OHTAC Recommendation

Clinical Utility of Vitamin D Testing

Presented to the Ontario Health Technology Advisory Committee in November 2009, February, and May 2010

Revised June 2010

OHTAC Ontario Health Technology Advisory Committee

Background

The Medical Advisory Secretariat (MAS) evaluation "Clinical Utility of Vitamin D Testing," on which this document is based, was intended to evaluate the clinical utility of vitamin D testing . As a separate analysis, the MAS evaluation also included a systematic literature review of the prevalence of vitamin D deficiency.

The MAS evaluation did not set out to determine the serum vitamin D thresholds that might apply to non-bone health outcomes. For bone health outcomes, however, the review found no high or moderate quality evidence to support a target serum level above 50 nmol/L. Similarly, no high or moderate quality evidence of vitamin D's effects on non-bone health outcomes (other than falls) could be found.

Vitamin D

Vitamin D stimulates intestinal calcium absorption and is important for bone mineralization. It may also be involved in the regulation of cell growth, proliferation, apoptosis (programmed cell death), and other effects. Vitamin D deficiency may lead to rickets in children and osteomalacia in adults. Factors believed to be associated with vitamin D deficiency include living at higher latitudes, darker skin pigmentation, the winter season, and conditions such as kidney disease and malabsorption syndromes.

Vitamin D alone or in combination with calcium has been shown to improve bone heath outcomes including the risk of fractures in postmenopausal women and elderly men. It has also been shown to reduce the risk of falls in community-dwelling seniors by improving muscle function and strength.

For non-bone health outcomes (other than falls), however, studies have yielded inconsistent results for vitamin D's effects, whether alone or in combination with calcium. (1) Such studied outcomes include cancer (including cancer in general, colorectal, breast, pancreatic, and prostate cancers), all-cause mortality, and cardiovascular disease. (1) In each of these cases, there is no high or even moderate quality evidence to support an association with vitamin D. Given the uncertainty surrounding vitamins D's effect on non-bone health outcomes, the evaluation conducted by MAS focused on falls and vitamin D's effect on bone health. Excluded from this examination are patients with conditions in which vitamin D is implicated as a contributing factor such as osteoporosis, rickets, osteopenia, malabsorption syndromes or drugs that affect vitamin D metabolism.

Target Serum Levels

Vitamin D deficiency is defined by serum levels below 25 nmol/L based on the risk of disease such as rickets and osteomalacia. The optimal serum level of vitamin D to maintain bone and overall health, however, has not been established. Therefore, two conservative thresholds were adopted for this evaluation:

> 25 nmol/L based on a reduction in the risk of rickets and osteomalacia, and

> 40 to 50 nmol/L based on vitamin D's interaction with parathyroid hormone (PTH).

The latter was based on several studies that showed little or no variation in serum PTH with serum vitamin D levels > 40 to 50 nmol/L. Publications of other National organizations have used similar thresholds for the general population, including the United States Office of Dietary Supplements (latest update, November 2009), (2) the Health Council of the Netherlands (2008), (3) and the Food Safety Authority of Ireland (2007). (4)

Ontario Context

Canada's Food Guide (issued by Health Canada in 2007) recommends that Canadians over the age of 2 consume 2 cups (500 ml) of milk or fortified soy beverages daily in order to obtain an adequate amount of vitamin D (200 IU). (5;6) In addition, men and women over the age of 50 should take a daily vitamin D supplement of 400 IU. (5;6) Additional recommendations are available for breastfed infants and children 0 to 12 months old. (6;7) Health Canada is currently reviewing the evidence concerning the safety and effectiveness of vitamin D in order to decide if the current recommended levels need to be updated. (6)

In Ontario, the volume of laboratory vitamin D tests has increased over the past 5 years, from approximately 30,000 tests in 2004, to 400,000 tests in 2008, to over 730,000 in 2009. The total amount billed for vitamin D tests in 2008 was $21.0M, an amount that is expected to surpass $38.0M in 2009.

OHTAC Findings

The research questions of the MAS evaluation were:

1. What is the clinical utility of vitamin D testing?

2. What is the prevalence of vitamin D deficiency in the general population in Canada?

3. What is the prevalence of vitamin D deficiency in subjects with kidney disease in Canada?

A total of 20 publications met the inclusion criteria for the evaluation of the prevalence of vitamin D deficiency, most of which were cross-sectional studies. Briefly, based on low quality evidence, studies of the general population found that approximately 5% had vitamin D deficiency and between 10% and 25% had serum vitamin D levels below 40 to 50 nmol/L. Factors that were found to affect vitamin D status were darker skin pigmentation and testing during winter/spring season. Individuals with kidney disease also appeared to be at higher risk for low serum vitamin D.

Melanin, a pigment that is present in higher amounts in darker skin, may act to filter ultraviolet radiation, possibly leading to lower dermal production of vitamin D. Notwithstanding the biological plausibility for the higher risk in individuals with darker skin pigmentation, a causal-effect relationship could not be demonstrated as the studies did not account for other possible factors affecting serum vitamin D. For instance, it is unclear if confounding variables such as dietary effects could have accounted for the lower serum levels in individuals with darker skin pigmentation.

The 2004 Canadian Community Health Survey on Nutrition showed that in Ontario, less than 50% of females ages 9 to 50 maintained a daily dietary vitamin D intake equal to or above the 200 IU recommended by Health Canada (it was as low as 25% in the 19 to 30 age group). (8) Approximately 44% to 69% of males in the same age groups met Health Canada's requirements. (8) Similarly, four studies included in the MAS evaluation observed a mean vitamin D intake that was below Health Canada's recommendations. (9-12)

The clinical utility of laboratory vitamin D tests was defined as the ability to improve bone health outcomes with MAS' focus being on the average risk population (excluding osteoporosis) and patients with kidney disease. A high quality systematic review published by the Agency for Healthcare Research and Quality (AHRQ) on the association between serum vitamin D levels and bone health outcomes and falls could not determine a precise target serum vitamin D level across all age groups due to study limitations and inconsistencies. (13) No new studies on these outcomes were identified in an updated systematic review published in July 2009. (1)

The fact that an optimal vitamin D level to improve bone health outcomes and the risk of falls has not been established undermines the clinical utility of vitamin D testing. Given this important limitation, as well as the limitations of the assays themselves, the routine use of vitamin D testing cannot be justified. Even if there is any residual uncertainty, there is no evidence that testing vitamin D levels encourages adherence to Health Canada's guidelines. A threshold for vitamin D levels to prevent non-bone health related conditions cannot be established until a causal effect or correlation has been demonstrated between vitamin D and these health conditions. This is as an ongoing research issue around which there is currently too much uncertainty to base any conclusions that would support routine vitamin D testing.

Health Canada has made recommendations on the adequate daily intake of vitamin D for healthy Canadians. (5;7) Since these recommendations are evidence-based and take into account both the safety and health effects of vitamin D among healthy persons (14), they should therefore be followed and promoted.

At present, it seems that the most efficient way to ensure adequate serum vitamin D levels in healthy individuals is to promote Health Canada's recommendations. This is especially important given that Canadian publications, such as the Canadian Community Health Survey (Ontario data) (8), showed that a considerable proportion of the population does not meet the minimum dietary vitamin D intake amount of 200 IU that is currently recommended by Health Canada. This excludes individuals with conditions such as renal disease, osteoporosis, malabsorption syndromes, or taking medications affecting vitamin D metabolism.

Decision Determinants

Based on the evidence found in the MAS report, *Clinical utility of vitamin D testing: an evidence based analysis. Ontario Health Technology Assessment Series 2010; 10(2)*, OHTAC has made the following ratings with respect to the decision determinants criteria:

	Vitamin D Testing in the Healthy Population	Vitamin D Testing for osteoporosis and other conditions and drugs that affect vitamin D absorption or metabolism
Overall clinical benefit	 Low/small	 Unknown (not subject to this analysis)
Consistency with expected societal and ethical values	 Unknown	 Unknown
Value for money	Not evaluated	Not evaluated
Feasibility of adoption into the health system	 Low/small	 High/large

For information on the decision determinants criteria and details on the meaning of the above symbols, please refer to the OHTAC website at http://www.health.gov.on.ca/english/providers/program/ohtac/decision_frame.html .

OHTAC Recommendations

The results of studies included in the evidence-based analysis suggest that individuals with darker skin pigmentation are at a higher risk of low serum vitamin D levels compared to those with lighter skin pigmentation and may need to be specifically targeted with regards to optimum vitamin D intake. Health Canada should be informed of these findings with a view to re-examining the existing guidelines for this population as part of their current review.

There is no moderate to high quality evidence to support vitamin D's effects in non-bone health outcomes such as different types of cancer (colorectal, breast, prostate, pancreatic), all-cause mortality, and some cardiovascular outcomes. The results of a comprehensive, high quality [based on the AMSTAR checklist (15)] systematic review published in August 2009 by the AHRQ do not support a link between vitamin D and different non-bone health outcomes such as different types of cancer, all-cause mortality, and some cardiovascular outcomes. (1) The use of vitamin D with or without calcium has been shown to reduce the risk of fractures and falls in elderly men and postmenopausal women. Therefore the present recommendations are based on the effects of vitamin D in bone health and falls.

Based on the available evidence, OHTAC recommends that:

- Vitamin D intake and supplementation as recommended by Health Canada should be followed and promoted through education of healthcare providers and the general population.
- OHTAC does not recommend routine vitamin D testing*.
- The Ministry of Health Promotion should be informed of the results of this evaluation.

* Excludes patients with conditions such as osteoporosis, rickets, osteopenia, malabsorption syndromes, and renal disease or drugs that affect vitamin D metabolism.

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