



The complexities of vitamin D

It seems so simple. Almost half the US population has a low circulating level of vitamin D, and patients with conditions as diverse as systemic lupus erythematosus and congestive heart failure (as discussed by Hajar et al on page 290 in this issue of the *Journal*) seem to fare worse if they have lower vitamin D levels. But this seeming simplicity of association belies several levels of complexity, with resultant clinical controversy.

First, vitamin D behaves more like a hormone than a vitamin. With adequate sunlight exposure, most humans synthesize sufficient vitamin D without dietary supplementation. But, much of the year, those of us living in Cleveland and the northern United States do not get enough sun. Our 25-hydroxyvitamin D₃ levels (the measured “storage” and substrate form of the vitamin) dip below what is considered normal. People with highly pigmented skin need additional sun exposure to activate the vitamin D precursors into the 25-hydroxy form. Those housebound with debilitating disorders (eg, heart failure) or told to limit their sun exposure (eg, patients with lupus) are at additional risk of having low circulating levels of 25-hydroxyvitamin D₃.

But how should normal be defined, and will raising the level of circulating 25-hydroxyvitamin D₃ actually make any difference?

Plasma vitamin D levels vary with the season, and when considering nonacute effects on calcium and parathyroid hormone (both influenced in the short term by active vitamin D levels), we do not have the advantage of a biomarker analogous to hemoglobin A_{1c} in diabetes that can give us a broader view of the effect of “low” vitamin D levels. Nor do we have biomarkers to reflect the effect of vitamin D supplementation on the cardiovascular and immune systems. Thus, we do not know with certainty how to define biologically normal with regard to the cardiovascular system or whether we should worry about isolated low levels of 25-hydroxyvitamin D₃.

As for supplementation, from our experiences with estrogen replacement therapy, I hope we have learned that epidemiologic data cannot predict the outcome of clinical intervention trials. We cannot assume, based on epidemiologic data alone, that giving vitamin D supplements to patients with heart failure will lessen their risk of death or of cardiovascular events.

Once again, biologic complexity warrants placebo-controlled therapeutic trials. Epidemiologic data and assumptions are not enough to guide our prescribing decisions.

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