



Invited Commentary

Recommendations on vitamin D needs in multiple sclerosis from the MS Society of Canada

As exemplified by papers in this special journal issue on vitamin D, achieving optimal vitamin D status is a global health issue that pertains to healthy populations of all ages as well as for people living with a variety of health problems. In North America, the dietary reference intake values for vitamin D from infancy to the elderly were revised in 2011⁽¹⁾ based primarily on bone health outcomes. However, speculation exists of the possibility of higher intakes of vitamin D being required for non-bone health outcomes, owing to the emerging evidence of functions of the active metabolite of vitamin D – 1,25-dihydroxyvitamin D (1,25(OH)₂D) – in relation to some cancers, immune disorders, cardiovascular and neurodegenerative diseases, and glucose homeostasis⁽²⁾. While intakes of vitamin D above that recommended for the healthy population have been implicated in relation to a variety of diseases, the optimal amount of vitamin D intake for specific non-bone functions in the body is not well delineated⁽¹⁾. This is certainly the case for vitamin D in relation to multiple sclerosis (MS).

The biological plausibility supporting a role for vitamin D in MS was based on ecological research that associated the prevalence of MS in areas of high *v.* lower latitude (i.e. low *v.* high sun exposure) even within the United States^(3,4). Further support for the vitamin D–MS linkage relied on observations of vitamin D's role in immunomodulation, postulating that vitamin D deficiency plays a role in the pathophysiology of autoimmune diseases such as MS⁽⁵⁾. From a genetic basis, Mendelian randomisation analyses have predicted a causal relationship between low vitamin D status as measured by serum 25-hydroxyvitamin D (25(OH)D) and the risk of MS, although published data have been inconsistent⁽⁶⁾. Collectively, such information led to much speculation about whether MS could be prevented or the disease modified by high doses of vitamin D. The internet, social media and lay press were sources of various opinions on the topic⁽⁷⁾.

As an active health charity involved in support of persons affected by MS, the MS Society of Canada recognised the confusion about vitamin D needs among the people at risk of or living with MS, their families and healthcare professionals. To address this information gap, in 2016, the MS Society of Canada convened a panel of expert scientists, clinicians, a patient advocate and staff

from other national MS patient organisations to review the evidence for an association between vitamin D status and MS prevention and/or disease modification. The goal was to develop clear and accurate guidelines on optimal vitamin D intake and status for people affected by MS for use in clinical practice and public health policy. The target audience was people at risk of developing MS and those living with MS, with separate consideration for children and adults.

The panel first set out specific objectives to develop recommendations related to the prevention and/or disease modification of MS as well as to identify potential co-morbidities and toxicities associated with vitamin D and relevant to persons affected by MS. The objectives were then explored by reviewing the existing literature and, where possible, applying a formal evidence grading system⁽⁸⁾. The identified literature spanned 2003–2016 and primarily composed of case–control, cohort and longitudinal observational studies. The few randomised trials identified primarily related to disease modification in persons living with MS, but interpretation was constrained by heterogeneity across trials in design, subjects, duration and drugs used as immunomodulatory therapy. Based on the literature search, the panel concluded that a formal systematic review and meta-analysis was not possible due to a paucity of relevant published studies, especially randomised clinical trials.

From the review and grading of literature combined with expert opinions of panel members, a consensus report was prepared for the Society that contained statements related to prevention, disease modification, consideration of co-morbidities related to MS and toxicity of vitamin D. They also provided opinion statements on specific questions requested by patient advocates related to the need to test their vitamin D status, whether supplementation is necessary and, if so, how much supplementation is required and the best sources of vitamin D. The report of the expert panel was used by the MS Society of Canada to develop a set of recommendations that were approved by the MS Canada Medical Committee and endorsed by the Canadian Network of MS Clinics and the Consortium of Multiple Sclerosis Centres and published on the Society's website in November 2018. Details of the recommendations targeted at health professionals can be viewed



online⁽⁹⁾. A separate online publication of recommendations targeted at the general public is also available online⁽¹⁰⁾. The latter includes background information of vitamin D, its origin, metabolism and function and is presented in a question-and-answer format.

The general theme of the recommendations is that persons either at risk or living with MS should ensure normal vitamin D status from birth as for healthy populations. The advice is to follow the dietary reference intakes for daily consumption and upper limits of intake from Health Canada⁽¹¹⁾, which are based on the 2011 report of the US Institute of Medicine (IOM)⁽¹⁾. To achieve a normal vitamin D status, a normal target range for serum 25(OH)D was suggested as 50–125 nmol/l, also as recommended by the IOM⁽¹⁾. Recommendations for the prevention of MS for at-risk populations and for those with MS generally followed the same guidance as provided by Health Canada, noted above – to maintain serum 25(OH)D in the target range by ensuring intake of vitamin D within the age-related range of recommended dietary allowance and the tolerable upper limit (15–100 µg/d for >8 years of age)^(1,11). In practical terms, this would require the use of vitamin D supplements as vitamin D fortification of foods in both Canada and the USA is presently only mandatory for milk, and most Canadians do not consume sufficient amounts to meet recommended intakes through food alone⁽¹¹⁾. A special note was made that for all people the benefit of vitamin D supplementation depends upon baseline vitamin D status, ethnicity and adiposity, but vitamin D intake should not exceed 100 µg/d unless for treatment of hypovitaminosis D. Finally, high-dose vitamin D supplementation for prevention, disease modification or treatment was not substantiated by the literature reviewed. The potential for adverse effects of excessively high doses of vitamin D in a person living with MS was recently underlined in a case report⁽¹²⁾.

The major limitation for persons affected by MS is that this recommendation for vitamin D is not based on a systematic review and risk of bias, and meta-analysis was not conducted because available evidence was not appropriate for such analysis. By default, the guidelines reflect the consensus of an expert panel based on grading of individual papers and expert opinion of panel members. The strength is that the demands for reasoned recommendations on vitamin D intake and status among the patient population were provided and translated into appropriate formats separately for health professionals and the lay public. The MS Society of Canada achieved their goal of meeting the request of their target population. The recommendations are likely applicable to persons affected by MS in countries beyond the USA and Canada where dietary guidance on vitamin D is similar to the IOM report⁽¹⁾. The revision of the MS Society's recommendations will depend on the availability of clinical trial evidence in the future before more disease-specific recommendations can be developed.

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