Key-Words:
Albumin, angiotensin, chronic kidney disease, endocytosis, hypertension, megalin, proximal tubule.

INTRODUCTION

The presence of abnormal amounts of albumin in the urine has evolved from a diagnostic marker in kidney disease into a prognostic marker important for establishing prognosis and treatment options not only in kidney disease, but also in a number of other conditions including diabetes and cardiovascular disease. Treatment of albuminuria is based on clinical trials that have established the benefit of blood pressure control and inhibition of the renin-angiotensin system. Despite greater understanding of the molecular mechanisms regulating urinary excretion of albumin, the fundamental changes that lead to increased albumin excretion in such a variety of different conditions are still poorly understood. This review will focus on some of the potential pathophysiological mechanisms involved emphasising the emerging evidence for a significant role of renal proximal tubule cell function.

IDENTIFYING ALBUMINURIA – WHAT SHOULD WE MEASURE?

The gold standard for measurement of albuminuria is a timed, usually 24-hour urine collection. The current cut-off values (Table I) defining albuminuria and microalbuminuria has been challenged by several studies showing an increased risk of cardiovascular disease associated with even lower levels of urinary albumin excretion\(^1\)\(^-\)\(^3\) also suggesting that there may not be a well-defined lower limit for the association between albumin excretion in the urine and cardiovascular risk. An albumin-creatinine ratio correlates well with 24-hour urine collections and may serve as a substitute for the diagnosis and quantitation of albuminuria\(^4\) and is recommended by most guidelines\(^5\)\(^,\)\(^6\). A morning spot urine sample representing overnight urine production is a better estimate of 24-hour urine collection than a random sample\(^7\). Urine creatinine excretion is

<table>
<thead>
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<th>24 h urine</th>
<th>Albumin/creatinine-ratio</th>
<th>Albumin/creatinine-ratio (male)</th>
<th>Albumin/creatinine-ratio (female)</th>
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</thead>
<tbody>
<tr>
<td>Normal albumin-excretion</td>
<td>130 mg/24 h (20 to 200 μg/min)</td>
<td>13.5 mg/mmol (30 mg/g)</td>
<td>12.5 mg/mmol (20 mg/g)</td>
<td>13.5 mg/mmol (30 mg/g)</td>
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<tr>
<td>Micro-albuminuria</td>
<td>30 to 300 mg/24 h (20 to 300 μg/min)</td>
<td>3.5 to 35 mg/mmol (30 to 300 mg/g)</td>
<td>2.5 to 25 mg/mmol (20 to 200 mg/g)</td>
<td>3.5 to 35 mg/mmol (30 to 300 mg/g)</td>
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<tr>
<td>Albuminuria</td>
<td>&gt;300 mg/24 h (1000 μg/min)</td>
<td>&gt;155 mg/mmol (1300 mg/g)</td>
<td>&gt;125 mg/mmol (1200 mg/g)</td>
<td>&gt;135 mg/mmol (1300 mg/g)</td>
</tr>
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dependent on a number of factors including sex, age, and muscle mass. Thus, when estimating 24-hour urine albumin excretion using albumin-creatinine ratio, the reference interval is sex- and age-dependent. While this has been documented in many laboratories, it is not always applied in clinical practice, and there is limited documentation of clinical benefit from applying sex- and age-related reference intervals. Studies indicate that significant amounts of albumin fragments are excreted in the urine, possibly resulting from tubular degradation of filtered albumin, followed by luminal secretion of albumin fragments. Although the clinical implication of this has not been established, changes in the relative excretion of albumin fragments to intact albumin have been identified in diabetes, possibly reflecting changes in tubular function. This could indicate that measurements of urinary albumin fragments could provide further information about kidney dysfunction.

**MECHANISM OF ALBUMINURIA – WHAT IS THE CONCERN?**

Proteinuria has been a long standing indicator of kidney disease. In this setting proteinuria is believed to reflect a change in the balance between glomerular filtration and tubular reabsorption of protein on the basis of increased filtration, or decreased tubular reabsorption, or both. Endothelial dysfunction is associated with microalbuminuria and may in fact precede the development of the latter, suggesting that vascular changes play a role both in the development of microalbuminuria and associated cardiovascular risk. Albumin is the major plasma protein and constitutes about 75% of urinary protein in many case of proteinuria. The amount of albumin normally filtered in the glomerulus has been the focus of recent controversy. Several micropuncture studies have estimated the concentration of albumin in the ultrafiltrate between 1 and 50 μg/ml, corresponding to a filtered load of albumin between 170 mg and 9 g per 24-hour in humans. A controversial study in rats based on two-photon confocal microscopy has suggested the normal filtration of very large amounts of albumin corresponding to 1100 g of albumin per day in humans. This, however, could not be confirmed by others. Despite these controversies it is apparent that normal tubular reabsorption of albumin is crucial to prevent albuminuria and filtered albumin is readily reabsorbed by efficient proximal tubule reabsorbptive mechanisms. Receptor mediated endocytosis involving two large, multiligand receptors, megalin and cubilin, has been identified as the major mechanism responsible for the proximal tubule reabsorption of albumin. This process involving the interaction between multiple membrane proteins constitutes a powerful apparatus for the uptake of a large number of different proteins. In addition to an essential role in tubular uptake of proteins, these receptors are important regulators of lysosomal activity and possess intracellular signalling potential establishing a link between these receptors and changes in tubular function. Tubular dysfunction has been identified in a number of conditions associated with albuminuria, including early diabetes. Furthermore, experimental studies have shown that albumin causes tubular changes eventually leading to the induction of inflammation, tubular epithelial-mesenchymal transformation and interstitial fibrosis. Overload albuminuria in rats and mice results in interstitial inflammation and fibrosis and albumin exposure in vitro induces the expression of a number of inflammatory and fibrogenic mediators and causes apoptosis and fibrosis. The exact cascade of events leading to changes in proximal tubule phenotype has not been fully identified and may involve signalling pathways dependent and/or independent on the tubular endocytosis of albumin.

**TREATMENT OF ALBUMINURIA – WHAT ARE WE TREATING?**

Non-nephrotic proteinuria in general causes no symptoms and thus the aim of treatment is to prevent the associated renal and cardiovascular morbidity and mortality. There is a strong association between the reduction of albuminuria and attenuation of renal deterioration in patients with renal disease, almost irrespective of cause. Similarly there is strong clinical evidence that treatment of microalbuminuria in diabetes is associated with a decreased risk of morbidity. These clinical observations constitute the rationale for treating albuminuria in these patients. Despite the association between microalbuminuria and cardiovascular disease, there is currently no compelling clinical evidence for the specific treatment of microalbuminuria outside the...
Albuminuria is an important indicator and prognostic factor in kidney disease and other conditions. The mechanisms of albuminuria include glomerular, tubular, and possibly vascular dysfunction. Several treatment strategies aimed at reduction in albuminuria has been established and shown to be effective in clinical studies, however, our understanding of the mechanism(s) by which this effect is mediated is still not fully elucidated. Whereas experimental studies to some extent allows for the separation of various pathophysiological mechanisms, this is difficult in the setting of human disease confounded not only by multiple coexisting disease mechanisms but also by the heterogeneity in disease presentation and background. A major challenge is to identify reliable markers of glomerular, vascular and tubular dysfunction which can be used to separate these in a clinical setting and facilitate the development and evaluation of targeted therapy.

Conflict of interest statement. None declared.

References


Perspectives

Albuminuria is an important indicator and prognostic factor in kidney disease and other conditions. The mechanisms of albuminuria include glomerular, tubular, and possibly vascular dysfunction. Several treatment strategies aimed at reduction in albuminuria has been established and shown to be effective in clinical studies, however, our understanding of the mechanism(s) by which this effect is mediated is still not fully elucidated. Whereas experimental studies to some extent allows for the separation of various pathophysiological mechanisms, this is difficult in the setting of human disease confounded not only by multiple coexisting disease mechanisms but also by the heterogeneity in disease presentation and background. A major challenge is to identify reliable markers of glomerular, vascular and tubular dysfunction which can be used to separate these in a clinical setting and facilitate the development and evaluation of targeted therapy.


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