



## A Review to Differentiate Acute Kidney Injury from Chronic Kidney Disease

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### Authors' contributions

*This work was carried out in collaboration between all authors. All authors contributed the literature search, writing of the paper and the design. All authors read and approved the final manuscript.*

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### ABSTRACT

The symptoms and signs of kidney disease are generally nonspecific to the underlying kidney disease. A considerable amount of these patients admit only with elevation in serum urea and creatinine. It is essential to first determine whether the disease is acute, subacute, or chronic for the differential diagnosis in a patient who presents with an elevated serum creatinine. The distinction between acute kidney injury (AKI) and chronic kidney disease (CKD) may be difficult in cases with no recent measurements of serum creatinine. Herein, we discussed the role of anamnesis, physical exam, routine laboratory tests, carbamylated hemoglobin, parathyroid hormone, hyaluronic acid, levels of 1,5-anhydroglucitol (AG), two-dimensional analysis of urinary dipeptidase, versus serum creatinine, creatinine levels of fingernails, and ultrasound in differential diagnosis of uremic subjects. The combination of data from medical anamnesis, physical exam, and routine laboratory test will be sufficient for diagnosis in most of the cases. Adding data from other markers in selected subjects may be useful in differential diagnosis of challenging cases admitted with uremia for the first time.

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## 1. INTRODUCTION

Kidney diseases do not cause specific symptoms which leads delayed diagnoses. Therefore, many patients admit only with elevation in serum urea and creatinine which necessitates determining the acuity of the event. Differential diagnosis of kidney failure is often facilitated by the availability of a previous serum creatinine concentration. If it is documented to be normal a few days previously the patient labeled as an acute kidney injury, whereas a patient who presents with a previously elevated serum creatinine that has been rising gradually over the past several months may easily be labeled as a chronic kidney disease. However, the distinction between acute kidney injury (AKI) and chronic kidney disease (CKD) may be difficult in cases with no recent measurements of serum creatinine. Although developed countries with good medical registry systems may be helpful in this regard, the challenge exist for nephrologists in developing countries where the patients with CKD do not admit hospitals until the end stage of the disease, and then present 'acutely' for the first time in advanced renal failure requiring emergent dialysis [1]. Herein, we aimed to review the clinical features, laboratory parameters, biomarkers, and sonography of these patients used to differentiate acute kidney injury from chronic kidney disease.

## 2. MEDICAL HISTORY AND CLINICAL FEATURES

A medical history of pre-morbid serum urea and creatinine concentration is the most valuable tool to evaluate the acute or chronic nature of the disease. A history of the most common causes of CKD should be investigated. Long duration diabetes, hypertension, polycystic kidney disease, urologic disorders, and refractory nephritis should be included in medical history. Some clinical features can help in deciding whether renal failure is acute or chronic: a history of vague ill health of some month's duration, of nocturia, of pruritus; the symptoms of anemia, evidence of long-standing hypertension or neuropathy, would suggest chronicity [2].

A history of the factors that may cause AKI such as events associated with volume loss, sepsis, recent surgery, nephrotoxic medications, signs of heart and liver failure, herbal medication, and

obstructive urologic disorders may favor diagnosis of AKI in a subset of these patients [3,4].

## 3. PHYSICAL EXAMINATION

The presence of fever, orthostatic hypotension, tachycardia, poor skin turgor, ascites, caput medusae, spider angiomas, edema, rash, oral ulcers, drug-related rash, livedo reticularis, purple toes, some fundoscopic findings, abdominal bruits, globe vesicale, and findings of prostate enlargement may be clues of various etiology of AKI [3-5].

Measurement central venous pressure may also be useful. Detecting skin pigmentation, presence of band keratopathy, fundoscopic findings of diabetic and hypertensive retinopathy may favor a diagnosis of chronicity in some of the cases with uremia. Unfortunately, in a considerable number of cases differential diagnosis of renal failure cannot be made on this basis because some of them had low sensitivity whereas others have low specificity to diagnose AKI or CKD.

Urine output is a good tool for evaluation of kidney function. It has become standard in definition of AKI [6]. Patients with AKI can also present with oliguria (urine output less than 400 mL per day), anuria (urine output less than 100 mL per day), or normal volumes of urine (nonoliguric acute kidney injury). Up to half of cases with AKI requiring RRT had nonoliguric acute kidney injury [7]. Advanced CKD patient may also admit with some degree oliguria. Therefore, urine output may useful for the differential diagnosis in hospitalised cases whose urine output is recorded. It would be more difficult to use urine output to diagnose AKI or CKD in outpatients.

## 4. ROUTINE LABORATORY PARAMETERS

Low hemoglobin, hyperphosphatemia, and hypocalcemia on presentation may be useful pointers of chronicity of the event. However, they may also be encountered in prolonged AKI [3]. So, it is difficult to differentiate acute from chronic case on these parameters. Cardiac size assessed on chest roentgenogram and ECG may be used as a clue to diagnose long standing hypertension as a cause of chronic kidney

disease. Unfortunately, it is neither sensitive nor specific to differentiate acute from chronic kidney disease.

## 5. CARBAMYLATION OF HEMOGLOBIN IN CIRCULATING RED CELLS

Carbamylation of proteins by isocyanic acid, the reactive form of cyanate derived from urea, is time dependent reaction which is increased in uremic subjects. Therefore, it may be a good marker to differentiate AKI and CKD which have different durations of uremia by the definition. Davenport et al. used carbamylated hemoglobin to differentiate acute from chronic renal failure and reported a sensitivity of 80% and specificity of 75% at the cutoff set at 125 microgram valine hydantoin (VH)/gHb [8]. Another study [9] found that CarbHb levels of 80 microgVH/gHb provided the best statistical values (sensitivity of 89% and specificity of 82%). At the final study, Wynckel A, et al. investigated carbamylated haemoglobin concentrations in 28 patients with AKI and 13 with CKD and reported a cut-off CarHb value of 100 microg CV/gHb had a sensitivity of 94% and a positive predictive value of 94% for differentiating AKI from CKD [10]. Although, the authors reported good results, it has not been widely used and not attractive for investigation since there has been no papers on PubMed for the differential role of Carbamylated hemoglobin since the year of 2000. However, if available it may be useful for differential diagnosis AKI and CKD in difficult cases.

## 6. CREATININE LEVELS OF FINGERNAILS

Because fingernail creatinine reflects serum creatinine at the time of nail formation, it may be indicator of the duration of uremia and may be useful for differential diagnosis uremic subjects. A study involved 60 normal individuals, 35 patients with CKD and 33 patients with AKI reported that the nail creatinine level of patients with AKI was similar to that in the normal group and significantly lower than that in the chronic group. They recommended to measure the nail creatinine for distinguishing acute from CKD [11].

Sud K et al. [12] also found mean fingernail creatinine concentration significantly higher in patients with chronic renal failure (93.7 +/- 83.7 micrograms/g) and end-stage renal disease on maintenance hemodialysis (118.4 +/- 46.8 micrograms/g) in comparison to those with acute renal failure (36.6 +/- 23.7 micrograms/g) and

controls. However, because of large variability in the values of fingernail creatinine concentrations within each group, the test lacked specificity. They concluded it as an unreliable indicator of duration of azotemia in individual patients and not likely to be of much clinical use.

On the final study, it was revealed that patients with AKI and controls had similar mean fingernail creatinine level, 30.9 mg/100 g of nail, and 30.1 mg/100 g of nail, respectively. Patients with known CKD had a mean fingernail creatinine level of 69.2 mg/100 g. which was significantly higher than patients AKI patients and normal controls [13]. Although, the authors reported significant differences between chronic and acute cases regarding mean fingernail creatinine levels, it has not become established as standard method in clinical practice since it is not easy to perform, widely available, large variability [12], and not practical.

## 7. TWO-DIMENSIONAL ANALYSIS OF URINARY DIPEPTIDASE VERSUS SERUM CREATININE

Renal dipeptidase is glycosylated phosphatidylinositol located in the microvilli of kidney proximal tubules. Its activity may be measured in urine which was tried to differentiate acute from chronic kidney disease. When the mass test of 246 individuals was examined on a 2-dimensional plot of urinary dipeptidase (y-axis) versus Scr (x-axis) with the data obtained from healthy volunteers (n = 189), AKI (n = 19) and CKD (n = 38) patients, it was observed that healthy volunteers are distributed along the y-axis and the AKI patients the x-axis, thus separating the two groups 90 degrees apart. The CKD patients are scattered away from both x-, and y-axis. Therefore, Lee et al. suggested this 2-dimensional approach to distinguish acute from chronic kidney disease [14].

Fukumura Y et al. [15] investigated the mean urinary renal dipeptidase activities in healthy subjects, patients with diabetes and patients with chronic renal failure. the mean urinary renal dipeptidase activities were 2.56, 2.46 and 0.78 U/mol creatinine, respectively. The renal dipeptidase activity was significantly lower in the chronic renal failure group.

No further investigation on the role of urinary dipeptidase versus serum creatinine for differential diagnosis patients with uremia has been published except these 2 studies.

## 8. LEVELS OF 1,5-ANHYDROGLUCITOL (AG)

1,5AG is a metabolically inactive monosaccharide that reaches steady state between ingestion and urinary excretion with near complete renal reabsorption at a specific fructose-mannose active transporter. Due to structural similarity, glucose competitively inhibits this reabsorption, such that in times of significant glycosuria [16,17].

1,5-AG also showed negative correlation to renal function and recommended for as a new blood glucose control marker reflecting temporary glucose elevations, [18] or to differentiate subtypes of diabetes [17]. The mean serum 1,5-AG in CKD patients [60 +/- 23  $\mu\text{mol/L}$ ] was significantly reported to be lower than normoglycemic controls (155 +/- 7  $\mu\text{mol/L}$ ) [19].

Serum 1,5-AG had been used as a marker for the differential diagnosis of nondiabetic AKI and CKD [20]. Serum 1,5-AG in patients with serum advanced renal failure was less than the lowest limit of the normal range in 14 of 15 CKD patients, but only 2 of 12 AKI patients. From these results, it was proposed that it can be useful to distinguish acute from chronic kidney disease in nondiabetic subjects. However, that is only one study with low number of subjects and results needs to be validated in further studies.

## 9. HYALURONIC ACID

Hyaluronic acid (HA) is a high molecular weight protein composed of N-acetylglucosamine and glucuronic acid unit. It is an important component of extracellular matrix. HA synthesis has been shown to increase in liver disease (hepatic fibrosis) [21] and inflammatory disease (rheumatoid arthritis) [22]. Because fibrosis is the main process underlying CKD, HA may be a valuable tool to differentiate acute from chronic kidney disease. Unfortunately, urinary HA was increased in post-operative AKI subjects, too [23]. Therefore, new studies are warranted to define the limits of HA in this context.

## 10. PARATHYROID HORMONE

Increased intact parathyroid hormone (iPTH) concentrations are present even in some CKD patients whose glomerular filtration rate ranges from 60 to 80 ml/min [24]. Many patients with AKI have hypocalcaemia and hyperphosphatasemia,

probably secondary to disordered vitamin D metabolism and failure of phosphate excretion, respectively [25]. Although, iPTH increases in patients with AKI, the magnitude of this increase is not well known. A lower iPTH increase is expected in AKI because there is not sufficient time for parathyroid glands hyperplasia which may make iPTH useful in differential diagnosis of subjects with uremia.

We investigated magnitude of iPTH increase in AKI and the potential role of iPTH for differential diagnosis of AKI (n=64) and CKD (n=58) in new patients with uremia. The mean iPTH level was 430±280 pg/ml in CKD group and significantly higher than those in AKI group 102±64 pg/ml. ( $p<0.0001$ ) [1]. A cutoff set at 170 pg/ml for iPTH is able to discriminate patients with CKD with high sensitivity (88%) and specificity (89%) values. These high sensitivity and specificity values make this cutoff a useful tool for differentiate acute from chronic kidney disease (Fig. 1).

Measurement of iPTH is widely available and cheaper than the other markers studied previously with the same aim. It may be useful in a subgroup of subjects. Unfortunately, the prevalence of dynamic bone disease is increasing in relative to other forms of renal bone disease [26] which may limit diagnostic role of iPTH to differentiate acute from chronic kidney disease.

## 11. ULTRASOUND

US is an accessible, inexpensive and fast aid for decision-making in patients with renal disease [27]. It is first choice of imaging of kidneys and provide useful information regarding, assessing renal dimensions and parenchymal thickness, rule out obstruction, parenchymal echogenicity [27,28]. Renal ultrasound examination has also been proposed as a method for distinction between AKI and CKD, because small kidneys usually indicate CKD [28]. The diagnostic aid of ultrasound depends on operators experience and false negative results may be observed in patients with diabetes mellitus, myeloma, amyloid, and tumor infiltration.

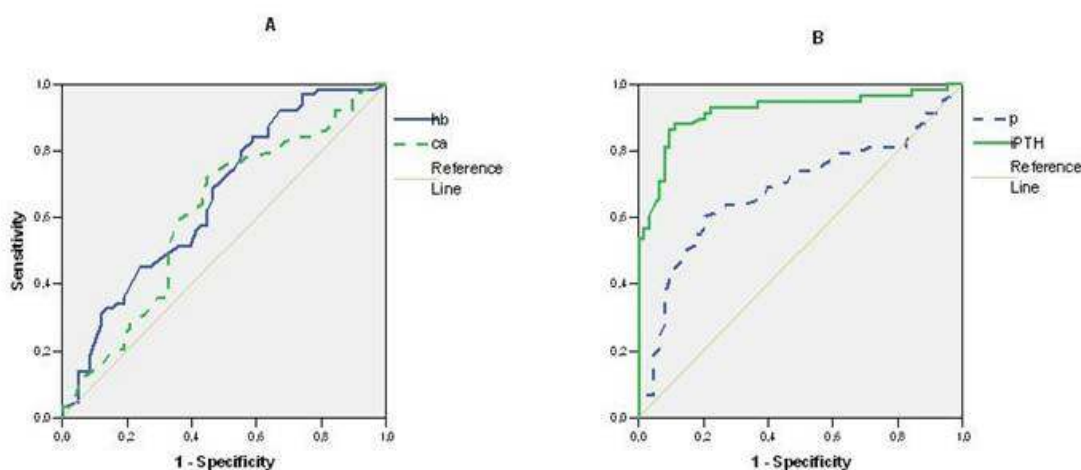
Renal length has a range of 10 to 12 cm for normal renal length at average body height. In the study [1] we investigated the role of iPTH, we had also evaluated the US findings. We found that a renal length less than 85 mm on ultrasound was present in 32.7% patients with CKD and that less than 100 mm in 44.8% of those patients.

In addition, in the study investigating the potential role of renal US to distinguish AKI from CKD in new patients, we were able to comprehensively analyse US features of patient with AKI and CKD [29]. The study revealed a mean renal length of  $112\pm 14$  mm in patients with AKI and  $90\pm 15$  mm in CKD. Cortical echogenicity was higher in CKD than AKI. Grade III renal cortex echogenicity was only present in patients with CKD. Slightly hyperechogenicity was the most common finding in sonography of both patients AKI and CKD in our study, therefore the value of echogenicity decreases in distinguishing acute from chronic kidney disease. The mean parenchymal thickness  $13.8\pm 3.4$  mm in patients with AKI and was significantly higher than patients with CKD ( $10.7\pm 4.2$  mm) in the same study (Table 1).

Diabetic subjects are different from the else of CKD patients [1,29]. Diabetic subjects are most

challenging one in context of in distinguishing acute from chronic ones. They have sonographic feature intermediate between acute and chronic kidney disease. Therefore, presence of diabetes mellitus should be known before making comment on sonographic findings of kidney. The areas under ROC curve of BSA-corrected mean renal length and BSA-corrected mean parenchymal thickness were 0.873 and 0.724 in the study. This result supports the practice using US to differentiate acute from chronic kidney disease with some limitations.

Nephrologist should be aware of a considerable overlap in size, and echogenicity of kidneys between acute and chronic conditions; therefore, the morphological appearance of kidneys does not always match the final diagnosis.



**Fig. 1. ROC analysis of PTH, Ca, P Hb curve for discriminating between AKI group and CKD group**

(A) ROC analysis curve for the optimal cut-off point of hemoglobin (line) and calcium (dashed line) for discriminating between AKI group and CKD group. AUC, areas under the curve are 0.66 and 0.61, respectively. (B) ROC analysis curve for the optimal cut-off point of iPTH (line) and Phosphorus (dashed line) for discriminating between AKI group and CKD group. AUC, areas under the curve are 0.92 and 0.68, respectively

**Table 1. Sonographic results of patients with AKI and CKD**

	AKI (n=62)	CKD (n=65)	p
Mean renal length (mm)	112±14	90±15	<0.0001
Mean parenchymal thickness (mm)	13.8±3.4	10.7±4.2	<0.0001
<b>Right-left cortical echogenicity</b>			
Grade 0	30.6-37.1%	6.1-4.6%	
Grade I-II	69.3-62.9%	90-87.7%	<0.0001
Grade III	0-0%	10.7-7.7%	
Cyst (%)	14.5	30.8	0.029
Stone (%)	21.0	20.0	ns
Ectasia (%)	16.1	12.3	ns

## 12. CONCLUSION

Distinguishing acute from chronic renal failure is often possible using premorbid serum creatinine concentration, if available. Although good medical registry systems in developed countries have decreased the magnitude of the problem, some of the patients with CKD often do not admit to hospitals until their kidney failure becomes advanced and uremic symptoms arise, and then they present “acutely” for the first time in advanced renal failure requiring emergent dialysis.

However, these tests have not become established in clinical practice since they are not easy to perform, widely available, not practical, and do not enable the distinction of acute from chronic kidney disease to be made in a satisfactory manner in a considerable number of patients. The combination of data from medical anamnesis, physical exam, and routine laboratory test will be sufficient for diagnosis in most of the cases. Adding data from other markers in selected subjects may be useful in differential diagnosis of challenging cases admitted with uremia for the first time.

## CONSENT

It is not applicable.

## ETHICAL APPROVAL

It is not applicable.

## COMPETING INTERESTS

Authors have declared that no competing interests exist.

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