Peer reviewed article

Effects of thyroxine replacement on serum creatinine and cystatin C in patients with primary and central hypothyroidism

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Summary

Background: Serum cystatin C (CysC) is a marker for kidney function, possibly superior to serum creatinine (Cr). Cr is increased and CysC decreased in primary hypothyroidism; these changes are reversed upon thyroxine (T4) replacement therapy. This (pilot) study was performed to see whether these opposing changes of CysC and Cr could be confirmed in patients with central hypothyroidism.

Methods: Prospective case series of consecutively referred patients with primary and central hypothyroidism. CysC and Cr were determined at the time of diagnosis and following T4 replacement therapy.

Results: 32 patients with newly diagnosed hypothyroidism were included. In 16 patients with primary hypothyroidism, mean fT4 was 4.4 ± 2.5 pmol/l (normal range 12 to 22) at diagnosis and increased to 20.1 ± 5.2 pmol/l (p <0.001) following T4 replacement. CysC increased from 0.79 ± 0.27 mg/l (normal range 0.63 to 1.33) to 1.03 ± 0.42 mg/l (p = 0.007) whereas Cr declined from 104 ± 21 µmol/l to 90 ± 19 µmol/l (p <0.001). In 16 patients with central hypothyroidism, mean fT4 was 6.5 ± 1.6 pmol/l at diagnosis and increased to 15.7 ± 3.3 pmol/l (p <0.001) following T4 replacement. CysC increased from 0.74 ± 0.27 mg/l to 0.83 ± 0.30 mg/l (p = 0.01) whereas Cr was not elevated at baseline (83 ± 11 µmol/l) and did not decrease following treatment (84 ± 10 µmol/l).

Conclusions: CysC was low at diagnosis of hypothyroidism and significantly increased following T4 replacement in patients with primary as well as central hypothyroidism. T4 replacement decreased Cr levels in patients with primary hypothyroidism whereas Cr remained unchanged in patients with central hypothyroidism. CysC may not accurately reflect kidney function in patients with primary and central thyroid dysfunction.

Key words: kidney function; replacement therapy; thyroid function

Introduction

Serum cystatin C (CysC) has been introduced as a marker of kidney function and considered to be an estimator of the glomerular filtration rate (GFR) at least as good as serum creatinine (Cr) [1, 2]. CysC is a more sensitive marker than Cr, especially in patients with mildly impaired GFR (in the "creatinine-blind" range) [3]. It is a low-molecular-weight protein produced at a constant rate

Abbreviations

Cr	serum creatinine
CysC	serum cystatin C
fT3	free triiodothyronine
fT4	free thyroxine
GFR	glomerular filtration rate
GH	growth hormone
IGF-1	insulin-like growth factor-1

No conflict of interest to declare.

by most nucleated cells independently of age, gender and lean tissue mass [3–5]. CysC is freely filtered by the glomerulus, reabsorbed and almost completely catabolised and destroyed by the tubular epithelial cells [6]. Therefore, GFR is the major determinant of CysC although the compound is barely excreted in the urine.

Although the production of CysC is not influenced by inflammatory states, serum levels of CysC may be influenced by hormones [4]. For instance, pharmacological glucocorticoid therapy increases CysC [7–9]. There is also an impact of thyroid dysfunction on CysC. CysC levels are lower in hypothyroid and higher in hyperthyroid states as compared with the euthyroid state, changes which are the opposite to those of Cr levels in patients with primary hypo- and hyperthyroidism [10–13]. Opposing changes of CysC and Cr could be confirmed even in patients with subclinical hypo- and hyperthyroidism [14]. Since the influence of T4 treatment on CysC in central hypothyroidism has not been investigated, the aim of this study was to test whether there might be a difference between the effects of thyroid hormone replacement on Cr and CysC in patients with primary and central hypothyroidism.

Materials and methods

Patients with newly diagnosed primary and central hypothyroidism referred to the Division of Endocrinology and Diabetes at the University Hospital in Zurich between 1998 and 2006 were included. Some of these patients also took part in two other studies at our institution [10,15]. Main inclusion criteria were untreated well-documented overt hypothyroidism at baseline as well as the possibility of follow-up visits and prospective collection of blood samples at our division. Patients with impaired renal function were not excluded. Oral informed consent to determine additional laboratory values had been obtained from all patients.

Free thyroxine (fT4), free triiodothyronine (fT3), TSH, CysC, Cr and insulin-like growth factor-1 (IGF-1) were measured in the hypothyroid state and following thyroxine replacement therapy after 4 ± 2 months in patients with primary and after 3 ± 2 months in patients with central hypothyroidism. Blood samples were taken before the intake of levothyroxine. In some patients with central hypothyroidism, blood samples were taken after glucocorticoids had been administered, either for replacement or treatment, depending on the condition in these patients.

fT4, fT3 and TSH were measured with electrochemoluminescence immunoassay technique on an Hitachi E170 system, Roche Diagnostics, Rotkreuz, Switzerland; fT4 with a normal range from 12 to 22 pmol/l and a coefficient of variation (= standard deviation/arithmetic mean) of 2.0% (16.9 pmol/l), fT3 with a normal range from 2.8 to 7.1 pmol/l and a coefficient of variation of 4.9% (5.1 pmol/l), TSH with a normal range from 0.27 to 4.2 mU/l and a coefficient of variation of 2.5% (1.56 mU/l). CysC was measured using an immunologic turbidimetric assay on a Cobas Integra 800 system, Roche Diagnostics, Rotkreuz, Switzerland, using DAKO reagents (DAKO Diagnostics, Zug, Switzerland) with a normal range from 0.63 to 1.33 mg/l and a coefficient of variation of 3.8% (1.35 mg/l). Cr was measured with the kinetic Jaffe reaction, rate-blanked with colour compensation on a Hitachi P-Modular system, Roche Diagnostics, Rotkreuz, Switzerland, with a normal range from 62 to 106 µmol/l for men and 44–80 µmol/l for women and a coefficient of variation of 1.7% (94 µmol/l) [16]. Based on the recommendations of the National Kidney Foundation the estimated glomerular filtration rate was calculated using the 4-v MDRD (IDMS) formula: GFR-IDMS [ml/min/1.73m^2] = 175 x (creatinine [µmol/l] / 88.4)$^{-1.154}$ x (age)$^{-0.203}$. For women the results were multiplied with 0.742; all of our patients were Caucasians. The MDRD (IDMS) results [ml/min/1.73 m^2 body surface area] were adjusted according to Du Bois' formula for adults (age >18 y.): body surface area (m^2) = weight [kg]$^{0.425}$ x size [cm]$^{0.725}$ x 0.007184.

IGF-1 was measured by RIA after removal of IGFBPs by chromatography; results are expressed in µg/l [15].

Data are presented as mean values ± SD when normally distributed and as median and interquartile range when not normally distributed (TSH). Values before and after treatment within the two groups were analysed using paired t-test. Unpaired t-test was performed to compare data between the two groups (primary hypothyroidism versus central hypothyroidism). Non-parametric tests (Wilcoxon signed rank test and Mann-Whitney U-test) were used for not normally distributed data (i.e. TSH). All statistical analyses were performed with WinSTAT for Excel software. P-values <0.05 were considered statistically significant.

Results

Primary hypothyroidism

16 patients (10 female) with primary hypothyroidism resulting from chronic autoimmune thyroiditis (all TPO antibody-positive) were included. Mean age at diagnosis was 44 ± 18 years and BMI was 25.7 ± 6.5 kg/m^2. All patients were treated with levothyroxine. 4 ± 2 months later, fT4, fT3, IGF-1 and CysC as well as heart rate had increased whereas TSH, Cr and diastolic blood pressure had fallen significantly. Seven of 16 patients at baseline met screening criteria for impaired renal function (estimated GFR ≤60 ml/min using the 4-v MDRD). At follow-up, the estimated GFR rose to >60 ml/min in two of the seven patients with impaired renal function at baseline. Laboratory results at baseline and following T4 treatment are shown in Table 1. With the exception of one patient with primary hy-

Table 1

Response to T4 replacement therapy.

		primary hypothyroidism (n = 16)	**central hypothyroidism** (n = 16)	central vs primary	
				difference (95% CI)	p values
fT4 (pmol/L, normal range 12–22)					
	baseline (hypothyroid)	4.4 ± 2.5	6.5 ± 1.6	2.1 (0.6–3.7)	0.01
	follow-up (euthyroid)	20.1 ± 5.2	15.7 ± 3.3	–4.4 (–7.7 to –1.2)	0.009
	follow-up vs baseline: p values	<0.001	<0.001		
	change (95% CI)	+15.7 (13.2–18.3)	+9.2 (7.2–11.1)		<0.001
fT3 (pmol/L, normal range 2.8–7.1)					
	baseline	2.1 ± 0.7	3.4 ± 1.1	1.3 (0.6–1.9)	<0.001
	follow-up	5.0 ± 1.2	4.0 ± 0.6	–1 (–1.7 to –0.3)	0.006
	follow-up vs baseline: p values	<0.001	0.02		
	change (95% CI)	+2.9 (2.1–3.7)	+0.6 (0.1–1.1)		<0.001
TSH (mU/L, normal range 0.27–4.2)					
	baseline	89 (62–319)	1.8 (1.1–2.6)		0.001
	follow-up	2.2 (0.38–3.35)	0.25 (0.1–0.48)		<0.001
	follow-up vs baseline: p values	0.001	0.01		
CysC (mg/L, normal range 0.63–1.33)					
	baseline	0.79 ± 0.27	0.74 ± 0.27	–0.05 (–0.25–0.15)	0.62
	follow-up	1.03 ± 0.42	0.83 ± 0.30	–0.2 (–0.47–0.07)	0.14
	follow-up vs baseline: p values	0.007	0.01		
	change (95% CI)	+0.24 (0.08–0.41)	+0.09 (0.03–0.16)		0.079
Cr (µmol/L)	baseline	104 ± 21	83 ± 11	–21 (–33 to –8)	0.003
	follow-up	90 ± 19	84 ± 10	–6 (–18–4)	0.21
	follow-up vs baseline: p values	<0.001	0.7		
	change (95% CI)	–14 (–19 to –8)	+1 (–3–4)		<0.001
IGF-1 (µg/L)	baseline	111 ± 57	64 ± 29	–47 (–81 to –14)	0.008
	follow-up	153 ± 45	99 ± 42	–54 (–86 to –21)	0.002
	follow-up vs baseline: p values	0.01	<0.001		
	change (95% CI)	+42 (12–72)	+35 (21–50)		0.684
Systolic blood pressure (mm Hg)	baseline	127 ± 19	123 ± 25	–4 (–20–11)	0.58
	follow-up	122 ± 14	125 ± 19	3 (–9–16)	0.58
	follow-up vs baseline: p values	0.07	0.37		
	change (95% CI)	–5 (–11 to –0.5)	+2 (–3.5–9.5)		0.058
Diastolic blood pressure (mm Hg)	baseline	80 ± 10	78 ± 11	–2 (–10–6)	0.57
	follow-up	72 ± 7	80 ± 9	8 (2–14)	0.009
	follow-up vs baseline: p values	0.006	0.34		
	change (95% CI)	–8 (–13 to –4.5)	+2 (–3–8)		0.002
Heart rate (beats/min)					
	baseline	64 ± 9	69 ± 8	5 (–1–11)	0.11
	follow-up	71 ± 7	71 ± 10	0 (–5–7)	0.81
	follow-up vs baseline: p values	<0.001	0.21		
	change (95% CI)	+7 (4.5 – 11.5)	+2 (-2–7.5)		0.072

Data are presented as mean values ± SD when normally distributed. Not normally distributed parameters are presented as medians and interquartile ranges (TSH).

pothyroidism whose blood pressure was not recorded at follow-up visit, the data for all outcome measures were available.

Central hypothyroidism

16 patients (9 female) with central hypothyroidism due to pituitary tumours or craniopharyngiomas were included. Mean age at diagnosis was 45 ± 18 years and BMI was 26.4 ± 4.5 kg/m^2. Four patients had a macro-prolactinoma, five had a non-functioning macro-adenoma and seven had a craniopharyngioma. In addition to TSH deficiency, all these patients were also lacking gonadotropins (and sex hormones) and most of them growth hormone (GH). 11 patients had ACTH deficiency. Among these 11 patients, four patients were on dexamethasone (pharmacological glucocorticoid treatment) and two patients on hydrocortisone (replacement) therapy when baseline values were determined. Five patients with ACTH deficiency were not on glucocorticoid treatment when the baseline blood samples were taken. At follow-up, 14 patients were on glucocorticoid replacement (three of them for safety reasons). Glucocorticoids were given for replacement and therefore at low doses in all patients at the time of follow-up.

All patients were treated with levothyroxine. At follow-up, fT4 had increased but heart rate and blood pressure remained unchanged. Laboratory results at baseline and following T4 treatment are shown in table 1.

In contrast to patients with primary hypothyroidism, Cr was not increased at baseline and did not change after T4 replacement whereas CysC increased in the same period. Two of 16 patients met screening criteria for impaired renal function (estimated GFR using the 4-v MDRD based formula ≤60 ml/min) both at baseline and at follow-up. Serum IGF-1 concentrations before and after T4 therapy were lower compared to patients with primary hypothyroidism but there was also a significant increase following T4 replacement. An increase in CysC in response to T4 was also observed in the six patients already on glucocorticoids at baseline (0.74 mg/l at baseline, 0.89 mg/l at follow-up) and in those (two patients) never treated with corticosteroids (0.54 mg/l at baseline, 0.65 mg/l at follow-up).

Discussion

Thyroid dysfunction has been associated with changes in kidney function, Cr, and CysC. Primary hypothyroidism results in an increase in Cr, reflecting a reduction in GFR most likely due to decreased renal blood flow [17–21] and T4 replacement results in a decrease of Cr levels. The changes of CysC concentrations in primary hypothyroidism are inverse to changes in Cr, i.e., CysC concentrations are low in the hypothyroid state and increase in response to T4 replacement. In this study we show that such inverse changes of Cr and CysC in patients with primary hypothyroidism cannot be confirmed in patients with central hypothyroidism.

At baseline, Cr was significantly higher in patients with primary hypothyroidism than in those with central hypothyroidism, and more of these patients had impaired renal function as judged by estimated GFR ≤60 ml/min using the 4-v MDRD. This difference between the two groups was no longer found after T4 replacement. Although thyroid hormone depletion was less severe in patients with central hypothyroidism, milder thyroid hormone deficiency cannot fully account for such a difference since Cr also increases in mild primary hypothyroidism [14]. In patients with central hypothyroidism, Cr levels were not increased at baseline and remained unchanged whereas CysC concentrations increased upon T4 replacement. This finding supports the hypothesis that the CysC production may be influenced by thyroid hormones. The absolute change of CysC levels in patients with central hypothyroidism was less pronounced than the changes observed in patients with primary hypothyroidism. This might be explained by smaller increase in fT3 concentrations in patients with central hypothyroidism compared to patients with primary hypothyroidism, indicating less severe hypothyroidism at baseline and less impact of T4 replacement in patients with central hypothyroidism.

CysC concentration may slightly differ between males and females. According to a study of Stevens et al [22], CysC was 9.2% lower in females than in males (after adjustment for GFR). Since we had almost an equal number of women in both groups (62.5 vs 56.3%), the influence of gender on the results will be minimal.

Thyroid hormone deficiency in patients with primary hypothyroidism results in endothelial dysfunction which can be corrected by T4 replacement [23, 24]. In our patients with central hypothyroidism, diastolic blood pressure, which is associated with endothelial dysfunction, was not increased at baseline and did not fall in response to T4 replacement therapy, whereas in patients with primary hypothyroidism, diastolic blood pressure was increased at baseline and fell significantly after T4 replacement therapy.

An obvious difference between patients with central vs patients with primary hypothyroidism is the TSH level (table 1) which is markedly increased in the latter only. In this context it may be of interest that TSH *per se* could possibly impair endothelium-dependent vasodilatation and could be partly responsible for the elevated blood pres-

sure and impaired renal function seen in patients with primary hypothyroidism [25].

Apart from TSH and thyroid hormones, other pituitary-dependent hormones could affect kidney function and Cr.

GH is the major stimulus for IGF-1 expression by hepatocytes. IGF-1 improves endothelial function, renal blood flow and raises GFR by a reduction of the efferent arteriolar resistance [26]. Serum concentration of IGF-1 is decreased in hypothyroidism and increased by T4 therapy in primary hypothyroidism and to somewhat lower levels in patients with central hypothyroidism reflecting that the patients with central hypothyroidism were (and remained) deficient in GH (table 1) [15]. In this context, it should be mentioned that GH and/or IGF-1 not only enhance the generation but also the biological actions of T3, possibly also explaining the smaller effects of T4 on CysC in patients with central hypothyroidism in our study [27]. Moreover, we cannot exclude the possibility that our empirical (symptom-, sign- and fT4-guided) T4-dosage was suboptimal with regard to normalising metabolism and CysC [28, 29].

Prolactin was not routinely assessed in patients with primary hypothyroidism but was markedly elevated at baseline in the four patients with macroprolactinoma, and moderately increased in some of the other patients with pituitary and thyroid disorders. Prolactin was not associated with changes in CysC, but due to the limited number of patients our data neither suggest nor exclude an influence of prolactin on CysC.

High dose glucocorticoid therapy has been reported to increase CysC. In renal transplant recipients CysC increased in patients with corticosteroid therapy after renal transplantation [30]. In such studies, however, nephrotoxic calcineurin inhibitor treatment could also contribute to differential increases in CysC and Cr after renal transplantation. In a more recent study, high-dose glucocorticoid therapy for nephrotic syndrome did not significantly increase CysC level in five children with high GFRs [8]. In vitro, dexamethasone produces a significant and dose-dependent increase in CysC expression in HeLa cells [31]. We confirmed stimulatory effects of dexamethasone on CysC mRNA in cultured bone and lung cells, and we found stimulatory effects of T3 in vitro [Schmid. et al., in preparation].

To our knowledge, there are no data on the effect of cortisol deficiency and replacement on kidney function, Cr or CysC. In our study, an effect of (low-dose) glucocorticoid replacement therapy on Cr and CysC in patients with central hypothyroidism is difficult to confirm or to exclude because of the heterogeneity of glucocorticoid deficiency and therapy at baseline and at follow-up. Apparently, it could not mask a stimulatory effect of T4, since CysC levels increased at follow-up even in the six patients on glucocorticoid therapy at baseline. The small number of patients in this subgroup precluded meaningful statistical analysis. We found that the impact of T4 replacement therapy on CysC level was important in both primary and central hypothyroidism, irrespective of glucocorticoid therapy.

A major limitation of our study is the fact that the analysis of kidney function was restricted to serum markers and did not include direct measurement of GFR by clearance of inulin, radionuclides or radiocontrast agents. Formulae such as the 4-v MDRD have been used for Cr-based estimation of GFR and have been validated in larger cohorts, including elderly people. However, these formulae lack precision for individuals with GFR >60 ml/min and they have not been validated for patients suffering from pituitary failure. The same is true for serum markers. Both CysC and Cr are remarkably low in central hypothyroidism and possibly overestimate GFR in these patients. CysC may not accurately reflect kidney function in patients with primary and central thyroid dysfunction. To fully elucidate the relationship between thyroid function, CysC and Cr concentration, further research with larger sample sizes is needed to correct the analysis for age, sex, body composition, renal function, differences in underlying disease, baseline, pattern and severity of pituitary failure and hormonal replacement therapies (in patients with central hypothyroidism). Furthermore, direct measurement of GFR should be considered. Our pilot study suggests that CysC may be among the more sensitive surrogate parameters reflecting thyroid hormone action not only in primary but also in central hypothyroidism.

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