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Paradoxical Changes in Cystatin C and Serum Creatinine in Patients with Hypo- and Hyperthyroidism,

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In the ongoing search for improved serum markers of impaired renal function (1), the low-molecular-weight protein cystatin C has been advocated as a promising and probably superior alternative to creatinine when used to assess glomerular filtration rate (GFR) (2, 3). Cystatin C possesses most of the properties of an ideal GFR test in that it is produced by all nucleated cells at an apparently constant rate, is freely filtered at the glomerulus, and is then fully destroyed in the proximal renal tubule (4). 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 (5). Indeed, studies to date would seem to confirm the potential of the marker in many clinical situations in which an accurate estimate of GFR is required in both adults (5–7) and children (8, 9).

Before cystatin C measurement became widespread, another low-molecular-weight protein, β_2-microglobulin, was promoted as a marker of GFR for similar reasons (10–12), but in contrast to cystatin C, its usefulness was subsequently found to be limited by the increased serum values found in inflammatory and neoplastic conditions (13). Thyroid disease has also been noted to affect β_2-microglobulin values through an influence on its rate of production (14), but no study has assessed whether this could also have an effect on cystatin C concentrations. We therefore measured concentrations of serum creatinine and cystatin C before and after treatment of patients with newly diagnosed hypo- and hyperthyroidism.

We measured serum cystatin C and creatinine in 17 patients (12 females and 5 males; median age, 51 years; range, 24–77 years) with newly diagnosed biochemical hypothyroidism [thyroid-stimulating hormone (TSH) >4.7 mIU/L (reference interval, 0.5–4.7 mIU/L) and free thyroxine (fT$_4$) <9 pmol/L (reference interval, 9–24 pmol/L)] and 19 patients (14 females and 5 males; median age, 48 years; range, 21–66 years) with newly diagnosed hyperthyroidism [TSH <0.05 mIU/L, fT$_4$ >24 pmol/L, and free triiodothyronine >5.3 pmol/L (reference interval, 0.5–5.3 pmol/L)] at baseline and when they subsequently became euthyroid (TSH <4.8 pmol/L; fT$_4$, 9–24 pmol/L). Hypothyroid patients were treated with 100 μg of thyroxine for 6 weeks. The four patients who were not rendered euthyroid on this regime became so when given 150 μg of thyroxine for a further 6 weeks. Twelve of the hyperthyroid patients became euthyroid after receiving 20 mg of carbimazole for 6 weeks. Five became hypothyroid at this stage and had 100 μg of thyroxine added; they were euthyroid by week 12 on the combination. Two patients required an increase in their carbimazole dose to 40 mg after 6 weeks and became euthyroid by week 18. The study had local Ethics Committee approval, and patients gave their written informed consent for participation.

All thyroid assays were performed on an Abbott Architect i4000 immunoassay analyzer (Abbott Diagnostics Division). Cystatin C was analyzed on a Dade-Behring BN2 analyzer (Dade Behring Ltd.), and serum creatinine was measured on a Beckman LX20 instrument (Beckman Coulter UK Ltd.) with a kinetic Jaffe method.

Mean (SD) serum creatinine was higher in the untreated hypothyroid patients when compared with hyperthyroidism [90.7 (18.0) vs 59.2 (20.7) μmol/L; P <0.0001; Fig. 1A]. After successful treatment, creatinine fell by 13% in the hypothyroid patients (P = 0.01 compared with pretreatment values) and increased by 22% in the hyperthyroid group (P <0.0001) to end with similar concentrations in both groups [78.8 (20.6) vs 72.3 (16.6) μmol/L; P = 0.30; Fig. 1A]. Paradoxically, cystatin C was lower in untreated hypothyroid patients than in those with hyperthyroidism [0.767 (0.125) vs 1.12 (0.25) mg/L; P <0.0001; Fig. 1B]. Treatment led to a 14% increase in cystatin C in hypothyroid patients (P = 0.0001) and a 21% decrease in the hyperthyroid group (P = 0.0003), producing similar final concentrations [0.874 (0.127) vs 0.891 (0.205) mg/L; P = 0.77; Fig. 1B]. The treated concentrations were within the reference intervals cited for both analytes (50–120 μmol/L for creatinine and 0.51–0.98 mg/L for cystatin C).

The creatinine data presented here confirm previous studies showing reduced values in untreated hyperthyroidism and increased values in hypothyroidism (15, 16). However, we have found that, in the same patients, cystatin C measurements point to the complete opposite. The magnitude of the difference is such that in hypothyroidism serum creatinine values are 53% higher than in
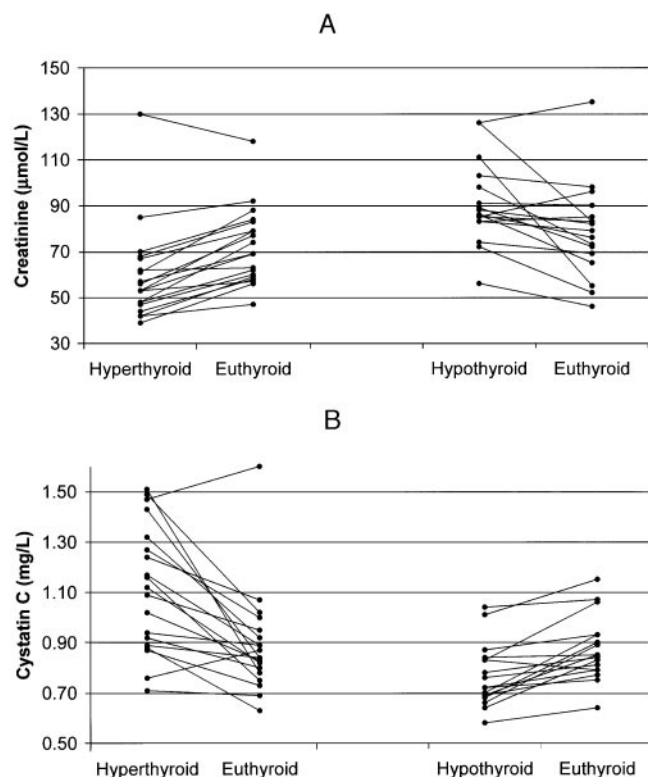
A

B

Fig. 1. Concentrations of serum creatinine (*A*) and cystatin C (*B*) before and after treatment of hypo- and hyperthyroidism.

hyperthyroidism, but the cystatin C values in hyperthyroidism are 46% higher than those in hypothyroidism. Existing literature suggests that it is creatinine that is providing the correct assessment of GFR changes *(17)*, but because definitive work formally assessing GFR in thyroid disease (using a "gold standard" marker) has yet to be performed, this cannot be stated categorically.

Until now, one of the most appealing aspects of using cystatin C as a marker of GFR has been the apparent lack of influence of medical conditions on its clinical utility, with the only debate being whether cystatin C concentrations are influenced by some metastatic malignancies or after renal transplantation *(18, 19)*. A likely explanation for our findings here is that hyperthyroidism is associated with a reversible increase in cystatin C production that is in excess of the expected increase in GFR, whereas in hypothyroidism, cystatin C production is reduced to a greater extent than is the GFR. The reasons for these changes in production remain speculative, but if similar to the cause suggested for β_2-microglobulin, then it would seem that it is simply through a metabolic-rate-mediated mechanism *(14)*.

In summary, this study has shown a clinically significant discrepancy between GFR assessed by serum creatinine and that found using cystatin C in untreated thyroid disease. This raises doubts as to the reliability of cystatin C measurement in these common conditions, but it also suggests that further work needs to be performed to confirm which marker is giving the true reflection of GFR.

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Quantification of Glutamine in Dried Blood Spots and Plasma by Tandem Mass Spectrometry for the Biochemical Diagnosis and Monitoring of Ornithine Transcarbamylase Deficiency, *Minh-Uyen Trinh,[1] Jennifer Blake,[1] J. Rodney Harrison,[1] Rosemarie Gerace,[1] Enzo Ranieri,[1] Janice M. Fletcher,[1,2] and David W. Johnson[1]** ([1] Department of Chemical Pathology, Women's and Children's Hospital, 72 King William Rd., North Adelaide, South Australia 5006, Australia; [2] University of Adelaide, North Terrace, Adelaide, South Australia 5000, Australia; * author for correspondence: fax 61-8-81617100, e-mail david.johnson@ adelaide.edu.au)

A notable deficiency in the use of tandem mass spectrometry (MS/MS) for newborn screening is the inability to screen for urea cycle defects. The most common of these,