TESTING AND TREATING VITAMIN D DEFICIENCY

Case study 68 report

August 2011

Independent, not-for-profit and evidence based, NPS enables better decisions about medicines and medical tests. We are funded by the Australian Government Department of Health and Ageing.

Level 7/418A Elizabeth St
Surry Hills NSW 2010
PO box 1147
Strawberry Hills NSW 2012

P. 02 8217 8700
F. 02 9211 7578
info@nps.org.au
www.nps.org.au

NPS Better choices ▹ Better health Professional

ABN 61 082 034 393

NPSCS1118

Suggested citation

National Prescribing Service Limited. Case study report. Case study: 68 Testing and treating vitamin D deficiency. Sydney: NPS, August 2011.

Acknowledgments

NPS, Better choices, Better Health would like to acknowledge expert commentaries provided by the following reviewers:

- Professor Rebecca Mason, Deputy Director, Bosch Institute, President, ANZ Bone and Mineral Society, University of Sydney, Sydney
- Dr. Simon Vanlint, Assistant Dean, Lecturer, Discipline of General Practice, University of Adelaide, South Australia

Contents

CASE STUDY 68
TESTING AND TREATING VITAMIN D DEFICIENCY

SCENARIO

Alima is a 35-year-old housewife who arrived to Australia with her family from the Middle East 2 years ago. She had a cold two weeks ago and feels her cough is getting worse. She is looking after three little children, feels tired, stressed and came with her husband to have her general checkup. Alima spends most of her time indoors and when she goes out she wears long clothes down to her ankles and her wrists and has a veil over her face. Her medical history is unremarkable.

1. Would you consider testing Alima for vitamin D level?

☐ yes ☐ no

Why? (tick all that apply)

☐ patient's request

☐ opportunistically in addition to other blood tests

☐ Alima is at high risk of vitamin D deficiency

☐ as a screening test for all patients

☐ other (specify)

2. What 3 questions would you ask to identify other risk factors for vitamin D deficiency?

_____

_____

_____

Two weeks later Alima has come to discuss her blood test results ordered at the previous visit. Her full blood count and glucose levels are in the normal range; serum vitamin D level (25-OHD) is 25 nmol/L (normal range 50–150 nmol/L).

3. What factors would you consider when interpreting vitamin D test results? (tick all that apply)

☐ time of the year when the test was performed

☐ level of skin pigmentation

☐ degree and consistency of skin covering (reduced exposure to sunlight)

☐ method used to measure vitamin D level

☐ other (specify)

4. **What lifestyle modifications would you recommend to Alima? Why?**

_____

_____

_____

5. **Would you recommend a vitamin D supplement to Alima? Please give a reason for your response?**

☐ yes ☐ no

Reason: _____

6. **If you answered yes in Question 5, which vitamin D preparation would you recommend??**

Supplement	Dose	Duration

_____

SUMMARY OF RESULTS

At the time of publication 1447 responses had been received from all participants, and 200 of those received from doctors have been compiled for feedback in this report.

CASE SYNOPSIS

Alima is a 35-year-old housewife who arrived in Australia 2 years ago from the Middle East and looks after three children. Her main concern is worsening cough and tiredness. She visits the GP to have a general checkup and the doctor orders blood tests, including vitamin D level. Alima spends most of her time indoors and when she goes out she wears long clothes down to her ankles and her wrists and has a veil over her face. Alima returns two weeks later to discuss her blood test results, and her serum vitamin D level (25-OHD) was 25nmol/L. Her medical history was unremarkable and all other tests were within the normal range. (See page 3 for more details.)

Testing for vitamin D deficiency

- Most respondents (98%) identified that Alima was at high risk of vitamin D deficiency and should be tested for it.
- Fewer than half (44%) of respondents stated that they may test Alima for vitamin D level when ordering other routine blood test.

Identifying risk factors for vitamin D deficiency

- Eighty-six per cent of respondents listed at least three risk factors for identifying vitamin D deficiency.
- Use of certain medicines (66%), lack of sunlight exposure (50%) and malabsorption syndrome (49%) were the most common risk factors reported by participants.

Interpreting vitamin D test results

- Most respondents (96%) reported that time of the year was an important factor when interpreting vitamin D test results.
- Eighty-six per cent and 83% of respondents, respectively, stated that degree and consistency of skin covering and skin pigmentation should be considered when interpreting vitamin D test results.

Lifestyle modifications

- More than half of respondents (53%) would recommend that Alima increase her sunlight exposure; while 18% would recommend that she engage in regular physical activity. Additionally, 17% of respondents recommended that Alima increase her dietary intake of calcium (dairy) and vitamin D (eggs, oily fish and other fortified sources).

Vitamin D supplementation

- Most respondents (95%) recommended a vitamin D supplement for Alima. More than half of respondents (57%) stated that Alima was vitamin D deficient (level of vitamin D 25 < nmol/L) and 51% of participants highlighted that Alima may be unable to get enough sunlight exposure due to cultural reasons.
- All respondents recommended a vitamin D_3 supplement; 56% recommended ostelin, while 39% recommended cholecalciferol.

RESULTS IN DETAIL

Testing for vitamin D deficiency

Respondents were asked whether they would test Alima for vitamin D deficiency. Most (98%) indicated they would order a vitamin D test. Of those who ordered a vitamin D test, most (95%) listed Alima as being at high risk of vitamin D deficiency.

TABLE 1: RATIONALE FOR TESTING VITAMIN D

Reason	% of respondents (n = 200)*
Alima is at high risk of vitamin D deficiency	95
Opportunistically, in addition to other blood tests	44
Patient's request	31
As a screening test for all patients	3
Other	4

* Respondents may have more than one response

Practice points

- Investigate for vitamin D deficiency only in at-risk populations. These include people who:
  - cover themselves for religious or cultural reasons[1,2]
  - have naturally dark skin[3]
  - are housebound, particularly those over the age of 65 who are in residential care facilities[4–6]
  - deliberately avoid sun exposure because they may be at an increased risk of skin cancer[7,8]
  - have limited access to sunlight due to chronic illness or disability or because of working conditions such as shiftwork
  - have malabsorption syndrome or are obese.[4,9–11]

Identifying risk factors for vitamin D deficiency

Respondents were asked to identify possible risk factors for vitamin D deficiency. Most (99%) identified at least one risk factor, while 98% listed two risk factors, and 86% listed three.

TABLE 2: RISK FACTORS FOR VITAMIN D DEFICIENCY IDENTIFIED BY RESPONDENTS

Risk factors	% of respondents (n = 198)*
Use of certain medicines	66
Lack of sunlight exposure	50
Malabsorption syndrome	49
Dietary habits	27
Past medical history	22
Level of skin pigmentation	13
Extent of skin covering	12
Others†	12
Regular physical activity	11
Family history	8
Age and weight	8

* Respondents may have more than one response

† Others included previous history of vitamin D deficiency and supplementation, use of sunscreen, housebound and occupation, time of the year when the test was conducted, previous history of tests and method used to investigate vitamin D deficiency,

Practice points

- Assess individuals for risk factors for vitamin D deficiency. These include:
  - lack of sunlight exposure, which is the main source of vitamin D for Australians[4]
  - level of skin pigmentation, as increased melanin reduces the cutaneous production of vitamin D_3[14]
  - extent of skin covering for cultural or religious reasons, as clothing effectively absorbs ultraviolet B (UV-B) radiation[1,2]
  - dietary habits (intake of vitamin-D-rich foods such as salmon, herring, mackerel, eggs, and fortified foods such as margarines and milk)[7]
  - malabsorption syndrome (investigate for coeliac disease and inflammatory bowel disease)[7]
  - checking previous and current medication history (e.g. use of anticonvulsants may interfere with vitamin D metabolism)[7].

Interpreting vitamin D test results

Two weeks later Alima has come to discuss her blood test results, and her serum vitamin D level (25-hydroxyvitamin D [25-OHD]) is 25 nmol/L (normal range 50–150 nmol/L).

Respondents were asked to highlight factors they would consider when interpreting vitamin D test results. Ninety-six per cent chose the time of year as an important factor, while 86% chose degree and consistency of skin covering as factors to consider when interpreting vitamin D test results. Skin pigmentation was also considered as an important factor by 83% of participants.

TABLE 3: FACTORS CONSIDERED BY RESPONDENTS WHEN INTERPRETING VITAMIN D TEST RESULTS

Factors	% of respondents (n = 200)*
Time of the year when the test was performed	96
Degree and consistency of skin covering (reduced exposure to sunlight)	86
Level of skin pigmentation	83
Method used to measure vitamin D level	64
Other†	3

* Respondents may have more than one response

† Other included vitamin D supplementation (last three months), medication history, renal function of the patient, diet, and ethnic background. One participant also recommended that the vitamin D test should be repeated.

Practice points

- Use the guide below when diagnosing individuals with vitamin D deficiency.[4,8]

Vitamin D status	25-OHD level (nmol/L)
Vitamin D adequacy	50
Mild deficiency	25–50
Moderate deficiency	12.5–25
Severe deficiency	15–25

- Consider time of the year when interpreting vitamin D test results. The amount of UV-B radiation in sunlight changes substantially with season, latitude and time of the day. Serum vitamin D levels (25-OHD) are highest at the end of summer and lowest at the end of winter.[12,13]
- Consider inter-laboratory variability when interpreting vitamin D test results, as it may have clinical implications such as diagnosing a patient with vitamin D deficiency.[15–19]
- Assess vitamin D status 3–4 months after starting treatment.[4]

Lifestyle modifications

Respondents were asked to suggest lifestyle modifications for Alima. Fifty-three per cent recommended Alima to increase sunlight exposure if culturally acceptable, while 18% advised Alima to engage in regular physical activity. Seventeen per cent would advise an increased dietary intake of calcium- and vitamin-D-rich foods. Participants highlighted that lifestyle modifications will promote vitamin D production.

TABLE 4: LIFESTYLE MODIFICATIONS SUGGESTED BY RESPONDENTS

Suggestions	% of respondents (n = 197)*
Increase sun exposure	53
Increase physical activity	18
Improve dietary intake of calcium-rich and vitamin-D-fortified foods	17
Recommend a vitamin D supplement	8
Others†	4

* Respondents may have more than one response

† Others included avoiding medication that may interfere with vitamin D metabolism, avoiding risk factors for osteoporosis, and trying to assess cultural rigidity regarding clothing issues, and weight reduction

Practice points

Sun exposure

- Recommend short walks of 10 minutes or less in the morning or afternoon most days of the week. Longer periods of sunlight exposure may be needed in winter, particularly in the southern states (15 minutes at lunchtime in Sydney or 30 minutes at lunchtime in Hobart).[4]
- Advise longer periods of sunlight exposure for individuals with naturally dark skin.[4]
- Recommend exposing the face, hands and arms to sunlight in private, for individuals who wear body coverings for religious or cultural reasons.
- Advise people that prolonged sun exposure is counterproductive, as it increases the risk of skin cancer.[4,8,20] Further information about sun exposure can be found on the Cancer Council Website: www.cancer.org.au/cancersmartlifestyle/SunSmart/VitaminD.htm

Role of diet

- Recommend increased dietary intake of calcium and vitamin-D-rich food (e.g. dairy products and fatty fish such as salmon, trout and sardines) especially to those at high risk of vitamin D deficiency.

Vitamin D supplementation

Respondents were asked whether they would recommend a vitamin D supplement to Alima and also to provide a reason for their recommendation. Tables 5 and 6 summarise the types of vitamin D supplements, and reasons for supplementation, respectively.

- 95% of respondents recommended vitamin D supplementation. More than half (57%) stated that Alima was vitamin D deficient (based on vitamin D level of 25 nmol/L) and about 51% highlighted that Alima may be unable to get enough sunlight exposure due to cultural or religious reasons.
- 66% of respondents recommended 1000–3000 IU of cholecalciferol, while 21% of participants prescribed 3000–6000 IU of cholecalciferol daily. Additionally, 65% of participants recommended vitamin D supplementation should be continued for at least 6–12 weeks.
- 12% of respondents suggested that a vitamin D test should be repeated at least 12 weeks after treatment.
- A further 68% of respondents recommended 1000–3000 IU of cholecalciferol for 6–12 weeks.

TABLE 5: VITAMIN D SUPPLEMENTS RECOMMENDED BY RESPONDENTS

Supplements	% of respondents (n = 197)
Vitamin D_3:	95
- Ostelin	56
- Other brands of cholecalciferol products	39
Others (including, vitamin D and vitamin D_3 drops, and combinations of calcium and vitamin D)	5

Practice points

Vitamin D supplementation

- Recommend vitamin D supplements for people at high risk of vitamin D deficiency.
- Recommend 3000–5000 IU of cholecalciferol daily for 6–12 weeks for individuals with a moderate–severe deficiency of vitamin D.4 Diet alone does not provide an adequate amount of vitamin D, so ongoing supplementation may be necessary for people at high risk of vitamin D deficiency.[4]
- Reserve calcitriol, the active form of vitamin D, for specific indications such as renal failure only. Calcitriol has a narrow therapeutic index and is not recommended in the treatment of vitamin D deficiency.[4,21]

TABLE 6: REASONS FOR VITAMIN D SUPPLEMENTATION SUGGESTED BY RESPONDENTS

Reasons	% of respondents (n = 197)*
Vitamin D level-25nmol/L	57
Unlikely to get enough sunlight exposure due to cultural reasons	51
Reduce risk of osteomalacia	9
Others†	4

* Respondents may have more than one response

† Others included high risk of vitamin D deficiency, childbearing age and level of skin pigmentation

Practice points

- Help your patients understand more about vitamin D. Download NPS resources, available in many different languages from www.nps.org.au/health_professionals/order_free_information/order_now
- Be aware that supplements containing 200 IU or less of vitamin D (which includes many multivitamins) are inadequate to treat vitamin D deficiency.[4]

Professor Rebecca S Mason
Deputy Director, Bosch Institute
President, ANZ Bone and Mineral Society
University of Sydney

COMMENTARY 1

Key points

- Patients at high risk of inadequate vitamin D include:
  - people who spend most of their time indoors or who do not expose their skin to sunlight (includes older people, people who wear modest dress, those who are ill and shift workers)
  - people with naturally dark skin
  - people with conditions such as obesity or malabsorption)
  - those using medications (such as anticonvulsants), which affect vitamin D storage or breakdown.
- The target level of > 50nmol/L for 25-hydroxyvitamin D (25-OHD), the major circulating vitamin D metabolite, is recommended for adequate calcium homeostasis and bone and muscle function. Although there is emerging evidence that levels up to 75nmol/L may be optimal for other health effects, there is currently inad-equate evidence to recommend this.
- Since 25-OHD values decrease at the end of winter, target values at the end of summer may need to be higher (>60nmol/L) to accommodate this.
- Since there is little vitamin D in most foods, where increased sunlight exposure is impractical or inadvisable, supplements are likely to be needed.

Alima's presentation is not uncommon. Frank vitamin D deficiency (<25nmol/L) has been reported in 60–80% of heavily pigmented and/or veiled young Australian women attending ante-natal clinics.[2,23]

Testing for vitamin D and risk factors for vitamin D deficiency

The most important source of vitamin D is exposure to sunlight. Energetic ultraviolet-B (UV-B) light rays are absorbed by 7-dehydro-cholesterol in skin and provide energy for a chemical reaction that produces vitamin D.

People at risk for vitamin D deficiency are those who spend most of their time indoors during the day, reducing sun exposure to bare skin, which includes:

- many older people
- those who are ill
- people at high risk of skin cancer, including very fair people
- many office and shift workers
- those who wear modest dress and/or avoid sunlight for religious or cultural reasons.

The pigment melanin absorbs UV-B and prevents it from reaching the vitamin D substrate.

Although sunscreens also absorb UV-B, in practice their use makes little difference to 25-OHD levels,[24] probably because people using sunscreens are at least likely to be going out into the sun, and sunscreens are typically applied inadequately.

25-hydroxyvitamin D levels are reduced in obese individuals, as vitamin D is sequestered in fat, and reduced in patients with malabsorption (due to disease or induced by agents such as Orlistat). Some medications, such as certain anticonvulsants (e.g. phenytoin) accelerate the degradation of vitamin D and its metabolites, as does a low calcium intake and the resultant hyperparathyroidism.[25] While there is no evidence to support population screening at present, the extensive list of evidence-based risk factors means that many patients are likely to warrant testing for vitamin D.

Interpreting vitamin D results

Vitamin D is converted, mainly in the liver, to 25-OHD, the major circulating metabolite and the compound measured to assess vitamin D status. While assays for vitamin D are not particularly precise, and should be done in an accredited laboratory, they show no major systematic errors.[26] From extensive studies in the literature on suppression of excess

parathyroid hormone and on bone and muscle function, there is a reasonable consensus that target levels of 25-OHD for these classic effects should be at least 50 nmol/L or possibly 60 nmol/L.[4,22,27] Since there is a significant drop in 25-OHD levels over winter,[28] the test result should be interpreted with the season in mind. Regardless of the reason for a low value, adverse effects on bone turnover, secondary hyperparathyroidism, bone density and muscle function have been demonstrated in many studies when the 25-OHD is < 50nmol/L. Osteomalacia and rickets are not generally seen until 25-OHD levels are < 12.5nmol/L or so.[4,22] There is emerging evidence from epidemiological and other studies that optimal vitamin D levels for other health outcomes may be ≥ 75nmol/L, but to date the evidence is not sufficiently robust to recommend this as a target for the population.[29]

Lifestyle modifications

If recommending increased sun exposure, it is worth bearing in mind that Australia has high rates of skin cancer, at least in the Caucasian population, and that vitamin D in skin is broken down by continued exposure to UV light. For these reasons, particularly in summer, short exposures of about 6–8 minutes of sunlight to face, arms and hands, around mid-morning or mid-afternoon, most days, are likely to be enough to maintain vitamin D levels. For people with dark skin, 3–6 times longer exposures may be required.[24] In winter, for most of Australia, to get the energetic UVB rays required to make vitamin D, sun exposure should be around noon, with times varying from 7 minutes in Cairns to about 30 minutes in Hobart. The area of skin exposed in winter is also likely to be smaller, though exercise, like a brisk walk, may allow people to uncover more.

There is some evidence that increased dietary calcium intakes may slow the rates of degradation of 25-OHD and so contribute to better vitamin D status.[25] Although fish and some other foods have a little vitamin D, it is difficult to get more than 5–10% of adequate vitamin D input from the diet. The most recent recommended dietary intakes for people aged 1–70 years are 600 IU/day, and for those over 70, 800 IU/day.[22]

For many people, like Alima, advice to increase sun exposure is impractical. This also includes:

- people at high risk of skin cancer, for example, patients taking immuno-suppressants
- older people or those who are ill, who may not be physically able to get outdoors on a regular basis
- people who wear modest dress
- people who have a cultural aversion to becoming pigmented, such as women from Asia.

For all these people, supplements seem to be a reasonable alternative.

Vitamin D supplementation

Given the problems with sun damage, for people with low vitamin D levels treatment with supplements may be more practical too. On average, 25-OHD levels increase by about 10-20 nmol/L after about 8–12 weeks for each 1000 IU (25 micrograms)/day given as a supplement, though with wide variation.[30] For this reason, supplements of 3000–5000 IU/day for 6–12 weeks may be reasonable for people with moderate (<25 nmol/L) to severe (<12.5 nmol/L) deficiency, followed by a repeat test at 9–12 weeks.[4] An upper tolerable level of vitamin D intake of 4000 IU/day has been recommended,[22] but short-term higher doses seem to be well tolerated.

To get around problems of cost and adherence, weekly or monthly dosing is possible.[31] High-dose supplements are not generally available in Australia, except through compounding chemists, where quality control may be an issue and the long-term effects of intermittent high-dose vitamin D have not yet been adequately studied.[32,33]

Dr Simon Vanlint
Assistant Dean
Lecturer, Discipline of General Practice,
University of Adelaide
Adelaide, SA

COMMENTARY 2

Key points

- Exposure to UV light from sunlight is the principal source of vitamin D for most Australians. Anyone who is institutionalised, 'shut-in', dark-skinned or who spends little time outdoors with exposed skin is at risk of insufficiency or frank deficiency. Even in south-east Queensland nearly half of the population may lack adequate vitamin D.
- Unless an individual is willing to eat significant amounts of oily fish it is very difficult to obtain sufficient vitamin D through diet. This means that many people will need supplementation.
- While there is a reasonable consensus that levels of 50–60 nmol/L are adequate for bone health, there is growing speculation that other tissues and disease states may require higher levels. Clinicians face the difficult task of deciding what is best for each patient, trying to reconcile trial evidence, population-level recommend-ations and the patients' specific require-ments. Given that vitamin D is cheap and very safe, many will choose a higher target level.

Who to test for vitamin D — the clinician's dilemma

While the evidence for wholesale population screening is lacking, at an individual patient level there are often reasons to consider vitamin D testing. People at risk of inadequate vitamin D levels include the elderly, those in residential care and those like Alima with dark skin and who cover themselves for religious or cultural reasons. People who have been hospital inpatients for 7 days or more could also be tested.

Renal disease may also affect the activation of vitamin D. Because vitamin D levels may affect specific disease states, people with these diseases could be tested, even in the absence of these risk factors. These diseases include:

- diabetes
- depression
- multiple sclerosis
- cardiovascular disease
- some cancers
- COPD/asthma
- skin diseases
- cognitive impairment.[34]

There is also evidence that vitamin D levels may influence susceptibility to infections such as tuberculosis and respiratory infections, including influenza.[35] Finally, the likely con-sequences of inadequate vitamin D in pregnancy for both mother and child are such that routine antenatal testing has been recommended.[36]

What target level should be aimed for?

For the best-understood target tissue, bone, there is reasonable consensus that 50–60 nmol/L is adequate.[37] This is based on biochemical markers, such as parathyroid hormone and bone turnover markers, and prospective clinical trials. The list of diseases outside of bone in which vitamin D may play a role is large, and growing.[38]

There is good evidence that vitamin D supplementation prevents falls in the elderly by exerting a beneficial effect on muscle,[39,40] but it has been difficult to transform a reduction in falls to a reduction in fractures, mainly due to issues of study design, size and cost.

There is intense speculation that levels of 75 nmol/L or more may be beneficial in the preventing and/or treating a wide variety of diseases and may even reduce all-cause mortality,[41] largely on the basis of studies showing an association between inadequate vitamin D levels and these diseases. Good evidence is available for falls, some cancers, depression and respiratory disease, with reasonable evidence also available for cardiovascular disease and chronic

musculoskeletal pain. It will be several years before high-quality, prospective interventional studies provide additional evidence to guide practice.

How to treat and follow up

The obvious approach is to recommend additional sun exposure. This may raise concerns about skin cancer and photo-ageing, and at present lacks an evidence base as a therapy, despite its likely role in prevention.

Oral supplements of 1000 IU daily are widely recommended, although people with moderate to severe deficiency may require higher initial doses. Because vitamin D is highly fat soluble, obese individuals may also require loading doses. People with active malabsorption (e.g. poorly managed coeliac disease) may not absorb oral supplements and may require specialist referral with a view to parenteral treatment.

Compounding chemists can prepare high oral doses on prescription, typically 100,000 IU per dose in an oily medium. It is possible that quality control of the precise dose may be an issue, although whether this is clinically meaningful is unclear. There is evidence that giving very high doses (500,000 IU as an annual stat dose) temporarily increases the risk of falls and fractures in older individuals,[33] although the mechanism for this is unknown. Although 100,000 IU given every 3–4 months is probably safe,[42] the precise limits of dose and frequency have not been defined, and caution should be exercised, especially in older individuals.

In general, vitamin D supplements are very safe and have a wide therapeutic window. There is a theoretical risk of renal stones, although this is uncommon in day-to-day practice even at high doses.[43] It seems reasonable to check vitamin D levels 6–8 weeks after supplementation begins, although once again this lacks a strong evidence base.

Calcium and vitamin D

Although this review is primarily concerned with vitamin D, many preparations also contain calcium agents, and many individuals use them in combination. A recent meta-analysis has suggested that calcium supplementation may result in adverse cardiovascular outcomes.[44] It is worth noting that this meta-analysis excluded those taking vitamin D and that the studies included did not have cardiovascular disease as a primary outcome. Another recent review found no adverse effect from calcium,[45] while a study specifically investigating the effect of calcium on cardiovascular disease found no effect overall, with a decreased relative risk in individuals with previous atherosclerotic disease.[46]

While it is reasonable to be cautious when advising patients about calcium supplementation, for many individuals the possible cardiovascular risks will be outweighed by the proven benefits.

REFERENCES

1. Diamond TH, Levy S, Smith A, et al. High bone turnover in Muslim women with vitamin D deficiency. Med J Aust 2002;177:139–41.
2. Grover S, Morley R. Vitamin D deficiency in veiled or dark-skinned pregnant women. Med J Aust 2001;175:251–2.
3. McGillivray G, Skull S, Davie G, et al. High prevalence of asymptomatic vitamin D and iron deficiency in East African immigrant children and adolescents living in a temperate climate. Arch Dis Child 2007;92:1088–93.
4. The Australian and New Zealand Bone and Mineral Society, Endocrine Society of Australia and Osteoporosis Australia. Vitamin D and adult bone health in Australia and New Zealand: a position statement. Med J Aust 2005;182:281–5.
5. Sambrook P, Cameron I, Cumming R, et al. Vitamin D deficiency is common in frail institutionalised older people in northern Sydney. Med J Aust 2002;176:560.
6. Flicker L, Mead K, MacInnis R, et al. Serum Vitamin D and Falls in Older Women in Residential Care in Australia. J AmGeriatr 2003;51:1533–8.
7. Pearce SH, Cheetham TD. Diagnosis and management of vitamin D deficiency. BMJ 2010;340:142–7.
8. Australian and New Zealand Bone and Mineral Society, Osteoporosis Australia, The Australasian College of Dermatologists, et al. Risks and benefits of sun exposure: Position Statement. The Cancer Council of Australia; Sydney, 2007.
9. van der Mei IAF, Ponsonby AL, Dwyer T, et al. Vitamin D levels in people with multiple sclerosis and community controls in Tasmania, Australia. J Neurol 2007;254:581–90.
10. Snijder MB, van Dam RM, Visser M, et al. Adiposity in relation to vitamin D status and parathyroid hormone levels: a population-based study in older men and women. J Clin Endocrinol Metab 2005;90:4119–23.
11. Vilarrasa N, Maravall J, Estepa A, et al. Low 25-hydroxyvitamin D concentrations in obese women: their clinical significance and relationship with anthropometric and body composition variables. J Endocrinol Invest 2007;30:653–8.
12. Pasco J, Henry M, Nicholson G, et al. Behavioural and physical characteristics associated with vitamin D status in women. Bone 2009;44:1085–91.
13. Kimlin M, Harrison S, Nowak M, et al. Does a high UV environment ensure adequate Vitamin D status? J Photochem Photobiol B 2007;89:139–47.
14. Clemens TL, Adams JS, Henderson SL, et al. Increased skin pigment reduces the capacity of skin to synthesise vitamin D3. Lancet 1982;1:74–6.
15. Snellman G, Melhus H, Gedeborg R, et al. Determining vitamin D status: a comparison between commercially available assays. PLoS One 2010;5:e11555.
16. Lai J, Lucas R, Clements M, et al. Assessing vitamin D status: pitfalls for the unwary. Mol Nutr Food Res 2010;54:1062–71.
17. Wallace A, Gibson S, de la Hunty A, et al. Measurement of 25-hydroxyvitamin D in the clinical laboratory: current procedures, performance characteristics and limitations. Steroids 2010;75:477–88.
18. Harrison S, Nowak M, Buettner P, et al. Public health and clinical dilemmas resulting from imprecise vitamin D tests. J Rural Trop Public Health 2009;8:53–8.
19. Binkley N, Krueger D, Cowgill C, et al. Assay variation confounds the diagnosis of hypovitaminosis D: a call for standardization. J Clin Endocrinol Metab 2004;89:3152–7.
20. Nowson C, Diamond T, Pasco J, et al. Vitamin D in Australia. Issues and recommendations. Aust Fam Physician 2004;33:133–8.
21. Rossi S, ed. Australian Medicines Handbook. Adelaide: Australian medicines Handbook Pty Ltd, 2011.
22. Institute of Medicine. Dietary reference intakes for calcium and vitamin D. Washington DC: Institute of Medicine 2011, (accessed 20 July 2011)
23. Bowyer L, Catling-Paull C, Diamond D, et al. Vitamin D, PTH and calcium levels in pregnant women and their neonates. Clin Endocrinology 2009;70:372–7.
24. Springbett P, Buglass S, Young AR. Photoprotection and vitamin D status. Journal Photochem Photobiol 2010;101:160–8.
25. Davies M, Heys SE, Selby PL, et al. Increased catabolism of 25-hydroxyvitamin D in patients with partial gastrectomy and elevated 1,25-dihydroxyvitamin D levels. Implications for metabolic bone disease. J Clin Endocrinol Metab 1997;82:209–12.
26. de la Hunty A, Wallace AM, Gibson S, et al. UK Food Standards Agency Workshop Consensus Report: the choice of method for measuring 25-hydroxyvitamin D to estimate vitamin D status for the UK National Diet and Nutrition Survey. Brit J Nutr 2010;104:612–9.
27. Henry HL, Bouillon R, Norman AW, et al. 14th Vitamin D Workshop consensus on vitamin D nutritional guidelines. J Steroid Biochem Mol Biol 2010;121:4–6.
28. van der Mei I, Ponsonby AL, Engelsen O, et al. The High Prevalence of vitamin D insufficiency across Australian populations is only partly explained by season and latitude. Environ Health Perspect 2007;115:1132–9.
29. Heaney RP, Holick MF. Why the IOM recommendations for vitamin D are deficient. J Bone Miner Res 2011;26:455–7.
30. Aloia JF, Patel M, Dimaano R, et al. Vitamin D intake to attain a desired serum 25-hydroxyvitamin D concentration. Am J Clin Nutr 2008;87:1952–8.
31. Ish-Shalom S, Segal E, Salganik T, et al. Comparison of daily, weekly, and monthly vitamin D3 in ethanol dosing protocols for two months in elderly hip fracture patients. J Clin Endocrinol Metab 2008;93:3430–5.

32. Trivedi DP, Doll R, Khaw KT. Effect of four monthly oral vitamin D3 (cholecalciferol) supplementation on fractures and mortality in men and women living in the community: randomised double blind controlled trial. BMJ 2003;326:469.
33. Sanders KM, Stuart AL, Williamson EJ, et al. Annual high-dose oral vitamin D and falls and fractures in older women: a randomized controlled trial. JAMA 2010;303:1815–22.
34. Plum LA, DeLuca HF. Vitamin D, disease and therapeutic opportunities. Nat Rev Drug Discov 2010;9:941–55.
35. Cannell JJ, Vieth R, Umhau JC, et al. Epidemic influenza and vitamin D. Epid Infection 2006;134:1129–40.
36. Viljakainen HT, Korhonen T, Hytinantti T, et al. Maternal vitamin D status affects bone growth in early childhood--a prospective cohort study. Osteoporosis International 2011;22:883–91.
37. Lips P. Which circulating level of 25-hydroxyvitamin D is appropriate? J Steroid Biochem Mol Biol 2004;89:611–3.
38. Heaney RP. The case for improving vitamin D status. J Steroid Biochem Mol Biol 2007;103:635–41.
39. Bischoff-Ferrari HA, Dawson-Hughes B, Staehelin HB, et al. Fall prevention with supplemental and active forms of vitamin D: a meta-analysis of randomised controlled trials. BMJ 2009;339:b3692.
40. Flicker L, MacInnis RJ, Stein MS, et al. Should older people in residential care receive vitamin D to prevent falls? Results of a randomized trial. J AmGeriatr 2005;53:1881–8.
41. Autier P, Gandini S. Vitamin D supplementation and total mortality: a meta-analysis of randomized controlled trials. Arch Intern Med 2007;167:1730–7.
42. Wigg AE, Prest C, Slobodian P, et al. A system for improving vitamin D nutrition in residential care. Med J Aust 2006;185:195–8.
43. Diamond TH, Ho KW, Rohl PG, et al. Annual intramuscular injection of a megadose of cholecalciferol for treatment of vitamin D deficiency: efficacy and safety data. Med J Aust 2005;183:10–2.
44. Bolland MJ, Grey AB, Gamble GD, et al. Effect of osteoporosis treatment on mortality: a meta-analysis. J Clin Endocrinol Metab 2010;95:1174–81.
45. Wang L, Manson JE, Song Y, et al. Systematic review: Vitamin D and calcium supplementation in prevention of cardiovascular events. Ann Intern Med 2010;152:315–23.
46. Lewis JR, Calver J, Zhu K, et al. Calcium supplementation and the risks of atherosclerotic vascular disease in older women: results of a 5-year RCT and a 4.5-year follow-up. J Bone Miner Res 2011;26:35–41.