

## THE ROLE OF ALPHA-1-MICROGLOBULIN IN THE EVALUATION OF TUBULAR IMPAIRMENT AND AS A PARAMETER SUPERIOR TO CREATININE IN THE ESTIMATION OF GLOMERULAR FILTRATION RATE

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### Summary

In 350 patients  $\alpha_1$ -microglobulin ( $\alpha_1$ M), a new low molecular weight glycoprotein (normal range in urine 3.5–8mg/L, in serum 20–42mg/L) was measured by single radial immunodiffusion. In 90 patients with low molecular weight proteinuria, increased urinary  $\alpha_1$ M concentrations were found, but serum levels were only elevated in patients with renal insufficiency. We also observed that a reduction of glomerular filtration rate alone (<70ml/min) leads to increased urinary concentrations of  $\alpha_1$ M. Conclusions on tubular impairment can only be drawn in cases of normal or slightly reduced renal function. Serum  $\alpha_1$ M proved to be a more sensitive indicator of renal insufficiency than creatinine even in the 'creatinine-blind' region of the glomerular filtration rate.

### Introduction

Microglobulins ( $\alpha_1$ -microglobulin,  $\beta_2$ -microglobulin) belong to the class of low molecular weight proteins (MW <68K) that are filtered by the glomerulus and reabsorbed in the proximal renal tubule where they are catabolized. Renal insufficiency leads to elevated serum concentrations of microglobulins. As a parameter for the assessment of renal function microglobulins are reported to be superior to the traditional estimation of endogenous creatinine [1,2] since their serum concentrations seem to be less dependent on the state of nutrition, muscular mass, body surface, sex and age of the patients than creatinine concentrations. Furthermore, no diurnal variations of the serum concentrations have been observed [3].

Disturbances in the tubular reabsorption of microglobulins and other low molecular weight proteins lead to increased concentrations of these proteins in the urine ('tubular proteinuria'). Therefore microglobulins seem to be suited as indicators of proximal tubular impairment [4,5]. However,  $\beta_2$ -microglobulin instability in pathological urine has been reported [6].

We have evaluated the measurement of  $\alpha_1$ -microglobulin ( $\alpha_1$ M) from a single serum specimen as a new parameter for the assessment of renal function. We also studied urine concentrations of  $\alpha_1$ M as sensitive indicators of tubular damage.  $\alpha_1$ M is a low molecular weight glycoprotein (MW 33K; 20% carbohydrate) first isolated by Ekström [7], further characterized by the group of Takagi [8], and whose physiological functions are as yet unknown. Its pH stability in the urine has been recently reported by Yu [5].

## Methods

In 100 apparently healthy subjects and in 350 patients with various renal and hypertensive diseases serum, spontaneous urine and 24-hour urine samples were investigated.  $\alpha_1$ M was determined by single radial immunodiffusion (SRID; LC-Partigen  $\alpha_1$ M test, Behringwerke, Marburg, FRG), creatinine by an automated Astra analyser (Beckman Instruments, Munich, FRG), glomerular filtration rate by endogenous creatinine clearance corrected for body surface, and the urinary protein pattern (high/low molecular weight) by SDS-microelectrophoresis (micro-PAGE) in 10 $\mu$ l capillary gradient polyacrylamide gels (0–30%) according to Neuhoff [9].

## Results

Normal ranges for  $\alpha_1$ M were established in serum (20–42mg/L) and urine (3.5–8mg/L). Ninety patients with low molecular weight proteinuria and either with or without renal insufficiency had elevated urinary concentrations of  $\alpha_1$ M, whereas increased serum values were only found in patients with renal insufficiency ( $C_{CR} < 100$ ml/min) (Figure 1). Independently of these results, we were able to establish that increased urinary  $\alpha_1$ M values are found at decreased glomerular filtration rates ( $C_{CR} < 70$ ml/min;  $r = -0.8$ ) (Figure 2).

In all of the 350 patients the correlation between the  $\alpha_1$ M and creatinine concentrations in serum to the creatinine clearance was determined. The regression curves for  $\alpha_1$ M (1;  $r = -0.9$ ) and creatinine (2;  $r = -0.74$ ) are presented in Figure 3. Using the  $\chi^2$ -test significant differences ( $p < 0.001$ ) were observed in the frequency of pathologic  $\alpha_1$ M values ( $> 42$ mg/L) and creatinine concentrations ( $> 1.2$ mg/dl) with respect to the glomerular filtration rate. For all glomerular filtration rates  $< 100$ ml/min, elevated serum  $\alpha_1$ M levels were found in 96 per cent of the cases, whereas pathologic creatinine concentrations were only seen in 70 per cent of the cases. Only at glomerular filtration rates  $< 60$ ml/min were creatinine concentrations elevated in all cases.

## Discussion

Our normal values for  $\alpha_1$ M concentrations in serum and urine are comparable with those of other groups [5,8] who employed the same  $\alpha_1$ M standards in their test systems. In normal people there are no diurnal variations in serum  $\alpha_1$ M concentrations [3].

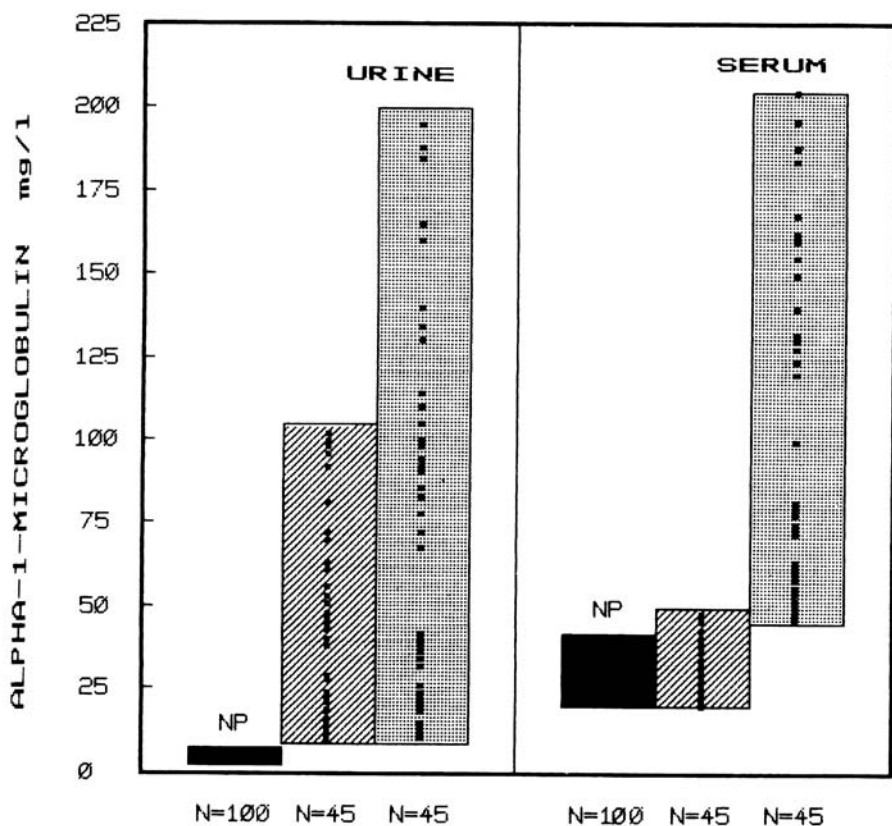


Figure 1. Distribution of serum and urine  $\alpha_1$ M concentrations in normal persons (NP), patients with low molecular weight proteinuria without renal insufficiency (hatched box) and with renal insufficiency (stippled box)

Pathological  $\alpha_1$ M concentrations in urine were found in all patients with low molecular weight proteinuria irrespective of the degree of renal insufficiency. This finding is in agreement with the observations of Yu [5]. As with other microproteins such as  $\beta_2$ M and retinol binding protein [10],  $\alpha_1$ M should be suitable as an indicator of disorders in tubular resorption. In contrast to  $\beta_2$ M, however,  $\alpha_1$ M is extremely stable in the clinically relevant pH range of urine (pH 4–10) [5]. Since  $\alpha_1$ M is filtered through the glomerulus, a reduction in glomerular filtration rate causes an increase in serum  $\alpha_1$ M concentrations. In our investigations, however, both the serum and urine concentrations showed a good correlation to the endogenous creatinine clearance. According to our results, when the glomerular filtration rate drops to below 70ml/min then the tubular resorption capacity for  $\alpha_1$ M is exceeded. Pathologically elevated  $\alpha_1$ M concentrations in urine under these conditions are not diagnostic of isolated tubular damage. Yu [5] also recommended on the basis of his own observations that increased urine  $\alpha_1$ M concentrations can only be considered indicative

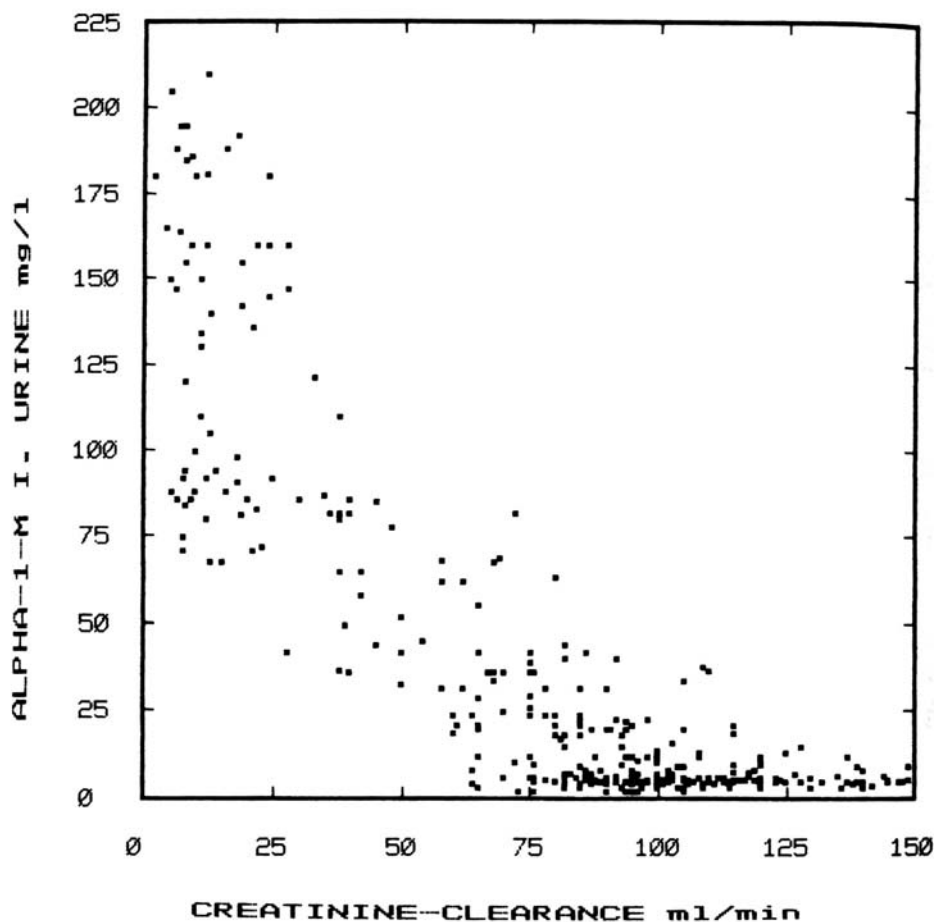


Figure 2. Correlation between endogenous creatinine clearance and urine  $\alpha_1$ M concentration in 350 patients with various renal and hypertensive diseases

of tubular proteinuria at serum creatinine concentrations  $<200\mu\text{mol/L}$ .

A better correlation was found in our patients between serum  $\alpha_1$ M concentrations ( $r = -0.9$ ) and creatinine clearance than between endogenous creatinine ( $r = -0.74$ ) and creatinine clearance. These results are in accordance with the observations reported by Itoh [2]. As can be seen from Figure 2,  $\alpha_1$ M shows a significantly better predictive ability of renal insufficiency than endogenous creatinine, even in the so-called 'creatinine-blind' range (60–100 ml/min) of the glomerular filtration rate.

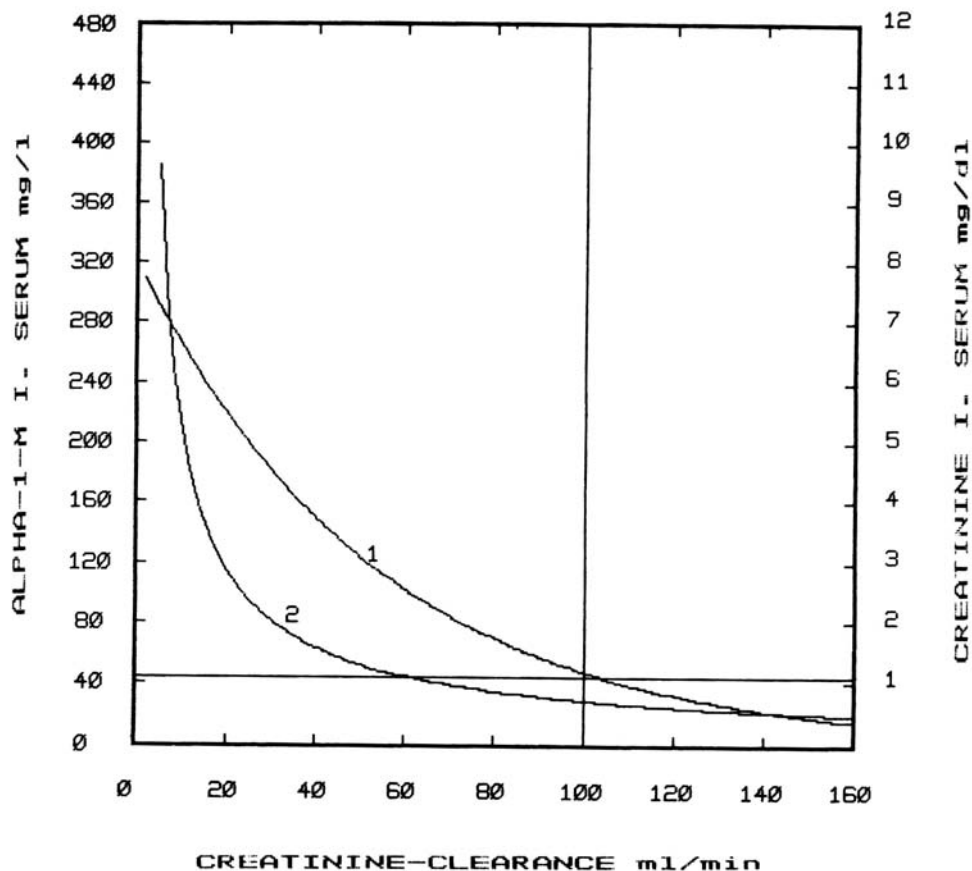


Figure 3. Regression analysis of creatinine clearance with either serum creatinine ( $r = -0.74$ ) or serum  $\alpha_1\text{M}$  ( $r = -0.9$ ) levels in 350 patients with various renal and hypertensive diseases. The normal ranges are represented by the unbroken lines

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