Editorial

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Albumin-adjusted ("corrected") calcium should no longer be reported: a position statement from the Joint IOF Working Group and IFCC Committee on Bone Metabolism and EFLM Committee on CKD

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Calcium is a tightly regulated analyte that is essential for neuromuscular excitability, coagulation, intracellular signalling and mineralization. Total calcium in the circulation reflects several fractions: a protein-bound component (predominantly albumin-bound), a fraction complexed to small anions, and ionized, which is the biologically active fraction. In an ideal world, ionized calcium would therefore be the preferred measurand. In routine practice, however, it is not measured systematically (despite being widely available on blood-gas analysers in many settings), and laboratories rely mainly on total calcium. This immediately raises a well-known limitation: because a substantial fraction of calcium is albumin-bound, total calcium shifts with albumin concentration, even when the biologically active ionized fraction does not change to the same extent. A pragmatic response has thus been to "adjust" total calcium using albumin-based equations. In 1973, Payne et al. proposed such an adjustment and suggested that accurate interpretation of serum calcium without it was not possible [1]. Their equation was derived from 200 routine specimens submitted for liver function testing and was not validated against ionized calcium. Yet, because of its simplicity, the practice of reporting an albumin-adjusted ("corrected") calcium became embedded in laboratory information systems, routine practice, scientific publications and clinical teaching, largely without systematic reappraisal. Over time, several alternative equations were proposed, including the approach described by Barth et al. [2]. Albumin-adjusted calcium also continues to appear in large datasets and publications, for example in reference interval work based on UK Biobank [3]. At the same time, contemporary health-system data confirm that albumin-adjusted calcium is still used in routine care and remains a common basis for interpretation in clinical practice [4].

The underlying premise is that albumin is the dominant, sufficiently stable determinant of the relationship between total and ionized calcium across patients and clinical contexts. This premise often fails in practice: it is precisely when albumin, pH, renal function or inflammatory status is altered that albumin-adjusted calcium becomes least reliable, and most likely to misclassify patients.

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This position statement addresses routine laboratory reporting of calcium with the aim of reducing harm from outdated default calculations in high-risk patients. The rationale for abandoning the practice of routine albumin-correction is now difficult to ignore. In a large contemporary dataset with paired ionized and total calcium, unadjusted total calcium performed at least as well as commonly used adjustment formulas overall, and adjustment increased misclassification, particularly in the presence of hypoalbuminemia [4]. In practice, "correction" can normalize true hypocalcaemia and generate spurious hypercalcaemia, which is exactly the opposite of what clinicians expect when they ask for a "truer" value.

Independent datasets in hospital and critical-care populations point in the same direction [4–7]. Specifically, in the Alberta cohort [4], unadjusted total calcium had the highest overall agreement with ionized calcium (74.5 %), whereas agreement decreased to 63.0 % with the original Payne formula and to 58.7 % with the simplified Payne formula. In patients where acid–base disturbances, inflammation, hypoalbuminemia and renal dysfunction are common, albumin-adjusted calcium shows poorer agreement with ionized calcium, and performance often deteriorates precisely in these settings. This is consistent with physiology: because pH shifts calcium–protein binding and therefore the ionized fraction, a formula that adjusts only for albumin cannot restore the relationship between total and ionized calcium when the binding equilibrium itself has changed. For the same reason, *when ionized calcium is measured, it should be interpreted at the patient's actual pH*: reporting ionized calcium adjusted to pH 7.40 is physiologically difficult to justify and may add further confusion. In other words, the more complex the patient, the more tempting the correction, and the less defensible it becomes.

The correction is even harder to justify in patients with advanced chronic kidney disease (CKD) or on haemodialysis (HD). Notably, in Payne's original work, samples from the renal unit were excluded. In these patients, small differences in calcium status influence treatment decisions (dialysate calcium, vitamin D analogues, calcimimetics, and calcium-based phosphate binders) and therefore the broader management of CKD-mineral and bone disorder (CKD-MBD). KDIGO has recently emphasised that the risks of hypocalcaemia should not be overlooked and that investigating and correcting hypocalcaemia is reasonable; at the same time, KDIGO clearly states that albumin-adjusted calcium equations do not accurately estimate ionized calcium and that clinically relevant abnormalities may be missed when relying on them [8]. In practice, adjustment may move results upward and blunt recognition of true hypocalcaemia, whilst dialysis cohorts consistently show poor agreement between corrected and ionized calcium and a high frequency of "hidden" abnormalities with prognostic implications [9, 10].

The same message applies outside nephrology. In chronic hypoparathyroidism, a recent analysis of the French Épi-Hypo cohort (using 1,215 paired ionized and total calcium measurements) showed that simple total-calcium cut-offs can classify ionized-calcium status with high predictive value, without any albumin correction [11]. The authors therefore argue explicitly for moving away from corrected calcium and for using total calcium as the default measure, reserving ionized calcium for borderline or discordant situations. Multiple myeloma is a good example of why albumin-based correction can be misleading. In myeloma, paraproteins may bind calcium; therefore, an albumin-only adjustment does not reflect the underlying binding situation. In the study by Buege et al., albumin-corrected calcium did not reliably identify ionized-calcium-defined hypercalcaemia in patients with myeloma and could be falsely reassuring despite an elevated ionized calcium [12]. The practical implication is simple: when calcium status matters in myeloma, relying on "corrected calcium" is risky, and ionized calcium should be considered.

From a laboratory standpoint, albumin adjustment is not a refinement: it adds a second measurement and, with it, extra uncertainty. In the era of traceability and measurement uncertainty, "albumin-adjusting total calcium" is a backward step: it replaces a defined measurand with a derived estimate that can vary depending on the albumin method and on changing binding and complexation. When albumin is included in the calculation, the analytical variation of adjusted calcium increases to about 3.6–4.7 %, which can blur small but clinically relevant changes, and compromise classification around decision limits. It also resists harmonisation: performance depends on local albumin methods (Payne's equation was developed using bromocresol green, which is known to overestimate albumin compared with bromocresol purple or immunometric methods) and on case-mix, so acceptable behaviour would require population- and method-specific calibration, and repeated revalidation over time [6]. Finally, a brief survey of European and international members of the IOF-IFCC Committee on Bone Metabolism, the EFLM Committee on CKD, and the Royal Belgian Society of Laboratory Medicine (RBSLM) highlights substantial heterogeneity in current practice. Some laboratories never report albumin-adjusted calcium; others report it only on explicit clinician request,

apply it routinely in certain clinical settings, or generate it automatically when calcium and albumin are ordered together. Notably, this variability can be observed even within the same country or region, which may contribute to inconsistent interpretation and avoidable confusion for clinicians. Encouragingly, responses also suggest that in some countries albumin adjustment is not used at all.

Taken together, these data support a clear position: the Joint IOF Working Group and IFCC Committee on Bone Metabolism and EFLM Committee on CKD recommend that *laboratories should no longer report albumin-adjusted ("corrected") calcium*, for those centres where it remains part of routine reporting. Total calcium should be the default result, and ionized calcium should be ordered up front when clinical decisions depend on calcium status or when interpretation of total calcium is likely to be unreliable. In severe hypoalbuminemia and in patients on dialysis, ionized calcium should be considered the first line test, provided it is measured within an appropriate quality framework and pre-analytical requirements (including appropriate sampling with balanced/low-concentration heparin and rapid handling) are strictly controlled.

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