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Vitamin D and Cardio-Metabolic Disease

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There has been an explosion in the number of investigations focused on the role of vitamin D in metabolic and cardiovascular diseases. Accompanying this growth and concentration of scientific reports has come a significant degree of confusion and uncertainty. This is largely attributed to the fact that large-scale randomized studies to evaluate the impact of vitamin D interventions on metabolic outcomes are still few and insufficient. While many studies support the role of vitamin D therapy in reducing cardio-metabolic risk factors, others do not, and notable limitations exist in almost all studies reported to date. Until definitive well-designed prospective intervention studies are completed, we at *Metabolism* have remained committed to reporting the latest scientific findings by publishing novel original articles, and summary reviews and editorials, focused on this constantly evolving field. Our goal has been to serve as a platform for advancing and distributing scientific knowledge in this arena, and providing clarity and editorial interpretations on the most contemporary data available. In this regard, this editorial highlights recent updates on studies that evaluate the role of vitamin D in cardio-metabolic diseases, with an emphasis on those studies published in *Metabolism* in the past two years, thereby extending upon our prior summaries for our readers. Notably, recent issues of *Metabolism*, including this current one, have published novel studies focused on the interactions between vitamin D and the renin-angiotensin system, adiposity, insulin sensitivity, and genetics.

The main implicated mechanistic link between vitamin D metabolites and cardio-metabolic diseases is the renin-angiotensin system (RAS), however, inflammatory mediators, such as the TGF- β pathway, are also potential intermediates[1, 2]. One of the proposed functions of the vitamin D receptor (VDR), when activated by its ligand 1,25-dihydroxyvitamin D (1,25[OH]₂D), is down regulation of RAS activity[3, 4]. Since RAS activity is known to mediate vascular disease and implicated in the control of insulin secretion and sensitivity, the vitamin D-VDR-RAS interplay has gained much attention[1, 2].

Obesity and states of increased adiposity are risk factors for vitamin D deficiency, enhanced RAS activity, and cardio-metabolic diseases[1, 5]. Prior studies have suggested that the

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influence of vitamin D therapy may therefore be most evident in states of obesity; low 25-hydroxyvitamin D (25[OH]D) levels have been associated with increased vascular RAS activity[6] and incident diabetes[7, 8], particularly in states of high adiposity. The limitation of such association studies has been the concern for confounding factors since low vitamin D status and high adiposity are highly correlated occurrences. Other studies have reported associations between low 25(OH)D levels and favorable adipocytokine profiles that were independent of adiposity status[9–11]. Even intervention studies, performed to evaluate these cross-sectional findings, displayed interesting and confusing results. Obese and diabetic patients undergoing 3 months of dietary vitamin D₃ fortification were observed to have an increase in adiponectin levels[12]; findings that support the aforementioned association studies. In contrast, earlier this year *Metabolism* published the results of a high-dose vitamin D₃ therapy intervention that substantially raised 25(OH)D and 1,25(OH)₂D levels in morbidly obese individuals over one month[13]. Despite this aggressive supplementation protocol, concentrations of adiponectin, resistin, leptin, and other inflammatory markers, remained unchanged. While the jury may still be out on the influence of vitamin D therapy on adipocytokines and inflammatory profiles as a function of adiposity status, in this issue of *Metabolism*, Sulistyoningrum et al. report their investigations on the inter-relationships between 25(OH)D concentrations, blood pressure, and adiposity[14]. Although their study design was cross-sectional, they used multiple modalities to assess adiposity (including computed tomography to assess visceral abdominal fat) and a large diverse sample size. Using multiple linear regression models to minimize confounding and bias, they show that the inverse relationship between 25(OH)D concentrations and blood pressure remains robust and independent of adiposity. Indeed, these findings are supported by the outcomes of recent intervention studies[15–17] and meta-analyses[18] focused on the blood pressure lowering effects of vitamin D.

The involvement of vitamin D and the VDR in glycemic control is still debated. In our previous issues of *Metabolism*, we provided detailed summaries of the many observational and interventional studies that have demonstrated conflicting results on whether the vitamin D-VDR complex influences insulin secretion or peripheral sensitivity[1, 5, 19]. Recent intervention studies employing high-dose vitamin D₃ therapy and direct VDR-agonist therapy have failed to show notable modulations in insulin secretion or peripheral sensitivity[13, 20, 21]. In contrast, studies evaluating high risk patients (such as those with polycystic ovarian syndrome[19], metabolic syndrome[22], and/or at-risk demographics[22, 23]) have observed metabolic improvements with vitamin D therapy or higher vitamin D concentrations. Al-Daghri et al. recently reported in *Metabolism* that dietary and environmental fortification of vitamin D could improve components of the metabolic syndrome in non-diabetic Saudis[22]. While intervention studies are often lauded as the gold-standard in determining therapeutic effects, small sample sizes can often introduce significant bias, particularly when studying complex systems such as vitamin D metabolism. In this regard, analyses of large cross-sectional and prospective cohorts may also provide valuable insights. In this issue of *Metabolism*, we publish results from the Cardiovascular Health Study that examined the cross-sectional and longitudinal relationships between 25(OH)D and indices of insulin resistance in a large cohort[24]. In over 1,400 relatively healthy adults, higher 25(OH)D concentrations displayed a cross-sectional association with

lower HOMA-IR, however, they did not predict HOMA-IR over a four year follow-up. Whether modulation of insulin sensitivity requires larger changes in 25(OH)D concentrations or longer follow-up warrants more investigation.

Ultimately, the discrepancies between these studies may be attributed to factors that determine individual responses to vitamin D concentrations and supplementation: intra-individual genetic variation and environmental exposures may represent crucial factors in designing and interpreting studies focused on vitamin D-mediated clinical outcomes. The interplay between genetic variation in the VDR, bone metabolism, the RAS, and insulin sensitivity has been previously reported[23, 25]. For example, the functional polymorphism *FokI* alters the length and activity of the VDR and has been shown to influence RAS activity[1, 26, 27] and the risk for incident diabetes[28]. In last year's *Metabolism* report, Jain et al. demonstrated that high-dose vitamin D3 supplementation could improve insulin sensitivity; however, this effect was best evidenced when stratifying by *FokI* genotype[23, 29]. Other studies in our journal have shown that variation in VDR gene alleles may predict adolescent height[25]; however, pharmacogenetic studies to evaluate the impact of vitamin D supplementation on height by genotype status are needed to confirm this finding. Indeed large-scale longitudinal and interventional studies have confirmed that the association between vitamin D and clinically relevant outcomes is best seen when accounting for genotype, and furthermore, these findings may even be obscured when genetic variation is not accounted for[30, 31].

Many additional studies are needed to clarify whether vitamin D supplementation represents an important and safe clinical therapy to modulate cardio-metabolic risk. In particular, future studies will likely require designs that are more involved than simply administering vitamin D as an exposure and assessing a long-term clinical outcome. Vitamin D metabolism and regulation of the RAS are complex processes that involve multiple genes, gene-products, and environmental inputs; genetic variation[30, 31], vitamin D dosing[32], dietary intake, and other environmental exposures for each individual have all been shown to alter the balance of each of these hormonal systems. In addition, accruing evidence continues to support the production of 1,25(OH)₂D outside the kidney[33]; this local-tissue production of the active VDR-ligand under the control of local hydroxylases further complicates the number of factors that may contribute to a vitamin D-mediated clinical outcome.

As we continue to follow the explosion of vitamin D-related studies here at *Metabolism*, we will maintain a keen interest in those investigations that recognize the complexity of this unfolding landscape and employ designs to maximize the interpretability of their results and underlying mechanisms of action.

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