Approach to Renal Tubular Disorders

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Abstract. The renal tubule plays an important role in fluid and electrolyte homeostasis. Renal tubular disorders may affect multiple (*e.g.,* Fanconi syndrome) or specific (*e.g.,* nephrogenic diabetes insipidus, renal glucosuria) tubular functions. Most conditions are primary and monogenic but occasionally are secondary to other disorders (focal segmental glomerulosclerosis, cystinosis, Lowe syndrome). Tubular dysfunction should be considered in all children with failure to thrive, polyuria, refractory rickets, hypokalemia and metabolic acidosis. Careful clinical and laboratory evaluation is essential for appropriate diagnosis and specific management of these conditions. **[Indian J Pediatr 2005; 72 (9) : 771-776]** *E-mail : arvindbagga@hotmail.com*

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Renal tubules play an important role in fluid, electrolyte and acid-base homeostasis. Normal reabsorption of electrolytes, glucose, calcium, magnesium, phosphates and aminoacids and secretion of protons occur in various specialized parts of the renal tubule. Renal tubular disorders manifest with dysfunction that might be focal or generalized. Important tubular functions and disorders associated with their dysfunction are shown in table 1.

The dysfunction may be secondary to a glomerular disease (*e.g*., focal segmental glomerulosclerosis) or be a primary defect in tubular function. Distinction between primary and secondary causes and precise characterization of the disorder is necessary for specific treatment.

Features Suggesting Tubular Disorders

Considering the spectrum of tubular functions, these disorders result in varied manifestations emphasizing the need for their consideration in many clinical conditions[1]. Non-specific features mandate the need for high index of suspicion for these disorders[2]. Tubular dysfunction should be considered in all children with failure to thrive, polyuria, refractory rickets, hypokalemia and metabolic acidosis (Table 2).

Assessment of Tubular Functions

Tubular function tests involve evaluation of functions of the proximal tubule (*i.e.*, tubular handling of sodium, glucose, phosphate, calcium, bicarbonate and aminoacids) and distal tubule (urinary acidification and concentration). The initial assessment of a child with suspected tubular disorder includes estimating blood levels of sodium, potassium, phosphate, pH and bicarbonate. Urine should be examined for pH and osmolality, and excretion of electrolytes, proteins, sugar and calcium. These tests provide information on renal tubular handling of sodium, potassium, bicarbonate and calcium, and ability to concentrate and acidify urine.

Depending on the clinical profile, abnormal screening tests are followed up with tests for specific tubular functions and evaluation for a possible underlying condition.

Tests for Urinary Acidification

Renal tubular acidosis (RTA) and diarrhea are important causes of metabolic acidosis in children. These disorders can be readily differentiated from most other causes of metabolic acidosis by estimation of the plasma anion gap. The following tests are useful in diagnosis and characterization of RTA.

Plasma anion gap: Anion gap represents the difference of unmeasured anions and cations in the plasma, and is measured as follows:

$$Anion\ gap = Na^+ - (Cl^- + HCO_3^-)$$

The normal value of the plasma anion gap is 10-12 mEq/L. Accumulation of organic acids like lactate and acetoacetate, as in diabetic ketoacidosis, and poisoning due to ethylene glycol are characteristically associated with metabolic acidosis and an increased anion gap. Normal anion gap in the presence of acidosis (hyperchloremic metabolic acidosis) suggests increased urinary (proximal RTA) or gastrointestinal loss (diarrhea) of bicarbonate or impaired excretion of H^+ ions (distal RTA).

Urine anion gap: Urine anion gap (net charge) (urine $Na^+ + K^+ - Cl^-$) provides an estimate of urinary ammonium (NH_4^+) excretion and is important in the evaluation of hyperchloremic acidosis. Under normal circumstances, urine anion gap is positive due to the presence of

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TABLE 1. Common Disorders of Tubular Functions

Segment	Function	Disorder
Proximal tubule*	Phosphate transport	Hypophosphatemic rickets
	Glucose transport	Renal glucosuria
	Aminoacid transport	Isolated, generalized aminoaciduria
	Bicarbonate transport	Proximal RTA
Ascending limb of Henle	Sodium, potassium, chloride transport	Bartter syndrome
Distal tubule	Proton (H^+) secretion	Distal RTA
	Sodium, chloride transport	Gitelman syndrome
Collecting duct	Sodium, potassium transport	Pseudohypoaldosteronism
		Liddle syndrome
	Water transport	Nephrogenic DI

*Generalized dysfunction of the proximal tubule (Fanconi syndrome) may be primary or secondary to various disorders (*e.g.,* galactosemia, Lowe syndrome)
RTA renal tubular acidosis; DI diabetes insipidus

TABLE 2. Features Suggestive of Renal Tubular Disorders

Clinical
- Growth retardation, failure to thrive
- Polyuria, polydipsia; preference for savory foods
- Refractory rickets
- Renal calculi, nephrocalcinosis
- Unexplained hypertension*

Laboratory
- Hyperchloremic metabolic acidosis
- Metabolic alkalosis with or without hypokalemia
- Hyponatremia with hyperkalemia
- Hypercalciuria with normal serum calcium

* As in Liddle's syndrome, syndrome of apparent mineralocorticoid excess

dissolved anions ***e.g.,*** sulfates, phosphates. Metabolic acidosis is associated with a compensatory rise in NH_4^+ production, resulting in a negative urine anion gap. Patients with RTA typically show impaired renal NH_4^+ excretion and a positive urine anion gap.

Urine pH: Urine pH is an estimate of the number of free H^+ ions in the urine which are secreted in response to metabolic acidosis. The presence of alkaline urine during metabolic acidosis suggests defective renal acidification, as in distal RTA.[3] However, alkaline urine may also be found in patients with metabolic acidosis due to extrarenal disorders, as in acute or chronic diarrhea. Occasionally, metabolic acidosis may need to be induced by oral administration of ammonium chloride (0.1 g/kg) before determining urine pH. This test is however cumbersome and not commonly used**.**

Urine to blood CO_2 difference*:* Based on the observation that urinary CO_2 excretion is an indicator of H^+ secretion, urine to blood CO_2 difference is considered a satisfactory index of distal renal acidification. In the presence of normal blood bicarbonate, low urine to blood CO_2 difference (< 10 mm Hg) suggests distal RTA; the levels are normal in proximal RTA (> 20 mm Hg). It is necessary that the difference be determined after adequate alkalinization with oral sodium bicarbonate (2-4 mEq/kg/day) (in order to achieve normal blood pH and bicarbonate, and urine pH > 7.4).

Fractional excretion of bicarbonate: Fractional excretion of bicarbonate is a marker of proximal tubular handling of bicarbonate. The proximal tubule normally reabsorbs almost all filtered bicarbonate (fractional excretion below 5%). A value greater than 15% indicates proximal RTA while levels are in the normal range in distal RTA. The fractional excretion of bicarbonate should be calculated only after adequate alkalinization (see above).

$$\text{Fractional excretion of bicarbonate} = \frac{\text{urine bicarbonate} \times \text{plasma creatinine}}{\text{plasma bicarbonate} \times \text{urine creatinine}} \times 100$$

Tests for Phosphate Handling

Phosphate homeostasis is chiefly regulated at the level of the proximal renal tubule. Plasma phosphate levels are thus indicators of renal tubular handling. The fractional excretion of phosphate determined on a timed (6-hr, 12-hr, 24-hr) urine specimen, is a widely used investigation for phosphate handling.

$$\text{Fractional excretion of phosphate (\%)} = \frac{\text{urine phosphate x plasma creatinine}}{\text{plasma phosphate} \times \text{urine creatinine}} \times 100$$

Tubular reabsorption of phosphate (%) = 100 - fractional excretion of phosphate

Tubular reabsorption of phosphate depends on plasma phosphate and glomerular filtration rate and is not a satisfactory indicator of tubular phosphate handling. This has led to increasing use of 'tubular maximum for phosphate corrected for GFR (TmP/GFR)', a factor independent of plasma phosphate and renal functions for assessment of renal phosphate handling. TmP/GFR (normal 2.8- 4.4 mg/dL) is an index of renal threshold for phosphate which can be determined by a nomogram[4] (on timed urine samples) or directly as follows:

$$\text{TmP/GFR (mg/dL)} = \text{Plasma phosphate} - \frac{\text{urine phosphate} \times \text{plasma creatinine}}{\text{urine creatinine}}$$

Tests for Urinary Concentration

Repeated early morning urine examination for osmolality or specific gravity should be performed in a child with suspected urinary concentration defect. Urine osmolality greater than 800 mOsm/kg (or specific gravity greater than 1015) excludes a significant defect in urinary concentration. Individuals with low urine osmolality should undergo a water deprivation test after excluding RTA and chronic renal failure. The presence of low urine osmolality (< 300 mOsm/kg) in patients with elevated plasma osmolality (osmolality > 300 mOsm/kg, serum sodium > 145 mEq/L) is diagnostic of diabetes insipidus. Distinction between central (neurogenic) and nephrogenic diabetes insipidus is necessary, based on response to administration of vasopressin. Vasopressin can be administered intranasally (10-20 μg) or subcutaneously (1-3 μg) and the urine osmolality assessed at 1-2 hr. A rise in urine osmolality by more than 50% of baseline, one hour after vasopressin administration, is diagnostic of central diabetes insipidus; the increase of urine osmolality in patients with nephrogenic diabetes insipidus is nil or minimal.

Water deprivation test: Patients with polyuria with no evidence of dehydration and normal serum sodium are kept off fluids for 6-8 hr, until weight loss exceeds 3% or until 3 consecutive hourly urine osmolality values are within 10% of each other. Urine osmolality more than 750 mOsm/kg at the end of the evaluation is suggestive of primary polydipsia. Osmolality less than 750 mOsm/kg after water deprivation should be further evaluated after administration of vasopressin.

Tests for Potassium Handling

Renal tubular disorders may be associated with both hypokalemia and hyperkalemia. Renal handling of potassium depends on the total body content of the mineral, its daily intake, delivery of sodium and water to the distal nephron and the action of aldosterone. Random urine potassium exceeding 20 mEq/L in patients with hypokalemia indicates renal potassium wasting. The fractional excretion of potassium (FEK) may also be used as an indicator of tubular function; FEK values exceeding 40% (normal 10-20%) indicate tubular wasting.

The action of aldosterone mediated sodium-potassium exchange in the distal renal tubule is evaluated by the transtubular gradient of potassium (TTKG), as given below:

$$\textit{Transtubular gradient of potassium} = \frac{\textit{urinary potassium} \times \textit{plasma osmolality}}{\textit{plasma potassium} \times \textit{urinary osmolality}}$$

TTKG should be estimated when urinary osmolality exceeds plasma osmolality; values below 5-7 in subjects with hyperkalemia imply impaired potassium secretion due to aldosterone deficiency or resistance. TTKG greater than 10 shall be found in patients with appropriate action of aldosterone, with hyperkalemia attributed to an increased potassium load.

TUBULAR SYNDROMES

Tubular disorders can be classified into distinct syndromes based on their presenting features.

Metabolic Acidosis and Hypokalemia

Hypokalemia is usually associated with metabolic alkalosis. The occurrence of metabolic acidosis and hypokalemia suggests RTA or gastrointestinal loss of bicarbonate (diarrhea, ureterosigmoidostomy). Distal RTA is characterized by decreased proton excretion due to a proton pump defect or back diffusion of protons. The primary defect in proximal RTA is the reduced renal threshold for bicarbonate, resulting in bicarbonaturia. Proximal RTA may represent isolated or generalized proximal tubular dysfunction; the latter (Fanconi syndrome) is characterized by bicarbonaturia, phosphaturia, sodium and potassium wasting, glucosuria and aminoaciduria. Fanconi syndrome may be primary or frequently associated with inherited disorders like Wilson disease, galactosemia, cystinosis and Lowe syndrome.

Evaluation: The first step in the evaluation of a child with hypokalemia and metabolic acidosis is to differentiate gastrointestinal bicarbonate loss from RTA. The presence of polyuria, preference for savory foods, failure to thrive and rickets, are suggestive of RTA. Gastrointestinal bicarbonate losses can be differentiated from RTA by estimating the urine anion gap. Negative urine anion gap indicates increased renal NH_4^+ production (extrarenal cause for metabolic acidosis), while positive gap suggests RTA. Once the diagnosis of RTA is established, it can be categorized further (Fig. 1)[5]. Children with proximal (type 2) RTA should undergo evaluation for other proximal tubule functions (phosphate, electrolytes, glucose and aminoacid excretion) and screening for an underlying etiology (*e.g.*, Wilson disease, cystinosis). Investigations in children with distal (type 1) RTA include estimation of urine calcium excretion, ultrasound for renal calcification and work-up for secondary causes (*e.g.*, obstructive uropathy, reflux nephropathy, chronic tubulointerstitial nephritis).

Management: Management of RTA includes correction of metabolic acidosis with bicarbonate supplements [sodium bicarbonate 7.5% (1 mEq/ml); Shohl solution (1 mEq/ml); Polycitra solution (2 mEq/ml)]. Bicarbonate requirement is more in patients with proximal RTA (5-6 mEq/kg/day) compared to distal RTA (1-2 mEq/kg/day). Alkali therapy is usually combined with potassium replacement to avoid severe hypokalemia. Potassium supplements in patients with acidosis are usually administered as citrate salts. Long-term potassium replacement is however not required in subjects with distal RTA. Patients with proximal RTA often requires supplements of phosphate

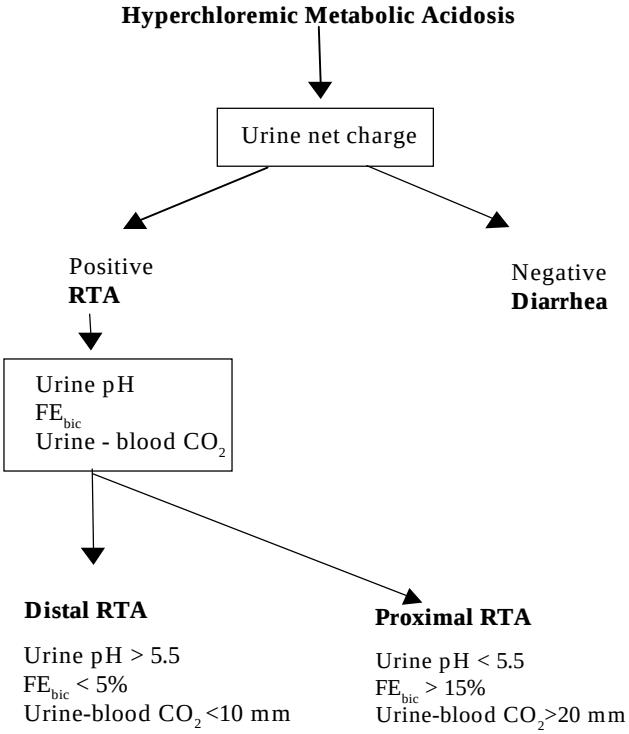

Fig. 1. Approach to a patient with metabolic acidosis and hypokalemia. Urine net charge (urinary $Na^+ + K^+ - Cl^-$) provides an estimate of renal ammonium production, differentiating between renal and extrarenal causes of hyperchloremic acidosis.
RTA renal tubular acidosis; FE_{bic} Fractional excretion of bicarbonate

(Joulie solution, neutral phosphate solution) and small doses of vitamin D. Specific therapy for an underlying disorder (cysteamine for cystinosis, D-penicillamine for Wilson disease and lactose free diet in galactosemia) is possible in few patients. Follow-up includes regular assessment for growth and blood levels of electrolytes, pH and bicarbonate. Subjects with distal RTA are at risk for nephrocalcinosis, which should be screened for by ultrasound.

Metabolic Alkalosis and Hypokalemia

Renal tubular causes of hypokalemia with alkalosis include a spectrum of conditions involving reduced electrolyte reabsorption (Bartter, Gitelman syndromes) or increased mineralocorticoid action (Liddle syndrome, syndrome of apparent mineralocorticoid excess, glucocorticoid remediable aldosteronism). These disorders should be differentiated from systemic causes including vomiting, hypomagnesemia, cystic fibrosis and diuretic use.

Evaluation: Initial evaluation should include history of upper gastrointestinal loss (vomiting and nasogastric drainage), diuretic use and measurement of blood pressure. Urine chloride helps in differentiating non-renal (< 10 mEq/L)) from renal causes (> 20 mEq/L) of hypokalemic alkalosis. The presence of elevated blood pressure suggests true (hyperaldosteronism, glucocorticoid remediable aldosteronism, congenital adrenal hyperplasia) or apparent mineralocorticoid excess (Liddle syndrome, syndrome of apparent mineralocorticoid excess) (Fig. 2). These disorders can be classified further by determining blood levels of aldosterone and renin and assessing the response to treatment with corticosteroid and/or spironolactone. Low blood levels of aldosterone and lack of response to glucocorticoid and spironolactone is suggestive of Liddle syndrome. Bartter syndrome can be differentiated from Gitelman syndrome by presence of hypercalciuria in the former and hypomagnesemia in the latter.

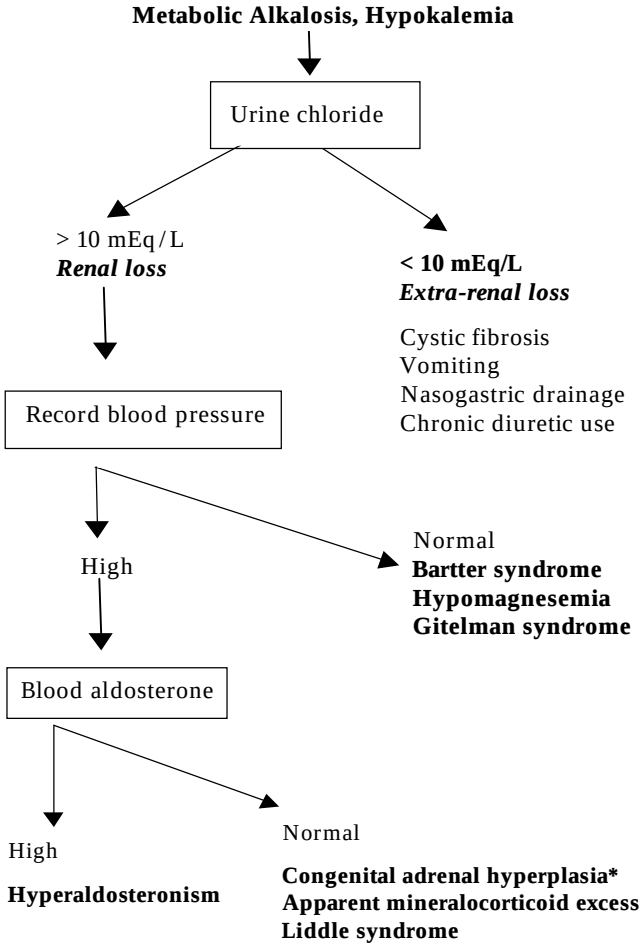

Fig. 2. Approach to a patient with metabolic alkalosis and hypokalemia.
* Due to deficiency of the enzymes, 11β hydroxylase or 17α hydroxylase

Management : Treatment of Bartter syndrome consists of ensuring adequate hydration and potassium supplementation (as chloride salts) along with indomethacin (2-4 mg/kg/day). Specific therapy with magnesium (50-100 mg/kg/day) in Gitelman syndrome and amiloride in Liddle syndrome ameliorate biochemical features of respective diseases.

Hypercalciuria

Patients with hypercalciuria may present with a variety of features including renal stones and nephrocalcinosis, hematuria, 'frequency dysuria' syndrome, and abdominal pain. Hypercalciuria is defined as urinary calcium excretion of more than 4 mg/kg/day. Calcium excretion may also be determined on spot urine samples; ratio of calcium to creatinine greater than 0.2 mg/mg beyond infancy is significant. Common causes of hypercalciuria are shown in table 3.[6]

Evaluation: Initial evaluation of a patient with hypercalciuria includes estimation of blood levels of

TABLE 3. Causes of Hypercalciuria

Secondary to Hypercalcemia
- Hyperparathyroidism
- Inactivating mutations of the calcium sensing receptor
- Vitamin D excess
- Granulomatous disorders - sarcoidosis, tuberculosis

Without Hypercalcemia
- Idiopathic hypercalciuria
- Distal RTA
- Bartter syndrome
- Therapy with loop diuretics, corticosteroids
- Familial hypomagnesemia

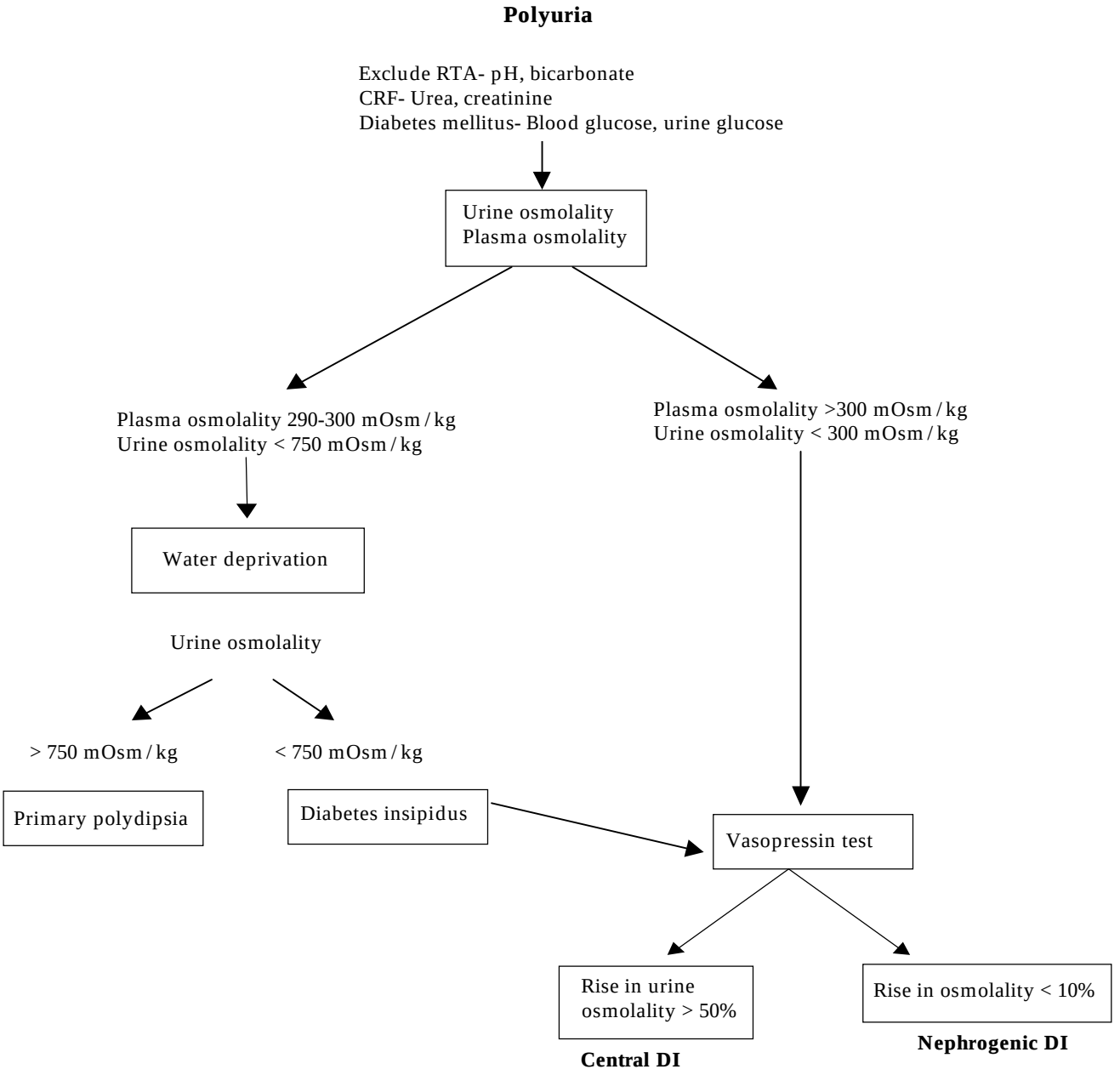

Fig. 3. Approach to a patient with polyuria. DI diabetes insipidus

calcium, phosphate, creatinine, pH and bicarbonate. Parathormone (PTH) and vitamin D (25-OH vitamin D) levels should be estimated in patients with hypercalcemia.

Management: The initial treatment for idiopathic hypercalciuria includes ensuring a high fluid intake and restriction of dietary sodium and animal protein. Administration of oral potassium citrate is beneficial in reducing hypercalciuria and risk of formation of calculi. Dietary restriction of calcium intake is not only ineffective but also harmful. A low calcium diet promotes oxalate reabsorption from the gut, resulting in its increased urinary excretion (enteric hyperoxaluria) and risk of forming calcium oxalate stones. Patients who do not respond satisfactorily to the above treatment may benefit from thiazide diuretics (hydrochlorothiazide 1-2 mg/kg/day). These cases should be monitored for dyselectrolytemia, hyperuricemia and dyslipidemia. All patients should be regularly followed-up with estimation of urine calcium excretion and imaging for renal stones and calcification.

Specific treatment for RTA and Bartter syndrome also results in reduced excretion of urinary calcium.

Polyuria

Polyuria (daily urine output > 2 L/m^2) is a presenting feature of a variety of tubular disorders including RTA, resistance to the action of antidiuretic hormone (ADH) (nephrogenic diabetes insipidus) or aldosterone (pseudohypoaldosteronism), and specific transport defects (Bartter and Gitelman syndromes).[7] These disorders should be distinguished from other causes of polyuria including diabetes mellitus, central diabetes insipidus and adrenal insufficiency.

Evaluation: The initial evaluation of patients with polyuria includes estimation of blood levels of glucose, electrolytes, pH, bicarbonate, calcium, creatinine and osmolality. Urine osmolality should be examined on an early morning specimen. Patients with high plasma osmolality (> 300 mOsm/kg) and low urine osmolality (< 300 mOsm/kg) have deficiency or resistance to the action of ADH, which should be clarified further based on response to the hormone (Fig. 3).[8] The water deprivation test should be done to distinguish between psychogenic polydipsia and diabetes insipidus.

Management: Patients with nephrogenic DI benefit from treatment with indomethacin (2-3 mg/kg/day) and thiazide diuretics. Solute restriction reduces renal solute load and obligate water losses. Alkali replacement in patients with RTA and administration of indomethacin and potassium supplements in Bartter syndrome is effective in reducing polyuria. Care must be taken to avoid dehydration; free access to fluids is necessary.

CONCLUSIONS

Physicians should be aware of the protean clinical features of renal tubular disorders. Early recognition, appropriate evaluation and specific management enable relief of symptoms in many conditions. Patients need to be followed up for prolonged periods for adequacy of growth and renal functions.

REFERENCES

1. Rodriguez-Soriano J. Tubular disorders of electrolyte regulation. In Avner ED, Harmon WE, Niaudet P, eds. *Pediatric Nephrology*. 5th edn. Baltimore; Lippincot Williams & Wilkins, 2004: 729-756.
2. Van't Hoff W. Renal tubular disorders. In Webb NJ, Postlethwaite RJ, eds. *Clinical Pediatric Nephrology*. 3rd edn. New York; Oxford Press, 2003: 103-112.
3. Herrin TJ. Renal tubular acidosis. In Avner ED, Harmon WE, Niaudet P, eds. *Pediatric Nephrology*. 5th edn. Baltimore; Lippincot Williams & Wilkins, 2004: 757-776.
4. Walton RJ, Bijvoet OL. Nomogram for the derivation of renal tubular threshold concentration. *Lancet* 1975; 2: 309-310.
5. Postlethwaite RJ. The approach to a child with metabolic acidosis or alkalosis. In Webb NJ, Postlethwaite RJ, eds. *Clinical Pediatric Nephrology*. 3rd edn. New York; Oxford Press, 2003: 61-72.
6. Jones C, Mughal Z. Disorders of mineral metabolism and nephrocalcinosis. In Webb NJA, Postlethwaite RJ, eds. *Clinical Pediatric Nephrology*. 3rd edn. New York; Oxford Press, 2003: 73-102.
7. Muglia LJ. Majzoub JA. Disorders of the posterior pituitary. In Sperling MA, eds. *Pediatric Endocrinology*. 2nd edn. Philadelphia; WB Saunders, 2000; 289-322.
8. Diabetes insipidus. In Bajpai A, Sharma J, Menon PSN, eds. *Practical Pediatric Endocrinology*. 1st edn. New Delhi; Jaypee 2003: 17-23.