

Commentary

Vitamin-D & prediabetes: a promising ménage in the Indian Scenario

Vitamin-D deficiency represents a global health problem affecting individuals across all life stages¹. Hypovitaminosis D is largely due to inadequate cutaneous production from 7-dehydrocholesterol and, to a lesser degree, from low dietary intake or impaired intestinal absorption of vitamin-D. The physiological production in the skin of this vitamin-hormone is affected by the exposure to sunlight which depends, in turn, on seasonal changes, latitude, clothing, skin pigmentation and use of sunscreens. However, many newly recognized interfering factors are gaining growing attention, such as obesity epidemic and high levels of environmental pollution. These new factors pave the way for the association of vitamin-D deficiency to the worldwide detrimental changes in lifestyle related to the effect of industrialization and migration to urban environment from rural settings. Thus, obesogenic environment and industrial pollution might exert an important role in promoting vitamin-D deficiency in countries with developing economy, like India, where industrialization and urbanization are growing at an exponential rate.

A remarkable similarity exists between a number of the risk factors for hypovitaminosis D and those for diabetes. Despite the lack of large well-planned national studies truly representative of India as a whole, the estimates of existing studies regarding the number of people with diabetes in India reported by Anjama *et al*² is 1.1-2.9 per cent, with a projection of around 51 million people with diabetes. In line with other developing countries, India is currently facing an epidemiologic transition of communicable vs non-communicable diseases².

Vitamin-D has been primarily recognized for its role in calcium homeostasis and bone health since its identification in 1921³. In recent years, along with the discovery of the growing number of extra-skeletal pleiotropic effects of this hormone, it has become increasingly evident that vitamin-D regulates the functions of over 200 genes. In particular, vitamin-D deficiency is associated with insulin resistance, diabetes mellitus and increased cardiovascular risk. The concurrent global epidemics of type 2 diabetes and

vitamin-D deficiency raise the question whether the vitamin-D deficiency might be included among the risk factors for diabetes⁴. Indeed, robust epidemiological evidence demonstrates the association between circulating 25-hydroxyvitamin-D [25(OH)D] and risk of type 2 diabetes⁵. Recently, the European Prospective Investigation into Cancer (EPIC)-Norfolk study reported an inverse association between circulating 25(OH)D and incident type 2 diabetes⁶. However, data from this very comprehensive meta-analysis, that failed to demonstrate any evidence of causality between vitamin-D status and risk for type 2 diabetes, cannot be extrapolated fully to other ethnic groups.

Prediabetes indicates a category of individuals with impaired fasting glucose or impaired glucose tolerance (IGT), whose risk for the future development of diabetes is relatively high⁷. In that, it would be of strategic importance to unravel the state of vitamin-D deficiency among individuals with prediabetes. So far, differences among the cohort studies in race, body weight, glucose homeostasis, or exposure to sunlight might account for the substantial degree of controversy surrounding the prevalence of vitamin-D deficiency in patients at risk for diabetes, such as those having IGT or metabolic syndrome.

In the present issue, Dutta *et al*⁸ have investigated the relationship between vitamin-D status and insulin resistance among adult individuals with prediabetes by evaluating the circulating levels of 25(OH)D, as the best indicator of vitamin D status⁹. In the study, the authors found that the occurrence of vitamin-D deficiency/insufficiency was 73.25, 66.6 and 78.57 per cent among individuals with prediabetes, diabetes and normal glucose tolerance, respectively, and that the prevalence of severe vitamin-D deficiency (<10 ng/ml) was about twice for individuals with prediabetes compared with both normal and diabetic groups. The prevalence of vitamin-D deficiency/insufficiency reported by Dutta *et al*⁸ appeared in line with data obtained in India from various studies published earlier^{10,11}. Despite the adequate sunshine in India, there are many factors involved in the epidemic of hypovitaminosis D, and

it has been well summarized elsewhere¹². Using the classification proposed by Holick *et al*¹³, the authors evidenced that individuals with severe vitamin-D deficiency have the highest insulin resistance. Because of the limited sample size, the association between vitamin-D status and 1-hour post-load glucose ≥ 155 mg/dl, a parameter considered as a strong predictor for future risk of type 2 diabetes¹⁴, did not reach a statistical significance. Of interest, Dutta *et al*⁸ also showed that the association between vitamin-D deficiency and measures of insulin resistance in their prediabetic individuals was independent of BMI and HbA1c. It is well-known that vitamin-D status is inversely related to body fat. Various factors, including the predominant storage of this fat soluble vitamin in the adipose tissue, have been proposed for this negative association. The independent association between vitamin-D deficiency and measures of insulin resistance could support the hypothesis that hypovitaminosis D might represent *per se* an adjunctive risk factor for the progression to overt diabetes and suggested that the determination of serum 25(OH)D could provide a practical complementary approach in the early diagnosis of type 2 diabetes.

Based on the data presented by Dutta *et al*⁸, it is tempting to speculate that worsened insulin resistance in prediabetes individuals with lower vitamin-D actually resulted in increased progression to diabetes. However, the cross-sectional design of the present study did not allow to unravel any causal association between insulin resistance and risk for progression to diabetes, being this report a pilot study to provide initial data on the relationship of insulin resistance with vitamin-D status primarily in individuals with prediabetes. Thus, the question about the putative inclusion of vitamin-D status as an independent risk for type 2 diabetes remains unsolved. Further studies, including a more careful evaluation of the “Calcium-vitamin D-parathyroid hormone” endocrine axis, are mandatory to pinpoint the real extent of the relationship between 25(OH)D and the risk for diabetes in the Indian scenario¹² and to clarify the possible preventive role of vitamin-D supplementations among prediabetes individuals.

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