Debate: PRO Position

Should Microalbuminuria Ever Be Considered as a Renal Endpoint in Any Clinical Trial?

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One of the earliest signs of asymptomatic kidney damage is the presence of small amounts of albumin in the urine, also termed microalbuminuria i.e. 30–300 mg/day. These small amounts of albumin tell an important story about the future of the kidneys: if microalbuminuria is present, patients have a greater chance of premature loss of filtration power and eventually renal failure. However, more important than establishing the presence of renal risk, is the question of whether we can do something about this risk. Thus, there is increased interest in using the change in albuminuria as a surrogate marker for risk change. We postulate that microalbuminuria is indeed a valid so-called ‘surrogate endpoint’ in renal intervention trials.

A surrogate endpoint is a biomarker that is correlated with the clinical endpoint and is intended to substitute for the clinical endpoint. Although such a biomarker is not itself important for a patient, it is associated with a clinically meaningful outcome and is expected to predict harm or benefit. Clinical trials with surrogate endpoint require fewer patients and are generally of shorter duration. It is therefore tempting to use surrogate endpoints trials for registration purposes in order to reduce the time and financial resources to develop new drugs. However, in this era of evidence-based medicine, a surrogate endpoint can only substitute a clinical outcome if it fulfills the criteria for validation of a surrogate end-

point, as outlined in the ‘Statistical Principles for Clinical Trials’ of the International Conference on Harmonisation [1]. According to these criteria, a biologically plausible relationship between the surrogate and outcome should exist. Prognostic evidence of the surrogate endpoint with patient outcome must be available, and finally, clinical trial data must demonstrate that the effect of interventions that change the surrogate endpoint is directly associated with the same change in patient outcomes. We will illustrate that microalbuminuria fulfills each criterion.

Mechanisms Linking Albuminuria to Renal Disease

The classical view on the relationship between albuminuria and progressive renal function loss is that increased urinary albumin excretion is the consequence of an impaired glomerular filter. The glomerular filter plays a dominant role in retaining macromolecules in the vascular compartment. Under physiological circumstances, the amount of albumin leaking into the urinary space is modest. The albumin molecules that escape the glomerular barrier do not appear in the urine because they are effectively reabsorbed by the proximal tubule. The barrier preventing albumin from leaking out of the vascular space has been studied extensively. A recent review re-

veals that next to the well-known charge and size selectivity of the glomerular filter, a large part is attributable to the glycocalyx [2]. The glycocalyx is a negatively charged layer that covers the endothelial glomerular cells and repels the transglomerular passage of negatively charged albumin. Thus, damage to the glomerular filter and changes in glycocalyx composition (endothelial dysfunction) are reasons for excessive leakage of albumin into the urinary space. This means an extra burden for mesangial cells, as well as tubular cells, when they reabsorb this excess albumin. In turn, this may lead to an intrarenal inflammatory response leading to activation of TGF- β , proinflammatory cytokines, glomerulosclerosis and tubulointerstitial fibrosis, ultimately leading to end-stage renal disease (ESRD) [3].

Microalbuminuria Predicts Renal Outcome

There is ample evidence that the albuminuria level is associated with the rate of renal disease progression. For practical purposes, albuminuria is categorized into different classes: normoalbuminuria (<30 mg/day), microalbuminuria (30–300 mg/day), and macroalbuminuria (>300 mg/day). Changes between these states are considered a hallmark of progression or regression of disease. Numerous prospective studies have shown that the magnitude of increased urinary albumin excretion is linearly associated with the risk for progression (or regression) between these states.

The association between albuminuria and risk for renal disease was first described in the diabetic population. Viberti et al. [4] found that after 14 years' follow-up, 7 out of 8 subjects with initial albuminuria levels between 30 and 140 μ g/min (45–210 mg/day) developed clinical diabetic nephropathy, whereas only 2 out of 55 subjects with initial albuminuria below 30 μ g/min developed clinical diabetic nephropathy. Several studies followed this initial report and confirmed the significance of albuminuria in predicting the long-term risk for renal disease [5].

Recently, the largest study conducted in patients with type 2 diabetes, the ADVANCE trial, was completed. The majority of the patients (69%) enrolled in this trial had albuminuria levels in the normoalbuminuric range. The baseline albuminuria level was linearly associated with renal outcome independent of other renal risk markers. This relationship extended even into the normoalbuminuric range (fig. 1a) [6].

Similar associations between albuminuria and the long-term risk for kidney disease have been described in

the nondiabetic and general populations. In the African-American Study of Kidney Disease and Hypertension (AASK), the level of albuminuria, expressed as protein creatinine ratio, was a strong independent risk marker for progression of renal disease. The relationship also held true in the microalbuminuric range. For every twofold increase in albuminuria, a 1.80-fold increased risk for ESRD was noted (fig. 1) [7]. Further evidence that microalbuminuria is an early indicator for the long-term risk of renal disease comes from a retrospective cohort study in 141 hypertensive patients [8]. The results of this study showed that the rate of renal function decline in individuals with microalbuminuria was significantly higher compared to those with normoalbuminuria (12.1 ± 2.77 ml/min vs. 7.1 ± 0.88 ml/min). Analyses from the community cohort Prevention of Renal and Vascular End-Stage Disease (PREVEND) study have provided further insight into the relationship between low levels of albuminuria and renal disease in the general population. In this cohort, elevated albuminuria is associated with a higher rate of decline in eGFR and an increased risk for renal replacement therapy. Again, the relationship extended into the low micro- and normoalbuminuric range [9].

These data from multiple studies in a broad range of patients demonstrate that increased albuminuria is consistently associated with risk for renal impairment. It is important to emphasize that there is no published study available demonstrating that diminished albuminuria levels are associated with an increased risk for renal replacement therapy, highlighting the strong and consistent association between albuminuria and renal disease progression. Another important point is the fact that the strong relation between albuminuria and renal outcome does not mean that albuminuria is the sole factor associated with renal progression. Studies stating that patients without microalbuminuria can have progressive renal function loss just indicate that other factors can play a role as well [10]. However, the available evidence clearly shows that increased levels of albumin (when present) are an excellent predictor of later renal problems in diabetes and non-diabetic conditions.

Albuminuria Reduction Predicts Renal Protection

The other important question to answer is 'whether a change in albumin level or albuminuria category is a predictor for renal protection?' For all accepted surrogate risk markers for renal disease progression, such as high

Fig. 1. a Association between albuminuria level and the risk for renal outcomes in different populations. Data show the risk for the occurrence of ESRD (death) for the general population (PREVEND [9]), type 2 diabetes (ADVANCE [6]) and hypertensive nephrosclerosis (AASK [7]). The protein:creatinine ratio, measured in the AASK trial, was converted to the albumin:creatinine ratio. The center of the squares are placed on the average al-

buminuria level in each population. **b** Associations between the proportional change in albuminuria and the risk for renal outcomes. Renal endpoint in the IRMA-2 trial is diabetic nephropathy. The renal endpoint in the AASK trial is ESRD. The two x-axes indicate the ranges of albuminuria reduction for the two different individual trials.

blood pressure, increased HbA1c and high cholesterol, risk profiles similar to increased albuminuria are observed. Interestingly, targeting all the accepted surrogate markers (blood pressure, HbA1c, cholesterol) towards normalcy have all been associated with a reduction in the long-term risk of renal or cardiovascular disease. It would be highly unlikely that the lowering of albuminuria is not associated with renoprotection. Furthermore, drugs that induce a fall in one of the accepted surrogate risk markers are accepted as renoprotective treatments, despite the fact that exceptions are published! One should thus have strong evidence to disallow albuminuria as a surrogate.

Analyses from different clinical trials have indeed shown that the magnitude of albuminuria reduction during pharmacological therapy within the microalbuminuric range is associated with renal protection. The Irbesartan in Micro-Albuminuria-2 (IRMA-2) trial demonstrated a dose-dependent effect of angiotensin receptor blockade on albuminuria reduction and progression to nephropathy: the higher the initial degree of albuminuria reduction during angiotensin receptor blocker treatment, the lower the risk for diabetic nephropathy in the long-term (fig. 1b) [11]. In line with these results is the study

of Gaede et al. [12], who randomly assigned patients to intensive or standard multifactorial intervention. This study showed that intensive treatment reduced albuminuria and slowed the progression of nephropathy. Interestingly, the rate of GFR decline was significantly lower in patients who regressed from microalbuminuria to normoalbuminuria compared to those who remained microalbuminuric or progressed to macroalbuminuria [12]. Similar results were obtained in nondiabetic patients with hypertension participating in the AASK trial. Modifying proteinuria levels even in the very low range ameliorated the rate of GFR decline and attenuated the progression to ESRD, independent of other renal risk markers (fig. 1b) [7].

Not all studies unambiguously demonstrate that the change in albuminuria during therapy is associated with improved outcomes. The recent ONTARGET trial has shown that dual agent RAAS-blockade slows the increase in albuminuria. Unexpectedly, dual agent RAAS-blockade did not lower the incidence of the prespecified renal outcome. This should, however, not be interpreted that (micro)albuminuria is not a valid endpoint for trials in nephrology, as extensively discussed in the literature [13].

A possible explanation for the ONTARGET findings is that dual agent RAAS-blockade had other effects, including inducing hyperkalemia and/or hypotension. These effects may have increased the risk for renal disease and may have offset the potential benefit of albuminuria lowering. Good examples for such a phenomenon come from antihypertensive drugs tested for cardiovascular protection. Diuretics may lower blood pressure, but if they induce hypokalemia they may not turn out to be cardioprotective [14]. This has never been a reason to dismiss blood pressure as a valid surrogate marker. Thus, we should not negate the value of microalbuminuria as a useful surrogate endpoint based on a single trial, including a specific population, and not being designed to study renal outcomes.

It is generally acknowledged that early intervention has a greater impact to delay the progression of renal function loss [15]. Consequently, health campaigns focus on early detection and appropriate treatment of patients with early signs of kidney damage. However, progression of renal disease occurs at a slow but relentless rate. Therefore, intervention trials testing the effectiveness of interventions in delaying the progression from early renal impairment to ESRD need to follow patients for many more years than current trial settings and finances allow. We have illustrated that the presence of microalbuminuria is a valid surrogate for clinical outcomes. As such, its use as a surrogate endpoint is essential in order to produce new affordable drugs for patients at an early stage of renal disease.

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