Vitamin D and Diabetes

Joanna Mitri, MD, MS[a,*], Anastassios G. Pittas, MD, MS[b]

KEYWORDS

• Vitamin D • Type 2 diabetes • Insulin resistance • Insulin sensitivity
• 25-hydroxyvitamin D

KEY POINTS

- Observational studies suggest a link between vitamin D and diabetes.
- The potential effect of vitamin D appears to be more prominent among persons at risk for diabetes.
- The optimal blood 25-hydroxyvitamin D concentration associated with reduced risk of type 2 diabetes is not clear.
- The evidence from randomized controlled trials to support the hypothesis that vitamin D supplementation prevents type 2 diabetes is lacking.

INTRODUCTION

Type 2 diabetes mellitus is a significant global health care problem, and pharmacotherapies to treat the disease continue to emerge. However, the increasing burden of type 2 diabetes calls for an urgent need for innovative approaches to prevent its development. Recently, vitamin D has risen as a potential diabetes risk modifier.

The potentially significant extraskeletal role of vitamin D is highlighted in several recently published studies, including the demonstration of the expression of the vitamin D receptor in a large number of nonskeletal cells, including pancreatic beta cells. Additional evidence has strongly suggested that vitamin D plays an important role in modifying the risk of type 2 diabetes, an effect that is likely mediated by an effect of vitamin D on beta cell function, insulin sensitivity, and systemic inflammation. The evidence comes primarily from cross-sectional and longitudinal observational studies reporting on the association between vitamin D status and risk of type 2 diabetes or glycemia among patients with established type 2 diabetes.

Source of Funding: By research grants R01DK76092, U34DK091958 and U01DK098245 (to A.G. Pittas) from the National Institute of Diabetes and Digestive and Kidney Disease, the Office of the Director, National Institutes of Health, and the National Institutes of Health Office of Dietary Supplements.

[a] Division of Endocrinology, Diabetes and Metabolism, Prima CARE Medical Center, 277 Pleasant Street, Fall River, MA 02721, USA; [b] Division of Endocrinology, Diabetes and Metabolism, Tufts Medical Center, 800 Washington Street, Boston, MA 02111, USA
* Corresponding author.
E-mail address: joannamitri@hotmail.com

Endocrinol Metab Clin N Am 43 (2014) 205–232
http://dx.doi.org/10.1016/j.ecl.2013.09.010 **endo.theclinics.com**
0889-8529/14/$ – see front matter

More recently, short-term, small randomized trials have reported the effect of vitamin D supplementation with or without calcium on diabetes risk and glycemia with mixed results.

The aims of the review are to (1) describe the biologic plausibility behind the potential association between vitamin D and diabetes, with emphasis on type 2 diabetes where most of the evidence exists and (2) summarize and synthesize the evidence from observational studies that report on the association of vitamin D status and risk of diabetes and from randomized trials that report on the effect of vitamin D supplementation on glycemia in patients with diabetes or at risk for diabetes.

REVIEW OF VITAMIN D PHYSIOLOGY

Vitamin D exists in 2 forms: cholecalciferol (vitamin D3) and ergocalciferol (vitamin D2). Vitamin D3 is synthesized in the skin on exposure to solar ultraviolet B (UVB) radiation. During exposure to solar UVB radiation, 7-dehydrocholesterol in the skin is converted to previtamin D3, which is immediately converted to vitamin D3 in a heat-dependent nonenzymatic process. Excessive exposure to sunlight degrades previtamin D3 and vitamin D3 into inactive phyto-products (photo-degradation), avoiding vitamin D toxicity in the setting of excess sunlight. Vitamin D3 is also found is certain foods, such as fatty fish. Vitamin D2 is synthesized by plants and is found mostly in nutrients supplemented with vitamin D (eg, milk) or dietary supplements. Whether endogenously synthesized or ingested through diet or supplements, vitamin D in the circulation is bound to the vitamin D-binding protein (DBP), which transports it to the liver, where vitamin D is converted by vitamin 25-hydroxylase to 25-hydroxyvitamin D (25OHD). This form of vitamin D is biologically inactive and must be converted primarily in the kidneys by 25-hydroxyvitamin D-1alpha-hydroxylase (CYP27B1) to the biologically active form, 1,25-dihydroxyvitamin D (1,25$[OH]_2$D). The presence of CYP27B1 in extra-renal tissues suggests that vitamin D may have an important role beyond the musculoskeletal system. The 25-hydroxyvitamin D is the major circulating form of vitamin D and is an excellent biomarker of exposure, either from cutaneous synthesis or dietary intake.

CLASSIFICATION OF VITAMIN D STATUS

Clinicians and researchers use blood concentration of 25OHD as a biomarker to determine vitamin D status. However, there is no consensus on the 25OHD thresholds for vitamin D deficiency or insufficiency. The main guidelines by the Institute of Medicine (IOM) and the Endocrine Society differ on classification of vitamin D status, as shown in **Table 1**.[1,2] The differences are explained by what populations were targeted by the guidelines and how the evidence was synthesized. The IOM guidelines concentrated

Table 1
Guidelines for vitamin D status by blood 25-hydroxyvitamin D concentration

Cutoff, ng/mL[a]	Institute of Medicine	Endocrine Society
<12	Deficiency	Deficiency
12–19	Inadequacy	Deficiency
20–29	Sufficiency	Insufficiency
30–49	Sufficiency	Sufficiency
>50	Reason for concern	Sufficiency

[a] To convert 25(OH)D concentration from ng/mL to nmol/L multiply by 2.459.