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OPINION LETTER

VITAMIN D – ANALYTE OF THE MILLENNIUM

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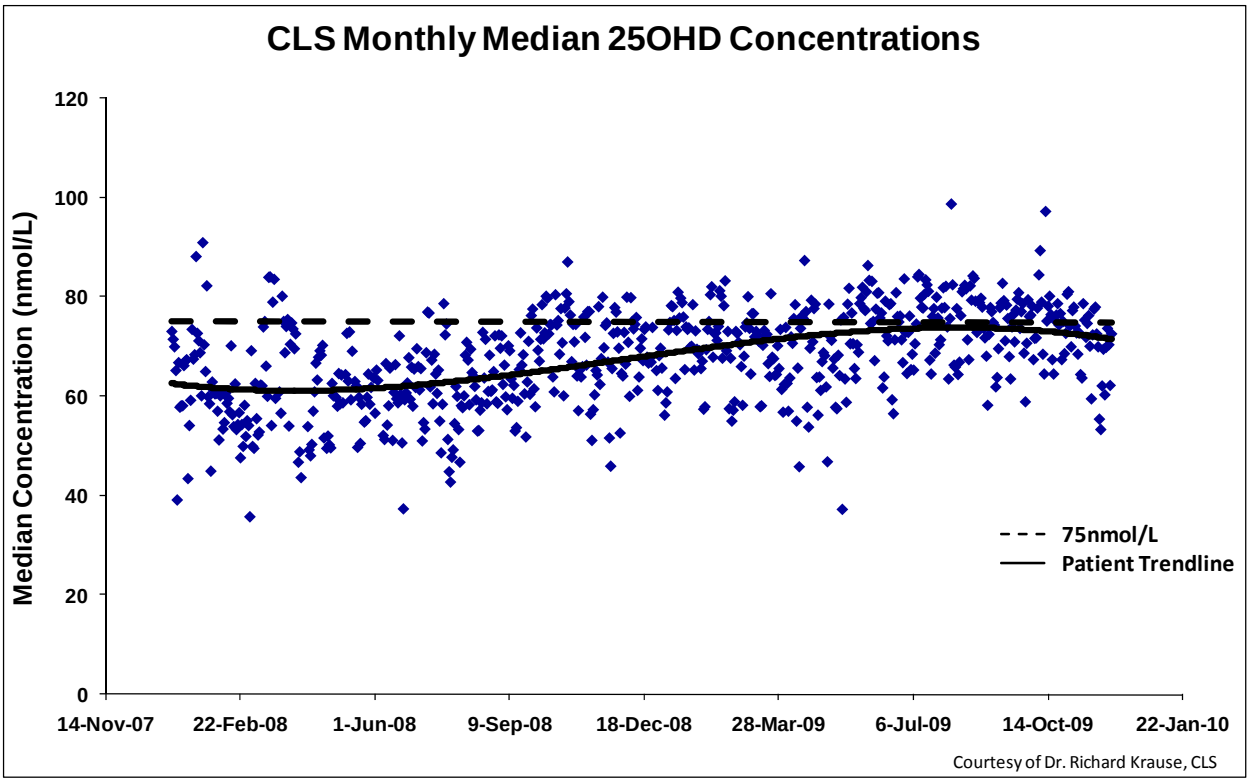
INTRODUCTION

Vitamin D deficiency is a common worldwide phenomenon and has been attributed to a number of factors such as lack of adequate sun exposure and/or use of sunscreen, aging population, obesity, and reduced supplementation. In addition, seasonal variations play a key role in vitamin D status, such as in Calgary and surrounding area, where the extended winter forces people indoors **(Fig. 1).** Furthermore, people with darker skin pigmentation are more likely to be deficient due to less efficient production of endogenous vitamin D (1). Patients suffering from malabsorptive syndromes such as inflammatory bowel disease, celiac disease, Whipple's disease, and Cystic Fibrosis are also prone to vitamin D deficiency (2-4). Previous research has well established that adequate vitamin D intake prevents skeletal deformities in children and while in adults, it reduces the risk of osteopenia and osteomalacia, improves lower extremity function, and reduces falls (5-8). However, more recent evidence has demonstrated the existence of vitamin D receptors in a variety of tissues and ongoing research suggests that vitamin D may play a more extensive role in preventing the onset of many chronic illnesses. Given this renewed interest, there has been a rapid escalation in laboratory testing and the subsequent development of high throughput methods to determine vitamin D status.

Figure 1. Seasonal fluctuations in vitamin D status in Calgary and the surrounding area.



Determination of Vitamin D Status

Vitamin D consists of either D2 or D3 forms which are derived from plant sources or from cutaneous UV-B irradiation of 7-dehydrocholesterol stores in the skin, respectively. The major circulating product of vitamin D metabolism is 25-hydroxyvitamin D (25OHD) from the liver, while 1,25-dihydroxyvitamin D from the kidney is the active hormone. In order to determine vitamin D status, 25OHD is measured since it is more abundant and has a longer half life of several weeks (5). Currently, controversy remains on the recommended levels of total vitamin D. Many experts agree that 75nMol/L (30ng/mL) is considered to be the optimal level for calcium absorption (5-6), while individuals with lower concentrations are considered to be vitamin D insufficient or deficient. While it is possible that these recommended levels may change as future studies continue to address the expanded role of vitamin D in disease prevention, current monitoring should be limited to assessment of skeletal health.

Guidelines for Monitoring Vitamin D Status

Recently, a report from the Canadian Medical Association Journal (CMAJ) highlighted the central issue of 25OHD test utilization (6). This report, which was approved by the Osteoporosis Canada Scientific Advisory Council, was a systematic evaluation of reviews of randomized controlled trials and observational studies assessing the role of vitamin D in fractures, falls, death and extraskeletal outcomes. According to the report, the clinician should approach testing according to three scenarios pertaining to risk for vitamin D insufficiency. Low risk patients who are less than 50 years old and do not have any comorbidities affecting vitamin D absorption or action, should be supplemented with 400-1000IU (10-25□g) daily and should not be monitored for vitamin D status. Conditions affecting vitamin D absorption or action include significant renal or liver disease, malabsorption syndromes, obesity, or medications affecting vitamin D metabolism (eg. phenobarbitol, carbamazepine, phenytoin, valproate). Moderate risk patients who are 50 years or older who do not have any comorbidities affecting vitamin D absorption or action should be given 800-2000IU (20-50□g) daily and should not be monitored for 25OHD levels. However, moderate risk patients who are receiving standard vitamin D supplementation for osteoporosis treatment should only be monitored for 25OHD after three to four months, to reach a plateau and should not be retested if the optimal level is achieved. Indeed, following

a change in vitamin D intake, 25OHD steady state levels are attained after three to four months, therefore monitoring should be performed accordingly (9). High risk patients who have recurrent fractures or bone loss despite treatment for osteoporosis, or have comorbid conditions affecting vitamin D absorption or action should initially be assessed for 25OHD levels and be supplemented according to test results. It may often be necessary for high risk patients to receive vitamin D doses greater than 2000IU (50□g), which is Health Canada's "tolerable upper intake level" and close monitoring for vitamin D toxicity may be especially important for these patients considering that oral or parenteral doses of more than 500,000IU can quickly lead to 25OHD peaks within one month (10). These guidelines are summarized in Table 1.

Table 1. Current recommendations by the Osteoporosis Canada Scientific Advisory Council on vitamin D testing.

Clinical Scenario	Recommendation
Low risk patient <50 years old with no comorbidities affecting vitamin D absorption or action	Supplementation with 400-1000IU (10-25µg) daily 25OHD levels should **not** be monitored
Moderate risk patient > 50 years old:	
a.) With no comorbidities affecting vitamin D absorption or action	Supplementation with 800-2000IU (20-50µg) daily 25OHD levels should **not** be monitored
b.) Receiving vitamin D supplementation for osteoporosis treatment	25OHD levels should be monitored every **three to four** months until optimal level is achieved
High risk patient Recurrent fractures or bone loss despite treatment for osteoporosis, or have comorbid conditions affecting vitamin D absorption or action	**Initial** assessment for 25OHD levels followed by supplementation according to test results For vitamin D doses greater than 2000IU (50µg), which is Health Canada's "tolerable upper intake level", close monitoring for vitamin D toxicity every month may be warranted (3)

VITAMIN D TESTING AT CALGARY LABORATORY SERVICES (CLS)

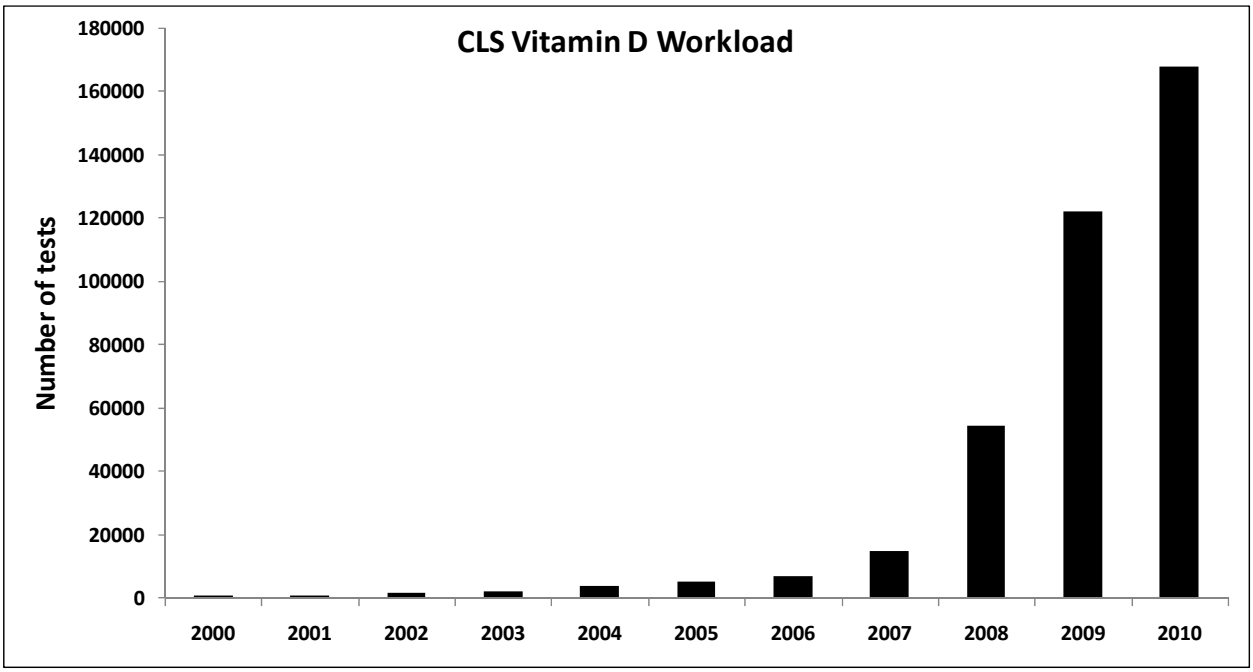
Currently, there are a variety of different methods to quantify 25OHD and that results do not match across different platforms. This general lack of standardization and harmonization, which would otherwise encourage accuracy of 25OHD measurement, poses potential problems on how patients may be treated depending on where their tests were performed, especially if medical decision points do not match across testing platforms. While efforts are already underway to address possible differences in assay performance, all 25OHD testing in Calgary and the surrounding area is performed at CLS by high-throughput automated immunoassay which measures total 25OHD. Consolidation of 25OHD testing and subsequent elimination of discrepant results associated with different methodologies should facilitate focused testing as outlined above. At CLS, we are performing over 12,000 tests per month which indicates the growing popularity of vitamin D testing and have exceeded 160,000 tests in 2010, approximately 10% of the

Calgary and surrounding area population, at a cost of almost $2 million (Fig. 2). The increasing volume of testing and associated spending imposes considerable strain on regional health resources and care must be taken to prevent overutilization. Indeed, the federal medicare program in the United States is proposing to limit vitamin D testing, while more recently, the Ontario government went further and imposed restrictions except for certain medical conditions such as osteoporosis, rickets, renal disease, osteopenia, and malabsorption syndromes.

CONCLUSION

In light of the evidence provided by clinical trials, vitamin D status should be monitored in only higher risk patients. Supplementation with vitamin D, which is available at lower cost and has a wide therapeutic window, within the tolerable upper intake level should be implemented for the rest of the population. Until further research establishes the extraskeletal benefits of vitamin D, vitamin D testing should be implemented for the purpose of assessing skeletal health and for the maximum benefit of our patients.

Figure 2. Exponential growth in vitamin D testing at Calgary Laboratory Services.



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