The assay of PTH and blood has evolved. Please discuss the intricacies of various PTH measurement assays. This is compounded by the fact that there is no universally accepted PTH preparation as an assay standard. It is therefore necessary to know the details of the particular assay in use, so that one may put the results obtained into proper perspective. Thus, some assays recognize N-terminally truncated PTH fragments to a great extent and yield high values, whereas others minimize the interaction with these peptides and result in lower values. Appropriate “target values” for PTH will thus vary widely depending on the assay used.

This problem is exemplified by the PTH recommendations laid out by the Kidney Disease: Improving Global Outcomes (KDIGO), which state that a reasonable target range for intact PTH in the setting of ESRD would range from two to nine times the upper limit of normal. This recommendation is somewhat problematic because of the accumulation of these fragments in patients with advanced kidney disease out of proportion to that seen in patients with normal renal function; therefore, the use of multiples of the upper limit of normal is likely not appropriate. The best advice at present is to be familiar with the particular assay in use and with knowledge of its performance to construct a reasonable range for targeting the control of hyperparathyroidism.

What is your take on the administration of vitamin D supplements (including calcitriol) to CKD patients? It is well recognized that there is a progressive decline in the levels of 1,25-dihydroxyvitamin D throughout the course of CKD. Many mechanisms are involved in this process, including phosphate retention, increases in FGF-23 levels, decreases in renal mass, suppression of 1-hydroxylase by uric acid toxins, and, importantly, decreases in 25-hydroxyvitamin D, which are quite common in patients with CKD, particularly in those with proteinuria. Thus, levels of 25-hydroxyvitamin D below the lower limits of normal, estimated to be 30 ng/mL, are common in patients with CKD.

The practice guidelines of KDOQI recommend trying to supplement nutritional forms of vitamin D to correct the low levels of 25-hydroxyvitamin D. And they include recommendations for the therapeutic use of ergocalciferol. However, these recommendations perform poorly in clinical practice: correction of low levels of 25-hydroxyvitamin D to above 30 ng/mL is achieved in only approximately 50 percent of patients. More recent studies indicate that the use of cholecalciferol might be more effective because this results in a longer half-life for 25-hydroxyvitamin D in plasma. The implications of correcting the low levels of 25-hydroxyvitamin D to normal are not yet fully clear, although it appears that this will allow for a decreased need for active vitamin D sterols, and there may be other benefits as well. Although there are not yet any definitive studies, ergocalciferol and cholecalciferol are widely used in clinical practice, and further studies of the optimal regimen to achieve vitamin D repletion are required.

In your practice, do you use the recommended target PTH levels? Please discuss target PTH levels for stage V CKD in relation to the KDOQI and KDIGO recommendations. The KDOQI practice guidelines recommended a desirable PTH range of 150–500 pg/mL based on the results of bone biopsy studies that demonstrated that this range was associated with a relatively normal bone turnover. However, there was wide variation in the data on which it was based, and the particular PTH assay that was used for these studies is no longer available. The later recommendations from KDIGO have broadened this range as a multiple of the upper limits of normal, that is, two to nine times the upper limits of normal as a reasonable target range. As discussed above, this is complicated by the accumulation of various PTH fragments that may not be recognized in various PTH assays. These recommendations reflect the frustration with, and variability in, PTH assays such that this broad range has recently come to be associated with considerable uncertainty with regard to treatment targets.

A large body of epidemiologic evidence, however, both in the United States and more recently from South America and Europe, looking at overall mortality of the patients, shows that the lowest mortality appears to be associated with PTH ranges more in keeping with the original KDOQI recommendations. It is reasonable to consider these outcome-related ranges as targets rather than to focus on one parameter of bone turnover, for which it is now recognized that PTH is a relatively poor marker. Accordingly, in our current practice, using the intact PTH assay that is widely used among large dialysis providers, we believe that a reasonable range is 150–300 pg/mL. It should be emphasized that these ranges should be considered “soft,” and may be extended, particularly on the higher side, without obvious detriment to clinical care. The PTH assay results should be considered in conjunction with other parameters of bone and mineral metabolism, such as calcium and phosphate and alkaline phosphatase measurements, and with existing comorbidities. These considerations may move the desired range up or down according to the clinical circumstances.

When is a bone biopsy required in these patients? Bone biopsy is not widely used in clinical practice because it is an invasive technique and requires specialized laboratory facilities for analysis. It is generally recommended that one might consider biopsies when the biochemical markers are indeterminate. Thus, a patient who describes bone pain, and whose PTH is within the target range, but in whom alkaline phosphatase is elevated, may well have hyperparathyroidism, and a bone biopsy would be helpful in guiding treatment. It was formally recommended that a bone biopsy is required in patients who are scheduled to undergo parathyroidectomy, but in the absence of aluminum-based phosphate binders, and if serum aluminum is low, this is probably not necessary.

What is calciphylaxis? What are the available treatment options for these patients? Is there a role for parathyroidectomy? Calciphylaxis is a syndrome of vascular calcification, small vessel thrombosis, and tissue necrosis that is seen almost exclusively in patients with advanced kidney disease. The cause of calciphylaxis is not precisely known, although several risk factors are known to be associated with it. Because of the poor prognosis associated with calciphylaxis, many treatment options are initiated, often in combination. Thus, the treatment options may include aggressive phosphate control by the use of non–calcium-containing phosphate binders, more frequent or longer dialysis, and consideration of parathyroidectomy, if the calciphylaxis is associated with moderate to severe hyperparathyroidism. Calcitriol, a calcimimetic, may be considered as an alternative to parathyroidectomy. In recent years, it has been noted that much of the calciphylaxis that occurs is proximal in the thighs or abdomen and is often not associated with severe hyperparathyroidism.

Anticoagulation with warfarin should be discontinued, and active vitamin D sterols should also be withdrawn. Hyperbaric oxygen may be helpful in achieving wound healing. More recently, the use of sodium thiosulfate has been advocated and appears to be efficacious, at least in some instances. Given that many thera-
With regard to CKD-MBD, what is your treatment approach to patients with stage III-IV CKD and stage V CKD?

Inasmuch as abnormalities in bone and mineral metabolism begin early in the course of CKD, it is desirable to initiate treatment as early in the course of kidney disease as possible. Current practice recommendations are to screen for abnormalities in bone and mineral metabolism by the early measurement of intact PTH and, if PTH is elevated, to consider initiating treatment.

The initial step in treatment would be to modulate dietary intake of vitamin D and, if they are low, to try to bring them into the normal range. If this is not sufficient to control the hyperparathyroidism, beginning an active form of vitamin D, such as calcitriol, paricalcitol, or doxercalciferol, should be considered. Although studies in experimental animals have shown the efficacy of phosphate restriction even in the early stages of CKD, one could consider efforts to decrease dietary phosphate intake or consider the use of phosphate binders, although these are not yet approved for use in early CKD.

As kidney disease advances, the need for active forms of vitamin D becomes more common, and phosphate binders are indicated when hyperphosphatemia occurs. In stage V CKD, or in patients receiving dialysis, the initial approach is to control phosphate first, then to correct hypocalcemia, to use active vitamin D sterols, and if this is insufficient to control PTH to target values, then to consider the use of a calcimetic agent. In terms of the type of phosphate binders used, one has to be cognizant of the existence of vascular calcification and the risk of its progression and to consider limiting the ingestion of calcium-containing phosphate binders. Although this approach is somewhat evolutional at present, it appears to be a prudent one, especially in the presence of existing vascular calcification.

When do you usually start calcimetic therapy?

In patients receiving dialysis, it is our practice to try to control hyperparathyroidism with phosphate control and active vitamin D sterols. As you know, there is a broad spectrum of patients, some who are hypercalcemic and some of whom have serum calcium values at the upper limits of normal. The former are easily treated with active vitamin D sterols, whereas in the latter, the use of active vitamin D sterols may be limited by a tendency to hypercalcemia. If hyperparathyroidism cannot be controlled to target values, then the addition of a calcimetic agent is indicated. It is our practice to use this in addition to the other measures.

What changes can be expected with CKD-MBD after successful kidney transplantation?

In general, the abnormalities associated with CKD-MBD begin to improve after successful kidney transplantation. The abnormalities may be influenced by concomitant therapy, and, indeed, by a previous history of CKD, such that many patients come to transplantation with adynamic bone disease, which may be the result of the time spent receiving hemodialysis, or indeed with complicating factors, such as prior steroid therapy or postmenopausal status. Parathyroidectomy is not usually performed early in the course of CKD and is associated with bone loss, and it should be assessed in terms of fracture risk and treatment undertaken if necessary. The extent of the improvement in CKD-MBD after transplantation will, of course, vary according to the level of kidney function achieved.

What are the treatment options for osteoporosis with CKD? Please discuss bisphosphonates, PTH, and denosumab.

Osteoporosis and other causes of low bone density often occur in patients with CKD throughout the entire spectrum of patients seen. Many of the agents used for the treatment of osteoporosis, such as bisphosphonates, are problematic, mainly because of a scarcity of studies, the long half-life of bisphosphonates in bone, and the possible presence of adynamic bone disease. In general, a precise diagnosis should be made before therapy is initiated. In recent years, other options for the treatment of osteoporosis have included intermittent injections of PTH, and there are a few data to support this approach in patients with CKD. The most recent therapy with denosumab has not been studied in detail in osteoporosis associated with CKD, but it may be a reasonable option, at least in some patients.

What criteria do you use to recommend patients for parathyroidectomy?

Parathyroidectomy should be considered for patients who have severe hyperparathyroidism that cannot be controlled by medical means. The failure to control hyperparathyroidism may be from inability to control serum phosphorus or persistent hypercalcemia, which limits the use of active vitamin D sterols. As you know, there is a broad spectrum of patients, some who are hypercalcemic and some of whom have serum calcium values at the upper limits of normal. The former are easily treated with active vitamin D sterols, whereas in the latter, the use of active vitamin D sterols may be limited by a tendency to hypercalcemia. If hyperparathyroidism cannot be controlled to target values, then the addition of a calcimetic agent is indicated. It is our practice to use this in addition to the other measures.

Practice Pointers continued

Sodium-dependent glucose co-transporter 2 (SGLT2) inhibitors and bile acid sequestrants hold promise for the treatment of type 2 diabetes. Both were among the agents highlighted in the symposium, “Novel Therapies for Type 2 Diabetes – Today and Tomorrow,” at the American Diabetes annual meeting in San Diego.

SGLT2 inhibitors, eight of which are in clinical trials, are the first class of drugs to target renal glucose reabsorption for treating diabetes, said Ernest M. Wright, PhD, DSc, of UCLA. By increasing the urinary excretion of glucose, SGLT2 inhibition reduces blood glucose levels.

“Reabsorption of glucose in the kidney is not essential for life,” as illustrated by the benign nature of familial renal glycosuria, Wright said. However, this novel class of therapies may have a downside. “So far, there are no remarkable adverse effects, but since SGLT2 expression occurs throughout the body, we need to be curious about off target sites,” he said.

Among the SGLT2 compounds in development for blood glucose control are dapagliflozin. Researchers presented results of a 104-week phase 3 study of dapagliflozin. Sustained reductions in blood glucose levels as well as body weight characterized study patients taking dapagliflozin added to metformin. In contrast, patients taking glipizide added to metformin gained weight. Change from baseline in HbA1c in patients receiving glipizide plus metformin was 0.02 percent, compared to -0.48 percent for those treated with dapagliflozin (dap) 2.5 mg plus metformin (met); -0.58 percent for patients on dap 5 mg plus met; and -0.78 percent for those on dapagliflozin 10 mg plus met. However, genital infections were more common in patients taking dap added to metformin. The former are easily treated with active vitamin D sterols. As you know, there is a broad spectrum of patients, some who are hypercalcemic and some of whom have serum calcium values at the upper limits of normal. The former are easily treated with active vitamin D sterols, whereas in the latter, the use of active vitamin D sterols may be limited by a tendency to hypercalcemia. If hyperparathyroidism cannot be controlled to target values, then the addition of a calcimetic agent is indicated. It is our practice to use this in addition to the other measures.

New Agents Hold Promise in Diabetes Treatment

BASs absorb bile acids (BAs) in the intestine of BAs by preventing their reabsorption, resulting in increased excretion of BAs in the stool. In order to produce more BAs to compensate for the stool loss, the liver converts cholesterol into BAs, thereby lowering blood levels of cholesterol. BASs promote glucose homeostasis by suppressing glucagon-like peptide 1 (GLP-1), a potent anti-hyperglycemic hormone that induces glucose-dependent stimulation of insulin secretion while suppressing glucagon secretion. When plasma glucose concentration is in the normal fasting range, GLP-1 no longer stimulates insulin release while suppressing glucagon secretion. While there are numerous targets for PPARs, however, is accompanied by substantial caution owing to the side-effects associated with the agents. They include bone fractures, fluid retention, weight gain as well as bladder cancer and cardiovascular risk.

“We face the issue of separating PPARs as a target from the issues seen with various PPAR-targeting drugs, but biologic studies continue to underscore the importance of the target itself,” said Platzky.

Charles F. Burant, MD, PhD, of the University of Michigan Medical concluded the symposium by highlighting fatty acid elongates, β3-adrenergic agonist, and G-protein-coupled receptors.

While there are numerous targets for diabetes drug development, “there is no perfect drug,” he said. “There is no perfect target. Expecting that there is one is unreasonable.”

The introduction of HMG-CoA reductase inhibitors, or statins, has reduced the clinical use of BAs in tackling hyperlipidemia. However, these agents may play a role in type 2 diabetes therapy. The scientific—and pharmaceutical—community’s interest in PPARs as drug targets is based on their effects on insulin sensitivity, atherosclerosis, and inflammation, said Jorge Plutzky, MD, of Harvard Medical School. Studies have shown that activating PPAR-γ may help prevent diabetes and nephropathy by blocking the effects of glucose and resistin-antinodostin-inhibitor-1 system (RAAS) in triggering podocyte apoptosis.

Researchers’ interest in the PPARs, however, is accompanied by substantial caution owing to the side-effects associated with the agents. They include bone fractures, fluid retention, weight gain as well as bladder cancer and cardiovascular risk.