Vitamin D Deficiency and Insufficiency

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25-Hydroxyvitamin D is the most abundant circulating metabolite of vitamin D. Almost all vitamin D produced in the skin or obtained from food or supplements is converted in the liver to 25-OHD. Moreover, the serum half-life of 25-OHD is almost 2–3 weeks. Thus, serum 25-OHD level is a sensitive index of vitamin D status [1]. The development of radioassays for 25-OHD 40 years ago has made it possible to measure serum 25-OHD concentration and to define an individual's vitamin D status [1-3]. Early studies indicated that serum 25-OHD under 5–8 ng/ml is invariably associated with rickets in children and with osteomalacia in adults, and levels under 12–15 ng/ml are usually associated with secondary hyperparathyroidism or subtle osteomalacia. These cutoff levels of 25-OHD have been used for the definitions of vitamin D deficiency and insufficiency respectively.

In the last 15 years a newer definition of vitamin D deficiency and insufficiency has emerged, which is supported by several research groups [4,5]. It has been suggested that vitamin D deficiency should be defined as a serum 25-OHD level < 20 ng/ml (50 nmol/L) and vitamin D insufficiency < 30 ng/ml (75 nmol/L). This position is based on several lines of evidence. There is an improvement in intestinal calcium absorption efficiency as serum 25-OHD levels rise to the range of 30–35 ng/ml [6]. Priemel et al. [7], in their autopsy study, found that about 40% of bone samples from individuals with serum 25-OHD of 20–32 ng/ml still had elevated osteoid volumes typical for vitamin D deficiency. However, no osteomalacia was found in samples taken from individuals with serum levels higher than 32 ng/ml. In a meta-analysis, Bischoff-Ferrari and colleagues [8] showed that a significant fracture risk reduction occurs only in individuals with serum 25-OHD levels > 30 ng/ml.

In addition to the roles of vitamin D in calcium homeostasis and bone health, newer data have demonstrated the association between vitamin D status and the prevalence of extra-skeletal diseases, such as cancer, cardiovascular diseases and autoimmune diseases [9,10]. Those who support the newer higher definition of vitamin D insufficiency (25-OHD between 20 and 30 ng/ml) indicate that the lowest risk for such diseases is found in subjects with serum 25-OHD levels above 30 ng/ml [11].

Contrary to the newer definitions of vitamin D deficiency and insufficiency, the Institute of Medicine, a division of the American National Academy of Science, indicated in a recent report [12] that serum 25-OHD level ≥ 20 ng/ml (50 nmol/L) is enough to sustain normal calcium absorption and bone density and to minimize the risk of osteomalacia and rickets, and that there is no evidence base to establish the optimal level of 25-OHD at > 30 ng/ml for the extra-skeletal diseases. Bouillon [13] also supports the position that intestinal calcium absorption and bone density are already optimal when 25-OHD level exceeds 20 ng/ml and that only marginal further improvement is achieved by higher serum 25-OHD levels. Moreover, although the extra-skeletal health effects of vitamin D are highly plausible, causality has not yet been proven by large-scale well-designed clinical randomized controlled trials, which are needed.

How then can we define the optimal serum level of 25-OHD? The available data indicate that a serum 25-OHD concentration of 20–25 ng/ml (50–62.5 nmol/L) in children should be achieved to maintain calcium homeostasis and healthy bones. However, since there is no evidence of harm associated with 25-OHD levels of 30–35 ng/ml, which may reduce the risks of extra-skeletal diseases, choosing such a level may be of benefit.

In their study reported in this issue of *IMAJ*, Korchia et al. [14] used the newer definition of vitamin D deficiency and insufficiency and demonstrated that 70% of 247 children studied had vitamin D deficiency or insufficiency. However, 42% of the studied children had serum 25-OHD levels between 20 and 30 ng/ml, which may be considered suboptimal but are sufficient to sustain normal intestinal calcium absorption and minimize the risk of rickets. Moreover, had they used the previous more conservative definition of vitamin D insufficiency, about 70% of the children would have been defined as vitamin D sufficient.

I believe that the large number of children with serum 25-OHD levels below 20 ng/ml (28%) is a major health problem. It is imperative that we address this issue. The high prevalence of vitamin D deficiency among children in Israel and other populations at risk – such as ultra-Orthodox Jewish woman [15], elderly people [16], the Bedouin [17], and Ethiopian female immigrants [18] – raises the question whether vitamin D supplements should be given to all children until the age of

25-OHD = 25-hydroxyvitamin D

18, as recommended recently [19,20], as well as to adult populations at risk, on a routine basis, even in a sunny country such as Israel.

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Capsule

Gut metagenome in European women with normal, impaired and diabetic glucose control

Type 2 diabetes (T2D) is a result of complex gene-environment interactions, and several risk factors have been identified, including age, family history, diet, sedentary lifestyle and obesity. Statistical models that combine known risk factors for T2D can partly identify individuals at high risk of developing the disease. However, these studies have so far indicated that human genetics contributes little to the models, whereas socio-demographic and environmental factors have greater influence. Recent evidence suggests the importance of the gut microbiota as an environmental factor, and an altered gut microbiota has been linked to metabolic diseases including obesity, diabetes and cardiovascular disease. Karisson et al. used shotgun sequencing to characterize the fecal metagenome of 145 European women with normal, impaired or diabetic glucose control. The authors observed compositional and functional alterations in the metagenomes of women with T2D, and develop a mathematical model based on metagenomic profiles that identified T2D with high accuracy. They applied this model to women with impaired glucose tolerance and show that it can identify women who have a diabetes-like metabolism. Furthermore, glucose control and medication were unlikely to have major confounding effects. They also applied the model to a recently described Chinese cohort and show that the discriminant metagenomic markers for T2D differ between the European and Chinese cohorts. Therefore, metagenomic predictive tools for T2D should be specific for the age and geographical location of the populations studied.

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Eitan Israeli

"What lies behind us and what lies before us are tiny matters compared with what lies within us"

Ralph Waldo Emerson (1803-1882), American essayist, lecturer and poet, who was a champion of individualism and critic of the countervailing pressures of society

"It is not the strongest of the species that survive, nor the most intelligent, but the one most responsive to change"

Charles Darwin (1809-1882), English naturalist who established the theories of evolution and natural selection