Hypothyroidism as an Obstacle to the Resolution of Acute Kidney Injury

Akut Böbrek Hasarı İyileşmesini Engelleyen Önemli Bir Neden: Hipotiroidism

ABSTRACT

We described the clinical course of 4 patients with acute kidney injury (AKI) in whom kidney function improvement was delayed because of concomitant hypothyroidism. After initiating thyroid hormone replacement therapy, the kidney function improved partially or completely. We discussed the underlying possible pathophysiological mechanisms of delayed recovery. A 33-year-old female presented with kidney failure following severe preeclampsia. She was diagnosed with hypothyroidism. The second case was a 70-year-old male who was healthy previously, and presented with elevated serum creatinine. The third patient was a 72-year-old female, who was admitted with non-oliguric AKI associated with aminoglycoside and non-steroid anti-inflammatory drug exposure. The fourth patient was a 60-year-old female under amiodarone treatment after coronary bypass grafting who presented with fatigue, and AKI. We suggest that delayed recovery of kidney dysfunction might be associated with hypothyroidism that prevents regeneration of tubular cells.

KEY WORDS: Acute kidney injury, Hypothyroidism, Thyroid hormone replacement therapy

ÖZ

Akut böbrek hasarının (ABH) mortalite ve morbiditesi yüksektir. Eşlik eden sistemik hastalık varlığında iyileşmesi zorlaşır ve gecikir. Hipotiroidi, tanı konulmadığı ve tedavi edilmediği durumda ABH iyileşmesini engelleyebilir. Eşlik eden hipotiroidi nedeni ile iyileşmesi geciken 4 ABH olgusunu takdim ettik. İlk olgu olan, ciddi pre-eklampsi sonrası ABH gelişen 33 yaşındaki kadın hastada hipotiroidi tespit edildi. İkinci olgu hiçbir sistemik hastalığı olmayan 70 yaşında bir erkek, diğeri ise aminoglikozid ve non-steroid anti inflamatuvar ilaç kullanımına bağlı non-oligürik ABH gelişen 72 yaşında kadın hastaydı. Son olgu ise koroner bypass operasyonu sonrası amiodaron tedavisi altında ABH ile başvuran 60 yaşında kadın hastaydı. Tüm hastalarda, eşlik eden hipotiroidi tespit edildi. Tiroid hormon replasman tedavisi başlandı ve sonrasında ABH tam ya da kısmi olarak iyileşti. Yazımızda ABH iyileşmesinin gecikmesinde hipotiroidi ile ilişkili olabilecek patofizyolojik mekanizmalar tartışıldı. Hipotiroidism, tübüler hücrelerin rejenerasyonunu engelleyerek böbrek fonksiyonlarının iyileşmesinin gecikmesine neden olabilir. Ayrıca tedavi edilmediği durumlarda ABH iyileşmesini engelleyebilir.

ANAHTAR SÖZCÜKLER: Akut böbrek hasarı, Hipotiroidi, Tiroid replasman tedavisi

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INTRODUCTION

An association between impaired kidney function and hypothyroidism has been reported in a few case reports. This important association is usually overlooked. Kidney injury might be secondary to rhabdomyolysis. If ischemic or nephrotoxic acute kidney injury (AKI) due to other causes is superimposed with hypothyroidism, recovery of kidney function deteriorates. Histological changes, water and electrolyte disorders, altered intrarenal hemodynamics are established effects of hypothyroidism on kidney function.

Acute injury of renal tubular cells by ischemia or nephrotoxic medications results in necrosis, apoptosis, and detachment of cells from the tubular basement membrane.

Recovery from ischemic and nephrotoxic AKI depends on regeneration of damaged tubular cells. Renal stem or progenitor cells outside the nephron migrate into the damaged nephrons and then regenerate the tubules (1, 2). Several studies suggest that there is a very delicate and dynamic relationship between tissue repair and progression or regression of renal injury (2). A number of renal tissue derived growth factors such as hepatocyte growth factor (HGF) and insulin-like growth factor 1 (IGF-1), which act as autocrine or paracrine regulators, are involved in the repair process. Triiodothyronine (T3) has been shown to modify the expression of various genes/proteins involved in the cell cycle, regeneration and the repair process (3, 4). There are reports suggesting deterioration of kidney function in association with hypothyroidism (5). Herein we present 4 cases of AKI with different etiologies where the renal function did not improve at expected time. The patients were diagnosed with profound hypothyroidism. After thyroid hormone replacement therapy (THRT), the renal dysfunction partially or completely improved.

Case 1: A 33-year-old female patient developed severe preeclampsia at the 30th week of pregnancy. Pregnancy was terminated via urgent caesarean section due to in utero fetal death and HELLP syndrome (urea: 73 mg/dL, creatinine: 2.4 mg/dL, AST: 394 IU/L, ALT: 73 IU/L, LDH: 1300 IU/L). Urea and creatinine levels continued to increase for 5 days after delivery despite 4000-4500 cc diuresis per day (urea: 350 mg/dL, creatinine: 7.4 mg/dL) and remained high for 3 weeks. The patient underwent 4 sessions of hemodialysis (HD). Routine thyroid hormone profile (THP) revealed hypothyroidism (TSH: 16.3 uIU/ml (0.350-4.940), free T3: < 1pg/ml (1.71-3.71), free T4: <0.25 pg/ml (0.70-1.48). Thyroid hormone replacement therapy (THRT) was started and her AKI completely recovered in parallel with thyroid function tests after 3 weeks.

Case 2: A 70-year-old male patient presented with oliguric AKI. Antibiotic-associated interstitial nephritis was diagnosed. After 2 sessions of HD treatment, his urine output increased to 9000 cc/day and the kidney function started to resolve. On the 8th day, complete anuria developed. Renal artery thrombosis, urinary obstruction and prerenal factors were ruled out. THP was checked and showed hypothyroidism (TSH: 107 uIU/ml, free T3: 1.58 pg/ml, free T4: 0.49 pg/ml). THRT was started and the kidney function recovered completely in parallel with the thyroid function in two weeks.

Case 3: A 72-year-old female was admitted with non-oliguric AKI associated with aminoglycoside and non-steroid anti-inflammatory drug usage. The patient did not need HD and her creatinine level persisted around 5 mg/dl for 1 month. Hypothyroidism was suspected and THP revealed TSH: 23 uIU/ml, sT3: <1 pg/ml, and sT4: 0.69 pg/ml. After onset of THRT, the kidney function partially improved and the creatinine level decreased to 2.5 mg/dL and stabilized.

Case 4: A 60-year-old female patient with coronary heart disease developed AKI 5 months after coronary by-pass surgery. No obvious etiology could be found. The patient had a recent 4-month history of amiodarone treatment. THP was checked and revealed hypothyroidism (TSH: 215 uIU/ml, sT3: <1 pg/ml, and sT4: 0.4 pg/ml). After THRT, the kidney function completely recovered in three weeks.

DISCUSSION

In contrast to the heart and brain where ischemia results in permanent cell loss, the kidney has huge regenerative potential and can repair completely after injury; however, recovery from renal injury requires complex mechanisms and the recovery process may not be complete. Incomplete recovery may result in chronic and end-stage renal disease. Some growth factors, cell cycle and anti-apoptotic factors, and renal progenitor cells are included in this process (2). Epidermal growth factor (EGF), hepatocyte growth factor (HGF), and insulin-like growth factor I (IGF-1), administered to animals subjected to renal ischemia, reduce the extent of renal dysfunction and accelerate the recovery of the kidney (6, 7). Thyroid hormone is essential for normal development, growth, neural differentiation, and metabolic regulation in humans. Thyroid hormone receptors (THR) therefore have a wide distribution throughout the body, as also shown in the kidney (8). Using a rat hepatic stellate cell line, T3 was shown to stimulate HGF measured by ELISA (3). Furthermore, T3 directly stimulates transcription of the IGF-1 gene in osteoblast-like cells prepared from neonatal rat calvariae (9). A few experimental studies have evaluated the response of EGF to T3 replacement. Both studies have shown an increased level of EGF with the action of T3 (10, 11). Although AKI has been reported with hypothyroidism, these cases were generally secondary to rhabdomyolysis (12, 13). In our cases, although there was adequate urine output after recovery from the oligoanuric period, we did not observe the expected improvement in renal function and the dialysis requirement continued in some cases. Our first patient developed polyuria after termination of pregnancy due to preeclampsia and was free of hemolysis findings but uremic symptoms continued. Thyroid function tests were requested on suspicion of hypothyroidism and profound hypothyroidism was diagnosed. After replacement therapy with the T4/T3 mixture, the renal function rapidly improved. With this experience, we looked for hypothyroidism in patients whose renal function had not improved at the expected time. In the light of experimental studies, we thought that impaired regenerative capacity of tubular cells or migration of progenitor cells may cause delayed healing or incomplete improvement of kidney function.

In conclusion, hypothyroidism should be considered in AKI patients with no obvious etiology and in patients with a delayed healing period of AKI due to any cause.

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