Case Report

Hyperkalemia with mild azotemia in a post-thyroidectomized patient: A case report and literature review

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บทคัดย่อ

ภาวะไทรอยด์ทำงานลดลง นอกจากจะทำให้เกิดภาวะโซเดียมในเลือดต่ำแล้ว ยังพบภาวะของเสียคั่งในเลือดได้จากหลายกลไก เช่น ระดับครีแอทินินในเลือดสูงลวง ลดการขับครีแอทินินโดยท่อไต ภาวะไตวายเฉียบพลันที่สามารถหายได้จากปริมาณเลือดที่สูบฉีดจากหัวใจลดลง การหดตัวของหลอดเลือดฝอยไต การเพิ่มขึ้นของแรงต้านทานของหลอดเลือดทั่วร่างกาย หรือการบาดเจ็บของท่อไตและเนื้อไตอย่างถาวรซึ่งนำไปสู่โรคไตเรื้อรังได้ นอกจากนี้ภาวะโพแทสเซียมในเลือดสูงอาจพบได้ในผู้ป่วยที่มีภาวะไทรอยด์ทำงานลดลงบางราย โดยยังไม่ทราบกลไกแน่ชัด เนื่องจากรายงานผู้ป่วยส่วนใหญ่ไม่ได้ประเมินระดับเกลือแร่ในปัสสาวะ ผู้วิจัยรายงานผู้ป่วยที่มีภาวะไทรอยด์ทำงานต่ำมาก และรับประทานอาหารที่มีไอโอดีนต่ำ เพื่อเตรียมการประเมินการทำงานของต่อมไทรอยด์ทางเวชศาสตร์นิวเคลียร์ ผู้ป่วยมีภาวะของเสียคั่งในเลือดในระดับไม่รุนแรง และมีระดับโพแทสเซียมในเลือดสูง ผลการตรวจระดับโพแทสเซียมในปัสสาวะไม่พบความผิดปกติของการขับโพแทสเซียม และความผิดปกติดังกล่าวยังกลับสู่ภาวะปกติภายหลังจากผู้ป่วยได้รับประทานฮอร์โมนไทรอยด์ทดแทนอีกครั้ง ผู้วิจัยสรุปความเป็นไปได้ของกลไกการลดการขนส่งโพแทสเซียมเข้าสู่เซลล์เป็นปัจจัยหลักของภาวะโพแทสเซียมในเลือดสูงในผู้ป่วยกลุ่มดังกล่าว โดยอาจกระตุ้นด้วยปริมาณโพแทสเซียมที่สูงกว่าปกติ ในอาหารที่มีไอโอดีนต่ำ และได้ทบทวนการศึกษาในอดีตถึงความผิดปกติในการทำงานของไตอื่น ๆ ในผู้ป่วยที่มีภาวะไทรอยด์ทำงานลดลง เช่น การพบโปรตีนรั่วในปัสสาวะ และการขับกรดโดยไตที่ลดลง โดยสรุป รายงานผู้ป่วยฉบับนี้ทำให้เห็นถึงความสำคัญของการติดตามการทำงานของไต และระดับเกลือแร่ในเลือดในผู้ป่วยที่มีภาวะไทรอยด์ทำงานลดลงอย่างรุนแรงหรือมีความเสี่ยง และนึกถึงสาเหตุจากภาวะไทรอยด์ทำงานลดลงในผู้ป่วยที่มีภาวะโพแทสเซียมในเลือดสูงหรือไตวายโดยไม่มีสาเหตุอื่นชัดเจน

คำสำคัญ: hyperkalemia, azotemia, hypothyroidism, low-iodine diet

Case Report

Hyperkalemia with mild azotemia in a post-thyroidectomized patient: A case report and literature review

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Abstract

Background: Apart from hyponatremia, azotemia has been found to be associated with hypothyroidism by inconclusive mechanism, possibly falsely elevated creatinine, decreased tubular secretion of creatinine, reversible pre-renal kidney injury from decreased cardiac output, renal vasoconstriction, increased systemic vascular resistance, or irreversible tubulo-interstitial injury which can lead to chronic kidney disease. Hyperkalemia is also an infrequent manifestation in some hypothyroid patients with unproven mechanism since previous case reports have not explored urinary electrolyte analysis.

Case report: We report a patient with mild azotemia and hyperkalemia in profound hypothyroid state while taking low-iodine diet. Urinary electrolyte analysis reveals no impairment in potassium excretion. Moreover, the abnormalities were normalized after thyroid hormone supplementation. Hence, we propose a possible mechanism of decreased intracellular potassium shift as a cause of hyperkalemia in hypothyroid patient, which may be aggravated by high potassium content in low-iodine diet. We also review other renal manifestations in hypothyroidism including proteinuria, hyperuricemia, and renal acidification defect.

Conclusions: Our case report emphasizes the importance of monitoring renal function and serum electrolytes in profound or high-risk hypothyroid patients, and awareness of thyroid dysfunction in patients with unexplained hyperkalemia or azotemia.

Keywords: hyperkalemia, azotemia, hypothyroidism, low-iodine diet

Introduction

Thyroid hormone has long been demonstrated as an important factor for maintenance of body metabolism and development of many organs including kidneys by numerous animal models and clinical human studies[1]. Moreover, in postnatal period, the hormone also affects cardiovascular, metabolic, and renal functions by mean of various mechanisms[2]. Effect of TH on renal function has been primarily thought to be from hemodynamic effect, both directly from disturbance in cardiac output and indirectly from altered intra-renal hemodynamics as a result from aberrant renal vasodilator synthesis and activity, aberrant renin-angiotensin-aldosterone system, and altered renal autoregulation via tubuloglomerular feedback[3]. In other words, all these effects on renal function are 'pre-renal' in nature, as evidenced by many clinical studies demonstrating changes in RPF and GFR in patients with thyroid dysfunction[1]. However, growing body of evidence has raised the possibility that thyroid dysfunction might also affect renal structures, both glomeruli and renal tubules[4,5]. These might, in contrast to the pre-renal manner, lead to irreversible

kidney damage or even CKD in some patients with thyroid dysfunction and partly explain the higher prevalence of thyroid disorders in patients with ESRD[3,6]. Moreover, TH is well known for affecting renal water and sodium homeostasis, rendering routine thyroid function testing in patients with unexplained hyponatremia[1,2].

Hypothyroidism is classified as OH or clinical primary hypothyroidism, which has TSH concentration above the reference range and free thyroxine concentration below the reference range, or SCH which has elevated TSH concentration and normal free thyroxine concentration, or central hypothyroidism in a much lower prevalent. The prevalence of OH varies by studied populations, between 0.2% - 10%, with much higher in women and elderly[7]. Etiologies of primary hypothyroidism in iodine-sufficient area include post-surgical thyroidectomy or post-ablation with radioactive iodine, some medications such as lithium and amiodarone, immune-mediated process with circulating antithyroid antibodies with or without other autoimmunities which increases in prevalence in elderly[8].

There is no controversy in treating patients with overt hypothyroidism with TH supplementation, such as levothyroxine. However, TH supplementation in patients with mild subclinical hypothyroidism remains controversial since some studies demonstrate benign prognosis in SCH albeit growing evidence has suggested cardiovascular benefit in treating patients with SCH[9]. In the context of renal function, hypothyroidism associates with multiple manifestations as shown in **table 1**, and TH supplementation can reverse many of these abnormalities. Not only restricted to OH, SCH has been shown by many studies to associate significantly with decreased GFR in equal or lesser extent to that of OH[6,10-12]. There is even an observational study demonstrating that TH supplementation can attenuate progression of CKD in patients with SCH although more randomized studies are needed before the implementation of this practice[13].

Table 1 Renal manifestations in adult patients with hypothyroidism

Manifestations	Proposed mechanism	Supporting evidences	Reversibility after thyroid hormone supplementation	Remarks
Elevated serum creatinine concentration with normal GFR (pseudo-azotemia)	False elevation due to increased muscle creatinine production	Normal iothalamate and creatinine clearance[14]	Fully reversible	Elevated CPK, LDH, and aldolase
	Decreased tubular creatinine secretion	Animal model[15]	N/A	
AKI (truly decreased GFR) with or without rhabdomyolysis[4,16,17]	Pre-renal process • Systemic hemodynamics: decreased cardiac output (inotropic, chronotropic, systolic, and diastolic dysfunction), increased systemic vascular resistance • Altered intra-renal hemodynamics • Decreased renal sodium and water reabsorption by proximal tubule	• Decreased directly measured RPF and GFR[1] • Decreased renal vasodilator synthesis and activity[3] • Reduced RAAS activation[1,3] • Impaired renal autoregulation: increased tubuloglomerular feedback from increased distal chloride delivery[2] • Paracrine and endocrine, such as VEGF, signaling[10]	Mostly recovered in 4 weeks to 10 months, lower recovery rate in elderly, diabetic or hypertensive patients[5]	• Can occur within 2 weeks of decreased TH • Serum creatinine level is mostly within 1.5-2.5 mg/dL but can be as high as 6 mg/dL or dialysis needed[5].

Manifestations	Proposed mechanism	Supporting evidences	Reversibility after thyroid hormone supplementation	Remarks
	Intra-renal structural change	• Decreased BUN to serum creatinine ratio but no report of urinary indices and injury biomarkers[18] • Kidney biopsy specimens showing interstitial fibrosis and tubular atrophy[5]	Might not completely recovered	Might progress to CKD
CKD[3]	Prolonged or undetected AKI from untreated hypothyroidism	Negative correlation of TSH level and GFR in dose-dependent manner, even with TH supplementation[6,10]	No, but rate of GFR decline might be attenuated[13]	Decreased GFR also affects thyroid function per se
Proteinuria	Immune- or immune complex-mediated process since most cases have autoimmune thyroiditis (non-immune mediated mechanism is uncertain)	• Kidney biopsy specimens showing MCD, MN, MPGN, IgAN, FSGS [5,19] • Positive IHC staining for anti-thyroglobulin and thyroid peroxidase in GBM[20,21]	Various, from completely reversed, partially reversed, to persistent or steroid needed[4]	Various degree, from subnephrotic proteinuria to nephrotic syndrome
Hyponatremia	Vasopressin action (may be stimulated by decreased cardiac output)	Increased non-osmotic vasopressin release and vasopressin sensitivity of collecting duct[2]	Reversible	May also be aggravated by decreased GFR, hence decreased water clearance
	Decreased renal sodium and water reabsorption	• Reduced RAAS activity • Impaired multiple tubular sodium cotransporters[1]		
Hyperuricemia with or without arthritis[10]	Decreased renal clearance	Decreased urinary uric level[22]	Reversible	
	Increased production from myopathy[14]			
Impaired urinary acidification[23]	Decreased expression of tubular H^+-ATPase, sodium-H^+, and sodium-bicarbonate exchanger[1]	Impaired response after acid loading test (a small study)[23]	N/A	
CV risk	Hypothyroidism associates with additional CV morbidity and mortality in CKD patients[3]. This may results from increased arterial stiffness, decreased nitric oxide production, endothelial dysfunction, atherosclerosis from dyslipidemia, or cardiac myocyte dysfunction[1].			

AKI, acute kidney injury; BUN, blood urea nitrogen; CKD, chronic kidney disease; CPK, creatinine phosphokinase; CV, cardiovascular; FSGS, focal segmental glomerulosclerosis; GBM, glomerular basement membrane; GFR, glomerular filtration rate; IgAN, immunoglobulin A nephropathy; IHC, immunohistochemistry; LDH, lactate dehydrogenase; MCD, minimal change disease; MN, membranous nephropathy; MPGN, membranoproliferative glomerulonephritis; N/A, not applicable; RAAS, renin-angiotensin-aldosterone system; RPF, renal plasma flow; VEGF, vascular endothelial growth factor

Apart from these manifestations, potassium disorder in the absence of significant GFR decline is not well established in hypothyroidism. There is only one case series demonstrating severe hyperkalemia in some post-thyroidectomized patients who took low-iodine diet. However, the mechanism of hyperkalemia was difficult to identify in the study due to its lack of urinary potassium profile[24]. Herein, we report a case of post-thyroidectomized patient taking low-iodine diet in preparation for thyroid scintigraphy who developed hyperkalemia with mild azotemia along with urinary electrolytes analysis to propose the possible mechanism in addition to knowledge from previous studies.

Case report

A 55-year-old post-thyroidectomized woman presented in September 2020 with asymptomatic hyperkalemia and mild azotemia from routine blood test after 4 weeks of TH discontinuation along with low-iodine diet in preparation for thyroid scintigraphy to evaluate residual thyroid function after total thyroidectomy due to papillary thyroid carcinoma. She was diagnosed with thyroid carcinoma with cervical lymph node involvement 1 year before this presentation from accidental finding of solitary thyroid nodule on head and neck magnetic resonance imaging prescribed after mild head trauma. There was no evidence of distant metastasis. One month after the diagnosis, she received total thyroidectomy and modified radical neck dissection followed by Iodine-131 ablation. Since then, she developed hypothyroidism and had taken levothyroxine supplement and had been in euthyroid state. Her another underlying disease is dyslipidemia, and she takes a stable dose of statins. There were no other insults that could explain azotemia or hyperkalemia such as leukocytosis, thrombocytosis, metabolic acidosis, new medications, or herbal use. Her serum albumin, creatine phosphokinase, parathyroid hormone, serum calcium and phosphate were within normal limit. Later thyroid scintigraphy revealed no thyroid tissue remnant. We also measured urinary electrolytes level and urinary indices in her hyperkalemic and azotemic period which are shown in **figure1**. All abnormalities were reversible after resumption of levothyroxine supplementation following the thyroid scintigraphy.

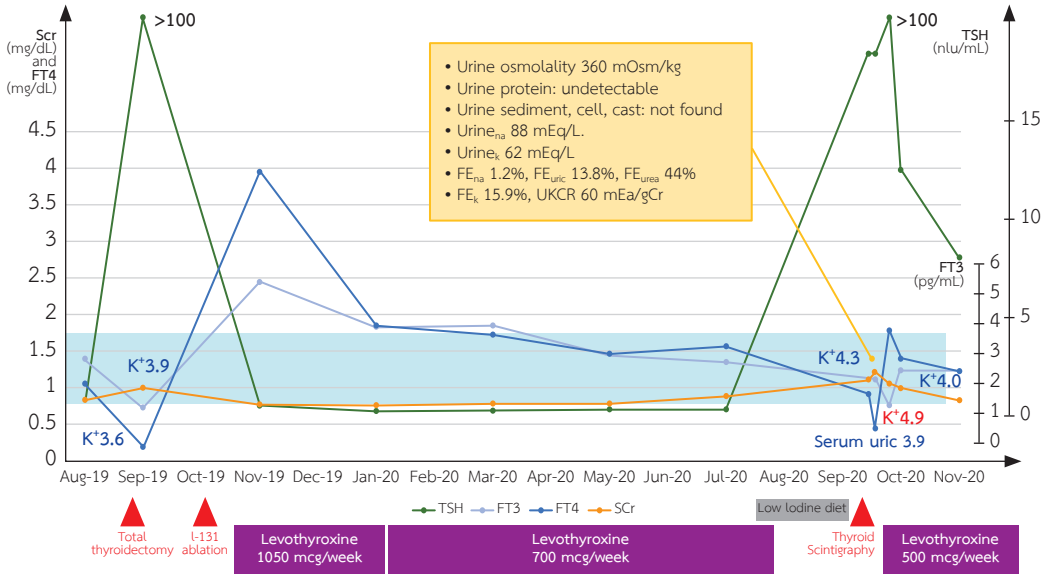

Figure 1 Timeline of patient investigations and interventions; Hypothyroid period was confirmed by marked elevated TSH level and decreased FT4 level followed shortly by decreased FT3 level. The blue-shaded area represents normal range of TSH, FT4, and FT3. Levothyroxine supplementation periods are depicted in purple bars. Urinary electrolyte levels and indices at presentation are shown in the box. Abbreviations: SCr, serum creatinine concentration; FE_K, fractional excretion of potassium; FE_{Na}, fractional excretion of sodium; FE_{urea}, fractional excretion of urea; FE_{uric}, fractional excretion of uric acid; FT3, free T3 level; FT4, free T4 level; I-131, iodine-131; K^+, serum potassium concentration; TSH, thyroid stimulating hormone level; UKCR, urinary potassium in mEq to urinary creatinine in gram ratio; $Urine_K$, urinary potassium concentration; $Urine_{Na}$, urinary sodium concentration

Discussion

Our case report is the first to report hyperkalemia and azotemia in a hypothyroid patient along with urinary indices and urinary electrolytes measurement.

Increased serum potassium level

Our patient developed transient mild hyperkalemia that cannot be solely explained by the decreased GFR. Moreover, the urinary potassium level and UKCR are not in the lower range. This reflects preserved renal potassium excretion. So, there must be other mechanisms leading to hyperkalemia in thyroidectomized patients.

Considering previous report in Japan[24], about 5% of thyroidectomized patients taking low-iodine diet develop reversible hyperkalemia, and some of them have electrocardiographic change. Although all of them also have elevated serum creatinine concentration to more than 0.3 mg/dL, their estimated GFR are not low enough to cause decreased potassium filtration. All patients with severe hyperkalemia were more than 60 years of age and received angiotensin receptor antagonists which are absent in our patient and these factors might make the patients more susceptible to hyperkalemia.

The most plausible mechanism, especially when consider our urinary potassium profile, is decreased transcellular potassium shift. There were studies demonstrating hyperkalemia and decreased skeletal muscle Na^+-K^+ ATPase concentration in thyroidectomized animal without evidence of rhabdomyolysis[25] and in hypothyroid human without preexisting renal disease which was reversible within 4-10 weeks of thyroid hormone supplementation[26]. Whether this is from an intrinsic effect of thyroid hormone itself or from an accompanying increased alpha-adrenergic action, opposing to mechanism of transient hypokalemia in thyrotoxicosis[(27)], necessitates further study.

Whether aberrance in skeletal muscle Na^+-K^+ ATPase concentration is the only mechanism of hyperkalemia in hypothyroid patient or there are other precipitating

factors such as exercise[25] or increased dietary potassium is uncertain. There is no data on exact potassium amount in low-iodine diet but, since the diet is fruit- and vegetable-enriched, it might provide large amount of dietary potassium. This might explain the absence of hyperkalemia on her first hypothyroid period soon after the thyroidectomy.

Although many studies have shown that thyroid hormone is correlate with RAAS activity[1]. Hypoaldosteronism cannot be the cause of hyperkalemia in our patient, whose urinary potassium profile was not low and blood pressure as well as serum bicarbonate level did not change significantly. In addition, a previous study has demonstrated normal plasma aldosterone concentration and plasma renin activity in hyperkalemic hypothyroid animals[25].

Increased serum creatinine concentration

Whether mild azotemia with rapid recovery after TH supplementation in our patient resulted from falsely elevated serum creatinine or tubular injury remains unproven since we did not measure direct GFR directly by clearance technique nor tubular injury biomarkers, and both mechanisms were possible in the light of previous studies[5,14,15]. However, the low urea to creatinine ratio, like the finding from previous report[18], along with relatively high fractional excretion of sodium, urea, and uric, indicate that the azotemia might not be solely explained by pre-renal process from decreased renal perfusion.

Conclusion

Our case report, in association with current evidence, supports the important of regular renal function and serum electrolytes monitoring in hypothyroid patients, especially in elderly, diabetic or hypertensive patients, who are at high risk of persistent renal damage and CKD, since the symptoms of hypothyroidism might be confused with or masked by uremia (anemia, fatigue), nephrotic syndrome (edema, macroglossia, hyperlipidemia), medication adverse effects, or normal aging. Moreover, we are the first to raise the possibility of TH effect on intracellular potassium shift. So, hypothyroidism should also be in the differential diagnoses in patients with unexplained kidney damage, CKD progression, hyponatremia, or hyperkalemia with normal urinary potassium profile. Since hypothyroidism is a treatable disease, TH supplementation may prevent the renal involvement, or even prevent ESRD in hypothyroid patients.

Abbreviations: CKD, chronic kidney disease; ESRD, end stage renal disease; GFR, glomerular filtration rate; Na^+-K^+ ATPase, sodium-potassium ATPase protein; OH, overt hypothyroidism; RAAS, renin-angiotensin-aldosterone system; RPF, renal plasma flow; SCH, subclinical hypothyroidism; TH, thyroid hormone; TSH, thyroid-stimulating hormone; UKCR, urinary potassium (mEq) to urinary creatinine (gram)

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Ethics approval: Publication of this case report is according to the local ethics committee's policy. The image and clinical details of the participant are presented anonymously. Written informed consent was obtained from the patient for publication of this case report.

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