Albuminurina and Diabetic Nephropathy: an Evolving Story

The lifetime risk of diabetic nephropathy is ~45% for patients with Type I (insulin-dependent) diabetes (1) and at least 30–35% for patients with Type II (non-insulin-dependent) diabetes (2, 3). In Type I diabetes, the incidence of readily detectable nephropathy rises steeply 10 years after the onset of diabetes (4). The progression from the appearance of "clinical proteinuria" (a positive test for protein upon routine urinalysis) to end-stage renal failure requiring dialysis or kidney transplantation occurs over about five years. This progression is usually relentless (4), but the rate of deterioration may be slowed or stabilized with improved glucose control (5–7), by the use of angiotensin-converting enzyme inhibitors (8, 9), diltiazem (10) [but not nifedipine (11)], and dietary protein restriction (12). Early intervention, before the development of clinical proteinuria, appears to be much more effective than later treatment.

Until about 10 years ago, diabetic nephropathy was usually first recognized when protein could be detected in urine with the dipsticks used for routine urinalysis (a protein concentration of 200 to 300 mg/L). It is now clear that concentrations of urinary albumin below the limit of detection by dipsticks are associated with progression to "overt" nephropathy and on to end-stage renal disease. Attention was first directed to patients with albumin excretion between 20 and 200 mg/day (albumin excretion rates of 14 to 140 μg/min), who were shown to be likely to progress to established "dipstick-positive" proteinuria and further to renal failure (13–16).

The study of Chase et al., published in this issue (17), extends our understanding of this problem to patients who have lower rates of excretion of urinary albumin than have been addressed by other investigators. Normal individuals have urinary albumin excretion rates up to 7 or 8 μg/min (~10 mg/24 h) (18, 19). Chase et al. show that patients with Type I diabetes who have urinary albumin excretion rates only slightly above normal are likely to progress to higher rates of albumin excretion, and, by extrapolation, are more likely to develop end-stage renal disease. Their study adds to the evidence that diabetic nephropathy is a continuum. Any increase of albumin excretion is likely to indicate diabetic nephropathy; the greater the increase, the more likely that there will be progression to clinically significant disease (conversely, the less likely that intervention will stop or reverse the progression).

The term "microalbuminuria" is often used to refer to small amounts of albumin that fall below the detection limit of older assays for albumin. This term is misleading; it implies that there is a small molecular species of albumin, when in fact, the albumin in the urine of these patients is qualitatively no different from urinary albumin in other conditions. "Incipient nephropathy" is also a misnomer, because diabetic patients with even slightly increased albumin excretion already have the glomerular changes of diabetes by light microscopy (20). Albuminuria indicates definite nephropathy, not incipient disease; the possibility that the nephropathy is reversible at this stage is exciting, but reversibility does not make this an "incipient" condition. Moreover, the absence of an increased albumin excretion does not exclude diabetic nephropathy; some patients with diabetic glomerular changes on kidney biopsy do not have albuminuria (20).

Biological factors make it difficult to apply this information in the clinic. There is a significant diurnal variation of albumin excretion: albumin excretion is lower overnight than during the day (21–23), at least in nondiabetic individuals. Albumin excretion may fluctuate substantially over a period of weeks or months (24, 25). High urine volumes in poorly controlled diabetic patients may cause false-negative results when albumin concentration is measured (26, 27). Although some investigators believe that calculating an albumin/creatinine ratio (23, 28, 29) will correct for variations in urine volume, others disagree (24, 26). It is difficult to draw definite conclusions from the literature on this subject. Some investigators have measured albumin in 24-h urine samples, others on overnight samples, others on a first-morning voiding, and still others for some fraction of the day. Most have expressed results as the amount of albumin excreted over time (albumin excretion rate; AER), but some have used milligrams per day and others have used micrograms per minute. Lack of a "gold standard" test for diabetic nephropathy or a clear indication of when nephropathy may or may not be reversible, there is no agreement regarding which method of testing has the best predictive value. Clearly, some patients will be classified differently under different conditions of sampling.

More work is needed in this important area, especially long-term studies to determine the predictive value of different testing conditions for identifying patients who are at risk for rapid progression to end-stage renal disease. Despite the gaps in our current knowledge, some form of testing for urinary albumin is still the best way of identifying patients with early diabetic nephropathy (30). The American Diabetes Association recommends that "total urinary protein excretion should be measured yearly, by a microalbuminuria method if possible (31)," for all patients with Type II
diabetes and for all patients with Type I diabetes of five years or more duration.

Several simple and inexpensive tests of albumin concentration can be used for screening random (untimed) urine samples, which are easier to obtain from ambulatory patients than are timed samples. Patients with abnormal screening results should have either 24-h or overnight albumin excretion rates, or both, determined on several occasions, weeks or months apart. Patients with a consistently increased albumin excretion should be viewed as having diabetic nephropathy and managed accordingly. Even though this approach is imperfect, it will be more beneficial to our diabetic patients than just waiting for the appearance of clinical proteinuria before taking notice.

References


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