Dysphoria Induced in Dialysis Providers by Secondary Hyperparathyroidism

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We returned from Kidney Week in Philadelphia in November in a distinctly dysphoric mood. We were heading toward rounds in the Hemodialysis Unit of the New York Harbor Veterans Affairs Health Care System and wondering what exactly we were going to do about secondary hyperparathyroidism (SHPT) in our population of veterans with ESRD. Our dysphoria (a generalized state of feeling unwell or unhappy) was the result of the conflicting messages communicated by the meeting and this issue of CJASN. The meeting was suffused with scholarly research churning out new findings and radiated a jovial air of commercial enthusiasm for reducing levels of parathyroid hormone (PTH) and phosphate. CJASN, on the other hand, published two papers with a less cheery message about our daily practice.

While making rounds on our dialysis patients, we attempt to adhere to guidelines based on observational data that are not clearly supported by relatively negative randomized, controlled trials (RCTs). A lack of convincing trial data may be met with different responses by different clinician phenotypes. For instance, some clinicians get a bit anxious if a laboratory parameter is out of the normal range and respond by doing something to fix it. Others take a more lackadaisical or nihilistic approach.

The younger of the two of us, a recent nephrology fellow, observes that rounding with different attending nephrologists offered the rich opportunity to learn from varying perspectives. Will she develop into the sort of clinician who struggles to keep the PTH in a strict target range or the more liberal type who does not respond to every out-of-range laboratory value with an immediate titration of medication? Will she relent and allow the Centers for Medicare and Medicaid Services Quality Improvement Program to dictate practice? (They seem pretty certain that they know what is good for patients on hemodialysis!) Our practice today may be as much on the basis of personal idiosyncrasies as on the basis of the idealized (if less than evidence-based) guidelines. The most confused party may be the patients who wonder why the serum phosphate and PTH remain higher than the doctor desires and merit so much attention.

With this dysphoria-inducing background, Tentori et al. (1), in this issue of CJASN, examine whether current trends in practices directed at CKD-mineral and bone disorder (CKD-MBD) are affecting outcomes. The Dialysis Outcomes and Practice Patterns Study (DOPPS) includes an international sample of patients on hemodialysis. Tentori et al. (1) report on changes in PTH levels in patients treated for SHPT in DOPPS phases 1–4 (covering 1996–2011) and the associations between PTH and the outcomes of all-cause and cardiovascular hospitalization and mortality. Median PTH increased substantially in DOPPS phases 1–4 in all regions except Japan. Consistent with earlier DOPPS analyses (2), mortality risk was higher for PTH=301–450 pg/ml and >600 pg/ml compared with the group with values of PTH=150–300 pg/ml. Cardiovascular mortality and risk of hospitalization were higher for PTH>600 pg/ml. PTH<50 pg/ml was also associated with mortality, especially among patients with diabetes and those with lower body mass index.

The particularly interesting result is not simply what happened to the patients but also, the glimmers of what might have been going on in the clinicians’ minds. The medical directors of dialysis units reported that their targets for an upper limit of PTH rose and did so before the Kidney Disease Improving Global Outcomes (KDIGO) recommendations of 2009 (3). The paper states that ‘it appears that clinicians’ attitude and overall management of SHPT may have changed. Given the lack of strong evidence to advocate for tighter control, clinicians may have grown to accept relatively higher PTH targets... reflecting clinicians’ attitudes and real world practice as opposed to specific clinical practice guidelines’ (3).

Were the clinicians sanguine about the PTH levels of their patients on dialysis? The Evaluation Of Cinacalcet HCl Therapy to Lower Cardiovascular Events Trial (EVOLVE) essentially failed to show improvement in clinical outcomes (risk of death or major cardiovascular events) when cinacalcet or placebo was used to treat SHPT (4). Observational studies have linked elevated PTH with mortality, but no RCT has shown whether treatment to a specific PTH target improves outcomes.

The rates of parathyroidectomy decreased over the studied period, which no doubt contributed to an extent to the increases in PTH levels.

However, before concluding that clinicians were overcome by ennui, we note that the prescription of intravenous vitamin D analogs and cinacalcet increased. Interpretation of providers’ prescribing behaviors is speculative. As any nephrology fellow knows, they are responding in many different ways to the conflicting
data, guidelines, RCTs, bundled payment plans, and commercial influences. It may be too simple to view the cumulative data as indicative of some mass trend rather than the amalgamation of individual strategies.

The KDIGO guidelines stated that “[t]he patients with CKD stage 5D, we suggest maintaining iPTH levels in the range of approximately 2–9 times the upper reference limit . . . We suggest that marked change in PTH levels in either direction within this range prompt an initiation or change in therapy to avoid progression to levels outside of this range” (3). The Kidney Disease Outcomes Quality Initiative commentary on this guideline was generous to the befuddled clinicians and suggested that “[t]his recommendation gives flexibility to US practitioners in using and adjusting treatments that are effective in decreasing PTH levels despite lack of proof for clinical benefit from a specific PTH range” (5).

There are many other variables that contribute to our collective cognitive dissonance regarding management of CKD-MBD. Questions persist about the appropriate assay for PTH measurement (6,7). KDIGO guidelines are based on second generation assays, which initially were said to detect only the intact PTH molecule. The assay also detects fragments, particularly the 7–84 fragment, that antagonize the actions of intact PTH (8). The relative importance of oxidized and nonoxidized PTH has not been resolved (9). These shortcomings mean that we may be overestimating parathyroid function and allowing them to influence our clinical decisions.

PTH is possibly no more than a surrogate and not properly an outcome by itself. We use circulating PTH as a marker for bone turnover, but it cannot reliably predict bone turnover states (10). The fact that patients with CKD show skeletal resistance to PTH leads to the current recommendations that PTH levels be at least two times the normal range (11). Bone biopsy may be the gold standard for the diagnosis of MBD, but it is infrequently performed. Biomarkers may have practical use, and quantitative computed tomography may find its place (12,13). Phosphorus, calcium, and low vitamin D levels have been linked with increased mortality, but evidence is lacking that lowering phosphorus and maintaining normal calcium levels improve clinical outcomes (14). Other than the possibility that PTH is of interest because of its imperfect correlation with bone findings, all of this information is inextricably wrapped up with vascular calcification, perhaps the true cause of death in patients with CKD (15). Finally, we have yet to incorporate fibroblast growth factor (FGF)-23 into a therapeutic model of CKD-MBD (16). It is, therefore, not surprising that rounds in the dialysis unit lead to some dizzying contradictions.

The DOPPS data show a falling rate of parathyroidectomy, presumably because a looser regimen of PTH control was promulgated. Another paper in this issue of CJASN highlights the complications that follow that procedure (17). Using data from the US Renal Data System, Ishani et al. (17) compared adverse events that occurred during the hospitalization and the 30-day and 1-year postoperative periods with the 1-year preceding the surgery for 4435 of 7707 patients after applying exclusion criteria. Parathyroidectomy was associated with significant morbidity and 2% mortality. (In this study, sponsored by Amgen, Ishani et al. [17] refer to the procedure as “surgical parathyroidectomy,” implying that a medical parathyroidectomy, with cinacalcet, is an alternative, although of course, the drug does not lower PTH as effectively.) We find this a rather harrowing result: 41 (0.9%) patients died during the index hospitalization, and 48 (1.1%) patients died within 30 days after discharge. Parathyroidectomy was associated with high rehospitalization rates and more intensive care unit and emergency room visits requiring treatment for hypocalcemia compared with the preceding year. Hospitalizations were higher for acute myocardial infarction and dysrhythmia (17).

The study fails to provide the indications (other than an elevated PTH) for performing parathyroidectomy and the long-term follow-up of the surviving patients after 1 year (17). We do not know if the clinicians who ordered the procedure were satisfied with the result (other than being pleased that the elevated PTH presumably fell) or if the patients lived long enough to somehow benefit. Ishani et al. (17) describe a greater relative increase in adverse outcomes in patients without comorbid conditions, presumably because those with comorbidities had higher adverse event rates before the procedure as well.

Where are we dialysis providers after these two interesting papers? Should we exercise our obsessive-compulsive tendencies and micromanage the PTH levels (as well as the calcium, phosphate, and vitamin D levels) as per KDIGO and CMS guidelines? Or should we relax and give our patients some dietary and medication leeway, recognizing that their quality of life (and ours) as it is affected by those guidelines has yet to be effectively assessed? We certainly do not want to order parathyroidectomies any time soon, and higher PTH levels are consistently associated with adverse events. Therefore, the plan to address (in an admittedly nonevidence-based manner) PTH levels early to avoid the highest values and keep levels in a middle range as the KDIGO guidelines suggest seems like a prudent course, pending more definitive RCT data.

Disclosures
None.

References

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See related articles, “Clinical Outcomes after Parathyroidectomy in a Nationwide Cohort of Patients on Hemodialysis,” and “Recent Changes in Therapeutic Approaches and Association with Outcomes among Patients with Secondary Hyperparathyroidism on Chronic Hemodialysis: The DOPPS Study,” on pages 90–97 and 98–109 respectively.