A formula to predict corrected calcium in haemodialysis patients

Arsh Jain1,2, Shelly Bhayana3, Meghan Vlasschaert2 and Andrew House1

1Division of Nephrology, Department of Medicine, 2Department of Epidemiology and Biostatistics, University of Western Ontario, London Health Sciences Centre, London, UK and 3Division of Endocrinology and Metabolism, University of Calgary, Canada

Abstract

Background. The conventional calcium correction formula (corrected total calcium (mmol/L) = TCa (mmol/L) + 0.02 [40 (g/L) – albumin (g/L)]) is broadly applied for the estimation of serum calcium in haemodialysis (HD) patients, despite the fact that it was not derived or validated in a HD population. A novel formula was derived and validated for corrected serum calcium in HD patients.

Methods. Total calcium (TCa), ionized calcium (iCa2+), magnesium, phosphate, albumin and bicarbonate were collected from 60 HD patients to derive the formula. A validation set of 237 stable HD patients was then examined, and subjects were classified as hyper-, hypo- and normocalcaemia based on the iCa2+. Agreement of the new formula was calculated with iCa2+ as the gold standard, using the intraclass correlation coefficient (ICC). This was compared to the agreement between iCa2+ and the following: uncorrected total serum calcium (TCa), the conventional correction formula, the Orrell formula and the Clase formula.

Results. Using multiple linear regression the following formula was derived: corrected total calcium (mmol/L) = TCa (mmol/L) + 0.01 [30 (g/L) – albumin (g/L)]. The new formula had superior agreement compared to all of the other formulae. There was a statistically significant greater agreement between the new formula and the iCa2+ as compared to the conventional formula (P < 0.01). However, the new formula did not significantly outperform the Orrell formula, the Clase formula or Total calcium.

Conclusions. The use of our simple new formula should enable more appropriate decision making compared to the conventional formula in the highly complex HD population.

Keywords: corrected calcium; haemodialysis; ionized calcium; serum calcium

Introduction

Calcium regulation and homeostasis are important in the clinical management of patients with end-stage renal disease on haemodialysis (HD). Both hyper- and hypocalcemia have been identified as independent predictors of mortality in HD patients [1,2]. However, measuring a serum calcium level is not as easy as it may at first seem; while total serum calcium (TCa) can be measured, it is the ionized fraction which is not protein bound that is biologically active. Ionized calcium (iCa2+) is neither easily nor routinely measured in all laboratories. Thus a number of formulae have been derived to estimate the iCa2+ or the ‘corrected’ total calcium (TCacorr) from TCa [3–10].

Clinical practice guidelines suggest that corrected calcium be targeted in the low normal range for patients on HD [11]. The guidelines unfortunately do not state which calcium correcting equation should be used.

The medical community has embraced a formula for calcium correction based on an article published in the British Medical Journal by an anonymous author in 1977 [12]. This correction formula, TCa_corr = TCa (mmol/L) + 0.02 [40 (g/L) – albumin (g/L)], was a crude simplification combining seven previous publications, although it is often incorrectly attributed to Payne et al. [8]. This formula has been applied ubiquitously in health care, and is referenced in numerous medical textbooks and journals [13–15]. Of note, Payne’s original study excluded patients from the renal medicine department [8]. Numerous authors have demonstrated the poor performance of the Payne formula and other correction formulae, particularly when applied to HD patients, compared to the gold standard of iCa2+ [4,16–18]. Yet, the conventional formula continues to be applied broadly for the estimation of calcium exposure in HD patients. Developing a simple and accurate estimate of corrected serum calcium in this patient population was highly desirable.

The objective of this study, therefore, was to derive and subsequently validate a novel and simple formula to estimate corrected TCa in HD patients. A gold standard of iCa2+ was compared to our new formula, as well as to the conventional correction formula, uncorrected TCa, Orrell formula and Clase formula. We hypothesized that our new formula would outperform the conventional formula.
A formula to predict corrected calcium in haemodialysis patients

Subjects and methods

This experiment was divided into two parts following suggested guidelines for the development of clinical prediction rules [19]. The first was the derivation of a new formula for corrected serum calcium and second was the validation of the new formula in an independent data set.

Patients and sample analysis

Blood samples were collected from 297 chronic stable HD outpatients at three tertiary care hospitals. The derivation set comprised 60 patients from London Health Sciences Centre, University Campus, London, Canada. The validation set comprised 237 patients from St. Joseph’s Health Centre and London Health Sciences Centre, Westminster Campus, London, Canada. Samples were collected pre-dialysis on days of routine monthly biochemical testing. Arterialized venous blood was collected without a tourniquet from the patient’s fistula or graft. If the patient had a tunneled heparin-primed catheter, an initial sample of blood equal to or greater than the volume of the catheter was discarded to avoid contamination. All blood was collected in lithium heparin tubes. Plasma was used for sodium, potassium, phosphate, magnesium, albumin and TCa measurements and whole blood was used for iCa\(^{2+}\), pH and total CO\(_2\) (HCO\(_3\)\(^{-}\)). Samples for iCa\(^{2+}\) were transported anaerobically and on ice if they were not going to be tested within 20 min. The iCa\(^{2+}\) was measured using the ion-selective electrode method. The quoted laboratory reference range for iCa\(^{2+}\) is 1.09–1.30 mmol/L and the between day coefficient of variation (CV) ranged from 1.1 to 3.3%. The brom cresol purple (BCP) dye-binding assay was performed on fresh plasma for albumin measurements. Both total calcium and albumin were measured using the LX20 Beckman Coulter analyser. The quoted laboratory reference range for albumin were measured using the ion-selective electrode method. The quoted laboratory reference range for albumin were measured using the LX20 Beckman Coulter analyser. The quoted laboratory reference range for albumin were measured using the LX20 Beckman Coulter analyser. The quoted laboratory reference range for albumin were measured using the LX20 Beckman Coulter analyser.

Statistical analysis

Using the derivation set (n = 60), stepwise multiple linear regression with backward elimination was performed to determine the effect of the potential explanatory variables TCa, albumin, phosphate, magnesium and bicarbonate on iCa\(^{2+}\). For purposes of simplification, we assumed that the TCa\(_{corr}\) was equal to twice the iCa\(^{2+}\) as has been considered by others [4,10,20]. Thus the dependent variable was (2 × iCa\(^{2+}\)). Subjects were classified as hyper-, hypo- and normocalcaemic based on the iCa\(^{2+}\) reference range.

As physicians, we are more interested in the degree to which a patient deviates from the norm rather than whether a measure correctly dichotomizes a patient as being normal or abnormal. Thus, to assess the agreement between the gold standard and the various formulae we followed the methodology of Clase et al. [4]. To directly compare iCa\(^{2+}\) with the formula-based values we first needed to normalize the data. In order to do this we first assumed that the normal ranges (iCa\(^{2+}\): 1.09–1.30 mmol/L; TCa: 2.12–2.62 mmol/L) represented the respective 95% confidence interval [i.e. mean ± 1.96 standard deviations (SD)]. Each measure was then converted to a z-score zCa = (Ca\(_{measured}\) − mean)/SD. The z-scores were then compared to assess how extreme each measure was from the mean/normal range. We then used intraclass correlation coefficient (ICC) to assess the level of agreement between each of the formulae and iCa\(^{2+}\). ICCs were compared following methodology described by Donner et al. [21] for testing the equality of dependent ICCs. We also present data on the number of patients who were misclassified for each of the formulae tested. We present a summation of both the false negatives and false positives for each formula using iCa\(^{2+}\) as the gold standard. This value is then converted to a percentage to give us the percent disagreement (or 100% − percent agreement).

All analyses were performed using SPSS 11.0 statistical software (SPSS, Inc., Chicago, IL, USA) and SAS version 9.0 (SAS Institute, Cary, NC, USA).

Results

Derivation

In the original model total calcium, albumin, magnesium and phosphate were significantly associated with the dependent variable at P < 0.05. The numeric contribution of phosphate and magnesium to the equation was small, and for the sake of parsimony, a model excluding these two variables was constructed. The final regression equation was (2 × iCa\(^{2+}\)) = 0.18 + 1.038 (TCa) − 0.0093 (albumin) (see Table 1).

Using means for values of TCa and albumin from the derivation set and forcing them into the model, the formula was then simplified algebraically into the final model: TCa\(_{corr}\) (mmol/L) = TCa (mmol/L) + 0.01 [30 (g/L) − albumin (g/L)].

Validation

The mean values and ranges for iCa\(^{2+}\), TCa and albumin in the 237 subjects comprising the validation set are summarized in Table 2. The point-prevalence of hypercalcaemia in the validation set, defined as iCa\(^{2+}\) > 1.30 mmol/L, was

<table>
<thead>
<tr>
<th>Variable</th>
<th>β</th>
<th>Standard error β</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constant</td>
<td>0.181</td>
<td>0.103</td>
<td>0.086</td>
</tr>
<tr>
<td>Total calcium</td>
<td>1.038</td>
<td>0.002</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Albumin</td>
<td>−0.0093</td>
<td>0.047</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Mean ± SD</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ionized calcium (mmol/L)</td>
<td>1.14 ± 0.12</td>
</tr>
<tr>
<td>Total calcium (mmol/L)</td>
<td>2.31 ± 0.20</td>
</tr>
<tr>
<td>Albumin (g/L)</td>
<td>34 ± 5</td>
</tr>
</tbody>
</table>
The point-prevalence of hypocalcaemia, defined as iCa$^{2+} < 1.09$ mmol/L, was 27%.

The ICCs for the formulae compared with iCa$^{2+}$ are as shown in Table 3. The ICC was highest with the new formula with a value of 0.689 and was fairly poor for the conventional formula 0.480 [22]. However the Orrell formula, Class formula and total calcium preformed fairly well, with ICCs of 0.668, 0.642 and 0.642, respectively. No other estimator was noted to perform better than the new formula. When assessing percent disagreement the new formula continued to outperform the other formulae as seen in Table 4.

The correlation for the conventional formula with iCa$^{2+}$ was significantly lower than the new formula ($P < 0.01$). However, the new formula did not significantly outperform the Orrell formula, the Class formula or the uncorrected total calcium.

**Discussion**

Since the first algorithm by McLean and Hastings in 1935 [23] that predicted a corrected iCa$^{2+}$ from total calcium and protein, numerous formulae have followed in an attempt to improve this estimation [3–10]. A significant relationship between albumin and serum calcium has been reported [3,7,8] and therefore many formulae have adjusted total calcium for albumin. Of the various formulae to date, the crude modification formula, $\text{TCa}_{\text{corr}} = \text{TCa} (\text{mmol/L}) + 0.01 [30 (\text{g/L}) – \text{albumin (g/L)}]$, has been the most widely applied [8]. It continues to appear in the medical literature, including the discipline of nephrology, despite the lack of validation in populations with advanced renal disease. Goransson et al. have suggested the abandonment of albumin correct Ca measurements due to its poor performance as compared to the gold standard or iCa$^{2+}$ [24]. However, until iCa$^{2+}$ calcium can be measured without a significant impact on resources this may not be widely adopted.

We derived a simple formula, $\text{TCa}_{\text{corr}} = \text{TCa} (\text{mmol/L}) + 0.01 [30 (\text{g/L}) – \text{albumin (g/L)}]$, to estimate the calcium level in HD patients, using a derivation set of 60 HD patients. We subsequently validated our formula in an independent set of 237 HD patients, and demonstrated superiority over the conventional correction formula, as well as a suggestion of increased performance as compared with the Orrell formula, the Class formula and the uncorrected TCa. Agreement was greatest between the gold standard and our new formula. Given the varied ranges of normal for iCa$^{2+}$ at different centres [4,24], we preformed a sensitivity analysis with an alternate reference range for iCa$^{2+}$ (1.15–1.35 mmol/L). The new formula continued to outperform all other formulae. In fact with this reference range, it was found to have significantly greater agreement with the gold standard than the conventional formula as well as the Class formula.

We chose the iCa$^{2+}$ as the gold standard and not pH corrected iCa$^{2+}$. Much of the recent literature on this subject has suggested that there is significant degree of metabolic acidosis in the dialysis patient. Thus correcting for pH will underestimate the true concentrations of iCa$^{2+}$ [4,24].

With specific reference to the HD population, the applicability of existing correction formulae has increasingly come into question. This population is unique in that patients are often hypoalbuminaemic and subject to altered calcium homeostasis [25,26]. Class et al. reviewed the performance of various correction strategies in HD patients [4]. Of the four formulae examined, only the Orrell formula provided a superior prediction of iCa$^{2+}$ than the uncorrected TCa. Two of the formulae, including the original unsimplified Payne formula, consistently overestimated iCa$^{2+}$ while the formula by Orrell et al. [7] tended to underestimate iCa$^{2+}$ at low albumin levels and underestimate iCa$^{2+}$ at high albumin levels. Our novel formula outperformed the conventional correction formula, the uncorrected TCa as well as the Orrell and Class formulae.

It is interesting to note that, as in our study, other studies have shown that uncorrected TCa agrees well with iCa$^{2+}$. A review by Ladenson et al. among a variety of patients found that, of 13 published formulae that corrected TCa for protein, albumin and pH, none, including the original Payne formula, performed any better than the uncorrected
TCa alone [16]. Our study, as well as Clase et al., found that uncorrected total serum agrees with iCa\(^{2+}\) to a degree that is similar to other correction formulae. This brings into question the need to correct for albumin at all. Particularly, considering that the ICC for uncorrected total serum was not significantly different from the best performing formulae.

Varying degrees of hypoalbuminemia in the HD population may be one contributor to the inaccuracy of previous correction formulae. In fact, Payne and others have suggested that their formulae may be unreliable in low albumin states such as nephrotic syndrome or at extremes of calcium ranges [3,9,27,28]. There is an inverse relationship between the amount of calcium bound to non-albumin proteins and serum albumin levels [29]. Specifically, there is a greater proportion of calcium bound to non-albumin binding proteins as albumin levels fall [9]. Formulae derived from patients within a narrow range of albumin levels would likely overestimate the correction for low albumin by failing to account for this increased affinity of calcium to non-albumin proteins. Hence, these formulae will tend to overestimate calcium in hypoalbuminemic states such as renal failure.

Our formula also provides a methodological advantage over previous formulae in that BCP staining was used to measure albumin versus bromcresol green (BCG). Reported difficulties with the use of BCG include non-specific binding with globulins, and falsely elevated albumin levels in serum samples containing heparin or fibrinogen [30–32]. Also, a few studies have demonstrated the difficulties of measuring albumin using BCP in specific clinical situations [33,34]. However, two large studies in HD patients that compared albumin measurements by BCP and BCG with the gold standards of nephelometry and immunoturbidimetry found better correlation of BCP with the respective gold standards [35,36]. Carfrey et al. showed that the use of BCP resulted in systematic overestimation of albumin in HD patients, with the greatest discrepancies seen in hypoalbuminemic HD patients [36]. Increased non-specific binding of other proteins to BCG in uraemic patients was implicated in reduced serum albumin concentrations in patients with hypoalbuminemiae [37,38]. Increased non-specific binding of other proteins to BCG in uraemic patients was suggested as a possible explanation for the error. Clase et al. have suggested a correction formula, based on 50 stable HD patients [4]. These investigators used BCG to measure albumin, which may explain the poorer performance in our validation set.

Conclusion

The correction formula for serum calcium TCa\(_{corr}\) (mmol/L) = TCa (mmol/L) + 0.02 [40 (g/L) – albumin (g/L)] [8], which is currently in widespread use, has very poor agreement with the gold standard of iCa\(^{2+}\) in HD patients. None of the currently available formulae have been both derived and subsequently validated in the HD population. Our novel formula, TCa\(_{corr}\) (mmol/L) = TCa (mmol/L) + 0.01 [30 (g/L) – albumin (g/L)], independently derived and validated in HD patients for the correction of serum calcium for albumin, results in significantly better agreement with iCa\(^{2+}\) compared to the conventional formula. Although not significantly, our formula performs better than the Orrell formula, the Clase formula, as well as uncorrected TCa. We recommend that the use of the conventional correction formula be abandoned in HD patients, and suggest that the use of our novel and simple formula for calcium correction will enable more appropriate decision making in this highly complex population.

Acknowledgements. We would like to thank the editors, reviewers, Dr Amit X Garg and Dr G Y Zou, for their useful advice and feedback on the manuscript.

Conflict of interest statement. None declared.

References

22. Landis JR, Koch GG. The measurement of observer agreement for categorical data. *Biometrics* 1977; 33: 159–174