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25-Hydroxyvitamin D Level Prediction Models – Is Further Optimization Feasible?

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A poor vitamin D status is increasingly associated with higher risks of numerous diseases such as the autoimmune diseases multiple sclerosis (MS) [1], type I diabetes [2], cancer [3], and cardiovascular diseases [4]. Many association studies, however, rely on a single vitamin D measurement, while fluctuation is to be expected in most, if not all, populations. To understand a true causal association between vitamin D status and risk of disease, modelling of vitamin D status is an important issue. The authors Šaltytė Benth et al. [5] address this issue and introduce a model to predict vitamin D status, as measured with 25-hydroxyvitamin D (25(OH)D) in MS patients.

There are several options to better model 25(OH)D levels. First, the number of 25(OH)D measurements could be increased to calculate the mean value. Second, and more neatly, a sinusoidal model removing the seasonal fluctuation as described by van der Mei [6] could be applied. Fluctuations in 25(OH)D levels are due to sun exposure because ultraviolet (UV) radiation is the major source of vitamin D. This implies seasonal variation, but ideally should take into account cloudiness and possibly air pollution. In addition, habits with regard to sun exposure are prone to change due to changing public opinion. This change includes sun-bathing behaviour (use of sunscreen) and way of dressing. Vitamin D status also depends on the intake of fatty acids, since vitamin D₃ is manufactured from UV radiation of 7-dehydrocholesterol [7]. In addition, there is increased attention on vitamin D and thereby a raising awareness of vitamin D deficiency, resulting in more vitamin D supplement use. Altogether, this makes it hard to estimate vitamin D status based only on seasonal fluctuation.

In addition to seasonal variation, the model introduced by Šaltytė Benth et al. [5] takes into account inter-individual variations. This is important, since it has been suggested that vitamin D status is dependent on individual parameters such as age and body mass index (BMI), with lower 25(OH)D levels in higher age

and higher BMI [8]. In addition, genetic factors including polymorphisms in vitamin D receptor (VDR), hydroxylizing cytochrome P enzymes (CYP27B1 and CYP24A1), and vitamin D-binding protein may influence the inter-individual fluctuation of 25(OH)D levels. In MS patients, a skewed distribution of genetic polymorphisms of VDR [9, 10] and CYP27B1 [11] has been described. In particular, genetic polymorphisms may affect the amplitude of the sinusoidal curve.

As well as the inter-individual variation, intra-individual variation might also explain part of the seasonal fluctuation of vitamin D status. Within an individual, dietary habits can vary during the year and thereby might affect the intake of vitamin D. In addition, habits affecting sun exposure, in particular outdoor activities, can change. Finally, individuals that are aware of their vitamin D status are more likely to take vitamin D supplements during the winter months.

Altogether, several drawbacks should be considered with respect to the proposed modelling of the vitamin D status. The patient cohort described by the authors was a rather homogeneous population with regard to disease course, disease duration and disability score. Patients in the Norwegian cohort were included in thirteen centres from north to south Norway, reflecting a large variation in latitude. This is in contrast to the population in which the seasonal model was applied [6]. This population consisted of MS patients with any disease course or disease duration as well as a control population. In addition, both patients and controls were included in a relatively small geographical area, i.e. Tasmania. Finally, part of the Norwegian patient population was supplemented with fatty acids. Therefore, to validate the model introduced by Šaltytė Benth et al. [5] it should be repeated in large MS cohorts. In addition, validation of prediction models of vitamin D status should include both healthy and diseased populations.

To conclude, a vitamin D prediction model should ideally include both seasonal and individual parameters. Considering all the individual factors that should be included in this prediction model, it might be even more effective to increase the number of vitamin D measurements instead of measuring all the individual factors that influence vitamin D status. However, studies that do not have multiple vitamin D measurements available will profit from optimal modelling of vitamin D status, although further improvements and appropriate validation will remain mandatory.

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