

## Vitamin D and Multiple Sclerosis Recommendations

### BACKGROUND

The association between vitamin D status and risk for multiple sclerosis (MS) prevention and/or disease modification has been the centre of considerable research and public discussion over the last decade. Studies ranging from mechanistic (cell and animal models) to population health to clinical trials have explored how low vitamin D status influences MS risk and whether vitamin D can be used as a standalone or add-on treatment for MS. To date, varying study approaches and inconsistencies in findings have limited the capacity to develop evidence-informed, clear recommendations on vitamin D for people affected by MS.

Despite the lack of definitive recommendations, people living with MS are vocal regarding their interest in vitamin D and its relationship to the disease. They want to know whether they should test their vitamin D status, whether supplementation is necessary, and if so how much supplementation is required and what the best sources of vitamin D are. They access various sources to obtain this information such as their healthcare team, organizations like the MS Society of Canada, friends and family, the internet and social media. It is therefore imperative that they are provided with clear, accurate information to make the best decisions for them regarding vitamin D.

### DEVELOPING STATEMENTS AND ESTABLISHING CONSENSUS

In early 2016, the MS Society of Canada convened a panel of scientific and clinical experts, staff from other national MS patient organizations, and a person affected by MS to discuss the available evidence on the link between vitamin D and MS. The purpose of the meeting was to begin the process of developing evidence-driven statements that can help guide people affected by MS in making informed decisions about their health. The recommendations will also support healthcare professionals and policy makers by providing them with a detailed assessment of the evidence on vitamin D and MS that will guide clinical practice and public health policy.

Discussions at the in-person meeting led to the creation of key statements on vitamin D and MS that would provide guidance in four areas: prevention, disease modification, comorbidities (presence of more than one condition), and toxicity. Following the meeting, email exchanges and teleconferences were held during which members of the panel identified and graded scientific publications relevant to each statement (see grading system in Appendix). The relatively small number of relevant published studies, particularly randomized clinical trials, limited the panel's ability to conduct a formal systematic review and meta-analysis. The statements were then discussed and revised in a follow-up teleconference, and final grades were assigned based on thoughtful assessment of the level of evidence supporting each statement and expert consensus.

## INTRODUCTION

### Vitamin D for General Health

Vitamin D plays an essential role in human health, primarily in calcium and phosphate regulation to support bone health. Before vitamin D can act at the tissue level it must first be converted to 25-hydroxyvitamin D in the liver and then to 1,25-dihydroxyvitamin D – the active hormone that is the main functioning unit. An individual's vitamin D status can be measured in two ways – vitamin D dietary intake and vitamin D levels in the blood. The latter gives a true picture of vitamin D status, and is determined by measuring the amount of 25-hydroxyvitamin D in the blood<sup>1</sup>.

In addition to the well documented role in bone health, evidence is emerging from ecological and observational studies that the active form of vitamin D – 1,25-dihydroxyvitamin D – also has functions in immune, cardiovascular, and neurological systems, as well as glucose regulation and placental function. This is supported by knowledge that the active vitamin D hormone is synthesized not only in the liver but in cells in the placenta, pancreas, prostate, breast, and in immune cells such as macrophages. Such information has been the basis of observations of the association of vitamin D status in humans and certain cancers, immune disorders, cardiovascular disease, abnormal glucose metabolism, and neurodegenerative diseases.

### Recommended Vitamin D Intake

Health Canada has published [recommendations](#) for daily consumption of vitamin D which are based on a 2010 report from the U.S. Institute of Medicine: Infants 0-1 year - 400 IU (10 µg)/day; children and adults 1-70 years - 600 IU (15 µg)/day; adults over 70 years - 800 IU (20 µg)/day. The recommended intake is the same for males and females. For pregnant and lactating women, the recommendation is the same as for adults. For adults over 50 years, Health Canada recommends a daily vitamin D supplement of 400 IU since aging may reduce the efficiency of vitamin D synthesis in the skin. Too much vitamin D can be harmful, so Health Canada also recommends an upper intake limit of 4000 IU (100 µg)/day unless there is a medical reason such a malabsorption or bone disease that requires higher intakes as directed by a physician.

### Sources of Vitamin D

Vitamin D can be obtained from food and supplements, and humans are able to synthesize vitamin D in the skin when exposed to ultraviolet radiation from the sun in the summer months. Black pigment in skin reduces the production of vitamin D, therefore people with pigmented skin are more at risk of low vitamin D status and may need supplements to acquire adequate vitamin D, especially during Canadian winters. While skin exposure to the sun can result in obtaining sufficient vitamin D, excessive exposure has been associated with risk of skin cancer, therefore one should follow [Health Canada](#)

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<sup>1</sup> Provinces and territories do not cover the cost of vitamin D tests for the general public. Certain health conditions are exempt from the cost, though multiple sclerosis is not currently one of them.

[recommendations](#) for safe sun exposure. Coverage of the skin with low SPF (<30) sunscreen will allow some vitamin D to be produced in the skin.

Food sources of vitamin D are primarily fatty fish (e.g. salmon and mackerel), egg yolks and vitamin D fortified foods. In Canada, cow's milk and margarine have mandatory regulations for vitamin D fortification. Voluntary fortification is also done for some orange juice and plant milk products.

In Canada, vitamin D supplements are primarily found in pill form as vitamin D3 (cholecalciferol) – the form that is made in the skin. Vitamin D2 (ergocalciferol) is derived from plant sources and is used in foods and supplements but primarily in the United States. It is thought that vitamin D3 is the most biologically active form but this is debated. Of note, the Food and Drug Administration does not regulate Vitamin D supplements, hence the potency of supplements may vary between preparations. To absorb the largest amount of vitamin D from a supplement or vitamin D fortified food source, it should be taken with the meal that contains the highest amount of fat since vitamin D is soluble in fat. The time of day of vitamin D supplementation does not appear to affect the absorption of vitamin D. Vitamin D can also be taken as an emulsion and obtained from cod liver oil, however it's important to discuss these applications with a healthcare professional to understand dosing, benefits and safety.

### **Vitamin D and Multiple Sclerosis**

As new research evidence emerges, experts are assessing the role vitamin D plays in the development and course of MS. The recommendations in this report are based on assessment of the available evidence, and are intended for those who are at risk – as defined in the following section – of developing MS and those who live with MS.

## VITAMIN D AND MS RECOMMENDATION STATEMENTS

### 1. Multiple Sclerosis prevention for at-risk populations

1-1 Adults deemed to be at risk<sup>2</sup> of developing multiple sclerosis (MS) are advised to achieve and maintain a normal vitamin D status defined as serum 25-hydroxyvitamin D in the target range of 50-125 nmol/L (20-50 ng/ml). Once this level has been achieved, they are encouraged to consult with their primary care physician about the frequency of monitoring on the basis of changes in health status. Vitamin D testing is advisable but not essential.

**(Level 3 evidence, Grade C recommendation)**

#### *Additional considerations*

- *Additional evidence provided by genetic studies (e.g. Mendelian Randomization) supports the epidemiological evidence that there is an association between higher vitamin D status and reduced MS risk.*
- *Although these genetic studies are unable to prescribe target vitamin D status for at risk populations, they eliminate confounding factors and strengthen the epidemiological observations.*
- *Careful language is needed to avoid the term “genetic risk” which may mislead the public to think that they can be genetically screened for MS risk based on vitamin D alleles.*

1-2 Due to limited direct evidence for supplementation, and variable responses to supplementation, adults at risk of developing MS should follow the Health Canada recommended daily vitamin D3 supplementation range for healthy people (600 up to 4000 IU for individuals at risk of lower vitamin D status) to achieve target vitamin D status of 50-125 nmol/L (20-50ng/ml) for reducing MS risk.

**(IOM supplementation range: Level 1+ evidence, Grade A recommendation)**

**(Optimal risk reduction status: Level 4 evidence, Grade D recommendation)**

1-3 Given evidence that low serum 25-hydroxyvitamin D levels during childhood and adolescence are associated with increased MS risk, it is proposed that all children and youth consume vitamin D supplements (see [Health Canada](#) and [American Academy of Pediatrics](#) recommendations). Children of parents with MS have a higher MS risk than the general population, thus it is suggested that children have serum 25-hydroxyvitamin D levels monitored and their practitioners ensure that their serum levels remain in the recommended range for target vitamin D status (serum 25-hydroxyvitamin D levels of approximately 75 nmol/L (30ng/ml)).

**(Current standard of practice)**

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<sup>2</sup> “at risk” population defined as first-degree relatives (parents, children, and siblings) of a family member with MS. Children with a first degree relative with MS (i.e. parent or sibling) have a 3-5% absolute risk of developing MS, which is higher than the general population. Individuals should bear in mind other lifestyle factors that could modify one’s risk of developing MS, including past exposure to Epstein - Barr virus, smoking and second-hand tobacco exposure, and obesity.

Also, of note, obesity may result in lower vitamin D levels, hence, obese people may need higher doses of vitamin D to achieve the same serum level as those with normal weight.

1-4 All women of childbearing age should take a prenatal multivitamin that includes vitamin D to achieve intakes of 600 IU/day up to 4000 IU/day. Vitamin D supplementation should continue throughout pregnancy and in women who are breastfeeding. Health Canada recommends that all breastfed, healthy term babies receive a vitamin D supplement of 400 IU/day.

**(IOM supplementation range: Level 1+evidence, Grade A recommendation)**

## 2. Multiple Sclerosis disease modification

2-1. Some evidence suggests that vitamin D can modify disease course in adults with MS. Optimal levels of vitamin D to achieve this are unknown and are currently being evaluated in clinical trials. Observational evidence suggests that serum 25-hydroxyvitamin D levels in the range of 50 – 125 nmol/L (20-50 ng/ml) may be beneficial. Vitamin D3 supplementation up to 4000 IU per day in adults is well tolerated and, as this is the recommended daily upper intake, should not cause harm.

**(Level 3 evidence, Grade C recommendation)**

### *Additional considerations*

- [Clinical trials](#) studying vitamin D supplementation as a treatment for MS to date have not been powered to sufficiently evaluate disease outcomes; these were primarily pilot trials designed to evaluate safety and follow-up times were short. Ongoing trials that are scheduled for completion over the next few years are expected to provide more clarity about efficacy of vitamin D as an intervention (either alone or as an add-on therapy) for disease modification.

2-2. In children and adolescents under the age of 18, serum 25-hydroxyvitamin D status should be measured upon diagnosis of a first clinical demyelinating event, and levels should be monitored every 6 months on follow-up.

**(Level 4 evidence, Grade D recommendation)**

2-3. Children and adolescents diagnosed with MS should be advised to start with daily vitamin D3 supplementation of 600 up to 1000 IU, with the dose increased under the guidance of their physician incrementally until target range of 75 nmol/L (30 ng/ml) is achieved and maintained. Status should be monitored every 6 months on follow-up, although more frequent monitoring may be required if health status or body weight are changing.

**(Level 3 evidence, Grade C recommendation)**

2-4. Administration of vitamin D should not be used as a standalone treatment for multiple sclerosis.

**(Level 3 evidence, Grade B recommendation)**

## 3. Multiple Sclerosis and comorbid conditions

3-1. People living with MS are at increased risk of osteoporosis, falls and bone fractures; this risk is attributable to an increased propensity for mobility and balance impairments and a sedentary

lifestyle. Although there is no definitive association between vitamin D supplementation and bone fractures in MS, people living with MS should supplement with vitamin D at levels recommended by Health Canada to achieve minimum serum 25-hydroxyvitamin D levels that are protective for bone health in the general population.

**(IOM supplementation range: Level 1+ evidence, Grade A recommendation)**

#### 4. Toxicity

4-1. The tolerable upper intake level (amount not to be exceeded in one day) for vitamin D in individuals living with or at risk of MS should be aligned with current Health Canada recommendations for the general population which is 4000 IU (100µg)/day. Intake at this level should be safe and not require continued monitoring.

**(Level 2 evidence, Grade B recommendation)**

*Additional considerations*

- *Greater precautions must be taken in individuals with renal disease, parathyroid disease and endocrine malignancies who have an increased risk of hypercalcemia; supplementation should be done under careful monitoring of a physician.*
- *To correct vitamin D deficiency, weekly doses may be as effective as daily doses. However, monthly high doses may not be adequate to correct deficiency although may maintain normal status once it is achieved. Monthly high doses to 50,000 IU vitamin D appear to be safe.*
- *For any supplement of vitamin D, but especially if the source is a liver oil such as cod, check that the dose of vitamin A contained in the prescribed pro does not exceed the following Health Canada recommended upper levels of intake: Infants to 3 years = 600 ug/day; children 4-8 years = 900 ug/day; 9-13 years = 1700 ug/day; 14-18 years - 2800 ug/day; and adults = 3000 ug/day.*

4-2. Short-term, high-dose vitamin D supplementation above the tolerable upper intake level (i.e. loading dose) is acceptable clinical practice in the treatment of individuals living with MS who present with hypovitaminosis D, provided appropriate monitoring of the individual's health status is followed.

**(Level 2 evidence, Grade B recommendation)**

*Additional considerations*

- *A loading dose approach is unnecessary unless: (1) serum 25-hydroxyvitamin D < 30 nmol/L (12 ng/ml) and (2) the patient is unresponsive to oral dosing. Loading dose would be maintained at least until values of serum 25-hydroxyvitamin D exceed 50 nmol/L (20 ng/ml).*

#### ENDORSED BY:



## Vitamin D and MS Evidence Grading System

Level or grade	Criteria
<b>Evidence</b>	
1+	Systematic overview or meta-analysis of randomized controlled trials
1	Randomized controlled trial with adequate power
2+	Randomized controlled trial that does not meet level 1 criteria
3	Nonrandomized clinical trial or cohort study
4	Before–after study, cohort study with noncontemporaneous controls, case–control study
5	Case series with controls
6	Case series without controls
<b>Recommendation</b>	
A	Supported by level 1 or 1+ evidence plus consensus
B	Supported by level 2 or 2+ evidence plus consensus
C	Supported by level 3 evidence plus consensus
D	Any lower level of evidence supported by consensus

*Adapted from 2002 recommendations for the management of osteoporosis published by Osteoporosis Canada*

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