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Impact of thyroid dysfunction on serum cystatin C

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Background. Serum cystatin C (CysC) is a novel marker for kidney function that has been claimed to be superior to serum creatinine. Thyroid dysfunction may alter creatinine, which has been found to be increased in hypothyroidism and decreased in hyperthyroidism. This study was performed to evaluate whether changes in CysC and creatinine are parallel during the treatment of hypo- and hyperthyroidism, respectively.

Methods. Prospective case series of 22 consecutively referred patients with thyroid dysfunction. Creatinine and CysC were determined at the time of diagnosis of hypo- and hyperthyroidism, and when free thyroxine (fT4) returned into the normal range. Hypothyroid patients were treated with levothyroxine. Hyperthyroid patients were treated with antithyroid drugs, surgery, or radioiodine.

Results. Nine patients with hypothyroidism and 13 patients with hyperthyroidism were included. In patients with hypothyroidism mean fT4 (±SD) was 4.9 ± 2.5 pmol/L (reference, 12 to 22) at diagnosis and increased to 16.6 ± 3.6 pmol/L when patients were treated with levothyroxine. Creatinine decreased from 86 ± 13 μmol/L (reference, 70 to 105) in the hypothyroid state to 76 ± 16 μmol/L when fT4 normalized ($P = 0.062$), whereas CysC increased from 0.84 ± 0.17 mg/L (reference, 0.63 to 1.33) to 1.1 ± 0.28 mg/L ($P < 0.001$). In patients with hyperthyroidism, mean fT4 was 54.6 ± 22.7 pmol/L (reference, 12 to 22) at diagnosis and decreased to 15.8 ± 3.6 pmol/L following treatment with antithyroid drugs, thyroid surgery, or radioiodine. Creatinine increased from 67 ± 15 μmol/L at diagnosis of hyperthyroidism to 75 ± 9 μmol/L when fT4 normalized ($P = 0.004$), whereas CysC declined from 1.32 ± 0.17 mg/L to 0.95 ± 0.19 mg/L ($P < 0.001$).

Conclusion. Thyroid dysfunction has a major impact on CysC levels. Therefore, thyroid function has to be considered when CysC is used as a marker of kidney function. In contrast to creatinine concentrations, CysC levels are lower in the hypothyroid and higher in the hyperthyroid state as compared with the euthyroid state.

Thyroid dysfunction is known to influence serum creatinine levels. Decreased creatinine clearance and eventually increased creatinine release by muscle cells seem to be responsible for elevated serum creatinine levels observed in patients with hypothyroidism [1–3]. In contrast, decreased serum creatinine levels may be encountered in patients with hyperthyroidism [3, 4].

In 1985, serum cystatin C (CysC) was introduced as a new marker of kidney function [5]. CysC is a low molecular weight, basic protein that functions as a physiologic inhibitor of cysteine proteinases [6]. CysC is considered to be produced at a constant rate by most nucleated cells [7]. The structure of its gene is of the housekeeping type and the production of CysC is not influenced by inflammatory states [7]. The protein is freely filtered at the glomerulus and practically completely reabsorbed and catabolized by tubular cells [8]. Compared to serum creatinine, CysC has a lower interindividual variability and is not correlated to lean tissue mass, gender, and age [9, 10]. CysC has proved to be a reliable marker of glomerular filtration rate (GFR) in healthy adults and children as well as in patients with renal disorders of rheumatologic, nephrologic, hepatic, and neoplastic origin [11–14]. In a review of 24 studies, CysC was found to be an estimator of the GRF at least as well as serum creatinine in the population at large and likely even superior in specific patient populations [15].

To the best of our knowledge, an influence of thyroid dysfunction on serum CysC levels has not been described before. The aim of this study was to evaluate whether parallel changes in CysC and serum creatinine could be observed in patients with hypothyroidism and hyperthyroidism, reflecting presumed effects of thyroid hormones on kidney function.

METHODS

Patients with newly diagnosed hypo- or hyperthyroidism who had been referred to the Division of Endocrinology and Diabetes at the University Hospital in Zurich between February 2000 and March 2002 were included. Only patients with follow-up at our division were included.

Key words: serum cystatin C, thyroid dysfunction, creatinine.

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Patients with subclinical hypo- or hyperthyroidism and patients with altered kidney function at study end (defined as serum creatinine above the normal range) were excluded from the analysis. Informed consent to determine additional laboratory values (serum creatinine and CysC) was obtained from all patients. CysC, serum creatinine, and free thyroxine (fT4) were measured in the hypo- or hyperthyroid state, respectively, and when fT4 had returned into the normal range. Thyroid function was monitored with fT4 because patients with secondary hypothyroidism were also included in the study and because thyroid-stimulating hormone (TSH) often remains suppressed in previously hyperthyroid patients for a longer period of time. Blood samples were taken before the intake of the daily medication (i.e., levothyroxine). Samples were immediately centrifuged and analyzed on the same day.

fT4 was measured by a electrochemoluminescence immunoassay (Elecsys, Roche, Rotkreuz, Switzerland) with a reference range from 12 to 22 pmol/L and a coefficient of variation (CV = standard deviation/arithmetic mean) of 14.5% (measured at a value of 5.1 pmol/L). CysC was measured by an immunologic turbidimetric assay (Cobas Integra, DAKO Diagnostics, Zug, Switzerland) with a reference range from 0.63 to 1.33 mg/L and a CV of 3.8% (1.35 mg/L). Serum creatinine was measured by a kinetic Jaffé reaction (Hitachi Modular System, Roche, Rotkreuz, Switzerland) with a reference range from 60 to 105 μmol/L and a CV of 1.7% (94 μmol/L).

Statistical analyses were performed using SAS Version 8.2 (SAS institute, Inc., Cary, NC, USA). Mean and standard deviation were used for descriptive statistics. Values before and after treatment within the two groups were analyzed using paired Student *t* test. A P value <0.05 was considered statistically significant.

RESULTS

Hypothyroidism

Nine patients (eight female and one male) with hypothyroidism were included; seven with primary hypothyroidism and two with secondary hypothyroidism due to pituitary disorders. Primary hypothyroidism resulted from chronic autoimmune thyroiditis in five patients and from thyroid surgery or radioiodine (I^{131}) ablation in two patients. Median age (range) at diagnosis was 34 (14 to 52) years. Mean fT4 at diagnosis was 4.9 ± 2.5 pmol/L. Mean TSH in patients with primary hypothyroidism was 198 ± 224 mU/L (reference, 0.27 to 4.2). All patients were treated with levothyroxine. Thyroxine substitution increased fT4 levels to 16.6 ± 3.6 pmol/L within 13 ± 5 weeks. TSH decreased in patients with primary hypothyroidism to 2.6 ± 2.5 mU/L. Serum creatinine declined from 86 ± 13 μmol/L at diagnosis to 76 ± 16 μmol/L ($P = 0.062$) when fT4 had normalized. In contrast, CysC increased from 0.84 ± 0.17 mg/L to 1.1 ± 0.28 mg/L ($P < 0.001$) in the same period. Changes of serum creatinine and CysC of all individual patients are demonstrated in the Figure 1 A and B. Two patients with impaired kidney function due to hypertension at study end were excluded from the analysis; they showed the same change of serum creatinine and CysC on a higher level. The exclusion of these patients had no influence on the conclusion of our study.

Hyperthyroidism

Thirteen patients (nine female and four male) with primary hyperthyroidism were included. Hyperthyroidism resulted from Graves' disease in 11 patients, from toxic multinodular goiter in one patient, and in another patient from suppressive therapy with levothyroxine. The median age (range) at diagnosis was 43 (22 to 86) years. One patient was known to have glomerulonephritis, but her serum creatinine was within the normal range. Mean fT4 at diagnosis of hyperthyroidism was 54.6 ± 22.7 pmol/L. TSH levels were undetectable in 12 patients, one patient had a TSH level of 0.07 mU/L (reference, 0.27 to 4.2). Nine patients were treated with antithyroid drugs, two patients underwent thyroid surgery, and one patient received radioiodine. Doses of levothyroxine were reduced in the patient with suppressive therapy. In all patients, fT4 returned to normal (fT4 15.8 ± 3.6 pmol/L) within 12 ± 8 weeks; TSH levels remained undetectable in eight patients and were below the normal range in five patients. Serum creatinine increased from 67 ± 15 μmol/L at diagnosis of hyperthyroidism to 75 ± 9 μmol/L ($P = 0.004$) when fT4 had normalized. In contrast, CysC decreased from 1.32 ± 0.17 mg/L to 0.95 ± 0.19 mg/L ($P < 0.001$) during the same period. Changes of serum creatinine and CysC are shown in Figure 1 C and D.

DISCUSSION

Thyroid dysfunction is associated with changes in serum creatinine. In agreement with previous reports, serum creatinine values in our study were higher in hypothyroidism and lower in hyperthyroidism as compared with the values of the same individual in the euthyroid state. By contrast, we observed inverse changes of CysC levels in patients with thyroid dysfunction. CysC levels were significantly lower in hypothyroidism and significantly higher in hyperthyroidism compared to the euthyroid state. The inverse changes in CysC and serum creatinine seen in patients with thyroid hormone deficiency and excess, respectively, suggest that the effects of thyroid hormones on GFR are overridden by the effects of thyroid hormones on CysC. Medications with

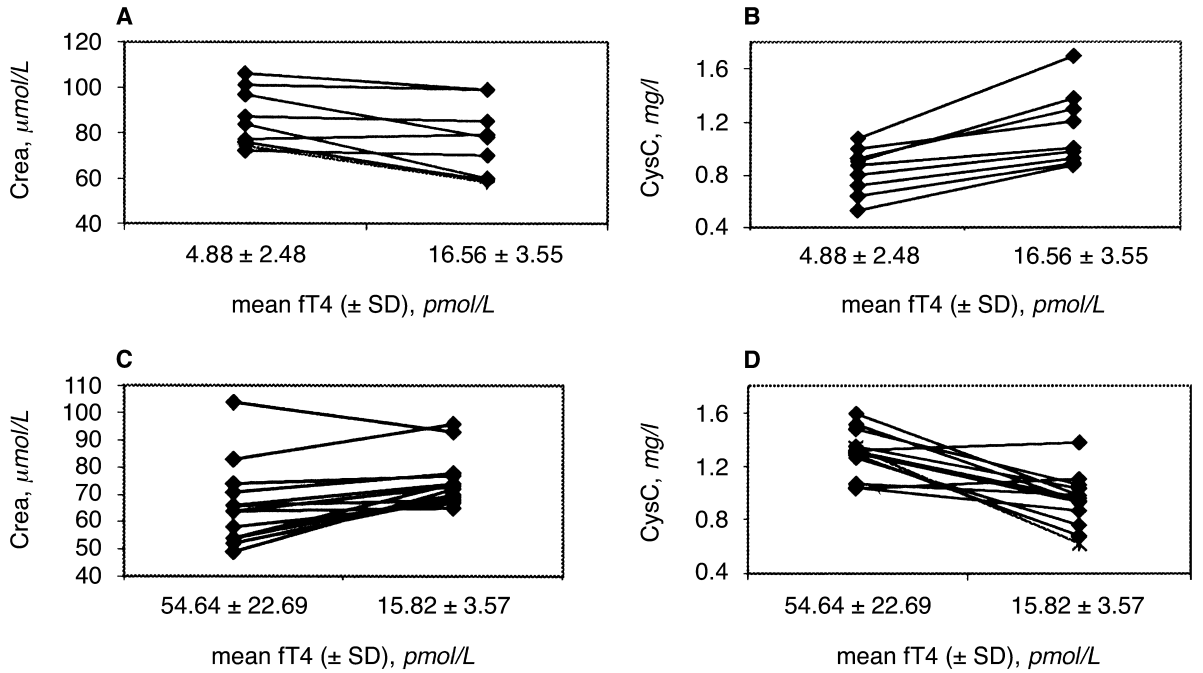

Fig. 1. Serum creatinine and cystatin C (CysC) in patients treated for hypothyroidism (*A* and *B*) and hyperthyroidism (*C* and *D*). Values are shown at diagnosis of hypothyroidism and hyperthyroidism, respectively, and when free thyroxine (fT4) returned into the normal range.

a relevant influence on serum creatinine have not been prescribed to our patients.

CysC is considered to be produced in all nucleated cells at a constant rate [7]. The influence of thyroid hormones on CysC observed in our study may be explained by an altered production rate of CysC in the context of a changed cell turnover and/or metabolic rate in thyroid dysfunction. Because we included patients with thyroid disorders of different origin, a direct effect of thyroid hormones on CysC appears to be the most likely explanation. Despite a rather small number of patients included, the effect of thyroid hormones on CysC was highly significant ($P < 0.001$) since it was consistently found in each individual patient except two patients with hyperthyroidism. The correlation between fT4 and CysC in patients with overt thyroid dysfunction is highly significant. However, the effect of mild thyroid dysfunction (subclinical hypo- and hyperthyroidism) on CysC remains unknown.

Thyroid function may be altered in patients without characteristic symptoms of hypo- or hyperthyroidism, respectively. Therefore, thyroid dysfunction should be considered when CysC is used as marker of kidney function. We suggest that thyroid function be documented when CysC is determined scientifically. There have been other reports on factors influencing CysC levels. CysC may underestimate creatinine clearance in transplant patients and may be increased in cancer patients due to increased cell turnover or death [16, 17]. However, thyroid function was not assessed systematically in studies investigating the utility of CysC as a marker of kidney function.

Due to the major impact of thyroid hormones on CysC demonstrated in our study, we recommend that altered thyroid function should be considered when CysC is determined.

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