The cause of metabolic acidosis

To the Editor: As a case of 'make your diagnosis', Chang *et al.*[1] presented a case with metabolic acidosis. Although the authors attributed the acid–base disorder of the case to D-lactic acidosis, the laboratory findings would indicate that the case had hyperchloremic acidosis in addition to D-lactic acidosis. The case might also have had respiratory alkalosis.

Having an anion gap of 21.1, the case would have an anion-gap increase of 9.1–11.1 according to the indicated reference value (10–12), although the value might need adjustment by the plasma-albumin concentration and the pH.[2] The increase would reflect the sum of L-lactic acid and D-lactic acid ($9.4 = 2.6 + 6.8$) and indicate the metabolic acidosis caused by these acids (mainly by D-lactic acid). However, the case had the corrected bicarbonate of 13–15, the sum of bicarbonate (3.9) and anion-gap increase, which is less than the reference for bicarbonate (22–26). The low range of corrected bicarbonate shows that the case had hyperchloremic acidosis, which could have been caused by bicarbonate loss due to intestinal malabsorption or renal tubular dysfunction, because the decrease in corrected bicarbonate reflects the increase in chloride.

For a decrease of bicarbonate (18.1–22.1), the expected decrease of $PaCO_2$ from its reference range (35–45) would be 18.1–26.5, and the predicted $PaCO_2$ would be 8.5–26.9. Having a $PaCO_2$ of 9.6, a predicted value, the case would have had an appropriate ventilatory response to metabolic acidosis. However, considering the limit of respiratory compensation for metabolic acidosis (a $PaCO_2$ of 15–20), the case might also have had respiratory alkalosis.

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Amino-terminal form of parathyroid hormone in CKD

To the Editor: We read with great interest the review by Souberbielle *et al.*[1] on the practical issues of measuring parathyroid hormone (PTH) in chronic kidney disease patients. Here we would like to raise a few issues regarding the amino-terminal form of PTH (N-PTH) that was briefly mentioned in their review.

As described in the article, N-PTH is detectable by the whole PTH assay (third-generation assay) but is less well reactive in 'intact' PTH assays (second-generation assays), presumably due to a modification in the 15–20 amino-acid region. Therefore, in patients with N-PTH overproduction, PTH values measured using the third-generation assays are paradoxically higher than those measured using the second-generation assays. Although not addressed in this review, it is important to note that such an overproduction of N-PTH can also occur in chronic kidney disease patients,[2] making this issue of critical importance in the evaluation of secondary hyperparathyroidism.

Considering the potential impact of N-PTH on patient care, one of the important issues is whether this molecule has a biological effect on bone turnover. Although still unclear, it is implicated that N-PTH has a significant bioactivity, because this molecule contains the very first N-terminus that is essential for interaction with the PTH/PTH-related protein receptor. Indeed, most patients with N-PTH overproduction or its corresponding reversed whole PTH/intact PTH ratio (>1) presented with severe parathyroid hyperplasia and high-turnover bone disease despite low intact PTH levels.[2,3] It is also noteworthy that in one of such patients, treatment with calcimimetics resulted in normalization of the reversed whole PTH/intact PTH ratio.[4] This finding underscores the possibility that the calcium-sensing receptor may regulate the secretion of not only 1–84 PTH but also this N-PTH variant.

Although it is too early to draw a conclusion from these data, they at least suggest that further insights into the nature of N-PTH would provide useful information in the management of secondary hyperparathyroidism. For the precise evaluation of parathyroid function in chronic kidney disease patients, further research on N-PTH is needed, as well as a precise understanding of the characteristics of each assay.

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3. Komaba H, Takeda Y, Shin J *et al.* Reversed whole PTH/intact PTH ratio as an indicator of marked parathyroid enlargement: five case studies and a literature review. *NDT Plus* 2008; **1**(Suppl 3): iii54–iii58.
4. Komaba H, Shin J, Fukagawa M. Restoration of reversed whole PTH/intact PTH ratio and reduction in parathyroid gland vascularity during cinacalcet therapy for severe hyperparathyroidism in a uraemic patient. *Nephrol Dial Transplant* 2010; **25**: 638–641.

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The Authors Reply: We thank Drs Komaba and Fukagawa for their remarks[1] and for giving us the opportunity to add to our review[2] some comments on amino-parathyroid hormone (N-PTH). Determining the exact nature of N-PTH and understanding its regulation and action(s) is an exciting but challenging field for future research. Although a very excessive production of N-PTH can be easily evidenced by the finding of a third/second-generation PTH ratio >1, we would like to underline an important technical point. As several automated third-generation assays will become available soon, it is likely that many studies will focus on the third/second-generation PTH ratio. However, this ratio cannot be calculated from any coupling of PTH assays (one third-generation and one second-generation assay). Indeed, both assays must be calibrated similarly (i.e., must produce the same concentration in a solution of rh1–84 PTH), and the second-generation assay must measure both 7–84 and 1–84 PTH with 100% cross-reactivity, but must not measure N-PTH. To our knowledge, this could currently be achieved only with the Ti-PTH assay (second-generation) and the CA-PTH assay (third-generation) from Scantibodies Laboratories (Santee, CA, USA). Nevertheless, a third/second-generation PTH ratio >1 is a very rare feature,[3] and the best way to improve our knowledge in N-PTH physiology would be to develop a simple and direct N-PTH assay. Indeed, the only published method is complicated and reserved to highly specialized research laboratories.[4] Having said that, the finding by Drs Komaba and Fukagawa of the normalization of a reversed ratio during calcimimetic therapy is striking and deserves further study.[5]

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Statins: do we definitely know whether they are completely inefficacious in ESRD?

To the Editor: We wish to submit a letter concerning the paper by Lam *et al.* in *Kidney International*.[1] Although the data are certainly of interest, we feel that some note of caution will put the argument of the authors into a slightly different perspective.

The paper of Lam *et al.*[1] reports that prescription of statins in dialysis patients continued unchanged despite the negative outcome in hemodialyzed patients of one study (4D; Wanner *et al.*,[2] and in the meantime even in a second one: AURORA[3]).

The observation is certainly of interest, but we wish to raise a note of caution regarding the interpretation of the evidence for the inefficacy of statins.

In the past, it had appeared *a priori* pathogenetically plausible that lipid lowering in uremic patients should reduce cardiac events. That pathophysiological plausibility does not necessarily translate into evidence-based outcomes of adequately powered prospective intervention trials has recently been impressively shown by the TREAT study on erythropoietin treatment.[4]

The issue we wish to raise here is the absolute requirement that studies must be adequately powered before the conclusion is drawn that a given treatment is ineffective. Indeed both the 4D and the AURORA study were underpowered to provide biostatistical proof for the efficacy of statins on myocardial infarction. In both studies the primary outcome was a composite comprising sudden death and death from other cardiac causes, including myocardial infraction and stroke. When planning the studies it was assumed that lipid lowering by statins would reduce such a combined cardiac and cerebrovascular end point. *Post hoc* we noted that statins had definitely no significant effect with respect to sudden death and heart failure. However, as we had pointed out elsewhere,[5] the study was presumably underpowered to exclude efficacy for all types of cardiac death. The *post hoc* analysis even pointed to a suggestive benefit for adjudicated coronary end points that were lower by 19% per 1 mmol lowering of low-density lipoprotein-cholesterol—surprisingly identical with what had been observed previously in studies on nonrenal cardiac patients.[6]

It is also remarkable that both in 4D and the AURORA study, a trend was seen for separation of the survival curves approximately 3 years after start of the study—in stark contrast to the almost immediate effect of statins seen in nonrenal patients with coronary heart disease. It is possible that in hemodialyzed patients statins don't affect inveterate