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Microalbuminuria in Diabetes Mellitus

Identifying individuals at risk for cardiovascular disease and end-stage renal disease

Diabetes mellitus, characterized by abnormally high blood glucose levels, is the result of insufficient insulin secretion by the pancreas, inadequate insulin function, or both. Insulin is the hormone responsible for the absorption of glucose into the body for immediate energy requirements or for energy storage. There are two main types of diabetes mellitus: Type 1, or insulin-dependent diabetes mellitus (IDDM), and Type 2, non-insulin-dependent diabetes mellitus (NIDDM). Combined, IDDM and NIDDM afflict approximately 15.7 million people in the United States — nearly 6% of the US population — and 135 million people worldwide.[1,2]

IDDM is the more severe but less common type of diabetes, accounting for approximately 5 - 10% of diabetes cases. It usually develops in young individuals — between ages 10 and 16 — and results from the destruction of the insulin-secreting cells of the pancreas. The destruction of these cells is often due to immunological attack, brought about by a viral infection. In such cases, insulin production ceases completely and the afflicted individual requires supplemental insulin therapy.

NIDDM is much more common, accounting for 90 - 95% of diabetes cases. It typically develops in older individuals — after age 40 — and is the result of insufficient insulin production. In most cases, insulin therapy is not required as the disease can often be managed by dietary modification, weight loss and/or control, and oral medication. NIDDM is often asymptomatic in its early stages and frequently goes undiagnosed; in the US, it is estimated that approximately one-third (5.4 million) of the total NIDDM cases are currently undiagnosed.[1]

The complications associated with diabetes include cardiovascular disease, peripheral vascular disease, retinopathy, and nephropathy. Cardiovascular disease is the leading cause of mortality in diabetes mellitus, present in approximately 75% of all diabetes-related deaths. Also significant is diabetic nephropathy, which progresses to end-stage renal disease (ESRD) in approximately one-third of both IDDM and NIDDM cases; worldwide, diabetic nephropathy is the leading cause of ESRD.[3,4,5] In the US, these and other diabetes-related afflictions account for an astonishing $98 billion in total medical costs.[6]

Recent studies indicate that if detected early, renal damage due to diagnostic nephropathy can be minimized, halted, or in some cases reversed by therapeutic interventions such as the administration of antihypertensive medication. Likewise, early intervention in diabetes-related cardiovascular disease can also minimize mortality. With over 5 million undiagnosed diabetes mellitus cases in the US alone, it is evident that effective screening procedures would identify those asymptomatic diabetics who are candidates for early intervention therapy, potentially avoiding the more serious, and costly, diabetes-related complications.

Microalbuminuria

Perhaps the most-studied marker of diabetes mellitus and diabetes-related complications is microalbuminuria, the presence of small amounts of albumin in the urine. In healthy individuals, urinary protein excretion ranges from 50 - 150 mg/day and consists primarily of Tamm-Horsfall mucoprotein, β_2-microglobulin, immunoglobulin light chains, other small globulins, and very little albumin (0 - 30 mg/day).[7] Excessive albumin excretion has long been associated with renal dysfunction and urinary dipstick-type assays for albumin have been available for quite some time.[8] Until recently, however, these assays were only capable of detecting urinary albumin concentrations representative of albumin excretion of approximately 300 mg/day. As such, clinical albuminuria was defined as urinary albumin excretion exceeding 300 mg/day. Clinical significance is now associated with smaller quantities of urinary albumin excretion, primarily in diabetes, and the term "microalbuminuria" has been introduced and defined as daily albumin excretion that exceeds the normal range, but is less than 300 mg/day. Correspondingly, albumin excretion that exceeds 300 mg/day is now defined as "macroalbuminuria." In diabetes mellitus, microalbuminuria (MA) develops in 20 – 40% of both IDDM and NIDDM patients and is predictive of nephropathy and cardiovascular disease.[5]

MA in insulin-dependent diabetes

In IDDM, diabetic nephropathy is the major life-threatening complication. Clinical symptoms include MA, an increase in arterial blood pressure, and a steady decline in glomerular filtration rate (GFR), which ultimately leads to ESRD.[9] In IDDM patients, MA often appears, then regresses back to normoalbuminuria, especially within the first 5 – 10 years after diagnosis of diabetes.[5,9] As such, a distinction is made between 'intermittent' MA and 'persistent' MA. In a majority of IDDM patients, once persistent MA is diagnosed, the patient's urinary albumin excretion rate (AER) continues to increase between 15 – 40% per year, ultimately reaching macroalbuminuric levels.[5,10,11]

Studies conducted in both adult and adolescent patients with IDDM indicate that persistent MA is significantly predictive of progression to diabetic nephropathy.[9,12,13,14] The positive predictive value of persistent MA in predicting the development of

Abbreviations:

A/C Ratio	-	Albumin:creatinine ratio
ACE Inhibitors	-	Angiotensin converting enzyme inhibitors
AER	-	Albumin excretion rate
ESRD	-	End-stage renal disease
GFR	-	Glomerular filtration rate
IDDM	-	Insulin-dependent diabetes mellitus
MA	-	Microalbuminuria
NIDDM	-	Non-insulin-dependent diabetes mellitus

diabetic nephropathy is reportedly as high as 80% over a 10-year period.[15,16] In fact, persistent MA is so closely associated with diabetic nephropathy that it is now thought of as early stage nephropathy, or "incipient" nephropathy, rather than merely a risk factor for the development of diabetic nephropathy.[7,17]

Persistent MA is also predictive of cardiovascular complications in IDDM.[12,18,19,20] Although IDDM patients are typically very young and the risk of developing diabetes-related cardiovascular complications thought to be low, a significant 23-year follow-up study demonstrated that IDDM patients with persistent MA were at a much greater risk of cardiovascular mortality compared to those without MA.[14] In addition, normotensive IDDM patients with persistent MA were shown to be at greater risk of developing left ventricular diastolic dysfunction than those without persistent MA.[21]

MA in non-insulin-dependent diabetes

Cardiovascular disease is the most significant cause of mortality in NIDDM, and persistent MA is the most powerful predictor of cardiovascular-related deaths.[7,12,22,23] In fact, NIDDM patients with persistent MA are approximately twice as likely to develop cardiovascular disease than normoalbuminuric patients.[24] This is despite the lack of any association between persistent MA and conventional indicators of cardiovascular disease.[25]

Many of the cardiovascular deaths in NIDDM occur without the development of clinical symptoms, presenting a diagnostic challenge. A recent study examined the prevalence of such "silent" myocardial ischemia in asymptomatic NIDDM patients with and without persistent MA.[26] Exercise stress testing on a treadmill revealed the presence of a silent ischemic response in both groups of patients, but at a significantly higher rate (65%) in those with persistent MA. Evaluating several other clinical parameters, persistent MA was the single strongest independent predictor of a silent ischemic response.

Persistent MA also predicts the development of diabetic nephropathy in NIDDM patients.[12,27] Specifically, persistent MA in NIDDM patients has been associated with a decreased GFR, an indicator of renal dysfunction.[28,29] Another study, however, found no association between the presence of persistent MA and a reduced GFR.[30] It should be noted that several clinical factors may complicate the tracking of MA progression in NIDDM patients. Because NIDDM can go undiagnosed for several years, the actual date of onset of NIDDM is often unknown; without a valid baseline AER value, an accurate assessment of MA progression is more difficult. In addition, nondiabetic renal disease is often present in NIDDM patients and may increase the AER to MA levels, unrelated to diabetes. And lastly, the high cardiovascular mortality present in NIDDM patients, may cause death before persistent MA develops.[7] It is not clear whether these factors contributed to the discrepant results of these studies, but future studies should take such considerations into account.

Histologic study of MA

The underlying physiology of MA and its affect on clinical outcome in diabetes mellitus is unclear. However, two hypotheses have been proposed to explain the difference between the predictive value of MA in IDDM, where persistent MA predicts ESRD and to a lesser degree cardiovascular disease, and that in NIDDM, where just the opposite is true. First, it is possible that MA is in fact indicative of renal dysfunction, but because NIDDM patients are older, they are more prone to the development of cardiovascular disease and may die before renal complications develop. It is also possible that the follow-up period for these older patients is not long enough to detect the onset of diabetic nephropathy.[31] Second, persistent MA may reflect a systemic, endothelial and vascular disorder, rather than reflect only glomerular structural abnormalities. A wide range of clinical symptoms have been noted in NIDDM patients, including MA, insulin resistance, hypertension, renal and cardiac hypertrophy, and abnormal cation membrane transport. It is possible that NIDDM patients, being older, are most susceptible the cardiovascular complications.[31]

The latter hypothesis does not, however, exclude the possibility that MA is directly reflective of histologic renal abnormalities in NIDDM patients. In an evaluation of diabetic renal structure, light microscopy revealed significant heterogeneity in the renal cells of NIDDM patients.[32] One-third of the patients studied had normal renal structure despite the presence of MA, another one-third showed atypical patterns of renal injury, and the remaining one-third had typical diabetic glomerulopathy. It has been proposed that the hyperglycemia observed in NIDDM patients may cause different patterns of renal injury, observed as histologic heterogeneity, as compared with IDDM patients, where diabetic glomerulopathy is the hallmark change of the disease.[31]

Therapeutic intervention

With the grave outcomes associated with both IDDM and NIDDM, early detection and intervention are instrumental in preventing progression to ESRD or to cardiovascular disease. Typical intervention for treating diabetes includes metabolic/glycemic control (insulin therapy if necessary) and reducing protein intake to moderate levels (e.g., 0.9 – 1.1 g protein / kg body weight). These treatments, however, usually have little effect on MA,[9,33] and once persistent MA has been diagnosed, additional measures must be implemented to minimize the amount of renal damage.

Several antihypertensive medications have been demonstrated to be effective in controlling the progression of MA in diabetic patients.[34,35,36] In particular, angiotensin converting enzyme (ACE) inhibitors have been shown to reduce the AER and slow the progression of persistent MA in both IDDM and NIDDM patients, independent of the presence or absence of hypertension.[33] In a recent study, five years of enalapril treatment, an ACE inhibitor, effectively slowed the progression of persistent MA, reduced the AER, and preserved the GFR of normotensive NIDDM patients.[37] Similarly, another ACE inhibitor, lisinopril, was shown to reduce the AER in those IDDM patients with an AER in the high normal range.[38] These effects appear to be long-lasting, but at present it is unclear whether ACE inhibitors simply postpone the onset of ESRD or will actually reduce ESRD mortality.

Screening for MA

Reports of cost-benefit analyses indicate that screening for MA is justified, at least in diabetic outpatient clinics, with the hope that early therapeutic intervention will retard the development of ESRD and cardiovascular disease.[4,12,39] Such screening procedures should involve serial measurements of the AER because, as mentioned before, MA often regresses back to normal AER levels and aggressive therapies should only be administered to those individuals with persistent MA. It has been proposed that a diagnosis of persistent MA should not be made until at least two or three urine samples test in the MA range over a 3 – 6 month period.[7,9] Semi-quantitative dipstick-type assays have been shown useful in preliminary screening procedures, as they are capable of detecting individuals with an AER in the MA range.[5,40] These assays should be follow-up, however, with quantitative assays which allow more accurate monitoring of MA progression.

From a clinical standpoint, the most accurate method of determining the urinary albumin excretion rate (AER) is by

obtaining several urine samples from a patient overnight at timed intervals. The normal range of AER values determined by this method is 20 - 200 µg/min. This is equivalent to a total albumin excretion of 30 - 300 mg/day, or 20 - 200 mg/liter in individuals with normal urine concentration.[9] Due to the difficulty of patient compliance in obtaining such timed samples, unless the patient is hospitalized, obtaining the first morning urine sample is also a reliable method. To correct for inter-patient variations in urine concentration, which would obviously affect absolute albumin concentrations, the albumin:creatinine ratio (A/C ratio) is often determined.

The range of A/C ratio values for MA has been described as 2 – 20 mg/mmol for men and a slightly higher 2.8 – 28 mg/mol for women to account for the lower creatinine excretion observed in females. Other ranges have been described for MA, with threshold values of 2.5 mg/mmol reported for men[9,41] and 3.5 mg/mmol[9] and 4.5 mg/mmol[41] reported for women. Further study is required to better define clinically appropriate ranges for each gender.

Using such AER determinations, it is possible to diagnose persistent MA at the very early stages of diabetic nephropathy, perhaps as much as a decade before the onset of diabetes-related complications. Therapeutic intervention could then be implemented in these high risk individuals, hopefully reducing the high mortality associated with diabetes mellitus.

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