CLINICAL VIGNETTE

Effect of Hypothyroidism and Thyroid Replacement on Renal Function Biomarkers

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Abstract

Over the last century, multiple studies emerged showing the correlation between thyroid diseases and renal function. The kidney-thyroid disease interplay could be bidirectional; altered kidney function may contribute to thyroid disorders and the thyroid hormones may directly affect the kidney.[1] Thyroid hormones influence the renal function by altering kidney structure, development, hemodynamics and salt and water homeostasis, as well as systemic metabolic, hemodynamic, and cardiovascular effects.[2] As a result of this close link between the two organs many patients with a history of hypothyroidism are misdiagnosed with chronic kidney disease.

We report a young male adult with a history of hypothyroidism who presented for an annual physical examination when he was found to have decreased estimated glomerular filtration rate (eGFR), elevated serum creatinine, and normal cystatin C levels. We noticed a significant change in the kidney function markers after normalization of thyroid tests with administration of levothyroxine.

Case Presentation

A 23-year-old male with past medical history of obesity, prediabetes, beta-thalassemia minor, and Graves' disease status post radioiodine ablation presented for an annual physical examination with the complaint of generalized fatigue. He had a history of thyrotoxicosis at age 16 in 2017 at which time he had his first ablation and again in 2018. The patient was placed on levothyroxine 150 mcg daily at the time, but in July 2019, he stopped the medication on his own when he moved to the West Coast. Over the subsequent three months while off levothyroxine, he noted a 20-lb weight gain, generalized fatigue, and constipation. He did not have difficulty urinating, flank pain, or a history of recurrent urinary tract infections or nephrolithiasis. The patient denied taking any medication or drugs including nonsteroidal anti-inflammatories, herbal supplements or synthetic marijuana. Vital signs were within normal limits and physical examination was generally unremarkable. His body mass index was 32.1 kg/m2 (6 ft 1 in and 244 lb. Lab work initially showed a markedly elevated TSH >200 mcIU/mL (0.3-4.7 mcIU/mL) with an undetectable T4. His serum creatinine was 1.66mg/dL with eGFR 57 mL/min/1.73m2 using CKD EPI-creatinine equation. He was also noted to have a microcytic anemia with a hemoglobin 11.7 g/dL. Over the next two weeks, the patient had repeated testing confirming an elevated serum creatinine (1.62 and 1.99 mg/dL) and showed cystatin C within normal limits (0.6 and 0.7 mg/L). The eGFR using the CKD EPI-creatinine cystatin equation was 94 and 79 mL/min/1.73m2, respectively. Urinalysis was unremarkable with no red or white blood cells. Urine albumin/creatinine and protein/creatinine were not detectable.

The patient restarted levothyroxine 175mcg daily. His symptoms improved and he lost 8 lb. Lab testing was repeated at 7 weeks and 5 months. Thyroid studies showed a mild elevation in TSH 11.9 and 10.5 mcIU/mL and normalization of free T4 1.6 and 1.6 ng/dL (0.8 - 1.7 ng/dL), respectively. Kidney function biomarkers showed a decrease in serum creatinine to 1.03 and 1.01 mg/dL with an increase in cystatin C to 0.9 and 0.8 mg/L, respectively. The eGFR using the CKD EPI-creatinine equation was 102 and 104 mL/min/1.73m2; the eGFR using CKD EPI-creatinine cystatin equation was 102 and 112 mL/min/1.73m2. The patient noted adherence to levothyroxine during this period in time but did not follow up with endocrinology until 5 months after re-initiation of levothyroxine to discuss an adjustment in dose.

Discussion

The physiological link and functional relationship between the kidneys and thyroid gland has been the subject of many publications in the past, it was noted that renal manifestations in thyroid disorders are reversible with treatment, and using serum creatinine to evaluate renal function may be deceiving in patients with hypothyroidism as it decreases back to baseline once the euthyroid state is achieved. The underlying mechanism may be a decrease in creatinine clearance and increase in creatinine release from muscle cells.[3] This raised a question about the reliability of specific kidney function biomarkers used to assess renal function in thyroid diseases. Renal function in the clinical setting is evaluated widely through the use of serum creatinine and less frequently but in many situations more accurately, serum cystatin C.

Cystatin C is a low molecular weight protein that is produced by most of the nucleated cells at a constant rate. It is freely filtered at the glomerulus and completely reabsorbed and catabolized by cells of the tubules. Its production is not influenced by inflammatory states and has no correlation to muscle mass. Compared to serum creatinine, it has a lower inter-individual variability. Cystatin C can be a reliable marker for estimation of GFR in healthy individuals, children and in

patients with renal disorders of rheumatologic, nephrologic, and neoplastic origin, and is likely superior to serum creatinine in those populations.[3] However, cystatin C levels are affected by thyroid states. It is lower in hypothyroidism and elevated in hyperthyroidism.[3-5] The production rate of cystatin C may be altered in the setting of thyroid dysfunction from a change in cell turnover and/or metabolic rate.[6]

Our patient case is consistent with findings in previous studies that the serum creatinine rises and cystatin C decreases in hypothyroidism. To determine which renal function biomarker is more reliable in thyroid dysfunction, gold standard testing for GFR has been studied. Karanikas et al performed 51Cr-EDTA isotopic renal scans in patients with severe hypothyroidism due to thyroidectomy before and after thyroid hormone replacement. Both a fall in serum creatinine (1.30±0.44 versus 1.04±0.32 mg/dl) and an increase in GFR (61±18 versus 75±23 ml/min) by 51Cr-EDTA clearance were seen.[7] In another study of hypothyroid patients, GFR measured by 52Cr-EDTA clearance increased from 99.6±32.2 to 125.76±41.2 ml/min after thyroid hormone replacement. The renal plasma flow rate measured by 131I-hippuran clearance was shown to increase as well.[8] A third pediatric case report from Japan evaluated the GFR using inulin clearance in one hypothyroid and one hyperthyroid patient and the results were consistent with the above.[9]

The findings from gold standard testing for GFR confirm that changes in serum creatinine in patients with hypothyroidism do reflect actual changes in GFR. Cystatin C should not be used in the assessment of GFR in thyroid disease. In addition, screening for hypothyroidism should be considered in patients with unexplained elevations in serum creatinine.

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