Diabetes mellitus and hyperkalemic renal tubular acidosis: case reports and literature review

Diabetes mellitus e acidose tubular renal hipercalêmica: relatos de caso e revisão da literatura

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Abstract

Hyporeninemic hypoaldosteronism, despite being common, remains an underdiagnosed entity that is more prevalent in patients with *diabetes mellitus*. It presents with asymptomatic hyperkalemia along with hyperchloraemic metabolic acidosis without significant renal function impairment. The underlying pathophysiological mechanism is not fully understood, but it is postulated that either aldosterone deficiency (hyporeninemic hypoaldosteronism) and/or target organ aldosterone resistance (pseudohypoaldosteronism) may be responsible. Diagnosis is based on laboratory parameters. Treatment strategy varies according to the underlying pathophysiological mechanism and etiology and aims to normalize serum potassium. Two clínical cases are reported and the relevant literature is revisited.

Keywords: acidosis; acidosis, renal tubular; *diabetes mellitus*; hyperkalemia; hypoaldosteronism.

Resumo

Apesar de comum, o hipoaldosteronismo hiporeninêmico continua a ser uma entidade sub-diagnosticada, com maior prevalência em pacientes com *diabetes mellitus*. A doença cursa com hipercalemia assintomática acompanhada de acidose metabólica hiperclorêmica sem disfunção renal significativa. O mecanismo fisiopatológico subjacente não é entendido em sua totalidade, mas postula-se que a deficiência de aldosterona (hipoaldosteronismo hiporeninêmico) e/ou a resistência à aldosterona no órgão-alvo (pseudo-hipoaldosteronismo) possam ser responsáveis. O diagnóstico é fundamentado em parâmetros laboratoriais. A estratégia terapêutica varia de acordo com o mecanismo fisiopatológico subjacente e a etiologia, mas seu objetivo é normalizar o potássio sérico. O presente artigo relata dois casos e analisa a literatura relevante sobre o assunto.

Palavras-chave: acidose; acidose tubular renal; *diabetes mellitus*; hiperpotassemia; hipoaldosteronismo.

Introduction

Renal tubular acidosis (RTA) comprises relatively frequent forms of hyperchloremic metabolic acidosis. This medical condition is underdiagnosed and poorly understood due to the complexity of the involved pathophysiological mechanisms. It is characterized by the occurrence of hyperchloremic metabolic acidosis, fluid and electrolyte balance disorders (involving potassium in particular), and absence of significant renal impairment. The glomerular filtration rate (GFR) of affected individuals is relatively preserved, while tubular impairment is the main element responsible for the observed alterations. Renal tubular acidosis is divided into three forms of involvement:

- Type 1 RTA (distal RTA) - impaired distal hydrogen ion secretion.
- Type 2 RTA (proximal RTA) - impaired proximal reabsorption of filtered bicarbonate.
- Hyperkalemic RTA - aldosterone deficiency or resistance (Type 4 RTA or hypoaldosteronism); or impaired distal sodium reabsorption (voltage-dependent distal RTA).

In RTA, impaired hydrogen ion secretion and/or bicarbonate reabsorption at a tubular level are the bases for the onset of acidosis.[1] Potassium serum levels vary depending on the subtype of RTA, but high potassium levels are observed only in hyperkalemic (or Type 4) RTA.

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Though relatively common, hyperkalemic RTA is an underdiagnosed condition. It has been estimated to affect 3.8% of hospitalized individuals with hyperkalemia.[2] The clinical manifestations of the disease are mild, and usually revolve around various degrees of hyperkalemia and hyperchloremic metabolic acidosis without significant glomerular filtration rate drops. Hyperkalemia secondary to renal involvement requires a GRF below 15mL/min/1.73m^2.[3] Hyperkalemia and metabolic acidosis are usually mild (potassium < 6.5mmol/L and bicarbonate > 17mmol/L), although exacerbation may occur in the event of acute kidney injury and/or undesired drug interactions.[2] The consequences of Type-4 RTA beyond the electrophysiological risks introduced by hyperkalemia are largely unknown.

Hypoaldosteronism and distal tubular voltage defects have been described as the pathophysiological mechanisms causing hyperkalemic RTA.[3,4] Hypoaldosteronism may stem from decreases in the stimulus to release aldosterone (hyporeninemic hypoaldosteronism), reduced aldosterone synthesis and secretion (heparin, congenital adrenal hyperplasia or hypoplasia, adrenoleukodystrophy) and/or aldosterone resistance in the target organ (pseudohypoaldosteronism).[5] Several studies enrolling diabetic individuals showed they had lower-than-expected aldosterone and renin levels, particularly in subgroups with diabetic nephropathy and neuropathy.

Clinical cases

Case 1

A 58-year-old male patient diagnosed with type 2 DM for three years had high blood pressure, dyslipidemia, coronary artery disease (underwent angioplasty and bypass surgery), stage 3bA2 chronic kidney disease (CKD) (estimated GFR of 40mL/min and occasional albuminuria of 160mg/g), and peripheral artery disease. The patient was taking linagliptin, isosorbide mononitrate, bisoprolol, acetylsalicylic acid, allopurinol, and rosuvastatin. He was referred to an endocrinologist on account of having DM type 2 and CKD. His blood pressure was 136/90 mmHg and he was euvolemic, without signs of peripheral edema. His workup showed HbA1c at 6.8%, creatinine at 1.8mg/dL (estimated GFR by the CKD-EPI of 41mL/min/1.73m^2), potassium at 6.5mmol/L, and a urine pH of 5.5. The arterial blood gas test revealed that he had metabolic acidosis - pH 7.36; HCO_3^- = 18mmol/L; base deficit = 7.2; $paCO_2$ = 32mmHg; paO_2 = 100mmHg; and anion gap = 9). His transtubular potassium gradient (TTKG) was decreased - 3.93. Renin levels were within reference values (renin = 2.4 uU/mL, reference values (RV) 1.1-16.5; and aldosterone = 6.9 ng/dL, RV 1-16). An electrocardiogram did not reveal *de novo* relevant alterations and, given that he was clinically stable and probably had hypoaldosteronism, treatment with calcium polystyrene sulfonate twice a day, oral fluids, furosemide 40mg/day, and low-potassium diet was initiated.

The patient was assessed a week later after having significantly improved his workup - K^+ = 5.8mmol/L and HCO_3^- = 20mmol/L. Two years after the initial assessment the patient was taking an ion exchange resin twice a day and furosemide 40 mg/day; his potassium levels were under control (K^+ = 5.6mmol/L and creatinine = 1.6mg/dL), but the TTKG was still altered.

Case 2

A 56-year-old male patient diagnosed with DM type 2 for six years had stage 3aA3 CKD (estimated GFR = 47mL/min/1.73m^2, albuminuria = 3300mg/g), high blood pressure, dyslipidemia, a toxic thyroid adenoma, and peripheral artery disease. He was initially taking insulin glargine once a day (20 units bedtime), pentoxifylline, clopidogrel, and perindopril.

He was referred to an endocrinologist on account of having primary hyperthyroidism. Workup findings indicated the patient had hyperkalemia (K^+ 6.1mmol/L), a creatinine level of 1.8mg/dL (GFR = 42; usually 47mL/min/1.73m^2); the blood gas test showed a pH of 7.35; paO_2 = 90mmHg; $paCO_2$ = 42mmHg; HCO_3^- = 23.2mmol/L; base deficit 2.6; anion gap = 10. Perindopril was discontinued and a week later the patient came in for additional tests, which revealed he still had hyperkalemia (K^+ 6.21mmol/L), urine pH = 5.5, TTKG = 0.5 and renin and aldosterone levels within the reference range (renin = 2.8 uU/mL, RV = 1.1-16; aldosterone = 2.2 ng/dL, RV 1-16).

The therapeutic strategy then prescribed to the patient included a low potassium diet, chlorthalidone, and calcium polystyrene sulfonate until his workup was normalized. The ACE inhibitor was not reintroduced. Eighteen months after the initial assessment the patient had his potassium serum level under control (K^+ 4.73mmol/L) and stable renal function (GFR 50mL/min/1.73m^2).

Discussion

Hyporeninemic hypoaldosteronism (HH) is the most frequent cause of hyperkalemic RTA.[6] It typically

appears on the sixth or seventh decade of life and is more prevalent in females.[7] Most patients have *diabetes mellitus* and mild to moderate involvement of the glomerular filtration rate - 30-90mL/min/1.73m^2). HH occurs in conjunction with asymptomatic chronic hyperkalemia, and with hyperchloremic metabolic acidosis in about 50% of the cases.[2] Renin deficit and primary adrenal disorders related to the synthesis of aldosterone lie on the basis of the workup alterations. Hyperkalemia is the finding responsible for generating and sustaining metabolic acidosis.

The mechanisms associated with renin depression include hypervolemia (directly precluding the release of renin); diabetic autonomic neuropathy (inhibiting the conversion of prorenin into renin, reducing adrenergic response to postural changes, and inducing beta-adrenergic receptor desensitization, thus affecting juxtaglomerular apparatus function); prostaglandin deficiency (namely prostacyclin, whose deficiency leads to reduced renin secretion and decreased conversion of prorenin into renin). Metabolic acidosis stems from impaired ammoniagenesis and is partly mediated by hyperkalemia.[5]

The diagnosis is based on the confirmation of hyperkalemia (K^+ greater than 5.2mmol/L) accompanied by hyperchloremic metabolic acidosis (pH typically normal, bicarbonate at 17-20mmol/L, and anion gap < 12mmol/L) in the absence of significant renal function impairment (GFR > 30mL/min/1.73m^2) or drugs that may induce hyperkalemia (non-steroid anti-inflammatory drugs, renin-angiotensin-aldosterone system inhibitors, calcineurin inhibitors or potassium supplements). Urine pH is typically lower than 5.5, reflecting the preservation of distal acidification capacity shown when the concentration of urine buffer (NH4+) for excreted acid valences is decreased.

The impact of hypoaldosteronism (absolute and/or relative) at a tubular level may be assessed indirectly through the transtubular potassium gradient (TTKG). The TTKG reflects the distal tubular potassium secretion ability (in the collecting duct)[5] and is calculated as follows:

TTKG = (Urine Potassium x Serum Osmolality)
(Serum Potassium x Urine Osmolality)

In the presence of hyperkalemia, the TTKG is physiologically expected to reach values above 7, reflecting compensatory hyperaldosteronism. In hyperkalemic RTA, the TTKG is lower than 7.[6,8] TTKG variations with therapy (for example, with fludrocortisone) help differentiate between aldosterone deficiency and resistance:

- Aldosterone deficiency: early normalization (2-4h) of the TTKG after physiological doses of fludrocortisone (0.1mg/day).
- Aldosterone resistance: late normalization (> 24h) of the TTKG after supraphysiological doses of fludrocortisone (> 0.1mg/day).

Some authors claimed that the TTKG formula is based on incorrect assumptions and challenged its validity. Therefore, additional measures must be taken to investigate cases of hyperkalemia.[7]

Since hyperkalemic RTA occurs in conjunction with impaired renal ammoniagenesis, indirect markers of renal ammonia excretion were developed: urine anion gap (UAG) and urine osmolal gap (UOG) (Table 1).

In patients without functional tubular disorders, acidosis usually decreases the UAG and increases the UOG. However, these formulas have their limitations. The calculation of the UAG is based on the principle that the ammonia secreted via the kidneys is bound to chlorine. Increases in urine ammonia levels are followed by increases in urine chlorine levels, and consequently decreases in the UAG. The UAG is, therefore, a surrogate marker of urine ammonia.

However, the UAG is not very reliable in the presence of urine Na^+ levels below 25mmol/L (frequently seen in cases of prerenal acute kidney injury), increased excretion of non-measured anions (ketoacidosis, bicarbonate therapy, D-lactacidemia, poisoning by toluene or paracetamol), and during the neonatal period (a stage in which non-measured anions are excreted in large quantities).[9]

In these situations, the UOG might be more reliable. The UOG is based on the fact that ammonia is an element in the anions not considered in the calculation of urine osmolality. In the presence of metabolic acidosis, urine ammonia increases as part of a compensatory mechanism, thus increasing the UOG. The limitations of the UOG include situations in which there is overexcretion of anions not bound to ammonia (alcohols and mannitol) and urinary tract infections (by bacteria producing urease, which catalyzes the formation of NH_4^+).[9]

Additionally, renin and aldosterone levels are useful to differentiate the mechanism of the underlying hypoaldosteronism (Table 2).

The absence of aldosterone and renin nomograms adjusted for serum potassium limits the analytical appreciation of these clinical scenarios, since the thresholds defining what might be considered normal are unclear. Given

Table 1 Reference values (RV) for urine anion and urine osmolal gap in physiological situations without acidosis (column showing normal values), in clinical situations with metabolic acidosis without hyperkalemic RTA (column showing acidosis RV), and values expected for hyperkalemic RTA (column showing ATR ↑K+). uNa - urine sodium; UK - urine potassium; uCl - urine chlorine; uOsm urine osmolality

	Formula	Normal values	Acidosis RV	ATR ↑ K+
Urine anion gap	$(uNa^+ + uK^+) - (uCl^-)$	20-90mEq/L	< 0mEq/L	> 0mEq/L
Urine osmolal gap	Measured uOsm - calculated uOsm	80-100mOsm/kg	> 100mOsm/kg	< 100mOsm/kg

Table 2 Typical workup changes in the subtypes of hyperkalemic RTA

	Renin	Aldosterone
Hyporeninemic hypoaldosteronism	N/↓	N/↓
Isolated congenital hypoaldosteronism	↑	N/↓
Pseudohypoaldosteronism (aldosterone resistance)	↑	↑

Table 3 Summary of workup findings typically seen in hyperkalemic renal tubular acidosis. HH - hyporeninemic hypoaldosteronism; PHA - Pseudohypoaldosteronism; GFR - glomerular filtration rate; TTKG - transtubular potassium gradient; UAG - urine anion gap; UOG - urine osmolal gap

	HH	PHA
K^+	> 5.1mmol/L	
pH	> 7.3	
HCO_3^-	17-21 mmol/L	
TFG	30-90 ml/min/1.73m^2	
GTTK	< 7	
HAU	> 0 mEq/L	
HOU	< 100 mOsm/L	
Aldosterona	N/↓	↑
Renina ativa	N/↓	↑

the lack of accurate dynamic data, with the exception of the TTKG, the reference values for renin and aldosterone (ignoring the possible fact that they resided in the upper or lower limit of normality and equally neglecting their variations with baseline values) are assumed to provide enough evidence for the differentiation between aldosterone deficiency and resistance as the cause of hyperkalemia. Table 3 summarizes the workup findings related to hyperkalemic renal tubular acidosis.

Treatment options are limited and aim to normalize potassium levels and acidosis. Different strategies have been described depending on the severity of workup findings and underlying etiology:

In moderate de novo (K^+ 6.5-7.4mmol/L) or severe hyperkalemia ($K^+ \geq$ 7.5mmol/L), patients are managed in a level 2 unit to have electrocardiograms done and undergo electrocardiographic follow-up and more detailed tests (confirmation of hyperkalemia through serum and urine ionograms and additional tests for renal function, complete blood count, TSH, serum and urine osmolality, and arterial blood gas.

If needed, other tests for aldosterone, renin, cortisol, digoxin levels, uric acid (tumor lysis), CK, and myoglobin (rhabdomyolysis) should be carried out. The treatment of more severe cases requires the correction of the underlying cause of the disease, the stabilization of the myocardial membrane (calcium gluconate) and the introduction of measures to decrease potassium circulating levels by promoting the intracellular entry of K^+ (insulin, dextrose solution, bicarbonate (in the event of acidosis) and salbutamol) and/or K^+ loss (ion-exchange resins, furosemide, and hemodialysis).[10]

In cases of mild hyperkalemia (K^+ 5.2-6.5mmol/L) without electrocardiographic repercussions, outpatient treatment with regular follow-up may be proposed. The choice of therapeutic strategy depends on the underlying cause of the disease:

Drug-induced hyperkalemia: suspend the drug, if possible. If the drug causing hyperkalemia is indispensable (cyclosporine in transplant patients, for instance), ion-exchange resins (sodium/calcium polystyrene sulfonate 1-3 times a day), diuretics (loop or thiazides), low-potassium diets may be used, and in cases of extreme necessity, fludrocortisone.[11]

Hyporeninemic hypoaldosteronism: although the underlying cause is aldosterone deficiency, the treatment does not consist necessarily of fludrocortisone. Since affected patients often suffer with high blood pressure, CKD, coronary artery disease (CAD), and heart failure (HF), the fluid overload induced by mineralocorticoids might be potentially deleterious and counterproductive for these patients. To make matters worse, in these

situations treatment with renin-angiotensin-aldosterone system (RAAS) inhibitors (which improve the prognosis of patients with CKD, HF, and CAD) is often suspended due to its hyperkalemic effects. Therefore, patients are not only exposed to neurohormonal stimuli that generate, perpetuate, and aggravate the injuries to the target organ (activating the RAAS), but also to a "toxic" overload of aldosterone. Thus, treatment with fludrocortisone is typically reserved for cases refractory to diuretic therapy (loop or thiazides), low potassium diets, and ion-exchange resins. The dose of fludrocortisone needed is usually supraphysiological (0.2 to 1mg/day), and possibly reflects some degree of associated aldosterone resistance.[12]

Aldosterone resistance: fludrocortisone therapy is recommended in doses of 0.2 to 1mg/day. An interesting exception is Gordon's Syndrome (pseudohypoaldosteronism type 2), in which hyperkalemia stems from WNK4 (*with no lysine kinase 4*) functional impairment or WNK1 functional gain. The described alterations cause functional gains in the Na^+-Cl^- cotransporter in the distal convoluted tubule decreasing Cl^- in the distal nephron, in addition to decreasing the supply of Na^+ to the collecting duct, producing a lower electric gradient in these segments of the nephron and, consequently, lower distal tubular secretion of K^+. Treatment includes the use of thiazides.[12]

The two case reports are typical accounts of hyporeninemic hypoaldosteronism. The patients had no clinical manifestations, and their workup showed mild to moderate hyperkalemia, moderate renal impairment, and hyperchloremic metabolic acidosis. Differences were found in TTKG values, as numbers closer to what should be expected in cases of hyperkalemia (> 7) were found in the first case, revealing a likely relationship with higher aldosterone levels.

However, in both cases aldosterone and renin levels were unexpectedly normal in the presence of hyperkalemia and unable to sustain ion homeostasis. Hypertension and the need to take multiple drugs to manage blood pressure, the presence of *diabetes mellitus* type 2 and the absence of typical clinical signs make corticoadrenal insufficiency an unlikely diagnostic possibility. Treatment with diuretics and ion-exchange resins effectively controlled hyperkalemia, thus allowing the resolution of metabolic acidosis and the attainment of a state of workup stability.

Conclusion

Hyporeninemic hypoaldosteronism is a frequent underdiagnosed medical condition. It manifests with hyperkalemia and hyperchloremic metabolic acidosis, in the presence of relatively preserved renal function (GFR) and no specific associated symptoms. Risk derives principally from the order of magnitude of hyperkalemia. It is more prevalent in individuals with diabetes with mild to moderate renal impairment (CKD stages 2-3). Diagnosis is achieved with the aid of transtubular potassium gradient (TTKG) and serum aldosterone and renin levels. The purpose of treatment is to normalize potassium levels, and may include a low-potassium diet, fludrocortisone, ion-exchange resins, and even hemodialysis. Given the lack of specific studies and the fact that this is an underdiagnosed condition, many questions still persist concerning the long-term consequences (with or without therapy) and the ideal treatment for the disease.

References

1. Rodríguez Soriano J. Renal tubular acidosis: the clinical entity. J Am Soc Nephrol 2002;13:2160-70. DOI: http://dx.doi.org/10.1097/01.ASN.0000023430.92674.E5
2. Haas CS, Pohlenz I, Lindner U, Muck PM, Arand J, Suefke S, et al. Renal tubular acidosis type IV in hyperkalaemic patients--a fairy tale or reality? Clin Endocrinol (Oxf) 2013;78:706-11. DOI: http://dx.doi.org/10.1111/j.1365-2265.2012.04446.x
3. Karet FE. Mechanisms in hyperkalemic renal tubular acidosis. J Am Soc Nephrol 2009;20:251-4. DOI: http://dx.doi.org/10.1681/ASN.2008020166
4. Lehnhardt A, Kemper MJ. Pathogenesis, diagnosis and management of hyperkalemia. Pediatr Nephrol 2011;26:377-84. DOI: http://dx.doi.org/10.1007/s00467-010-1699-3
5. Arai K, Chrousos GP. Aldosterone Deficiency and Resistance. In: De Groot LJ, Chrousos G, Dungan K, eds. Endotext [Internet]. South Dartmouth: MDText.com, Inc.; 2000 [citado 2017 Out 27]. Disponível em: https://www.ncbi.nlm.nih.gov/books/NBK279079/
6. Choi MJ, Ziyadeh FN. The utility of the transtubular potassium gradient in the evaluation of hyperkalemia. J Am Soc Nephrol 2008;19:424-6. DOI: http://dx.doi.org/10.1681/ASN.2007091017
7. Kamel KS, Halperin ML. Intrarenal urea recycling leads to a higher rate of renal excretion of potassium: an hypothesis with clinical implications. Curr Opin Nephrol Hypertens 2011;20:547-54. DOI: http://dx.doi.org/10.1097/MNH.0b013e328349b8f9
8. West ML, Marsden PA, Richardson RM, Zettle RM, Halperin ML. New clinical approach to evaluate disorders of potassium excretion. Miner Electrolyte Metab 1986;12:234-8.
9. DeFronzo RA. Hyperkalemia and hyporeninemic hypoaldosteronism. Kidney Int 1980;17:118-34. DOI: http://dx.doi.org/10.1038/ki.1980.14
10. Kovesdy CP. Management of Hyperkalemia: An Update for the Internist. Am J Med 2015;128:1281-7. DOI: 10.1016/j.amjmed.2015.05.040 DOI: http://dx.doi.org/10.1016/j.amjmed.2015.05.040
11. Sousa AG, Cabral JV, El-Feghaly WB, de Sousa LS, Nunes AB. Hyporeninemic hypoaldosteronism and diabetes mellitus: Pathophysiology assumptions, clinical aspects and implications for management. World J Diabetes 2016;7:101-11. DOI: http://dx.doi.org/10.4239/wjd.v7.i5.101
12. Young WF Jr. Etiology, diagnosis, and treatment of hypoaldosteronism (type 4 RTA). Uptodate [citado 2017 Out 27]. Disponível em: https://www.uptodate.com/contents/etiology--diagnosis-and-treatment-of-hypoaldosteronism-type-4-rta