Albumin-Adjusted Calcium and Ionized Calcium

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To the Editor:

In a recent study, Smith et al. *(1)* compared albumin-adjusted calcium (Adj-Ca)[1] with ionized calcium (Ca^{++}) in the laboratory records of 2 large cohorts of adult hospital patients, many with renal impairment. They used a bromocresol purple (BCP) albumin method with a "modified Payne formula" for Adj-Ca but did not define the patients used to derive their equation. I am concerned that their suggestion that Adj-Ca should not be used when albumin concentration is <3.0 g/dL (30 g/L) may obscure results of clinical importance. For example, nausea and vomiting in a patient with carcinomatosis, marked hypoalbuminemia, and a normal total calcium may be attributed to a direct effect of the cancer, whereas a raised Adj-Ca indicates that Ca^{++} would reveal medically treatable cancer-induced hypercalcemia.

Not that Ca^{++} is a perfect "gold standard." In 1984 we reported significant correlations between serum Ca^{++} and bromocresol green (BCG) albumin both in laboratory staff and in 2 hospital populations with no obvious disturbance of calcium homeostasis *(2)*. (Patients from renal and intensive care units and those with abnormal Adj-Ca values had been excluded.) A reduction in albumin of 1.0 g/dL (10 g/L) was associated with a reduction in Ca^{++} of more than one third of its reference range. A clinical study subsequently confirmed experimental evidence that Ca^{2++} correlation with albumin is caused by positive protein interference at the reference electrode of analyzers *(3)*.

Smith et al. *(1)* said that Adj-Ca should not be used when albumin is <3.0 g/dL because there was an inflexion in their plot of the differences between BCP Adj-Ca and Ca^{++} at about this point. In 1996 we confirmed an earlier report by Ashby et al. of the nonlinear relationship between total calcium and BCG albumin *(4)*. We had searched a large laboratory computer database for adult patients from limited departments with normal urea and creatinine and requests for serum calcium and albumin, but with no other data suggestive of disturbed calcium homeostasis. With at least 100 data points at each albumin between 2.0 and 5.1 g/dL, we found 2 significantly different straight lines that intersected at 8.8 mg/dL (2.2 mmol/L) for calcium and 3.7 g/dL for BCG albumin, each at its respective lower reference limit. However, average Adj-Ca values using the overall slope differed little from values using the slope for albumin values <3.7 g/dL, being higher by 0.02 mg/dL (0.005 mmol/L) at 2.5 g/dL and lower by 0.044 mg/dL (0.011 mmol/L) at 3.0 g/dL, differences of little or no clinical significance.

In the same study *(4)*, we reported significant differences between adjustment equations derived as described above from 2 additional databases from hospital laboratories using different analytical instruments and reagents. Each laboratory's equation was verified by its production of an Adj-Ca distribution, which, after the exclusion of a small number of outliers by probit analysis, was identical with its total calcium reference range. We recommended that laboratories should derive adjustment equations from their own data.

Laboratory-based adjustments are supported by the evidence from Bachmann et al. *(5)* that 24 laboratory methods produced differing median albumin results. Additionally, the immunochemical reference method gave similar albumin values in pooled predialysis renal sera and nonrenal sera, whereas 20 of the 21 commercial automated BCG and BCP systems gave lower ranges in predialysis renal sera. These observations support our practice to not include renal specimens when deriving adjustment equations. As many laboratories' interpretive comments warn and Smith et al. *(1)* confirm, adjusted calcium values may be too high in renal failure.

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[1] Nonstandard abbreviations: Adj-Ca, albumin-adjusted calcium; Ca^{++}, ionized calcium; BCP, bromcresol purple; BCG, bromocresol green.

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