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http://www.racgp.org.au/afp/2014/october/letters-to-the-editor/

What is the optimal level of vitamin D?

Dear Editor

The paper by Robyn Lucas and Rachel Neale addresses the question: What is the optimal level of vitamin D?[27] Unfortunately, they seem to have chosen papers from the literature to support their idea that 50 nmol/L is adequate, ignoring other papers that support higher levels. The purpose of my letter is to point out some of the problems with the papers they cited and present some of the findings in papers they overlooked.

The Institute of Medicine committee based its recommendations on vitamin D randomised controlled trials (RCTs) published by the end of 2010, ignoring observational studies except to point out that some showed evidence of adverse effects at higher 25-hydroxyvitamin D [25(OH)D] levels. Lucas and Neale also misinterpreted one key paper on bone condition with respect to 25(OH)D levels.[27] The authors of that paper clearly stated that 75 nmol/L, not 50 nmol/L, was the cut-off point for healthy bones. As for RCTs, vitamin D RCTs have largely been poorly designed and conducted as they have been designed on the pharmaceutical drug model: that is, that the agent used in the study is the only source of the compound and that there is a linear dose-response relationship between intake and effect. Neither is satisfied for vitamin D due to the abundant other sources. The proper way to design vitamin D RCTs has been outlined in a pair of recent papers.[28,29] Thus, observational studies provide better evidence for now than RCTs regarding the optimal 25(OH)D levels. As for the relationship between 25(OH)D level and parathyroid hormone (PHT), a paper based on over 310,000 measurements found that PTH decreased monotonically as 25(OH)D level increased out to 187 nmol/L.[31] The decrease of PTH for 25(OH)D increasing from 50 to 187 nmol/L was 35%.

As to possible risks for higher 25(OH)D levels, two things should be kept in mind. One is that for health outcomes, for which there are many studies, the meta-analysis of all available studies should be considered, not single studies. For prostate cancer, the result of meta-analyses is that there is no general relationship between low and high 25(OH)D levels and risk of prostate cancer,[32] but there is increased risk of aggressive prostate cancer at low 25(OH)D levels.[33] For all-cause mortality rate, while there may be a slight upturn at higher 25(OH)D levels based on studies to date, it is not significant.[34] The second thing is that some of the increased risk of adverse health outcomes could be due to enrolling people in the cohort studies who were recently told to take more vitamin D due to a health condition such as osteoporosis. This effect was demonstrated in a pair of studies on frailty:[35,36] for elderly men, there was an inverse correlation of frailty status with respect to 25(OH)D level several years after enrolling in the

study,[35] whereas for elderly women, there was a U-shaped relationship with higher frailty status associated with both low and high 25(OH)D levels.[36] Elderly women are much more likely to be advised to take vitamin D than elderly men in the United States.

Another concern regarding observational studies is that 25(OH)D levels change with time. Thus, the longer the time since blood draw, the less likely that the level measured corresponds to the average value. This effect has been observed for breast and colorectal cancer[32] and all-cause mortality rate.[37] Thus, the statement 'the strength of the evidence for an association between 25(OH)D levels and breast cancer decreased as the quality of the study design increased' is incorrect. What was reported in the referenced study was that the odds ratio for highest quantile versus lowest quantile 25(OH)D level was 0.86 (95% confidence interval, 0.75–1.00) for nested case-control and retrospective studies, 0.35 (0.24–0.52) for population-based case-control studies, and 0.08 (0.02–0.33) for hospital-based case-control studies.[38] When it is also considered that breast cancer can develop very rapidly, as evidenced by the fact that breast cancer diagnoses peak in spring and fall,[39] and that a meta-analysis of breast cancer survival with respect to 25(OH)D levels at time of diagnosis found a hazard ratio of 0.50 (0.45–0.58),[40] the designation of quality of study for 25(OH)D levels is actually the inverse of what is commonly accepted.

On the basis of 25(OH)D level–health outcome relationship, I estimated that if population mean 25(OH)D levels were increased from 54 to 110 nmol/L, all-cause mortality rates would decrease by 7–17%, depending on the continent, and life expectancies would increase by 2 years.[41] The bases for the calculations were subsequently supported by the 25(OH)D level–outcome relations from meta-analyses for cardiovascular disease[42] and diabetes mellitus.[43]

As for optimal 25(OH)D levels, many reviews by individuals and groups have recommended 75 nmol/L or higher, on the basis of the best evidence available at the time.[44–51] Given the concern about the risk of skin cancer and melanoma in Australia, vitamin D supplements might be preferred to solar ultraviolet-B irradiance. However, it is noted that there is considerable variability in changes in 25(OH)D level for any given oral vitamin D intake.[52] Thus, measurement of 25(OH)D level before and after commencing a vitamin D supplementation program might be in order.

William Grant
Sunlight, Nutrition and Health Research Center
San Francisco, CA

References

27. Lucas R, Neale R. What is the optimal level of vitamin D? Separating the evidence from the rhetoric. Aust Fam Physician 2014;43:119–22. Search PubMed
28. Priemel M, von Domarus C, Klatte TO, et al. Bone mineralization defects and vitamin D deficiency: histomorphometric analysis of iliac crest bone biopsies and circulating 25-hydroxyvitamin D in 675 patients. J Bone Miner Res 2010;25:305–02. Search PubMed
29. Lappe JM, Heaney RP. Why randomized controlled trials of calcium and vitamin D sometimes fail. Dermatoendocrinol 2012;4:95–100. Search PubMed

30. Heaney RP. Guidelines for optimizing design and analysis of clinical studies of nutrient effects. Nutr Rev 2014;72:48–54. Search PubMed
31. Valcour A, Blocki F, Hawkins DM, Rao SD. Effects of age and serum 25-OH-vitamin D on serum parathyroid hormone levels. J Clin Endocrinol Metab 2012;97:3989–95. Search PubMed
32. Grant WB. Effect of interval between serum draw and follow-up period on relative risk of cancer incidence with respect to 25-hydroxyvitamin D level; implications for meta-analyses and setting vitamin D guidelines. Dermatoendocrinol 2011;3:199–204. Search PubMed
33. Gilbert R, Metcalfe C, Fraser WD, et al. Associations of circulating 25-hydroxyvitamin D with prostate cancer diagnosis, stage and grade. Int J Cancer 2012;131:1187–96. Search PubMed
34. Zittermann A, Iodice S, Pilz S, Grant WB, Bagnardi V, Gandini S. Vitamin D deficiency and mortality risk in the general population: A meta-analysis of prospective cohort studies. Am J Clin Nutr 2012;95:91–100. Search PubMed
35. Ensrud KE, Blackwell TL, Cauley JA, et al. Circulating 25-hydroxyvitamin D levels and frailty in older men: the osteoporotic fractures in men study. J Am Geriatr Soc 2011;59:101–06. Search PubMed
36. Ensrud KE, Ewing SK, Fredman L, et al. Circulating 25-hydroxyvitamin D levels and frailty status in older women. J Clin Endocrinol Metab 2010;95:5266–73. Search PubMed
37. Grant WB. Effect of follow-up time on the relation between prediagnostic serum 25-hydroxyitamin D and all-cause mortality rate. Dermatoendocrinol 2012;4:198–202. Search PubMed
38. Chen P, Li M, Gu X, et al. Higher blood 25(OH)D level may reduce the breast cancer risk: evidence from a Chinese population based case-control study and meta-analysis of the observational studies. PLoS One 2013;8:e49312. Search PubMed
39. Oh EY, Ansell C, Nawaz H, Yang CH, Wood PA, Hrushesky WJ. Global breast cancer seasonality. Breast Cancer Res Treat 2010;123:233–43. Search PubMed
40. Mohr SB, Gorham ED, Kim J, Hofflich H, Garland CF. Meta-analysis of vitamin D sufficiency for improving survival of patients with breast cancer. Anticancer Res 2014;34:1163–66. Search PubMed
41. Grant WB. An estimate of the global reduction in mortality rates through doubling vitamin D levels. Eur J Clin Nutr 2011;65:1016–26. Search PubMed
42. Wang L, Song Y, Manson JE, Pilz S, et al. Circulating 25-hydroxy-vitamin D and risk of cardiovascular disease: a meta-analysis of prospective studies. Circ Cardiovasc Qual Outcomes 2012;5:819–29. Search PubMed
43. Song Y, Wang L, Pittas AG, et al. Blood 25-hydroxy vitamin D levels and incident type 2 diabetes: a meta-analysis of prospective studies. Diabetes Care 2013;36:1422–28. Search PubMed
44. Souberbielle JC, Body JJ, Lappe JM, et al. Vitamin D and musculoskeletal health, cardiovascular disease, autoimmunity and cancer: Recommendations for clinical practice. Autoimmun Rev 2010;9:709–15. Search PubMed
45. Holick MF, Binkley NC, Bischoff-Ferrari HA, et al. Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. J Clin Edoncrinol Metab 2011;96:1911–30. Search PubMed
46. Pérez-López FR, Brincat M, Erel CT, et al. EMAS position statement: Vitamin D and postmenopausal health. Maturitas 2012;71:83–88. Search PubMed

47. Pludowski P, Holick MF, Pilz S, et al. Vitamin D effects on musculoskeletal health, immunity, autoimmunity, cardiovascular disease, cancer, fertility, pregnancy, dementia and mortality- a review of recent evidence. Autoimmun Rev 2013;12:976–89. Search PubMed
48. Płudowski P, Karczmarewicz E, Bayer M, et al. Practical guidelines for the supplementation of vitamin D and the treatment of deficits in Central Europe – recommended vitamin D intakes in the general population and groups at risk of vitamin D deficiency. Endokrynol Pol 2013;64:319–27. Search PubMed
49. Hossein-Nezhad A, Holick MF. Vitamin D for health: A global perspective. Mayo Clin Proc 2013;88:720–55. Search PubMed
50. Spedding S, Vanlint S, Morris H, Scragg R. Does vitamin D sufficiency equate to a single serum 25-hydroxyvitamin d level or are different levels required for non-skeletal diseases? Nutrients 2013;5:5127–39. Search PubMed
51. American Geriatrics Society Workgroup on Vitamin D Supplementation for Older Adults. Recommendations Abstracted from the American Geriatrics Society Consensus Statement on Vitamin D for Prevention of Falls and Their Consequences. J Am Geriatr Soc 2014;62:147–52. Search PubMed
52. Garland CF, French CB, Baggerly LL, Heaney RP. Vitamin D supplement doses and serum 25-hydroxyvitamin D in the range associated with cancer prevention. Anticancer Res 2011;31:617–22. Search PubMed

Reply

Dear Editor

We thank Dr Grant for his comments on our manuscript and agree that different interpretations of the existing data are possible. Below we address some of the issues that Dr Grant has raised.

Priemel and colleagues interpreted the results of their study of 25(OH)D and bone morphology in autopsy specimens to imply that a 25(OH)D level of at least 75 nmol/L is needed to optimise bone health.[53] However, we contend that the results did not provide sufficient data to support such a concrete recommendation. Firstly, a very low proportion of people (<1%) with 25(OH)D concentration between 50 and 74 nmol/L had evidence of mineralisation defects, compared with none in the group of people with 25(OH)D >75 nmol/L. In addition to the very small difference in this proportion, the total number of people with 25(OH)D >50 nmol/L was low. There was no statistical analysis to confirm that the differences in the proportion of people with mineral defects in the two groups with 25(OH)D over 50 nmol/L was not due to chance. Importantly, the vast majority of people with a level below 50 (or even 25 nmol/L) showed no evidence of bone mineralisation defects, so this metric cannot be used to define a 25(OH)D cut-off.

The threshold at which parathyroid hormone (PTH) is minimised is not clear, with studies finding a range of different thresholds and others a continuously decreasing risk.[54] The study to which Dr Grant referred did indeed show that there was no 25(OH)D threshold beyond which levels of PTH stabilised.[55] The implication is that indefinitely increasing 25(OH)D to the limit of toxicity will be beneficial, which is almost certainly inadvisable given the potential risks at higher levels (see below). Interestingly, a

surprising proportion of people (49%) had normal PTH despite frank vitamin D deficiency. Thus, use of PTH in isolation to determine a 25(OH)D cut-point is not appropriate.

Regarding the U-shaped curves we highlighted, we agree that the evidence is inconsistent. This is almost certainly due to the nature of epidemiology – differences in the population, timing of measurement, measurement of both 25(OH)D and confounding variables, data analysis and interpretation could all lead to different results. Meta-analyses can solve this problem to some extent, but a number of studies showing the increased risk at higher levels have been published since the relevant meta-analysis, and data are constantly changing. For example, manuscripts have very recently been published which suggest a U-shaped curve for prostate cancer (minimum risk at a 25(OH)D level of approximately 50–75 nmol/L[56] and fragility fractures (minimum risk at a 25(OH)D level of 60–72 nmol/L).[57] With respect to total mortality, a meta-analysis did confirm that there appears to be a turning point.[58] While we agree that any increased risk of disease at higher levels of 25(OH)D is not well established, we feel that there is sufficient evidence to warrant sounding a note of caution.

Different types of observational studies, and indeed trials, have advantages and disadvantages. However, we do not believe that studies of vitamin D should be exceptions to the commonly accepted wisdom that cohort studies provide more reliable data in most circumstances than case-control studies. In case-control studies, when blood is collected after diagnosis of disease, any association is likely to be due to reverse causality. Using breast cancer as an example, if patients have been sitting in waiting rooms, consulting with multiple health professionals, and undergoing surgery or other treatment, their 25(OH)D levels will almost certainly decline due to reduced sun exposure and possibly due to the effects of the disease or treatment. Studies have shown seasonally adjusted 25(OH)D levels to be stable over time, suggesting that baseline levels in cohort studies are a good marker of longer-term exposures.[59]

There is no doubt that frank vitamin D deficiency is a health risk, but beyond that it is currently unclear where 25(OH)D cut-off should lie. At this point we concur with the Institute of Medicine and Osteoporosis Australia that a level of 50 nmol/L is probably sufficient for most people. If this threshold is used, most Australians do not have low 25(OH)D levels (23% of the Australian population, across all seasons, in the recent Australian Health Survey). Therefore, routine population screening, which is currently costing upwards of $140 million per annum, is not warranted and general practitioners should follow published guidelines to determine whom to test.

Professor Robyn Lucas
Canberra, ACT
Dr Rachel Neale
Brisbane, QLD

References

53. Priemel M, von Domarus C, Klatte TO, et al. Bone mineralization defects and vitamin D deficiency: histomorphometric analysis of iliac crest bone biopsies and circulating 25-hydroxyvitamin D in 675 patients. J Bone Miner Res 2010;25:305–12. Search PubMed

54. Sai AJ, Walters RW, Fang X, Gallagher JC. Relationship between vitamin D, parathyroid hormone, and bone health. J Clin Endocrinol Metab 2011;96: E436–46. Search PubMed
55. Valcour A, Blocki F, Hawkins DM, Rao SD. Effects of age and serum 25-OH-vitamin D on serum parathyroid hormone levels. J Clin Endocrinol Metab 2012;97:3989–95. Search PubMed
56. Kristal AR, Till CA, Song X, et al. Plasma Vitamin D and Prostate Cancer Risk; Results from the Selenium and Vitamin E Cancer Prevention Trial. Cancer Epidemiol Biomarkers Prev 2014; doi:10. 1158/1055-9965.EPI-14-0115. Search PubMed
57. Bleicher K, Cumming RG, Naganathan V, et al. U-Shaped Association Between Serum 25-Hydroxyvitamin D and Fracture Risk in Older Men: Results from the Prospective Population Based CHAMP Study. J Bone Miner Res 2014; doi: 10.1002/jbmr.2230. Search PubMed
58. Zittermann A, Iodice S, Pilz S, Grant WB, Bagnardi V, Gandini S. Vitamin D deficiency and mortality risk in the general population: a meta-analysis of prospective cohort studies. Am J Clin Nutr 2012;95:91–100. Search PubMed
59. Hofmann JN, Yu K, Horst RL, Hayes RB, Purdue MP. Long-term variation in serum 25-hydroxyvitamin D concentration among participants in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial. Cancer Epidemiol Biomarkers Prev 2010;19:927–31. Search PubMed