Cystatin C: A Promising Marker of Glomerular Filtration Rate to Replace Creatinine

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Dear Sir

The determination of serum creatinine is commonly used for the estimation of glomerular filtration rate. However it is well known that serum creatinine concentration increases only at a reduction of about 50% of the glomerular filtration rate. The determination of low-molecular-mass proteins in serum seems to be a suitable approach for detecting reduced glomerular filtration rate within the so-called creatinine-blind range.

In previous investigations concerning the determination of ribonuclease, we showed its superior diagnostic validity compared to creatinine and β 2-microglobulin [1]. However, the determination of ribonuclease is easily flawed by contamination. A circumstance which hampers its use in routine practice. Thus, we read with great interest the papers of Grubb et al. [2-5] on the usefulness of cystatin C as low-molecular mass protein. Human cystatin C has a molecular mass of about 13 kD and inhibits cysteine protein-ases [2]. It is present in very low concentrations in human serum, urine, cerebrospinal fluid, saliva, semen, colostrum, ascitic and pleural fluid, and thus demands highly sensitive tests. Löfberg and Grubb [3] developed the first enzyme immunoassay for the quantitation of cystatin C. Cystatin C was proposed as an ideal marker of glomerular filtration rate because of its constant production rate and its catabolism in the proximal renal tubules [4, 5]. However, the diagnostic value of cystatin C has not clearly been confirmed by other authors up to now.

Meanwhile, we developed a sensitive sandwich enzyme immunoassay by using commercially available anti-human cystatin

Table 1. Diagnostic validity of cystatin C compared to creatinine and other low-molecular-mass proteins for the detection of reduced glomerular filtration rate

Parameter	Sensitivity	Specificity
%	%	
85.7	92.9	
100		
100		
Cystatin C	88.2	
β 2-Microglobulin	76.5	β 2-Microglobulin 64.7
52.9		
Creatinine		

31 patients suffering from chronic renal diseases were investigated. The cut-off limit of 1.36 ml/s was selected as indicator of the reduced glomerular filtration rate (measured by ^{99m}Tc -diethylenetriaminopentaacetic filtration clearance) and was used for the calculations of sensitivity and specificity. 17 patients had values below that cut-off limit. For the other parameters, the following limits were used as cut-off limits: cystatin C, 2.29 mg/l for women, 2.75 mg/l for men; β_2 -microglobulin, 2.75 mg/l; creatinine 97 $\mu\text{mol/l}$ for women, 106 $\mu\text{mol/l}$ for men.

C antibodies and established reference values [6]. The cut-off values were 2.75 mg/l for men and 2.29 mg/l for women [6]. Cystatin C shows a typical behavior in relation to glomerular filtration rate (fig. 1). Comparison of the diagnostic validity of cystatin C and both standard renal parameters (^{99m}Tc -diethylenetriaminopentaacetic acid clearance; creati-

0 0.5 1 1.5 2 2.5
Glomerular filtration rate (ml/s)

Fig. 1. Relationship between the glomerular filtration rate using ^{99m}Tc -diethylene-triaminopentaacetic acid and cystatin C in serum. The dotted lines correspond to the limits of the 95% reference intervals.

nine) and further low-molecular-mass proteins (β_2 -microglobulin, α_2 -microglobulin) proves that cystatin C more sensitively reflects a reduction of glomerular filtration rate than the other parameters measured (table 1).

In summary, we believe that these results are promising and support the view that cystatin is in principle suited to replace creatinine as a standard marker of kidney function. In addition to its clinical validity, a recently developed particle-enhanced immuno-turbidimetric assay for cystatin C offers all necessary analytical advantages of a modern laboratory method applicable in routine clinical practice: it can be automated, allows a rapid determination within a few minutes and shows a high degree of precision [7].

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