25-OH Vitamin D: Is It the Universal Panacea for Metabolic Syndrome and Type 2 Diabetes?

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Obesity has become a global epidemic. Consequently, there are increasing rates of obesity-related diseases such as diabetes, cardiovascular diseases, sleep disorders, and associated morbidity and mortality. Although there is growing debate on the etiopathogenesis of the global pandemic of obesity, there is no question that increasing calories, concomitant decreases in physical activity, and increasing sedentary lifestyle are major contributors. Typically, obesity is associated with insulin resistance/hyperinsulinemia, which has been implicated in the increased cardiovascular diseases, metabolic syndrome, and type 2 diabetes. Metabolically, obesity is associated with reduced high-density lipoprotein cholesterol and high triglycerides and increases in serum total cholesterol, low-density lipoprotein, and small, dense, low-density lipoprotein cholesterol particles. In addition, obesity is regarded as a proinflammatory state with increases in the oxidative stress burden, free oxygen radicals, and F2-isoprostanes.

However, the associations of obesity and metabolic derangements are very complex. Although there are direct causal relationships of some of these metabolic derangements with obesity, in some situations, the metabolic change can be a consequence of the obesity per se. Recently, several epidemiological studies have reported increasing prevalence of low serum 25-hydroxy vitamin D (25-OH vitamin D) levels in several communities around the globe. In contrast to old literature, where specific demographic populations such as elderly patients living in higher latitudes and altitudes, geographical areas with low sun exposure, religious practices, etc. posed greater risk, there are alarming rates of low serum 25-OH vitamin D levels among seemingly healthy populations, especially in the elderly in the Western industrialized world. This has raised several health concerns with regard to the etiologies of the low vitamin D levels and the disease consequences of serum 25-OH vitamin D level alterations in these populations.

Traditionally, vitamin D has been the key regulator of serum calcium metabolism either directly via absorption of calcium from the gut (hence its major role in bone metabolism) or indirectly through PTH on bone metabolism and renal calcium absorption. Vitamin D receptors are ubiquitous, being found on several tissues including, gut, adipose tissues, cardiac and skeletal muscles, and β-cells. Until recently, there were only sporadic reports on the effects of vitamin D on glucose homeostasis (1–3) and cardiovascular diseases (4, 5). This association has both physiological and mechanistic attributes that make vitamin D a potential key player in common metabolic and cardiovascular diseases worldwide. In this regard, Alvarez and Ashraf (1) in their meta-analysis of both cross-sectional and prospective studies point out that vitamin D insufficiency (20–29 ng/ml) and deficiency (less than 20 ng/ml) have direct and indirect effects on insulin secretion and insulin action. In this regard, vitamin D has been directly linked to the development of type 2 diabetes and type 1 diabetes, but the mechanism(s) remains controversial (2, 3). Furthermore, Pilz et al. (5) have reported in a large cross-sectional study that both low serum 25-OH vitamin D and 1,25-hydroxy vitamin D were associated with higher prevalence of myocardial dysfunction, deaths due to heart failure, and sudden cardiac death. In this context, Schleithoff et al. (4) have reported that vitamin D supplementation improves cytokine profiles in patients with congestive heart failure in a double-blind, randomized, placebo-controlled trial. In their study, IL-10 was...
higher after vitamin D supplementation, whereas TNF-α was not changed. The authors concluded that vitamin D reduces the inflammatory milieu in congestive heart failure patients and suggested that the vitamin D–PTH axis may be involved in the progression of congestive heart failure. In this regard, Wang et al. (6) reported in cross-sectional and prospective study that individuals with vitamin D deficiency (<15 ng/ml) have a 62% increase in the first incidence of a cardiovascular disease event, especially in patients with hypertension.

Insulin insensitivity and β-cell secretory defects are critical to the development of impaired glucose tolerance and type 2 diabetes. Although there is a genetic basis for the dysfunction in both parameters, there is definitely a major role of environmental factors (i.e., acquired). In this regard, obesity has become dominant in the global pandemic of type 2 diabetes due to less participation in leisure time physical activity and increasing sedentary lifestyle, especially in the Western countries. It has been hypothesized that low serum 25-OH vitamin D could play a significant role in the pathogenesis of glucose intolerance and type 2 diabetes. Chiu et al. (7) studied 126 healthy Californians to determine insulin sensitivity index and first and second phases of insulin secretion using the hyperglycemic clamp method. Using univariate analyses and multiple regression analyses, serum 25-OH vitamin D was positively associated with insulin sensitivity and negatively associated with first- and second-phase insulin secretion. Most importantly, subjects with hypovitaminosis (20 ng/ml) had a higher risk of insulin resistance and metabolic syndrome. These studies suggested and, indeed, implicated vitamin D in glucose homeostasis in humans, but this remains controversial.

In this edition of JCEM, Tzotzas et al. (8) have reported rising serum 25-OH vitamin D levels after weight loss in obese women. The authors studied 44 obese women with modest obesity (age, 40.6 ± 11.4 yr; body mass index, 36.7 ± 4.9 kg/m²) and compared their pre-and postintervention serum 25-OH vitamin D with those of healthy normal controls (body mass index, 23.8 ± 1.5 kg/m²). The study found lower 25-OH vitamin D levels in obese subjects when compared with the nonobese controls, whereas PTH levels were not different. The serum 25-OH vitamin D was associated with insulin and insulin resistance in the obese subjects. After 20 wk of weight loss that reduced initial body weight by 10%, insulin resistance was reduced whereas 25-OH vitamin D increased (18.3 ± 5.1 vs. 15.4 ± 6.0 ng/ml; P < 0.05). Clearly, in the obese patients, 25-OH vitamin D level was low, and it increased but did not normalize with weight reduction in their study. Nevertheless, 25-OH vitamin D correlated inversely with improvement in insulin resistance. This paper attempted to bridge the knowledge gap on the potential mechanisms of the increasing prevalence of low 25-OH vitamin D in the obese populations.

The reason for the emerging epidemic of low serum 25-OH vitamin D in seemingly well-nourished U.S. populations remains uncertain but appears to be multifactorial. It is worth noting that 25-OH vitamin D is a fat-soluble vitamin. Thus, increasing adiposity may serve as a repository (or metabolic sink) for vitamin D storage. Hence, it is tempting to postulate that the emerging pandemic of overweight/obesity can itself result in increasing prevalence and incidence of insufficient or deficient serum 25-OH vitamin D levels. Because the 25-OH vitamin D is avidly stored in the body fat and is physiologically available, it is difficult to assess whether the serum level actually reflects the tissue levels in individuals who have diminished bioavailable serum 25-OH vitamin D levels. Two other important factors in low serum 25-OH vitamin D level are race and ethnicity. In this regard, there is higher prevalence of hypovitaminosis vitamin D in ethnic populations such as African-Americans, Hispanics, etc., who are at greater risk of insulin resistance, obesity, type 2 diabetes, and cardiovascular diseases than Caucasians. However, National Health and Nutrition Examination Survey III data did not show any significant association between 25-OH vitamin D and insulin resistance (homeostasis model of assessment for insulin resistance) in African-Americans but showed significant association in Caucasians and Hispanic-Americans (2). Whether the disparities in the relationship between 25-OH vitamin D and insulin resistance in some previous studies are due to race/ethnicity-specific differences in serum 25-OH vitamin D levels or tissue responsiveness or thresholds remains to be investigated using randomized, double-blind, placebo-controlled study design. Unlike many previous cross-sectional and epidemiological studies, future studies on the role of vitamin D and glucose homeostasis in African-Americans should use highly sensitive measures of insulin sensitivity and β-cell function.

Regardless of the mechanism(s), however, the demonstration that 25-OH vitamin D supplementation enhances insulin sensitivity and improves glucose homeostasis is of great clinical interest. This gives more credence to the important role of 25-OH vitamin D. Most importantly, the potential 25-OH vitamin D effect on reduction of incident cardiovascular events and congestive heart failure and type 2 diabetes have huge public health implications. The major question is, given the epidemic of hypovitaminosis D in the United States, should we recommend adding more vitamin D to our diets, drinks, and nutritional formula, and if so, what should be the required daily intake? If so, should the required daily intake of 25-OH vitamin D be
race/ethnicity-specific? At face value, this will probably be one of the most cost-effective public preventive strategies for cardiovascular diseases, impaired glucose tolerance, and type 2 diabetes. Thus, further prospective and systematic intervention studies of supplementation of 25-OH vitamin D on glucose homeostasis, metabolic syndrome, and cardiovascular disease are warranted. In particular, studies on the role of serum 25-OH vitamin D in predicting the risk of type 2 diabetes and insulin resistance in various ethnic populations such as African-Americans, Africans, Asians, and continental southeast Asians and Indians are urgently warranted.

Before making any general recommendation regarding further 25-OH vitamin D fortification of our dietary products, there are other issues that need to be considered, especially with respect to glucose homeostasis, insulin secretion, and insulin sensitivity in the general population (2, 3, 7, 8). First, there is no universally accepted definition of optimal serum levels of 25-OH vitamin D levels. Second, there appear to be different therapeutic thresholds for different diseases. For example, for prevention of osteomalacia and rickets, a serum 25-OH vitamin D level of 10 ng/ml is regarded as sufficient. On the other hand, to prevent osteoporosis and achieve optimal calcium absorption, a concentration of 30 ng/ml is perhaps needed. With regard to glucose homeostasis, it is unknown what length and duration of intervention would be required to increase the tissue insulin sensitivity and β-cell secretion in humans. We should note that in the study by Tzotzas et al. (8) in this edition of JCEM, insulin resistance (homeostasis model of assessment for insulin resistance) improved by wk 4, at the time when the serum 25-OH vitamin D was still insufficient (16.9 ng/ml). Most importantly, at wk 20, the serum 25-OH vitamin D of 18.3 ng/ml was still subnormal and deficient. Thus, in obese individuals it appears that achieving the optimal 25-OH vitamin D levels may require greater weight loss as well as oral supplementation over an extended period during weight loss intervention. Finally, the ultimate target tissue of insulin sensitization, i.e. liver vs. skeletal muscles, by 25-OH vitamin D needs to be investigated in future studies in obese patients with and without type 2 diabetes.

In summary, several observational and short-term studies clearly show that vitamin D deficiency and insufficiency are associated with several metabolic and cardiovascular perturbations. With increasing obesity and the attending metabolic syndrome and type 2 diabetes, it is imperative that placebo-controlled, randomized studies should be performed to determine the dose, duration of supplementation of 25-OH vitamin D, and the ultimate health outcomes in high-risk populations. The impetus for such studies is clear. Oral vitamin D is very inexpensive (indeed, cheap!), easily available, and has a documented long-term safety record. The question is whether vitamin D is the long-awaited panacea for prevention of type 2 diabetes and cardiovascular diseases in the general population? Time will tell.

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References