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PERSPECTIVES

Measuring what we cannot interpret: Vitamin D thresholds in the Chilean population

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When the Ministry of Health published the vitamin D findings of the National Health Survey 2016–2017 (ENS 2016-2017, Encuesta Nacional de Salud 2016-2017) [1], it did so with a caveat that those citing the figures have almost universally disregarded: no cutoff points exist for epidemiological studies in the Chilean adult population; the thresholds applied were agreed at a meeting of experts and established only preliminarily; and they served a descriptive rather than a diagnostic function [2]. The report closes by naming a Chilean cutoff as an outstanding task. The laboratory that performed the determinations is no less explicit, recording under reference interval that none is available [3].

Eight years later, the task is still pending, and those provisional thresholds—set at 12, 20,20 and 29 ng/mL, with a secondary dichotomy at 20 ng/mL [2]—have acquired the standing of diagnostic criteria. Two analyses of the same survey applied incompatible definitions, one adopted a cutoff at 20 ng/mL [4] and the other reserved sufficiency for concentrations above 29 ng/mL [5], neither tracing its choice to Chilean evidence.

WHAT THE ENS 2016-2017 MEASURED, AND WHAT IT DID NOT

The survey's findings are commonly reported as though they characterized the Chilean population, which they do not. Serum vitamin D was measured in two subsamples only, women aged 15 to 49 and adults aged 65 and over [6], so that no national data exist for men below 65, to whom the 20 ng/mL threshold is nonetheless applied daily.

Among women of reproductive age, the mean concentration was 20.2 ng/mL and the median 19.8; among older adults the mean was 17.7 ng/mL and 59.5% fell below 20 ng/mL [2]. The threshold most frequently applied in Chile thus lies near the center of the distribution it is meant to divide. Every other laboratory threshold in routine clinical use is a reference interval, obtained by measuring a healthy population and designating the tails as abnormal, whereas a cutoff situated at the median of a distribution does not separate disease from health but partitions a population and assigns illness to one half of it. Vitamin D thresholds were constructed differently, and for a defensible reason. Serum 25-hydroxyvitamin D is not a fixed characteristic of the individual but a reflection of sunlight exposure and of dietary or supplemental intake, so that in a population with little of either, the whole distribution shifts downward. A reference interval derived from such a population would therefore describe what is common rather than what is adequate, and would define deficiency out of existence in precisely the setting where it is most likely to occur — much as a hemoglobin range derived from a population with endemic iron deficiency would establish anemia as the norm. The internationally adopted alternative was to anchor the threshold to skeletal outcomes rather than to the observed distribution. That escape from circularity came at a price of its own: the Institute of Medicine's 20 ng/mL denotes a planning target meeting the bone health requirement of 97.5% of the population [7], while the Endocrine Society's 30 ng/mL was formulated for the evaluation of patients already identified as being at risk [8]. Neither was intended as a diagnostic criterion for a whole country.

Nor is a single determination as definitive as it appears. The survey used the most accurate laboratory method available, yet the analytical variation inherent in any such measurement means that a person whose true concentration lies near 20 ng/mL may be reported as deficient on one occasion and

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sufficient on the next, with nothing whatever having changed in the interval [3,9].

A BIOMARKER ASKED TO PERFORM TWO FUNCTIONS

A more fundamental difficulty should concern those of us who teach evidence-based medicine: serum 25-hydroxyvitamin D is not an outcome but a biomarker asked to perform two distinct functions, each failing a different test of validity. As a surrogate endpoint it sustains the inference that raising a concentration confers benefit, the reasoning against which Fleming and DeMets cautioned three decades ago [10]; a surrogate acquires that standing only when intervention upon it reliably alters the outcome that matters to patients, and the suppression of ventricular ectopy remains the canonical case of a marker that satisfied every mechanistic expectation while increasing mortality [11]. As a diagnostic criterion, it does something arguably more consequential, for whereas a failed surrogate endpoint misleads investigators, a surrogate dichotomized into a disease definition creates patients. It is worth considering, too, what is being chained together in this reasoning: a biomarker stands as a proxy for vitamin D status, vitamin D status stands as a proxy for skeletal health, and bone density, the customary next step, is itself a surrogate.

WHAT THE TRIALS SHOW, AND WHAT THEY CANNOT

Vitamin D is unusual among surrogates in having been not merely unvalidated but examined and found wanting across the range in which it is chiefly applied. VITAL randomized 25,871 adults who were not selected for vitamin D deficiency to 2,000 IU daily and found no reduction in total, nonvertebral or hip fracture, with no modification of effect according to baseline concentration; in the lowest prespecified quartile, at or below 24.0 ng/mL, the hazard ratio for total fracture was 1.04 (95% CI, 0.80 to 1.36) [12]. Nor are higher doses reliably safer: an annual high dose having increased falls and fractures among older women [13] and three years of high-dose supplementation having reduced volumetric bone density relative to a lower dose without any gain in bone strength [14].

Two qualifications are owed, and both bear directly on practice.

The first is that the argument does not hold across the whole range of the marker. Below approximately 12 ng/mL, low concentrations do track real disease: rickets in children and osteomalacia in adults are genuine conditions with a genuine biochemical antecedent, and the ENS 2016-2017 found 21.5% of older adults and 16% of women of reproductive age below that concentration [2]. Nothing argued here suggests that such results should be disregarded.

The second is that the trials have little to say about that same range. VITAL's subgroup below 12 ng/mL was exploratory and small, comprising 401 participants and 15 fractures in all, and yielded a hazard ratio of 1.03 with a confidence interval running from 0.36 to 2.95 [12]. Such a wide interval is compatible with both a substantial reduction in fractures and with a near-tripling of them; the result therefore establishes nothing in either direction, and is an absence of evidence rather than evidence of absence.

Together these produce an uncomfortable asymmetry. The marker is most defensible at the low concentrations where it is least often measured, and least defensible between 12 and 30 ng/mL — the range in which roughly two thirds of Chilean older adults are found [2], and in which almost all diagnostic labeling consequently occurs.

GUIDANCE AND PRACTICE HAVE DIVERGED

It would be convenient to attribute the resulting cascade to professional guidance, but in Chile that explanation does not survive examination. The Chilean Society of Endocrinology and Diabetes stated in 2022 that no consensus exists on an optimal value, recommended against measuring vitamin D in persons outside defined risk groups (e.g. metabolic bone disease, malabsorption, bariatric surgery, morbid obesity, reduced sun exposure, and use of anticonvulsants, corticosteroids, antiretrovirals or antifungals), advised explicitly against including the determination as part of a general health check, and proposed supplementing adults over 65 with 800 IU daily without prior measurement [15]. The Endocrine Society reached a comparable position two years later [16]. The difficulty lies not in guidance that has fallen behind the evidence, but in a practice largely undisturbed by the guidance that exists.

That practice is not without consequence. In one primary care cohort, non-indicated vitamin D testing generated an average of 1.6 downstream services per patient over the following 24 months, among them repeat determinations, parathyroid hormone, densitometry, and calcium and osteoporosis medications, many of which were themselves of low value; 62% of those tested received a new diagnosis of deficiency or insufficiency, and a fifth of those so diagnosed had never had an abnormal result [17]. Such cascades are better understood as a property of the system than of the individual practitioner. Once a laboratory designates a value as falling below a reference limit, the conventions of clinical practice supply the remainder: confirmation, treatment, and re-measurement.

WHAT WE MIGHT REASONABLY ASK OF OURSELVES

Chile now requires the fortification of milk and wheat flour with vitamin D, a measure enacted in 2022 and in force since June 2026 [18]. The editorial that welcomed the decree in the Chilean endocrinological literature cited Finland, where fortification sustained since 2003 raised mean serum concentrations from 19 to 26 ng/mL [19]. That figure merits attention. The most sustained national fortification program yet undertaken moved a population to a mean that still falls below the sufficiency threshold that the same editorial applies to Chileans. A standard which the most successful policy of its kind does not attain is better understood as an aspiration than as a clinical criterion.

Fortification will nonetheless shift the Chilean distribution upward, and the natural way to judge whether it has succeeded is to compare concentrations before and after. That comparison requires a measurement framework the country does not possess. Three requirements seem modest enough to adopt: documented traceability to international reference standards, so that values obtained now remain comparable with those obtained later; prevalence reported at more than one threshold, so that estimates remain comparable across studies; and explicit identification of any cutoff as either a population target or a diagnostic criterion, these being incompatible uses of a single number.

Responsibility here is widely distributed, and rests least of all with the clinicians who order the test. It rests with those of us who write, review, edit and teach, and who allowed a preliminary and explicitly descriptive threshold to pass into diagnostic use without asking where it came from. Until Chilean evidence links this marker to outcomes that matter to patients, the best-supported position is also the least demanding: in a healthy adult, the determination should not be requested at all, since a surrogate that cannot be interpreted is not information but an invitation to act.

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