Influence of Thyroid Function on Different Kidney Function Tests

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Key Words

Chronic Kidney Disease Epidemiology Collaboration equation • Creatinine • Creatinine clearance • Cystatin C • Neutrophil gelatinase-associated lipocalin • Thyroid dysfunction

Abstract

Background/Aims: The commonly used kidney function tests have limitations, especially in thyroid dysfunction. Therefore, we studied the most commonly used kidney function tests in patients with hypo- and hyperthyroidism and after reaching euthyroidism. **Methods:** Prospective case series in 16 patients with thyroid dysfunction. Serum creatinine, 24-hour creatinine clearance, calculated glomerular filtration rate (GFR) by Cockcroft-Gault, estimated GFR (eGFR) by the Chronic Kidney Disease Epidemiology Collaboration equation, serum cystatin C, eGFR based on cystatin C, eGFR based on a combined (cystatin C and creatinine) formula and plasma neutrophil gelatinase-associated lipocalin (NGAL) were measured in hypo- and hyperthyroidism and after gaining euthyroidism. **Results:** When free thyroxine (fT₄) normalized in hypothyroid patients, creatinine decreased and creatinine-based eGFR increased significantly. In contrast, cystatin C increased and eGFR based on cystatin C decreased significantly. There was no significant change in NGAL levels. When fT₄ normalized in patients with hyperthyroidism, cre-

atinine increased and creatinine-based eGFR decreased significantly. In contrast, cystatin C decreased and cystatin-C-based GFR increased significantly. There was no significant change in NGAL levels. **Conclusions:** Thyroid function has a major influence on the vast majority of kidney function tests. Cystatin C is strongly influenced by the thyroid function and should be avoided in thyroid disorders. There was no effect on the plasma NGAL levels. The recommended kidney function test is a measurement of creatinine-based eGFR.

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Introduction

There is a well-known interaction between thyroid and kidney functions. Thyroid hormones are involved in the growth, development and the physiology of the kidney [1]. Thyroid dysfunction is known to cause significant changes in kidney function: hypo- and hyperthyroidism affect glomerular filtration rate (GFR), renal blood flow, tubular function, water and electrolyte balance and kidney structure [2]. There is a broad discussion on the best kidney function test in different populations [3]. In the absence of known chronic kidney disease, the most commonly used kidney function tests in everyday clinical practice are the two biomarkers serum creatinine and serum cystatin C. The next step in testing is estimat-

Table 1a. Clinical characteristics and laboratory results (serum or plasma) in patients before and after therapy of hypothyroidism

Parameter		Normal	Hypothyroidism		Normal thyroid function	
			mean $\pm$ SD	range	mean $\pm$ SD	range
<i>Study population</i>						
Gender	3 females, 6 males					
Age, years	42 $\pm$ 14 (22–65)					
<i>Clinical characteristics</i>						
BMI		28.0 $\pm$ 4.7	21.5–27.0	27.4 $\pm$ 4.1	22.3–34.9	
Weight, kg		87.1 $\pm$ 15.0	65.0–104.0	85.0 $\pm$ 13.5	67.5–104.5	
<i>Laboratory results</i>						
TSH, mU/l	0.47–4.7	39.50 $\pm$ 26.20**	11.1–100.5	0.24 $\pm$ 0.46	0.01–1.46	
T ₃ , pmol/l	0.7–2.3	0.16 $\pm$ 0.32***	0–1	1.69 $\pm$ 0.3	1.0–2.2	
fT ₄ , pmol/l	11.7–28.0	4.8 $\pm$ 0.3***	4.5–5.1	24.1 $\pm$ 5.3	13.7–33	
Urea, mg/dl	20–50	26.4 $\pm$ 6.50	19–39	28.3 $\pm$ 7.3	16–37	
Creatinine, mg/dl	0.5–1.4	1.2 $\pm$ 0.20***	0.9–1.4	0.9 $\pm$ 0.1	0.8–1.1	
Creatinine clearance over 24 h collected, ml/min	80–120	86 $\pm$ 23**	44–118	115 $\pm$ 36	63–179	
Creatinine clearance (Cockcroft-Gault), ml/min	80–120	92 $\pm$ 14***	78–115	117 $\pm$ 16	97–149	
eGFR by CKD-EPI (creatinine based), ml/min	80–120	68 $\pm$ 12***	52–95	93 $\pm$ 15	70–121	
Cystatin C, mg/l	0.53–0.95	0.80 $\pm$ 0.09*	0.68–0.93	0.88 $\pm$ 0.09	0.77–1.04	
eGFR based on cystatin C, ml/min	80–120	103 $\pm$ 15*	82–125	90 $\pm$ 11	74.0–106.0	
eGFR based on creatinine and cystatin C, ml/min	80–120	81 $\pm$ 10*	66–97	90 $\pm$ 11	71–106	
NGAL, ng/ml	<50	39 $\pm$ 27	30–112	38 $\pm$ 16	30–68	

All parameters measured in serum or plasma samples. Age is given as median $\pm$ standard deviation, with range in parentheses, all other results as means $\pm$ standard deviation. BMI = Body mass index; TSH = thyroid-stimulating hormone. * $p < 0.05$, ** $p < 0.003$, *** $p < 0.0001$.

ing the GFR by collected and calculated clearances [creatinine clearance measured in a 24-hour collection, calculated GFR by Cockcroft-Gault or the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation, estimated GFR (eGFR) based on cystatin C and eGFR based on both (creatinine and cystatin C)]. In case of chronic kidney disease (GFR <60 ml/min), the eGFR rate by formulas, like the MDRD (Modification of Diet in Renal Disease), is the most common, best-validated approach [4]. In case of acute kidney injury the best-validated biomarkers are cystatin C and neutrophil gelatinase-associated lipocalin (NGAL) [5, 6]. All kidney function tests have their well-known limitations, and different effects have been described in thyroid dysfunction: in case of the well-established serum creatinine an increase in hypothyreotic state and a decrease in hyperthyroidism have been shown [7], whereas serum cystatin C has been shown to decrease in hypothyroidism and to increase in hyperthyroidism [8–10]. Recently, the newer proposed acute kidney injury marker NGAL has been shown to be a survival factor for thyroid neoplastic cells [11].

None of the previous studies have included several kidney function tests in a single patient cohort. The aim of this study is to compare 8 different kidney function tests [serum creatinine, 24-hour creatinine clearance, calculated creatinine clearance by Cockcroft-Gault, calculated GFR by the CKD-EPI equation, serum cystatin C, calculated GFR based on cystatin C, calculated GFR based on both (cystatin C and creatinine) and NGAL] in parallel in a case series of patients with hypo- and hyperthyreosis before and after treatment.

Methods

Patients

Hypothyroidism. Nine patients who were under replacement therapy with L-triiodothyronine (L-T₃, Thybon®) because of total strumectomy for thyroid cancer were recruited for the study. All patients underwent complete medical examination including laboratory tests and vital signs. Two to 6 (median 4) weeks before radioiodine therapy L-T₃ replacement was stopped, and the diagnosis of hypothyroidism was confirmed by appropriate clinical and biochemical criteria: thyroid-stimulating hormone

Table 1b. Clinical characteristics and laboratory results (serum or plasma) in patients before and after therapy of hyperthyroidism

Parameter		Normal	Hyperthyroidism		Normal thyroid function	
			mean $\pm$ SD	range	mean $\pm$ SD	range
<i>Study population</i>						
Gender	6 females, 1 male					
Age, years	46 $\pm$ 11 (34–57)					
<i>Clinical characteristics</i>						
BMI		23.77 $\pm$ 4.63	20.6–34.0	24.49 $\pm$ 4.37	21.2–34.2	
Weight, kg		69.54 $\pm$ 7.84	57.5–83.8	71.69 $\pm$ 7.57	59.0–84.3	
<i>Laboratory results</i>						
TSH, mU/l	0.47–4.7	<0.00 $\pm$ 0.0	<0.00–0.02	0.93 $\pm$ 1.80	0.01–4.86	
T ₃ , pmol/l	0.7–2.3	3.89 $\pm$ 2.36*	2.5–9	1.30 $\pm$ 0.46	0.8–2.0	
fT ₄ , pmol/l	11.7–28	27.10 $\pm$ 8.34*	18.3–41.0	11.63 $\pm$ 4.28	5.0–17.4	
Urea, mg/dl	20–50	29.14 $\pm$ 7.34	22–43	30.14 $\pm$ 8.11	15–38	
Creatinine, mg/dl	0.5–1.4	0.63 $\pm$ 0.10**	0.5–0.8	0.77 $\pm$ 0.13	0.7–1.0	
Creatinine clearance over 24 h collected, ml/min	80–120	132 $\pm$ 26*	89–165	104 $\pm$ 11	85–114	
Creatinine clearance (Cockroft-Gault), ml/min	80–120	126 $\pm$ 14*	110–150	103 $\pm$ 8	94–116	
eGFR by CKD-EPI (creatinine based), ml/min	80–120	110 $\pm$ 6*	102–116	98 $\pm$ 8	83–107	
Cystatin C, mg/l	0.53–0.95	1.07 $\pm$ 0.21*	0.85–1.43	0.82 $\pm$ 0.08	0.69–0.94	
eGFR based on cystatin C, ml/min	80–120	73 $\pm$ 16**	49–93	100 $\pm$ 12	85–120	
eGFR based on creatinine and cystatin C, ml/min	80–120	93 $\pm$ 8*	81–105	94 $\pm$ 6	89–107	
NGAL, ng/ml	<50	50 $\pm$ 25	30–81	41 $\pm$ 29	30–107	

All parameters measured in serum or plasma samples. Age is given as median $\pm$ standard deviation with range in parentheses, all other results as means $\pm$ standard deviation. BMI = Body mass index; TSH = thyroid-stimulating hormone. * $p < 0.05$, ** $p < 0.003$, *** $p < 0.0001$.

above normal (0.47–4.7 mU/l), T₃ equal to or below normal (0.7–2.3 pmol/l), thyroxine (T₄) below normal (11.7–28.0 pmol/l; table 1a).

After radioiodine therapy and when patients had received replacement treatment with levothyroxine (Euthyrox®, Merck, Darmstadt, Germany; 150–250 µg/day), they were studied again after 13.7 $\pm$ 10.7 weeks. Normal thyroid function was confirmed by appropriate laboratory tests (table 1a).

Hyperthyroidism. Seven patients suffering from hyperthyroidism (3 Graves' disease, 4 toxic adenomas) were included in the study. Diagnosis was confirmed by appropriate clinical and biochemical tests. Three patients got drug therapy with carbimazole, 4 got a radioiodine therapy (table 1b). The patients were studied again after normalization of thyroid function after 15.7 $\pm$ 6.7 weeks.

The local ethics committee and regulating government authorities approved the study. Written informed consent was obtained from all patients.

Kidney Function Tests

In all patients (all Caucasian), the kidney function was measured at each of the 2 time points: in thyroid dysfunction (hypo- or hyperthyroidism) and after therapy in euthyroidism by the following 8 methods:

- (1) serum levels of creatinine were measured enzymatically;
- (2) 24-hour creatinine clearance was calculated after 24-hour urine collection;
- (3) calculated creatinine clearance according to the formula of Cockcroft and Gault [12];
- (4) GFR was estimated based on creatinine by the CKD-EPI equation (no black patients) [13];
females with serum creatinine ≤ 0.7 mg/dl: $\text{eGFR} = 144 \times (\text{serum creatinine}/0.7)^{-0.329} \times (0.993)^{\text{age}}$;
females with serum creatinine > 0.7 mg/dl: $\text{eGFR} = 144 \times (\text{serum creatinine}/0.7)^{-1.209} \times (0.993)^{\text{age}}$;
males with serum creatinine ≤ 0.9 mg/dl: $\text{eGFR} = 141 \times (\text{serum creatinine}/0.9)^{-0.411} \times (0.993)^{\text{age}}$;
males with serum creatinine > 0.9 mg/dl: $\text{eGFR} = 141 \times (\text{serum creatinine}/0.9)^{-1.209} \times (0.993)^{\text{age}}$;
- (5) serum cystatin C was measured by nephelometry;
- (6) GFR was estimated based on cystatin C calculation by: $\text{eGFR} = 74.835/(\text{serum cystatin C})^{1.333}$;
- (7) GFR was estimated based on cystatin C and creatinine by: $\text{eGFR} = 177.6 \times (\text{serum creatinine})^{-0.65} \times (\text{serum cystatin C})^{-0.57} \times \text{age}^{-0.20} \times (0.82 \text{ if female})$ [14];
- (8) plasma NGAL by immunoassay on the Triage platform (point of care system) [5]; levels below the limit of detection (60 ng/ml) were set to 30 ng/ml.

Statistical Analysis

Data are presented as means $\pm$ SD. Values before and after treatment within the 2 groups were analyzed using the paired Student *t* test. A *p* value below 0.05 was considered to be statistically significant. Correlations were calculated by the Spearman test. Statistical analyses were conducted with Graph Pad Prism (Graph Pad Software, San Diego, Calif., USA).

Results

Hypothyroidism

In the hypothyroid patients (*n* = 9), the mean free T_4 (fT_4) was 4.8 ± 0.3 pmol/l (reference 11.7–28.0) at diagnosis and increased to 24.1 ± 5.3 pmol/l when patients were treated with levothyroxine. When fT_4 normalized, serum creatinine decreased significantly (*p* < 0.001) from 1.2 to 0.9 mg/dl (reference 0.5–1.4) and creatinine-based GFR estimations (reference 80–120 ml/min) increased significantly (table 1a and fig. 1a): 24-hour creatinine clearance from 86 ± 23 to 115 ± 36 ml/min (*p* < 0.001), calculated GFR by Cockcroft-Gault from 92 ± 14 to 117 ± 16 ml/min (*p* < 0.001) and eGFR by the CKD-EPI equation from 68 ± 12 to 93 ± 15 ml/min (*p* < 0.001). The combined (cystatin C and creatinine) formula for estimating GFR increased significantly from 81 ± 10 to 90 ± 11 ml/min (*p* = 0.01) as shown in table 1a and figure 2a. In contrast, serum cystatin C increased significantly (*p* = 0.02) from 0.80 ± 0.09 to 0.88 ± 0.09 mg/l and eGFR based on cystatin C decreased from 103 ± 15 to 90 ± 11 ml/min (*p* = 0.02) as shown in table 1a and figure 3a. There was no significant effect (*p* = 0.9) on the low plasma NGAL levels (39 ± 27 ng/ml in hypothyroidism vs. 38 ± 16 ng/ml in euthyroidism) as shown in figure 4.

Hyperthyroidism

In patients with hyperthyroidism (*n* = 7), the mean fT_4 was 27.1 ± 8.34 pmol/l (reference 11.7–28.0) at diagnosis and decreased to 11.63 ± 4.28 pmol/l following treatment with antithyroid drugs (*n* = 3) or radioiodine (*n* = 4). When fT_4 normalized, serum creatinine increased significantly (*p* < 0.001) from 0.63 ± 0.10 to 0.77 ± 0.13 mg/dl (reference 0.5–1.4), and creatinine-based GFR estimations (reference 80–120 ml/min) decreased significantly (table 1b and fig. 1b): 24-hour creatinine clearance from 132 ± 26 to 104 ± 11 ml/min (*p* = 0.03), calculated GFR by Cockcroft-Gault from 126 ± 14 to 103 ± 8 ml/min (*p* = 0.01) and eGFR by the CKD-EPI equation from 110 ± 6 to 98 ± 8 ml/min (*p* = 0.02). In contrast, serum cystatin C decreased significantly (*p* = 0.01) from 1.07 ± 0.21 to 0.82 ± 0.08 mg/l, and GFR based on cystatin C

increased significantly (*p* < 0.001) from 73 ± 16 to 100 ± 12 ml/min as shown in table 1b and figure 3b. There was no significant change (*p* = 0.76) for the combined (cystatin C and creatinine) GFR equation in patients with hyperthyroidism and after treatment, when reaching an euthyroid state as shown in table 1b and figure 2b. There was no significant effect (*p* = 0.61) on the low plasma NGAL levels (50 ± 25 ng/ml in hyperthyroidism versus 41 ± 19 ng/ml in euthyroidism) as shown in figure 4.

Correlations between Thyroid Function and Kidney Function Tests

There is a positive, highly significant correlation (*r* = 0.76, *p* < 0.001) between fT_4 and cystatin C in patients with overt hypo- and hyperthyroidism as shown in figure 5.

Discussion

Thyroid and kidney function are known to interact, and thyroid dysfunction is known to cause significant changes in kidney function, especially to affect GFR [1, 15, 16]. Different kidney function tests are used in everyday clinical practice: biomarkers like serum creatinine, serum cystatin C, plasma NGAL and estimations of the GFR by collected and calculated clearances (creatinine clearance measured in a 24-hour collection, calculated GFR by Cockcroft-Gault or the CKD-EPI equation, estimated GFR based on cystatin C and estimated GFR based on both creatinine and cystatin C). In case of chronic kidney disease (GFR < 60 ml/min), the eGFR rate by the MDRD formulas is the best-validated approach [4]. The ‘gold standard’ tests for assessing kidney function are the more invasive tests like inulin clearance or isotopic studies.

Our study included several creatinine-based kidney function tests (serum creatinine, collected 24-hour creatinine clearance, calculated GFR by Cockcroft-Gault, eGFR by the CKD-EPI equation); no previous study included collected 24-hour urine clearances and calculated GFRs. Our results on the 4 creatinine-based kidney function tests are in line with the previous reports [7]: in all 4 tests there was a significant decline of the eGFR in hypothyroidism and an increase in hyperthyroidism. The 24-hour collected creatinine clearance was increased by 28 ml/min to 132 ml/min in our hyperthyroid patients and decreased by 25 ml/min to 86 ml/min in our hypothyroid patients. These GFR values are very similar to the GFR by isotopic studies reported in the literature [17]. The Cockcroft-Gault formula was published in 1976 [12], and nowadays it is still used very frequently for drug dosing, be-

Fig. 1. Creatinine-based kidney function tests: 24-hour creatinine clearance, calculated creatinine clearance by Cockcroft-Gault, eGFR by CKD-EPI. **a** Hypothyroidism before (fT_4 4.8 ± 0.3 pmol/l) and after treatment (fT_4 24.1 ± 5.3 pmol/l). **b** Hyperthyroidism before (fT_4 27.10 ± 8.34 pmol/l) and after treatment (fT_4 11.63 ± 4.28 pmol/l).

cause of its use in pharmacological studies and regulatory recommendations. Therefore, GFR calculation by Cockcroft-Gault was included in the study protocol and provided very similar results to the 24-hour collected creatinine clearance. The widely used MDRD equa-

tions are limited to chronic kidney disease (with GFR < 60 ml/min), because of the well-known GFR underestimation in a population with normal GFR. Therefore, we chose the recently recommended CKD-EPI equation for our study population without known chronic kidney dis-

Fig. 2. eGFR based on a combined creatinine and cystatin C formula. **a** Hypothyreosis before (fT_4 4.8 ± 0.3 pmol/l) and after treatment (fT_4 24.1 ± 5.3 pmol/l). **b** Hyperthyreosis before (fT_4 27.10 ± 8.34 pmol/l) and after treatment (fT_4 11.63 ± 4.28 pmol/l).

Fig. 3. Cystatin-C-based kidney function tests: serum cystatin C and eGFR. **a** Hypothyreosis before (fT_4 4.8 ± 0.3 pmol/l) and after treatment (fT_4 24.1 ± 5.3 pmol/l). **b** Hyperthyreosis before (fT_4 27.10 ± 8.34 pmol/l) and after treatment (fT_4 11.63 ± 4.28 pmol/l).

ease [13]; nevertheless, the estimation of the GFR was lower than by 24-hour collected creatinine clearance and Cockcroft-Gault estimation. Studies on serum creatinine in thyroid disease indicate that GFR is rising in hyperthyroidism and falling in hypothyroidism [7]. This is in line

with a significantly higher inulin clearance reported in patients with hyperthyroidism and a reduced GFR assessed by isotopic renal function studies reported in patients with hypothyroidism – both were reversible after normalizing fT_4 [17–20]. In patients with extreme thyroid

Fig. 4. Plasma NGAL. **a** Hypothyreosis before (fT_4 4.8 ± 0.3 pmol/l) and after treatment (fT_4 24.1 ± 5.3 pmol/l). **b** Hyperthyreosis before (fT_4 27.10 ± 8.34 pmol/l) and after treatment (fT_4 11.63 ± 4.28 pmol/l).

dysfunction, like those with myxedema, serum creatinine could probably underestimate the renal function, because creatinine depends on the metabolism of muscles [21, 22].

In the study protocol we included the well-established newer biomarker cystatin C for the measurements of kidney function [3]. Cystatin C may be superior to creatinine as a marker for GFR, and a more accurate marker in acute kidney injury. Cystatin C has advantages because concentrations in blood are not influenced by muscle mass, but several known factors, other than GFR, affect serum cystatin C levels [23–26], and there is an ongoing discussion about its widespread use. In our study, the cystatin-C-based kidney function test showed complete inverse changes compared to the changes described above in creatinine-based kidney function tests: serum cystatin C levels and eGFR based on cystatin C were significantly lower in hypothyroidism ($p = 0.02$ and $p = 0.02$) and significantly higher in hyperthyroidism ($p = 0.01$ and $p < 0.001$). Furthermore, there is a highly significant positive correlation ($r = 0.76$, $p < 0.001$) between fT_4 and cystatin C in patients with overt hypo- and hyperthyroidism. These observations are in line with the findings from other groups [8, 9, 27], indicating that cystatin C is a better marker of thyroid function than a kidney function test in this setting. It was speculated that the thyroid function is involved in the metabolism of cystatin C [28], as it has been described for β_2 -microglobulin [29].

In the situation described above, with inverse behavior of creatinine and cystatin C in thyroid dysfunction, it is exciting to study a GFR equation based on both biomarkers, creatinine and cystatin C. We used the equation proposed by Stevens et al [14], and indeed there was no

Fig. 5. Correlation between serum cystatin C and fT_4 .

significant change of estimated GFR before and after treatment of hyperthyroid patients. In hypothyroid patients there was a predominant ‘creatinine effect’ with a significant decrease in hypothyroidism compared to the euthyreotic state ($p = 0.01$). Nevertheless, cystatin C seems to be worthless as a kidney function test in thyroid dysfunction; therefore, any cystatin-C-based equation should be avoided in this setting.

The impact on thyroid dysfunction on cystatin C is of special interest on the background of its recommended use as an earlier biomarker of acute kidney injury in emergency [30] and intensive care medicine [6, 31]. In the emergency department [32] and especially in the intensive care unit, the prevalence of abnormal thyroid function tests is extremely high with more than 70% of the

intensive care patients showing low total T₃, and around 50% have low total T₄ [33].

Several recent studies demonstrate that NGAL, measured in plasma or urine, is an earlier biomarker in acute injury [34–36]. Nevertheless, there are several known limitations, the clinically most important one is an increase in NGAL in inflammation [37]. NGAL is an NF- κ B-regulated gene and is furthermore known to be a survival factor for thyroid neoplastic cells [11]. In contrast to cystatin C, there was no significant change in NGAL levels before and after treatment of thyroid disorders.

In summary, thyroid function has a major influence on the vast majority of kidney function tests. Cystatin C is strongly influenced by the thyroid function and should be avoided in thyroid disorders, but there was no effect of the thyroid function on the low NGAL levels in patients without acute kidney injury. The recommended kidney

function test in thyroid dysfunction is a creatinine-based GFR estimation (24-hour creatinine clearance, calculated GFR by Cockcroft-Gault or the CKD-EPI equation). Furthermore, kidney and thyroid function should always be used together to avoid misleading interpretations.

Acknowledgment

This study was supported by the Robert Bosch Foundation Stuttgart, Germany.

Disclosure Statement

No conflict of interest declared.

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