Dawson-Hughes, B. A pooled analysis of vitamin D dose requirements for fracture prevention. N Engl J Med, 2012. 367(1): 40-9.
48. Avenell, A, Gillespie, WJ, Gillespie, LD, and O'Connell, DL. Vitamin D and vitamin D analogues for preventing fractures associated with involutional and post-menopausal osteoporosis. Cochrane Database Syst Rev, 2005(3): CD000227.
49. Prentice, RL, Pettinger, MB, Jackson, RD, Wactawski-Wende, J, Lacroix, AZ, Anderson, GL, Chlebowski, RT, Manson, JE, Van Horn, L, Vitolins, MZ, Datta, M, LeBlanc, ES, Cauley, JA, and Rossouw, JE. Health risks and benefits from calcium and vitamin D supplementation: Women's Health Initiative clinical trial and cohort study. Osteoporos Int, 2013. 24(2): 567-80.
50. Rizzoli, R, Biver, E, Bonjour, JP, Coxam, V, Goltzman, D, Kanis, JA, Lappe, J, Rejnmark, L, Sahni, S, Weaver, C, Weiler, H, and Reginster, JY. Benefits and safety of dietary protein for bone health-an expert consensus paper endorsed by the European Society for Clinical and Economical Aspects of Osteopororosis, Osteoarthritis, and Musculoskeletal Diseases and by the International Osteoporosis Foundation. Osteoporos Int, 2018.
51. Jennings, A, MacGregor, A, Spector, T, and Cassidy, A. Amino Acid Intakes Are Associated With Bone Mineral Density and Prevalence of Low Bone Mass in Women: Evidence From Discordant Monozygotic Twins. J Bone Miner Res, 2016. 31(2): 326-35.
52. Hannan, MT, Tucker, KL, Dawson-Hughes, B, Cupples, LA, Felson, DT, and Kiel, DP. Effect of dietary protein on bone loss in elderly men and women: the Framingham Osteoporosis Study. J Bone Miner Res, 2000. 15(12): 2504-12.
53. Promislow, JH, Goodman-Gruen, D, Slymen, DJ, and Barrett-Connor, E. Protein consumption and bone mineral density in the elderly : the Rancho Bernardo Study. Am J Epidemiol, 2002. 155(7): 636-44.
54. Munger, RG, Cerhan, JR, and Chiu, BC. Prospective study of dietary protein intake and risk of hip fracture in postmenopausal women. Am J Clin Nutr, 1999. 69(1): 147-52.
55. Wengreen, HJ, Munger, RG, West, NA, Cutler, DR, Corcoran, CD, Zhang, J, and Sassano, NE. Dietary protein intake and risk of osteoporotic hip fracture in elderly residents of Utah. J Bone Miner Res, 2004. 19(4): 537-45.
56. Delmi, M, Rapin, CH, Bengoa, JM, Delmas, PD, Vasey, H, and Bonjour, JP. Dietary supplementation in elderly patients with fractured neck of the femur. Lancet, 1990. 335(8696): 1013-6.
57. Tucker, KL, Hannan, MT, Chen, H, Cupples, LA, Wilson, PW, and 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.
58. Sahni, S, E, Z, McLean, RR, and Hannan, MT. Non-D vitamins and bone health in adults. IBMS BoneKEy, 2010. 7(12): 431-446.
59. Thorning, TK, Bertram, HC, Bonjour, JP, de Groot, L, Dupont, D, Feeney, E, Ipsen, R, Lecerf, JM, Mackie, A, McKinley, MC, Michalski, MC, Remond, D, Riserus, U, Soedamah-Muthu, SS, Tholstrup, T, Weaver, C, Astrup, A, and Givens, I. Whole dairy matrix or single nutrients in assessment of health effects: current evidence and knowledge gaps. Am J Clin Nutr, 2017. 105(5): 1033-1045.
60. Beck, BR and Weis, LJ. Effective exercise for osteoporosis in the real world: Three year observations from The Bone Clinic. J Bone Miner Res. 33:2018, from American Society of Bone and Mineral Research. 2018. Montreal, Canada.