The set point of calcium—another view

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In a recent editorial in this journal, Drs Goodman and Salusky questioned whether the set point of calcium, as defined as the serum calcium at 50% of the maximal PTH, provides relevant information [1]. Their editorial concluded by stating that until evidence becomes available that in vivo estimates of alternative methods of calculating the set point of calcium correspond to data obtained in parathyroid tissue in vitro using the four-parameter model, the relevance of alternative methods remains uncertain. It would seem to us that this logic is not entirely correct since the purpose of in vitro studies is to reflect in vivo physiology and not the opposite; considering that the in vitro measurement of the set point has varied considerably even with normal parathyroid tissue [2], it is unlikely that in vitro studies will consistently reflect in vivo PTH responses.

We are pleased to have the opportunity to address the concerns of Drs Goodman and Salusky about the methods for calculating the set point of calcium. As opposed to the four-parameter model, in which the set point is obtained at the mid-range between the minimal and maximal PTH [1,3], the set point in our method is obtained at 50% of the maximal PTH. In general, we believe that both methods for the calculation of the set point provide similar information and intend to present data which demonstrate this conclusion. However, it is also important to discuss conceptual differences between the two methods and discuss why mathematical models may not always provide the most relevant information with respect to the abnormal PTH–calcium curve in dialysis patients.

In the four-parameter model, the mathematical formula for calculating the set point and slope elongates the PTH–calcium curve by setting the minimal PTH to zero and the set point is then obtained at the 50% value of the elongated curve. As illustrated in Figure 1,

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Fig. 1. The figure has been adapted from the editorial by Drs Goodman and Salusky (reference 1) which was originally published in reference 6. The PTH–calcium curves were obtained in normal humans and dialysis patients with marked secondary hyperparathyroidism. The set points (calculated by the four-parameter model) of the two PTH–calcium curves were stated to be not significantly different.

with maximal PTH as 100% and minimal PTH at 5% (normal human), the mid-range would be 52.5%; for a dialysis patient in whom the minimal PTH is 20%, the mid-range would be 60%. While mathematically correct, the question could be asked whether the four-parameter model has the potential to distort biological reality. As shown in Figure 1 which is reproduced from the editorial by Drs Goodman and Salusky [1], it can be observed that the minimal PTH, as a percentage of maximal PTH, is considerably different between normal humans and dialysis patients; this has been shown many times previously [4–6]. Our inspection of this figure suggests to us that the two PTH–calcium curves appear to be different; thus it would not surprise us if the set points, which are supposed to reflect the PTH–calcium curve, were different for the two curves.
model would select against finding any difference in the two set points, since in the dialysis patients the set point was obtained at 60% of the maximal PTH and in normal humans at 52.5% of the maximal PTH. In addition, it is also conceptually difficult to appreciate how the two PTH-calcium curves would not be different since for the same basal serum calcium (1.22 mmol), the basal PTH as a percentage of maximal PTH was considerably greater in the dialysis patients than normal humans, 25 versus 56% respectively (Figure 1). Furthermore, it is mathematically difficult to conceive how with the same basal calcium and more than a 30% difference in basal PTH values, the set points could actually be the same. While without the original data it is not possible to know whether the calculation of the set point at 50% of the maximal PTH would detect a difference in set points, such an approach would increase the probability of finding a difference because the two PTH-calcium curves are more widely divergent at 50% of the maximal PTH. Thus, while the approach advocated by Drs Goodman and Salusky is based on a mathematical model, it could be questioned whether in this instance it is missing important biological information.

While the set point as calculated by the two methods may have some minor conceptual differences, the important question is to answer whether, in general, each method for calculating the set point provides similar information in the clinical setting. In two recent studies, we have calculated the set point by both methods and have observed a high degree of correlation. As shown in Figure 2, the correlation coefficient for the comparison of the two methods was $r=0.98$ in 21 dialysis patients in whom total calcium was measured [5] and $r=0.97$ in 55 dialysis patients in whom ionized calcium was measured (unpublished data). Thus, if the two set points are so highly correlated with each other, it would be expected that each would be similarly correlated with other parameters. Furthermore, we have also used a statistical method designed to assess the agreement between two correlated methods and have determined that a high degree of agreement was present between the two methods for the calculation of the set point [7]. Finally, as would be expected, the correlations between the two set points and the predialysis serum calcium, basal PTH, maximal PTH, minimal PTH, and the basal/maximal PTH ratio were virtually identical (Table 1); these results have also been confirmed in a unpublished study of 55 haemodialysis patients in whom ionized calcium was measured instead of total calcium. Thus our results indicate that the two set points provide similar information in the clinical setting.

In their editorial [1], Drs Goodman and Salusky would seem to use specious reasoning in suggesting that since no difference in the set point, as calculated by the four-parameter model, was observed in studies between normal humans and azotaemic patients [6,8], this would mean that reports of differences in the set point, as calculated at 50% of the maximal PTH, observed between patients with different forms of renal osteodystrophy [4], as a result of calcitriol treatment [9,10], or following parathyroidectomy [10], may be flawed. Our response to this argument is that the results of our recent studies have suggested that the set point may not be a fixed property in the dialysis patient and is modified by sustained changes in the existing serum calcium [5,9,11]. As has been shown in

![Set Point of Calcium (mg/dl) - Brown](image)

**Fig. 2.** The correlation between the two set points is shown for two separate studies in which A. total calcium (reference 5) and B. ionized calcium (unpublished data) measurements were used.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Set point (50%)</th>
<th>Set point (Brown)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Predialysis calcium</td>
<td>$r=0.85$, $P&lt;0.001$</td>
<td>$r=0.83$, $P&lt;0.001$</td>
</tr>
<tr>
<td>Basal PTH</td>
<td>$r=0.35$, $P=0.12$</td>
<td>$r=0.35$, $P=0.12$</td>
</tr>
<tr>
<td>Maximal PTH</td>
<td>$r=0.31$, $P=0.17$</td>
<td>$r=0.30$, $P=0.18$</td>
</tr>
<tr>
<td>Minimal PTH</td>
<td>$r=0.37$, $P=0.10$</td>
<td>$r=0.35$, $P=0.12$</td>
</tr>
<tr>
<td>Basal/maximal PTH</td>
<td>$r=-0.26$, $P=0.26$</td>
<td>$r=-0.25$, $P=0.27$</td>
</tr>
</tbody>
</table>
Table 1, the correlation between the two set points and the serum calcium was \( r = 0.85 \) (SP) and \( r = 0.83 \) (SP-B) \[5\]; these results would suggest the intriguing possibility that PTH secretion adapts to sustained changes in the existing serum calcium. In a recently published study \[9\], PTH–calcium curves were obtained in 11 haemodialysis patients at baseline, 6–10 weeks after the predialysis serum calcium was intentionally increased by either calcitriol treatment or a high-calcium dialysate, and 6 weeks after discontinuation of the calcium-modifying treatments, at which time the predialysis serum calcium had returned to baseline values. In this study in which changes in serum calcium were deliberately produced, the correlation between the two set points and serum calcium was \( r = 0.72 \), \( P < 0.001 \) (SP) and \( r = 0.71 \), \( P < 0.001 \) (SP-B). Finally, in another study \[11\] in which the predialysis serum calcium was changed by modifying the dialysate calcium concentration, the change in calcium correlated with the change in set point \( (r = 0.87, P < 0.001 \) (SP) and \( r = 0.82, P < 0.001 \) (SP-B)). These results would serve to support the concept that the set point is modified by the existing serum calcium. Thus, the likely reason that a difference in the set point was not observed between normal humans and azotaemic patients \[6,8\] was that the serum calcium was not different and not because the set point was calculated with the four-parameter model.

Finally we would like to address the comments of Drs Goodman and Salusky regarding the calculation of the slope of the PTH–calcium curve and emphasize that we must be careful not to be victimized by mathematical correctness. To calculate the slope with the four-parameter model, the PTH–calcium curve is elongated because the minimal PTH is set to zero and the slope is calculated at the mid-point, which is the set point of the elongated curve \[1,3\]. As stated by Drs Goodman and Salusky, relatively few data points are generally available at the mid-point, which is the set point of the elongated curve \[1,3\]. As stated by the rule rather than the exception. Thus, if only the two data points closest to the mid-range are used to calculate the slope, this has the potential to introduce considerable error. As shown in Figure 3, this concern becomes even more problematic when, as commonly observed in dialysis patients, variation in the minimal PTH as a percentage of maximal PTH is present. In Figure 3A, three superimposable PTH–calcium curves with visually identical slopes and also containing multiple aligned data points have been drawn to represent potential results in the study of normal humans and dialysis patients; the only difference in the curves is a difference in the minimal PTH as a percentage of maximal PTH. When the slope of these curves was calculated with the four-parameter model (Figure 3B), the regression lines representing the three slopes show a marked divergence. While it is true that the slope is calculated from the points nearest to the set point (line at 0), this calculation then depends on a virtually perfect alignment of the data points. Thus since, as stated by Drs Goodman and Salusky, relatively few data points are generally available at the set point \[1\] and rarely are these data points perfectly aligned, this could potentially result in a significant error.

Consequently we believe that our approach for calculating the slope of the PTH–curve may be more reasonable because it is possible to account for variation in data points and it is not affected by differences in the minimal PTH as a percentage of maximal PTH.
To calculate the slope, maximal PTH is converted to 100% and minimal PTH is represented as a percentage of maximal PTH and the slope is measured directly as a linear measurement in the steepest part of the PTH–calcium curve. This is accomplished by eliminating the asymptotic portions at both ends by subtracting 10% from the maximal PTH and adding at least 10% to the minimal PTH. The resulting measurement should provide a reasonable determination of the change in PTH for the change in serum calcium [5].

In summary, we believe that as recently stated by Brown [12], who first popularized the application of the four-parameter model for the study of PTH–calcium curve, and as we have shown in this editorial, both methods for the calculation the set point of calcium provide similar information in the clinical setting. In addition, we believe that it is time to end this contentious debate about the definition of the set point and proceed with the more exciting subject of learning more about the dynamics of PTH secretion.

References

2. Fitzpatrick LA, Leong DA. Individual parathyroid cells are more sensitive to calcium than a parathyroid cell population. Endocrinology 1990; 126: 1720-1722

Editor's note

Please see also the ‘Exchange of Opinion’ by Goodman (pp. 1725–1727 in this issue).

Nephrology Dialysis Transplantation is happy to provide a forum for exchange of opinion on topics where the definite scientific evidence is apparently not yet in. We give the authors of the original article the opportunity to reply.

The set point revisited, again

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The response to our recent editorial [1] about the interpretation of results obtained from in vivo studies of parathyroid gland function in patients with chronic renal failure contains factual errors that warrant attention [2].

When comparing experimental models, an accurate description of the components of each and their underlying tenets is required. Figure 1, which is reproduced from our editorial [1], demonstrates that presenting results according to the four-parameter model does not artificially extend the inverse sigmoidal calcium–PTH curve by setting minimum PTH levels to values of zero; rather, minimum PTH levels at high ionized calcium concentrations are approximately 5% of maximum values in normal subjects, whereas minimum levels are about 20% of maximum in patients with secondary hyperparathyroidism [3]. These findings were initially reported by Ramirez et al. in patients undergoing regular dialysis [3], and they have subsequently been confirmed by Messa and co-workers in