Is the Presence of Microalbuminuria a Relevant Marker of Kidney Disease?

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Abstract Levels of urinary albumin excretion that are below the usual limit of detection by qualitative testing, but are above normal levels (microalbuminuria; MA), can be readily identified by simple measures, such as the urinary albumin to creatinine ratio in untimed urine samples. Such measurements, particularly when combined with assessment of estimated glomerular filtration rate (eGFR), have utility as biomarkers for enhanced risk of all-cause mortality, cardiovascular events, progressive chronic kidney disease, and end-stage renal disease in diabetic and nondiabetic subjects. However, it is controversial whether "isolated" MA (MA in the absence of a clear reduction in eGFR, urine sediment abnormalities, or structural renal disease) should be regarded as kidney disease. Such MA could also be regarded as a manifestation of a diffuse endothelial (microvascular) injury and thereby collateral kidney damage. This article reviews the current evidence concerning MA as a marker of kidney disease or kidney damage.

Keywords Microalbuminuria · Chronic kidney disease · Cardiovascular events · End-stage kidney disease · Albuminuria · Estimated glomerular filtration rate · All-cause mortality

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Introduction

Microalbuminuria (MA) was delineated many years ago to describe the appearance of small quantities of albumin, too little to detect by standard "dipstick" methods, in urine samples from subjects with diabetes [1, 2]. According to recent guidelines, MA may be defined as the urinary excretion of 30–300 mg/d in a timed urine collection in adults [3]. When spot urine samples are used, the recommended definitions of MA are the excretion of 17–250 mg/g of creatinine in men and 25–355 mg/g of creatinine in women. This measurement is known as the urinary albumin to creatinine ratio (UACR). The gender-associated differences in definition result from variation in daily creatinine generation—females have lower creatinine generation than males [4]. In addition, variations in the quantification of albuminuria for these definitions of MA may need to be applied to the elderly (who have greatly decreased creatinine generation) or to excessively muscular individuals (who have high creatinine generation) [3]. Urinary albumin concentration in untimed urinary collections may also be used to define MA—values of 3–30 mg/dL generally are regarded as fulfilling the definition. Albumin in urine is most often measured by immuno-turbidimetry using antibodies reactive with intact albumin. Alternatively, high-pressure liquid chromatography can be used, but this method also measures nonimmunologically reactive albumin and albumin fragments, which yields higher values than immuno-turbidimetry [5]. In general, MA corresponds to a "trace" reading on dipstick testing of urine, but results depend on the degree of urine concentration. Dye-impregnated strips that have enhanced sensitivity for albumin are also available [6]. Simple, portable, "point-of-service" instruments that measure small

amounts of albumin make assessment of MA readily available, reliable, and inexpensive [7].

The precise organ of urinary albumin remains somewhat controversial. The dominant viewpoint is that albumin is normally filtered by the glomeruli in small but significant amounts, about 1 to 2 mg/min (~ 2 g/d), but the great majority (99%) of filtered albumin is reabsorbed and degraded by the proximal tubule, leaving less than about 5 μg/min (7 mg/d) to be excreted [8]. A minority view is that larger amounts of albumin are filtered, as much as 200 g/d, but a retrieval pathway in the proximal tubule reclaims the filtered albumin intact and delivers it to the circulation, except for small amounts of intact and partially or fully degraded albumin [9]. In pathologic states, the glomeruli may become increasingly permeable to circulating albumin by virtue of disturbances in endothelial cell function, basement membrane abnormalities, or podocyte (visceral epithelial cell) disorders. Currently, the focus is on disturbances of endothelial or podocyte function as causes of excessive albumin glomerular permeability, rather than disturbances of basement membrane physiology [8]. Albumin is negatively charged at physiologic pH and may be impeded in transglomerular passage by the anionic residues in endothelial cell, glomerular basement membrane, or podocyte [8]. However, the existence of a charge-selective permeability barrier has been challenged [10]. A reduction in proximal tubule reclamation or reabsorption of filtered albumin can also cause albuminuria [9]. Finally, physicochemical alterations in the circulating albumin molecule can affect its permeation through the glomerular capillary wall, by altering the shape or possibly the electrical charge [11]. Thus, the mechanisms underlying increased urinary albumin excretion are complex and it is often difficult to ascribe MA in specific patients to a unique pathophysiologic process; however, endothelial cell dysfunction, a podocytopathy, or both seem to underlie most instances. Nevertheless, it remains possible that alterations in proximal tubular function may contribute to albuminuria in some circumstances, such as during poorly controlled glycemia in diabetes mellitus. These considerations are important when one attempts to relate albumin excretion rates to the definition of kidney disease, because albuminuria arising from diffuse endothelial cell injury (eg, in atherosclerosis and hypertension) might best be regarded as a sign of a systemic disease process, affecting many organs and systems, rather than one originating in the kidneys. Alternatively, albuminuria arising from a podocyte dysfunction could legitimately be regarded as a manifestation of a kidney disease. Regardless of the underlying mechanisms and interpretation of the pathophysiologic meaning of albuminuria, important associations exist between the quantities of albumin excreted in the urine and progressive chronic kidney disease (CKD) and cardiovascular (CV) events.

Microalbuminuria: Association with Progressive "Generic" CKD and CV Events

Microalbuminuria, as defined above, has been consistently associated with an increased likelihood of progression of generic CKD to more advanced stages or even to end-stage renal disease (ESRD) in large epidemiologic studies [12••, 13•, 14••, 15]. These observations have been used to justify the inclusion of MA in the definition of generic CKD in the original classification schema of the Kidney Disease Outcome Quality Initiative (KDOQI) of the National Kidney Foundation (NKF) in 2002 [3]. Indeed, the presence of MA (defined as UACR of 30–299 mg/g creatinine without gender or age adjustments) as the *sole* reason for diagnosing generic CKD accounted for 90% of those with stage 1 CKD and 87% of those with stage 2 CKD in the US National Health and Nutrition Examination Survey (NHANES) conducted from 1999 to 2004 [16]. In this cohort ($N=13,233$), 6.8% had self-reported diabetes and 27% had diagnosed hypertension. Thus, the great majority of subjects designated as having stage 1 or 2 CKD in NHANES had isolated MA (MA without a clear reduction in estimated glomerular filtration rate [eGFR], urine sediment changes, or structural kidney disease) as the defining abnormality. It is natural to ask whether such isolated MA is sufficient reason to designate a person as having generic CKD.

As shown by a recent, very large, collaborative meta-analysis (Chronic Kidney Disease Prognosis Consortium; $N=105,872$ subjects), the hazard ratio (HR) for all-cause mortality and cardiovascular mortality (adjusted for the effects of age, ancestry, history of CV disease, systolic blood pressure, diabetes, smoking, and total cholesterol concentration) rises progressively above a UACR of about 10 mg/g [17••]. In subjects with normal renal function (eGFR=90–104 mL/min/1.73 m^2), the HR for CV mortality is 1.63 at a UACR of 10–29 mg/g, 1.82 at 30–299 mg/g, and 4.77 at greater than 300 mg/g. A decrease in eGFR magnifies the effect of an increased UACR on both all-cause and CV mortality, especially at an eGFR of 45 mL/min/1.73 m^2 or lower. Thus, there is little or no doubt that increased albumin exertion, even below the conventional MA range, is associated with an increased likelihood for mortality, both all-cause and CV-related. The causal direction for this association cannot be determined from this epidemiologic data. Is elevated albumin excretion a biologic marker of underlying systemic disease (eg, cancer, atherosclerosis), or is it somehow involved in the causal pathway for fatal events, including CV disease?

Similarly, the risk of developing a progressive form of CKD is linked somehow to the presence of elevated albumin exertion. A large, community-based study from Alberta, Canada, ($N=920,875$) showed that subjects with

normal or nearly normal renal function (eGFR≥60 mL/min/ 1.73 m^2, average age 46 years) and MA had event rates of ESRD of 1.5 and doubling of serum creatinine of 2.8 times those of subjects with "normal" albumin excretion (<30 mg/g UACR) [14••]. Absolute events rates were low: 0.06 per 1000 person-years of follow-up for ESRD in the normo-albuminuric group versus 0.09 per 1000 patient-years for the MA group. A lowered eGFR magnified the effect of MA on the occurrence of ESRD and doubling of the serum creatinine, especially at levels below 45 mL/min/ 1.73 m^2. In another community-based study (N=65,589 adults; 3.3% diabetic; average age, 50.1 years), researchers noted that the likelihood of developing (and surviving long enough) to receive treatment for ESRD among subjects with MA and eGFR≥60 mL/min/1.73 m^2 was 27 times that of subjects with normo-albuminuria and similar eGFR levels [13•]. A reduced eGFR greatly magnified the effect of MA on risk for ESRD. Subjects with an eGFR less than 60 mL/min/1.73 m^2 and MA had a 5.4-fold to 81-fold increased risk of ESRD compared to those with an eGFR≥ 60 mL/min/1.73 m^2, depending on the degree of decrease in eGFR. Thus, the addition of MA to eGFR greatly enhances the ability to detect and quantify risk of progressive CKD, particularly when eGFR is less than 60 mL/min/1.73 m^2. These observations call for a revision of the 2002 version of the KDOQI-NKF classification schema for CKD that does not include albuminuria for diagnosis of stage 3 or above CKD [3]

Taken together, these findings from epidemiologic studies using large databases strongly support the view that MA needs to be considered as a "biomarker" of adverse outcomes, even among those subjects with normal or nearly normal renal function. However, the strength of this association between MA and outcomes may vary by subject age and underlying disease (eg, diabetic or nondiabetic) or by concomitant illness known to influence albumin excretion rates (eg, obesity). For example, in the aforementioned meta-analysis conducted by the Chronic Kidney Disease Prognosis Consortium [17••], the pooled estimates of fully adjusted HR for CV mortality tended to be higher in those younger than 65 years of age compared to those older than 65 years with apparently equivalent degrees of MA. An analysis of the impact of MA on outcomes in the old-old (>75 years of age) has not been conducted; however, as stated above, UACR has a tendency to increase with normal aging, predominantly because of the effects of sarcopenia on creatinine generation, not necessarily because of an absolute increase in albumin excretion with aging. Furthermore, the association of MA with adverse outcomes in subjects with normal or nearly normal renal function (eGFR≥60 mL/min/1.73 m^2), after adjustment for the effects of aging may simply reflect the

overall burden of atherosclerotic vascular disease in this group of subjects. As recently pointed out by Kalaitzidis and Bakris [18], untangling the influences of metabolic disturbances and hypertension in diabetic and nondiabetic subjects with concomitant MA can be problematical. It is still uncertain if MA is an integral part of the pathophysiologic pathways for CV disease or simply a bystander.

Microalbuminuria: Association with Progression of "Specific" CKD

The sine qua non of "specific" forms of CKD in which MA is present is that of diabetes mellitus. Indeed, the concept of MA arose from studies of the natural history of diabetic nephropathy during the period 1981 to 1982 [1, 2]. Shortly after its initial description in type 1 diabetes, MA was believed to be a harbinger of overt diabetic nephropathy and progressive CKD. We now recognize that MA in type 1 diabetes is a dynamic process with frequent spontaneous regression to normo-albuminuria [19, 20]. We also recognize the wide array of extra-renal factors that can influence albumin excretion, such as obesity, age, gender, distant inflammation, and certain drugs (eg, rosuvastatin) [21•, 22, 23]. Furthermore, studies done at the Joslin Clinic over many years indicate that more advanced stages of CKD are not uniformly associated with progression of MA to overt microalbuminuria [19, 24]. Pathologic abnormalities indicative of diabetic nephropathy (eg, increased mesangial fractional volume) precede the development of MA, and very clearly renal functional decline can occur in the absence of MA, at least in type 1 diabetes [25]. Type 2 diabetes may be another story, because the relationship of MA and renal functional decline is not as well studied or understood as in type 1 diabetes, and this relationship is confounded by concomitant accelerated atherosclerotic macrovascular disease. Nevertheless, several studies showed that progression of type 2 diabetes can occur in the absence of MA [21•, 22–26]. Interventions designed specifically to reduce MA have not consistently shown a reduction of later progression to advanced CKD or ESRD. Some recent interventional trials (eg, the Avoiding Cardiovascular Events through Combination Therapy in Patients Living with Systolic Hypertension [ACCOMPLISH] trial) involving type 2 diabetic subjects showed that the change in albumin excretion rates can be disassociated from risk of progression to ESRD under the influence of combined renin-angiotensin system blockade and calcium channel antagonism [21, 27•]. Taken together, these observations in type 1 and type 2 diabetes suggest, but do not prove, that MA may not be a reliable marker of kidney disease or its progression.

Microalbuminuria: A Synthesis of its Relevance to Kidney Disease

Among patients with well-established kidney disease (ie, eGFR <45–50 mL/min/1.73 m^2), the magnitude of albuminuria can be viewed as a marker of a more progressive course and a more rapid loss of renal function (a "risk marker" rather than a "risk factor") for both diabetic and nondiabetic renal disease [28, 29]. This finding may well be a manifestation of "lead-time bias," in that those with lower levels of albumin excretion have disease in its earlier stages and thus a greater reserve of functioning nephrons, whereas those with higher levels of albuminuria have no reserves and with each loss of nephrons, a corresponding decline in renal function becomes evident. In this sense, the level of albumin excretion is a relevant marker of kidney disease and risk of its progression. A conundrum exists when renal function is entirely or nearly normal: no overt structural renal disease is evident, yet albumin excretion is elevated into the MA range. Such patients might be described as having "isolated" MA. No doubt this circumstance somehow predisposes to, or is a marker of a predisposition to, CV disease. The exact pathophysiologic connection between isolated MA and CV disease is not fully clarified. For example, albuminuria correlates with parameters of aortic stiffness and carotid plaque formation but not with carotid intima-media thickness as a surrogate for widespread atherosclerosis [30]. On the other hand, MA does correlate with signs of altered endothelial function, such as endothelium-dependent vascular dilatation [31–33]; however, it is often difficult to disentangle the effects of alterations in renal function and concomitant metabolic and dyslipidemia states in identifying direct relationships between MA and endothelial dysfunction. Isolated MA may well be a biomarker of widespread vascular injury and atherosclerotic burden. In this sense, it is not measuring a "kidney disease" per se, but only a secondary and indirect effect of a distant disease process on kidney physiology. Although this conclusion may appear to be semantic rather than reality-based, it has immediate relevance for the diagnosis of CKD using current classification schema (ie, KDOQI-CKD). Stage 1 and 2 CKD in this schema cannot be reliably distinguished on the basis of eGFR alone because current creatinine-based eGFR formulas are imprecise. Whether newer cystatin C–based formulas will correct this deficiency remains to be seen; preliminary findings are encouraging, but not uniformly so [34, 35]. Most cases of stage 1 and 2 CKD are currently defined on the basis of MA, typically in an isolated form. This definition is useful to stratify the eventual risk of CV events and all-cause mortality; however, does it have the same utility for defining the presence of and risk for progressive CKD and eventual ESRD at all levels of eGFR and in all ages? Current evidence suggests that the utility of MA in predicting renal outcomes is most pronounced in those with well-established kidney disease (eg, eGFR <45–50 mL/min/1.73 m^2) and in younger subjects (eg, <65 years of age). In my opinion, whether it is appropriate to regard isolated MA as equivalent to kidney disease is still an open question. A compromise position would be to regard this laboratory finding as an indication of kidney "damage" rather than giving it the more ominous label of "disease." This issue is not trivial—about 30% of those diagnosed as having CKD in epidemiologic studies have their kidney disease identified by the finding of MA and eGFR ≥60 mL/min/1.73 m^2 in the absence of a self-reported diagnosis of diabetes.

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