Low-Molecular Weight Proteins as Markers for Glomerular Filtration Rate

To the Editor:

Inulin clearance (C_{in}) is the usual gold standard for evaluating glomerular filtration rate (GFR), but technical difficulties and patient inconvenience prevent its widespread use (1). The most commonly used marker for GFR is serum creatinine, but muscle wasting and tubular secretion may lead to overestimation of GFR (2, 3). Serum concentrations of the low-molecular weight proteins cystatin C (CysC) (4), β_{2}-microglobulin (B_{2}M) (5, 6), and β-trace protein (BTP) (7) maybe useful alternatives for detecting reduced GFR, but no study to date has compared all of these proteins directly to C_{in}.

We studied 62 patients (20 females, 42 males). All had their GFR determined by steady-state C_{in} as described previously and adjusted to a standard body surface of 1.73 m². We had reported on CysC and creatinine in 44 patients with various degrees of liver cirrhosis (1). We include here 41 of these patients for whom samples were available and 3 new patients with liver diseases; 31 had alcoholic etiologies; 10 had viral hepatitis, and 3 had other etiologies. The remaining 18 patients had renal diseases: 5 with chronic renal failure, 2 with acute renal failure, and 11 others.

After an overnight fast, GFR was tested with participants in a supine position. Serum creatinine was determined by a Jaffe method (1). Serum CysC, B_{2}M, and BTP were analyzed by fully automated, latex-enhanced immunonephelometric methods (N latex Cystatin C, N latex β_{2}-microglobulin, N latex β-trace protein, respectively, on a nephelometer II; Dade-Behring). Central 95% reference intervals established from a representative cohort of 100 female and 100 male healthy blood donors (median age, 31 years; 2.5–97.5 percentiles, 19.0–60.5 years) were 0.402–0.738 mg/L for BTP, 1.085–2.015 mg/L for B_{2}M, 0.475–0.820 mg/L for CysC, and 53.04–106.08 μmol/L for creatinine (1).

Statistical analysis was performed with Statview 4.5 for Macintosh (Abacus Concepts) and MedCalc® for Windows. P <0.05 (two-tailed) was considered significant. The study was performed in accordance with the Helsinki Declaration of 1975, as revised in 1985.

The mean [95% confidence interval (CI)] age of our patient cohort was 49.4 (45.7–53.2) years; the mean GFR was 40.3 (34.6–46.0) mL·min⁻¹·1.73 m². The mean (2 SD) concentrations of CysC, B_{2}M, BTP, and creatinine were 1.15 (1.035–1.264) mg/L, 2.68 (2.386–2.974) mg/L, 0.894 (0.797–0.991) mg/L, and 91.75 (82.0–101.5) μmol/L, respectively.

The reciprocals of CysC, B_{2}M, and BTP correlated significantly with GFR [1/CysC, \( r = 0.686 \) (95% CI, 0.525–0.80), \( P < 0.0001 \); 1/B_{2}M, \( r = 0.646 \) (95% CI, 0.471–0.772), \( P < 0.0001 \); 1/BTP, \( r = 0.567 \) (95% CI, 0.368–0.717), \( P < 0.0001 \)]. Although 1/creatinine also correlated with GFR \( [r = 0.392 \text{ (95% CI, 0.155–0.586), } P = 0.0016 \] this correlation coefficient was the weakest. Only 1/CysC correlated significantly better with GFR than did 1/creatinine (\( P = 0.021 \); z-statistic, 2.29). The reciprocals 1/BTP and 1/B_{2}M showed statistically insignificantly higher correlation coefficients than 1/creatinine alone (1/BTP, \( P = 0.22 \); z-statistic, 1.23; 1/B_{2}M, \( P = 0.056 \); z-statistic, 1.91).

ROC plots for CysC, B_{2}M, BTP, and creatinine assessed their ability to detect a GFR ≥70 mL·min⁻¹·1.73 m² (Fig. 1). GFR was >70 mL·min⁻¹·1.73 m² in 8 patients and lower in 54 patients. The ROC areas for CysC and B_{2}M were significantly greater than the ROC area for creatinine (CysC, \( P = 0.014 \); B_{2}M, \( P = 0.028 \); BTP, \( P = 0.062 \), paired statistical comparisons). The 95% CIs for the areas under the curves for creatinine and CysC did not overlap (Fig. 1).

The first study that described increased BTP in renal insufficiency showed only a weak linear correlation with creatinine in the serum of controls (8), but we found a rather good and significant correlation for the reciprocals of both analytes with the GFR (data not shown). The correlations of CysC and B_{2}M with GFR were in the range of previously published studies (4, 6, 9).

Our data are at variance with a study by Priem et al. (7), which showed a higher diagnostic efficiency for BTP to detect a reduced GFR. However, this investigation evaluated only B_{2}M and BTP in comparison with creatinine and C_{in}. The production rate of B_{2}M varies considerably with immune reactions because it is part of the histocompatibility antigen complex and is produced predominantly by lymphocytes; this may account for the divergent study results (10–12). With respect to BTP, we found a lower area under the ROC curve than did Priem et al. (7), despite the fact that we used the same assay. Therefore, differences in the results may be attributable to patient characteristics. Their study population comprised solely diabetics, whereas our patient cohort included patients with various degrees of liver cirrhosis, renal disease, and only two patients with diabetes (7).

BTP is filtered by the kidney, and its concentrations in urine range from 600 to 1200 μg/L (13). It seems likely that increased BTP concentrations in serum reflect reduced clearance of the protein (8). Unlike CysC, which is catabolized in the kidney, other mechanisms may influence the serum concentration of BTP, especially because this 25-kDa protein can serve as a lipophilic transporter (14).

In summary, our data support the view that CysC, although not an ideal marker, is better than B_{2}M and BTP as an indicator of reduced GFR and as a possible replacement for creatinine in clinical practice.

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Fig. 1. ROC curves for CysC (———), B2M (— − −), BTP (· · ·), and creatinine (− − −), demonstrating the ability of each analyte to detect GFR < 70 mL·min^{-1}·1.73 m^2.

The cutoffs shown for each analyte are those with the highest diagnostic accuracy (minimum false-negative and positive results) with the corresponding 95% CIs (in parentheses). For CysC, the area under the ROC curve is 0.880 (0.772–0.948; SE, 0.049), and the cutoff is 0.93 mg/L [sensitivity, 77.8% (64.4–87.9%); specificity, 100.0% (100–100%)]. For B2M, the area under the ROC curve is 0.859 (0.747–0.934; SE, 0.056), and the cutoff is 2.26 mg/L [sensitivity, 72.2% (58.4–83.5%); specificity, 100.0% (100–100%)]. For BTP, the area under the ROC curve is 0.809 (0.689–0.898; SE, 0.067), and the cutoff is 0.762 mg/L [sensitivity, 64.8% (50.6–77.3%); specificity, 100.0% (100–100%)]. For creatinine, the area under the ROC curve is 0.647 (0.515–0.764; SE, 0.096), and the cutoff is 76.908 μmol/L [sensitivity, 64.8% (50.6–77.3%); specificity, 87.5% (47.4–97.9%)].

References

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