Increased Plasma Levels of Alpha-1-Acid Glycoprotein in Chronic Renal Failure Are Unlikely to Be Due to Decreased Renal Elimination

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Dear Sir,

We read with interest the paper 'Serum alpha-1-acid glycoprotein in chronic renal failure', by Docci et al. [Nephron 39: 160–163, 1985] and would like to make some comments.

In the introduction, the authors state that as some AAG is eliminated by the kidney, serum concentrations of AAG should rise as renal function falls. If decreased renal clearance of AAG is the only change in AAG handling in chronic renal disease, the degree to which plasma levels rise is determined by the fraction of renal clearance to total clearance. We do not know of any specific data on the latter, but believe that it can be estimated from available data.

The half-life ($t_{1/2}$) of ^{125}I -labelled AAG is approximately 5 days [1]. From the formula $t_{1/2} = 0.693 \text{ Vd} / \text{Cl}$, and using the smallest possible distribution volume (Vd), i.e. plasma volume, approximately 2.5 liters, the estimated value of AAG clearance is 0.24 ml/min. Many small MW proteins like AAG are in fact distributed outside the vascular space, and the Vd is likely to be greater than plasma volume. Hence, the above-estimated value of plasma AAG clearance is the minimum.

We have been measuring urinary AAG concentrations in subjects with the nephrotic syndrome, using radial immunodiffusion plates made with commercial antibody (Atlantic antibodies). The limit of sensitivity of this assay is 0.01 g/l. Using these plates, AAG could not be detected in the urine of normal subjects. Using the limit of sensitivity of the assay as the value of normal urinary AAG concentration (which is likely to be an overestimate by a factor of 10), a urinary volume of 1.5 l/day, and an average plasma AAG concentration of 1 g/l, renal clearance of AAG is at most 0.01 ml/min. Hence, using the minimum value for total clearance and the maximum value for renal clearance, renal clearance makes up approximately 4% of total clearance. This means that if all other factors remain constant, even total loss of urinary AAG clearance would only cause a 4% increase in plasma AAG levels, an insignificant amount, and probably not clinically detectable.

The authors state that none of the subjects had 'detectable proteinuria'. All normal subjects have proteinuria if one looks hard enough, and in our experience the vast majority of patients with chronic renal disease have considerably greater than normal degrees of proteinuria despite a decrease in GFR. The authors do not state the method used for detection of proteinuria, nor

whether the subjects had high, normal or low amounts of AAG in their urine. It cannot be assumed that as GFR falls, renal protein excretion falls, as handling of protein and creatinine by the kidney is different: damage to glomerular basement membrane and altered blood flow may increase protein loss but decrease filtration.

The authors claim that they have demonstrated from the data in figure 1 a linear correlation between serum creatinine and log serum AAG concentration. However, they do not appear to have checked whether the confidence intervals for the slope of the regression line include slope = 0, which, by inspection, seems almost certain. If this is the case, they cannot say whether log serum AAG concentrations rise, fall, or are unchanged as serum creatinine rises. We find it unusual that the abscissa in figure 1 is serum creatinine: it is well known that there is a hyperbolic relationship between serum creatinine and renal function (GFR).

In summary, then, our major comments on this paper are: (1) the conclusion in the discussion section, viz, that there is an exponential increase in the serum concentration of AAG as renal function falls, is not supported by the data; (2) we are not clear whether the subjects had high, normal or low rates of urinary AAG excretion; (3) even if urinary AAG excretion is decreased in patients

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with chronic renal disease, a rise in serum AAG concentration cannot be explained by this mechanism, and either a decrease in non-renal clearance or an increase in production would be responsible.

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References

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