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Is Cystatin C a Marker of Glomerular Filtration Rate in Thyroid Dysfunction?

In the recent literature, cystatin C has been advocated as a new and more accurate estimate of glomerular filtration rate (GFR) *(1)*. Cystatin C is a 13-kDa endogenous cysteine proteinase inhibitor produced by all nucleated cells at a constant rate and broken down completely in the renal tubuli *(2)*. Cystatin C concentrations are independent of age and body weight, and there is no need for urine collection for clearance estimations. Furthermore, serum concentrations of cystatin C are not influenced by malignancy or inflammation. In contrast, the often-used serum creatinine concentration is supposedly influenced by dietary intake, renal tubular metabolism, age, and variations in muscle mass. There are also various analytical difficulties with the widely used Jaffe colorimetric assay for creatinine. A slight decrease in GFR has been found in patients with hypothyroidism, which improved significantly after treatment *(3–5)*. We wondered whether cystatin C would also be a good marker of renal function in case of thyroid dysfunction. Because thyroid hormones have general metabolic effects, the thyroid state could influence plasma cystatin C concentrations.

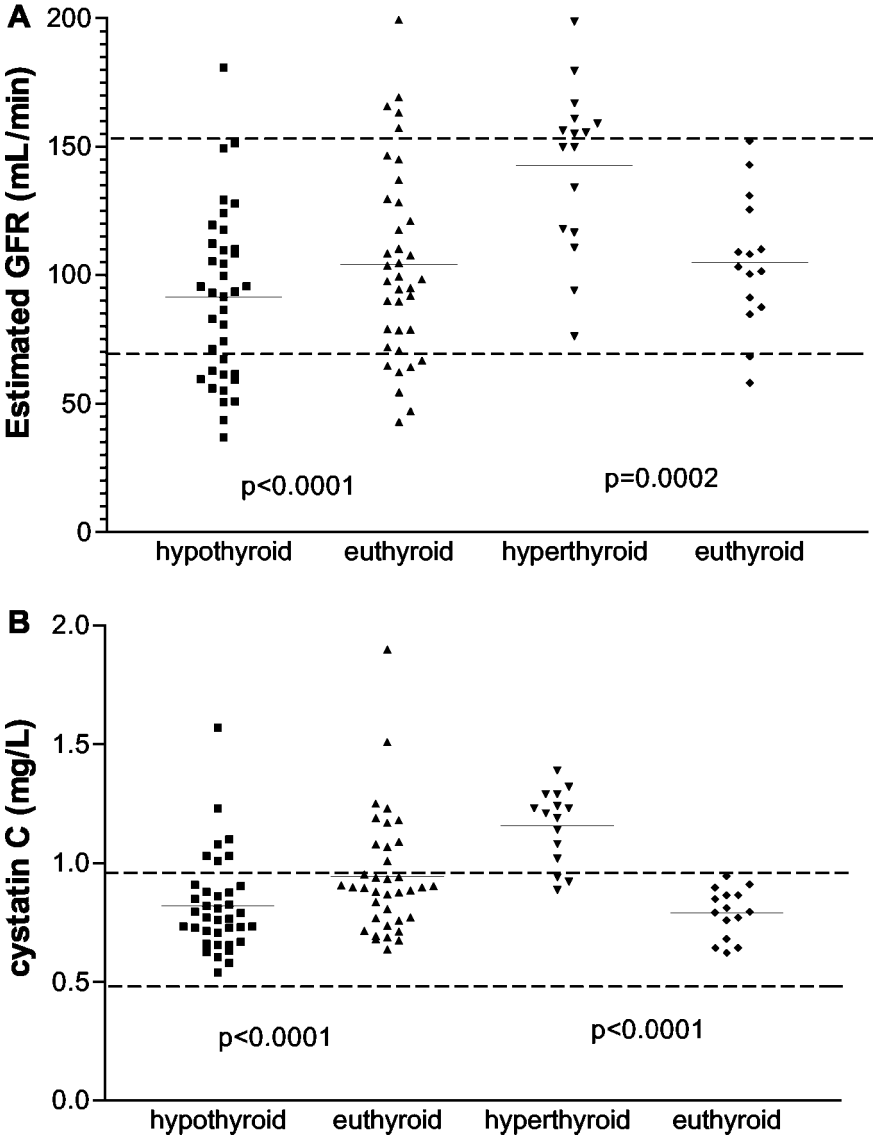

Fig. 1. Relationships between thyroidal state and estimated GFR (*A*) and cystatin C concentrations (*B*).

We reanalyzed patient data from earlier trials. All patients gave written informed consent, and the earlier studies were approved by the local ethics committee. The study groups consisted of consecutive patients seen at our clinics for primary hypothyroidism based on autoimmune thyroiditis (n = 37; 10 males and 27 females; median age, 46 years; range, 22–72 years) and for hyperthyroidism caused by Graves disease (n = 14; 1 male and 13 females; median age, 41 years; range, 23–73 years). Blood samples were taken at diagnosis, before start of treatment, and after euthyroidism had been regained for at least 3 months. Samples were assayed for thyroid-stimulating hormone (range, 0.4–4.0 mIU/L), free thyroxine (10–24 pmol/L), and serum creatinine (ranges, 40–80 μmol/L for females and 45–90

μmol/L for males) by routine assays. Cystatin C (range, 0.53–0.95 mg/L) was measured on a BN-Prospec analyzer (Dade-Behring). GFR was estimated with the Cockcroft–Gault formula *(6)*. Statistical analysis of the data before and after treatment was performed with the paired *t*-test ($P < 0.05$ considered significant).

In the patients with hypothyroidism, after treatment mean (SD) serum creatinine decreased from 90 (22) μmol/L to 77 (18) μmol/L ($P < 0.0001$); accordingly, estimated GFR increased ($P < 0.0001$; Fig. 1A). On the other hand, cystatin C increased after treatment (Fig. 1B). In the patients with hyperthyroidism, serum creatinine increased from 50 (13) μmol/L to 72 (18) μmol/L ($P < 0.0001$), and the estimated GFR decreased accordingly after treatment (Fig. 1A). Cystatin C, however, decreased significantly after treatment (Fig. 1B). Paradoxically, cystatin C decreased in hypothyroidism, in contrast to the values for creatinine and GFR. The values for all three markers moved toward reference values for euthyroidism. This finding was consistent for both hypo- and hyperthyroid patients.

We offer the following possible explanations for our findings. In hypothyroidism, creatinine increases; accordingly, the estimated GFR, which is based on creatinine, decreases. We could find only one study that calculated GFR by use of isotopes, i.e., the plasma clearance of CrEDTA, in patients with hypothyroidism *(3)*. That study demonstrated a diminished GFR in hypothyroidism, which was reversible in the euthyroid state. Thyroid hormones have significant effects on renal hemodynamics, renal handling of salt and water, and the active tubular transport processes for Na^+, K^+, and H^+ *(7)*. It is possible that tubular creatinine secretion is diminished in hypothyroidism, thereby increasing serum creatinine concentrations. We observed the opposite effect in the hyperthyroid patients. In addition, because the thyroid state influences metabolism in general, it may influence the production of cystatin C. This would lead to lower cystatin C concentrations in hypothyroidism and higher concentrations in hyperthyroidism. In that case, the production rate of cystatin C may not be constant, as reported recently.

In summary, in patients with thyroid dysfunction, plasma creatinine concentrations could be influenced by effects of thyroid hormones on the renal tubular cells, and plasma cystatin C concentrations could be influenced by the effects of thyroid hormones on cystatin C production. On the basis of our data and the data presented in two very recently published reports *(8, 9)*, we conclude that serum creatinine and estimated GFR by the Cockcroft–Gault formula remain better estimates of GFR than does cystatin C and that cystatin C cannot be used without knowledge of the thyroidal state. However, more investigation is needed because none of the studies used a "golden standard" for GFR determination.

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Microscopic Urinalysis and Automated Flow Cytometry in a Nephrology Laboratory

To the Editor:

In their recent report, Ottiger and Huber *(1)* compared the UF-100 flow cytometer and the KOVA system and suggested an algorithm for the selection of samples for microscopic analysis. They found that urine samples from nephrology patients had higher microscopic review rates. We agree with them that automated systems foster rapid and standardized analysis of formed elements and offer significant labor savings *(2–4)*, but we think that such a study may lead to different results in a laboratory of nephrology, where the prevalence of renal diseases and pathologic findings is higher.

We collected 298 consecutive midstream urine samples from patients with known or suspected renal diseases. The samples were first examined with a Sysmex UF-50 (software version 0.5; TOA Medical Electronics) and then with a phase-contrast microscope *(5)*, according to the European guidelines, at low (×100) and high (×400) magnification, by the same team (one biologist and one nephrologist, who independently analyzed the samples and then compared and discussed the results). The upper reference limits for phase-contrast microscopy used in our laboratory are as follows: erythrocytes, <2/high-power field (HPF); leuko-