Microalbuminuria as a Risk Predictor in Diabetes: The Continuing Saga

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OBJECTIVE

The rationale for this study was to review the data on microalbuminuria (MA), an amount of albumin in the urine of 30–299 mg/day, in patients with diabetes in the context of cardiovascular risk and development of kidney disease. The objective was to review the pathophysiology of MA in patients with diabetes and review the data from trials regarding MA in the context of risk for cardiovascular events or kidney disease progression.

RESEARCH DESIGN AND METHODS

Data sources were all PubMed-referenced articles in English-language peer-reviewed journals since 1964. Studies selected had to have a minimum 1-year follow-up and be either a randomized trial linking MA to cardiovascular or kidney disease outcome, a meta-analysis/systematic review, or a large observational cohort study.

RESULTS

The data suggest that MA is a risk marker for cardiovascular events and possibly for kidney disease development. Its presence alone, however, does not indicate established kidney disease, especially if the estimated glomerular filtration rate is >60 mL/min/1.73 m^2. An increase in MA, when blood pressure and other risk factors are controlled, portends a poor prognosis for kidney outcomes over time. Early in the course of diabetes, aggressive risk factor management focused on glycemic and blood pressure goals is important to delay kidney disease development and reduce cardiovascular risk.

CONCLUSIONS

MA is a marker of cardiovascular disease risk and should be monitored per guidelines once or twice a year for progression to macroalbuminuria and kidney disease development, especially if plasma glucose, lipids, and blood pressure are at guideline goals.

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REVIEW ARTICLE

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The term "microalbuminuria" (MA) originated in 1964 when Professor Harry Keen first used it to signify a small amount of albumin in the urine of patients with type 1 diabetes (1). The next mention of MA in the literature was 5 years later when Keen et al. (2) examined MA in the context of oral glucose tolerance testing. However, it was not until the late 1970s when Mogensen and Vittinghus (3) and Viberti et al. (4) assessed the effects of insulin treatment on exercise-induced MA and examined albumin excretion in the context of glycemic control. An explosion of studies by these authors and their respective coworkers followed in the 1980s, examining the associations of MA and end-organ injury as well as trying to understand the pathophysiology of MA (5–9).

Almost a half century later, the status of MA has evolved because of insights into the mechanism and associations with disease outcomes. Whereas early research focused on the relevance of MA as a risk factor for diabetic kidney disease, research over the past 2 decades has shifted to examine whether MA is a true risk factor.

To appreciate fully the contribution of MA to overall cardiorenal risk, it is important to distinguish between a risk factor and risk marker. A risk marker is a variable that identifies a pathophysiological state, such as inflammation or infection, and is not necessarily involved, directly or causally, in the genesis of a specified outcome (e.g., association of a cardiovascular [CV] event with fever, high-sensitivity C-reactive protein [hs-CRP], or MA). Conversely, a risk factor is involved clearly and consistently with the cause of a specified event (e.g., a CV event associated with persistently elevated blood pressure or elevated levels of LDL). Both a risk marker and a risk factor can predict an adverse outcome, but only one lies within the causal pathway of a disease. Moreover, a reduction (or alteration in a beneficial direction) of a risk factor (i.e., achievement of blood pressure goal) generally translates into a reduction of adverse outcomes, such as CV events; this is not necessarily true for a risk marker. As we will see, data demonstrating that MA is a risk marker for both CV events and chronic kidney disease (CKD) development in people with and without diabetes have emerged.

Before discussing the studies and the evolution of disease concepts surrounding MA in diabetes, it is also important to note that the terminology of MA has changed recently. The Kidney Disease Improving Global Outcomes group suggested that the term "MA" be replaced by the term "high albuminuria" (10). MA still refers to urinary albumin excretion of 30 to $<$300 mg/day as estimated from the urinary albumin-to-urinary creatinine ratio (UACR) in a spot morning urine specimen (unadjusted for sex). For the purposes of this discussion, however, we will still use the term "MA." Additionally, to assess for presence of MA, the American Diabetes Association recommends that at least two morning urine specimens collected within 3 months of each other should be abnormal to consider patients as having MA (11).

RESEARCH DESIGN AND METHODS

The data sources included in this article were all PubMed-referenced articles in English-language peer-reviewed journals since 1964. Studies selected had to have a minimum follow-up of 1 year; include at least 100 participants; be either a randomized trial, a systematic review, a meta-analysis, or a large observational cohort study in patients with any type of diabetes; or be trials of high CV risk that included at least 50% of patients with diabetes. All studies had to assess changes in MA tied to CV or CKD outcomes and not purely reflect changes in MA related to blood pressure, unless they were mechanistic studies. On the basis of these inclusion criteria, 31 studies qualified and provide the data used for this review. This review highlights the clinical trials as well as discusses the other studies.

RESULTS

Epidemiology

Early studies in patients with diabetes supported the concept that as MA increases to higher levels, the risk of CKD progression and CV risk also increases (12–14) (Fig. 1). Moreover, evidence from epidemiological studies in patients with diabetes suggested that the magnitude of urine albumin excretion should be viewed as a continuum of CV risk, with the lower the albumin excretion, the lower the CV risk (15,16). However, MA values can vary daily up to 100% (11). These large biological variations are a result of a variety of conditions, with a central core tied to inflammation associated with factors ranging from increased blood pressure variability, high blood glucose levels, high LDL cholesterol, and high uric acid levels to high sodium ingestion, smoking, and exercise (17) (Fig. 2). Additionally, any febrile illness, regardless of etiology, will increase urine albumin excretion (18). Taken together, these data support the concept that MA is highly variable and that values over a short time period (i.e., 3–6 months) are meaningless in predicting any CV or kidney disease outcome.

Pathophysiology

Initial studies to understand the mechanisms of MA examined changes in glomerular membrane permeability as a key determinant in patients with diabetes (4,19). Many factors affect the genesis and level of MA, most of which are linked to inflammatory conditions (Fig. 2). A good evidence base, however, supports the concept that MA directly reflects the amount of inflammation and vascular "leakiness" present in patients with diabetes (16,18,19).

More recent studies have found a number of other factors that affect glomerular permeability by modifying cytokines that affect permeability. Increased amounts of glycated albumin reduce glomerular nephrin and increase vascular endothelial growth factor (20). Additionally, increases in sodium intake (21) as well as intraglomerular pressure secondary to high protein intake or poorly controlled blood pressure (22,23) increase glomerular permeability in diabetes and, hence, MA levels.

In individuals with diabetes, albumin is glycated and associated with the generation of reactive oxygen species. In addition, many other factors such as advanced glycation end products, reactive oxygen species, and other cellular toxins contribute to vascular injury. Once such injury occurs, the effect of pressor hormones, such as angiotensin II, is magnified, resulting in a

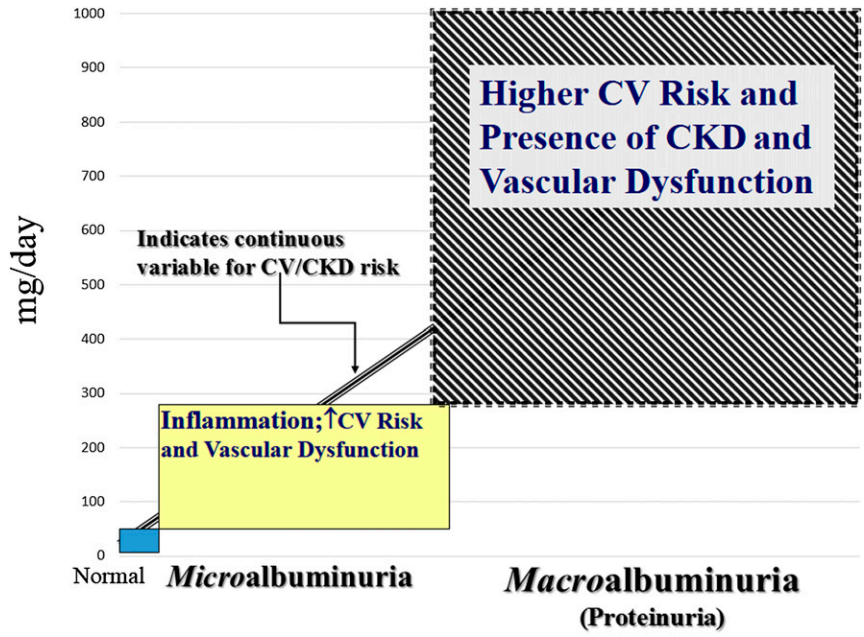

Figure 1—The spectrum of albuminuria and its associated CV risk and kidney disease presence.

faster progression of vascular injury. The end result is direct injury to the vascular smooth muscle cells, endothelial cells, and visceral epithelial cells (podocytes) of the glomerular capillary wall membrane as well as to the proximal tubular cells and podocyte basement membrane of the nephron (20,24,25). All these contribute to the development of MA.

The magnitude of hyperinsulinemia secondary to insulin resistance is associated with CV risk and higher probability of CV events. The prevalence of MA and level of albuminuria are higher in patients with isolated impaired glucose tolerance than those with impaired fasting glucose (26). However, not all studies confirm an independent association between insulin resistance and MA. A 13-year follow-up study of individuals with long-standing hypertension demonstrated that increases in MA did not predict increased insulin resistance, impaired insulin secretion, or increases in traditional or novel biomarkers of inflammation and endothelial dysfunction. Increases in MA into the macroalbuminuria range were associated with the rate of CKD progression (27). Despite these disparate results, elevated insulin levels are associated with increased vascular inflammation and, hence, the connection with MA regardless of diabetes status (28).

To illustrate the importance of glycemic control on MA development and progression, data from the prospective

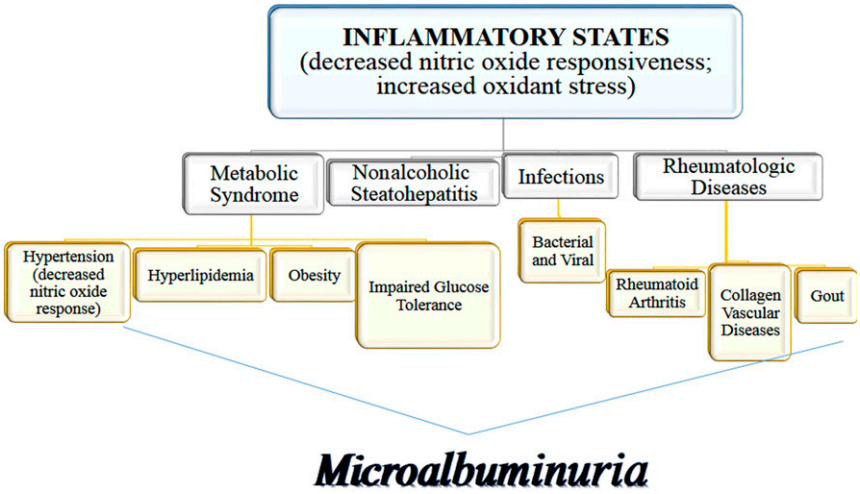

Figure 2—The disease spectrum of MA and its role as an indicator of inflammation.

Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) study provide a perspective. The DCCT/EDIC study quantified the incidence of and risk factors for the initial development of MA, its progression to macroalbuminuria (urine albumin >300 mg/g creatinine), and long-term CKD progression after the development of MA (29). Random assignment of 1,441 patients with type 1 diabetes to either intensive or conventional diabetes therapy demonstrated that after a median 13-year follow-up of persistent MA, the intensive treatment group was more likely to have a lower risk of worsening kidney function and a 40% regression to normoalbuminuria. This finding is further supported by data from the UK Prospective Diabetes Study (UKPDS), demonstrating that better glycemic control retards the development of MA. In UKPDS, more intensive blood glucose control resulted in both a 33% reduction in relative risk of MA development at 12 years and a significant reduction in the proportion of patients doubling their plasma creatinine levels (30). These results are not surprising because better glycemic control is associated with far lower levels of inflammatory markers (31). Moreover, a careful analysis of the DCCT/EDIC study did not demonstrate significance regarding the presence of MA as a predictor of CKD progression. Of the 1,439 type 1 diabetic patients in DCCT/EDIC, stage 3 nephropathy (estimated glomerular filtration rate [eGFR] <60 mL/min/1.73 m^2) developed in 89, of whom 34 (38%) had either normoalbuminuria or MA and 54 (61%) had macroalbuminuria. The analysis clearly demonstrates that macroalbuminuria (i.e., >300 mg/day) was indicative of not only the presence of nephropathy, but also a greater likelihood of CKD progression. In contrast, MA was not associated with this finding (32). Thus, very early in the course of diabetes, the presence of MA would argue for good glycemic control but not the presence of nephropathy.

The most significant insight to date, however, is the finding of a genetic abnormality that predicts MA development. Consequently, there is altered tubular reabsorption of albumin related to cubilin, a proximal tubule receptor protein responsible for albumin reabsorption (33). A meta-analysis of data from 63,153 individuals of European ancestry from genome-wide association studies identified susceptibility loci and a missense variant in the cubilin gene (33). Similar associations were noted among 6,981 African Americans (33). This missense variant was associated with a 41% increased risk for persistent MA development over 20 years among 1,304 participants with type 1 diabetes in the DCCT/EDIC study. This 41% risk increase of MA compares with a 10% risk among those without the missense variant (33). Thus, very early in the course of diabetes, the presence of MA would argue for good glycemic control to prevent progression to macroalbuminuria and subsequent CKD progression. Note that MA itself, however, does not indicate the presence of nephropathy.

MA and CV Risk

MA is accepted as a CV risk marker for myocardial infarction and stroke, regardless of diabetes status. Although there is good evidence in those with type 2 diabetes that the presence of MA >100 mg/day is associated with higher CV events and greater likelihood of kidney disease development (6). Evidence for this association comes from many studies and meta-analyses (Table 1). Patients with long-standing, poorly controlled diabetes are more likely to have MA than those without diabetes (34,35). Likewise, people with MA are at greater risk for developing hypertension, a risk factor known to increase CV risk (35). Regardless of diabetes status, individuals whose nocturnal blood pressure does not dip on 24-h ambulatory blood pressure monitoring for any reason, including sleep apnea, are more likely to have MA (36). Finally, a meta-analysis by Perkovic et al. (37) demonstrated a dose-response relationship between the level of albuminuria and CV risk. In this meta-analysis, individuals with MA were at 50% greater risk of coronary heart disease (risk ratio 1.47 [95% CI 1.30–1.66]) than those without. Those with macroalbuminuria (i.e., >300 mg/day) had more than a twofold risk for coronary heart disease (risk ratio 2.17 [95% CI 1.87–2.52]) (37). Despite these data indicating a higher CV risk in patients with MA regardless of diabetes status and other CV risk factors, there is no consensus that the addition of MA to conventional CV risk stratification for the general population (e.g., Framingham or Reynolds scoring systems) is of any clinical value, and that includes patients with diabetes (38).

The Heart Outcomes Prevention Evaluation (HOPE) trial provides a strong rationale for MA to be a risk marker for CV disease. Among >9,000 participants in the HOPE trial, the presence of MA increased the relative risk of the primary aggregate end point (myocardial infarction, stroke, or CV death) in those with and without diabetes (1.97 and 1.61, respectively) (39). To further support the concept of MA as a CV risk marker in patients with diabetes the Microalbuminuria, Cardiovascular, and Renal Outcomes (MICRO)-HOPE study demonstrated that the reduction in MA

Table 1—MA and CV risk/outcome studies linking outcome to MA change

Clinical trial	Participants with diabetes (%)	MA planned analysis	Median duration (years)	Positive correlation between MA reduction and CV outcomes
ROADMAP (41)	100	Primary, prospective	3.2	No
UKPDS (60)	100	Secondary, prospective	12	Yes
MICRO-HOPE (40)	100	Secondary, prospective	4.5	Yes
ONTARGET (57)	50	Secondary, post hoc	4.6	No
ACCOMPLISH (56)	63	Secondary, prospective	2.9	No

leads to improved CV disease outcomes. Among the 1,140 patients with diabetes and MA, patients treated with ramipril had a 20% lower UACR accompanied by a 21% reduction in the primary outcome (myocardial infarction, stroke, or CV death) and a lower risk of developing overt nephropathy. These effects were independent of baseline levels of MA (40).

Given that MA was evaluated in a post hoc manner in almost all interventional studies, it is likely that the reduction in MA simply reflects the effects of either renin-angiotensin system (RAS) blockade on endothelial function or significant blood pressure reduction rather than the MA itself being implicated as a CV disease risk factor (18). The aforementioned associations of lowering MA with angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) does not prove a direct benefit on CV event lowering associated with MA reduction in diabetes. A trial that had a primary end point of blunting increases in MA linked to the secondary end point of CV events was the Randomized Olmesartan and Diabetes Microalbuminuria Prevention (ROADMAP) (41). In this trial, olmesartan showed a significant benefit for reducing increases in MA but was associated with a fivefold higher CV event rate in the group with the blunted rise in MA, a finding that cannot be explained. Four long-term, appropriately powered trials demonstrated an inverse relationship between reductions in MA and primary event rates for CV events (Table 1).

Taken together, these studies support the concept that MA is a risk marker in diabetes and is consistent with data of other inflammatory markers, such as hs-CRP, such that the higher the level, the higher the risk (15,39,42). The importance of MA as a CV risk marker is exemplified further by another meta-analysis that showed that MA has a similar magnitude of CV risk as hs-CRP and is a better predictor of CV events (43). Thus, the data supporting MA as a risk marker for CV events are relatively consistent, clearly indicate that an association exists, and help to identify the presence of underlying inflammatory states, regardless of etiology.

MA and CKD Risk

CKD progression is defined in two ways: as a progressive decline in eGFR faster than the normal decline of 0.8–1 mL/min/year or as an increase in albuminuria to >300 mg/day. This increase in albuminuria may occur in the presence or absence of therapy to reduce established risk factors for CKD progression (i.e., blood pressure, glucose).

It is generally accepted that lower eGFR and higher levels of albuminuria (e.g., >300 mg/day) independently predict mortality and faster progression to end-stage renal disease (ESRD) among individuals with stage 3 CKD (eGFR <60 mL/min/1.73 m^2) or higher, with the associations stronger for ESRD than for mortality (44). Thus, these relationships are consistent with the most recent CKD stage classifications based on eGFR and suggest that albuminuria level provides additional prognostic information among individuals with CKD (10).

Early animal studies suggested that hyperfiltration (higher-than-normal glomerular filtration rate [GFR]) would be associated with a higher risk of CKD development and progression to ESRD. Studies were performed to try to reverse hyperfiltration with ACE inhibitors and better glycemic control in patients with type 1 diabetes but with little success (45,46), although MA levels went down or even normalized in these studies. A more recent post hoc analysis of two separate studies in type 2 diabetes demonstrated that hyperfiltration predicts declines in only a subgroup of patients and does not predict nephropathy onset or progression in all patients (47). Hence, MA is not yielding a correct signal of protection because there is a dissociation between reductions in MA and changes in hyperfiltration status with either glycemic control or ACE inhibitors.

Before discussing MA in diabetic nephropathy, it is important to note that all clinical outcome trials of nephropathy progression positive for antihypertensive intervention with RAS blockade recruited patients with >300 mg/day of albuminuria and not MA (48). Moreover, prospective trials powered for CKD outcomes included only patients with diabetes who had an eGFR range of 28–59 mL/min/1.73 m^2 and a mean baseline albumin excretion of >500 mg/day (16). In people with early stage nephropathy (i.e., stage 2 or 3a [GFR 45–89 mL/min/1.73 m^2]) and MA, there is no clear benefit on slowing GFR decline by reducing MA with drugs that block the RAS independent of lowering blood pressure (16). This is exemplified by many trials discussed in this section (Table 2). Thus, blood pressure lowering is the key goal for all patients with early stage nephropathy associated with normoalbuminuria or MA.

The initial prospective study that solidified MA as the earliest clinical finding of diabetic nephropathy in patients with type 1 diabetes was published in 1989. In this 5-year trial, MA was found to be the only laboratory correlate to track with mesangial volume expansion, the earliest biopsy-associated pathologic change in the kidney of patients with diabetes (49). A little more than a decade later, however, another prospective renal biopsy trial by the same group showed that MA was only indicative of CKD progression in ~30% of patients with type 1 diabetes. Thus, 70% of people with MA did not progress, thus negating any further assumption that MA is the definitive clinical correlate of CKD (50).

To clarify further the role of MA as an indicator and predictor of CKD progression, another prospective 5-year renal biopsy trial performed in normotensive, normoalbuminuric, type 1 diabetic patients confirmed the previous trials' findings (51). Moreover, the results demonstrated that the effects of RAS blockade with an ACE inhibitor or ARB did not uniformly reduce the initial development of MA (51). Finally, Mauer et al. (51) failed to show protection against development of the earliest pathological change of diabetic nephropathy—mesangial expansion—as well as MA development with use of either an ACE inhibitor or an ARB. Thus, three separate prospective, 5-year biopsy studies proved that MA is not synonymous with pathological presence of diabetic nephropathy

Table 2—MA and CKD progression

Clinical trial	Participants with diabetes (%)	Type	Design	Median duration (years)	Positive correlation between MA reduction and CKD outcomes
Chavers et al. (49)	100	1	Secondary, prospective	5	Not evaluated
Steinke et al. (50)	100	1	Secondary, prospective	5	Not evaluated
Mauer et al.* (51)	100	1	Secondary, prospective	5	Not evaluated
DCCT/EDICT (29)	100	1	Secondary, prospective	10	No
ABCD (53)	100	2	Secondary, prospective	7.5	No
BENEDICT (54)	100	2	Primary, prospective	5	Not evaluated
ACCOMPLISH (56)	63	2	Secondary, prospective	2.9	No
UKPDS (60)	100	2	Secondary, prospective	12	Not evaluated

*Intervention with RAS blocker failed to prevent mesangial expansion and did not block increases to development of MA.

(Table 2). Consequently, MA may represent either a defect in cubilin, as previously described, or an underlying inflammatory state much like the elevation of hs-CRP reflects inflammation in patients with high CV risk, diabetes, or both.

When albuminuria levels are in the very high or macroalbuminuria range (i.e., >300 mg/day), it is accepted that the patient has CKD and is likely to progress ultimately to ESRD, unless they die of a CV event (39,52). However, only one prospective randomized trial evaluated the role of early intervention to reduce blood pressure with an ACE inhibitor versus a calcium channel blocker in CKD progression by assessing change in MA and creatinine clearance in people with type 2 diabetes (Appropriate Blood Pressure Control in Diabetes [ABCD] trial) (23). After >7 years of follow-up, there was no relationship between changes in MA and CKD progression. Moreover, there was regression to the mean of MA. Blood pressure, however, was well controlled in both treatment groups to levels <130/80 mmHg (23,53).

Another trial that intervened early in the course of type 2 diabetes to prevent progression based on reduction in MA was the Bergamo Nephrologic Diabetes Complications Trial (BENEDICT) (54,55). Like in ABCD, subjects in BENEDICT had diabetes but were normoalbuminuric, but unlike in ABCD, all subjects were hypertensive. The BENEDICT groups were randomized to two different approaches to achieve blood pressure control and followed for 3 years. The primary outcome was development of persistent MA (overnight albumin excretion ≥20 μg/min at two consecutive visits). After the main trial was completed, a cohort study of those in whom MA developed was followed for another 2 years (55). The primary trial demonstrated that the combination of verapamil and trandolapril was better than verapamil alone for delaying the development of MA. Neither the primary nor the follow-up trial, however, assessed change in eGFR, so no data are available on CKD outcomes. However, the long-term follow-up showed no difference among an ACE inhibitor, trandolapril alone, or verapamil with the ACE inhibitor on MA reduction or CV events (55).

Two CV outcome trials examined MA change in the context of CKD progression in a subgroup of patients with diabetes either as a prespecified secondary end point (Avoiding Cardiovascular Events through Combination Therapy in Patients Living with Systolic Hypertension [ACCOMPLISH]; *n* = 6,946 of 11,506) (56) or as a post hoc analyses (ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial [ONTARGET]; *n* = 6,982 of 17,078) (57). These trials demonstrated an inverse relationship between reductions in MA and primary event rates for CKD or CV events (Tables 1 and 2). Moreover, ONTARGET showed that combining therapy of an ACE inhibitor with an ARB not only increased reduction in MA, but also increased the incidence of acute kidney injury. In ONTARGET, the geometric mean of UACR increased from baseline to last observation by 31% (95% CI 26–35%) in groups randomized to ramipril, 24% (95% CI 20–28%) in those randomized to telmisartan, and 21% (95% CI 17–25%) in those randomized to combination therapy. Of those with MA at baseline, progression to very high albuminuria (>300 mg/day) occurred in 2.12% on ramipril, 1.77% on telmisartan, and 1.61% on combination therapy, with a significant difference between those on ramipril versus combination, although CKD outcome (need for dialysis, faster rate of eGFR decline) was worse in the combination group (57).

Many observational studies used development of MA as indicating the presence of early stage CKD. Early studies by the individual groups of Mogensen and Parving demonstrated a relationship between increases in MA and progression to nephropathy in type 1 diabetes. These groups also showed that use of ACE inhibitors, blood pressure reduction, and glucose control reduced MA (9,58,59). However, more recent studies in both type 1 and type 2 diabetes demonstrated that only a subgroup of patients progress from MA to >300 mg/day albuminuria, and this subgroup accounts for those destined to progress to ESRD (29,32,60–63). Thus, the presence of MA alone is not predictive of CKD progression.

The progressive rise in albuminuria levels associated with nephropathy may relate to genetic susceptibility of nephropathy in a subgroup of patients because an increase in MA is a known marker of nephropathy progression, especially in those with a family history of nephropathy (64–66). However, some patients with type 2 diabetes progress to ESRD without ever having developed albuminuria levels of ≥300 mg/day (67).

One insight into why only certain subgroups of people with diabetes show CKD progression related to albuminuria level change comes from the Family Investigation of Nephropathy and Diabetes (FIND) study (68). Strong evidence for linkage to diabetic nephropathy was detected on chromosome 6p. Moreover, in FIND, regions of different chromosomes in different ethnic and racial groups showed evidence of linkage to the level of MA. The linkage peak on chromosome 22q, one of the linkages associated with MA, overlaps the MYH9/APOL1 gene region, which was previously implicated in diabetic and nondiabetic nephropathies in African Americans (68). Thus, subgroups with this genotype are the most likely to progress to ESRD and have increases in albuminuria regardless of therapy.

MA as a marker of nephropathy is a major topic of debate in the nephrology literature. One side contends that MA is a marker of inflammation and higher CV risk and not indicative of kidney disease in people with diabetes (69), and the other side supports the hypothesis that MA is a clear marker of CKD, even at low levels, regardless of diabetes presence (70). The arguments against MA as a risk marker for CKD are derived from prospective outcome studies on drugs that block the RAS that focused on time to dialysis, kidney biopsy specimen changes, and doubling of serum creatinine (69). The side supporting MA as a risk marker for CKD is exclusively based on observational data and post hoc analyses in primarily people without diabetes (70).

Taken together, data from outcome trials, meta-analyses, and observations demonstrate that MA alone is not synonymous with the presence of clearly defined CKD in diabetes, although it is used as part of the criteria for the diagnosis of CKD in the most recent CKD classification and staging (71). Note that only a subgroup of ~25–30% of people with diabetes who also have MA will likely progress to more advanced stages of CKD.

Predictors of progression to ESRD, apart from family history, and many years of poor glycemic and blood pressure control are still not well defined. Although there are some genetic markers, such as CUBN and APOL1, their use in practice is not well established. A family history of CKD is a powerful predictor of risk for CKD development and progression in patients with MA. Therefore, all patients should be asked about family history of CKD or members requiring dialysis. Low birth weight is another risk predictor of CKD progression, especially in diabetes, although this is not proven (72). Additionally, continued increases from MA into the macroalbuminuria range (>300 mg/day) when CV risk factors such as blood pressure, salt intake, and lipids are controlled to target values is most often indicative of progression of underlying CKD, irrespective of its cause.

CONCLUSIONS

Recent advances have allowed us to gain a better understanding of the epidemiology, pathophysiology, and clinical significance of MA among patients with and without diabetes. The current guidelines recommend that MA be assessed annually in all patients with diabetes or CKD (11). Thus, annual measurement of MA should be performed in all patients with diabetes and kidney disease. MA assessment should focus on high-risk patients, such as those who are obese, who are African American, or who have other CV risk factors, including family history of CKD.

In the context of the data presented in this article, MA should be viewed as a risk marker associated with an increase in CV risk and for kidney disease, but its presence alone does not indicate established kidney disease, especially if the eGFR is well above 60 mL/min/1.73 m^2. Increases in MA, with blood pressure and other CV risk factors controlled, are likely but not proven to portend a poor prognosis for CKD progression over time. Achieving target blood pressure (<140/80 mmHg) and target HbA_{1c} (<7%) should be priorities in treating patients with MA. Recent guidelines from both the American Diabetes Association and the National Kidney Foundation provide a strong recommendation for using agents that block the RAS, such as ACE inhibitors and ARBs, as part of the regimen for those with albuminuria levels >300 mg/day but not MA (73). Keep in mind, however, that maximal antialbuminuric effects will not be achieved with these agents unless a low-sodium diet is strictly followed.

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