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PTH-Vitamin D-Glycemia Interactions Reloaded

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Traditionally viewed as a key regulator of musculoskeletal health, recent studies also have pointed to pleiotropic roles of vitamin D in the modulation of metabolic and vascular functions (1). Hypovitaminosis D is associated with obesity (2), and low vitamin D states predict higher fasting glycemia and insulin resistance in population studies (3,4), yet other studies showed no relations between vitamin D status and glucose homeostasis after adjusting for adiposity (5,6). Vitamin D supplementation has not consistently benefited glycemia in intervention trials despite adequate increments into a "normal range" (7). The debate surrounding vitamin D and glucose metabolism continues. Aside from assay variability, subject population, and lifestyle confounders that could complicate data interpretation, a fundamental unanswered question is what constitutes vitamin D sufficiency.

Hormonal axes are classically evaluated on multiple levels, encompassing negative feedback and positive stimulation. The vitamin D hormonal system is chiefly under the regulation of the parathyroid hormone (PTH), which stimulates the conversion of circulating 25-hydroxyvitamin D (25-OH-D) to its active form, 1,25-dihydroxyvitamin D (1,25-$(OH)_2$D). While best known to occur in the kidneys, local tissue 1α-hydroxylase expression enables active vitamin D synthesis in a paracrine fashion (1). The interactions between endocrine and paracrine vitamin D systems are not well understood and may underscore the apparent dissociation between PTH and 25-OH-D levels in some clinical settings. For example, PTH responsiveness may determine the outcome among vitamin D–insufficient/deficient critically ill patients (8). In other words, PTH may be normal or elevated to different extents in patients with comparable 25-OH-D circulating status. Higher PTH response correlates with excess mortality in the elderly (9). Whether higher PTH is causal to morbidity and mortality; reflects more profound vitamin D deficiency, such as tissue-level deficiency (10); or is a biomarker of other yet-to-be defined secondary factors is not known. These possibilities have prompted the inclusion of PTH measurements in clinical investigations of vitamin D status in patients with dysmetabolism (11).

In this issue, Kramer et al. (12) tackled this conundrum within the context of vitamin D deficiency, parathyroid status, and insulin sensitivity changes postpartum. By prospectively evaluating predictors for evolution of β-cell function and insulin sensitivity, the authors identified vitamin D–deficient/insufficient states in conjunction with higher PTH levels (upper third tertiles but within normal range) 3 months postpartum, but not either alone, to be an independent predictor of worse glycemia, β-cell function, and insulin sensitivity 9 months later. Close to one-third of the participants with vitamin deficiency and third tertile PTH developed prediabetes/diabetes at 12 months postpartum. These results are provocative and shed novel insight on multiple clinical and mechanistic levels.

First, combined vitamin D and PTH status assessment has unveiled a state of functional vitamin D deficiency relevant to glucose homeostasis, not apparent by either alone. Greater PTH elevation among those with low circulating 25-OH-D levels could signify more severe vitamin D deficiency. Recognizing the aforementioned limitation of absolute 25-OH-D level in differentiating paracrine versus endocrine active vitamin D derivation, it is tempting to speculate that higher PTH levels reflect target tissue-level deficiency. Based on vitamin D action in the pancreas and other insulin-responsive end organs, tissue vitamin D deficiency could explain the observed worsening β-cell function and insulin sensitivity over time. In contrast, low circulating vitamin D level alone, without a rise of PTH into the upper third tertile, could be interpreted as adequate tissue active vitamin D derivation, rather than true deficiency per se.

Second, as adipose tissue is a major storage site of vitamin D, fat mass could impact both vitamin D and PTH levels. Intriguingly, the predictive power of low vitamin D/high PTH state was independent of baseline adiposity

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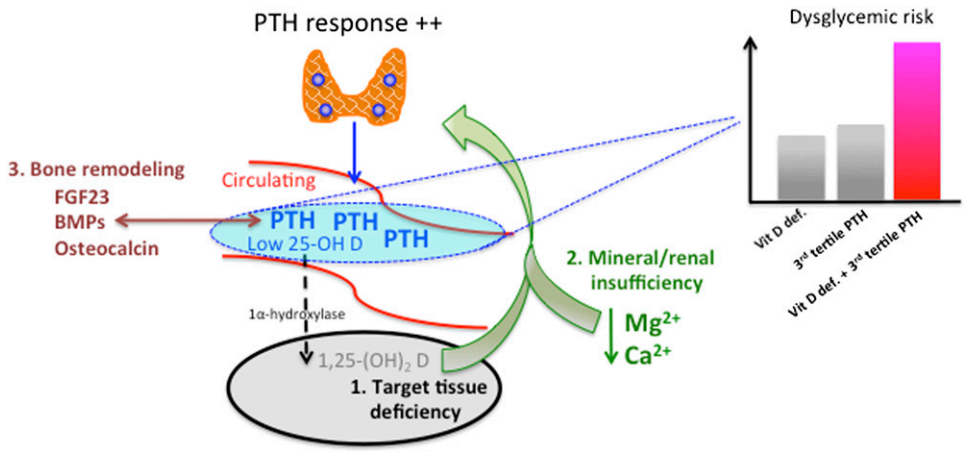

Figure 1—Putative dysglycemic mechanisms underlying vitamin D deficiency postpartum characterized by "heightened" PTH response as a result of *1*) more severe tissue level vitamin D deficiency, *2*) mineral and/or renal insufficiency, and *3*) bone-derived PTH-responsive insulin-sensitizing/antagonizing factors and cytokines. BMPs, bone morphogenetic proteins; FGF23, fibroblast growth factor 23; Vit D def., vitamin D deficiency.

and changes over the 9-month follow-up period. This implies a primary effect of PTH-vitamin D axis on glycemia, beyond the well-known adipose-driven impact.

Third, relative excess risk of dysglycemia and insulin resistance among women with combined vitamin D deficiency/third tertile PTH response exceeded either states in isolation, thus raising the question of whether other additional factors could be contributing. Kramer et al. did not examine for factors of secondary PTH rise, such as low calcium intake, hypomagnesemia, and/or renal insufficiency. Given known associations of all these conditions with worse β-cell function and insulin resistance (13–15), one could not exclude the possibility that the observed higher PTH state may harbor other overt dysglycemic factors. Furthermore, bone–pancreas cross talk is a newly recognized endocrine modulator of glucose homeostasis (16). Osteocalcin is a bone factor with direct stimulatory effects on β-cell function (17). As PTH is linked to higher bone resorption, common in the postpartum period, future studies should investigate whether heightened PTH secretion impacts bone turnover, thereby imparting adverse glycemic effects.

The longitudinal follow-up is a notable strength of the study; however, results obtained in the postpartum period may not be generalizable to other populations. Calcitropic hormones undergo significant changes throughout pregnancy (18). Calcitriol initially rises while PTH falls; after delivery, PTH increases to above prepregnancy levels and has been interpreted as a secondary response to relative calcium deficiency from lactation. Whether the adverse glycemic sequelae predicted by the low vitamin D/third tertile PTH state within the unique postpartum calcitropic hormonal milieu translates to other populations is unclear.

In addition to pinpointing the pivotal importance of PTH status in determining the impact of vitamin D deficiency on glucose and insulin metabolism, the study by Kramer et al. (12) illuminates the complex interplay among the myriad of calcitropic and glucose homeostatic hormones (Fig. 1). It is time to think beyond the realms of traditional liver-muscle-pancreas-adipose tetrad and consider other facets of the metabolic world. It is possible that PTH status is only one piece of the vitamin D-glucose-insulin puzzle, and other players, such as the newly discovered fibroblast growth factor 23 (19) and bone morphogenic proteins (20), also could exert modulatory effects on individuals with given vitamin D and PTH status.

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