Hypothyroidism-induced Acute Kidney Injury and Hyponatremia

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ABSTRACT

Thyroid hormones affect every organ system in the body including renal development and physiology, and electrolyte and water homeostasis. These effects happen as a consequence of the combination of direct effects of thyroid hormones on renal tubules and hemodynamic effects of thyroid hormones. As a consequence, both hypothyroidism and hyperthyroidism significantly affect renal function. This case describes a patient with hypothyroidism-related acute kidney injury without rhabdomyolysis, and no additional precipitating factor. While there are many case reports describing hypothyroidism-related rhabdomyolysis leading to acute kidney injury, there are only a handful of case reports on hypothyroidism-related acute kidney injury without rhabdomyolysis.

KEYWORDS: hypothyroidism, acute kidney injury, rhabdomyolysis, hyponatremia

INTRODUCTION

Hypothyroidism affects every organ system in the body, including the central nervous system, cardiovascular system, gastrointestinal system, musculoskeletal system, and the metabolic rate.[1] Hypothyroidism is associated with an underappreciated but clinically significant alteration of renal physiology.[1-2] While there are many case reports describing hypothyroidism-related to rhabdomyolysis leading to acute kidney injury (AKI),[3-9] there are only a handful of case reports on hypothyroidism-related AKI without rhabdomyolysis.[10-14] This case describes a patient with hypothyroidism and AKI without rhabdomyolysis, and no additional precipitating factor.

CASE PRESENTATION

An 82-year-old male with past medical history of colorectal cancer (in remission for 15 years), hypertension, hypothyroidism and hyperlipidemia, presented from home with a change in mental status. According to family, the patient lived alone but his daughter visited frequently. At his baseline, he was fully oriented and able to take care of himself. Two days prior to presentation, his daughter noted that the patient complained of lethargy and lower back pain, with poor appetite and decreased oral intake. His mental status continued to worsen, and so his daughter brought him to the emergency department. Upon presentation, the patient was unable to recall life events and did not know why he was in the hospital. He denied fever, chills, chest pain, shortness of breath, cough, nausea, vomiting, abdominal pain, diarrhea, constipation, dysuria, urgency, peripheral edema or any focal neurological complaint.

Daily medications included levothyroxine, aspirin, fenofibrate, lisinopril, omeprazole, and vitamin D supplements. The patient had a two-pack-year smoking history but quit smoking decades prior to presentation. The family reported he ingested 5–7 standard alcoholic drinks per week. He was retired and spent most days at home.

Initial vital signs were the following: temperature 97.2°F, heart rate 48 regular beats per minute, respiratory rate 20/min, blood pressure 152/63 mmHg and oxygen saturation was 97% on room air. The patient was alert but oriented only to self. Cardiac exam revealed bradycardic S1S2. On neurological exam he was able to follow commands and had no focal deficits. The rest of his physical examination was within normal limits.

Laboratory results are included in **Table 1**. Urinalysis was unremarkable. EKG showed decreased voltage in precordial leads. TSH was 132.994 uIU/mL (normal range 0.350–5.5 ulU/ml), with free T4 low at 0.16 ng/dl (normal range 0.8–1.8 ng/dl) and T3 low at <20.0 pg/dL (normal range 230–420 pg/dl). CT of the brain without IV contrast, renal ultrasound, chest x-ray and CT of the abdomen and pelvis without IV contrast were unremarkable. Due to the hyponatremia, acute kidney injury, and profound hypothyroidism, the patient was admitted to the medical service.

Both nephrology and endocrine were consulted for acute kidney injury, hyponatremia, and hypothyroidism. The patient received 500mL of intravenous 0.9% normal saline and was then fluid restricted to 1L/day. He was not given any maintenance intravenous fluids. He was also started on intravenous levothyroxine. His serum creatinine and serum sodium level normalized to 1.1 mg/dl and 138 meq/L, respectively, over the next 4–6 days. His mental status also improved by the time of discharge and remained stable at a 3 month follow-up visit. As a result of his rapid improvement with thyroxine and fluid restriction alone, his AKI and hyponatremia were thought to be directly related to myxedema.

Table 1. Laboratory results

Test Name	Results	Reference Range
White Blood cells	6.4 x10^9/L	3.5-11 x10^9/L
Hemoglobin	12.3 g/dl	13.5-16 g/dl
Hematocrit	36.1%	37%-47%
Platelets	228 x10^9/L	150-400x10^9/L
Sodium	125 meq/L	135-145 meq/L
Potassium	3.6 meq/L	3.5-5.1 meq/L
Chloride	93 meq/L	98-110 meq/L
Bicarbonate	18 meq/L	22-32 meq/L
Creatinine	4.06 mg/dl	0.6-1.2 mg/dl
Blood Urea Nitrogen	50 mg/dl	6-24 mg/dl
Glucose	104 mg/dl	67-99 mg/dl
AST	30 IU/L	10-42 IU/L
ALT	9 IU/L	6-45 IU/L
ALP	28 IU/L	34-104 IU/L
Albumin	3.6 g/dl	3.5-5 g/dl
Total Bilirubin	0.6 mg/dl	0.2-1.3 mg/dl
Total Protein	6.2 g/dl	6-8 g/dl
Ammonia	40 µmol/L	2-50 µmol/L
CPK	319 IU/L	20-210 IU/L
Serum Osmolality	281 mOsm/Kg	290-300 mOsm/Kg
Urine Osmolality	516 mOsm/Kg	

Figure 1. Effects of Thyroid hormone on Hemodynamics

Genomic effects
Upregulation of α-myosin heavy chain genes (fast myosin) → Increased contractility and hypertrophy
Downregulation of β-myosin heavy chain genes (slow myosin) → Increased contractility
Upregulation of SR Ca2+-ATPase (SRCa2) → Increase rate of myocardial relaxation in diastolic phase (Lusitropic effect)
Downregulation of phospholamban (PLB) → Inhibits SRCa2 → Increase in Lusitropic effect
Upregulation of b1-adrenergic receptors → Increase heart rate
Upregulation of Na+-K+-ATPase → Chronotropic effect??
Downregulation of Na+/Ca2+ exchanger (NCX1) → Inotropic affect
Upregulation of TRα1 → Increased eNO which leads to vasodilatation
Downregulation of angiotensin receptors → Vasodilation
Effect depends on type of voltage gated potassium channels
Increase in VEGF → Angiogenesis
Increase FGF → Hypertrophy
Nongenomic effects
Increases HIF-1 protein synthesis → Increase in blood volume
Activation of TRα1 through nongenomic pathways → Increased eNO which leads to vasodilatation
Thyroid hormone also activates multiple Ion channels (Na, K, Ca) and regulates multiple specific signal transduction pathways
Modulates sensitivity to adrenergic vasoconstrictors and endothelium-dependent vasodilators.

DISCUSSION

The principal mode of AKI in myxedema is thought to be due to the reduced renal blood flow (RBF) and glomerular filtration rate (GFR), but the exact pathogenesis remains unclear and is thought to be multifactorial.[1] Studies have described both genomic and nongenomic signaling by thyroid hormones.[15,16]

Effect of hypothyroidism on hemodynamics

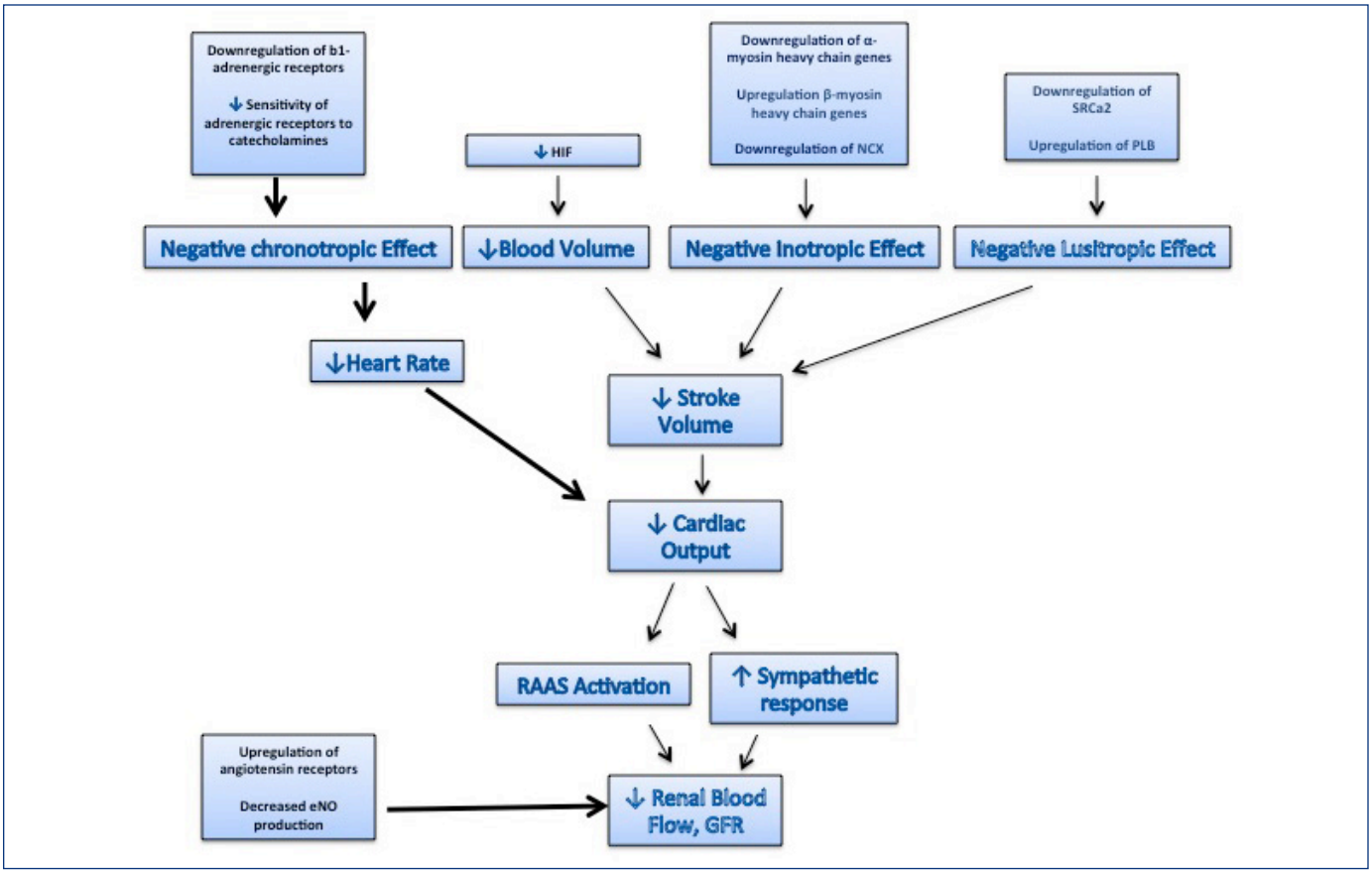
The effects of hypothyroidism on the cardiovascular system has been extensively studied and well documented. Thyroid hormones affect the cardiovascular system by both genomic and non-genomic pathways which widely overlap. (**Figure 1.**)[15,16] Thyroid hormones regulate positive and negative expression of genes for structural and regulating proteins of cardiomyocytes, thus affecting both contraction and electrochemical signaling pathways. Thyroid hormone fine-tunes the expression of genes for myosin heavy chain, which is the main structural part of the sarcomere.[16,17] Thyroid hormone regulates the expression of sarcoplasmic reticulum Ca2+-ATPase (which plays a role in relaxation time during diastole), b1-adrenergic receptors (increase receptor function and density), guanine nucleotide regulatory proteins, Na+-K+-ATPase, voltage gated potassium channels and Na+/Ca2+ exchanger.[18-22]

Thyroid hormones downregulate the expression of angiotensin receptors in vascular smooth muscles (leading to vascular relaxation).[23] Thyroid hormones also activates endothelial nitric oxide synthase through alpha 1 thyroid receptor (TRα1), which in turn leads to vasodilation.[24] Thus, thyroid hormones leads to decreased vascular resistance, which leads to increased vascular compliance, decreased blood pressure, and increased cardiac output (**Figure 2**).

Effect of Hypothyroidism on GFR

Subclinical and clinical hypothyroidism is a common problem in CKD patients. Elevated creatinine can be seen within two weeks of severe hypothyroidism. Creatinine often improves very quickly after appropriate treatment of hypothyroidism but sometimes patients can have slower

Figure 2.



response or incomplete renal recovery with prolonged and severe hypothyroidism.[25-29] Hypothyroidism may also causes increased glomerular capillary permeability which leads to proteinuria. Proteinuria often precedes the reduction in GFR in hypothyroidism.

Because creatinine-based equations are used to estimate GFR, it is unclear how much of an elevated creatinine level reflects the true drop in GFR. Creatinine levels can be altered by myopathy, decreased tubular secretion or creatinine metabolism. Cystatin C blood level cannot be used as a marker of GFR in this patient population as the levels are generally low in hypothyroid patients and elevated in hyperthyroid patients.[30] The exact mechanism is unknown but it is thought to be related to direct effects of thyroid hormone on cystatin C production. In one study, Villabona and colleagues noted increased renal plasma flow (from 542.8ml/min to 717 ml/min) and GFR (from 99.6 to 125.7 ml/min measured with Cr-EDTA clearance) after thyroid hormone replacement in overt hypothyroidism patients. [31]

Effect of hypothyroidism on Tubular function

Thyroid hormones affect renal tubular function by both genomic and nongenomic pathways.[1] Hypothyroidism affects renal tubular secretory and reabsorptive processes by upsetting the expression and activity of various ion channels/transporters. Thyroid hormones also influence the renal tubular physiology by alternating the responses to different hormones (Increased ADH sensitivity).

Hypothyroidism causes renal tubular down regulation of Na+-K+ ATPase, H+-ATPase, Na+-HCO3 exchanger, Na+-H+ exchanger, Na+-Pi IIa exchanger, Na+-sulfate exchanger, Na+-K+-2 Cl2 cotransporter, Na+-Ca2+ exchanger, Cl2 channel and up regulation of aquaporin (AQP) 1 and 2.[1,32,33] As one can imagine, hypothyroidism will lead to impaired urinary concentrating ability, increased urinary sodium excretion, increased fractional excretion of sodium and decreased free water clearance. Hypothyroidism results in low cardiac output which triggers the carotid baroreceptors and consequently increases the non-osmotic ADH secretion. All of these effects of hypothyroidism on sodium and water homeostasis will lead to hypothyroidism-induced hyponatremia.[33]

Effect of hypothyroidism on Skeletal muscle

Hypothyroidism causes rhabdomyolysis by inducing structural abnormalities in the setting of metabolic impairment. Structural abnormalities include decline in fast-twitch type II muscle fiber mass, increase in slow-twitch type I muscle fiber mass, decrease in muscle carnitine and glycosaminoglycan deposition. Metabolic abnormalities include inhibition of mitochondrial activity, decreased protein turnover,

impaired carbohydrate metabolism, low myosin ATPase activity and low ATP turnover. [34.] In turn, rhabdomyolysis causes AKI through intraluminal obstruction by myoglobin, uric acid casts, direct myoglobin toxicity and production of free radicals. [35]

CONCLUSION

This case illustrates how severe symptomatic hypothyroidism can lead to severe renal dysfunction without rhabdomyolysis. Clinicians should be aware of this rare association and patients with unexplained AKI should be worked up for hypothyroidism.

References

1. Mariani LH, Berns JS. The Renal Manifestations of Thyroid Disease. JASN. 2012; 23 (1) 22-26.
2. Klein I, Danzi S. Thyroid Disease and the Heart. Circulation. 2007;116:1725–1735.
3. Barahona MJ, Mauri A, Sucunza N, et al. Hypothyroidism as a cause of rhabdomyolysis. Endocr J. 2002, 49:621–23
4. Sekine N, Yamamoto M, Michikawa M, et al. Rhabdomyolysis and acute renal failure in a patient with hypothyroidism. Intern Med. 1993;32:269–71.
5. Naz A, Issa M. Rhabdomyolysis and acute renal impairment in a patient with hypothyroidism: A case report. Case Rep Med. 2014, 139170
6. Halverson PB, Kozin F, Ryan LM, Sulaiman AR. Rhabdomyolysis and renal failure in hypothyroidism. Ann Intern Med. 1979;91:57–58.
7. Ahmed GS, Zaid HM, Moloney M. Hashimoto's thyroiditis presenting as Hoffman's syndrome, rhabdomyolysis and acute kidney injury. BMJ Case Rep. 2014 pii: bcr2013203269.
8. Kisakol G, Tunc R, Kaya A. Rhabdomyolysis in a patient with hypothyroidism. Endocr J. 2003;50:221–23.
9. Altay M, Duranay M, Ceri M. Rhabdomyolysis due to hypothyroidism. Nephrol Dial Transplant. 2005;20:847–48
10. Weerakkody RM, Lokuliyana PN. Severe hypothyroidism presenting as reversible proteinuria: two case reports. *J Med Case Reports. 2019*;13, 270.
11. Rodrigo C, Gamakaranage CS, Epa DS, Gnanathasan A, Rajapakse S. Hypothyroidism causing paralytic ileus and acute kidney injury - case report. Thyroid Res. 2011; 4: 7.
12. Connor A, Taylor JE. Renal impairment resulting from hypothyroidism. NDT Plus. 2008;1:6, 440–441.
13. McAninch EA, Lagari VS. Acute-on-Chronic Kidney Injury in Thyroid Hormone Withdrawal: A Case with Possible Implications for Radioactive Iodine Planning. Case Reports in Endocrinology. 2015, Article ID 932372
14. Vikrant S, Chander S, Kumar S, Gupta D. Hypothyroidism presenting as reversible renal impairment: an interesting case report. Renal Failure. 2013; 35:9, 1292-1294
15. Danzi S, Dubon P, Klein I. Effect of serum T_3 on the regulation of cardiac gene expression: role of histone acetylation. Am J Physiol Heart Circ Physiol. 2005;*289*: 1506–1511.
16. Hiroi Y, Kim HH, Ying H, Furuya F, Huang Z, et al. Rapid nongenomic actions of thyroid hormone. Proc Natl Acad Sci U S A. 2006,103:14104-14109.
17. Haddad F, Bodell PW, Qin AX, Giger JM, Baldwin KM. Role of antisense RNA in coordinating cardiac myosin heavy chain gene switching. J Biol Chem. 2003; *278*: 37132–37138
18. Ketzer LA, Arruda AP, Carvalho DP, de Meis L. Cardiac sarcoplasmic reticulum Ca2+-ATPase: heat production and phospholamban alterations promoted by cold exposure and thyroid hormone. Am J Physiol Heart Circ Physiol. 2009 Aug;297(2):H556-63
19. Bahouth SW (1991) Thyroid hormones transcriptionally regulate the beta 1-adrenergic receptor gene in cultured ventricular myocytes. J Biol Chem 266: 15863-15869.
20. Hu X, Lazar MA. Transcriptional repression by nuclear hormone receptors. Trends Endocrinol Metab. 2000; *11*: 6–10.
21. Nishiyama A, Kambe F, Kamiya K, Seo H, Toyama J. Effects of thyroid status on expression of voltage-gated potassium channels in rat left ventricle. Cardiovasc Res. 1998, 40: 343-351.
22. Boerth SR, Artman M. (1996) Thyroid hormone regulates Na(+)-Ca2+ exchanger expression during postnatal maturation and in adult rabbit ventricular myocardium. Cardiovasc Res 31: E145 -E152.
23. Fukuyama K, Ichiki T, Takeda K, Tokunou T, Iino N, et al. Downregulation of vascular angiotensin II type 1 receptor by thyroid hormone. Hypertension. 2003, 41: 598-603.
24. Colin IM, Nava E, Toussaint D, Maiter DM, vanDenhove MF, Lüscher TF, Ketelslegers JM, Denef JF, Jameson JL. Expression of nitric oxide synthase isoforms in the thyroid gland: evidence for a role of nitric oxide in vascular control during goiter formation. Endocrinology. 1995 Dec;136(12):5283-90.
25. Iglesias P, Díez JJ. Thyroid dysfunction and kidney disease. Eur J Endocrinol 160: 503–515, 2009
26. Mooraki A, Broumand B, Neekdoost F, Amirmokri P, Bastani B. Reversible acute renal failure associated with hypothyroidism: Report of four cases with a brief review of literature. Nephrology (Carlton). 2003, 8: 57–60.
27. Montenegro J, González O, Saracho R, Aguirre R, González O, Martínez I. Changes in renal function in primary hypothyroidism. Am J Kidney Dis. 1996, 27: 195–198.
28. Kreisman SH, Hennessey JV. Consistent reversible elevations of serum creatinine levels in severe hypothyroidism. Arch Intern Med. 1999, 159: 79–82.
29. den Hollander JG, Wulkan RW, Mantel MJ, Berghout A. Correlation between severity of thyroid dysfunction and renal function. Clin Endocrinol (Oxf). 2005, 62: 423–427.
30. Fricker M, Wiesli P, Brändle M, Schwegler B, Schmid C: Impact of thyroid dysfunction on serum cystatin C. Kidney Int 63: 1944–1947, 2003
31. Villabona C, Sahun M, Roca M, Mora J, Gómez N, Gómez JM, Puchal R, Soler J. Blood volumes and renal function in overt and subclinical primary hypothyroidism. Am J Med Sci. 1999, 318: 277–280.
32. Li X, Misik AJ, Rieder CV, Solaro RJ, Lowen A, Fliegel L: Thyroid hormone receptor alpha 1 regulates expression of the Na+/H+ exchanger (NHE1). J Biol Chem. 2003, 277: 28656–28662
33. Schmitt R, Klussmann E, Kahl T, Ellison DH, Bachmann S: Renal expression of sodium transporters and aquaporin-2 in hypothyroid rats. Am J Physiol Renal Physiol. 2004, 284: F1097–F1104.
34. Wiles CM, Young A, Jones DA, Edwards RH. Muscle relaxation rate, fibre-type composition and energy turnover in hyper- and hypo-thyroid patients. Clin Sci (Lond) 1979;57:375–84.
35. Vanholder R, Sever MS, Erek E, Lameire N. Rhabdomyolysis. J Am Soc Nephrol 2000;11 (8):1553-61.

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