Should measurement of vitamin D and treatment of vitamin D insufficiency be routine in New Zealand?

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Abstract

Epidemiological studies have reported associations between lower vitamin D levels and a great variety of diseases, prompting calls for widespread treatment of individuals with low vitamin D levels.

Most of New Zealand's population have vitamin D levels for at least part of the year that are considered insufficient (25-hydroxyvitamin D <50–80 nmol/L). However, evidence for benefits of vitamin D supplementation in such populations is controversial and there is some evidence of harmful effects. Until adequately powered, randomised, controlled trials of vitamin D supplementation demonstrate safe improvements in health, clinicians should not focus on detecting/treating individuals with vitamin D insufficiency, instead treating those at high risk of vitamin D deficiency (25-hydroxyvitamin D <25 nmol/L), such as the frail elderly, and those with specific clinical indications. Treatment for such individuals does not require vitamin D measurements.

Requests for vitamin D measurements in Auckland have nearly quadrupled in the past decade, from 8500 in the year 2000 to 32,800 in 2010, with substantial increases in cost. Vitamin D measurement is often inaccurate and imprecise, and the vast majority of tests performed currently do not reveal vitamin D deficiency. Therefore, a move away from routine vitamin D measurements seems sensible, though they are still indicated when investigating suspected metabolic bone disease or hypocalcaemia.

Background

Vitamin D deficiency causes rickets in children and myopathy, osteoporosis, secondary hyperparathyroidism, and osteomalacia in adults.[1] The precise vitamin D level at which these conditions occur is not known and may be influenced by other factors such as dietary calcium intake, but a widely accepted definition of vitamin D deficiency is serum 25-hydroxyvitamin D (25OHD) <25 nmol/L.[1]

More recently, vitamin D insufficiency, variously defined as 25OHD <50-80 nmol/L,[2] has been associated in epidemiological studies with a very wide variety of diseases, including cancer, neurological disorders, vascular diseases, infectious conditions, autoimmune diseases, osteoporosis, type 2 diabetes mellitus and obesity.[3] These findings have prompted a substantial increase in requests for vitamin D measurements and led to calls for widespread treatment of individuals with "insufficient" vitamin D levels.[3]

Defining vitamin D insufficiency as 25OHD <80 nmol/L classifies most of New Zealand's population as vitamin D insufficient. In the 1997 National Nutrition survey, the mean 25OHD level was 50 nmol/L and only 25% of individuals had levels >70

nmol/L.[4] Thus, the implication of recommending treatment of vitamin D insufficiency is that most of New Zealand's population would be treated, at least in the winter and spring months when 25OHD levels are lowest.

A policy of such widespread use of vitamin D supplements should only be implemented in a context of rigorous evidence of the benefits and safety of vitamin D supplements in populations with vitamin D insufficiency. Here, we present 10 reasons why such a policy should not currently be implemented, and discuss a strategy for sensible policy on measurement of vitamin D.

Evidence for treating vitamin D insufficiency

Defining vitamin D insufficiency: many methods, much inconsistency, no consensus—Vitamin D insufficiency can be defined using surrogate endpoints such as intestinal calcium absorption, parathyroid hormone (PTH) levels, bone density, or clinical endpoints such as falls, fractures or cardiovascular events, and the definition can be based on data from randomised control trials (RCTs) or observational (non-experimental) studies.[2]

Most definitions are based on surrogate skeletal endpoints such as PTH, although there is little, if any, evidence that such surrogate endpoints are valid predictors of key clinical endpoints such as fracture, and it is not clear what surrogate endpoints should be used for non-skeletal clinical events. Moreover, definitions based upon data from observational studies vary substantially from those based upon RCTs, and definitions derived using different surrogate endpoints are also inconsistent.[2] Consequently, definitions of vitamin D insufficiency range from as low as 30 nmol/L to >100 nmol/L,[2] with some experts now recommending a threshold of 50 nmol/L and others 75-80 nmol/L.[2]

The Institute of Medicine recently concluded that a level of 40 nmol/L represents the median population requirement.[5] None of these definitions states how seasonal variation of 25OHD should be dealt with: the month of vitamin D measurement is the strongest determinant of 25OHD levels in populations distant from the equator.[6,7] Presumably these thresholds refer to the lowest 25OHD level throughout the year, which occurs in late winter or early spring. If this is the case, summertime 25OHD levels much higher than these thresholds are required to ensure year round vitamin D sufficiency. For example summertime 25OHD levels of 90-120 nmol/L can be required to ensure wintertime 25OHD >80 nmol/L.[8]

Measuring vitamin D is difficult and expensive—25OHD is the metabolite that best reflects overall vitamin D status, but measuring it is technically challenging, and there is substantial variation in results between assays, and between laboratories reporting 25OHD values.[9-11] The assays that are generally accepted as the most accurate [liquid chromatography tandem mass spectrometry (LC-MS/MS)] are not widely available.

Typical 25OHD immunoassays may give results differing by up to 40% from the LC-MSMS result,[10] meaning that clinicians cannot be certain that measurements of 25OHD in the insufficient range truly indicate low vitamin D status. A further drawback is that measurement of 25OHD is expensive, and a single measurement can cost substantially more than the annual cost of vitamin D supplements for an individual.

Interpreting observational studies- correlation is not causality—Almost all of the recent data linking vitamin D insufficiency with non-skeletal endpoints comes from observational studies, but by design, observational studies can only ever show associations between variables and cannot prove a causal relationship.[12]

Observational studies usually divide the cohort into various subgroups by 25OHD levels, and compare outcomes between the subgroups. However, the baseline characteristics of the subgroups vary- vitamin D insufficient subgroups are older and heavier, exercise less, have more co-morbidities and are more frail/less healthy than vitamin D sufficient subgroups.[13] Researchers usually try to account for these differences by adjusting for the variables which differ between the subgroups in their models. However, adjusting for healthiness is difficult, and such adjustments may not include all relevant variables in the model, and/or may not account for the differences in health between the groups.[14]

A further bias rarely considered is the constant risk fallacy. Adjusting for covariates assumes that the relationship between the covariate and the outcome is consistent for all values of the covariate.[15] However, this assumption is rarely tested and often untrue. For example, there has been a consistent secular trend for increasing life expectancy over recent decades, thus a cohort aged 60y will have a lower mortality rate than a cohort aged 70y even taking account of the 10y age difference between the groups. Similar differences may apply to other variables relevant to vitamin D insufficiency, such as obesity.

Interpreting observational studies- seasonal issues specific to vitamin D—In countries distant from the equator, 25OHD varies substantially throughout the year in a non-linear manner. This can lead to misclassification, for example when a 25OHD measurement in summer is classified as "sufficient" although, because of seasonal variation, a 25OHD measurement from the same subject in winter would be classified as "insufficient".[8] Some studies do not account for seasonal variation, others group individuals by season of measurement, ignoring the substantial changes in 25OHD that occur within each season, and others adjust for season using linear techniques even though the seasonal variation in 25OHD is non-linear. The effects of such misclassification have not been well studied.

Interpreting observational studies-conflicting results—While numerous observational studies report associations between vitamin D insufficiency and clinical endpoints, a substantial number do not. For example, while some studies have reported increases in fracture incidence with lower 25OHD levels,[16-19] others have not.[13,20-22] The *lack* of association between vitamin D insufficiency and clinical endpoints in such studies is rarely acknowledged, and often dismissed, by enthusiasts for vitamin D supplementation, and raises the possibility of publication bias in favour of studies reporting associations between vitamin D insufficiency and negative health outcomes.

Interpreting RCTs- calcium and vitamin D are not interchangeable—Many RCTs have tested the intervention of co-administered calcium and vitamin D supplements, yet positive results are attributed to vitamin D. For example, a study that is commonly cited as evidence for benefits of vitamin D on cancer incidence, was actually a comparison of 3 treatments: co-administered calcium and vitamin D, calcium alone,

or placebo.[23] Co-administered calcium and vitamin D had a relative risk of 0.4 for cancer incidence compared with the placebo group.

To determine whether there was an independent effect of Vitamin D, the appropriate comparison is to compare the co-administered calcium and vitamin D arm with the calcium alone arm. For this comparison, there was no significant between-groups difference in the risk of cancer. Similarly, in a meta-analysis of fracture outcomes in 17 trials of calcium with or without vitamin D supplementation, the relative risk of fracture was 0.9 with calcium alone, and was 0.87 with co-administered calcium and vitamin D.[24]

In this meta-analysis, all of the trials studied vitamin D in daily doses of ≤800 IU/day. Similarly, a meta-analysis of 18 trials of vitamin D supplements reported a 7% reduction in mortality.[25] However, 13/18 trials were of co-administered calcium and vitamin D, and vitamin D supplements by themselves did not reduce mortality in this or subsequent meta-analyses.[26,27]

These analyses suggest the addition of vitamin D to calcium supplements does not substantially impact upon either cancer incidence, or fracture incidence, and possible mortality benefits might require co-administered calcium and vitamin D supplements.

RCT evidence for benefit of vitamin D is inconsistent—Results from RCTs of vitamin D supplements for skeletal endpoints in community-dwelling populations with vitamin D insufficiency have been largely negative. Meta-analyses of these studies report no benefit of vitamin D supplements on hip or total fracture when vitamin D alone is the intervention or when calcium and vitamin D are co-administered.[26]

In contrast, in two studies of vitamin D deficient, institutionalised, elderly women at high risk of fracture, co-administered calcium and vitamin D supplements reduced hip and non-vertebral fracture incidence.[28,29] There are a number of RCTs that have reported data on non-skeletal endpoints but few have been adequately powered. While a number of RCTs have reported positive benefits from vitamin D, generally there are more studies, often larger in size and longer in duration, that report no effects. For example, systematic reviews have concluded there is no existing evidence that vitamin D supplements prevent cardiovascular disease,[27,30,31] type 2 diabetes,[27,31] or cancer,[32] or impact upon blood pressure, blood glucose or cholesterol.[27]

Individual RCTs have shown no benefits of vitamin D supplements on body weight,[33] and conflicting results for incidence of respiratory infections.[34,35]

Interpreting meta-analyses: proceed with caution—By mid 2009, there were at least 9 meta-analyses of the 17 RCTs of vitamin D and falls, and at least 14 meta-analyses of the 22 RCTs of vitamin D and fractures.[36] The conclusions vary substantially between analyses, with most reporting no effect, but some reporting strongly positive findings. These conflicting conclusions have generated substantial confusion. The differences between analyses mainly arise from the heterogeneous patterns of results from RCTs, so that methodological decisions regarding inclusion criteria and sub-grouping of studies in the meta-analysis largely determines the results obtained.[36]

Potential for harms from vitamin D supplementation—Discussion on harms from vitamin D supplements has focused almost exclusively on hypercalcaemia, which only occurs as a result of administration of very high doses of vitamin D. However, a recent placebo-controlled RCT of 2256 older women with median baseline 25OHD of 49 nmol/L reported that an annual dose of 500,000 IU vitamin D increased the risks of fractures and falls by 26% and 15%, respectively.[37]

Consistent with these results, another recent RCT of 173 people following hip fracture with mean 25OHD of ~30 nmol/L, compared daily 2000 IU vs. 800 IU vitamin D and reported a 28% (P=0.06, not significant) increase in falls with higher dose vitamin D.[38] Meta-analyses of RCTs of vitamin D used without co-administered calcium report an increase in risk of hip fracture of 15% (95% confidence interval -1% to 33%) of borderline statistical significance.[26]

Some observational studies have reported increased mortality in individuals with higher 25OHD levels compared with intermediate levels,[39,40] although there is no evidence of increased mortality with vitamin D supplementation in meta-analyses of RCTs,[25-27] in which the typical dose studied was 400–800 IU/day. The narrow focus on hypercalcaemia as the only possible and relevant harm of vitamin D supplements was never appropriate and can no longer be defended.

Recent history–déjà vu all over again—Finally, in the very recent past there has been similar enthusiasm for hormone replacement therapy, antioxidants, and folic acid/B vitamins for cardiovascular disease or cancer prevention, based upon promising results from observational studies. When the definitive RCTs have been carried out, harms[41–43] or no benefits[44–46] of these agents were observed.

Implications of vitamin D enthusiasm for health costs—In the Auckland region, there has been an increase of 380% in the number of requests for measurement of 25OHD in the past decade, from 8,500 in 2000 to 32,800 in 2010 (Figure 1). A large proportion of the requests come from a small number of individual requestors. In May and June 2010, 4508 vitamin D measurements were requested by 901 individuals. 50% of individuals requested one measurement over these 2 months, and 80% <5 measurements. However, these 80% of individual requestors only accounted for 26% of the total measurements. 2% of individuals requested 27% of the total measurements, and 9% and 19% requested 61% and 74% respectively of the total measurements (Figure 1).

Figure 1. Number of vitamin D requests per year and by individual requestors over a 2-month period
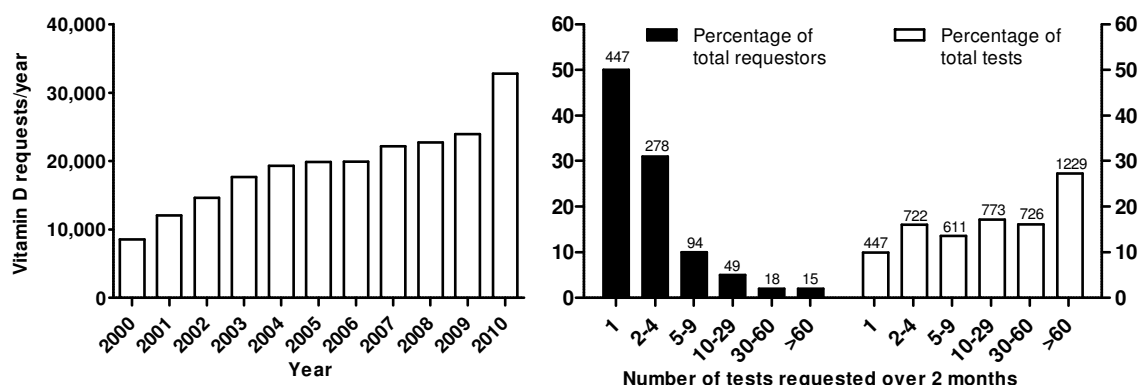
The left panel shows the total number of requests for vitamin D measurements between 2000 and 2010. The right panel shows the relationships between percentage of total requestors (dark bars) or percentage of total tests (open bars) and number of tests per requestor, over a two month period (May, June 2010). The numbers above each bar represent total number of individual requestors (dark bars) or the total number of vitamin D requests (open bars).

The current total cost of a single measurement of 25OHD is $31.10. Thus, the total cost of vitamin D measurement in 2010 in the Auckland region exceeded $1 million. In a previous analysis of >21,000 consecutive results in adults, 25OHD was <25 nmol/L in only 15%, and was ≥50 nmol/L in 52%,[47] suggesting that the considerable majority of tests are carried out in individuals at low risk of vitamin D deficiency.

There was considerable variation in vitamin D status by season: the proportion with vitamin D deficiency was 8%, 10%, 20%, and 21% in summer, autumn, winter, and spring, respectively. Six measurements were needed to detect 1 case with vitamin D deficiency, and the cost of these 6 tests was $186. In the summer months, 13 measurements were needed to detect 1 case, costing $404. In context, a treatment course of vitamin D 50,000 IU monthly for 1 year costs <$10 per patient.

Given that measurement of 25OHD is expensive and mostly identifies people with vitamin D levels in the range for which there is no compelling evidence of benefit from routine supplementation, the utility of 25OHD measurements must be questioned. Furthermore, as most of the 25OHD assays currently in use in New Zealand do not have high precision or accuracy, particularly at lower levels of 25OHD (Christchurch is the only centre that uses a LC-MS/MS assay), clinicians cannot be confident that the result of a single measurement of 25OHD accurately reflects their patient's vitamin D status. Thus, it can reasonably be argued that vitamin D measurements should only be requested when the result is likely to change patient management.

There are a few clear cut examples: investigation of rickets or osteomalacia and other uncommon metabolic bone diseases, and hypocalcaemia. For most individuals who are at high risk of vitamin D deficiency, which includes those with deeply pigmented skin, the frail elderly, and those who actively avoid the sun for cultural or medical

reasons, treatment with vitamin D supplements or encouraging sensible sunshine exposure is reasonable without the need for vitamin D testing.

ACC also recommends that people living in residential care do not require vitamin D testing before or during treatment.[48] For active, community-dwelling New Zealanders with regular sunlight exposure, no testing of vitamin D should be undertaken, and vitamin D supplements are not necessary. With the substantial increase in requests for vitamin D tests over the last decade, in the absence of a clear rationale for the increase in the requirement for these tests, it is likely that voluntary restrictions and education campaigns may be insufficient to halt the increase in vitamin D test requests.

The approach of enforced restriction of vitamin D tests has already occurred elsewhere- for example in several provinces in Canada where the tests are no longer publicly funded. One potential advantage of such restrictions is that the number of requests for 25OHD measurement would be likely reduced so that one or two sites in New Zealand with the most accurate assay (LC-MS/MS) could carry out all testing.

Conclusions

There are considerable uncertainties regarding diagnosis and definition of vitamin D insufficiency, and an absence of rigorous evidence that vitamin D supplementation improves health in vitamin D-insufficient populations. Several large RCTs are underway and hopefully will provide strong evidence of benefits or otherwise of vitamin D supplements.

Unless adequately powered RCTs do provide evidence of health improvement, clinicians should not routinely measure vitamin D or routinely prescribe vitamin D supplements in low-risk populations. However, routine treatment of individuals at high risk of vitamin D deficiency (frail elderly, deeply pigmented, veiled) is reasonable without measurement of 25OHD. Measurement of vitamin D is costly, inaccurate and imprecise, and the majority of tests do not reveal vitamin D deficiency. Therefore, vitamin D testing should be limited to the investigation of suspected metabolic bone disease and hypocalcaemia.

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