

Is Very Low Always Useful? The Case of Very Low-Grade Albuminuria in Kidney Disease



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Richard Bright¹ recognized almost 200 years ago that proteinuria accompanied renal failure. The detection limits of both proteinuria and reduced glomerular filtration rate (GFR) have moved ever lower since then. Even modest amounts of albuminuria above 30 mg/g of urine creatinine pose a risk of future renal function loss.² This raises the important question of whether screening for significant renal disease should include testing for even lower amounts of albuminuria.

Melsom *et al.*³ report the risk of renal function loss in subjects who have amounts of urinary albumin excretion that are below the accepted lower level of normal. Their population included 1278 white individuals aged 50 to 62 years, free of diabetes mellitus or cardiovascular disease, with normal measured GFR by iohexol clearance and followed for more than 5 years. The quality of the urine collection in their study was optimal by being

in the fasting state condition and taking the average of 3 first-void morning spot urines. The population showed very low albumin-to-creatinine ratios. An increased risk of loss of renal function is reported in this cohort, as their amount of albumin-to-creatinine ratio increased from none, to 0.1 to 0.45 and to 0.46 to 3.4 mg urine albumin/mmol urine creatinine. The results of Melsom *et al.*³ are intriguing, yet appear to have flaws of internal and external validity.

The assay method for albuminuria that was used in this report has a limit of quantitation that is 7.5 mg/l. That corresponds to approximately 7.5 mg/g of urine creatinine, which in turn corresponds to approximately 0.75 mg urine albumin/mmol urine creatinine. This assay's detection limit is 2 mg/l. In the range between 2.0 and 7.5 mg/l, this assay thus does not have quantitative precision. Melsom *et al.*³ report that subjects in their study with albuminuria in this range had increased loss of GFR over the 5-year follow-up time of their study, and this was in a graded fashion within that very low range of albuminuria. Their claims may thus be disputed because of the

expected imprecision of the assay in that very low range. The present report does not record whether the study subjects had urinalyses. If there was more microhematuria in those with greater albuminuria, or if there was pyuria, then there is likely to have been more urinary tract pathology that would explain the loss of renal function, rather than just a modestly increased amount of urine albumin.

External validity is another concern. The study population was entirely white. Their average baseline GFR was above 90 ml/min per 1.73 m². One may not be able to apply these findings to a more diverse population or to those with lower GFR. Also, the yearly incidence of new end-stage renal disease in Norway is 100/million population, which is well below that of the United States and also below that of Belgium, which is 380 and 180, respectively (https://www.usrds.org/2017/view/v2_11.aspx).

It is also worth considering the rates of loss of GFR over the study follow-up time, as shown in Figure 2 of Melsom *et al.*³ The rate of loss of GFR in those with no albuminuria was approximately 0.5 ml/min per year, and was approximately 1 ml/min per year in those with 0.1 to 3.4 mg albumin/mmol urine creatinine. These rates are well below the rates of loss of GFR in subjects with chronic progressive kidney disease (Figure 1). Also, the subjects of this study had an average age of 58 at the start of the study, so would be 63 years old at end of the study. On average, they will live for 20 more years. At a rate of 1 ml/min per year, the subjects in the 0.1 to 3.4 mg urine albumin/mmol urine creatinine group would have a GFR of approximately 78 ml/min at their 20-year follow-up time, when they will be in their early 80s.

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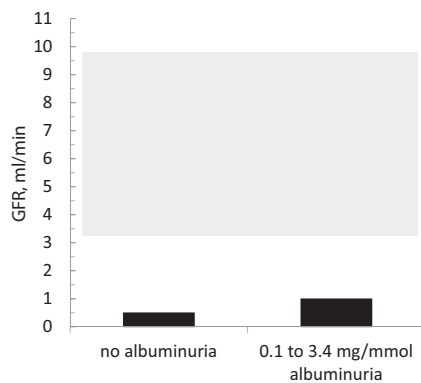


Figure 1. Rate of loss of glomerular filtration rate (GFR), in ml/min per year, as a function of degree of albuminuria. Data adapted from Melsom *et al.*³ The rates of loss of GFR for study subjects with no albuminuria and 0.1 to 3.4 mg albuminuria/mmol urine creatinine are shown as the left and right black columns. The grey shading shows rates of yearly loss of GFR in progressive chronic kidney disease. The rates of loss of GFR in the study subjects are well below those of patients with progressive chronic kidney disease.

A GFR in that range at that age is not renal failure and has no significant effect on all-cause mortality.⁴ The report by Melsom *et al.*³ may be telling us something about aging, but it may not be significant with regard to risk of renal failure or death.

In a broader perspective, the effort to categorize renal function according to estimated GFR and urinary albumin excretion may be distracting us from finding the cause of a patient's renal disease. We may have some satisfaction to record the precise label of stage as G2A1 or G4A3, for instance, but if we don't know the cause of our patient's renal disease, we are not much further in our understanding than was Bright,¹ 200 years ago. Diagnosis of chronic kidney disease and prediction of further loss of renal function depends on interpreting the urinalysis and graphing the fall in GFR versus time, to which are added the renal biopsy and even urine proteomics.⁵ This will move us beyond mere categories of chronic kidney disease, and will ensure better care of our patients. Measuring albumin-to-creatinine ratio remains useful for predicting the future loss of renal function, but at very low levels it appears of minor clinical interest.

DISCLOSURE

All the authors declared no competing interests.

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