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Hyperthyroidism influences renal function

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Abstract

Purpose While the effects of hypothyroidism on renal function have been studied extensively, there is less information concerning the effect of hyperthyroidism. We aimed to elucidate the effect of overt and subclinical hyperthyroidism, on estimated glomerular filtration rate (eGFR) with large number of patients treated for hyperthyroidism and after euthyroidism was achieved.

Method A total of 433 consecutive overt and subclinical hyperthyroid patients were included in the study. We assessed serum fT3, fT4, TSH, BUN, creatinine, and eGFR measurements during both hyperthyroid and euthyroid states of the same patients. The eGFR was calculated using the simplified modification of diet in renal disease (MDRD) Formula.

Results Among these patients, 367 had overt, and 66 had subclinical hyperthyroidism. fT3, fT4, and eGFR measurements decreased, meanwhile BUN, creatinine and TSH levels increased significantly after euthyroidism was achieved ($p < 0.0001$ for all). The correlation analyses revealed that eGFR in hyperthyroid state (eGFRh) and fT3 in hyperthyroid state (fT3h) ($r = 0{,}210$, $p < 0{,}0001$), and fT4 in hyperthyroid state (fT4h) ($r = 0{,}176$, $p < 0{,}0001$) were significantly correlated. ΔGFR did not differ between overt hyperthyroid group and subclinical hyperthyroid group.

Conclusions We observed a significant decline in eGFR measurements after the patients became euthyroid. Some of these patients had lower values than 60 mL/min/1.73 m^2, which mean that hyperthyroidism may be masking mild renal failure.

Keywords eGFR · Creatinine · Hyperthyroidism · Renal function

Introduction

Thyroid hormones stimulate renal growth and development, glomerular filtration rate (GFR), and sodium and water homeostasis. Hypothyroidism affects glomerular and tubular functions and also changes dynamics of the renin–angiotensin system. In experimental studies hypothyroidism has been associated with reduction in kidney weight and tubular mass, as well as adverse changes in glomerular architecture. Conversely, kidney to body weight ratios in hyperthyroid animals increase by as much as 30%. The mechanism is not fully understood but the role of the renin–angiotensin system has been proposed [1].

While the effects of hypothyroidism on renal function have been studied extensively, there is less information concerning the effect of hyperthyroidism. We have previously shown that eGFR measured in 706 hypothyroid patients, improved significantly after euthyroidism was achieved [2]. Thyroid hormone (TH) stimulates angiogenesis, increases cardiac output by positive inotropic and chronotropic effects, stimulates the renin-angiotensin system and increases renal blood flow [3]. All of these effects are expected to result in increased eGFR in hyperthyroidism. Very few studies with small number of patients investigated the effect of hyperthyroidism on eGFR. Hollander et al. investigated the effect of thyroid hormone abnormalities on renal function in 37 consecutive patients with untreated primary hypothyroidism (autoimmune thyroiditis) and 14 patients with untreated hyperthyroidism due to Graves' disease, and found that eGFR (calculated with MDRD formula) improved significantly during treatment of

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hypothyroidism, and decreased during treatment of hyperthyroidism [4]. Kimmel et al. compared different methods of eGFR in nine hypothyroid and seven hyperthyroid subjects [5]. When fT4 normalized, serum creatinine increased significantly, and creatinine-based GFR estimations decreased significantly in hyperthyroid patients.

As there is no clinical study on human subjects with enough power to determine the effect of hyperthyroidism on renal functions, we aimed to elucidate the effect of overt and subclinical hyperthyroidism, on eGFR with large number of patients treated for hyperthyroidism and after euthyroidism was achieved.

Materials and methods

We investigated retrospectively the files of 1115 adult Caucasian patients referred to Internal Medicine and Endocrinology departments for the evaluation of hyperthyroidism between January 2012 and December 2017. After excluding patients without serum BUN, serum creatinine, free T3 (fT3) and free T4 (fT4) in addition to TSH measurements, 433 overt and subclinical hyperthyroid patients were included in the study. Exclusion criteria were pregnancy, eGFR ≤45 ml/min/1.73 m^2, chronic liver failure, chronic heart failure, taking recently medications known to affect renal function such as contrast agents, nonsteroid anti-inflammatory drugs, antibiotics, and diuretics. The study was approved by Kecioren Teaching and Research Hospital Clinical Research Ethics Committee (number: 1515).

We assessed serum fT3, fT4, TSH, BUN, creatinine, and eGFR measurements during both hyperthyroid and euthyroid states of the same patients. The eGFR was calculated using the simplified modification of diet in renal disease (MDRD) formula described by the National Kidney Foundation as follows: eGFR (mL/min/1.73 m^2) $= 175 \times (S_{cr})^{-1.154} \times (Age)^{-0.203} \times$ (0.742 if female) × (1.212 if African American) [6]. Serum fT3 (normal 2.2–4.2 pg/ml), fT4 (normal 0.65–1.7 ng/dl), and TSH (normal 0.4–4.2 mIU/l) were measured by means of chemiluminescence methods (Liaison®; DiaSorin S.p.A., Saluggia, Italy). Serum creatinine (normal: 0.84–1.25 mg/dl) was measured by means of the alkaline picrate (Jaffe) method (Konelab, ThermoScientific Inc., Franklin, MA).

Distribution of the continuous variables was determined by the Kolmogorov–Smirnov test. Continuous variables with normal distribution were expressed as mean ± SD. Variables with skew distribution were expressed as median (minimum–maximum), and categorical variables were expressed as percentage. The paired sample *t*-test was used for normally distributed variables and the Wilcoxon rank-sum test for skew-distributed variables. Pearson and Spearman analysis was used to identify correlations between study parameters. For all statistics, a two sided p value <0.05 was considered to be statistically significant. All analyses were performed with SPSS 15.0 for Windows.

Results

Our study involved 433 adult patients (Age: median 47, minimum 20, maximum 76 years old), 254 of whom were female (58.7%), and 179 of whom were male (41.3%). Among these patients, 367 had overt, and 66 had subclinical hyperthyroidism. fT3, fT4, and eGFR measurements decreased, meanwhile BUN, creatinine and TSH levels increased significantly after euthyroidism was achieved ($p < 0.0001$ for all of the statistics with Wilcoxon rank-sum test in whole group, and in both subclinical and overt hyperthyroid subgroups), (Table 1 and Fig. 1). Male patients had higher eGFR in both hyperthyroid and euthyroid states than female patients ($p < 0.0001$).

The correlation analyses revealed that eGFR in hyperthyroid state (eGFRh) and fT3 in hyperthyroid state (fT3h) ($r = 0.210$, $p < 0.0001$), and fT4 in hyperthyroid state (fT4h) ($r = 0.176$, $p < 0.0001$) were significantly correlated. eGFR in euthyroid state (eGFRe) and fT3 in euthyroid state (fT3e) ($r = 0.103$, $p = 0.033$), except for fT4 in euthyroid state (fT4h), were significantly correlated. ΔeGFR were significantly higher in patients with Graves disease [−25.7(13.3–83.4)] than patients with toxic nodular goiter [−11.5(55.9–74.8)], and various types of thyroiditis [−11.1(22.9–62.5)], ($p < 0.0001$). ΔeGFR were significantly higher in younger (≤50 years old) and male patients than older (≥51 years old) and female patients ($p < 0.0001$, and p: 0.03 respectively). ΔeGFR and ΔfT3 levels ($r = 0.246$, $p < 0.0001$), and ΔfT4 levels ($r = 0.179$, $p < 0.0001$) were significantly correlated between hyperthyroid and euthyroid states. $BUN_{Hyperthyroid}/Creatinine_{Hyperthyroid}$ ratio (p: 0.001) and $BUN_{Euthyroid}/Creatinine_{Euthyroid}$ ratio (p: 0,007) were significantly higher in overt hyperthyroid group than subclinical hyperthyroid group. We stratified the whole group into two subgroups according to fT4h levels (subgroup 1 (fT4h < 3 ng/dl), and subgroup 2 (fT4h ≥ 3 ng/dl), in consideration for median fT4), ΔeGFR (p: 0.001) was significantly higher in subgroup 2 (ΔeGFR: −14.8 [minimum:−74.8, maximum: 31.3]) than subgroup 1 (ΔeGFR: −10.6 [minimum:−83.4, maximum: 55.9]), (Fig. 2). Ten patients who had eGFR values above 60 mL/min/1.73 m^2 when they were hyperthyroid, had lower eGFR values than this threshold after they became euthyroid.

Table 1 Demographic findings and comparison of the laboratory measurements in hyperthyroid and euthyroid states [median (minimum–maximum)]

	Hyperthyroid	Euthyroid	p
eGFR (ml/min/1.73 m^2)	103.4 (53.4–203.1) [male: 118 (70.5–203.1), female: 93.6 (53.4–171.2)]	91.1 (54.2–173.8) [male: 105 (67.1–173.8), female: 85.4 (54.2–138.4)]	<0.0001 (for all comparisons)
ΔeGFR (ml/min/1.73 m^2)	−12.2 (55.9−83.4)		NA
	Male: −13.9 (55.9−74.8), female: −9.7 (28−83.4)		0.03
	≤50 years old: −14.3 (55.9 −83.4), ≥51 years old: −9 (29.3 −50.3)		<0.0001
	Overt hyperthyroid: −12.3 (55.9−74.8), subclinical hyperthyroid: −11.2 (29−80)		0.252
BUN (mg/dl)	25 (10–64)	28.6 (11–77)	<0.0001
Creatinine (mg/dl) (*N*:0.84–1.25)	0.69 (0.44–1.06)	0.77 (0.53–1.1)	<0.0001
fT3 (pg/ml) (*N*:2.2–4.2)	6.61 (2.32–35.54)	2.91 (1.03–4.86)	<0.0001
fT4 (ng/dl) (*N*:0.65–1.70)	2.84 (0.71–10.0)	1.02 (0.487–2.89)	<0.0001
TSH (mIU/L) (*N*: 0.4–5)	0.004 (0–0.234)	1.02 (0.4–4.52)	<0.0001

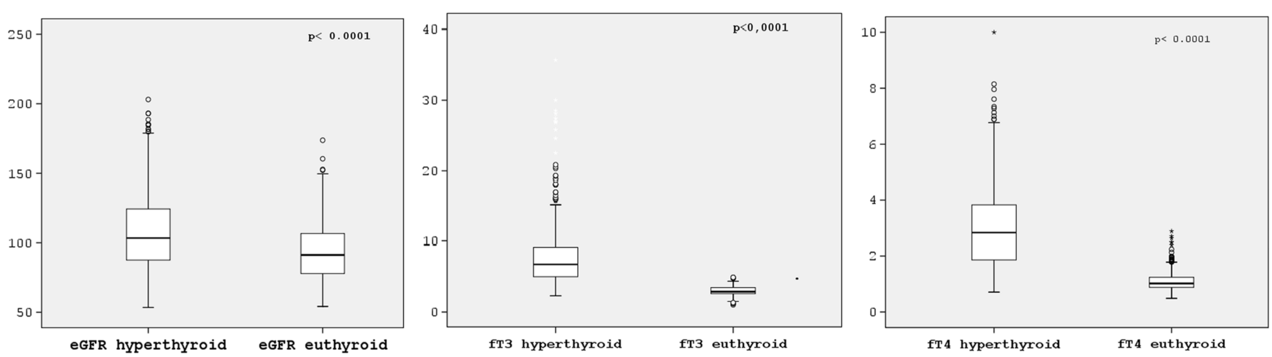

Fig. 1 Comparison of eGFR, fT3, and fT4 in hyperthyroid and euthyroid states

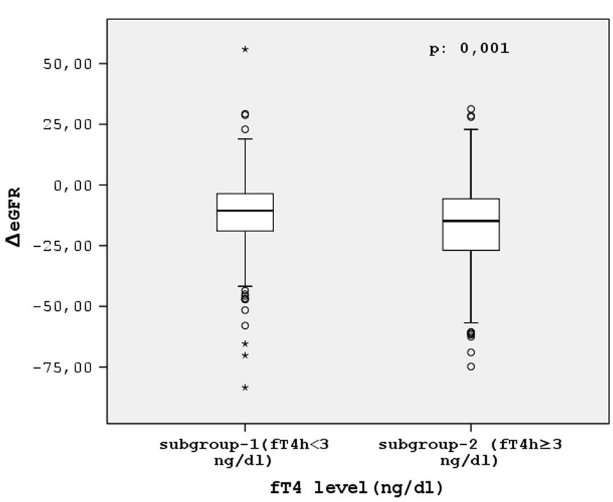

Fig. 2 ΔeGFR according to fT4 levels

Discussion

In this study, we investigated the effect of hyperthyroidism on renal function. We found that fT3, fT4, and eGFR measurements decreased, meanwhile BUN, creatinine, and TSH levels increased significantly after euthyroidism was achieved.

Although the relation between hypothyroidism and kidney function was investigated in several animal and human studies, there are very few studies about hyperthyroidism and kidney function in humans with limited number of subjects. Hollander et al. found that eGFR increased significantly during treatment of hypothyroidism, and decreased during treatment of hyperthyroidism in 37 hypothyroid and 14 hyperthyroid patients [4]. They also found, similar to our study, significant correlation between ΔeGFR and ΔfT4 levels. Kimmel et al compared different methods of eGFR in nine hypothyroid and seven hyperthyroid subjects [5]. When fT4 normalized, serum creatinine increased significantly, and creatinine-based GFR estimations decreased significantly in hyperthyroid patients. The cystatin C-based kidney function test showed complete inverse changes compared to the changes described in creatinine-based kidney function tests. Therefore, they advised that cystatin-C-based equations should be avoided in thyroid disorders. In a cross-sectional study from China, when other factors were eliminated, TSH was found to be significantly correlated with eGFR (MDRD Formula) in 8418 individuals [7]. The researchers concluded that TSH can be used as an independent factor of the chronic kidney disease in a middle-aged normoglycemic euthyroid Chinese population independent of BMI, waist circumference, blood pressure, lipid profile, and fasting blood glucose.

Although there are very few clinical studies, pathophysiology of the effect of hyperthyroidism on kidney was investigated in experimental animal studies. Several mechanisms were found playing roles on increasing both the size and functional capacity of kidney. In hyperthyroid animals beta-adrenergic receptors in kidney cortex, and synthesis and secretion of renin by juxtaglomerular cells are increased, which in turn enhance angiotensin-converting enzyme activity [3]. Previous experimental studies have also shown increased cardiac and renal capillarity and augmented vascularization of the mesenteric bed in hyperthyroid rats [3]. Thyroid hormone directly influences the expression and activity of most of renal transporters by direct binding of thyroid hormone to the promoter region of a transporter gene [1]. Hyperthyroidism increases systolic blood pressure by increasing heart rate, decreasing systemic vascular resistance, raising cardiac output, and increases nitric oxide production which all contribute to the hyperdynamic circulation. Hyperthyroidism results in increased renal blood flow. The activation of renin-angiotensin system and the decrease in the resistance of afferent glomerular arterioles lead to an increase in the glomerular hydrostatic pressure and GRF in animals [3]. We can explain the fall in eGFR in our study with these previous experimental studies, however increase in BUN is not an expected finding. In thyrotoxic state urine concentration capacity is lowered because of direct downregulation of aquaporin 1 and 2 [8]. Therefore one would expect a fall in BUN after euthyroidism was achieved. In a previous clinical study with 53 hyperthyroid patients, mean serum BUN levels decreased after euthyroidism was achieved, however *p* value was not noted before and after treatment of hyperthyroidism [9]. We have previously shown that brain natriuretic peptide (BNP) levels significantly increase in hyperthyroidism, and return to normal values after euthyroidism was achieved [10]. Takase et al. showed that eGFR was inversely correlated with both BNP, and NT-proBNP at all stages of kidney function [11]. Therefore BNP may have a role in increasing eGFR and decreasing BUN and creatinine in hyperthyroidism.

In conclusion, in this study we observed that both BUN and creatinine levels increased significantly after euthyroidism was achieved in hyperthyroid patients, these findings point out to true decline in renal function rather than a mere adaptation to hemodynamic changes. Although the mechanistic link between thyroid and kidney disease remains unclear, hyperthyroidism in addition to hypothyroidism may have significant effect on renal function.

We observed a decline in eGFR below 60 mL/min/1.73 m^2 in 10 patients, which brings about the idea that hyperthyroidism may be masking mild renal pathologies in some patients. It can be advised to check GFR measurements of the patients after they become euthyroid.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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. The study was approved by Kecioren Teaching and Research Hospital Clinical Research Ethics Committee (number: 1515).

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