

## ESTIMATION OF GLOMERULAR FILTRATION RATE FROM SERUM CYSTATIN C AND CREATININE IN PATIENTS WITH THYROID DYSFUNCTION

### ODREĐIVANJE JAČINE GLOMERULSKE FILTRACIJE NA OSNOVU SERUMSKE KONCENTRACIJE CISTATINA C I KREATININA KOD BOLESNIKA SA POREMEĆAJEM FUNKCIJE ŠTITASTE ŽLEZDE

Velibor Čabarkapa, Romana Mijović, Zoran Stošić, Nikola Ćurić, Radmila Žeravica, Branislava Ilinčić

Center for Laboratory Medicine, Clinical Center of Vojvodina, Novi Sad, Serbia

**Summary:** Given that thyroid function influences serum cystatin C and creatinine levels, the question arises as to whether it is possible to accurately estimate glomerular filtration rate (GFR) in patients with thyroid dysfunction. The objective of the study was to determine serum cystatin C and creatinine levels and estimate GFR in patients with thyroid dysfunction. The study included 32 cases with newly diagnosed hyperthyroidism and 27 cases with newly diagnosed hypothyroidism, as well as 20 healthy controls matched for sex and age with the cases. Serum concentrations of thyroid stimulating hormone (TSH), free triiodothyronine (fT3) and free thyroxine (fT4), creatinine and cystatin C were measured in all study subjects. GFR was estimated using the Modification of Diet in Renal Disease (MDRD), the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) and cystatin C-based equations. Serum cystatin C levels were significantly higher in hyperthyroid subjects compared to controls ( $1.32 \pm 0.31$  vs.  $0.89 \pm 0.15$ ;  $p < 0.01$ ). Serum creatinine levels were significantly lower in hyperthyroid subjects compared to controls ( $60.6 \pm 10.2$  vs.  $76.4 \pm 8.6$ ;  $p < 0.01$ ), and significantly higher in hypothyroid subjects compared to controls ( $94.5 \pm 13.2$  vs.  $76.4 \pm 8.6$ ;  $p < 0.01$ ). GFR estimated with the MDRD equations was significantly higher in hyperthyroid subjects compared to hypothyroid subjects ( $101.6 \pm 20.7$  vs.  $64.1 \pm 11.6$  mL/min/1.73m<sup>2</sup>;  $p < 0.01$ ). GFR estimated with the equation based on serum cystatin C was significantly lower in hyperthyroid subjects compared to hypothyroid subjects ( $59.2 \pm 22.1$  vs.  $92.1 \pm 16.0$  mL/min/1.73m<sup>2</sup>;  $p < 0.01$ ). Although serum cystatin C is regarded a reliable marker of GFR and more sensitive than serum creatinine, it has limitations in patients with thyroid dysfunction, due to significant changes in its serum concentrations

**Kratak sadržaj:** S obzirom na uticaj tireoidne funkcije na nivo cistatina C i kreatinina, postavlja se pitanje mogućnosti pravilne procene (GFR) brzine glomerularne filtracije kod bolesnika sa tireoidnom disfunkcijom. Cilj ove studije je evaluacija vrednosti cistatina C i kreatinina uz procenu (GFR) kod bolesnika sa poremećajem funkcije štitaste žlezde. U ispitivanje je uključeno 32 bolesnika sa novodijagnostikovanom hipertireozom i 27 bolesnika sa novodijagnostikovanom hipotireozom. Kontrolnu grupu sačinjava 20 zdravih ispitanika koji odgovaraju ispitivanoj grupi prema starosti i polu. Svim ispitanicima je određena koncentracija fT3, fT4, TSH, kreatinina i cistatina C. Procenjena je vrednost GFR jednačinama na osnovu serumske koncentracije kreatinina, kao i jednačinom baziranom na vrednosti cistatina C. Značajno su više vrednosti cistatina C u grupi hipertireoidnih bolesnika u odnosu na kontrolnu grupu ( $1,32 \pm 0,31$  vs.  $0,89 \pm 0,15$ ;  $p < 0,01$ ). Vrednosti kreatinina statistički su značajno niže u grupi hipertireoidnih bolesnika u odnosu na kontrolnu grupu ( $60,6 \pm 10,2$  vs.  $76,4 \pm 8,6$ ;  $p < 0,01$ ), za razliku od značajno viših vrednosti kreatinina u grupi hipotireoidnih bolesnika u odnosu na kontrolnu grupu ( $94,5 \pm 13,2$  vs.  $76,4 \pm 8,6$ ;  $p < 0,01$ ). GFR procenjena MDRD i CKD-EPI jednačinama u grupi hipertireoidnih bolesnika značajno je viša u odnosu na GFR u grupi hipotireoidnih bolesnika ( $101,6 \pm 20,7$  vs.  $64,1 \pm 11,6$  mL/min/1,73m<sup>2</sup>;  $p < 0,01$ ). GFR procenjena jednačinom baziranom na serumskoj koncentraciji cistatina C u grupi hipertireoidnih ispitanika statistički je značajno niža u odnosu na iste vrednosti u grupi hipotireoidnih subjekata ( $59,2 \pm 22,1$  vs.  $92,1 \pm 16,0$  mL/min/1,73m<sup>2</sup>;  $p < 0,01$ ). Iako se smatra da je cistatin C pouzdan parametar u proceni GFR, senzitivniji od serumske koncentracije kreatinina, njegova

*Address for correspondence:*

dr Velibor Čabarkapa  
Kornelija Stankovića 7  
21000 Novi Sad, Serbia  
Phone: +381652035741  
e-mail: veliborcabarkapa@gmail.com

*List of abbreviations:* GFR – Glomerular filtration rate, MDRD – Modification of Diet in Renal Disease, CKD-EPI – Chronic Kidney Disease Epidemiology Collaboration, TSH – thyroid stimulating hormone, fT3 – free triiodothyronine, fT4 – free thyroxine, PETIA – Particle-Enhanced Turbidimetric Immunoassay, CG – control group, HYPER – hyperthyroid subjects, HYPO – hypothyroid subjects, NS – non-significant.

regardless of renal function. In patients with thyroid dysfunction GFR should therefore be estimated using the equations based on serum creatinine.

**Keywords:** cystatin C, creatinine, glomerular filtration rate, thyroid dysfunction

## Introduction

Chronic kidney disease is a worldwide health problem. Early recognition of impaired renal function and timely initiation of treatment usually can slow down the progression of disease and/or prevent the development of numerous associated complications (1, 2).

The best parameter for evaluating renal function is glomerular filtration rate (GFR), which can be estimated using reliable and accurate methods employing clearances of exogenous substances such as iohexol,  $^{51}\text{Cr}$ -EDTA,  $^{125}\text{I}$ -iothalamate or  $^{99\text{m}}\text{Tc}$ -DTPA. Still, these methods are not part of routine diagnostic procedures (1, 2). The endogenous marker of GFR most commonly used in routine clinical and laboratory practice is serum creatinine (3). However, given that serum creatinine levels are influenced by non-renal factors such as age, sex, race, muscle mass and diet, this parameter is regarded insufficiently sensitive in the detection of mildly to moderately reduced GFR (2).

GFR is today usually estimated using prediction equations based on serum creatinine (2–4). The most widely used are the Cockcroft-Gault and the Modification of Diet in Renal Disease (MDRD) (4), as well as a modified MDRD equation called the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI), which is considered to yield a more precise estimation of GFR (3). Although the prediction equations have substantially improved routine estimations of GFR, none is ideal and unaffected by age, sex, pathology, and laboratory methods applied to determine serum creatinine.

Recent studies have suggested that cystatin C, a low molecular mass protein filtered by the glomerulus and completely reabsorbed by the proximal tubules, is a reliable parameter in GFR estimation. Serum cystatin C has been found superior to serum creatinine in estimating GFR in the range 60–90 mL/min/ $1.73\text{m}^2$  (4). It can be used in the prediction equations for estimating GFR, however, attention should be paid to appropriate laboratory methodology and possible presence of disease. In contrast to creatinine, serum cystatin C is not influenced by race, sex, muscle mass and diet (2). In addition, it has been found superior to creatinine in estimating GFR in patients after kidney transplantation (5), diabetics (6), patients receiving nonsteroidal antiinflammatory drugs and chemotherapy, and patients with liver cirrhosis (7).

upotreba je ograničena kod bolesnika sa tireoidnom disfunkcijom usled značajnih promena njegove serumske koncentracije nezavisno od bubrežne funkcije, odnosno, kod bolesnika sa tireoidnom disfunkcijom za procenu GFR treba koristiti jednačinu baziranu na serumskoj koncentraciji kreatinina.

**Ključne reči:** cistatin C, kreatinin, brzina glomerulske filtracije, tireoidna disfunkcija

On the other hand, serum cystatin C is influenced by other, non-renal factors, such as treatment with glucocorticoids (8) and thyroid dysfunction (6, 8), which limits its use in certain medical conditions.

Published data suggest the existence of numerous interactions between renal and thyroid function. Thyroid hormones are essential for the growth and development of the kidney; they participate in maintaining the homeostasis of fluids and electrolytes, and affect glomerular filtration rate, effective renal plasma flow, and tubular function (9).

In view of the possible effects of thyroid function on serum cystatin C and creatinine levels, regardless of renal function, the question arises whether it is possible to accurately estimate GFR using these markers in subjects with impaired thyroid function.

The objective of our study was to determine serum cystatin C and creatinine levels and estimate GFR in subjects with thyroid dysfunction.

## Materials and Methods

### Sample

This cross-sectional study was carried out at the Center for Laboratory Medicine of the Clinical Center of Vojvodina in Novi Sad, Serbia. The study group included a total of 59 subjects divided into two subgroups: one comprising 32 cases with newly diagnosed hyperthyroidism and the other comprising 27 cases with newly diagnosed hypothyroidism. None of the cases had a renal disease. The control group included 20 healthy subjects matched to the study group subjects for sex and age. Blood sampling was carried out in the morning on an empty stomach. Serum was kept at a temperature of  $-20\text{ }^{\circ}\text{C}$ , and measurements were performed in one series under the same conditions for all samples.

### Laboratory assays

Thyroid function was estimated in all subjects on the basis of determining thyroid stimulating hormone (TSH), free triiodothyronine (fT3) and free thyroxine (fT4) levels, using an Abbott Architect i2000SR instrument and Abbott commercially available assay kits, with the following reference ranges: TSH (0.35–4.94 mIU/L), fT3 (2.6–5.7 pmol/L) and fT4 (9.1–19.1 pmol/L).

Serum creatinine was determined according to the kinetic Jaffe's method, using an automated biochemical analyzer (Olympus AU400) and commercially available assay kits by the same manufacturer. Reference range for women was 30–96  $\mu\text{mol/L}$ ; for men < 50 years 30–110  $\mu\text{mol/L}$ ; and for men > 50 years 30–127  $\mu\text{mol/L}$ . Serum cystatin C was determined by an immunoturbidimetric method on the same analyzer (Olympus AU400) with Diazyme commercially available assay kits, with the reference range 0.50–1.03 mg/L.

GFR was calculated using the following prediction equations for

#### MDRD (4)

$\text{GFR} = 32.788 \times (\text{Scr})^{-1.154} \times (\text{age})^{-0.203} \times (0.742 - \text{women})$

GFR (in mL/min/1.73m<sup>2</sup>) Scr – serum creatinine (in  $\mu\text{mol/L}$ ), and for

#### CKD-EPI (10)

Women with serum creatinine  $\leq 62 \mu\text{mol/L}$ :

$\text{GFR} = 144 \times (\text{S}_{\text{Cr}}/0.7)^{-0.329} \times (0.993)^{\text{age}}$ ,

Women with serum creatinine > 62  $\mu\text{mol/L}$ :

$\text{GFR} = 144 \times (\text{S}_{\text{Cr}}/0.7)^{-1.209} \times (0.993)^{\text{age}}$

Men with serum creatinine  $\leq 80 \mu\text{mol/L}$ :

$\text{GFR} = 141 \times (\text{S}_{\text{Cr}}/0.9)^{-0.411} \times (0.993)^{\text{age}}$

Men with serum creatinine > 80  $\mu\text{mol/L}$ :

$\text{GFR} = 141 \times (\text{S}_{\text{Cr}}/0.9)^{-1.209} \times (0.993)^{\text{age}}$

GFR in mL/min/1.73m<sup>2</sup>, S<sub>Cr</sub> – serum creatinine (in mg/dL).

The prediction equation used for calculating GFR from serum cystatin C determined by the Particle-Enhanced Turbidimetric Immunoassay (PETIA) is as follows (4):

$\text{GFR (mL/min/1.73m}^2) = 84.69 \times [\text{cystatin C (mg/L)}]^{-1.68}$ .

Statistical analyses were performed using the Microsoft Office Excel 2003 software. All parameters were presented as mean  $\pm$  SD. Comparison of the groups was done using Student t-test. Interdependence of variables was tested using Pearson's correlation test. A P value of < 0.05 was regarded statistically significant.

## Results

Demographic and laboratory characteristics of the study subjects are listed in *Table I*.

There was no significant difference in sex and age between the cases and controls. There was a significant difference in serum cystatin C levels between hyperthyroid subjects and controls ( $1.32 \pm 0.31$  vs.  $0.89 \pm 0.15$ ;  $p < 0.01$ ) but no significant difference in serum cystatin C levels between hypothyroid subjects and controls ( $0.97 \pm 0.11$  vs.  $0.89 \pm 0.15$ ;  $p > 0.05$ ). Serum creatinine levels were significantly lower in hyperthyroid subjects compared to controls ( $60.6 \pm 10.2$  vs.  $76.4 \pm 8.6$ ;  $p < 0.01$ ) and significantly higher in hypothyroid subjects compared to controls ( $94.5 \pm 13.2$  vs.  $76.4 \pm 8.6$ ;  $p < 0.01$ ) (*Table I*).

A significant difference between hyperthyroid subjects and controls was found in GFR estimated with the MDRD ( $101.6 \pm 20.7$  vs.  $88.1 \pm 9.1$  mL/min/1.73 m<sup>2</sup>;  $p < 0.01$ ), the CKD-EPI ( $101.2 \pm 14.0$  vs.  $92.3 \pm 10.3$  mL/min/1.73m<sup>2</sup>;  $p < 0.01$ ), and the prediction equa-

**Table I** Demographic and laboratory characteristics of the study subjects

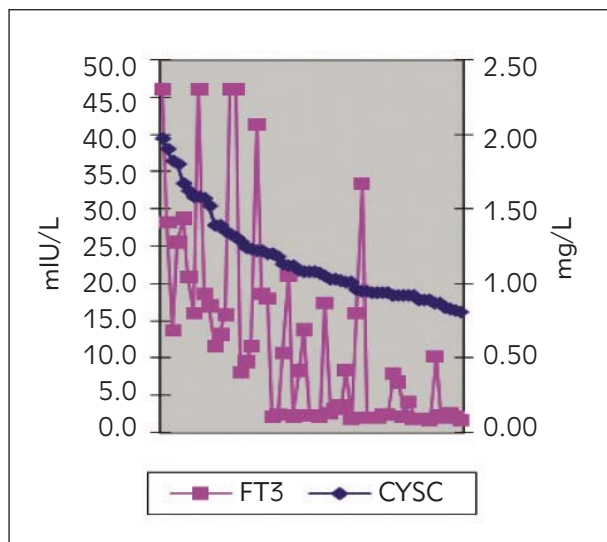
	CG	HYPER	HYPO	P value CG – HYPER	P value CG – HYPO
Age	49.6 $\pm$ 9.9	47.4 $\pm$ 11.3	51.2 $\pm$ 12.0	NS	NS
Men	4/20	6/32	6/27	NS	NS
Women	16/20	26/32	21/27	NS	NS
fT3 (pmol/L)	4.2 $\pm$ 0.3	20.5 $\pm$ 12.5	2.4 $\pm$ 0.5	<0.01	<0.01
fT4 (pmol/L)	14.2 $\pm$ 0.5	35.9 $\pm$ 12.8	5.7 $\pm$ 1.0	<0.01	<0.01
TSH (mIU/L)	1.55 $\pm$ 0.62	0.01 $\pm$ 0.01	61.99 $\pm$ 34.71	<0.01	<0.01
cystatin C (mg/L)	0.89 $\pm$ 0.15	1.32 $\pm$ 0.31	0.97 $\pm$ 0.11	<0.01	NS
creatinine ( $\mu\text{mol/L}$ )	76.4 $\pm$ 8.6	60.6 $\pm$ 10.2	94.5 $\pm$ 13.2	<0.01	<0.01

Legend: CG – control group; HYPER – hyperthyroid subjects; HYPO – hypothyroid subjects; NS – non-significant.

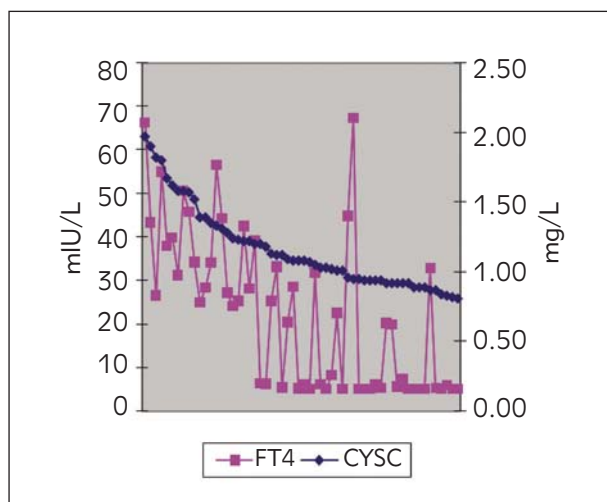
**Table II** Estimated GFR values in study subjects

	CG	HYPHER	HYPO	P value CG – HYPHER	P value CG – HYPO	P value HYPHER – HYPO
MDRD – GFR (mL/min/1.73m <sup>2</sup> )	88.1±9.1	101.6±20.7	64.1±11.6	<0.01	<0.01	<0.01
CKD – EPI – GFR (mL/min/1.73m <sup>2</sup> )	92.3±10.3	101.2±14.0	66.5±12.5	<0.05	<0.01	<0.01
CYS C – GFR (mL/min/1.73m <sup>2</sup> )	107.7±29.1	59.2±22.1	92.1±16.0	<0.01	<0.01	<0.01

Legend: CG – control group; HYPHER – hyperthyroid subjects; HYPO – hypothyroid subjects.



**Figure 1** Correlation between serum ft3 and cystatin C levels in subjects with thyroid dysfunction ( $r = 0.64$ ,  $p < 0.0001$ ).



**Figure 2** Correlation between serum ft4 and cystatin C levels in subjects with thyroid dysfunction ( $r = 0.67$ ,  $p < 0.0001$ ).

tion based on serum cystatin C ( $59.2 \pm 22.1$  vs.  $107.7 \pm 29.1$  mL/min/1.73 m<sup>2</sup>;  $p < 0.01$ ) (Table II).

Similarly, there was a significant difference between hypothyroid subjects and controls in GFR estimated with the MDRD ( $64.1 \pm 11.6$  vs.  $88.1 \pm 9.1$  mL/min/1.73 m<sup>2</sup>;  $p < 0.01$ ), the CKD-EPI ( $66.5 \pm 12.5$  vs.  $92.3 \pm 10.3$  mL/min/1.73 m<sup>2</sup>), and the prediction equation based on serum cystatin C ( $92.1 \pm 16.0$  vs.  $107.7 \pm 29.1$  mL/min/1.73 m<sup>2</sup>;  $p < 0.05$ ) (Table II).

GFR estimated with the MDRD and CKD-EPI equations was significantly higher in hyperthyroid subjects compared to hypothyroid subjects (MDRD:  $101.6 \pm 20.7$  vs.  $64.1 \pm 11.6$  mL/min/1.73m<sup>2</sup>;  $p < 0.01$ ; CKD-EPI:  $101.2 \pm 14.0$  vs.  $66.5 \pm 12.5$  mL/min/1.73 m<sup>2</sup>;  $p < 0.01$ ), whereas GFR estimated with the cystatin C equation was significantly lower in hyperthyroid subjects compared to hypothyroid subjects ( $59.2 \pm 22.1$  vs.  $92.1 \pm 16.0$  mL/min/1.73m<sup>2</sup>;  $p < 0.01$ ) (Table II).

Correlations between ft3 and ft4 levels and cystatin C levels in subjects with thyroid dysfunction are presented in Figures 1 and 2. A significant positive correlation was found between ft3 and ft4 levels and cystatin C levels. A significant negative correlation was found between TSH levels and cystatin C levels ( $r = -0.58$ ,  $p < 0.0001$ ).

### Discussion

The level of cystatin C production in nucleated cells remains constant from the age of one year to 50 years (4, 7). After the age of 50 serum cystatin C increases, reflecting a physiological decrease in GFR (7). Cystatin C production does not depend on sex, race, low muscle mass, and diet (8), and these characteristics make it superior to creatinine in the estimation of GFR in adults, in particular in the elderly and children (7). However, the fact that thyroid dysfunction influences serum cystatin C and creatinine levels questions the validity of estimating renal function in these patients.

Our results showing significantly higher cystatin C levels in hyperthyroid subjects compared to both healthy controls and hypothyroid subjects are consistent with the findings of previous similar studies (11–15). Elevated serum cystatin C may result from an increased cystatin C production rate due to accelerated metabolic activity and altered cellular metabolism seen in hyperthyroidism (13), although these mechanisms are still disputable. Stojanoski et al. reported that cystatin C levels in their hyperthyroid patients remained high, regardless of an increase in GFR estimated with  $^{99m}\text{Tc}$ -DTPA clearance, which may support the theory on the direct effect of thyroid hormones on increased cellular production of cystatin C (15). Furthermore, Wiesli et al. found that even mild changes in the levels of thyroid hormones had significant effects on cystatin C levels (13). Several prospective studies have shown that the elevated cystatin C levels in hyperthyroid patients decrease after the euthyroid state has been restored with thyroid suppression therapy (11–15).

In our study, hypothyroid subjects had statistically significantly lower cystatin C levels compared to hyperthyroid subjects, which is in agreement with the published data (11–15). In addition, cystatin C levels in our hypothyroid subjects were not below the reference range for the method applied, which is also consistent with several previous studies (13–16). The low cystatin C levels seen in hypothyroidism are likely a result of the decreased overall metabolic activity and decreased cystatin C production due to low levels of thyroid hormones (13, 15, 16). However, studies that followed the effects of thyroid hormone replacement therapy on serum cystatin C report that changes in the levels of cystatin C in hypothyroidism are transient and that its levels increase after restoration of the euthyroid state (13–17).

Our results showing a high positive correlation between the levels of free thyroid hormones (fT3 and fT4) and cystatin C and a negative correlation between this marker and TSH levels add proof to the statement that cystatin C levels are affected by changes in thyroid hormone levels and altered thyroid function.

In our hyperthyroid subjects, GFR estimated with the MDRD and CKD-EPI equations suggested intactness of renal function, whereas GFR estimated on the basis of serum cystatin C levels indicated moderate impairment of renal function. The difference in the GFR values estimated using the two types of prediction equations was statistically significant. Creatinine levels, although within the reference range, were significantly lower compared to our euthyroid controls, which is also in agreement with the published data (11–15). Elevated thyroid hormones are thought to cause reduced peripheral vascular resistance, vasodilatation of renal blood vessels, and increased effective renal

plasma flow. In addition, their effects include increased GFR, and increased clearance and tubular secretion of creatinine (15). Decreased creatinine levels seen in hyperthyroidism reflect the effects of thyroid hormones on renal hemodynamics in a given moment, whereas cystatin C elevation in hyperthyroid patients is probably explained by its increased production, reflecting the peripheral effect of thyroid hormones and not the state of renal function in these patients.

In our hypothyroid subjects, GFR estimated using the MDRD and CKD-EPI equations showed mildly reduced renal function, as opposed to GFR estimated on the basis of serum cystatin C that indicated preserved renal function. The GFR values estimated using the two types of equations were statistically significantly different and thus surprising. On the other hand, we found significantly higher serum creatinine levels in hypothyroid subjects compared to both healthy controls and hyperthyroid subjects, which was expected and is consistent with previous studies (11–15). Increased peripheral vascular resistance seen in hypothyroidism causes declines in GFR and effective renal plasma flow; the clearance and tubular secretion of creatinine are decreased, resulting in its increased serum concentration (15).

Studies on the effects of thyroid suppression therapy (11–15) and thyroid hormone replacement (11–16) in patients with thyroid dysfunction have shown that serum creatinine levels change significantly during the treatment.

A major limitation of our study, as well as of previous similar studies, is the lack of GFR estimation using the clearance of exogenous substances, which would provide a more precise estimation of GFR. Karawajczyk et al. also reported contradictory results with GFR calculations using the equations based on serum creatinine and cystatin C, but normal GFR estimated using iohexol clearance in hyperthyroid subjects (18), which suggests a possible solution to the problem of evaluating renal function in patients with thyroid dysfunction.

Although regarded a reliable marker of GFR and more sensitive than serum creatinine, serum cystatin C has limitations in patients with thyroid dysfunction, because of significant changes in its serum concentration regardless of renal function. In patients with thyroid dysfunction GFR should therefore be estimated using the equation based on serum creatinine.

### **Conflict of interest statement**

The authors stated that there are no conflicts of interest regarding the publication of this article.

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*Received: June 22, 2011*

*Accepted: September 6, 2011*