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Proteinuria in Diabetes: Bystander or Pathway to Cardiorenal Disease?

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ABSTRACT

The development of albuminuria in diabetics is closely associated with an enhanced risk of renal and cardiovascular disease. However, the role of albuminuria in the pathogenesis of these clinical conditions remains controversial. Whether albuminuria is simply a biomarker or qualifies as a surrogate endpoint for cardiorenal disease has wide-ranging implications from the monitoring and treatment of patients to the design of clinical trials and drug development. We critically review available data to determine whether the association between albuminuria and cardiorenal disease is causative. Current evidence suggests the significance of albuminuria depends on its severity (degree or level) and on the specific clinical outcome under consideration. For diabetic kidney disease, there is convincing epidemiologic and experimental evidence to assign clinical albuminuria status as a surrogate endpoint, but for lower levels of albuminuria (microalbuminuria and normoalbuminuria), the evidence is inconclusive or not available. Albuminuria of any degree is unlikely to be causally related to diabetic cardiovascular disease, but its onset might be useful to identify those subjects at cardiovascular risk and to detect and treat other modifiable risk factors.

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Diabetic kidney disease (DKD) is the most common chronic nephropathy worldwide and, with the rising prevalence of diabetes and obesity, is rapidly becoming a major public health problem. In diabetes, renal disease and cardiovascular disease are closely associated, and the development of DKD is an independent and powerful risk factor for morbidity and mortality from cardiovascular disease (CVD).[1,2]

Proteinuria is one of several markers of kidney damage in diabetes. The urine contains a large variety of different molecular weight proteins including albumin. For reasons that will not be addressed here, measurement of urine albumin, rather than total protein, is recommended for detection of renal disease in diabetics, and the term albuminuria will be used henceforth.[1,2] Sensitive and specific assays for albumin are now available for detection of urine albumin concentrations down into the normal range. The interassay variability of these methods is small, although there is as yet no standardized procedure across clinical laboratories.[2] Urine albumin excretion is generally reported as an albumin/creatinine ratio (ACR) in either milligrams per millimoles or millligrams per gram when spot, preferably early morning, urine samples are collected, or albumin excretion rates (AERs) in micrograms per minute or milligrams per 24 hours using timed urine collections.

The importance of albuminuria in diabetes resides in the consistent observation that elevations in this marker, independent of other functional or structural markers of kidney damage, are strongly related to the development of renal disease and CVD.[1,2] Although different categories of urine albumin excretion such as normoalbuminuria (ACR $<$ 30 mg/g), microalbuminuria (ACR from 30 to 299 mg/g), or clinical albuminuria (ACR $\geq$ 300 mg/g) are commonly used, the relationship between urine albumin excretion and cardiorenal risk is an exponential continuum without threshold. It is worth mentioning that the independent and log linear association of albumin excretion rate with renal disease and CVD also applies to conditions outside diabetes, such as other chronic glomerulopathies, arterial hypertension, and chronic heart failure, and the general population, but their discussion is beyond the scope of this article.

The pathophysiology of albuminuria is complex and likely to be heterogeneous even within a single disease entity such as diabetes, with different cell types in the glomerulus and possibly in the tubule contributing in different degrees and at different stages of disease to the leakage of albumin. The phenotype of diabetic albuminuria therefore may have multiple different etiologies and is unlikely to be a single entity.[3]

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EPIDEMIOLOGY OF ALBUMINURIA IN DIABETES

A large body of evidence shows that elevations of albuminuria, even below the arbitrary threshold for normality of an ACR of 30 mg/g, associate with progression to greater levels of albuminuria, lower estimated GFRs (eGFR) and subsequent decline in renal function, evidence of renal histologic damage, and increased risk of advancing renal failure even after adjustment for confounding risk factors.[1,2] One such factor of peculiar importance is arterial BP. Rises in albuminuria accompany increases in BP, initially occurring within the normal range. Higher BP values may precede and predict the development of greater levels of albuminuria, and indeed, the susceptible subset of diabetic subjects who develop albuminuria has a familial predisposition to arterial hypertension.[2]

This close association between albuminuria and renal disease is reproduced to a remarkably similar degree in relation to CVD. Even small increases in albuminuria predict an increased risk of CVD morbidity and mortality and all-cause mortality. As for renal disease, the diabetic subject susceptible to nephropathy has a strong familial predisposition to CVD.[2]

These clear and consistent epidemiologic associations question whether albuminuria is casually related to DKD and CVD and more importantly, from a clinical standpoint, whether albuminuria is a modifiable risk factor, the treatment or prevention of which would affect the clinical outcome of DKD and CVD. To answer this question, we must revisit the criteria that need to be satisfied to ascribe causality to the variable albuminuria, set them in the context of more recent statistical methodologies for validation of causality, and analyze the relationship of albuminuria separately with renal disease and with CVD. By doing this, we will form a clearer view of whether albuminuria represent a simple biomarker, an intermediate endpoint, or a surrogate endpoint, and how this applies to the separate context of renal disease and CVD.

DEFINITIONS OF ENDPOINTS AND CRITERIA FOR CAUSALITY

In clinical practice, measures of effectiveness of interventions should relate to meaningful clinical outcome such as mortality, disease morbidity (nonfatal cardiovascular or cerebrovascular events), functional status (exercise capacity in patients with chronic heart failure), and quality of life. Measures that are related to a clinical outcome but are distant from it come under the categories of biomarker, intermediate marker, or surrogate marker.[4,5] It is important to establish to which category albuminuria belongs, because this has clear implications for diagnostic, treatment, and monitoring purposes.

A biomarker is a laboratory or physiologic measure that is usually found in a pathologic condition and is commonly associated with it. Strictly speaking, a biomarker is not directly causal of the clinical condition: for example, elevated troponin in myocardial infarction or peek expiratory flow rate in lung disease. An intermediate endpoint is a biomarker that is part of the ontology of a certain clinical condition. Reduced GFR, for instance, is an intermediate endpoint because it is on the causal pathway to ESRD. A surrogate endpoint, on the other hand, is a laboratory or physical measure that is used as a substitute for a clinical outcome and for which there is convincing evidence of a casual relationship with clinical outcome. Examples of surrogate endpoints are raised BP and LDL cholesterol for CVD or doubling of serum creatinine for kidney failure.

To be assigned the status of surrogate endpoint would represent distinct advantages for a variable such as albuminuria. It would permit earlier, easier, precise, and more frequent measurements of a pathologic process (be it renal disease or CVD), reduce duration, sample size, and cost of clinical trials, and lead to faster therapeutic decisions. It would also help and facilitate drug development. However, a prime requisite for surrogate status is that there is incontrovertible evidence the variable is causally related to the outcome, and as a consequence, modification of the surrogate leads to proportionate changes in the outcome.

Nine criteria were proposed by Sir Austin Bradford-Hill that need to be satisfied to ascribe causality.[6] Analysis of these criteria not only can bring evidence for or against a cause and effect relationship but also helps decide whether, given the knowledge available, there is any other explanation equally or more likely than cause and effect:

Strength: Is Strength of Relationship between Variable and Outcome Present?

Diabetic subjects who develop albuminuria have between a 9- to 40-fold increased risk of progression to ESRD or ESRD-related death compared with diabetic subjects who maintain normoalbuminuria.[1,2,7,8] Recent *post hoc* analysis of data from subjects with type 2 diabetes mellitus (T2DM) and an eGFR between 30 and 59 ml/min shows an almost 5-fold greater risk of renal events in subjects with ACR $\geq$30 mg/g *versus* those with ACR $<$30 mg/g.[9] The degree of ESRD risk in diabetes varies depending on the level of albuminuria, ranging from three- to fivefold for microalbuminuria to ninefold for clinical albuminuria, which may simply reflect different stages of disease evolution.[8] The increase in risk of ESRD is greater in type 1 diabetes mellitus (T1DM) subjects compared with T2DM subjects, which is likely to be the result of competing risk factors for mortality from other causes in older T2DM patients.

T1DM subjects with albuminuria have a relative mortality from CVD that is nine times higher than T1DM subjects with normoalbuminuria, who in turn have a fourfold higher risk of CVD death than the general population.[1,8] T2DM subjects with microalbuminuria or albuminuria have significantly higher risks (1.7 and 2.6, respectively) for CVD mortality compared with those with normoalbuminuria.[10,11] Thus, the strength of the relationship seems robust between albuminuria and renal disease but slight between albuminuria and CVD, especially in T2DM subjects.

Consistency: Are Results Replicated by Different Researchers under Different Conditions?

Different investigators from different countries and in different ethnic groups have confirmed the association of albuminuria with renal disease in diabetes. Similarly, epidemiologic studies consistently indentify albu-

minuria as an independent risk factor for CVD and in particular chronic congestive heart failure. Importantly, this increased risk appears at levels of albuminuria that are currently defined as within the normal range.[1,10]

Specificity: Is the Variable Associated with a Specific Disease or Effect Rather than a Wide Range of Diseases or Multiple Effects?

In most cases, albuminuria is the earliest sign of renal disease and may represent glomerular and tubular damage. However, there are reports of functional renal impairment and changes in renal histology in the absence of albuminuria that have questioned the role of albuminuria as a specific marker of DKD.[12–14]

The specificity with which albuminuria relates to CVD is less clear in diabetes and seems confined to congestive heart failure. The Heart Outcomes Prevention Evaluation study reported that the presence of microalbuminuria at baseline resulted, after adjustments for other CVD risk factors, in a three- to fourfold increased risk of hospitalization for congestive heart failure but was considerably less specific for other CVD events and death, with an increased risk of only between 1.4 and 1.8.[10]

The importance of the specificity criterion should not be overemphasized in as much as diabetes, renal, or CVD outcomes have more than one cause, and lack of specificity is found in other conditions of proven cause and effect relationship such as smoking and lung cancer. Indeed smokers have a higher death rate than nonsmokers from many other causes than lung cancer.

Temporality: Does the variable precede the outcome?

Generally the onset of albuminuria precedes renal failure. This notion and historic evidence have been challenged by reports of diabetic subjects with impaired renal function without albuminuria.[12–14] In the UK Prospective Diabetes Study (UKPDS) cohort, 51% of those who developed renal impairment (defined as creatinine clearance $<$ 60 ml/min or doubling of plasma creatinine) did not have preceding albuminuria.[14] These data suggest a temporal uncoupling between albuminuria and renal failure. However, in these studies, the definition of renal failure was not robust, and detection of albuminuria was not systematically recorded. Of note, only a relatively small number of subjects developed renal endpoints (71, elevated plasma creatinine $\geq$ 175 μmol/L; 14 required renal replacement therapy), and the authors did not report how many of these 85 subjects had a prior history of albuminuria. We examined the evidence of albuminuria in 612 diabetic subjects (96 T1DM, 516 T2DM) with serum creatinine levels consistently $>$150 μmol/L or receiving renal replacement therapy ($n = 62$) who attended the diabetic renal clinic at Guy's Hospital between 2005 and 2007.[15] Albuminuria, which was systematically recorded every 6 to 12 months, was defined as ACR ratio $\geq$2.5 mg/mmol in men and $\geq$3.5 mg/mmol in women or AER $\geq$20 μg/min on timed overnight urine collections or positive urine protein dipstick. For 5 subjects with T1DM and 88 subjects with T2DM, there was histologic or clinical evidence of nondiabetic renal disease. Sixteen subjects (2 T1DM, 14 T2DM) had incomplete records. Of the remaining 503 subjects (89 T1DM, 414 T2DM), only 2 T2DM subjects with diabetic nephropathy had no recorded evidence of raised AER preceding the development of renal impairment (Figure 1). These recent data from a clinic-based cohort suggest a history of albuminuria almost invariably precedes the development of significant diabetic nephropathy and strongly support the historic evidence of a temporal relationship between albuminuria and renal failure.

Some workers have suggested that albuminuria reflects generalized endothelial dysfunction and generalized vascular damage, which presumably would occur before the onset of overt CVD.[16] The Bypass Angioplasty Revascularization Investigation 2 Diabetes study of T2DM with confirmed CVD reported only a 33% prevalence of albuminuria, which was associated with peripheral vascular disease and left ventricular dysfunction.[17]

Biologic Gradient: Is There Demonstration of a Dose–Response Curve to Support Causality?

There is a clear biologic gradient between clinical albuminuria and renal outcomes. T2DM subjects with high baseline albuminuria ($\geq$3.0 g/g) show an eightfold increased risk for progression to ESRD compared with the group with lower albuminuria ($<$1.5 g/g).[18] Moreover, a 50% initial reduction in albuminuria by treatment translated to a 45% risk reduction for ESRD. However, whether there is a dose–response curve within the microalbuminuria or normoalbuminuria range is unknown.

In T2DM subjects, there is also a biologic gradient between albuminuria and total mortality or cardiovascular mor-

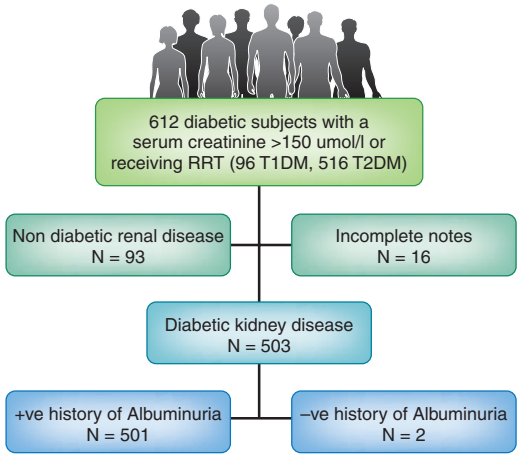

Figure 1. History of albuminuria in a cohort of 612 patients with diabetes and overt kidney disease.

bidity or mortality. In the Heart Outcomes Prevention Evaluation study, for every 1 mg/mmol rise of ACR, even below the level of microalbuminuria, the adjusted hazard of the primary outcome of CVD events or death increased by about 15%. Subjects with an ACR >1.62 mg/mmol had a 2.3-fold increase in the primary outcome compared with those with an ACR <0.22 mg/mmol.[10] Initial reduction of albuminuria by treatment with anti-hypertensive medications also decreases the risk of CVD outcomes by between 18 and 27%, although the dose–response curve is most clear for congestive heart failure and less for ischemic heart disease.[19] This graded relationship between reduction of albuminuria and CVD outcomes is confounded to a significant extent by the lowering of BP and whether even a dose–response curve for CVD exists within the micro- and normoalbuminuric range.

Biologic Plausibility: Is There a Plausible Mechanistic Link Between the Variable and the Outcome?

Evidence for biologic plausibility usually comes from *in vitro* and animal studies, which examine mechanisms of renal and cardiovascular damage in much greater detail than clinical human studies allow. Biologic plausibility is strongest when the variable is an intermediate in the causal pathway of disease, but this heavily depends on the biologic knowledge of the day. Although the phenotype albuminuria in diabetes may derive from multiple and different mechanisms, it has been proposed that albuminuria, rather than being a simple marker of damage, may actually be involved in the pathophysiology of progressive renal injury.[20] Urine albumin seems to be proinflammatory and, thus, once filtered and reabsorbed by the tubule, would induce a number of profibrotic cytokines that drive the process of glomerulosclerosis and, more importantly, tubulointerstitial fibrosis. In this context, a key factor is TGFβ, which is a mediator of renal fibrotic change in diabetes. In some animal studies, neutralizing the effects of TGFβ prevents or reverses renal fibrosis and preserves renal function but has no effect on albuminuria.[21] This may be because activation of TGFβ occurs downstream of albuminuria, after albumin has been filtered and partially reabsorbed, but it does prove the concept that it is possible to uncouple albuminuria (or changes thereof) from renal damage/repair or changes thereof. In this scenario, measuring effectiveness of a treatment by monitoring or targeting albuminuria as a marker of disease prevention or reversal would be useless.

It has been suggested that biologic plausibility is strengthened if long-term reduction of the variable persists after withdrawal of treatment, because this may indicate a beneficial effect on the underlying structural damage responsible for the disease clinical outcome.[22] This is questionable, however, in as much as the effect on structure may diminish over time with discontinuation of therapy, and therapy may be intended for long-term use. A case in point in T2DM subjects is that of hypertension, an accepted surrogate for CVD. Unless good control of BP is maintained by continuation of treatment, the clinical benefits of BP lowering are lost, as clearly shown in the observational follow-up of the UKPDS.[23] Unlike good control of blood glucose, good control of BP has no legacy effect, and the same may apply to albuminuria.[23,24]

The biologic mechanisms that link albuminuria to CVD are much less clear. It could be postulated that increased transcapillary escape of albumin, as measured in diabetic subjects with albuminuria,[25] may trigger an inflammatory reaction in the vessel wall, and there is some evidence that endothelial dysfunction precedes the onset of microalbuminuria or clinical albuminuria.[26] It is more likely that another factor, such as oxidative stress that upregulates the expression of inflammatory cytokines and induces endothelial dysfunction,[3,27] would result in albuminuria on the one hand and CVD on the other (Figure 2). This disconnect in the causal pathway between albuminuria and CVD is also underscored by the observation in T2DM subjects that drugs such as statins, which significantly reduce the risk of CVD, have inconsistent effects on albuminuria.[28]

Coherence: Is the Interpretation of a Causal Link between Albuminuria and Cardio-Renal Outcomes Consistent with the Known Natural History and Biology of the Disease?

Albuminuria is certainly part of the natural history of diabetic nephropathy and a good predictor of decline in renal func-

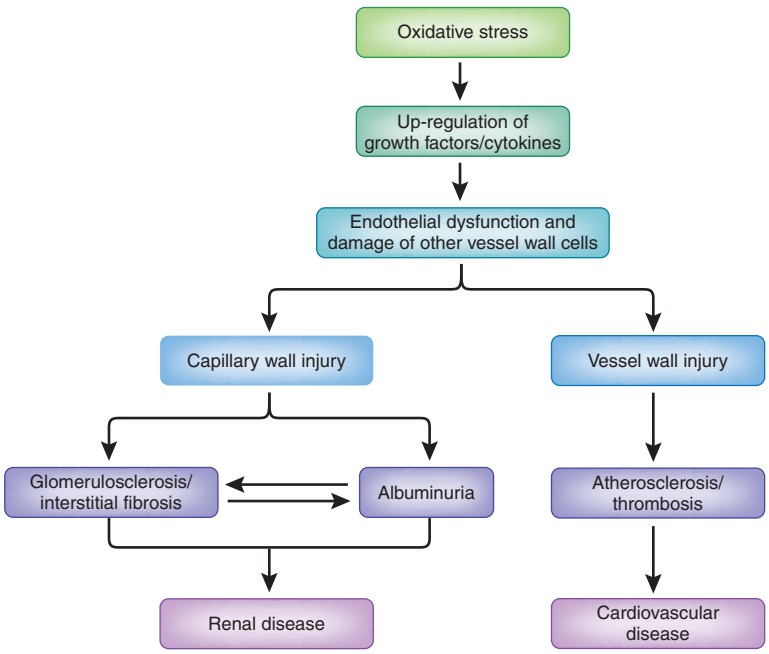

Figure 2. Putative pathophysiologic mechanism of the disconnect in the causal pathway between albuminuria and cardiovascular disease.

tion. However, the natural history of albuminuria has changed in the last few years, with increasingly aggressive glycemic and BP control in T1DM and T2DM subjects.[1] Some clinical data suggest that renal damage can develop in the absence of albuminuria, and animal data indicate that structural lesions and functional decline can be prevented by interventions that do not affect albuminuria.[12–14,21] Although albuminuria may reflect generalized vascular dysfunction, a precursor of overt CVD disease, there is no clear evidence to suggest that interventions that directly target albuminuria result in a lowering of CVD events. Furthermore, CVD in T2DM subjects can clearly occur in the absence of albuminuria.

Analogy: It May Help in Some Cases to Judge by Analogy to Infer Causality

Albuminuria and retinopathy often coexist in diabetes, and indeed, the diabetic origin of albuminuria and kidney disease is often doubted in the absence of retinopathy. A common pathophysiology has been suggested for diabetic microvascular disease,[27] but it is increasingly clear that local, organ-specific factors also play a role. In recent clinical trials, interventions that targeted the renin angiotensin system (RAS) prevented or retarded worsening retinopathy but had no effect on the development of microalbuminuria.[29–32] Although albuminuria is closely related to other microvascular conditions, the association of diabetic retinopathy or neuropathy with CVD is less robust, making analogy a weak criterion to judge the putative causal link of albuminuria with CVD.

Experimental Evidence: Does Correction of the Variable Predictably Reduce the Frequency of the Clinical Outcome?

Is albuminuria a modifiable risk factor? The answer to this question may depend on the level of albuminuria and on the stage of DKD or diabetic CVD.

Clinical Albuminuria.

In diabetic subjects with overt renal disease as defined by elevated serum creatinine and mild to moderate clinical albuminuria (nephrotic proteinuria $>$ 3.5 g/24 h is uncommon in diabetes), interventions with angiotensin-converting enzyme (ACE) inhibitors in T1DM, and angiotensin receptor blockers (ARBs) in T2DM, reduced the risk of progression to doubling of serum creatinine, ESRD, and death by between 50% (T1DM) and 25 to 30% (T2DM) compared with conventional anti-hypertensive treatment.[1,2,18] Blockade of the RAS reduces albuminuria to a significantly greater extent, by approximately 40% than other anti-hypertensive medications, and *post hoc* analyses in T2DM studies indicated that a 50% reduction in albuminuria in the first 6 months of treatment translates into a 45% lower risk of ESRD.[18] In all these studies, BP was reduced to lower values in subjects assigned to receive RAS blockade, and although the differences were small, albeit in some cases significant, a possible confounding effect of BP reduction on the renal outcome could not be fully excluded. A number of statistical techniques have been proposed to adjust for confounders to evaluate whether a variable, in this case albuminuria, is a surrogate endpoint for the clinical outcome, in this case renal failure.[4,5,22]

Ideally, one would test whether the estimate of the treatment effect (ACE inhibition or angiotensin receptor blockade) on the clinical outcome (renal failure) would be reduced to zero after statistical adjustment for the variable (albuminuria). Figure 3 shows graphically this eventuality and implies that, unless the treatment lowers albuminuria, it would have no impact on the clinical outcome. Unfortunately this condition only rarely applies, even for accepted surrogate endpoints such as raised cholesterol or hypertension. Less stringent statistical approaches have been proposed such as the evaluation of the proportion of the treatment effect on the clinical outcome explained by a putative surrogate and more recently the use of meta-analyses and systematic reviews of different trials.[22] All these approaches, although useful, have important limitations that have been described in detail elsewhere.[22,33,34]

Thus, although in overt diabetic renal disease, the experimental evidence for albuminuria as a potential surrogate for ESRD is reasonably robust, results of recent trials in which greater reductions in albuminuria were sought have raised some concern. In diabetes, short-term combination therapy with an ACE inhibitor and ARB, ACE inhibitor and diuretic, or ARB and direct renin inhibitor lowers albuminuria by a greater degree than respective monotherapies.[35–37] However, secondary analyses of CVD outcome studies in mixed populations, such as the Outcomes With Telmisartan, Ramipril, or Both, in People at High Vascular Risk and also the Avoiding Cardiovascular Events through Combination Therapy in Patients Living with Systolic Hypertension, showed that combination therapies that lower albuminuria to a greater degree result in worse renal disease outcomes (doubling of serum creatinine or ESRD or need for dialysis) in the overall population and afford no unique benefit in the smaller subset of subjects with diabetes. However, in these trials, the percentage of patients with clinical albuminuria (ACR $\geq$ 300 mg/g) was quite small.[38,39]

In the short term, studies of endothelin receptor antagonists reduce albuminuria in diabetic nephropathy independently of BP changes.[40] A recent randomized controlled trial with avosentan, a predominant

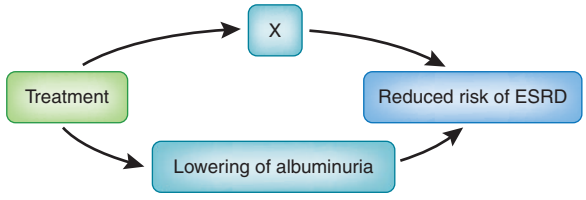

Figure 3. Example of a potential relationship between treatment, albuminuria, and ESRD. If albuminuria is causative of the development of ESRD, treatment would reduce the risk of ESRD only if it lowered albuminuria.

endothelin type A receptor antagonist, in T2DM subjects with clinical albuminuria and raised serum creatinine (chronic kidney disease stages 3 and 4) confirmed a further reduction by 40 to 50% of albuminuria over and above that achieved by ACE inhibition but was associated with a greater fall in eGFR in the short term and had to be terminated prematurely because of a significant excess of congestive heart failure, fluid overload, and a trend to higher mortality.[41] Other intervention strategies aimed at specifically lowering albuminuria have also failed to provide definitive evidence for surrogacy.[42] For a variety of reasons, none of the above studies met the ideal conditions to test fully the hypothesis that diabetic albuminuria is a surrogate endpoint, but they highlight the complexity of the issue under study and raise the possibility that apparently favorable changes in albuminuria may not be associated with concordant renal (or CVD) protection.

Even more problematic is the experimental evidence linking the reduction of albuminuria and CVD outcomes. No clinical trial has addressed this question directly. *Post hoc* analyses of the reduction of endpoints in T2DM subjects with overt nephropathy using losartan (Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan) suggested that, the greater the reduction in albuminuria in the first 6 months of therapy with losartan, the greater the decrease in risk of CVD events.[19] The strength of this relationship was predominantly driven by a reduction in the incidence of hospitalization for congestive heart failure, although a small residual significance was left for other CVD events. It is easy to see how an intervention such as inhibition of the RAS, which ameliorates congestive heart failure and improves cardiac performance, could lead to a reduction in albuminuria because of decreased renal stasis rather than an ARB-induced reduction of albuminuria being responsible for the lower incidence of congestive heart failure.

Microalbuminuria.
Numerous studies in both T1DM and T2DM subjects showed that strict glycemic control, reduction of BP, and use of ACE inhibitors or ARBs, at times independently of BP changes, are capable of reducing the rate of transition from microalbuminuria to clinical albuminuria and often revert microalbuminuria to normoalbuminuria.[1,2] With one exception, none of these studies has been of significant duration to establish whether these effects result in reduction of clinical renal or CVD events. In the Steno-2 study in T2DM subjects with microalbuminuria, a multifactorial intensive treatment strategy that included control of hyperglycemia, hypertension (often with ACE inhibitors or ARBs), dyslipidemia, use of aspirin, and behavioral modification lowered the rate of clinical albuminuria and was associated with a lower rate of declining GFR, reduced risk of CVD mortality and morbidity, and lower total mortality.[43,44] Even in this long-term study, however, it is hard to say whether the renal and CVD endpoints were concomitant effects or the consequence of a treatment-related effect on albuminuria. Furthermore, the many interventions at play, some of which would have no effect on albuminuria, make it even more difficult to prove cause and effect.

Normoalbuminuria.
In both T1DM and T2DM subjects, strict glycemic control reduces the risk of developing microalbuminuria and clinical albuminuria, and this beneficial effect seems to persist for years after the original glycemic difference between treatment groups has waned (glycemic legacy).[24,45] These primary prevention studies, however, have not linked the reduction in the risk of albuminuria with renal or CDV events. Moreover, there is a notable example of disconnect. In overweight T2DM subjects in the UKPDS and its 10-year observational follow-up, treatment with metformin improved glycemia and resulted in a significant reduction in CVD events and in lower mortality but had no effect on albuminuria and other microvascular endpoints.[24]

In T2DM subjects, control of arterial hypertension also decreases the transition rate of normoalbuminuria to microalbuminuria, and in The Bergamo Nephrologic Diabetes Complications Trial, the risk of developing microalbuminuria was reduced by about 50% with the use of the ACE inhibitor, trandolapril, but not with the calcium-channel blocker, verapamil, for the same lowering of BP.[46] In this same study, use of an ACE inhibitor reduced the risk of developing left ventricular hypertrophy.[47] Secondary analyses of other studies, which admittedly were designed with different primary endpoints, have reported discrepant results. In the Diabetic Retinopathy Candesartan Trial renal substudy in T1DM and T2DM subjects with normoalbuminuria, the ARB candesartan failed to reduce the risk of microalbuminuria, despite greater reduction in BP compared with the control group.[32] In the Renin Angiotensin System Study in normotensive T1DM subjects with normoalbuminuria, treatment with enalapril or losartan had no effect on or worsened the development of microalbuminuria compared with placebo.[29] The number of microalbuminuria events was very small, and interpretation is problematic. Inhibition of RAS in this same study had no effect on renal histology, the primary endpoint, but reduced the risk of retinopathy, a secondary endpoint.[29]

A recent clinical trial in T2DM subjects with normoalbuminuria specifically designed with time to onset of microalbuminuria as the primary endpoint showed that treatment with the ARB olmesartan reduced the incidence of microalbuminuria by 23%, an effect partly explained by a greater olmesartan-induced BP reduction, but was associated with a higher risk of CVD mortality, although the total number of secondary CVD events was small.[48]

The studies in diabetic subjects with microalbuminuria and normoalbuminuria are therefore largely inconclusive and fail to establish, thus far, whether treatments that target prevention or reversal of microalbuminuria would result in either protection from renal disease or CVD.

CONCLUSIONS

The criteria used to ascribe causality to a biomarker and to establish, in the spe-

cific, whether albuminuria is a valid surrogate endpoint for renal failure and CVD in diabetes and thus worth of targeted therapy cannot bring indisputable evidence for or against the cause–effect hypothesis. However, they help inform our decision-making process in the clinical management and monitoring of subjects with diabetes. In diabetic subjects with clinical albuminuria and impaired renal function, it is our view that a reduction in mild to moderate albuminuria may be a suitable surrogate for changes in renal disease outcome and kidney disease progression, at least in trials with ACE inhibitors and ARBs. Under these circumstances, targeting treatment to albuminuria is justified. For early diabetic nephropathy at the stages of micro- and normoalbuminuria, the situation is different. Although lower degrees of albuminuria are a biomarker of renal damage or dysfunction, there is inconclusive evidence of whether these lower levels represent an essential intermediate endpoint on the path to renal failure and even weaker evidence of whether they qualify as a surrogate endpoint. We fully subscribe to the conclusions of the National Kidney Foundation Kidney Disease Outcomes Quality Initiative working group that "there is insufficient evidence to assume that interventions that prevent or reverse microalbuminuria will necessarily lead to improvement in clinical outcomes and conversely that failure to reduce microalbuminuria precludes a beneficial effect of treatment on diabetic kidney disease."[22]

Albuminuria, even at the level of clinical albuminuria, is unlikely to be a surrogate endpoint for CVD but is more likely a concomitant manifestation of CVD. The notion that treating the kidney protects the heart,[49] in relation to lowering albuminuria, is not supported by sufficiently robust experimental evidence. However, although albuminuria may not be central in the process to CVD, it may be a useful tool to identify individuals at increased risk of CVD and to alert the physician in the detection and treatment of other risk factors.

These conclusions should be taken as a platform on which to base future research that continues to explore and unravel the relationship of albuminuria, particularly at low levels, with the clinical outcomes of renal disease and, in a wider context, CVD in diabetes.[22]

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