

Blast from the Past-using PTH to Differentiate Acute versus Chronic Kidney Disease

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Abstract

In these times of limited financial and human resources, physicians must be cognizant of the rising costs of healthcare. Expensive imaging studies should be reserved for conditions that are particularly challenging to diagnose using traditional laboratory tests. Consequently, we must revisit the use of alternative simple, inexpensive and readily available laboratory tests to help differentiate medical conditions. Therefore, we would like to revisit the use of intact PTH as a discriminatory lab value in evaluating chronic vs. acute kidney injury.

Keywords: Intact PTH; Acute versus Chronic Kidney Failure; Hyperkalemia; Phosphorus

Introduction

In the absence of imaging studies, it is difficult to determine if elevated creatinine is the result of an acute or chronic kidney insult. Many lab values have been utilized to determine this complex question with varying success. Previously, it has been ascertained that hyperkalemia is one of the best indicators of CKD, as the kidney is able to adjust for decreased GFR (glomerular filtration rate) by increasing colonic excretion of potassium [1-4]. Carbamylated Hemoglobin has also been used to differentiate the two conditions, [5,6] however this method has fallen out of favor due to the shortened red blood cell life span associated with uremia. Interestingly, intact parathyroid hormone (i-PTH) can be utilized similarly. However, the complex regulation of PTH in the setting of acute and chronic kidney injury has prevented its widespread use.

Assays that measure the full-length hormone comprised of 84 amino acids, or PTH (1-84), are known as “intact” PTH (i-PTH) assays [7]. Earlier radioimmunoassays commonly detected various fragments of PTH that accumulate in the serum/plasma of patients with CKD because their renal clearance and/or degradation are diminished. In contrast to the various fragments that are detected in more traditional assays, intact PTH is not metabolized by the kidney and should not give artificially high values [7].

The regulation of parathyroid hormone is a complex process involving the synchronization of the skeletal and endocrine systems as well as the kidneys. Not surprisingly, many peripheral disorders can affect PTH homeostasis resulting in secondary hyperparathyroidism (SHPT). Of these disorders, chronic kidney disease (CKD) is most commonly encountered [8]. Although CKD has long been associated with SHPT, the proposed mechanism for parathyroid dysfunction has been the subject of much debate. Nonetheless, several factors have been implicated in the pathogenesis.

CKD results in a dysregulation of calcium, phosphate, and vitamin D homeostasis. In this pathway, elevated phosphate concentration, low serum calcium concentration, and reduced 1,25 (OH)₂D₃ (calcitriol) lead to increased PTH synthesis [9,10]. Further, a more recent development in the understanding of SHPT describes the role of phosphatonin fibroblast growth factor (FGF-23) in controlling PTH levels. In response to elevated phosphate, FGF-23 diminishes renal 25 (OH)-1-hydroxylase, a vital enzyme responsible for the conversion to active vitamin D [10,11]. Interestingly, FGF-23 dysregulation does not appear to be limited to CKD and has been observed in AKI [12,13].

Further compounding the issue is a possible decrease in the activation of the vitamin D receptor [14].

Whatever the mechanism of altered homeostasis, elevated PTH has been linked to a variety of poor clinical outcomes reaching far beyond normal bone metabolism. These manifestations include increased risk for cardiovascular disease, decreased immune function, and an overall decreased quality of life [15,16]. Additionally, excess PTH appears to have neurotoxic effects as EEG abnormalities have been observed in patients with kidney failure [17]. Such toxic effects of PTH are proposed to occur secondary to an elevation of IL-6, C-reactive protein, and tumor necrosis factor- α , thus creating a state of inflammation [18].

Case 1

A 35 year-old African American female with a past history of pituitary adenoma status post surgery and no history of renal disease presented with a 3 day history of excessive drowsiness. In the ER the patient was found to be severely hypotensive and in septic shock. Acute kidney injury likely due to volume depletion was considered after sudden onset of elevated creatinine. Additionally, despite normal serum calcium and phosphorous, labs revealed a PTH (intact) of 163 pg/ml. The patient was continued on antibiotics and began to recover slowly (Table 1).

Case 2

A 69 year-old female with a history of hypertension and CVA was brought to the emergency department after falling and injuring her ankle. The patient was noted to have high creatinine and no history of renal disease prompting, renal consult. Acute kidney injury, likely due to volume depletion was considered. After a further rise in creatinine, i-PTH was noted to be elevated at 104 pg/ml. The patient was started on IV fluids and monitored. The creatinine began to decrease and the patient recovered (Table 2).

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Case 1	Day 1 12:45	Day 2 4:00	Day 2 13:30	Day 3 2:11	Day 5 5:10
Creatinine (mg/dL)	3.85	3.34		3.32	2.89
PTH(intact) pg/dL			163		
Calcium (mg/dL)	10.1	8.5		8.5	8.3
Phosphorus (mg/dL)			2.5		
Potassium (mg/dL)	3.6	4.6		3.9	3.5

Table 1: A 35 year-old African American female with a past history of pituitary adenoma status post surgery.

Case 2	Day 1 17:28	Day 2 5:44	Day 3 10:27	Day 4	Day 5
Creatinine (mg/dL)	3.42	3.43	2.25	1.82	1.49
PTH(intact) pg/dL		104			
Calcium (mg/dL)	9.4	9.1	8.2	8.7	8.8
Phosphorus (mg/dL)		4.7		3	
Potassium (mg/dL)	5	5.3	4.5	5.5	4.6

Table 2: A 69 year-old female with a history of hypertension and CVA.

Case 3	Day 1 4:03	Day 1 13:25	Day 2 5:05	Day 3 2:11	Day 4 4:00
Creatinine (mg/dL)	4.19	3.36	2.72	1.89	1.60
PTH (intact) pg/dL			75		
Calcium (mg/dL)	7.5	8.9	7.6	7.6	8.0
Phosphorus (mg/dL)			2.7	2.2	2.6
Potassium (mg/dL)	3.8	3.4	3.1		2.9

Table 3: A 55 year-old female with no history of renal disease.

Case 4	Day 1 11:50	Day 1 13:32	Day 2 5:01	Day 3 9:28	Day 4 3:50
Creatinine (mg/dL)	3.49		2.76	2.09	1.51
PTH (intact) pg/dL		135			60
Calcium (mg/dL)	10.7		9.9	9.4	8.2
Phosphorus (mg/dL)				1.1	
Potassium (mg/dL)	4.6		3.8	3.8	3.5

Table 4: A 57 year-old female with a history of seizures, CVA and hypothyroidism.

Case 5	Day 1 18:17	Day 2 14:41	Day 3 4:05	Day 3 15:16
Creatinine (mg/dL)	3.24	5.55	6.36	7.02
PTH(intact) pg/dL			332	
Calcium (mg/dL)	6.7	7.3	6.7	6.7
Phosphorus (mg/dL)	5.2	5.2	6.3	2.2
Potassium (mg/dL)	6	5.8	4.8	4.7

Table 5: A 34 year-old male with a history of alcohol abuse.

Case 6	Day 1 19:30	Day2 11:40	Day 2 14:51	Day 2 17:00	Day 3 18:00	Day 4 5:00	Day 5 5:20
Creatinine (mg/dL)	3.4	4.4	3.89	5.05		6.11	7.25
BUN (mg/dL)	28	46	35	47		58	65
PTH (intact) pg/dL		561			891		493
Calcium (mg/dL)	7.2	5.9	6.8	6.5			7
Phosphorus (mg/dL)		4.2					
25-Hydroxy Vitamin D (ng/mL)		26					

Table 6: A 34 year-old white male who was diagnosed with rhabdomyolysis due to drug intoxication.

Case 3

A 55 year-old female with no history of renal disease presented with a 2-3 day history of right upper quadrant pain and dizziness. She was referred for renal consult after emergency department evaluation

revealed hypotension and elevated BUN and creatinine. Further assessment revealed acute kidney injury, most likely secondary to volume depletion. Urine electrolytes were monitored and the patient was administered IV fluids and pressors. Subsequent labs revealed elevated i-PTH in the setting of hypocalcemia. Soon after the hypotension was corrected the patient's creatinine began to decline. The patient eventually regained renal function (Table 3).

Case 4

A 57 year-old female with a history of seizures, CVA and hypothyroidism arrived at the emergency department from a nursing home with complaints of weakness and fever. She was referred for renal consult after urinalysis revealed proteinuria, hematuria, and bacteriuria. Further assessment, suggested acute renal injury. In addition to creatinine, i-PTH was discovered to be elevated. After several days of IV fluids, the patient began to regain renal function. The creatinine began to decline and the PTH followed in a similar manner (Table 4).

Case 5

A 34 year-old male with a history of alcohol abuse presented after being found unresponsive by his family. He was brought to the emergency department where he was observed to have a high creatinine. Renal consult was obtained and the patient was diagnosed with acute renal failure likely secondary to rhabdomyolysis and volume depletion. Despite supportive treatment, the patient remained oliguric. PTH was still markedly elevated (332 pg/ml) on day 3. The patient was placed on dialysis and began to recover over the next several weeks (Table 5).

Case 6 final report

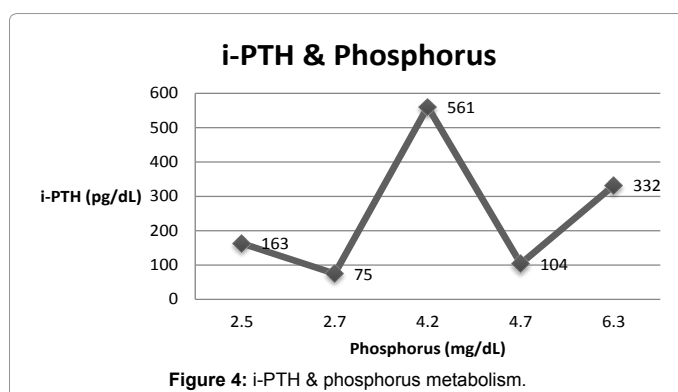
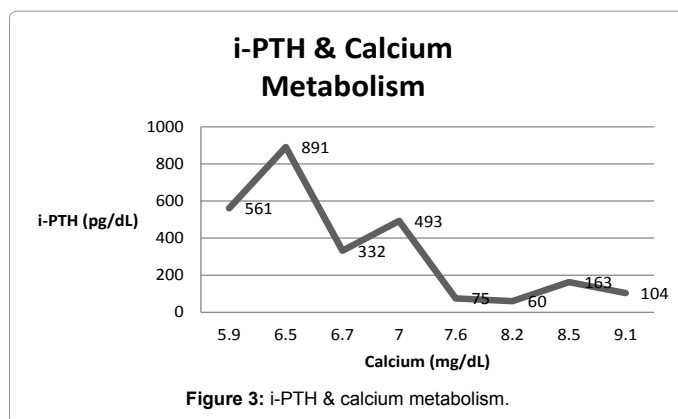
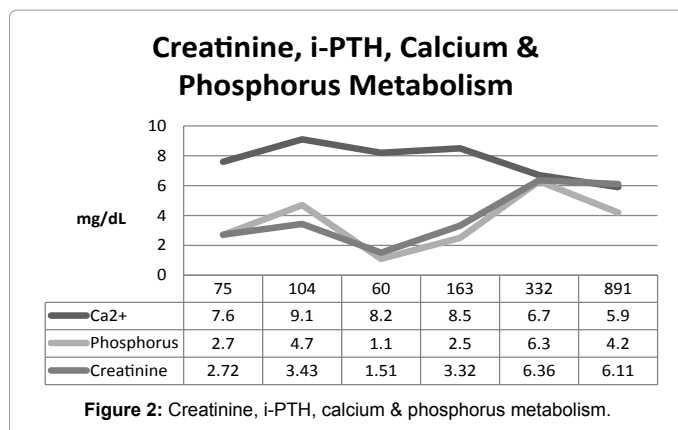
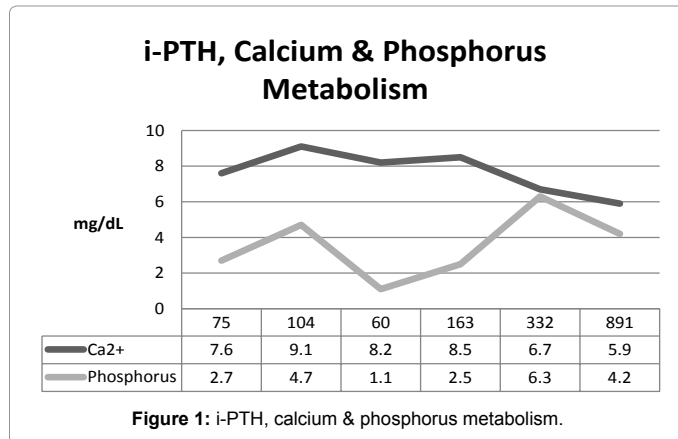
We describe the case of a 34 year-old white male who presented to the emergency department after being found unresponsive at home. The patient was diagnosed with rhabdomyolysis due to drug intoxication and was admitted to the ICU. The initial serum chemistry values revealed elevated serum potassium at 6.7 mg/dL and total CK of more than 124,000. BUN and creatinine were 24 mg/dL and 3.4 g/day respectively. Calcium was 7.2 mg/dL and ALT was 80 U/L. Subsequent assessments suggested acute kidney injury (AKI) likely due to rhabdomyolysis. Pre-renal azotemia was suspected due to the high hemoglobin and hematocrit, as well as the concentrated urine.

At this time it was decided that the patient would continue to receive aggressive IV hydration. Renal replacement therapy would not be necessary unless the patient remained oliguric. Serum BUN and creatinine were reviewed continuously and electrolytes were monitored. PTH (intact) and calcium were also assessed.

Despite supportive therapy, PTH remained significantly elevated on day 5. Additionally, the observed PTH elevation was not correlated with a significant increase in serum calcium. The relevant clinical data are given in (Table 6) (Figures 1-4).

Discussion

Our report of six cases at the local community hospital suggests that a high creatinine observed in CKD is often associated with a persistently elevated PTH. In contrast, patients with a high creatinine as a result of AKI that resolves quickly tend not to have persistently high PTH. Cases 1-4 represent the typical clinical picture of PTH elevation in AKI. In these cases, it is likely that a hypocalcemia-induced increase of plasma parathyroid hormone in early ARF is followed by a down-regulation of PTH during the renal function recovery period [19-22]. It seems that the exception to this rule is when the PTH on presentation



is above 250-300 pg/ml as observed in cases 5 and 6. In such patients with AKI and severe hyperparathyroidism, PTH may remain elevated despite recovering renal function.

In such rare cases, it seems that the prolonged duration of PTH elevation may be due to rhabdomyolysis and the persistent hypocalcemia observed in these patients. Although cases 5 and 6 provide insight into a unique presentation, further review is required. Specifically, the role of hyperphosphatemia and elevated creatine phosphokinase provoke further questions on the topic.

In similar cases of continued PTH elevation, several different well-studied markers should be employed to differentiate CKD from AKI, as prompt supportive therapy can be life saving. Alternative markers such as carbamylated hemoglobin may have a diagnostic role in discerning the two conditions [5,6]. Notably, it has shown acceptable sensitivity and positive predictive value in dividing patients with potentially reversible renal injury from those with CKD [6]. Additional markers such as serum 1, 5-anhydroglucitol (1,5-AG) may also be useful in such cases as elevated levels correlate well with AKI [23].

Furthermore, we propose that intact PTH should be more routinely screened in patients presenting with acute kidney injury. Despite showing a sensitivity of 88% and a specificity of 89% in dividing patients with CKD and AKI [24], a recent study indicated that PTH was evaluated in only 10% of patients presenting with presumed AKI [25]. Thus it is likely that increased utilization of this commonly ignored hormone may serve as a simple and inexpensive adjunct in making a more accurate diagnosis.

While CKD has long been associated with SHPT, there is a paucity of literature discussing similar sequela in the setting of AKI. However, the majority of existing literature regarding SHPT in acute kidney injury examines a subset of patients with rhabdomyolysis induced renal failure. In such cases, patients often present with biphasic calcium metabolism consisting of hypocalcemia during the oliguric phase, followed by hypercalcemia in the diuretic phase [26].

Several mechanisms have been proposed to contribute to SHPT in such patients. Of these, skeletal resistance to PTH remains an important common theme [27-29]. Although the precise mechanism for the resistance remains mostly unknown, recent data suggests that elevated FGF-23 may be largely responsible. FGF-23 has been proposed to play a role in both decreasing renal production of calcitriol as well as diminishing skeletal responsiveness to PTH [30]. Additionally calcium sequestration in skeletal muscle may trigger SHPT in these patients [31].

Conclusion

Continued hyperparathyroidism is a common complication of chronic kidney disease, but is rarely observed in acute kidney injury. Therefore, some degree of suspicion for AKI should be reserved particularly in the patient with elevated PTH despite declining creatinine. Further, we encourage the use of PTH as an inexpensive and readily available marker for differentiating AKI and CKD. Although this case provides an unusual presentation of a common clinical finding, this report is little more than a starting point. Further cases should be reviewed in order to provide a more accurate diagnostic picture and improved treatment plan.

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