Risk Factors for Acute Kidney Injury due to Severe Hypothyroidism

Adnan Batman[1], Muhammed Masum Canat[2], Emre Sedar Saygili[3], Ender Besler[2], Duygu Yildiz[4], Feyza Yener Ozturk[5], and Yuksel Altuntas[5]

[1]Koc University Hospital
[2] University of Health Sciences Turkey, Sisli Etfal Training and Research Hospital
[3]Canakkale Onsekiz Mart Universitesi
[4]Siirt Training and Research Hospital
[5]University of Health Sciences Turkey, Sisli Etfal Training and Research Hospital

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Abstract

Objective This study aims to investigate the factors affecting development of acute kidney injury (AKI) due to severe hypothyroidism. Methods This single-centre, retrospective observational study involved patients with primary hypothyroidism and thyroid stimulating hormone (TSH) levels of more than 50 mIU/L at their review in the endocrinology outpatient clinic, between January 2015 and April 2021. Patients whose medical history and laboratory data were complete were included in the study. Demographic and laboratory data of patients with AKI (case group) and without (control group) were compared. Factors affecting the development of AKI were examined by logistic regression analysis. Results A total of 100 patients, 20 (11 male (M), 9 female (F)) in the AKI (case) group and 80 (23 M, 57 F) patients in control group, were included in our study. The median age of the case group (56 years, interquartile range (IQR) 44.3–68.5) was significantly higher than the control group (49 years, IQR 32.3–60; p = 0.027), and the ratio of males to females was significantly higher in the case group (p = 0.001). Multivariate logistic regression analyses showed that hypothyroidism diagnosed after the age of 60 years (odds ratio (OR) 59.674, 95% confidence intervals (CI) 5.955–598.031; p = 0.001), free triiodothyronine (FT3) < 1.3 pg/mL (OR 17.151, 95% CI 2.491–118.089; p = 0.004) and creatine kinase (CK) > 1000 U/L (OR 1.522, 95% CI 1.602–82.848; p = 0.015) were predictors for the development of AKI due to severe hypothyroidism. Conclusion We recommend close follow-up and monitoring of patients with AKI caused by severe hypothyroidism if aged > 60 years, CK > 1000 U/L or FT3 < 1.3 pg/mL.

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Conclusion

We recommend close follow-up and monitoring of patients with AKI caused by severe hypothyroidism if aged > 60 years, CK > 1000 U/L or FT3 < 1.3 pg/mL.

KEYWORDS

Hypothyroidism, Acute kidney injury, Free T3**,** Creatine kinase.

INTRODUCTION

Thyroid and renal function have well-documented associations. Thyroid hormones (TH) are required for kidney growth and for development and maintenance of water and electrolyte balance. Thyroid dysfunction affects kidney function, and renal failure affects thyroid hormone metabolism in the peripheries as well as the hypothalamic-pituitary-thyroid axis (1). TH are necessary for the kidney to complete its functional growth and for the development, preservation and maintenance of glomerular function (2). Overt hypothyroidism in particular has been linked to a reduction in glomerular filtration rate (GFR) and renal blood flow (RBF) (3). Cases of acute kidney injury (AKI) due to severe hypothyroidism have been reported in the literature. Since AKI due to severe hypothyroidism is rare, the number of cases is insufficient for publication beyond case series (4). The glomerular function is more impaired than tubular function during severe hypothyroidism. In severe hypothyroidism, a reduction in RBF has been documented, which is most likely due to the overall hypodynamic circulation, reduced cardiac output due to myocardial impairment, sinus bradycardia, and the reduced inotropy and chronotropy due to lower levels of TH (5). However, the risk factors of AKI due to severe hypothyroidism has not been fully elucidated. This study aimed to investigate the factors that affect the development of AKI in patients with severe hypothyroidism.

MATERIALS AND METHODS

Study design

This study was designed as a retrospective, cross-sectional study. The local ethical committee approved the study protocol (07.07.2020/1601), and the study was conducted following the ethical principles stated in the Declaration of Helsinki.

The study included patients who were reviewed in our hospital between January 2015 and April 2021 and had primary hypothyroidism with thyroid stimulating hormone (TSH) levels of more than 50 mIU/L. At the time of presentation, each patient's demographic information (gender and age), medication history and atherosclerotic risk factors (history of smoking, alcohol use, dyslipidaemia, hypertension (HT) and diabetes mellitus (DM)) were documented. Patients were excluded if they were currently pregnant or under 18 years of age, with myxedema coma, had an GFR<15 mL/min/1.73 m2, were receiving maintenance renal replacement therapy, had chronic liver disease, concomitant malignancies, stroke, pulmonary embolism, immunological disease or chronic heart failure, or had recently received treatments known to affect renal function, such as nonsteroidal anti-inflammatory drugs, diuretics, contrast agents or certain antibiotics. The height and weight of the participants were recorded, and the body mass index (BMI) was calculated by dividing the weight (kg) by the square of their height (m).

All blood samples were taken after eight or more hours of fasting. All laboratory analyses were performed in the same laboratory. Free thyroxine (FT4), free triiodothyronine (FT3) and TSH were analysed using the

electrochemiluminescence immunoassay method (Roche Diagnostics GmbH, D-68298 Mannheim, Germany). The GFR was estimated using the National Kidney Foundation's simplified Modification of Diet in Renal Disease (MDRD) calculation, as follows (6,7):

GFR = 175 × (serum creatinine)-1.154 × (age)-0.203 × (0.742 if female) × (1.212 if African American).

where units for GFR are mL/min/1.73 m2 and creatinine mg/dL.

Acute kidney injury was defined as an increase in creatinine levels of 0.3 mg/dL (26.4 μmol/L) or 50% from baseline in less than 48 hours, or a reduction in urine output to less than 0.5 mL/kg/h for more than six hours (6). Patients with AKI were included in the case group and patients without AKI in the control group.

Statistical analysis

Kolmogorov-Smirnov and Shapiro-Wilk tests were used to test for normality. Correlation of risk factors with outcome were analysed independently (univariate analysis) by either Student's t-test or Mann-Whitney U-test where applicable. The differences in proportions between groups were compared by using the chi-squared or Fisher's exact test, where appropriate. Descriptive statistics were used to summarise the data and are presented as median (interquartile range (IQR) or odds ratio (OR)) for skewed continuous variables, and count with the percentage of total for categorical variables. In order to define risk factors for AKI secondary to severe hypothyroidism, univariate and multivariate binary logistic regression analyses were performed; ORs and confidence intervals (CI) were calculated. All statistical analyses were carried out on Windows using the SPSS v23 programme (SPSS Inc., Chicago, IL, USA). A p value of less than 0.05 was taken as statistically significant.

RESULTS

Between January 2015 and April 2021, 2226 patients with TSH > 50 mIU/L were identified. A total of 100 patients, with complete retrospective demographic and laboratory data were included in our study. Twenty patients (11 males (M), 9 females (F)) were included in the AKI group (cases) and 80 (23 M, 57 F) were included in the control group. The median age of the AKI group was 56 years (IQR 44.3–68.5), and the median age of the control group 49 years (IQR 32.3–60). The median age, the median age at diagnosis of hypothyroidism and the proportion of males were significantly higher in the cases than in the control group ($p = 0.027$, $p = 0.001$ and $p = 0.001$ respectively). There was no difference between the groups in weight, BMI, duration of hypothyroidism, rate of newly diagnosed or daily levothyroxine dose per kg. The rate of treatment (TH replacement therapy) discontinuation and treatment discontinuation time were significantly higher in the case group ($p = 0.040$ and $p = 0.049$ respectively). While there was no difference in the rates of cardiovascular disease (CVD), heart failure, obstructive sleep apnoea or hyperlipidemia, the rates of HT and DM were significantly higher in the case group ($p < 0.001$ and $p = 0.002$ respectively). Alcohol consumption, cigarette use, fibrate use as risk factors for rhabdomyolysis and AKI did not differ between the groups, but the rate of statin use was found to be higher in the case group ($p = 0.002$) (Table 1).

There was a significant difference between the groups in levels of urea, creatinine, GFR, creatine kinase (CK), uric acid, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, FT4, FT3 and potassium ($p = 0.001$, $p < 0.001$, $p < 0.001$, $p = 0.010$, $p < 0.001$, $p = 0.036$, $p = 0.047$, $p = 0.001$, $p < 0.001$ and $p = 0.027$ respectively) (Table 2).

The binary logistic regression analyses are shown in Table 3. In the univariate logistic regression analyses, male gender (OR 0.330, 95% CI 0.121–0.902; $p = 0.031$), age > 60 years (OR 0.222, 95% CI 0.080–0.621; $p = 0.004$), hypothyroidism diagnosed after age 60 years (OR 0.127, 95% CI 0.035–0.511; $p = 0.462$), presence of DM (OR 0.156, 95% CI 0.042–0.580; $p = 0.006$), presence of HT (OR 0.074, 95% CI 0.023–0.235; $p < 0.001$), hyperuricaemia (OR 0.110, 95% CI 0.024–0.503; $p = 0.004$), CK > 1000 U/L (OR 0.246, 95% CI 0.082–0.739; $p = 0.012$), FT4 < 0.2 ng/dL (OR 0.241, 95% CI 0.083–0.700; $p = 0.009$), FT3 < 1.3 pg/mL (OR 0.080, 95% CI 0.019–0.345; $p = 0.001$) and statin use (OR 0.120, 95% CI 0.026–0.557; $p = 0.007$) were statistically significant predictors for the occurrence of AKI due to severe hypothyroidism. Multivariate logistic regression analyses showed that age greater than 60 when diagnosed with hypothyroidism (OR 59.674,

95% CI 5.955–598.031; p = 0.001), FT3 < 1.3 pg/mL (OR 17.151, 95% CI 2.491–118.089; p = 0.004), CK > 1000 U/L (OR 11.522, 95% CI 1.602–82.848; p = 0.015) were predictors for the development of AKI associated with severe hypothyroidism.

DISCUSSION

This is the first study in the literature to examine the risk factors for AKI due to severe hypothyroidism. Male gender, age greater than 60 years, age at diagnosis of hypothyroidism greater than 60, statin use, presence of DM, presence of HT, hyperuricaemia, CK > 1000 U/L, FT4 < 0.2 ng/dL, FT3 < 1.3 pg/mL were identified as possible contributing factors to the development of AKI in the univariate analyses. In the multivariate analyses, age at diagnosis of hypothyroidism > 60 years, CK > 1000 U/L and FT3 < 1.3 pg/mL were observed as predictors for development of AKI.

Severe hypothyroidism can have various effects on the biological structure and functioning of the kidneys. In severe hypothyroidism, histological abnormalities such as thickening of both tubular and glomerular basement membranes have been observed (7). In some studies, proteinuria has been observed in hypothyroid patients and is associated with the severity of hypothyroidism (8). In addition, hypothyroidism has been linked to a variety of glomerulopathies, including membranous glomerulopathy, minimum-change nephropathy and membranoproliferative glomerulonephritis, with thyroxine therapy alleviating urine protein loss (9,10).

Rhabdomyolysis is an important and life-threatening complication of severe hypothyroidism. Cases of AKI due to rhabdomyolysis caused by hypothyroidism have been reported in the literature (11). The risk of rhabdomyolysis increases with a CK value of >1000 U/L (12,13), and that CK > 1000 U/L increases the risk of AKI three-fold (14). Supporting this, in our study, CK values were significantly higher in the AKI group, and CK > 1000 U/L was observed as a risk factor for the development of AKI.

Male gender was shown to be another factor that increased the risk of AKI due to severe hypothyroidism in our study. Epidemiological studies have observed that chronic kidney disease is more common in females (15). This is because females have a longer life expectancy than males and that GFR decreases with age. However, the risk of AKI and the proportion of patients with chronic kidney disease receiving renal replacement therapy were found to be higher in males in epidemiological studies . Possible reasons for this include the protective effects of oestrogen in women, the harmful effects of testosterone, and an unhealthy lifestyle and busy work-life in males (15,16,17).

Studies have reported that TSH levels increase with age, and follow-up is recommended until high TSH levels are <8 mIU/L, especially in older patients (18). As age increases, renal function decreases; patients become more susceptible to prerenal AKI, and GFR may decrease (19). Hypothyroidism has been linked to decreased renal plasma flow (RPF), and inadequate effective RBF. The hypodynamic condition of the vascular system caused by hypothyroidism is hypothesised to be the cause of the reduction in GFR and RBF (20). High TSH levels have been found to be negatively correlated with RPF, RBF and GFR due to high vascular resistance in afferent renal arterioles. It has also been shown that the TH relaxes arteries and reduces arterial resistance (3). The elderly are at risk of renal dysfunction due to the hypodynamic circulation caused by severe hypothyroidism. In support of this, our study showed that being over 60 years old or age greater than 60 at the time of diagnosis of hypothyroidism were risk factors for development of AKI due to severe hypothyroidism.

Although the TSH levels in the AKI and control groups were not different in our study, other studies has shown that an increase in TSH is related to a decrease in RBF and a decline in GFR (3). The fact that all of the patients in this study had severe hypothyroidism may explain for the lack of differences in TSH values. Besides, it has been observed that FT4 levels are strongly associated with changes in renal function changes, including after treatment with levothyroxine (21). Peripheral TH may cause activation of the renin-angiotensin and sympathetic systems, and affect renal vascular compliance through actions on the nuclear receptor (22). TH, especially FT3, are particularly associated with renal tubular function, which induces increased expression of mRNA encoding alpha and beta subunits of the Na+/K+-ATPase enzyme (23). Since there are no studies on this subject in the literature, it is not possible to define the level of FT3 or

FT4 that increases the risk of AKI. In our study, it was observed that FT3 below the median value in both the univariate and multivariate analyses was a statistically significant risk factor for the development of AKI secondary to severe hypothyroidism.

The length of time that a patient has been hypothyroid, independent of the TSH level, may also increase the risk of renal dysfunction. In our study, treatment discontinuation time in the AKI group was found to be statistically higher than in the control group. Although the discontinuation time does not appear to affect the development of AKI, the authors believe that a longer time of treatment discontinuation has a greater effect on the decrease in RBF and GFR. The hypodynamic circulation due to TH deficiency may also be implicated in AKI formation in the chronic period.

There are many studies in the literature regarding the relationship between serum uric acid levels and kidney function. A negative association has been found in most studies, but not confirmed in others (24). Furthermore, as an inflammatory marker, high blood uric acid levels have various physiological effects on renal function, hypertension, and CVD development, including endothelial dysfunction (24,25). In the current study, hyperuricaemia, in addition to the vascular and renal implications of severe hypothyroidism, was discovered to be a risk factor for AKI in the univariate analysis.

Due to the effects of hypothyroidism on the renal glomerular and vascular structure, the presence of a disease that may affect kidney baseline function may increase the risk of AKI. Hypertension and diabetes are the most common causes of chronic kidney disease and are associated with poor renal outcomes, including in patients with hypothyroidism (26). In diabetic patients, a reduction in GFR is seen in parallel with an increase in TSH. In addition, the incidence of diabetic nephropathy increases with increasing TSH values (27). It is already predictable that the presence of traditional AKI risk factors such as DM and HT will increase the risk of AKI due to severe hypothyroidism , as in our study.

Myopathy due to severe hypothyroidism, elevated CK, hypovolaemia and electrolyte abnormalities increases the risk of rhabdomyolysis (11). In cross-sectional studies, statin therapy increases the risk of rhabdomyolysis due to the possibility of inducing immune-mediated necrotising myopathy and CK elevation, and via other mechanisms (28,29). For these possible reasons, in our study, statin use was one of the factors affecting the development of AKI due to severe hypothyroidism.

The present study, being retrospective, and investigating a rare disease, has several limitations. First, all the patients were recruited from a single centre, and the sample size was relatively small. Second, several potentially relevant factors, such as the duration of chronic illness, genetic predisposition and race, were not investigated. However, there is little research on severe hypothyroidism; our study focused on patients with AKI due to severe hypothyroidism, which is rarer. Randomized prospective studies with more patients participating in terms of risk factors for AKI due to severe hypothyroidism independent of classical AKI risk factors (such as DM and HT) will contribute to the literature.

AKI due to severe hypothyroidism is an important and life-threatening complication. We recommend close follow-up and monitoring in hypothyroid patients who are diagnosed at age > 60 years, or whose CK is greater than 1000 U/L, or FT3 less than 1.3 pg/mL.

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ETHICAL APPROVAL

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This article does not contain any studies with animals performed by any of the authors. Institutional review board/Ethics Committee has approved the study.

INFORMED CONSENT

Informed consent was obtained from all individual participants included in the study. The article has not been presented at any conference or meeting.

DISCLOSURES

The authors declare that they have no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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