VITAMIN D DEFICIENCY: CAUSES, IMPLICATIONS, RECENT CLINICAL TRIALS

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Vitamin D is a threshold nutrient required for normal skeletal growth and maturation, as well as for normal calcium homeostasis in the adult. Vitamin D facilitates calcium absorption in the gastrointestinal tract and plays a vital role in mineral accrual in children and skeletal remodeling in the adult. Recognition of the importance of vitamin D became evident at the time of the industrial revolution in western Europe, in the late 1800's, when populations in England moved from rural to urban settings. Classical depictions of children with rickets were common then. Presumably, levels of vitamin D were below the threshold required for optimal skeletal growth and maturation. A threshold nutrient is defined by its beneficial effects in a dose-related manner until a level is reached beyond which no further benefits can be expected. We now recognize that vitamin D requires two activation steps: Vitamin D is hydroxylated in the liver to form 25-hydroxvitamin D (25-OH D) and then further hydroxylated in the kidney to form the active hormone, 1,25-dihydroxyvitamin D. Despite the fact that 25-OH D is not the active metabolite, it is the storage form of the vitamin D and is, thus, used clinically for measurements and for discussions about threshold nutrient values. There is controversy over what that threshold level of 25-OH D is in the adult, with 20 ng/mL (50 nmol/l) recommended by many organizations under normal conditions. Whether this is the 'right' concentration for someone who has a metabolic bone disease, such as osteoporosis or primary hyperparathyroidism, is uncertain. Many experts feel that 30 ng/mL (75 nmol/l) might be a more appropriate concentration of 25-OH D under those conditions. What is clear is that levels below 12 ng/mL (25 nmol/l) are clearly low and associated with rickets in childhood and osteomalacia in adults. World-wide epidemiological studies have documented that vitamin D insufficiency (25-OH D levels < 20 ng/mL) is very common, even in desert countries, like Saudi Arabia, and in others, like the United States, where fortification of food is common. Thus, one could consider the entire world's population to be at risk for vitamin D insufficiency. Adding to this discussion is the observation that there are vitamin D receptors and enzymatic conversion machinery that theoretically can activate vitamin D (i.e., produce 1,25-dihydroxyvitamin D) in many tissues. As a results, the idea that vitamin D may harbor non-skeletal actions and be important in diseases other than those targeting the skeleton has gained support. Some of these diseases include type 2 diabetes mellitus, cancer, and cardiovascular disease. Cross- sectional studies supporting an association between vitamin D insufficiency and these non-skeletal diseases led the design and implementation of several prospective, randomized, controlled studies to test the hypothesis that vitamin D has beneficial non-skeletal effects. Recently, these clinical trials have been published in major medical journals. The results of these trials and a critique of them will be a feature of the presentation.

KEYWORDS: Vitamin D; calcium homeostasis; vitamin D insufficiency.