Diuretics and secondary hyperparathyroidism in chronic kidney disease

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Secondary hyperparathyroidism (SHPT), one of the salient features of chronic kidney disease (CKD), has received substantial attention based on observational studies that indicate its association with increased mortality in both patients with end-stage renal disease (ESRD) [1] and with non-dialysis-dependent (NDD)-CKD [2]. As shown in Table 1, diverse conditions including medications are associated with relatively high or low serum PTH levels in

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Table 1. Factors associated with and/or consequences of relatively low or high serum intact PTH level in CKD patients using conventional PTH assays*

<table>
<thead>
<tr>
<th>Low PTH</th>
<th>High PTH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thiazide diuretics</td>
<td>Loop diuretics</td>
</tr>
<tr>
<td>Calcium-rich diet</td>
<td>Low-calcium diet</td>
</tr>
<tr>
<td>Lower dietary phosphorus</td>
<td>Higher dietary phosphorus</td>
</tr>
<tr>
<td>Vegetarian diet (phytate-based phosphorus)</td>
<td>High inorganic phosphorus in diet (additives, conservatives)</td>
</tr>
<tr>
<td>FGF-23 (?)</td>
<td>Hyperphosphatemia</td>
</tr>
<tr>
<td>Peritoneal dialysis</td>
<td>Inadequate dialysis treatment</td>
</tr>
<tr>
<td>High dialysate calcium concentration</td>
<td>Low dialysate calcium concentration</td>
</tr>
<tr>
<td>Adynamic bone disease</td>
<td>High turnover bone disease</td>
</tr>
<tr>
<td>Low alkaline phosphatase</td>
<td>High alkaline phosphatase</td>
</tr>
<tr>
<td>Advanced age</td>
<td>Younger age</td>
</tr>
<tr>
<td>Caucasian race</td>
<td>Black race</td>
</tr>
<tr>
<td>Higher eGFR</td>
<td>Lower eGFR</td>
</tr>
<tr>
<td>PTH assay errors</td>
<td>PTH assay errors</td>
</tr>
<tr>
<td>Malnutrition-inflammation complex</td>
<td>Obesity</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td></td>
</tr>
</tbody>
</table>

Medications: phosphorus binders, nutritional vitamin D, VDRA, vitamin D mimetics, calcimimetics, recombinant PTH\(^b\), RANKL modulators\(^c\) (?)

\(^a\)FGF-23, fibroblast growth factor-23; eGFR, estimated glomerular filtration rate; PTH, parathyroid hormone; VDRA, vitamin D receptor activator; RANKL, receptor activator of nuclear factor kappa-B ligand.

\(^b\)Administration of recombinant PTH, known as Teriparatide (injectable Forteo\(^\text{TM}\)) may suppress the measurable naïve PTH level based of the PTH assay employed.

\(^c\)No consistent data related to RANKL.

CKD patients. Among medications that lower PTH, the administration of active vitamin D and its analogs [3,4] is also associated with lower mortality in ESRD [1] and NDD-CKD patients [5]. Similar effects have also been suggested for calcimimetics [6]. Interestingly, both vitamin D derivatives and calcimimetics also lower serum alkaline phosphatase levels in CKD patients [7], which may be another pathways related to survival advantages of these agents [8,9]. Nevertheless, since at least part of the putative mechanism of action responsible for these observed survival benefits is the lowering of PTH [10], treatment of SHPT may also be considered a potential way to improve longevity in these patients [11,12]. Controversy still exists about what the ideal PTH levels should be [13], especially since dialysis patient outcome data from Japan, the country that has one of the highest dialysis patient survival in the world and where a low intact PTH of 60–180 pg/mL is targeted (as opposed to Western countries where guidelines recommend 150–300 or even 600 pg/mL [13]) indicates that patients with the lowest serum PTH have the lowest death rates [4].

SHPT emerges early during the course of CKD and progresses as kidney function declines; hence, an effective treatment strategy should consist of early detection and treatment as well as the identification and correction of factors that may aggravate SHPT. The basic underpinning of SHPT are the alterations in calcium, phosphorus and vitamin D, which occurs not only as a function of decreasing glomerular filtration rate (GFR) [14] but also as a result of patient demographics [3,15], comorbidities [16], protein-energy wasting [17] and obesity [18,19] (Figure 1). Many of these do not represent ‘modifiable’ factors, which has made it difficult to prevent SHPT by altering its risk factors. Indeed, current treatment paradigms concentrate on the administration of medications aimed at suppressing established SHPT. Addressing this shortcoming is the study by Isakova et al. [20] in this issue, which explores the link between the well-known effects of diuretic medications on calcium homeostasis and PTH levels in patients with moderate and advanced NDD-CKD. Decline in kidney function is often associated with sodium and water retention, which (among other factors) may lead to de novo or worsening hypertension [21]; hence, the application of diuretics to offset this pathophysiology is considered a sine qua non of hypertension management in CKD patients. Isakova et al. [20] report that loop diuretics are also associated with significantly higher risk of SHPT, while no such association seems to be present for thiazide diuretics; thiazides in fact appear to mitigate the impact of loop diuretics on PTH levels in those treated with both classes of medications [20]. These novel associations appear biologically plausible: a calciuric effect of loop diuretics [22] could facilitate hypocalcemia and thus promote SHPT, while a calcium-retentive effect of thiazides [23] could do the opposite.

Viewing the results of the paper purely from a bone mineral perspective, a logical conclusion is that the modulation of the diuretic regimens could be used as a tool to prevent the development and/or to mitigate the severity of SHPT. Not withstanding the merits of such an argument, we would like to take a broader view of this issue and examine what potential impact the results of the study by Isakova et al. [20] could have on clinical practice. First of all, one needs to be conservative in how to interpret the results of this epidemiologic study. The authors used methodologies aimed to offset limitations inherent of observational studies (including multivariate adjustments, stratification and propensity scores), but these still do not allow us to conclude that use of diuretics is the proximal cause of the differences in PTH levels. Whereas only clinical trials can provide definitive proof to this effect, the well-described effects of diuretics on calcium homeostasis make it more likely that the described associations are indeed a result of a cause–effect relationship.

Secondly, we need to examine what the consequences of a diuretic effect on SHPT might have on patient outcomes. Thiazide diuretics were shown to improve bone mineral density and to decrease the risk of bone fractures in patients with normal kidney function [24], but these results may not be extrapolated to patients with advanced CKD, given their much more complex bone and mineral homeostasis. The effects of a higher PTH on bone structure in CKD depend largely on how high PTH is; both very high and very low PTH levels have been linked to various histological abnormalities, and there is considerable debate about what an ‘ideal’ PTH level might be in NDD-CKD [25]. Based on these complex considerations, it is premature to conclude...
that an association of a certain drug class with higher or lower PTH levels means an association with worse or with better bone structure or fracture rates in patients with CKD. In regards to mortality, the association of higher PTH with increased mortality is based on observational data [2,4]; given the associative nature of these data, any discussion about the mortality effects of drugs that modulate PTH level remains speculative.

Finally, our third and perhaps most practically important point: could these results help us optimize diuretic use by including their effects on PTH level in our clinical decision making? Since the decision to use a loop diuretic over a thiazide when treating hypertension or congestive heart failure is usually based on the former's higher potency, it is less likely that one would opt for a thiazide when the clinical situation asks for a more potent agent, as it is often the case in patients with advanced CKD. If interchanging diuretic classes is not feasible, then combining loop diuretics with thiazides would seem the most logical strategy from a bone mineral standpoint, which could not only offer an offsetting effect of the two classes on calcium homeostasis and on SHPT [20], but would also represent a much more potent diuretic strategy. Indeed, clinical trials of combination diuretic regimens have shown significantly enhanced diuretic effects after the addition of thiazide diuretics in patients resistant to loop diuretics [26,27]. The downside of such combination strategies, however, is the potential for exaggerated volume loss, a sharp drop in GFR (with the potential risk of acute kidney injury) and hypokalemia [26,27]. Since these earlier clinical trials examining diuretic combinations were performed in patients who were resistant to the actions of loop diuretics [26,27], we can only speculate that an even more enhanced effect might occur if this strategy were to be applied more liberally, as one would need to do if SHPT were to be taken into consideration. Hence, any such application would have to be done with extreme caution to avoid untoward consequences.

In conclusion, we believe that the results presented by Isakova et al. shine a spotlight on an interesting and previously neglected link between commonly used medications and an important metabolic complication of CKD. These findings are hypothesis generating and could form the basis for future research, including clinical trials. Due to uncertainties about the clinical relevance of the presented associations and the potential risk of therapeutic strategies that involve changing diuretic regimens, caution is advised in the application of these findings to clinical practice.

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(See related article by Izakova et al. Diuretics, calciuria and secondary hyperparathyroidism in the Chronic Renal Insufficiency Cohort. Nephrol Dial Transplant 2011; 26: 1258–1265)

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