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Effects of Thyroid Hormone on Urinary Concentrating Ability

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Keywords
Hypothyroidism · Fluid deprivation · Urinary concentrating ability

Abstract
Background: Hypothyroidism has been associated with impaired urinary concentrating ability. However, previous reports on thyroid hormone and urinary concentrating ability in humans only studied a limited number of patients with autoimmune thyroid disease or used healthy controls instead of paired analysis within the same patients. ***Objective:*** To study the urinary concentrating ability in athyreotic patients with differentiated thyroid cancer on and off levothyroxine treatment as they are exposed to different thyroid states as part of their treatment in the absence of an autoimmune disease. ***Design and Methods:*** We studied 9 patients (mean age of 42.7 years) during severe hypothyroid state (withdrawal of levothyroxine before radioactive iodine therapy) and TSH-suppressed state (on levothyroxine therapy). At these two points, serum and urine samples were collected after 14 h of overnight fasting without any food or drink. ***Results:*** Serum and urine osmolality were not significantly different between on and off levothyroxine treatment. Serum creatinine levels were significantly higher in patients off versus on levothyroxine treatment (87.0 vs. 71.0 µmol/L, respectively; $p = 0.044$) and, correspondingly, the estimated glomerular filtration rate was significantly lower (89.6 vs. 93.1 mL/min, respectively; $p = 0.038$). ***Conclusion:*** Short-term, severe hypothyroidism has no effect on urinary concentrating ability. Our study confirms the well-known effects of thyroid hormone on serum creatinine concentrations.

Introduction

Thyroid hormone (TH) is indispensable for the metabolism of all tissues. The importance of TH in normal physiology is well illustrated by primary thyroid diseases in which abnormal TH concentrations affect the function of several organs resulting in a variety of clinical symptoms [1].

The ability to conserve water during periods of water deprivation is an important function of the kidney. Fluid deprivation increases serum osmolality and thereby causes a release of the antidiuretic hormone (arginine vasopressin [AVP]). In turn, in the principal cells of the collecting duct, vasopressin inserts preformed vesicles with the water channel aquaporin-2 into the

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apical plasma membrane to allow water reabsorption [2]. The counter-current mechanism creates the osmotic driving force for water reabsorption in the collecting duct.

Hypothyroidism has been associated with impaired urinary concentrating capacity in animals and humans [3–6]. Short-term hypothyroidism in rats results in a diminished medullary osmotic driving force for passive water movement across the collecting duct. This was associated with a significant decrease in the medullary sodium potassium chloride cotransporter type 2 (NKCC2) [4]. The impaired maximal urinary concentrating capacity in these rats with moderate hypothyroidism was readily reversed with TH replacement. On the other hand, long-term hypothyroidism in rats resulted in an impaired urine dilution capacity after water loading as a result of the nonosmotic release of vasopressin [3]. This defect was reversed by administering a vasopressin receptor antagonist.

Only a few studies on the urinary concentrating defect in hypothyroidism have been performed in patients with autoimmune thyroid disease [5, 6]. A small study ($n = 4$) of patients with hypothyroidism revealed a urinary concentrating defect after 16 h of water deprivation [5]. After adequate treatment with levothyroxine (LT4), this defect was corrected. Another study found similar defects in myxedema patients ($n = 10$) compared to healthy control subjects ($n = 15$) after 16 h of water restriction [6]. Treatment of a small group of these patients ($n = 3$) showed no improvement in urinary concentrating capacity. These studies on TH and urinary concentrating ability in humans only studied a very limited number of patients [5] or used healthy controls instead of paired analysis within the same patients [6]. Furthermore, detailed thyroid function tests were not performed.

The aim of this study was to extend the existing studies by investigating the urinary concentration ability for the first time in athyreotic patients, before and after LT4 treatment. We therefore studied patients with differentiated thyroid cancer (DTC), since they are exposed to different thyroid states as part of their treatment in the absence of autoimmune disease.

Subjects and Methods

DTC patients, 18–65 years old, were recruited from the outpatient clinic of the Erasmus Medical Center Rotterdam between November 2014 and October 2015. Initial therapy consisted of total thyroidectomy. Patients were eligible for inclusion if they were scheduled for treatment with radioactive iodine (RAI); did not use drugs interfering with TH metabolism or drugs influencing urinary concentration capacity (e.g., diuretics, lithium, nonsteroidal anti-inflammatory drugs); did not have a urinary tract infection; had no history of diabetes insipidus, diabetes mellitus or adrenal insufficiency; and had an estimated glomerular filtration rate (eGFR) >60 mL/min per 1.73 m^2. Patients were instructed to abstain from water and food for 14 h before their outpatient visit on two different occasions. The first measurement was scheduled after 4 weeks of TH withdrawal (before RAI therapy, to stimulate radioactive iodine uptake by malignant tissues) and the second a few months after restoring euthyroidism/TSH suppression. Our primary endpoint was the difference in urine osmolality between LT4 withdrawal and treatment. Peripheral blood samples and spot urine samples were obtained from all participants.

Table 1. Characteristics of study participants

Sex, *n* (%)	
Male	4 (44.4)
Female	5 (55.6)
Mean age ± SD, years	42.7±11.0
Median time between tests (25th–75th percentile), days	124 (91–161)
Mean LT4 dose (range), μg	204.2 (150–325)
Mean LT4 dose (range), μg/kg	2.27 (1.6–3.1)
Diagnosis, *n* (%)	
Papillary thyroid cancer	7 (82.5)
Follicular thyroid cancer	2 (12.6)

The Medical Ethics Committee of the Erasmus Medical Center approved the study protocol (MEC-2014-134), and written informed consent was obtained from all study participants.

Laboratory Measurements

Serum free T4 (FT4; reference range 11.0–25.0 pmol/L), total T4 (reference range 58.0–128.0 nmol/L), and total T3 (reference range 1.4–2.5 nmol/L) concentrations were measured by chemoluminescence assays (Vitros ECI Immunodiagnostic System; Ortho-Clinical Diagnostics, Rochester, MI, USA). Serum TSH (reference range 0.4–4.3 mU/L) was measured by immunometric assay (Immulite 2000 XPi, Siemens, The Hague, The Netherlands). Serum and urine osmolality were measured by OM 6050 Osmo Station from A. Menarini Diagnostic, and serum sodium, potassium, urea, creatinine, chloride and glucose concentrations were measured by Roche/Hitachi cobas c systems. The eGFR was computed automatically with the Chronic Kidney Disease Epidemiology Collaboration formula (CKD-EPI). Sodium, urea, and creatinine concentrations were also measured in urine samples by Roche/Hitachi cobas c systems.

Statistical Analysis

Based on the previous studies [5, 6], we postulated that a study in a sample of 10 patients on and off LT4 treatment would be sufficient in size to find a significant difference in urine osmolality. Data were expressed as median with 25th and 75th percentiles. For paired analysis between patients on and off LT4 treatment the Wilcoxon signed rank test was used. We used SPSS 20.0 for Windows (SPSS, Inc., Chicago, IL, USA). The Spearman rank correlation

Table 2. Changes in thyroid function tests and serum electrolytes, creatinine and osmolality

	Off LT4		LT4 treated		*p* value
	median	IQR	median	IQR	
TSH, mU/L	68.4	42.0–102.5	0.049	0.005–0.57	0.008
FT4, pmol/L	1.7	1.2–3.4	24.1	21.5–25.3	0.008
Total T4, nmol/L	17.0	14.0–28.0	146.0	132.0–170.5	0.008
Total T3, nmol/L	0.7	0.6–1.0	2.1	2.0–2.3	0.008
Creatinine, μmol/L	87.0	76.5–92.0	71.0	67.5–89.5	0.044
eGFR, mL/min	89.6	66.4–93.1	93.1	85.8–103.8	0.038
Urea, mmol/L	4.6	3.7–5.1	4.8	4.1–5.2	0.21
Sodium, mmol/L	141.0	138.5–141.5	143.0	142.0–144.5	0.011
Glucose, mmol/L	4.8	4.5–5.1	5.3	4.9–5.6	0.011
Potassium, mmol/L	4.3	4.2–4.5	4.4	4.1–4.6	0.5
Chloride, mmol/L	99.0	97.5–101.5	104.0	102.5–104.5	0.007
Osmolality, mosm/kg	282.0	279.0–284.0	287.0	281.5–288.0	0.09

Data are expressed as median and interquartile range (IQR, 25th–75th percentile).

Table 3. Changes in urine concentrations and osmolality

	Off LT4		LT4 treated		*p* value
	median	IQR	median	IQR	
Osmolality, mosm/kg	630.0	535.0–812.0	765.0	613.0–794.0	0.17
Sodium, mmol/L	84.0	54.5–146.0	141.0	95.5–157.5	0.21
Creatinine, mmol/L	17.2	12.3–28.5	13.7	12.1–20.6	0.09
Sodium/creatinine ratio	5.1	1.9–10.8	11.0	5.1–12.0	0.26
Urea, mmol/L	258.0	190.0–383.0	328.0	274.0–439.0	0.09

Data are expressed as median and interquartile range (IQR, 25th–75th percentile).

coefficient was calculated to evaluate the correlation between urine osmolality and age and thyroid function tests off and on LT4 treatment. A p value <0.05 was considered as statistically significant.

Results

We included 10 patients in the study. However, one of them had started treatment with a diuretic after the first visit and was therefore excluded. Nine patients with a mean age of 42.7 years (range 24–57 years) were analyzed (Table 1). As expected, thyroid function tests were significantly different on and off LT4 treatment (Table 2), reaching very low levels of FT4 (median 1.7 pmol/L) off LT4. Serum creatinine levels were significantly higher (87.0 vs. 71.0 μmol/L; p = 0.044) and the eGFR was significantly lower in the hypothyroid state than in the LT4-treated state (89.6 vs. 93.1 mL/min, respectively; p = 0.038). Serum glucose levels were significantly lower during hypothyroidism (4.8 vs. 5.3 mmol/L; p = 0.011). Serum sodium and chloride levels were significantly higher during LT4 treatment than during hypothyroidism (143 vs. 141 mmol/L; p = 0.011 and 104.0 vs. 99.0 mmol/L; p = 0.007, respectively), while serum osmolality remained similar (287.0 on LT4 vs. 282.0 mosm/kg off LT4; p = 0.09).

Table 3 shows that urinary osmolality was not significantly different between patients on and off LT4 treatment (765.0 vs. 630.0 mosm/kg, respectively; p = 0.17). Figure 1 shows the changes in urinary osmolality within each patient. There was also no significant difference in sodium, urea, and creatinine levels in the urine samples. There was no correlation between urinary osmolality and age, TSH, FT4, total T4, and total T3 levels neither during hypothyroidism nor during LT4 treatment (data not shown).

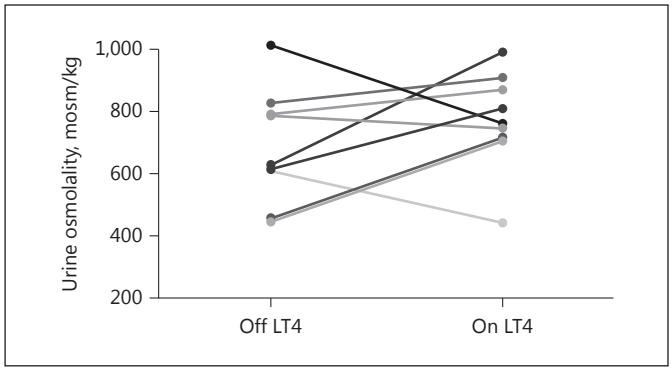

Fig. 1. Changes in urine osmolality off and on LT4 treatment. Each line between two dots represents a patient.

Discussion

In this prospective study in athyreotic DTC patients there was neither a significant difference in urine osmolality nor in serum osmolality on and off LT4 treatment after a water and food deprivation test of 14 h. Since we could not detect an impairment of urinary concentrating ability during severe hypothyroidism in our patients, we did not assess AVP and copeptin concentrations, a stable preprohormone of AVP. Our findings are in contrast with previously published studies in rats [4] and humans [5, 6]. In these previous studies on urinary concentrating ability in humans, detailed thyroid function tests were not performed. The severity of hypothyroidism was predominantly based on clinical characteristics, which is not very precise [7]. In the current study, we confirmed severe hypothyroidism biochemically with a median TSH level of 68 mU/L, and correspondingly low levels of FT4, total T4, and T3. Whereas previous studies were performed in patients with prolonged signs of hypothyroidism (i.e., myxedema), hypothyroidism was present in the current study only for 4 weeks. Although we cannot exclude that there would have been an impaired urinary concentrating ability after prolonged hypothyroidism, the current study excludes important acute consequences of altered thyroid hormone status.

Another speculative explanation for our findings could be that our patients were treated with relatively high dosages of LT4 to establish TSH suppression (median TSH concentration of 0.049 mU/L) because of their thyroid cancer. Although our patients were not overtly thyreotoxic, high TH levels are associated with a hyperdynamic circulation including increased cardiac output and blood pressure and decreased systemic vascular peripheral resistance [8]. These systemic hemodynamic alterations are known to be associated with increased renal hemodynamics and urine flow, which might have decreased the urine osmolality in our LT4-treated patients [9]. This mechanism is supported by Wang et al. [10], who observed in hyperthyroid rats a significant increase in solute excretion in the presence of an AVP-independent downregulation of aquaporin water channels. In healthy human subjects, water deprivation causes the plasma osmolality to rise above 280–290 mosm/kg, which leads to the release of AVP into the circulation. This results in increased water retention with a rise in urine osmolality to a maximum of 1,000–1,200 mosm/kg and restoration of plasma osmolality toward the reference range [11]. Since the median urine osmolality was lower than 1,000 mosm/kg in both thyroid states in our patients, it could be speculated that there was a concentrating defect in both thyroid states, and we were therefore not able to find a statistically significant difference in urine osmolality.

Serum creatinine levels were significantly higher in our patients during hypothyroidism than during LT4 treatment and, correspondingly, eGFR was significantly lower during hypothyroidism. This is in line with several case reports and case series [12–14]. Previous detailed studies have shown that the changes in serum creatinine reflect actual changes in GFR instead of alterations in creatinine metabolism [15–17].

A limitation of our study is the small number of patients, which is a consequence of the steadily growing number of DTC patients that are treated with RAI after preparation with recombinant TSH instead of LT4 withdrawal [18]. A second limitation is the low-iodine diet which patients had to adhere to in order to increase the effectiveness of RAI treatment. Although this diet is different from a "low-sodium" diet, any foods containing iodized salt and sea salt were not allowed [19]. Therefore, we cannot exclude that this diet might have influenced the sodium and chloride levels and hence osmolality in our patients during hypothyroidism. Indeed, the significantly lower serum sodium (without development of hyponatremia) and chloride levels and the decreased urinary sodium/creatinine ratio off LT4 therapy, thus during the low-iodine diet, support this notion. Similar results have been reported by Vannucci et al. [20], who also showed significantly lower serum sodium levels off LT4 prior to ablative RAI treatment without any correlation between serum TSH and sodium levels, suggesting that the reduction in sodium levels is unrelated to the hypo-

thyroid status. Finally, our study had an outpatient design which precludes strict control of adherence to the water deprivation protocol. However, in general, an anticipated adequate serum osmolality was observed, indicating adequate water deprivation.

In conclusion, although previous studies have shown an impaired urinary concentrating ability in patients with myxedema, we did not find any evidence for impaired urinary concentrating ability in patients with short-term but severe hypothyroidism.

Disclosure Statement

No competing financial interests exist.

References

1 Roberts CG, Ladenson PW: Hypothyroidism. Lancet 2004;363:793–803.
2 Knepper MA, Kwon TH, Nielsen S: Molecular physiology of water balance. N Engl J Med 2015;373:196.
3 Chen YC, Cadnapaphornchai MA, Yang J, Summer SN, Falk S, Li C, Wang W, Schrier RW: Nonosmotic release of vasopressin and renal aquaporins in impaired urinary dilution in hypothyroidism. Am J Physiol Renal Physiol 2005;289:F672–F678.
4 Cadnapaphornchai MA, Kim YW, Gurevich AK, Summer SN, Falk S, Thurman JM, Schrier RW: Urinary concentrating defect in hypothyroid rats: role of sodium, potassium, 2-chloride co-transporter, and aquaporins. J Am Soc Nephrol 2003;14:566–574.
5 Discala VA, Kinney MJ: Effects of myxedema on the renal diluting and concentrating mechanism. Am J Med 1971;50:325–335.
6 Vaamonde CA, Michael UF, Oster JR, Sebastianelli MJ, Vaamonde LS, Klingler EL Jr, Papper S: Impaired renal concentrating ability in hypothyroid man. Nephron 1976;17:382–395.
7 Canaris GJ, Manowitz NR, Mayor G, Ridgway EC: The Colorado thyroid disease prevalence study. Arch Intern Med 2000;160:526–534.
8 Klein I, Ojamaa K: Thyroid hormone and the cardiovascular system. N Engl J Med 2001;344:501–509.
9 Vargas F, Atucha NM, Sabio JM, Quesada T, Garcia-Estan J: Pressure-diuresis-natriuresis response in hyperthyroid and hypothyroid rats. Clin Sci (Lond) 1994;87:323–328.
10 Wang W, Li C, Summer SN, Falk S, Schrier RW: Polyuria of thyrotoxicosis: downregulation of aquaporin water channels and increased solute excretion. Kidney Int 2007;72:1088–1094.
11 Robertson GL, Shelton RL, Athar S: The osmoregulation of vasopressin. Kidney Int 1976;10:25–37.
12 Kreisman SH, Hennessey JV: Consistent reversible elevations of serum creatinine levels in severe hypothyroidism. Arch Intern Med 1999;159:79–82.
13 Montenegro J, Gonzalez O, Saracho R, Aguirre R, Gonzalez O, Martinez I: Changes in renal function in primary hypothyroidism. Am J Kidney Dis 1996;27:195–198.
14 El Ters M, Patel SM, Norby SM: Hypothyroidism and reversible kidney dysfunction: an essential relationship to recognize. Endocr Pract 2014;20:490–499.
15 Karanikas G, Schutz M, Szabo M, Becherer A, Wiesner K, Dudczak R, Kletter K: Isotopic renal function studies in severe hypothyroidism and after thyroid hormone replacement therapy. Am J Nephrol 2004;24:41–45.
16 Villabona C, Sahun M, Roca M, Mora J, Gomez N, Gomez JM, Puchal R, Soler J: Blood volumes and renal function in overt and subclinical primary hypothyroidism. Am J Med Sci 1999;318:277–280.
17 Mariani LH, Berns JS: The renal manifestations of thyroid disease. J Am Soc Nephrol 2012;23:22–26.
18 Schlumberger M, Ricard M, De Pouvourville G, Pacini F: How the availability of recombinant human TSH has changed the management of patients who have thyroid cancer. Nat Clin Pract Endocrinol Metab 2007;3:641–650.
19 Li JH, He ZH, Bansal V, Hennessey JV: Low iodine diet in differentiated thyroid cancer: a review. Clin Endocrinol (Oxf) 2016;84:3–12.
20 Vannucci L, Parenti G, Simontacchi G, Rastrelli G, Giuliani C, Ognibene A, Peri A: Hypothyroidism and hyponatremia: data from a series of patients with iatrogenic acute hypothyroidism undergoing radioactive iodine therapy after total thyroidectomy for thyroid cancer. J Endocrinol Invest 2017;40:49–54.