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Original Article

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Exogenous thyrotropin improves renal function in euthyroid patients, while serum creatinine levels are increased in hypothyroidism

Flore Duranton[1,*], Anouchka Lacoste[2,*], Patrick Faurous[3], Emmanuel Deshayes[3], Jean Ribstein[4], Antoine Avignon[5], Georges Mourad[2] and Àngel Argilés[1,2,6]

[1]SAS RD – Néphrologie, Montpellier, France, [2]Service de Néphrologie, Dialyse et Transplantation, Hôpital Lapeyronie, Université de Montpellier, Montpellier, France, [3]Institut Régional du Cancer (ICM), Montpellier, France, [4]Service de Médecine Interne, Hôpital Lapeyronie, Université de Montpellier, Montpellier, France, [5]Service de Nutrition-Diabète, Hôpital Lapeyronie, Université de Montpellier, Montpellier, France and [6]Néphrologie Dialyse St Guilhem, Sète, France

Correspondence and offprint requests to: Àngel Argilés; E-mail: argiles@rd-n.org

Abstract

Background. There is evidence showing that the hypothyroid state results in increased serum creatinine levels. However, whether this is only due to the peripheral thyroid hormones or if thyroid-stimulating hormone (TSH) is also involved is not known.

Methods. Serum creatinine levels and estimated glomerular filtration rate (eGFR) were assessed in thyroidectomized patients with varying thyroid hormones and TSH levels. Blood samples from Group 1 (21 patients) were obtained 1 month after complete thyroidectomy, while under a hypothyroid state (t1) and a sufficient time after thyroid hormones initiation (euthyroid state, t2). Group 2 (20 euthyroid patients) were sampled after recombinant human thyrotropin injections (rhTSH, t1) and later after rhTSH extinction (t2).

Results. In Group 1, serum creatinine levels decreased after correction of hypothyroidism (85.3 ± 4.3 versus 78.0 ± 3.9 µmol/L; P = 0.04). In Group 2, serum creatinine levels increased after rhTSH withdrawal (70.6 ± 5.7 µmol/L versus 76.5 ± 5.8 µmol/L; P = 0.007). Between t1 and t2, eGFR varied accordingly [Group 1, 71.7 ± 3.5 versus 81.2 ± 4.5 mL/min/1.73 m² (P = 0.02); Group 2, 97.7 ± 7.4 versus 87.5 ± 5.9 (P = 0.007)]. The changes in TSH and eGFR following supplementation with thyroxine were significantly correlated ($r = -0.6$, P = 0.0041).

Conclusions. Iatrogenic hypothyroidism significantly increases serum creatinine and reversibly impairs eGFR, while treatment with rhTSH enhances renal function in euthyroid patients, supporting the existence of an influence of TSH level on renal function. The mechanisms by which peripheral thyroid hormones and TSH influence GFR need to be identified in physiology-orientated studies.

Keywords: Glomerular Filtration Rate; Creatinine; Thyrotropin; Thyroxine; Hypothyroidism

Introduction

Hypothyroidism induces a hypodynamic state of the circulatory system, which would result in a decrease of renal function and particularly of glomerular filtration rate [1]. Several haemodynamic changes have been reported in hypothyroidism that may influence renal function, such as hyponatraemia, decrease in renal blood flow and renal plasma flow, which may decrease the glomerular filtration rate [2–9]. In addition to the haemodynamic changes, hypothyroidism also results in histological changes in the kidney that have been characterized as a decrease in the size of all its various compartments and particularly a decrease in the diameter of the tubular segments as well as of the height of the tubular cells and of the width of the brush borders [10–12].

Despite the increasing evidence showing the influence of thyroid metabolism on renal function, this association is seldom considered in internal medicine or in nephrology textbooks. Thus, neither renal physicians nor endocrinologists take into account the thyroid state routinely when interpreting renal function markers in patients with thyroid disease, or alternatively they do not check the thyroid state when caring for renal failure patients.

Following a few observations in our outpatient clinic of patients with an increased serum creatinine level concomitant to thyroid disease and for whom no other cause was identified to explain the decrease in the glomerular filtration rate, we were interested in assessing the influence of the thyroid state on renal function. In addition to assessing the effect of the peripheral hormones on the glomerular filtration rate, we were particularly interested in studying a putative effect of thyroid-stimulating hormone (TSH), as this compound, obtained from recombinant technology, has been recently introduced in clinical

*Equally participated.

oncology in the follow-up and treatment of thyroid tumours. We studied prospectively the first 41 consecutive patients admitted in the oncology department to be monitored for thyroid carcinoma, after total thyroidectomy.

Materials and methods

Forty-one patients operated on for a thyroid carcinoma were studied during their scheduled radioiodine therapy. Increased iodine avidity by thyroid cells is sought in thyroid oncology for screening and treatment purposes. In first intention radioiodine treatment, iodine avidity is enhanced by maintaining a protracted hypothyroid state after total thyroidectomy. In second intention treatment following a suspicion of thyroid cancer relapse, iodine avidity is increased by rhTSH injection. We studied these situations in two different groups of patients, whose characteristics are given in Table 1. The two groups were similar in terms of sex ratio, and mean age, weight, height and body mass index ($P > 0.05$). Group 1 consisted of 21 thyroidectomized patients in whom iatrogenic hypothyroidism was maintained for a month prior to radioiodine therapy and scanning. Group 2 consisted of 20 thyroidectomized patients in the euthyroid state with a suspicion of thyroid carcinoma relapse who were treated with two recombinant human αTSH injections (Thyrogen®; Genzyme SAS, Saint Germain en Laye, France) at a dose of 0.9 mg on Day 2 and one prior to radioiodine therapy and scanning. Patient tumour types and staging are detailed in Table 2. Blood controls were performed twice in both groups of patients: on the day of therapy which was during iatrogenic hypothyroidism in Group 1 or at Day 3 after the first rhTSH injection in Group 2 (t1 time point) and 4–12 weeks after radioiodine therapy (t2 time point). The study design is depicted in Figure 1.

Blood compounds assessed included creatinine, sodium, potassium, chloride, bicarbonate, CPK, TSH and triiodothyronine (T3). Creatininaemia was determined colorimetrically on the day of screening with a COBAS C501 device (Roche, Meylan, France). At t2, creatininaemia was enzymatically or colorimetrically determined by community laboratories. The serum levels of TSH were determined on the day of screening using an antibody-based assay, which reacts with endogenous as well as exogenous human recombinant TSH. Electro-chemiluminescence was measured after a sandwich antibody reaction in the module Elecsys of a COBAS C300 device (Roche).

Renal function was determined by the simplified Modification of Diet in Renal Disease (MDRD) formula [13]:

$$\text{eGFR} = 186.3 \times [(\text{serum creatinine in } \mu\text{mol/L})/88.4]^{-1.154} \times \text{age}^{-0.203}$$

With a correction factor for:

(i) race = 1.212 (black)

Table 1. Characteristics of the patients included in the study

	Group 1 ($n = 21$)	Group 2 ($n = 20$)	P-value
Age (years)	51.8 ± 3.1	54.5 ± 3.6	0.57
Sex (M/F)	3/18	5/15	0.98
Weight (kg)	67.8 ± 2.7	72.0 ± 3.6	0.35
Height (cm)	162.6 ± 1.8	167.1 ± 1.5	0.07
BMI (kg/m²)	25.5 ± 1.0	25.5 ± 1.0	0.39

Table 2. Tumour histology and staging.

	Group 1 ($n = 21$)	Group 2 ($n = 20$)	Total
Histology			
Papillary	18	16	34
Vesicular	2	2	4
Oncocytic	1	0	1
Unknown	0	2	2
TNM classification			
T			
1	10	12	22
2	4	3	7
3	4	0	4
4	1	0	1
X	2	5	7
N			
0	6	4	10
1	3	4	7
X	12	12	24
M			
0	19	18	37
1	0	1	1
X	2	1	3

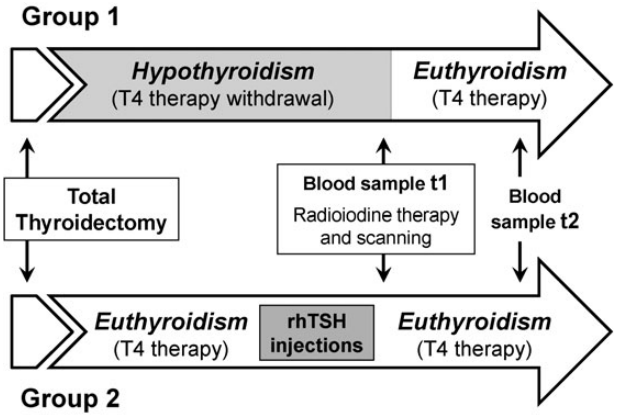

Figure 1. Study design and sampling time of the two groups of patients treated for thyroid carcinomas.

(ii) sex = 0.742 (female).

Statistics were performed with an SAS package 9.2 (SAS Institute, Cary, NC, USA). Student's tests were performed for unpaired and paired data accordingly. A P-value of <0.05 was considered significant. Results are given as mean ± standard error of the mean.

Results

Laboratory results are given in Table 3. At the first sampling time (t1), serum creatinine levels were significantly higher in patients from Group 1 with hypothyroidism than in euthyroid patients from Group 2 receiving rhTSH (Figure 2, $P = 0.046$). In Group 1, creatinine levels decreased when hypothyroidism was corrected by thyroxine (T4) administration (Figure 2, $P = 0.04$). In Group 2, serum creatinine levels significantly rose after rhTSH withdrawal ($P = 0.007$) to a level similar to that observed in Group 1 after correction of hypothyroidism with thyroxine ($P = 0.32$, Figure 2). When limiting the analysis to colorimetric determinations of creatinine, significant changes in serum creatinine remained observable in Group 1 ($n = 15$, mean difference = −10.9 ± 4.0 µmol/L, $P = 0.016$)

and Group 2 ($n = 15$, mean difference = 3.2 ± 1.5 µmol/L, P = 0.047).

The estimated glomerular filtration rate (eGFR) showed significant variations between t1 and t2 in both groups, with inverse patterns. The administration of thyroxine in hypothyroid patients resulted in a significant improvement in eGFR (Group 1, P = 0.019; Figure 3). TSH administration was associated with elevated eGFR, which decreased after TSH withdrawal (Group 2, P = 0.007; Figure 3). At the second sampling time (t2), eGFRs were similar in both groups (P = 0.33).

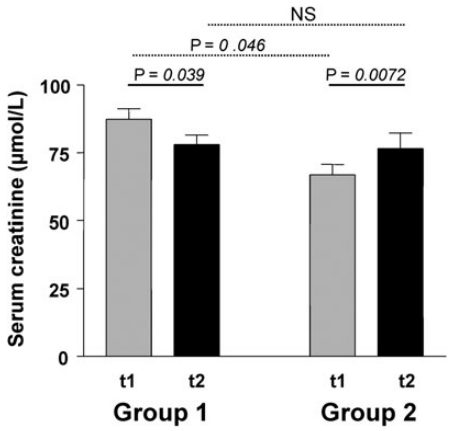

Figure 2. Mean serum creatinine levels by group and time point. Serum creatinine significantly decreased in patients who moved from the hypothyroid to the euthyroid state by supplementation with thyroxine (Group 1), whilst serum creatinine increased in euthyroid patients after rhTSH extinction (Group 2).

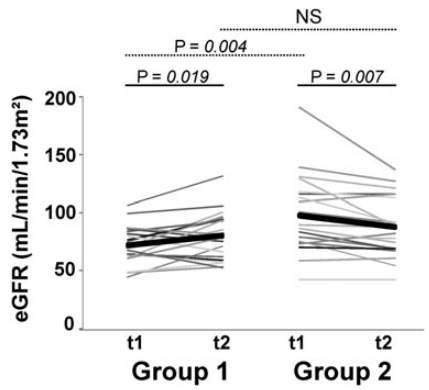

Figure 3. Individual variations of eGFR by group and time point. The thick line represents variations of mean eGFR. eGFR significantly increased in patients who moved from the hypothyroid to the euthyroid state by supplementation with thyroxine (Group 1), whilst eGFR decreased in euthyroid patients after rhTSH extinction (Group 2).

There was a clear difference in TSH levels between t1 and t2 in both groups of patients, with increased TSH levels at the first sampling time (both P < 0.001, Figure 4). However, the origin of the serum TSH in both groups was different. In Group 1, TSH was endogenous and was the consequence of the stimuli following total thyroidectomy. In Group 2 the TSH was exogenous and was given as required by the therapeutic schedule. In both groups, serum levels of TSH had returned to normal levels at t2 (Table 3 and Figure 4).

The hypothyroid state (Group 1 at t1) was associated with a significant increase in serum levels of creatine phosphokinase (CPK) and a significant decrease in serum potassium levels (P < 0.001 and P = 0.017, respectively; Table 3). For both compounds, levels were normalized after hypothyroidism correction and were similar to those observed in Group 2 (t2, Group 1 versus Group 2; P = 0.82 and P = 0.83, respectively; Table 3). There was an increase in sodium levels in euthyroid patients treated with rhTSH (Group 2, t1 versus t2, P < 0.001), which was normalized after rhTSH extinction (t2, Group 1 versus Group 2, P = 0.59; Table 3).

Variations in eGFR were significantly correlated with variations in endogenous TSH levels following the correction of hypothyroidism ($r = -0.652$, P < 0.003, Figure 5).

Discussion

The present study shows that hypothyroidism is associated with a decrease in creatinine-based estimations of the glomerular filtration rate. It further shows that TSH administration is associated with an improvement in eGFR in thyroidectomized patients previously rendered euthyroid by exogenous thyroxine treatment. Both the former data on hypothyroid patients and the latter new findings on TSH treated patients, support the existence of a link between thyroid metabolism and renal function and open new questions about the mechanisms underlying this link.

Although not widely considered, there is increasing evidence in the literature suggesting that hypothyroidism alters renal function, both the glomerular filtration rate [14] and the tubular function [15]. Recent publications illustrate the growing interest in the association between thyroid and renal functions [16, 17].

Table 3. Clinical characteristics of the two groups of patients

	Group 1 ($n = 21$)		Group 2 ($n = 20$)	
	Sample t1	Sample t2	Sample t1	Sample t2
Creatinine (µmol/L)	85.3 ± 4.3[a]	78.0 ± 3.9[b]	70.6 ± 5.7[c]	76.5 ± 5.8[b]
eGFR (mL/min/1.73 m²)	71.7 ± 3.5[a]	81.2 ± 4.5[b]	97.7 ± 7.4[c]	87.5 ± 5.9[b]
TSH (mUI/L)	92.6 ± 8.3[a]	3.54 ± 1.37[b]	114.5 ± 12.8[a]	0.20 ± 0.07[c]
T3 (ng/L)	–	4.66 ± 0.41	–	4.51 ± 0.35
CPK (UI/L)	225.2 ± 30.1[a]	87.1 ± 9.9[b]	105.7 ± 18.1[b]	90.4 ± 10.4[b]
Na (mmol/L)	141.4 ± 0.8[a]	141.6 ± 0.8[a]	143.9 ± 0.5[b]	141.2 ± 0.4[a]
K (mmol/L)	3.89 ± 0.08[a]	4.24 ± 0.07[b]	4.10 ± 0.08[a,b]	4.27 ± 0.09[b]
Cl (mmol/L)	100.2 ± 0.9[a]	98.6 ± 3.2[a,b]	102.4 ± 0.5[b]	101.9 ± 0.9[b]

The values are means and SEM. Different letters indicate values, which are significantly different
T3 was not titrated at t1. All patients had undergone thyroidectomy. At t1, patients from Group 1 had stopped thyroid hormone treatments for a month, their T3 levels are expected to be below 1 ng/mL. Patients from Group 2 were under hormonal treatment to achieve the euthyroid state at t1 and t2, their T3 levels are expected to be similar at both time points.

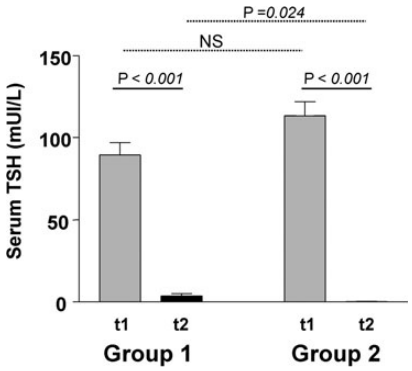

Figure 4. Mean serum TSH levels by group and time point. Both groups of patients had very high levels of TSH which sharply decreased after correcting hypothyroidism in Group 1 or rhTSH extinction in Group 2.

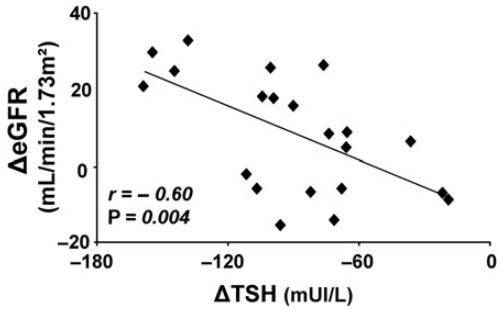

Figure 5. Association between changes in serum TSH levels and eGFR after correction of hypothyroidism in Group 1. Changes were calculated as the values at t2 minus values at t1. There was a significant correlation between changes in TSH and eGFR.

The increase in serum creatinine levels observed in hypothyroidism is relevant in clinical practice since it may mislead physicians in handling the care of the patients with thyroid dysfunction. As stressed by Kreisman and Hennessey [14], frankly abnormal serum creatinine levels may occur in some cases of hypothyroidism and not taking into consideration the association of thyroid metabolism and glomerular filtration rate may lead to unnecessary and costly investigations. On the other hand, in patients presenting mild renal failure without evident cause and a clinical record of hypothyroidism (as the ones that motivated our interest in thyroid metabolism), it may be helpful to determine thyroid metabolism and eventually to adapt the hormone therapy. Although not envisaged or proposed in internal medicine textbooks, the correction of the thyroid dysfunction will certainly be followed by an improvement of renal function. This has been documented by several isolated case reports in the literature, in childhood [18], or in adult patients with mild [19] or even with advanced renal failure [20]. This is also supported by a study using radiomarkers, which showed reversible reductions in glomerular filtration rates in hypothyroid patients [21]. Interestingly, Karanikas *et al*. [21] also showed that changes in measured GFR levels were consistent with changes in serum creatinine. In contrast, plasma cystatin C levels appear to be increased in hyperthyroidism and decreased in hypothyroidism rendering the use of cystatin C-based estimations of GFR inappropriate in these clinical situations [22].

Based upon the beneficial effect of thyroid hormones on renal function, thyroxine has also been proposed in acute renal failure and it has been shown to be effective in promoting recovery in a wide variety of animal models of acute renal failure [23–27]. However, its use has not spread into clinics as Acker *et al*. [28] observed a deleterious effect of thyroxine on the outcome of acute renal failure in critically ill euthyroid patients in a randomized prospective trial and they speculated that this might be due to the prolonged TSH suppression [28]. The lack of evidence of this treatment option was recently summarized [29].

Beyond the clinical interest of keeping in mind the association between thyroid and renal metabolisms, and the benefits on renal function of treating hypothyroidism, one is tempted to look for the mechanisms by which they are linked. It is believed that the decrease in the glomerular filtration rate would be due to the generalized hypodynamic state associated with hypothyroidism [1–9]. However, the present study shows that also in patients with thyroid replacement therapy, injecting recombinant human TSH improved eGFR.

Because hyperthyroidism has been shown to be associated with increased eGFR [30], we wondered whether the action of rhTSH on putative thyroid remnants could have influenced thyroid hormone levels and resulted in hyperthyroidism. In healthy patients receiving rhTSH injections, serum TSH, T3 and T4 levels increased and peaked within the next 2 days [31, 32]. In thyroidectomized patients treated with rhTSH injections, we found that on the day of radioiodine scanning (2 days after the first injection), thyroid hormone levels were consistent with euthyroidism (T3, 3.1 ± 0.1 ng/L; T4, 16.8 ± 0.4 ng/L; $n = 9$, *unpublished data*). On the day of screening, patients who underwent thyroxine withdrawal had lower thyroid hormone levels, which were consistent with hypothyroidism (T3, 0.9 ± 0.04 ng/L; T4, 1.58 ± 0.05 ng/L; $n = 10$, *unpublished data*). These results strongly argue that thyroid function was not responsible for the changes in eGFR observed in patients receiving rhTSH as it did not increase the thyroid hormone levels in these patients.

On the other hand, our study cannot rule out the possibility of an effect of exogenous TSH on creatinine synthesis or excretion leading to a decreased circulating level. In this case, endogenous TSH secreted during hypothyroidism would similarly affect creatinine levels, but this reduction would be masked by an even more important loss of glomerular filtration rate. In this case, creatinine-based eGFR would be over-estimated in hypothyroid patients to an extent which could be relevant in clinical practice.

Thyroid hormones are known for directly affecting water and sodium metabolism. Myxoedema and hyponatraemia may occur during hypothyroidism [33] and increased serum sodium levels have been observed in hyperthyroid rats [34]. In our study, however, thyroidectomized patients with or without thyroid hormone replacement had normal serum sodium levels. Surprisingly, the group of patients receiving both exogenous TSH and thyroxine was in a transient state of hypernatraemia. In euthyroid patients, TRH injection was shown to decrease levels of the anti-diuretic hormone arginine vasopressin (AVP) [35]. Experiments in rats showed that AVP as well as angiotensin II displayed thyrotropin-releasing effects [36,37]. In contrast, it has not been shown whether TSH could affect the production of AVP or angiotensin II. It may be that the link between hypothyroidism and water/sodium metabolism is not only due to thyroid hormones but also due to TSH through mechanisms not yet identified.

Therefore, our data challenge the view that renal function is solely modified by the hypodynamic state associated with thyroid dysfunction and provide new evidence that also TSH, with no previously known activity in renal physiology, could modify the glomerular filtration rate and water or sodium metabolism. However, it has not been demonstrated whether TSH could have a direct effect on renal function or if it is mediated by changes in peripheral hormones activities such as deiodonases.

TSH acts through binding to its receptor TSHR, which belongs to a family of G protein-coupled receptors with a large ligand-binding domain containing leucine, reach repeats, and a heptahelical transmembrane domain, that dimerize [38, 39]. The heptahelical receptor couples to Gs and Gq proteins, activating both Gs/cAMP and Gq/PLC/Inositol phosphates pathways [40, 41] resulting in differential effects that have been further characterized by the identification of familial mutations of TSHR [42]. TSHR was expressed in transfected MDCK cells [43] and it remains controversial whether it is normally present in renal cells. Sellitti *et al*. [44] observed the TSHR transcript in the renal cortex and also in mouse mesangial cells, while Busuttil and Frauman [45] and Urizar *et al*. [39] did not find TSHR in renal tissue.

Given the clear renal response to the TSH treatment in the studied population, further characterization of the TSH effects in the different renal compartments deserves to be assessed.

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Conflicts of interest statement. None to declare. The results presented in this paper have not been published previously.

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