Albuminuria and Management of Type 2 Diabetes Mellitus

Mohammad Reza Ganji

Nephrology Research Center, Tehran University of Medical Sciences, Tehran, Iran

See article on page 268

IJKD 2013;7:245-8
www.ijkd.org

In this issue of the *Iranian Journal of Kidney Diseases*, Zakerkish and colleagues' have reported a significant relationship between albuminuria and a series of factors in diabetic patients, including blood urea nitrogen, serum creatinine, lipid profile, serum hemoglobin A1c, systolic and diastolic blood pressure, glomerular filtration rate (GFR), and duration of diabetes mellitus.[1] The association between cardiac disease and albuminuria cannot be ascertained in this study due to study design and other confounding factors. The major complication of diabetes mellitus such as retinopathy could not be evaluated, and its correlation with albuminuria and rate of decline of GFR was not determined. Despite all these factors, the highlight of this study was that only 19.7% of their patients could reach a hemoglobin A1c less than 7%, and this can lead us to more aggressive treatment of hyperglycemia.

Diabetic nephropathy occurs in 20% to 40%of patients with diabetes mellitus and is the single leading cause of end-stage renal disease in many countries. Persistent microalbuminuria in the range of 30 mg/24 h to 299 mg/24 h has been shown to be the earliest stage of diabetic nephropathy in type 1diabetes and a marker for development of nephropathy in type 2 diabetes. It is also a well-established marker of increased risk of cardiovascular disease.[2] Patients with microalbuminuria who progress to more significant levels of urine albumin (> 300 mg/24 h; historically called macroalbuminuria) are likely to progress to end-stage renal disease.

The current worldwide prevalence of diabetes mellitus is estimated to be approximately 250 million people, and it is expected to reach 380 million by 2025.[3] The most recent data, which were derived from the 2005-2006 National Health and Nutrition Examination Survey in the United States with both fasting plasma glucose and 2-hour oral glucose tolerance test results showed a prevalence of diabetes in persons older than 20 years old of 12.9% (approximately 40 million).[4] From these individuals, 40% (approximately 16 million) were undiagnosed. The prevalence of diabetes has also increased in other parts of the world. For example, recent estimates suggest 110 million diabetic individuals live in Asia in 2007, but the true number is likely to be substantially greater, because China alone was thought to have 92.4 million adults with diabetes in 2008.[5]

The rate of decline in GFR exceeding that of normal aging (>1 mL/min/y) are associated with adverse outcome. In diabetic patients with chronic kidney disease, the level of proteinuria appears to be a strong marker predicting the rate of decline in GFR. There is some evidence that prevention of progression of proteinuria may be the hallmark of improved outcome of diabetic nephropathy, pointing out that with aggressive treatment, many persons can remain stable and do not progress to dialysis.[6]

Mechanisms of albuminuria can be explained as abnormalities of the glomerular endothelial barrier, causing excessive filtration, as well as reduction of renal tubular cell albumin degradation and reabsorption. Angiotensin II and mechanical stress are important factors contributing to intraglomerular hypertension, inflammation, and oxidative stress which worsen albuminuria. Multiple strategies for treatment of chronic kidney disease includes blood pressure reduction to less than 140/90 mm Hg, treatment with angiotensin-converting enzyme inhibitors and angiotensin receptor blockers, lowering albuminuria, glycemic control, treatment of anemia, aggressive lipid treatment, treatment of secondary hyperparathyroidism, smoking cessation,

weight control, and exercise.

There is strong evidence for genetic factors associated with chronic kidney disease development, as well. The Diabetes Control and Complications Trial[6] showed a relationship between a number of polymorphisms of the superoxide dismutase 1 gene and risks of macroalbumniuria and microalbuminuria among type 1 diabetic participants, suggesting that genetic variants in the propensity to oxidative injury may be related to development of diabetic nephropathy. In persons with diabetes, impaired glucose tolerance, and even with a family history of diabetes, kidney disease is associated with abnormalities of vasodilation mediated by endothelial-derived nitric oxide, suggesting a linkage between vascular and metabolic abnormalities. Angiotensin II increases nitric oxide metabolism to peroxynitrite, which is a potent oxidant injury stress.[7] The hemodynamic stress of systolic hypertension with loss of vascular compliance further impairs endothelial-derived vasodilatation.

Early detection of risk markers, such as albumin in the urine, formerly termed microalbuminuria, relies on tests for urinary excretion of albumin. Conventional qualitative tests (chemical strips or "dipsticks") for albuminuria do not detect the small increases of urinary albumin excretion. Recent data suggest that risk extends below the lower limit of 10 mg/g of albumin-creatinine ratio, reinforcing that this factor is a continuous variable for cardiovascular risk. Of note is that low levels of albuminuria alone indicate neither an increased risk for progression to end-stage renal disease nor kidney disease per se; hypertension needs to be present for the risk of progression.[8] Moreover, about 20% of people progress to end-stage disease without an increase in low levels of albuminuria.

Transient increases in urinary albumin excretion have been reported with short-term hyperglycemia, exercise, urinary tract infections, marked hypertension, heart failure, acute febrile illness, and hyperlipidemia.[9] To answer the question whether albuminuria or retinopathy are associated with rate of decline of GFR, in a new study, patients with type 2 diabetes in Japan with retinopathy or microalbuminuria had a much higher rate of annual decline in GFR. The authors analyzed data from 1475 patients with type 2 diabetes. After a median follow-up of 8 years, compared with the patients with neither microalbuminuria nor diabetic retinopathy at baseline, those who had at least 1 risk factor were much more likely to progress to macroalbuminuria, especially if they had microalbuminuria. The annual decline in the estimated GFR was 2 to 3 times faster in the group with both risk factors than in the other groups.[10]

Although greater albuminuria and lower estimated GFR both predict adverse prognosis, whether a synergistic prognostic interaction occurs in patients with diabetes has not been defined in a large national cohort study. In the 2000-2011 National Kidney Foundation's Kidney Early Evaluation Program on 42 761 participants with diabetes showed the association of estimated GFR, albumin-creatinine ratio, and their interaction with all-cause mortality and progression to end-stage renal disease at a median 4 years of follow-up. Of 42 761 participants with diabetes, 8618 (20.2%) had an estimated GFR less than 60 mL/min/1.73 m^2, 7715 (18.0%) had an albumin-creatinine ratio greater than 30 mg/g, and 2641 (6.2%) had both. The result disclosed that both estimated GFR and albuminuria were associated independently with mortality and progression to end-stage renal disease. An estimated GFR less than 30 mL/min/1.73 m^2 and macroalbuminuria together were associated with a 5-fold higher risk of mortality and a more than 1000-fold higher risk of progression to end-stage renal disease.[11] Recent results have challenged the concept that a decline in kidney function in patients with diabetes is always accompanied by increased albuminuria. Results from the Third National Health and Nutrition Survey have suggested that the finding of nonalbuminuric renal insufficiency is not an uncommon discovery for subjects with diabetes, especially those with type 2 diabetes. Patients with type 2 diabetes, microalbuminuria, and preserved kidney function who have typical and atypical renal structural pathology have a higher intrarenal resistance index when compared with those who have near normal renal structure.[12]

It is possible that a reduced GFR in normo-albuminuric subjects with type 2diabetes occurs predominantly due to an increase in intrarenal arteriosclerosis as opposed to the well-established pathological changes that affect the glomerulus in diabetic subjects with reduced GFR and an elevated albumin excretion rate. Now there is clear evidence in subjects with type2 diabetes who can develop

renal impairment in the absence of an increase in albuminuria. In one study, the prevalence of normoalbuminuric renal insufficiency defined as a GFR less than 60 mL/min/1.73 m^2 was 23% in subjects with type 2diabetes. This can be explained by premature senescence of the diabetic kidney, interstitial fibrosis, ischemic vascular disease, or cholesterol microemboli, as opposed to classical diabetic glomerulosclerosis. The mechanisms responsible for the increase in intrarenal resistance index and a reduction in systemic arterial compliance, at least in diabetes, are not fully understood but may involve impaired glycemic control, the glycation of structural proteins within the arterial wall, angiotensin-stimulated collagen deposition in vessel walls, autonomic nervous system dysfunction, or endothelial dysfunction.[13] There are many factors that are important for delaying or halting diabetic nephropathy beyond preventing albuminuria and retinopathy. The Diabetes Control and Complications Trial, a randomized controlled trial of intensive versus standard glycemic control in patients with relatively recently diagnosed type 1diabetes, showed definitively that improved glycemic control is associated with significantly decreased rates of microvascular (retinopathy and nephropathy) and neuropathic complications. Follow-up of the Diabetes Control and Complications Trial cohorts in the epidemiology of Diabetes Interventions and Complications study[14] demonstrated persistence of microvascular benefits in previously intensively treated subjects, even though their glycemic control approximated that of previous standard arm subjects during follow-up. The Veterans Affairs Diabetes Trial showed significant reductions in albuminuria with intensive (achieved median hemoglobin A1c of 6.9%) compared with standard glycemic control, but no difference in retinopathy and neuropathy.[15] The Action in Diabetes and Vascular Disease study of intensive versus standard glycemic control in type 2 diabetes found a significant reduction in albuminuria, but not in neuropathy or retinopathy, with an hemoglobin A1c target of 6.5% (achieved median hemoglobin A1c of 6.3%) compared with standard therapy achieving a median hemoglobin A1c of 7.0%.[16] Analyses from the Action to Control Cardiovascular Risk in Diabetes trial have shown lower rates of onset or progression of early-stage microvascular complications in the intensive glycemic control arm compared with the standard arm.[17] These analyses also suggest that further lowering of hemoglobin A1c from 7% to 6% is associated with further reduction in the risk of microvascular complications, albeit the absolute risk reductions become much smaller. Given the substantially increased risk of hypoglycemia, the concerning mortality findings in the Action to Control Cardiovascular Risk in Diabetes trial, and the relatively much greater effort required to achieve near normoglycemia, the risks of lower glycemic targets may outweigh the potential benefits on microvascular complications on a population level.

Hypertension is a major risk factor for both cardiovascular disease and microvascular complications. In type 1 diabetes, hypertension is often the result of underlying nephropathy, while in type 2 diabetes, it usually coexists with other cardiac and metabolic risk factors. The United Kingdom Prospective Diabetes Study provided strong evidence that control of blood pressure can reduce the development of nephropathy. In type 2 diabetes with hypertension and normoalbuminuria, renin-angiotensin-aldosterone system inhibition has been demonstrated to delay onset of microalbuminuria.[18] If the blood pressure is confirmed to be higher than 140/90 mm Hg, drug therapy should be initiated along with non pharmacological therapy. Patients with type 2 diabetes have an increased prevalence of lipid abnormalities, contributing to their high risk of cardiovascular disease. Multiple clinical trials demonstrated significant effects of pharmacological (primarily statin) therapy on cardiovascular disease outcomes in subjects with congestive heart faolure and for primary cardiovascular disease prevention.

Diabetic retinopathy is a highly specific vascular complication of both type 1 and type 2diabetes, with prevalence strongly related to the duration of diabetes. Serial examinations for type 1and type 2 diabetic patients should be repeated annually by an ophthalmologist or optometrist. Examinations will be required more frequently if retinopathy is progressing. Factors that increase the risk of retinopathy include chronic hyperglycemia, albuminuria and hypertension. Intensive diabetes management with the goal of achieving near normoglycemia has been shown in large prospective randomized studies to prevent and or delay the onset and progression of diabetic retinopathy. Lowering blood pressure has been shown to decrease the

progression of retinopathy although tight targets (systolic blood pressure < 120 mm Hg) do not impart additional benefit. A new study with longer follow up should be designed in Iranian subjects with type 2 diabetes for assessment of impact of retinopathy, hyperglycemia and albuminuria on progression of nephropathy in future.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Zakerkish M, Shahbazian HB, Shahbazian H, Latifi SM, Moravej Aleali A. Albuminuria and Its Correlates in Type 2 Diabetic Patients. Iran J Kidney Dis. 2013;7:268-76.
2. Klausen K, Borch-Johnsen K, Feldt-Rasmussen B, et al. Very low levels of microalbuminuria are associated with increased risk of coronary heart disease and death independently of renal function, hypertension, and diabetes. Circulation. 2004;110:32-5.
3. Cowie CC, Rust KF, Byrd-Holt DD, et al. Prevalence of diabetes and impaired fasting glucose in adults in the U.S. population: National Health And Nutrition Examination Survey 1999-2002. Diabetes Care. 2006;29:1263-8.
4. Cowie CC, Rust KF, Ford ES, et al. Full accounting of diabetes and pre-diabetes in the U.S. population in 1988-1994 and 2005-2006. Diabetes Care. 2009;32:287-94.
5. Chan JC, Malik V, Jia W, et al. Diabetes in Asia: epidemiology, risk factors, and pathophysiology. JAMA. 2009;301:2129-40.
6. Bloomgarden ZT. Diabetic nephropathy. Diabetes Care. 2008;31:823-7.
7. Sowers JR. Hypertension, angiotensin II, and oxidative stress. N Engl J Med. 2002;346:1999-2001.
8. Klausen KP, Scharling H, Jensen JS. Very low level of microalbuminuria is associated with increased risk of death in subjects with cardiovascular or cerebrovascular diseases. J Intern Med. 2006;260:231-7.
9. Glassock RJ. Debate: CON position. Should microalbuminuria ever be considered as a renal endpoint in any clinical trial? Am J Nephrol. 2010;31:462-5; discussion 6-7.
10. Moriya T, Tanaka S, Kawasaki R, et al. Diabetic Retinopathy and Microalbuminuria Can Predict Macroalbuminuria and Renal Function Decline in Japanese Type 2 Diabetic Patients: Japan Diabetes Complications Study. Diabetes Care. 2013.
11. Amin AP, Whaley-Connell AT, Li S, Chen SC, McCullough PA, Kosiborod MN. The synergistic relationship between estimated GFR and microalbuminuria in predicting long-term progression to ESRD or death in patients with diabetes: results from the Kidney Early Evaluation Program (KEEP). Am J Kidney Dis. 2013;61:S12-23.
12. MacIsaac RJ, Panagiotopoulos S, McNeil KJ, et al. Is nonalbuminuric renal insufficiency in type 2 diabetes related to an increase in intrarenal vascular disease? Diabetes Care. 2006;29:1560-6.
13. Kramer HJ, Nguyen QD, Curhan G, Hsu CY. Renal insufficiency in the absence of albuminuria and retinopathy among adults with type 2 diabetes mellitus. JAMA. 2003;289:3273-7.
14. [No author listed]. Retinopathy and nephropathy in patients with type 1 diabetes four years after a trial of intensive therapy. The Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Research Group. N Engl J Med. 2000;342:381-9.
15. Duckworth W, Abraira C, Moritz T, et al. Glucose control and vascular complications in veterans with type 2 diabetes. N Engl J Med. 2009;360:129-39.
16. Patel A, MacMahon S, Chalmers J, et al. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. N Engl J Med. 2008;358:2560-72.
17. Gerstein HC, Miller ME, Byington RP, et al. Effects of intensive glucose lowering in type 2 diabetes. N Engl J Med. 2008;358:2545-59.
18. Remuzzi G, Macia M, Ruggenenti P. Prevention and treatment of diabetic renal disease in type 2 diabetes: the BENEDICT study. J Am Soc Nephrol. 2006;17:S90-7.
19. Fong DS, Aiello LP, Ferris FL, 3rd, Klein R. Diabetic retinopathy. Diabetes Care. 2004;27:2540-53.

Correspondence to:
Mohammad Reza Ganji, MD
Department of Nephrology, Shariati Hospital, Tehran University of Medical Sciences, Tehran, Iran
E-mail: mrezaganji@yahoo.com