quantitative serum proteomics

"...correlating optimum 25(OH)D serum levels with modulated serological proteins and using well-characterized serum samples from randomized placebo controlled trials, may reveal clinically important surrogate markers."

Keywords: controversies ■ quantitative proteomics ■ serum ■ vitamin D ■ vitamin D deficiency ■ vitamin D optimization

There is a sustained and increasing biomedical interest in vitamin D deficiency and its extra-skeletal physiological implications to a wide spectrum of diseases [1–6]. However, there is no consensus on the true clinical efficacy of vitamin D, an essential pleiotropic hormone [1–3]. This Editorial aims to highlight the reasons for such lack of consensus.

Vitamin D physiology

The canonical notion of the secosteroidal vitamin D is that it plays a significant role in calcium and phosphate homeostasis [3–6]. Of particular physiological relevance to humans are vitamin D3 (cholecalciferol) and vitamin D2 (ergocalciferol) [1,2]. These vitamin D forms can be acquired through cutaneous production from a precursor molecule (7-dehydrocholesterol) after exposure to UVB radiation, and through nutritional means via consumption of naturally rich or fortified foods and supplements. Under physiologic conditions, vitamin D produced in the skin or acquired from the diet is transported to the liver where it is hydroxylated to form 25-hydroxyvitamin D [25(OH)D]. This serum metabolite, measured in ng/ml or nmol/l (1 nmol/l = 2.5 ng/ml), is routinely utilized as a reliable indicator of vitamin D status. A second hydroxylation step that takes place in the kidneys converts 25(OH)D to the active vitamin D form 1,25-dihydroxyvitamin D [1,2].

Vitamin D in health & disease

Despite a lack of consensus, serum 25(OH)D levels below 20 ng/ml are generally considered to reflect vitamin D deficiency [1–3]. Low vitamin D levels have been causally linked to skeletal abnormalities, such as osteomalacia in adults and rickets in children. Additionally, vitamin D deficiency has been identified as a risk factor for osteoporosis and fractures [1,2]. Much scientific focus has been attracted recently in the potential extra-skeletal actions of vitamin D [4–7]. Observational studies have associated hypovitaminosis D with several adverse health outcomes, including cardiovascular disease, Type 2 diabetes, neurodegenerative disease, autoimmune disease and cancer [4–7]. However, a definitive causal link between vitamin D status improvement and reduced risk of these pathologies has yet to be found. Of particular interest to our group is the relationship between vitamin D status and cardiovascular disease [8], the leading cause of death globally.

Vitamin D controversies

A randomized placebo controlled trial is the most widely accepted clinical design that can provide causal insight. To date, the results of randomized controlled trials on the effects of vitamin D on cardiovascular disease are either inconsistent or inconclusive [4–8]. We deem that this discrepancy is principally attributed to such factors as: the lack of significant duration of the nutritional intervention; the suboptimum doses of vitamin D administered; the lack of definitive clinical endpoints in the form of measurable phenotypic indicators or disease states; the existence of other confounding factors, such as obesity [9]; and lastly, the lack of effective bioanalytical methodologies to profile such indicators. These clinical study parameters are highly interwoven and interdependent. For example, a study with a short duration and/or low administered dose of vitamin D may not be sufficient to perturb changes at statistically significant levels for the clinical outcomes assessed.

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