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Podocyturia-A Reliable Marker for Early Diabetic Nephropathy

Mukherjee B*

Associate Professor, Hi-tech Medical College and Hospital, India

***Corresponding author:** Brijesh Mukherjee, Associate Professor, Hi-tech Medical College and Hospital, Rourkela, Odisha, India, Tel: 919437115479; Email: taararia@gmail.com

Mini Review

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Abstract

Constant efforts are ongoing to identify reliable and reproducible noninvasive biomarkers for acute and chronic kidney injury targeted toward identifying kidney injury not only in its early stages, but also in classifying kidney disease according to severity, predict disease outcomes, and monitor response to therapeutic interventions.

The number of podocytes in urine or podocyturia increases with active kidney disease even before proteinuria appears and seems to improve with treatment. Also, podocyturia seems to be confined to active disease, in contrast to proteinuria, which is present during both active and chronic phases of glomerular damage. It will be particularly interesting to explore podocyturia, as a marker of subclinical early renal damage, which may be a detectable way before the occurrence of overt proteinuria and development of full blown glomerular disease.

Keywords: Podocyturia; Diabetic Nephropathy; Normoalbuminuria

Mini Review

Diabetic nephropathy is the leading cause of end-stage renal disease (ESRD) worldwide, and it is estimated that ~20% of type 2 diabetic patients reach ESRD during their lifetime [1]. Kidney disease in diabetic patients is clinically characterized by increasing rates of urinary albumin excretion, starting from normoalbuminuria, which progresses to microalbuminuria, macroalbuminuria, and eventually to ESRD. Microalbuminuria is the earliest clinically detectable stage of diabetic kidney disease at which appropriate interventions can retard or even reverse the progress of the disease.

According to the most recent estimates published in the Diabetes Atlas 2006, India has the largest number of diabetic patients in the world, estimated to be ~40.9 million in the year 2007 and expected to increase to ~69.9 million by the year 2025. Type 2 diabetes in Asian Indians differs from that in Europeans in several aspects: the onset is at a younger age, obesity is less common, and genetic factors appear to be more common [2,3]. Some studies conducted in migrant Asian Indians in the U.K. and Europe have reported increased prevalence of diabetic nephropathy compared with white Caucasians. The few studies published on the prevalence of diabetic nephropathy in India have all been clinic based [4-7].

Indeed, the Diabetes Atlas 2006 does not list a single population-based study on diabetic nephropathy from South Asia [2].

Diabetes is becoming the major single cause of end stage renal disease in the world. Precise evaluation of renal function in early stages of diabetic kidney disease may indicate patients susceptible to progression to the end-stage renal disease. Intensification of the treatment in those patients might slow the progression of the disease. Implementation of behaviour modification and pharmacological therapy targeted especially at hyperglycemia and hypertension declines urinary albumin excretion rate and decreases the progression to end-stage renal disease [8]. Intensive treatment is associated with increased life expectancy and is more cost-effective than conventional treatment in patients with diabetic kidney disease [9]. Progressive renal function decline in diabetes is an early event that occurs in a proportion of patients without increased albumin excretion rate [10].

Estimation of the glomerular filtration rate (GFR) is the most widely used test of renal function and reflects the kidney's ability to clear a particular substance from plasma. GFR is defined as the quantity of glomerular filtrate formed per unit time in all nephrons of both kidneys. The most precise and accurate methods for estimating GFR are based upon determinations of plasma clearance of substances like 51Cr-EDTA, iothalamate or iohexol. These so called "gold standard" methods require injection of an exogenous radioactive or contrast agent, and are complex, laborious, expensive and impractical in the clinical setting and for larger research studies. Therefore, the measurement of endogenous blood substances to estimate GFR is common practice. For several decades clinicians have relied on measurements of serum creatinine as a rapid first-line test to determine GFR. This test is convenient and cheap, but results are affected by age, sex, muscle mass, diet, race and tubular creatinine secretion, particularly when GFR is reduced. Thus there is a need for ongoing research for identification of new markers for early diabetic nephropathy.

Traditionally, the appearance of microalbuminuria has been used to detect the onset of diabetic nephropathy (DN), and its appearance prompts aggressive treatment.

However, podocyte injury starts to occur in previously assumed unaffected populations of patients before microalbuminuria appears, and therefore podocyturia is an earlier marker of DN than microalbuminuria, researchers stated here on April 15 at the National Kidney Foundation (NKF) 2010 Spring Clinical Meetings.

Podocytes are highly differentiated cells with a complex cellular morphology. Podocyte cell body bulges into the urinary space and gives rise to long primary processes that extend toward the capillaries to which they affix by numerous foot processes (FPs). The FPs of neighbouring podocytes interdigitate, leaving between them filtration slits bridged by an extracellular structure, known as the slit diaphragm (SD). Our knowledge of the molecular structure of the SD has remarkably improved in the past few years. Several molecules, including nephrin, CD2AP, FAT, ZO-1, P-cadherin, Podocin, and Neph 1-3 have been shown to be associated with the SD complex, and some of these molecules are now known to be critical for its integrity. Podocyte structural abnormalities and loss have been described in DN. Furthermore, podocytes form an integral part of the glomerular filtration barrier and participate in GBM formation, and thus they may be implicated in GBM thickening and abnormal glomerular permeability to proteins. Primary podocytes undergo dedifferentiation and apoptosis in culture ; however cell lines of differentiated podocytes have recently become available, allowing the in vitro study of podocyte response to the insults relevant to DN Podocyte Apoptosis-Loss In the adult kidney podocytes are unable to undergo regenerative proliferation to compensate for a loss of podocytes or an increase in GBM surface area. It has been speculated that podocyte cell cycle quiescence is a prerequisite for a functional glomerulus as for podocytes reentry into the cell cycle a deconstruction of the highly structured cytoskeletal organization would be required with loss of glomerular permselectivity. In human DN there is a decrease in the number of podocytes per glomerulus. Furthermore, loss of podocytes correlates closely with the degree of progression with fewer podocytes per glomerulus in the rapidly progressing group compared with slow progressors. It is unclear whether in DN there is an absolute reduction in podocytes number or a relative reduction due to increased GBM surface area. In the first case, podocytes structural alterations and damage would be the primary event resulting in podocytes apoptosis and podocyturia. In the second case, both glomerular hypertrophy and enhanced glomerular volume expansion would cause an increase in GBM surface area with consequent reduction in podocytes density. FP broadening would be a compensatory response of the remaining podocytes in the attempt to

cover areas of bare GBM. Broadening, however, reduces FP adhesion to the GBM and may eventually result in podocyte detachment and loss.

Podocytes are normally absent or seen in small numbers in urine of normal individuals or those with inactive kidney disease. Although not visible utilizing a microscope, it is possible to visualize these podocytes in urine with immunofluoresence staining and after incubation with antihuman podocalyxin monoclonal antibody PHM-5 (Australian Monoclonal Development, Artarmon, New South Wales, Australia). The number of podocytes in urine or podocyturia increases with active kidney disease even before proteinuria appears and seems to improve with treatment [11]. Also, podocyturia seems to be confined to active disease, in contrast to proteinuria, which is present during both active and chronic phases of glomerular damage [12]. It will be particularly interesting to explore podocyturia, as a marker of subclinical early renal damage, which may be a detectable way before the occurrence of overt proteinuria and development of full blown glomerular disease. NOTE: Fresh urine is collected and urinary cell pellets were derived via centrifugation. Immunofluorescence is used to mark the presence of podocytes. The urinary podocytes are identified by co localisation of podocyte-specific markers. The podocytes-to-creatinine ratios can also be calculated in order to semi quantify the cases of podocyturia.

A glomerular epithelial cell antigen, podocalyxin, has been found in the urine of patients with glomerular disease [13,14]. Hara, et al. [15] detected podocalyxin-marked podocytes in urinary sediments of patients with various forms of glomerulonephritis by immunoflorescence and reported that the number of podocytes in the urine was a direct indication of the degree of glomerular epithelial cell injury

References

1. Ayodele OE, Alebiosu CO, Salako BL (2004) Diabetic nephropathy: a review of the natural history, burden, risk factors and treatment. J Natl Med Assoc 96(11): 1445-1454.

2. Sicree R, Shaw J, Zimmet P (2006) Diabetes and impaired glucose tolerance. In: Gan D (Ed.), Diabetes Atlas, 3rd (Edn.), International Diabetes Federation, Kortrijik (Heule), Belgium, pp: 15-103.

3. Mohan V, Alberti KGMM (1997) Diabetes in the tropics. In: Alberti KGMM, Zimmet P, Defronzo RA, Keen H (Eds.), International Text Book of Diabetes Mellitus, 2nd (Edn.), John Wiley and Sons, Chichester, UK, pp: 171-187.

4. Samanta A, Burden AC, Feehally J, Walls J (1986) Diabetic renal disease: differences between Asian and white patients. Br Med J 293(6543): 366-367.

5. Mather HM, Chaturvedi N, Fuller JH (1998) Mortality and morbidity from diabetes in South Asians and Europeans: 11-year follow-up of the Southall Diabetes Survey, London, UK. Diabet Med 15(1): 53-59.

6. Chandie Shaw PK, Baboe F, van Es LA, van der Vijver JC, van de Ree MA, et al. (2006) South-Asian type 2 diabetic patients have higher incidence and faster progression of renal disease compared with Dutch-European diabetic patients. Diabetes Care 29(6): 1383-1385.

7. Vijay V, Snehalatha C, Ramachandran A, Viswanathan M (1994) Prevalence of proteinuria in non-insulin dependent diabetes. J Assoc Physicians India 42(10): 792-794.

8. Gaede P, Vedel P, Larsen N, Jensen GV, Parving HH, et al. (2003) Multifactorial intervention and cardiovascular diseas in patients with type 2 diabetes. N Engl J 348(5): 383-393.

9. Gaede P, Valentine WJ, Palmer AJ, Tucker DM, Lammert M, et al. (2008) Cost-effectiveness of intensified versus conventional multifactorial intervention in type 2 diabetes: results and projections from the Steno-2 study. Diabetes Care 31(8): 1510-1515.

10. Perkins BA, Ficociello LH, Ostrander BE, Silva KH, Weinberg J, et al. (2007) Microalbuminuria and the risk for early progressive renal function decline in type 1 diabetes. J Am Soc Nephrol 18(4): 1353-1361.

11. Yu D, Petermann A, Kunter U, Rong S, Shankland SJ, et al. (2005) Urinary podocyte loss is a more specific marker of ongoing glomerular damage than proteinuria. J Am Soc Nephrol 16(6): 1733-1741.

12. Nakamura T, Ushiyama C, Suzuki S, Hara M, Shimada N, et al. (2000) Urinary podocytes for the assessment

of disease activity in lupus nephritis. Am J Med Sci 320(2): 112-116.

13. Hancock WW, Atkins RC (1983) Monoclonal antobodies to human glomerular cells: a marker for glomerular epithelial cells. Nephron 33(2): 83-90.

14. Kerjaschki D, Poczewski H, Dekan G, Horvat R, Balzar E, et al. (1986) Identification of a major sialoprotein in the glycocalyx of human visceral glomerular epithelial cells. J Clin Invest 78(5): 1142-1149.

15. Hara M, Yamamoto T, Yanagihara T, Takada T, Itoh M, et al. (1995) Urinary excretion of podocalyxin indicates glomerular epithelial cell injuries in glomerulonephritis. Nephron 69(4): 397-403..