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Clin Lab Med 26 (2006) 635–653

CLINICS IN
LABORATORY
MEDICINE

Microalbuminuria

Nitin Khosla, MD, Pantelis A. Sarafidis, MD,
George L. Bakris, MD*

Department of Preventive Medicine, Hypertension/Clinical Research Center, Rush University Medical Center, 1700 West Van Buren Street, Suite 470, Chicago, IL 60612, USA

Microalbuminuria (MA) is defined as the presence of albumin in the urine above the normal range (currently defined as <30 mg/d) but below the detectable range with conventional dipstick methodology (eg, >300 mg). MA is a well-recognized predictor of diabetic complications and is a marker of ischemic cardiovascular (CV) events that are related to the development of atherosclerosis [1–4]. Although MA clearly is associated with higher CV mortality in patients who have type 1 or type 2 diabetes, its role as a prognostic indicator of CV events in persons who do not have diabetes is less well defined [5–10].

Emerging research has focused on how MA may contribute to the pathogenesis of CV disease (CVD). These efforts have centered primarily on populations that have essential hypertension and do or do not have diabetes. Although several pathophysiologic mechanisms have been proposed as to how MA may contribute to the development of atherosclerotic vascular disease, evidence to support one clear mechanism remains elusive. The current proposed mechanisms primarily involve local injury to the vascular smooth muscle and endothelial cells through vessel shear stress, and subsequent changes in nitric oxide and increases in a variety of cytokines that culminate in cell proliferation and increases in vascular permeability.

This article reviews the role of MA in the context of atherosclerotic vascular disease development. It focuses on clinical and epidemiologic evidence regarding the significance of MA in patients who do or do not have diabetes. Additionally, there is a discussion about treatment modalities that are aimed at reducing MA and maximizing CV risk reduction.

* Corresponding author.
E-mail address: gbakris@earthlink.net (G.L. Bakris).

doi:10.1016/j.cll.2006.06.005

Definition and prevalence of microalbuminuria

Viberti and colleagues [3] first described MA as a predictor of nephropathy in type 1 diabetics in 1982. The definition of MA has been refined; the current National Kidney Foundation definition of MA is a urinary excretion rate of albumin between 20 μg/min and 200 μg/min or between 30 mg/d and 299 mg/d [11]. Although 24-hour collections were the traditional way to measure MA, a quick and comparably accurate way of measuring albuminuria was an albumin/creatinine ratio on a spot collection of morning urine in the fasting state [12]. With the growing use of the spot urine collection approach, the definition of MA was expanded to include a urinary albumin/creatinine ratio (UACR) of 2 to 20 mg albumin/mmol creatinine (30–299 mg/g); however, the use of this ratio requires knowledge of the factors that affect its measurement (Box 1). The range for the urinary excretion rate of albumin is 25% lower during sleep than during waking hours. Furthermore, MA can vary daily from 40% to 100% [13–16]. These are largely biologic variations that are due to inflammation that is associated with small injury (eg, toothaches) as well as increases in dietary sodium and protein intake [17]. Caution is required when interpreting the UACR in patients with higher muscle mass, African Americans, and men, because these populations have higher levels of creatinine excretion [18]. After taking all of these factors into account, the current guidelines recommend the use of the UACR in place of a timed urine collection. The imprecise nature of MA and creatinine measurement requires that at least three measures be made over a period of 2 to 3 months before determining the actual UACR for a particular patient. The intra-assay variation using radioimmuneassay is between 5% and 7%, and is less when using high-performance liquid chromatography (HPLC) [12].

Box 1. Factors that affect measurement of urine albumin/creatinine

Albumin excretion
Blood pressure
Time of day
Fasting versus nonfasting sample
Salt intake
Volume status

Creatinine excretion
Gender
Race
Muscle mass

Use of the HPLC method for assessing spot UACR is much more sensitive and specific when compared with radioimmune assay methodology; hence, only one measurement is required [12]. The cost and efficacy of HPLC is being compared with radioimmune assay in large clinical laboratories in the United States. Thus, it is clinically available upon request. Ideally, these measurements should be obtained in the fasting state and collected from the first morning void [19]. Repeat specimens should follow the same protocol because the dietary intake of sodium and protein can modify albuminuria.

Although early studies noted a high prevalence of MA in persons who had diabetes, later and larger clinical trials failed to confirm this observation [6,11,20–23]. Variations in prevalence are mostly due to patient selection or inclusion criteria biases, such as the severity of hypertension, age, race, coexisting renal disease, techniques used for detection of MA, and sampling size of the cohort. The prevalence of MA in people who have type 2 diabetes is about 20% (range, 12%–36%), and MA affects about 30% of people who have type 2 diabetes who are older than age 55 [6,24,25]. The rate of progression to diabetic nephropathy (ie, development of macroalbuminuria) in type 2 diabetes with MA is 5% per year, whereas it is 7.5% annually among those who are affected with type 1 diabetes [2,3]. Subsequent chronic renal failure occurs at a rate of 1% annually in patients who have type 2 diabetes, whereas the risk for persons who have type 1 diabetes approaches 75% after 10 years [8,26]. The rate of nephropathy progression and CV risk is far lower for those who have type 1 or 2 diabetes who have tight control of their glucose and blood pressure early in the course of their disease [27,28].

The prevalence of MA varies widely from 5% to 40% among nondiabetic persons who have essential hypertension [29–31]. The high variability relates to the factors that were discussed above and to the duration of blood pressure control and associated lipid abnormalities, especially low-density lipoprotein (LDL) levels (Box 2). An analysis of the Diabetes Control and Complications Trial and the Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) database illustrates that small LDL and elevated triglycerides, much like what is seen in the metabolic syndrome, are strong predictors of MA [32,33]. Moreover, a meta-analysis of small clinical studies documented decreases in MA when 3-hydroxy-3 methyl-glutaryl CoA reductase inhibitors are used to lower LDL levels [34]; however, these findings have not been confirmed in a large, prospective clinical trial.

Pathophysiology

The pathophysiologic role of MA as a participant in, or accelerant to, the atherosclerotic process is uncertain, but available evidence suggests that it is more a marker than a pathogenic factor. All patients who have MA have an elevated transcapillary escape rate of albumin, and the presence of the risk

Box 2. Factors known to influence the development of microalbuminuria

Increased body mass index
Elevated blood pressure (systolic, diastolic, mean)
Endothelial dysfunction
Decrease in high-density lipoprotein levels
Insulin resistance (hyperinsulinemia)
Smoking
Salt sensitivity
Increased age
DD ACE-genotype

factors that make up the metabolic syndrome (hypertension, hyperlipidemia, insulin resistance, procoagulant factors, and obesity) also is higher in these patients [11,20,23,35]. The current paradigm suggests that the mechanism of vascular injury that leads to MA is different in nondiabetic and diabetic populations, however [26,36,37].

In nondiabetic patients who have MA, generalized vascular leakiness is caused by alterations in the extracellular matrix. These alterations are triggered largely by increases in microvascular pressure, which lead to injury to the endothelium (Fig. 1). In response to this injury, excess protein is deposited in the extracellular matrix, and, as a result, the capillary basement membrane becomes sclerosed [26,38]. The resultant defect in endothelial permeability permits lipid influx into the vessel wall that causes atherosclerotic changes. This response is the final common pathway of many acute and chronic illnesses, and is mediated through various stimuli, including complement activation, macrophages, neutrophils, and endothelial stimulation from diverse inflammatory insults [36].

The presence of diabetes accelerates this process in a manner similar to "adding gasoline to an already burning fire." The glycated state in which albumin exists in diabetics transforms it into an antigenic-like molecule that is associated with generation of reactive oxygen species [38,39]. These free radicals cause direct injury to the epithelial cells of the glomerular membrane, vascular smooth muscle cells, and mesangial cells, and they chelate the proteins on the glomerular membrane. This impairs the ability of the glomerulus to filter proteins and albumin excretion is increased [40]. Further evidence from animal studies supports the notion that albumin must be glycated to be pathogenic. An interesting finding from these animal models is that intermittent elevation of serum glucose induces changes in cell membranes that are similar to those seen in people who have diabetes [38]. Thus, the link between diabetic and nondiabetic MA may be impaired insulin resistance, which leads to an increased amount of glycated albumin.

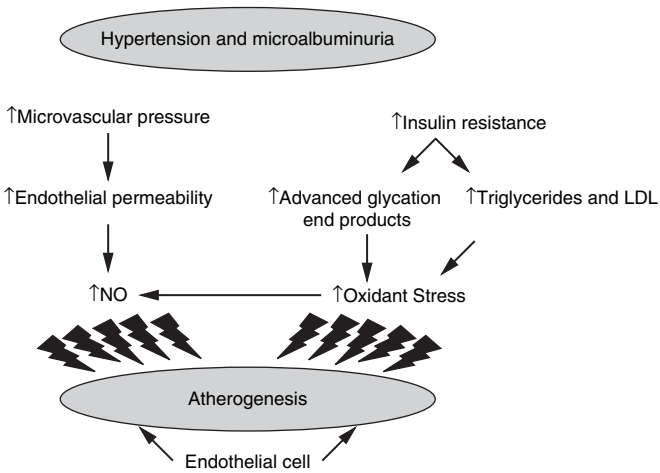

Fig. 1. Endothelial permeability defect from injury to the endothelium is triggered by increases in microvascular pressure, which cause atherosclerotic changes.

The presence of diabetes also increases MA by other mechanisms. Direct injury to the glomerular membrane by advanced glycosylation end products results in a loss of glomerular membrane size selectivity [5]; this has a direct effect of increasing albuminuria, but also allows for passage of more lipids into the vessel wall. The cycle is worsened by the body's increased production of albumin in response to renal losses [26,41]. This discussion represents the spectrum of events that can occur in diabetics; however, it is difficult to predict what form of dysfunction a particular diabetic will exhibit. This may explain the different course of diabetic renal diseases between different diabetics and patients who have the two types of diabetes.

Comorbid conditions associated with microalbuminuria

MA reflects widespread vascular disease and is associated with the presence of an unfavorable risk profile and target organ damage, especially in people who have diabetes. This section covers the major risk factors for CVD in the context of MA.

Hypertension

Several studies have shown that the level of MA correlates with blood pressure as measured by clinic or 24-hour ambulatory blood pressure monitoring [42,43]. This observation was corroborated by a clinical study of 387 nondiabetic, hypertensive patients that found that the level of MA was proportionate to the level of systolic, diastolic, and mean blood pressure measured at an office visit or on a 24-hour ambulatory monitor. Another study of untreated patients who had MA and essential hypertension found that patients with borderline levels of MA (28–30 mg/d) had higher diastolic

and mean blood pressure readings than did normoalbuminuric hypertensive subjects [23]. Furthermore, an Italian population study with 1567 participants revealed that systolic blood pressure was 18 mm Hg higher in nondiabetic people who had MA compared with those who did not have MA [20]. Circadian blood pressure abnormalities also were described in people who had MA [44,45]. A study of 63 hypertensive patients demonstrated that persons with a blunted (ie, $<10/5$ mm Hg) or absent nocturnal dipping of blood pressure had higher levels of MA than did patients with a normal dipping pattern.

Patients with MA and type 1 diabetes destined to develop nephropathy will have BP elevation >130 mm Hg [26]. Patients who have type 1 diabetes have elevations in their systolic and diastolic blood pressures that occur only after the development of nephropathy, manifested by MA. Conversely, type 2 diabetics may have elevations in systolic blood pressure that precede the development of MA. This suggests that the mechanism of MA in type 1 diabetics relates to incipient nephropathy, whereas in type 2 diabetics it relates to atherosclerosis. When these data are coupled with the analysis of the DCCT/EDIC studies, they support the concept that the level of MA reflects the duration of blood pressure control as well as lipid abnormalities in type 2 diabetics and patients who have essential hypertension. Hence, the degree of MA may serve as an indicator of blood pressure and lipid control as does the hemoglobin A, C for glucose control.

Hyperinsulinemia

The term "syndrome X" (metabolic syndrome) was coined by Reaven after he pointed out that insulin resistance and the accompanying hyperinsulinemia form a link between the CV risk factors of metabolic syndrome and the development of CVD [46]. Many investigators have called for the inclusion of MA in the definition of metabolic syndrome after studies showed higher levels of fasting insulin concentrations and greater plasma insulin response to a glucose load in hypertensive patients who had MA compared with those who did not have MA [47,48]. Moreover, MA has been included in the World Health Organization definition of metabolic syndrome. Furthermore, a recent study examined the relationship between the level of MA and varying responses to a 75-g glucose load; the level of urinary albumin excretion and prevalence of MA were higher in patients who had isolated impaired glucose tolerance than in those who had impaired fasting glycemia [49]. These findings were confirmed by the Australian Diabetes, Obesity, and Lifestyle Study, which found that MA increases as glycemic control worsens, and that this effect is seen even in patients who do not have frank diabetes [50]. The Hoorn Study confused the picture, however. It showed that MA was correlated with hypertension, waist/hip ratio, and frank diabetes, but was not related to the other components of the metabolic syndrome [51].

Despite these disparate results, elevated insulin levels may provide the connection for MA in diabetic and nondiabetic patients. The mechanism

of this link between insulin action and MA, however, remains largely speculative [42]. All of the proposed theories note that people who have diabetes, who also have hypertension and MA, show a greater abnormality of glucose intolerance and lipid metabolism and reiterate the relationship between elevated fasting insulin levels and MA in patients who do not have diabetes. Moreover, simultaneous occurrence of the aforementioned conditions of the metabolic syndrome in nondiabetic subjects identifies a group of people with an increased risk for CVD [52].

Endothelial dysfunction

Although endothelial dysfunction is not a discrete entity, it has been proposed that it represents a common final pathway for macro- and microvascular diseases. The endothelium, which is composed of the cells lining the inner layer of blood vessels, is responsible for the production of the components of the extracellular matrix, maintenance of the balance between coagulation and fibrinolysis, and regulation of the inflammatory activity of blood vessels [39]. Endothelial dysfunction is said to exist when there is an imbalance between the normal antithrombotic and vasodilatory properties of a blood vessel, and it is a main factor in atherogenesis.

Increased permeability of the endothelium allows atherosclerotic lipoprotein particles (oxidized LDL and others) to penetrate into the vessel wall. This influx generates oxygen free radicals, which are scavenged by nitric oxide. As the nitric oxide is consumed, the vessel loses its capacity to vasodilate and the vessel is compromised further by the impairment of insulin-mediated skeletal muscle vasodilation. The end result of this cascade of events is the creation of an ideal environment for development of atherosclerotic plaques [37,38].

The extent of endothelial dysfunction in humans can be determined directly by measuring endothelial-dependent regulatory mediators or indirectly by examining endothelial-dependent vasodilation [39]. Although many biochemical indices, such as angiotensin II, tissue-type plasminogen activator, plasminogen activator inhibitor-1, CD146, and endothelin, have been proposed as measures of endothelial dysfunction, von Willebrand factor (vWF) remains the most extensively studied potential marker of endothelial injury [39,53]. In nondiabetic patients who had essential hypertension and in diabetics, patients who had MA had higher plasma levels of vWF antigen than did patients with normal albumin excretion. Furthermore, individual vWF and urine albumin excretion values were correlated significantly. VWF has been associated with occlusive thrombosis, so that increased plasma vWF levels may contribute directly to the enhanced CV risk that is seen in patients who have endothelial dysfunction and MA [53,54].

Clausen and colleagues [55] did an elegant study to demonstrate that there is endothelial-dependent vasodilation in subjects who have MA. They compared the dilatory capacity of the brachial artery in 19 volunteers

who had MA (<150 μg/min and without clinically evident atherosclerotic disease) with a control group of clinically healthy participants who had normoalbuminuria (MA<6.6 μg/min). They found that flow-associated dilatation and nitroglycerine-induced dilation were impaired significantly in subjects who had MA. A recent study has contradicted these results, however. This study of 654 nondiabetic patients showed no change in flow-associated and nitroglycerine-induced dilation of the brachial artery vasodilation as the level of albumin excretion increased [56].

In conclusion, endothelial dysfunction seems to play a key role in MA genesis and atherosclerosis. Relevance of these biochemical markers in the development of endothelial dysfunction requires further investigation. In this ultramicrostructural molecular science age, endothelial cell dysfunction should be considered as "micro" target organ damage, rather than a marker of target organ damage or merely associated with target organ damage.

Dyslipidemia

The relationship between MA and abnormalities in serum lipoproteins has been documented well. These lipid abnormalities include higher levels of LDL, total triglycerides, and lipoprotein (a), but the abnormality that is seen most consistently in all patient populations is a low level of high-density lipoprotein [20,23,42,57,58]. This is exemplified by a recent study in type 1 diabetics that suggested that increased levels of high-density lipoprotein may protect against the development of MA [59]. Although the loss of the protective effects of good cholesterol, such as high-density lipoprotein, clearly plays a role in the development of MA, elevations of proatherogenic lipoproteins also have a significant contribution. A cross-sectional analysis of 1160 type 1 diabetic subjects in the DCCT showed that progressive increases in albuminuria were associated with elevations in intermediate-density lipoproteins and small dense LDL particles [60]. Furthermore, elevations of atherogenic lipoprotein (a) maintained a correlation with MA after a multivariate analysis in patients who had essential hypertension. Taken all together, these data support the notion that the mechanism of increased CV risk in patients who have MA is related, in part, to an overall adverse lipid subfraction profile. The picture is not entirely clear, however, because patients who have homozygous familial hypercholesterolemia do develop severe premature atherosclerosis and CVD without developing antecedent MA [61].

Genetic associations

People who have MA who also have essential hypertension or diabetes have shown a variety of genetic polymorphisms that are believed to contribute to developing MA [62–64]. Elevated activity of the renin-angiotensin system is an independent risk factor for CVD, and the United Kingdom Prospective Diabetes Study and others demonstrated that ACE gene polymorphism is associated with MA [62]. Patients with the DD ACE-genotype

show an increased albumin excretion rate, but it is unclear whether this genotype alone is enough to cause MA [63]. In type 1 diabetics, the expression of the same glomerular RNA has been shown in patients who have MA and those who have frank proteinuria [65]. This suggests that the progression to overt nephropathy in these patients is a continuum that begins with MA; however, extrapolating this to patients who do not have type 1 diabetes remains debatable.

Clinical applications

The presence of MA alone may have limited diagnostic value because it represents a sensitive, but disease-nonspecific, marker of increased vascular permeability and inflammation [37]; however, it has several applications in specific clinical situations. These applications include risk assessment, prognostic implications, disease severity evaluation, and as a marker of target organ damage (vasculature) that is associated increased CVD risk.

Vascular risk assessment

Since Yudkin and colleagues reported that MA was a predictor of vascular disease in nondiabetic subjects [64], several population-based studies have shown an association between increased urinary albumin excretion and several established adverse CV risk profiles [20,23,66,67]. In one report of 680 patients who did or did not have diabetes, the presence of hyperhomocysteinemia, a risk factor for atherosclerosis, was associated significantly with MA, independent of type 2 diabetes or hypertension [68]. The association of MA with an abnormal prothrombotic profile may not be surprising because some conditions, like endothelial dysfunction, are hypothesized as a common contributing factor in the pathogenesis of MA and atherosclerosis [5,37]. Lastly, MA also has an association with prohormone brain natrivretic peptide (BNP), an emerging marker for increased CV risk. A study of 537 patients showed that elevated levels of MA and prohormone BNP were predictors of overall mortality and first CV event. These relationships held even when plugged into the same model, and both factors were better predictors of CV mortality and events than was C-reactive protein [69].

The benefits of using MA in lieu of other markers to screen for target organ injury, endothelial injury, or CVD are that it is inexpensive and the results are available rapidly [5,7,69]. Although the usefulness of the assessment of MA in patients who have diabetes is clear, the routine determination of MA in the general population—as in people who have hypertension and do not have diabetes—is debatable. In part, this is due to the low prevalence of MA in the nondiabetic population and the uncertainty of the significance of its modification in these groups [70,71]; however, targeting high-risk patients may be of greater value. Moreover, a cost-effectiveness analysis was performed on MA use in the general population. Although it was found not

to be cost-effective to screen the entire cohort of patients that had hypertension, it was highly cost-effective to screen those who had diabetes, and those who had metabolic syndrome and obesity, in general [72].

Prognostic implications

If MA is associated with a higher CV risk, hypertensive target organ damage, and diabetic complications, its prevalence should be higher in these subjects. Not only do numerous overviews of the literature support this contention, but MA also has been shown to be a predictor of morbidity and mortality among various patient populations [6,9,10,20,23,35,52,71]. Agrawal and colleagues [66] reported a significantly higher prevalence of coronary artery disease, stroke, and peripheral vascular disease among people who had MA [66]. The prevalence of CVD was 31%, 6%, and 7%, respectively, in nondiabetic hypertensive subjects who had MA compared with 22%, 4%, and 5% in subjects who did not have MA. A clear increase in overall mortality was seen in the nondiabetic subgroup of the Losartan Intervention for Endpoint Reduction (LIFE) study, which showed that the primary composite end point (CV death, fatal and nonfatal stroke, and fatal and nonfatal myocardial infarction) increased continuously as albuminuria increased, and that there was no threshold level of MA associated with an increased risk [73]. A post hoc analysis of the nondiabetic cohort from the African American Study on Kidney Disease (AASK) demonstrated a similar trend for renal outcomes [74,75]. In this trial, a higher baseline level of proteinuria predicted the development of end-stage renal disease at 5 years. Although the analysis looked mostly at patients who had frank albuminuria, the predictive value of the baseline level of proteinuria was seen even in patients with urinary protein levels that were less than 300 mg/d [74].

Although these data are compelling, there are some data that contradict the association of MA with increased CV risk. In a prospective follow-up study of more than 300 treated hypertensive men that extended for an average of 3.3 years, Agewall and colleagues [76] showed no increased risk for CVD morbidity and mortality. These investigators found that although target organ damage was more common among patients who had MA than among those who did not have it, macroalbuminuria, not MA, showed prognostic value.

The data regarding MA in cohorts of people that have diabetes is clearer. A meta-analysis showed that the overall odds ratio is 2.4 for total mortality and 2.0 for CVD morbidity and mortality in type 2 diabetes [6]. Other studies observed that subjects who have MA and type 2 diabetes have a total mortality of approximately 8% and an annual CVD mortality of 4%. These values are up to four times higher than in patients who do not have MA [2,26]. Total and CV mortality was twice as high in people who had type 1 diabetes and MA compared with subjects who did not have MA [77]. Post hoc analyses of Reduction of Endpoints in Non-insulin dependent

diabetes mellitus with the Angiotensin II Antagonist Losartan (RENAAL) and Irbesartan Diabetic Nephropathy Trial (IDNT) showed a correlation between MA and renal outcomes. Just as in the nondiabetic cohort of AASK, these studies showed that the risk for reaching end-stage renal disease in diabetics has a continuous correlation with the baseline level of albumin excretion [78,79].

The best support for MA as a prognostic indicator in diabetics and nondiabetics may come from the Heart Outcomes Prevention Evaluation (HOPE) trial. Among more than 9000 participants, the presence of MA increased the relative risk for the primary aggregate end point (myocardial infarction, stroke, or CV death) similarly in subjects who did and did not have diabetes (1.97 and 1.61, respectively) [80]. Thus, routinely measuring MA in people who do or do not have diabetes who are at high risk for CV and renal morbidity and mortality is appropriate for determining the risk for a future event.

Disease severity assessment

Just as the level of MA has a correlation with long-term CV and renal mortality, it also is proportional to the severity of many other acute inflammatory processes, such as trauma, sepsis, and surgery [37]. Ischemia and reperfusion are other conditions that follow this rule. MA also is detected in the presence of an acute myocardial infarction or peripheral vascular disease and it is proportional to the severity of the infarct or of the claudication [81,82]. Recent trials have sought to use the level of MA as a predictor for worse clinical outcomes and as a target of therapy in the ICU, but, thus far, data have been disappointing [83].

Marker of target organ damage

In several studies, people who had MA had larger left ventricular mass and higher degrees of left ventricular hypertrophy [23,84–86]. This was documented by electro- and echocardiogram criteria. Even in hypertensive patients who are normoalbuminuric, patients with higher absolute levels of albumin excretion have greater left ventricular wall thickness and more frequent concentric left ventricular hypertrophy than do patients with lower levels of albumin excretion [87]. This association of MA with left ventricular hypertrophy likely is related to a higher blood pressure load that leads to both things, rather than a direct relationship between the two.

The expression of atherosclerotic disease in the carotid artery that is manifested as an increase in intimal-media thickness also was noted in nondiabetic and diabetic subjects who had MA [88,89]. Vascular retinal changes and coronary artery disease also are more common in hypertensive patients who have MA than in normoalbuminuria patients [23,90]. The incidence of hypertensive retinopathy is lower if MA is reversible with treatment. This

vascular remodeling may be related to endothelial dysfunction whose role in atherogenesis has been described well.

Therapeutic intervention

The merits of normalizing or reducing the level of MA in people who have diabetes are unquestionable, but there are several unanswered questions in nondiabetic patients [11,70]. Although not as effective as antihypertensive therapy, lifestyle modifications can slow the progression of diabetic renal disease. Low-protein diets and tight glycemic control can preserve renal function and prevent nephropathy in the early stages of renal disease, but these modalities are much less effective once kidney dysfunction is present (ie, serum creatinine > 1.3 mg/dL) [91–93].

Although good glycemic control and protein restriction have an effect on renal function that is partially independent of blood pressure, achieving target blood pressure is critical in preserving renal function in diabetics. In the United Kingdom Prospective Diabetes Study, blood pressure control yielded a greater reduction in stroke, all diabetes end points, death related to diabetes, and microvascular complications than did tight glucose control in people who had type 2 diabetes and nephropathy [92]. Thus, the most effective and reliable way to preserve kidney function and reduce CV events is achieving a blood pressure of less than 130/80 mm Hg in people who have any level of proteinuria and kidney disease or diabetes [94].

Because there is an established relationship between reductions in MA and the reduced risk for kidney disease progression and CV events in patients who have diabetes with antihypertensive regimens that are known to reduce albuminuria (ie, angiotensin-converting enzyme [ACE] inhibitor or augiotensin recepter block [ARB]), one of these agents should be part of the regimen that is used to achieve blood pressure goal in patients who have MA [94,95]. These agents reduce intraglomerular pressure and attenuate mesangial matrix expansion in models of diabetes, and prevent the development of atherosclerosis in cholesterol-fed rabbits [96–98]. The net result of these effects is the prevention of glomerulosclerosis in a manner that is independent of blood pressure and glucose control [97].

Further evidence to support the partial blood pressure lowering independent effects of ACE inhibitors can be seen in studies that involve normotensive type 2 diabetics. In one study of normotensive type 2 diabetics, the plasma creatinine concentration and the rate of protein excretion remained stable after treatment with an ACE inhibitor for 5 years [93]. By comparison, placebo-treated patients had a 13% increase in plasma creatinine concentration, a 2.5-fold increase in mean protein excretion (from 123 mg/d to 310 mg/d), and a higher rate of progression to overt proteinuria (42% versus 12% in the group that received ACE inhibitors) during this period. These differences were maintained at 7-year follow-up [95]. Another study noted similar findings in hypertensive type 2 diabetics who had MA. Over a

3-year period, administration of an ACE inhibitor was associated with less progression to overt proteinuria (7% versus 21% in a placebo-treated group) and a slower increase in the plasma creatinine concentration [99].

The substudy of the HOPE, the MA, CV, and renal outcomes HOPE, demonstrated that the reduction in MA that is seen with the use of ACE inhibitors leads to improved CV outcomes. Among the 1140 patients who had diabetes and MA, patients who were treated with ramipril had an approximately 20% lower UACR, which was accompanied by a 21% reduction in the primary outcome (myocardial infarction, stroke, or CV death), and a lower risk for developing overt nephropathy. These effects were independent of the baseline level of MA [24].

Although most American and international guidelines suggest that ACE inhibitors and ARBs can be used interchangeably, the data involving ARBs and outcomes are less plentiful. In much sicker cohorts, such as in the RENAAL trial, the use of losartan led to a 28% reduction in macroalbuminuria at 6 months in type 2 diabetics; for every 50% reduction in albuminuria there was a 36% reduction in the primary outcome of doubling of serum creatinine, ESRD, and death. The investigators concluded that all of the renoprotection from the use of the ARB was related to its antiproteinuric effect, and not to the achieved blood pressure [79]. This was confirmed in a similar cohort by the results of the IDNT, which showed that 36% of the renoprotection that was seen with irbesartan was related to its antiproteinuric effect [78]. Although these two trials demonstrated that ARBs impact renal outcomes, LIFE showed that losartan decreased the occurrence of CV death plus nonfatal myocardial infarction, and nonfatal stroke, and that 20% of this effect is related to its antiproteinuric effect [100]. Taken all together, these data support the notion that ACE inhibitors and ARBs have similar effects on outcomes. Generally, ARBs are tolerated better than are ACE inhibitors, because they are associated with a lower incidence of cough, angioedema, and hyperkalemia [101].

Several options are available if a patient should continue to have MA despite treatment with an ACE inhibitor or an ARB and achievement of goal blood pressure. Combining high doses of an ACE inhibitor with an ARB can be done safely and does lead to a significant reduction in protein excretion [102]. Although some preliminary data have suggested that nondihydropyridine calcium antagonists may reduce MA, clinical trials have failed to confirm this [103]. Emerging data have suggested that vasodilating β-blockers also can lead to a significant reduction in MA, independent of effects on blood pressure [104]. In short, although drugs that lower blood pressure by blocking the renin-angiotensin system seem to confer benefits that are not related totally to the effects of lower blood pressure, this is only seen in people who have advanced proteinuric nephropathy; even then blood pressure accounts for only about 25% of their benefit, the remainder being blood pressure lowering [105]. In people who have earlier stages of nephropathy and MA, no such independent relationship

holds in the context of outcomes [106]. Thus, blood pressure lowering is the key goal for all patients who have early-stage nephropathy and normoalbuminuria or MA.

Summary

Recent advances have allowed for a greater understanding of the epidemiology, pathophysiology, and clinical significance of MA among patients who have diabetes and essential hypertension, and the general population. MA is associated with a higher prevalence of diabetic complications and CV events as well as a risk for further deterioration of kidney function among patients who have essential hypertension. Although the routine measure and treatment of MA should be done in all persons who have diabetes and hypertension with the metabolic syndrome, such an approach should not be used in all patients who have essential hypertension. Lastly, achieving target blood pressure should be the priority in treating patients who have MA, and strong consideration should be given to using agents, such as ACE inhibitors, ARBs, and aldosterone antagonists, that independently reduce albumin excretion.

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