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Mini Review

Urinary Biomarkers for Early Diabetic Nephropathy in Everyday Practice

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Introduction

Diabetes Mellitus (DM) is a chronic disease that affects 6.4% of the adult population and is expected to rise to 552 million by 2030 [1]. This global increase in the prevalence of diabetes will inevitably lead to acceleration of micro- and macro vascular complications of diabetes. Diabetic Nephropathy (DN) is one the common micro vascular complication of diabetes mellitus- DM. It is a leading cause of end-stage renal disease in developed and developing countries and a contributor to significant morbidity and mortality in patients with diabetes [2]. Recent studies have demonstrated that the onset and course of DN can be ameliorated significantly by several interventions, but these interventions have their greatest impact if instituted at a very early stage in the course of the development of DN.

The last few years have provided a better insight into the complex pathophysiology of DN on a molecular level. Besides hemodynamic alterations such as hyper filtration and hyper perfusion, there is now clear evidence that these changes are only one aspect of a complex series of metabolic alterations caused by disturbed glucose homeostasis. All the kidney structure including glomerular endothelia, mesangial cells, podocytes, and tubular epithelia are affected in DN [3]. It is characterized by excessive accumulation of extracellular matrix with thickening of glomerular and tubular basement membranes and increased amount of mesangial matrix, which ultimately progresses to glomerulosclerosis and tubulointerstitial fibrosis [3,4]. Similar alterations occur in other organs, causing their damage, mainly cardiovascular, the leading cause of death in patients with DM. Even more, evidence support the hypothesis that early development of adverse vascular changes already existed prior to the development of overt diabetes i.e. in pre-diabetic conditions in both impaired fasting glucose and/or impaired glucose tolerance [5].

In order to detect early sign of DN all the available non-invasive techniques are in use. Some of them indirectly demonstrate the vascular and parenchymal renal damage by Doppler ultrasound such as quantification of arterial renal perfusion with Renal arterial Resistance Index (RRI) [6], detection of arterial stiffness by measurement of brachial-ankle pulse wave velocity (ba PWV), or carotid intimal-media thickness [7] as early markers of atherosclerosis. The others based on the urinary appearance of an excess of serum proteins that are not normally freely filtered through the glomerular. Many of these proteins (called biomarkers) in serum and urine have been studied that represent different mechanisms or structural damage in DN, based on which they have been classified as markers of glomerular injury, tubular injury, oxidative stress, inflammation, and endothelial damage [8,9]. They are listed in Table 1.

Many of these biomarkers are not specific for DN. Therefore, this paper aimed to review the most common urinary markers of glomerular injury associated with DN that are actually in use in the early diagnosis of DN.

Albuminuria

Albuminuria is the most widely used early clinical indicator of DN and has been recognized as a predictor of progression to ESKD in both type 1 and type 2 diabetes [10,11]. In addition, albuminuria is a marker of increased cardiovascular morbidity and mortality for patients with either type 1 or type 2 diabetes. Thus, the finding of albuminuria is an indication for screening for possible vascular disease and aggressive intervention to reduce all cardiovascular risk factors (e.g., lowering of LDL cholesterol, antihypertensive therapy, cessation of smoking, institution of exercise, etc.). In addition, there is some preliminary evidence to suggest that lowering of cholesterol may also reduce the level of proteinuria [12]. For practical purposes albuminuria is categorized into different classes—namely, normoalbuminuria (< 30 mg albumin per day or per g creatinine), albuminuria 30–300mg. Albumin per day or per g creatinine, and albuminuria >300 mg/24 h (previously macro albuminuria) [13]. The changes between these albuminuria states represent a hallmark of the progression or regression of disease [14]. More recent studies show that an increase in albuminuria, even within the range that is currently considered normal, indicates higher renal risk [15]. In patients with type 2 diabetes followed up for at least 5 years, higher albuminuria

Table 1: Urinary biomarkers of diabetic nephropathy that reflect kidney injury derived from ref 8, 9.

Glomerular damage	Albumin Trasferrin
Tubular damage	Alfa 1 microglobulin Retinol-binding protein Neutrophil gelatonase – associated lopocalin (NGAL) Kidney Injury Molecule (KIM 1) Cystatin C Glycosaminoglycan
Glomerular- tubular basement membrane	Type IV Collagen Type I Collagen fragments Matrix metalloproteinase 9 Fibronectin TGB Beta induced protein h3
Growth factors	Transforming growth factor 1 Connective tissue growth factor
Oxidative stress	8-hydroxy-2-deoxyguanosine 8-oxo-7,8-dihydro- deoxyguanosine
Inflammation	Soluble forms of receptors for Tumor Necrosis Factor alfa (1 and 2)
Intrarenal renin-angiotensin system	Renin

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at baseline was associated with a faster decline in renal function. Importantly, although within the normal range, a albuminuria of X10 mg/g in women or X5 mg/g in men was associated with a significantly greater rate of renal function decline [16]. Not only the albuminuria level itself but also changes in albuminuria (within 30-300 mg/g) over time predict renal or cardiovascular risk changes. In patients with type 2 diabetes and albuminuria 30-300 mg/g, it has been shown that those subjects in whom albuminuria declined by more than 50% over 2 years' follow-up had a subsequent renal function decline of -1.8ml/min per year. In contrast, in subjects without a 50% reduction in albuminuria long-term renal function decline was significantly larger, being -3.1ml/min per year [16].

On the other side, the absence of albuminuria or its progression to proteinuria does not signify that an individual patient is safe from a progressive decline in glomerular filtration rate. However, about 10-25 % of diabetic patients follow the "normoalbuminuria pathway" in which glomerular filtration rate progressively declines without worsening proteinuria [17]. In addition, moderate increases in albumin excretion are associated with a variety of other conditions, including obesity, posture, exercise, diet, smoking, gender, puberty, infection, and inflammation. Therefore, changes in albuminuria of 30-300 mg/g may reflect a modification of another disease process that possibly is not causally related to the development of kidney dysfunction [18]. All these indicate that albuminuria may not be an optimal marker for the early detection of DN.

Podocytes Injury

Glomerular epithelial cells (podocytes) directly cover the glomerular basement membrane and there is recent evidence that alterations in structure and function of podocytes (reduced number and podocytes density) occur early in DN before the onset of albuminuria [19-22]. Podocytes loss initiates the process of glomerulosclerosis by accelerating synechiae between podocytes and the glomerular basement membrane [23]. Also, altered expression of podocytes specific proteins such as synaptopodin [24], producing [25,26] and heparin have been described [27]. However, to date, quantification of podocytes injury, although strongly linked to the severity of albuminuria, has not been demonstrated to be an independent marker of GFR loss.

Cystatin C

According to the recent data, serum Cystitis C is a better marker of kidney function than serum creatinine concentration (sCr) and a significant predictor of progression to end-stage renal failure compared to estimated Glomerular Filtration Rate (GFR) based on sCr in adults [28]. Also, the filtered cystatin C is almost entirely reabsorbed in the proximal tubule, as with other low-molecular-weight proteins, with virtually no tubular secretion of cystatin C; as such, increases in urinary cystatin C, independent of serum cystatin C, suggest renal tubular damage rather than solely glomerular damage [29]. In addition, urinary Cystitis C was found increased with increasing degree of albuminuria and reached higher levels in macro albuminuria patients with DM. Moreover, increased urinary Cystitis C was associated with decline in GFR, particularly at the early stages of DN in patients with an eGFR of ≥60 mL/min/1.73 m^2, and that this was correlated with progression to CKD stage 3 or greater [30]. These findings suggest that urinary cystatin C may be a sensitive biomarker for early detection and prediction of kidney impairment in type 2 diabetic patients. However cystatin C is still unavailable in many laboratories.

Urinary Micro RNA (mi RNA)

In recent years, a class of naturally occurring short non coding RNA called micro RNA (mi RNA) has emerged as important post-transcriptional regulators of gene expression, capable of regulating numerous biological functions. Considerable attention has focused on the role of mi RNAs as mediators or biomarkers of diseases, including DN. Several mi RNAs in serum, plasma, urine and other body fluids, have now been identified, which may be up regulated or down regulated in the progression of DN, and their detection in very early stages may be of value in predicting the disease course. Argyropoulos et al. identified a set of 27 differentially expressed mi RNAs in urine samples from patients with type 1 diabetes in different stages of DN whose renal outcomes had been ascertained after >20 years of follow-up [31]. Further studies on a larger diabetic population are needed to characterize mi RNAs that are highly specific to DN in order to understand their role in the pathogenesis of diabetic nephropathy.

Urine Proteomics

Urine proteome analysis is rapidly emerging as a tool for facilitating the diagnosis and prognosis of disease states and the technology of high resolution protein separation by capillary electrophoresis together with mass spectrometry allows enables an unbiased search for potential new biomarkers. Recent studies using this approach identified a set of biomarkers for DN could distinguish individuals with type 1 diabetes from those with type 2 diabetes. Also, these studies identified urinary proteomic biomarkers that are distinct for patients who had albuminuria and diabetes and who subsequently progressed toward overt DN, and allow the early detection of DN, or its discrimination from other non diabetic CKD or the prediction of normoalbuminuria diabetic patients prone to develop DN [32].

Until now, the main limitations of the newer molecular technologies, such as quantitative PCR to detect urine mi RNAs and urine proteomics for their use are: they are expensive and currently available in rare laboratories.

Conclusion

Over the last few decades, there has been tremendous interest in the discovery of biomarkers of DN that allow for the detection of early stages of DN and progressive kidney function decline in diabetic patients. Usually these markers tested in small cross sectional studies, and are not applicable in daily practice. However, it is still difficult to determine which patients with diabetes will develop DN and progress to a state of declining glomerular filtration rate and the development of end stage renal disease. By getting the better marker/ s, the current standard for detection and prediction of diabetic nephropathy and cardiovascular risk remains albuminuria having in mind its limitations.

References

1. International Diabetes Federation: Diabetes Atlas Fifth Edition, International Diabetes Federation. Belgium: Brussels. 2011.

2. Gariani K, de Seigneux S, Pechère-Bertschi A, Philippe J, Martin PY. [Diabetic nephropathy: an update]. Rev Med Suisse. 2012; 8: 473-479.

3. Kanwar YS, Wada J, Sun L, Xie P, Wallner EI, Chen S, et al. Diabetic nephropathy: mechanisms of renal disease progression. Exp Biol Med (Maywood). 2008; 233: 4-11.

4. Lehmann R, Schleicher ED. Molecular mechanism of diabetic nephropathy. Clin Chim Acta. 2000; 297: 135-144.

5. Marco Matteo Ciccone, Pietro Scicchitano, Matteo Cameli, Annagrazia Cecere, Francesca Cortese, Ilaria Dentamaro, et al. on behalf of the Working Group on Hypertension, Prevention & Rehabilitation of the Società Italiana di Cardiologia. Endothelial Function in Pre-diabetes, Diabetes and Diabetic Cardiomyopathy: A Review. J Diabetes Metab. 2014; 5: 364.

6. Ciccone MM, Iacoviello M, Gesualdo L, Puzzovivo A, Antoncecchi V, Doronzo A, et al. The renal arterial resistance index: a marker of renal function with an independent and incremental role in predicting heart failure progression. Eur J Heart Fail. 2014; 16: 210-216.

7. Nakamura A, Shikata K, Hiramatsu M, Nakatou T, Kitamura T, Wada J, et al. Serum interleukin-18 levels are associated with nephropathy and atherosclerosis in Japanese patients with type 2 diabetes. Diabetes Care. 2005; 28: 2890-2895.

8. Matheson A, Willcox MD, Flanagan J, Walsh BJ. Urinary biomarkers involved in type 2 diabetes: a review. Diabetes Metab Res Rev. 2010; 26: 150-171.

9. Lee SY, Choi ME. Urinary biomarkers for early diabetic nephropathy: beyond albuminuria. Pediatr Nephrol. 2014.

10. Perkins BA, Ficociello LH, Roshan B, Warram JH, Krolewski AS. In patients with type 1 diabetes and new-onset microalbuminuria the development of advanced chronic kidney disease may not require progression to proteinuria. Kidney Int. 2010; 77: 57-64.

11. Adler AI, Stevens RJ, Manley SE, Bilous RW, Cull CA, Holman RR, UKPDS GROUP. Development and progression of nephropathy in type 2 diabetes: the United Kingdom Prospective Diabetes Study (UKPDS 64). Kidney Int. 2003; 63: 225-232.

12. American Diabetes Association- position statement. Nephropathy in diabetes. Diabetes Care. 2004; 27: 79-83.

13. American Diabetes Association: Clinical practice recommendations. Diabetes Care. 2014; 37.

14. Gansevoort RT, Matsushita K, van der Velde M, Astor BC, Woodward M, Levey AS, et al. Lower estimated GFR and higher albuminuria are associated with adverse kidney outcomes. A collaborative meta-analysis of general and high-risk population cohorts. Kidney Int. 2011; 80: 93-104.

15. Babazono T, Nyumura I, Toya K. Higher levels of urinary albumin excretion within the normal range predict faster decline in glomerular filtration rate in diabetic patients. Diabetes Care. 2009; 32: 1518–1520.

16. Araki S, Haneda M, Koya D, Hidaka H, Sugimoto T, Isono M, et al. Reduction in microalbuminuria as an integrated indicator for renal and cardiovascular risk reduction in patients with type 2 diabetes. Diabetes. 2007; 56: 1727-1730.

17. Macisaac RJ, Jerums G. Diabetic kidney disease with and without albuminuria. Curr Opin Nephrol Hypertens. 2011; 20: 246-257.

18. MacIsaac RJ, Jerums G, Cooper ME. New insights into the significance of microalbuminuria. Curr Opin Nephrol Hypertens. 2004; 13: 83-91.

19. White KE, Bilous RW, Marshall SM, E Nahas M, Remuzzi G, Piras G, et al. Podocyte number in normotensive type 1 diabetic patients with albuminuria. Diabetes. 2002; 51: 3083-3089.

20. Steffes MW, Schmidt D, McCrery R, Basgen JM, International Diabetic Nephropathy Study Group. Glomerular cell number in normal subjects and in type 1 diabetic patients. Kidney Int. 2001; 59: 2104-2113.

21. Meyer TW, Bennett PH, Nelson RG. Podocyte number predicts long-term urinary albumin excretion in Pima Indians with Type II diabetes and microalbuminuria. Diabetologia. 1999; 42: 1341-1344.

22. Wolf G, Chen S, Ziyadeh FN. From the periphery of the glomerular capillary wall toward the center of disease: podocyte injury comes of age in diabetic nephropathy. Diabetes. 2005; 54: 1626-1634.

23. Weil EJ, Lemley KV, Mason CC, Yee B, Jones LI, Blouch K, et al. Podocyte detachment and reduced glomerular capillary endothelial fenestration promote kidney disease in type 2 diabetic nephropathy. Kidney Int. 2012; 82: 1010-1017.

24. Turk T, Leeuwis JW, Gray J, Torti SV, Lyons KM, Nguyen TQ, et al. BMP signaling and podocyte markers are decreased in human diabetic nephropathy in association with CTGF over expression. J Histochem Cytochem. 2009; 57: 623-631.

25. Baelde HJ, Eikmans M, Lappin DW, Doran PP, Hohenadel D, Brinkkoetter PT, et al. Reduction of VEGF-A and CTGF expression in diabetic nephropathy is associated with podocyte loss. Kidney Int. 2007; 71: 637-645.

26. Wu Y, Dong J, Yuan L, Liang C, Ren K, Zhang W, et al. Nephrin and podocin loss is prevented by mycophenolate mofetil in early experimental diabetic nephropathy. Cytokine. 2008; 44: 85-91.

27. Doublier S, Salvidio G, Lupia E, Ruotsalainen V, Verzola D, Deferrari G, et al. Nephrin expression is reduced in human diabetic nephropathy: evidence for a distinct role for glycated albumin and angiotensin II. Diabetes. 2003; 52: 1023-1030.

28. Menon V, Shlipak MG, Wang X, Coresh J, Greene T, Stevens L, et al. Cystatin C as a risk factor for outcomes in chronic kidney disease. Ann Intern Med. 2007; 147: 19-27.

29. Herget-Rosenthal S, Feldkamp T, Volbracht L, Kribben A. Measurement of urinary cystatin C by particle-enhanced nephelometric immunoassay: precision, interferences, stability and reference range. Ann Clin Biochem. 2004; 41: 111–118.

30. Kim SS, Song SH, Kim IJ, Jeon YK, Kim BH, Kwak IS, et al. Urinary cystatin C and tubular proteinuria predict progression of diabetic nephropathy. Diabetes Care. 2013; 36: 656-661.

31. Argyropoulos C, Wang K, McClarty S, Huang D, Bernardo J, Ellis D, et al. Urinary microRNA profiling in the nephropathy of type 1 diabetes. PLoS One. 2013; 8: 54662.

32. Rossing K, Mischak H, Dakna M, Zürbig P, Novak J, Julian BA, et al. Urinary proteomics in diabetes and CKD. J Am Soc Nephrol. 2008; 19: 1283-1290.

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