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Impact of Thyroid Dysfunction on Serum Cystatin C, Serum Creatinine and Glomerular Filtration Rate

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Key words: cystatin C; creatinine; glomerular filtration rate; thyroid dysfunction.

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Abbreviations: Cys C - cystatin C, GFR - glomerular filtration rate, PTU -propiltiouracil, eC_{Cr} - estimated creatinine clearance rate.

Abstract

Aim. The aim of this cross-sectional, prospective, randomized, longitudinal study was to asses serum cystatin C (Cys C) and creatinine concentrations and glomerular filtration rate (GFR) in thyroid dysfunction.

Material and Methods. We have measured Cys C, creatinine and GFR using the ^{99m}Tc-DTPA technique in 35 patients (26 females and 9 males; 43 ± 11 years), 15 with newly diagnosed hyperthyroidism (TSH < 0.07 mIU/L, fT_4 > 24 pmol/L) and 20 with newly diagnosed hypothyroidism (TSH > 4.5 mIU/L, fT_4 < 9 pmol/L), at baseline and when they became euthyroid (TSH 0.4-4.5 mIU/L, fT_4 9–24 pmol/L). The patients had no history of kidney disease and were subdivided into 2 groups: age (>50 and <50 years) and fT_4 (40-100 pmol/L; >100 pmol/L) – hyperthyroid and TSH (4.5 - 48 mIU/L; > 48 mIU/L) – hypothyroid group. Thirty five age- and sex-matched normal subjects served as controls.

Results. Increased creatinine levels in hypothyroid patients 115 ± 12 μmol/L decreased after treatment to 95 ± 14 μmol/L and reduced values in hyperthyroid patients 53.6 ± 12 μmol/L increased after treatement to 75.2 ± 14 μmol/L ($p<0.05$). Cys C ranged from 0.88 ± 0.7 mg/L before to 1.24 ± 0.5 mg/L after treatment in hypothyroid and 1.65 ± 0.5 mg/L before to 0.96 ± 0.5 mg/L after treatment in hyperthyroid patients ($p<0.01$). Hyperthyroid subjects exhibited significant increase in GFR ranging from 144.1 ± 18 mL/min before to 123.7 ± 24 mL/min after treatment**.** Hypothyroid group exhibited significant decrease in GFR ranging from 81.1 ± 28 mL/min before to 103.7 ± 24 mL/min after treatment ($p<0.01$). The significant difference between GFR values assessed by the isotope technique and values assessed by the serum markers indicates that further work needs to be performed to confirm which method is giving the true reflection of GFR in thyroid dysfunction.

Introduction

Cystatin C (Cys C) is a single chain, non glicosylated, 13 kDa basic protein produced by all nucleated cells at constant rate, filtered at the glomerulus and fully destroyed at the proximal renal tubule. Its rate of production is not influenced by inflammation or malignancy and, unlike creatinine, is unaffected by the muscle mass, sex, or age of a patient [1]. Human Cys C is a potent cysteine protease inhibitor which is expressed in all human tissues and can be detected in the body fluids. It is considered as a novel marker for assessing glomerular filtration rate (GFR), claimed to be superior to serum creatinine [2, 3]. Until now, one of the most appealing aspects of using Cys C as a marker of GFR has been the apparent lack of influence of medical conditions on its clinical utility. Thyroid dysfunction may alter creatinine, which has been found to be increased in hypothyroidism

and decreased in hyperthyroidism. Several reports indicate that overt untreated thyroid disease affects also the levels of serum Cys C, being decreased in hypo- and increased in hyperthyroidism [4]. Wiesly et al. suggested that mild subclinical thyroid dysfunction also significantly influences Cys C concentrations [5]. The aim of our study was to asses the variations of serum Cys C and creatinine concentrations and GFR in overt thyroid dysfunction.

Material and Metods

Subjects

Thitry five consecutive patients (26 females and 9 males; 43 ± 11 years) which reffered to our Institution in the period (January 2007 – December 2009), were enrolled in the study. The study group included: 20 patients (14 females and 6 males) with newly diagnosed hypothyroidism (TSH > 4.5 mIU/L, fT_4 < 9 pmol/L) due to chronic autoimmune thyroiditis - Hashimoto and 15 patients (12 females and 3 males) with newly diagnosed hyperthyroidism (TSH < 0.07 mIU/L, fT_4 > 24 pmol/L) due to diffuse toxic goiter. The patients had no history of previous kidney disease or malignances and were subdivided into 2 subgroups: according to age (> 50 and < 50 years) and according to hormone levels (fT_4 40-100 pmol/L; fT_4 > 100 pmol/L) – the hyperthyroid group and (TSH 4.5 - 48 mIU/L; TSH > 48 mIU/L) – the hypothyroid group. Thirty five age- and sex-matched normal healthy subjects served as controls. We have measured Cys C and creatinine concentrations and GFR using the ^{99m}Tc-DTPA technique at baseline and when the patients became euthyroid (TSH 0.4-4.5 mIU/L, fT_4 9–24 pmol/L) after treatement with L – thyroxin (hypothyroid group) and propiltiouracil - PTU (hyperthyroid group). Informed consent was obtained from all patients.

Assays

Serum Cys C was measured by an immunologic turbidimetric assay using DakoCytomation Cystatin C immunoparticles (Cobas Mira Integra, DakoCytomation Denmark A/S) with reference range 0.65 – 1.15 mg/L (< 50 years) and 0.70 – 1.44 mg/L (> 50 years). All serum samples were analysed in duplicate. Serum creatinine was measured by the modifyed Jaffe method on Beckman Counter LX20 Pro Clinical Systems (Beckman Coulter Inc., Brea, CA) with reference range 55 - 105 μmol/L. Serum fT_4 was measured by DELFIA method on DELFIA^T Fluorometer (PerkinElmer and Analytical Sciences, Wallac Oy, Finland) with reference range 9 – 24 pmol/L and TSH was measured by IRMA method with reference range 0.4 - 4.5 mIU/L. GFR was measured using the ^{99m}Tc-DTPA technique according to the Gate's method and using the Sopha Vision DS7 single head spect system gamma camera. Calculated GFR was estimated using the equations [6]:

$$GFR\ (mL/min/1.73m^2) = [\ 84.69 \times cystatin\ C\ (mg/L)^{-1.680}\ ]$$

The equation results in the following relationship between cystatin C and GFR: Estimated creatinine clearance rate (eC_{Cr}) using Cockcroft-Gault formula when serum creatinine is measured in μmol/L [7]:

Table 1: Relationship between cystatin C and GFR (according to DakoCytomation instruction manual for Cystatin C Immunoparticles - Code No./Réf./Code-Nr.LX002).

Cystatin C (mg/L)	GFR (mL/min/1.73m^2)
0.6	200
0.7	154
0.8	123
0.9	101
1.0	85
1.1	72
1.2	62
1.3	55
1.4	48
1.5 - 1.6	41
1.7 - 1.8	33
1.9 - 2.0	28
2.1 - 2.3	23

$$eC_{Cr}\ (GFR) = (140 - age) \times Mass\ (in\ kilograms) \times Constant\ /\ Serum\ creatinine\ (in\ \mu mol/L)$$

Where Constant is 1.23 for men and 1.04 for women.

Statistical analysis

Data were expressed as mean ± SD for quantitative variables. Student's unpaired and paired t – test and linear regression analysis were used as appropriate. p values < 0.05 were considered as statistically significant.

Results

Creatinine levels showed reduced values in untreated hyperthyroid patients 53.6 ± 12 μmol/L which increased after treatement to 75.2 ± 14 μmol/L ($p<0.05$). However, cystatin C measurements pointed to the complete opposite ranging from 1.65 ± 0.5 mg/L before to 0.96 ± 0.5 mg/L after treatment ($p<0.01$). Finally, all hyperthyroid subjects exhibited a significant increase in

glomerular filtration rate ranging from 144.1 ± 28 mL/min before to 123.7 ± 24 mL/min after treatment (p<0.01). Calculated GFR estimations according to cystatin C values in hyperthyroid patients ranged from 41.3 ± 8 mL/min before to 101.2 ± 11 mL/min after treatment. Calculated GFR estimations according to creatinine values in hyperthyroid subjects ranged from 161.3 ± 21 mL/min before to 99.8 ± 15 mL/min after treatment (Table 2).

Table 2: Biochemical features of the hyperthyroid group.

Hyperthyroid patients (n=15)	GFR(ml/min)	Cys C(mg/l)	CREATININE (μmol/L)
Before therapy	144.1 ± 28	1.65 ± 0.5	53.6 ± 12
After therapy	123.7 ± 24	0.96 ± 0.5	75.2 ± 14
p	p<0.01	p<0.01	p<0.05

We have subdivided the patients into 2 subgroups in order to estimate whether age and severity of clinical features significantly affect GFR, cystatin C and creatinine levels. Cystatin C values according to age and severity of clinical features in the hyperthyroid group ranged from: 1.61 ± 0.3 mg/L before to 0.88 ± 0.4 mg/L after treatment – (subgroup fT_4 > 100 pmol/L), 1.51 ± 0.3 mg/L before to 0.9 ± 0.4 mg/L after treatment – (subgroup fT_4 40-100 pmol/L), 1.59 ± 0.3 mg/L before to 0.87 ± 0.3 mg/L after treatment – (subgroup > 50 years) and 1.49 ± 0.3 mg/L before to 0.92 ± 0.4 mg/L after treatment – (subgroup < 50 years) (Fig.1).

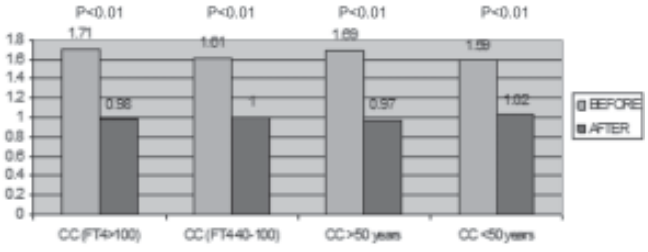

Figure 1: Cys C (CC) values according to age and severity of clinical features - hyperthyroid group.

Creatinine values according to age and severity of clinical features in the hyperthyroid group ranged from: 44 ± 16 μmol/L before to 64.3 ± 18 μmol/L after treatment – (subgroup fT_4 > 100 pmol/L), 42.3 ± 15 μmol/L before to 66.5 ± 14 μmol/L after treatment – (subgroup fT_4 40-100 pmol/L), 47.2 ± 13 μmol/L before to 65.1 ± 19 μmol/L after treatment – (subgroup > 50 years) and 44.3 ± 11 μmol/L before to 65.3 ± 18 μmol/L after treatment – (subgroup < 50 years) (Fig.2).

GFR values according to age and severity of

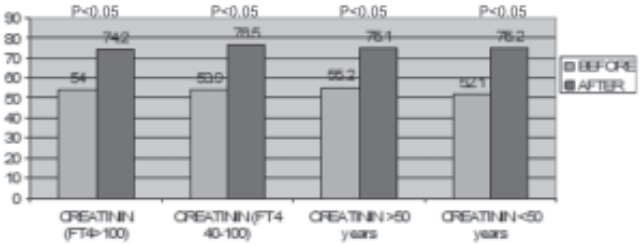

Figure 2: Creatinine values according to age and severity of clinical features - hyperthyroid group.

clinical features in the hyperthyroid group ranged from: 121.1 ± 13 mL/min before to 117.2 ± 11 mL/min after the treatment – (subgroup fT_4 > 100 pmol/L), 144.4 ± 16 mL/min before to 119.1 ± 12 mL/min after treatment – (subgroup fT_4 40-100 pmol/L), 122.3 ± 14 mL/min before to 116.4 ± 13 mL/min after treatment – (subgroup > 50 years) and 143.2 ± 18 mL/min before to 118.7 ± 13 mL/min after treatment – (subgroup < 50 years) (Fig. 3).

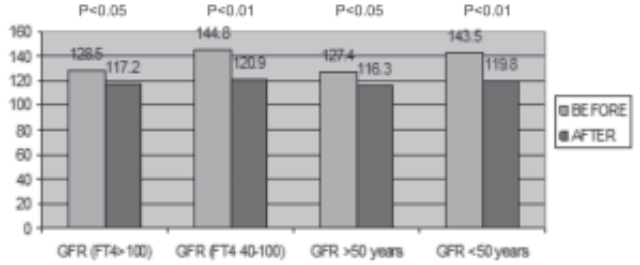

Figure 3: GFR values according to age and severity of clinical features - hyperthyroid group.

Creatinine levels showed increased values in untreated hypothyroid patients 115 ± 12 μmol/L which decreased after treatement to 95 ± 14 μmol/L (p<0.05). However, cystatin C measurements pointed to the complete opposite ranging from 0.88 ± 0.7 mg/L before to 1.24 ± 0.5 mg/L after treatment (p<0.01). Finally, all hypothyroid subjects exhibited a significant decrease in glomerular filtration rate ranging from 81.1 ± 28 mL/min before to 103.7 ± 24 mL/min after treatment (p<0.01). Calculated GFR estimations according to cystatin C values in hypothyroid patients ranged from 115.1 ± 12 mL/min before to 92.4 ± 11 mL/min after treatment (Table 3).

Table 3: Biochemical features of the hypothyroid group.

Hypothyroid patients (n=20)	GFR(ml/min)	Cys C(mg/l)	CREATININ (μmol/L)
Before therapy	81.1 ± 28	0.88 ± 0.7	115 ± 12
After therapy	103.7 ± 24	1.24 ± 0.5	95 ± 14
p	p<0.01	p<0.01	p<0.05

Calculated GFR estimations according to creatinine values in hypothyroid subjects ranged from 65.3 ± 10 mL/min before to 80.2 ± 17 mL/min after treatment. Cystatin C values according to age and severity of clinical features in the hypothyroid group ranged from: 0.86 ± 0.4 mg/L before to 1.21 ± 0.4 mg/L after treatment – (subgroup TSH > 48 mIU/L), 0.87 ± 0.4 mg/L before to 1.22 ± 0.4 mg/L after treatment – (subgroup TSH 4.5 – 48 mIU/L), 0.88 ± 0.3 mg/L before to 1.20 ± 0.4 mg/L after treatment – (subgroup > 50 years) and 0.9 ± 0.3 mg/L before to 1.23 ± 0.4 mg/L after treatment – (subgroup < 50 years) (Fig. 4).

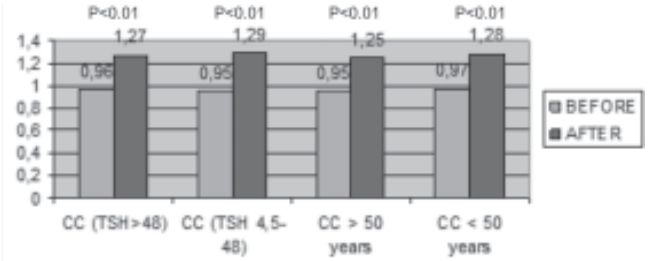

Figure 4: Cys C (CC) values according to age and severity of clinical features -hypothyroid group.

Creatinine values according to age and severity of clinical features in the hypothyroid group ranged from: 118 ± 16 μmol/L before to 88.3 ± 15 μmol/L after treatment – (subgroup TSH > 48 mIU/L), 113.1 ± 15 мmol/L before to 87.5 ± 14 μmol/L after treatment – (subgroup TSH 4.5 – 48 mIU/L), 116.1 ± 13 μmol/L before to 90.1 ± 14 μmol/L after treatment – (subgroup > 50 years) and 118.3 ± 11 μmol/L before to 88.3 ± 13 μmol/L after treatment – (subgroup < 50 years) (Fig. 5).

GFR values according to age and severity of clinical features in the hypothyroid group ranged from: 77.1 ± 13 mL/min before to 107.2 ± 16 mL/min after the treatment – (subgroup TSH > 48 mIU/L), 80.4 ± 16 mL/min before to 105.1 ± 12 mL/min after treatment – (subgroup TSH 4.5 – 48 mIU/L), 78.3 ± 14 mL/min before to 106.4 ± 17 mL/min after treatment – (subgroup > 50 years) and 79.2 ± 18 mL/min before to 108.7 ± 19 mL/min after treatment – (subgroup < 50 years) (Fig. 6).

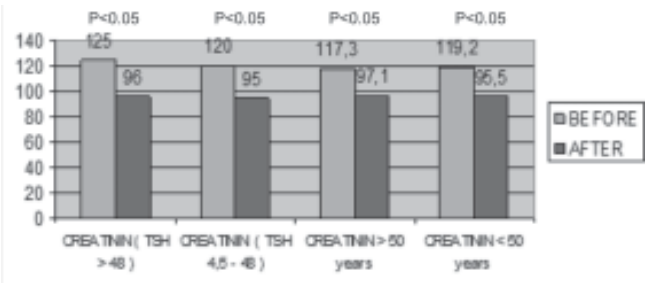

Figure 5: Creatinine values according to age and severitiy of clinical features - hypothyroid group.

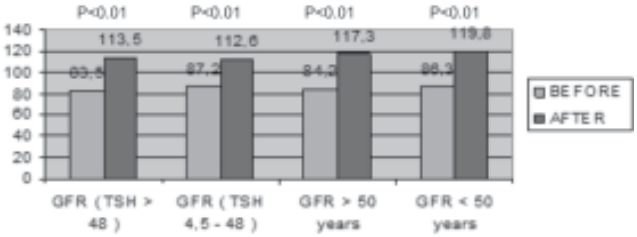

Figure 6: GFR values according to age and severity of clinical features - hypothyroid group.

Calculated GFR estimations using the equations, according to the serum markers concentrations in overt untreated thyroid dysfunction, showed no correlation with GFR values obtained by the radioisotope technique. Moreover, a significant difference was observed between GFR values assessed by the radioisotope technique and values assessed by the serum markers. Positive correlation between calculated and measured GFR ($r = 0.4$; $p < 0.05$) was found after the treatment (the euthyroid phase). No statistically significant difference was found between the Cys C and creatinine concentrations and GFR values according to age and severity of clinical features, except for the measured GFR values using the isotope technique in the hyperthyroid group.

The control group subjects had normal values of mean serum Cys C concentrations 0.85 ± 14 mg/L, normal creatinine concentrations 80 ± 12 μmol/L and normal values of GFR ranging 105 ± 15 mL/min. No significant variations between the mean serum markers concentrations and GFR values were observed at baseline and at the end of the study. Positive correlation for mean serum marker concentrations and measured GFR ($r = 0.4$; $p < 0.05$) was found between the control group and the patients with thyroid dysfunction after the treatment (the euthyroid phase). Inverse correlation for the above mentioned parameters ($r = 0.4$; $p < 0.01$) was found when the control group was compared with untreated thyroid patients.

Discussion

Thyroid dysfunction affects the metabolic processes in all organs and tissues, including the kidneys. This medical condition inflicts changes in the GFR, effective renal plasma flow and the kidney structure.

Hyperthyroidism is considered to increase the GFR by decreasing the peripheral vascular resistance, increasing the effective renal plasma flow, vasodilatation of the renal blood vessels and the positive ino- and chronotropic effect. Hypothyroidism decreases the GFR by increasing the peripheral vascular resistance, decreasing the effective renal plasma flow, vasoconstriction of the renal blood vessels and the negative ino- and chronotropic effect.

Ideally, GFR should be determined with a method that is convenient, inexpensive, and accurate. Up to date, several algorithms and methods have been proposed, but none is applicable as a valid GFR estimator in all clinical conditions. Estimations can be made from serum creatinine concentartions using the Modification of Diet in Renal Disease (MDRD) or Cockcroft–Gault equations [8, 9]. However, these equations are not aplicable in all clinical conditions, giving over- or underestimation of GFR in specific cases. Cys C is considered a novel marker for assessing GFR, claimed to be superior to serum creatinine. Studies have reported that cystatin C is less influenced by non renal factors including age, gender and muscle mass than serum creatinine [10, 11].

Thyroid dysfunction influences serum creatinine concentrations. Subjects with overt hyperthyroidism present lower serum creatinine concentrations, while patiens with overt hypothyroidism present higher values than controls. Increased thyroid hormone levels suggest increased intracellular creatine phosphate catabolism. The hypoenergetic state in hyperthyroidism blocks the process of creatine regeneration. This above mentioned, together with the increased GFR, increased creatinine clearance and increased creatinine tubular secretion explain the lower values of serum creatinine in hyperthyroidism. Decreased GFR, decreased creatinine clearance and decreased creatinine tubular secretion together with the increased releasing of creatinine from muscle cells explain the higher values of serum creatinine in hypothyroidism [12]. Serum Cys C concentrations indicate an opposite trend being significantly increased in hyperthyroidism and decreased in hypothyroidism. Restoration of euthyroidism is associated with normalisation of Cys C values. Most probably thyroid hormones affect the production rate of this protein, increasing it in hyper- and decreasing it in hypothyroidism [13]. In healthy subjects, if the kidneys work effectively and GFR is within normal range, serum Cys C values are normal. Negative correlation is established between Cys C values and GFR – high Cys C values indicate low GFR and viceversa [14]. Taking into consideration the influence of the thyroid disorders on GFR and Cys C levels separately, and the correlation between GFR and Cys C concentrations on the other hand, a very complex interaction thyroid gland – GFR – Cys C can be established, which demands further investigations in this field [15]. The dilemma, if the cellular production of Cys C in thyroid dysfunction is the main factor contributing to its serum concentration in this clinical condition and the correlation between GFR and Cys C levels in hypo- and hyperthyroidism, has not been cleared up to date [16]. Our study suggests that the cellular production rate of Cys C has the dominant role of determination on its serum concentration. This suggestion is based upon the fact that despite the increase in GFR in hyperthyroid patients, Cys C values remain high, and viceversa, in hypothyroid patients low Cys C values can be observed even though the GFR is decreased. However, further scientific research in this field should be performed in order to determine up to which degree thyroid hormones affect the production rate of this protein [13]. These scientific data, on the other hand, question the priority of Cys C as a valid marker for assessing GFR in patients with thyroid disorders. Furthermore, a big probability egsists that in future Cys C could be used as a valid indicator of thyroid hormone peripheral action.

Many experimental and clinical investigations suggest high positive correlation between the inulin clearance, being the gold standard for GFR assessment, and the radioisotope technique with ^{99m}Tc-DTPA. Furthermore, the thyroid dysfunction doesn‘t represent an obstacle in valid GFR estimation with this technique, which makes it a possible method of choice for patients with thyroid disorders [17-19].

In conclusion, the significant difference between GFR values assessed by the radioisotope technique and values assessed by the serum markers indicates that further work needs to be performed to confirm which method is giving the true reflection of GFR in thyroid dysfunction. Our study proposed that, unlike the effect that thyroid disease has on serum markers production rate, the accuracy of the radioisotope technique is not influenced by the thyroid disorders and might be the method of choice in this clinical condition. Serum Cys C might be proposed as a valid indicator of thyroid hormone periferal action, but since thyroid dysfunction affects its serum concentrations, it can‘t be used as a valid marker for assessing GFR in this category of patiens. Our study also suggests that the production rate of Cys C dominantly influences its serum concentration.

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