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Review Article

Predicting Diabetic Nephropathy Risk in Children: Microalbuminuria Versus Novel Glomerular Biomarkers

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Abstract

The present review aims to compare the abilities of microalbuminuria and other novel glomerular biomarkers in predicting diabetic nephropathy (DN) risk in diabetic pediatric patients.

Although overt DN and end stage renal disease (ESRD) complicating type 1 diabetes mellitus (T1DM) or type 2 diabetes mellitus (T2DM) are rare during childhood or adolescence, some previous reports have confirmed the occurrence of overt DN in these age groups. The use of microalbuminuria is the gold-standard method for predicting the onset of DN, but its predictive ability is limited. Thus, there is a paradigm shift to other novel urinary biomarkers which hold promise as more sensitive diagnostic tools for earlier detection of DN and prediction of progression to ESRD.

In fact, several biomarkers of glomerular or tubular dysfunction can precede microalbuminuria, suggesting that microalbuminuria is only present when significant renal damage has occurred. Glomerular biomarkers applicable to both T1DM and T2DM include transferrin, tumour necrosis factor-α (TNF-α), type-IV collagen and fibronectin, while N-acetyl β-glucosaminidase (NAG) and laminin are seen in only T2DM. All of them predict DN risk but with varying predictive abilities.

Remarkably, transferrin, TNF-α, and type-IV collagen appear in urine before microalbuminuria, although transferrinuria has low specificity for DN. Despite the ability offibronectin, NAG and laminin to predict DN risk, these biomarkers need validation by further studies.

Keywords: Microalbuminuria, Diabetic nephropathy, Glomerular biomarkers

Introduction

Diabetic nephropathy (DN) is one of the microvascular complications seen in both Type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM); T1DM commonly occurs in childhood or adolescence although the prevalence of T2DM is also rising globally in these age groups [1]. It may result in increased morbidity, as well as mortality from subsequent end stage renal disease (ESRD). Overt DN and ESRD complicating either type of diabetes mellitus are rare during childhood or adolescence, but diabetic kidney disease in susceptible patients almost certainly commences soon after the onset of diabetes and may rapidly progress during adolescence, leading to microalbuminuria or incipient DN [1]. In fact, some previous reports have confirmed the occurrence of overt DN in both childhood and adolescence [2-4].

Early detection of DN is therefore critical in improving the clinical management and outcome of diabetes mellitus in children. Despite the use of microalbuminuria as the gold-standard method for predicting the onset of DN, its predictive ability is limited. This observation has necessitated the search for other novel urinary biomarkers which hold promise as more sensitive diagnostic tools for earlier detection of diabetic kidney disease and prediction of progression to ESRD [5]. For instance, not all diabetic subjects with microalbuminuria will end up with ESRD [6, 7]. In fact, about one third of them may actually have normoalbuminuria [8], while several biomarkers of glomerular or tubular dysfunction can precede microalbuminuria, suggesting that microalbuminuria is only present when significant renal damage has occurred [9].

Furthermore, recent evidence reveals that a remarkable number of patients with macroalbuminuria or overt DN can revert to normoalbuminuria, while the concept of 'non-albuminuric' DN is also well-documented: underscoring the fact that diabetic patients can actually present with a reduced GFR without progressing from normo-to macroalbuminuria [10].

The present review aims to compare the abilities of microalbuminuria and other novel glomerular biomarkers in predicting DN risk in diabetic pediatric patients.

Microalbuminuria as a predictor of DN risk

Increased urinary albumin excretion (UAE) is a well-established biomarker of glomerulopathy [9]. Different degrees of UAE can occur: normoalbuminuria, microalbuminuria and macroalbuminuria. Normoalbuminuria refers to UAE of less than 30 mg/day or 20 µg/min whereas microalbuminuria and macroalbuminuria refer to UAE of 30-300 mg/day or 20-200 µg/min, and above 300 mg/day or 200 µg/min respectively [11].

Microalbuminuria is a risk factor for chronic kidney disease

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(CKD) and ESRD, as well as a powerful predictor of cardiovascular morbidity and mortality in diabetic subjects [12-14]. Because baseline albuminuria is the strongest predictor of ESRD and cardiovascular morbidity in T2DM [15,16], the American Diabetes Association recommended screening with annual UAE in all patients with T2DM, commencing at the time of diagnosis [17].

Glomerular hyperfiltration occurs in the early stage of DN and results in microalbuminuria. As the disease evolves, macroalbuminuria sets in and is followed by deterioration in renal function which may eventually require renal replacement therapy (RRT) [6]. Microalbuminuria is thus a strong predictor of DN risk and progression, as well as a predictor of cardiovascular disease risk in T1DM and T2DM [18] (Table 1). Previously, it was projected that 80% of patients with T1DM who have microalbuminuria will end up with overt nephropathy or macroalbuminuria within 10-15 years: 50% of whom will develop ESRD within 10 years and 75% within 20 years, if there are no appropriate therapeutic interventions like strict glycemic control [19]. However, a report now indicates that the rate of progression from microalbuminuria to macroalbuminuria over a 5- to 10- year period is about 15 to 30%, although as high as 45% in patients with less than 15 years of diabetes duration but much lower than the previously estimated figure [20].

Novel glomerular biomarkers as predictors of DN risk

During the evolution of DN, the functional derangement and structural remodeling of the kidney, initiated by hyperglycemic injury, are related to changes in several cellular events and activation of signaling pathways [21]. The identified activated pathways include: a hemodynamic pathway involving the renin-angiotensin-aldosterone system (RAAS) and urotensin system; profibrotic and inflammatory cytokines; several kinases, such as protein kinase C (PKC) and the Janus kinase (JAK) pathway; and oxidative stress mediators such as nicotinamide adenine dinucleotide phosphate oxidase (NADPH oxidase) [22].

These pathways interact by complex molecular mechanisms which result in the main pathogenic components of DN: renal fibrosis, mesangial expansion, glomerular hypertrophy, oxidative stress and tubular inflammation [22]. Because these pathophysiologic mechanisms contribute to the development of DN, biomarkers of glomerular injury, tubular injury, inflammation, and oxidative stress can thus form part of a biomarker panel for the prediction of the disease [23].

Apart from albuminuria, other novel glomerular biomarkers of DN are well documented. These include transferrin, tumour necrosis factor-α (TNF-α), type IV collagen, fibronectin, N-acetyl β-glucosaminidase (NAG), and laminin. Some of them apply to both T1DM and T2DM, and are better predictors of DN risk as they appear in urine prior to microalbuminuria, while others need validation by further studies (Table 1).

First, some authors report that prior to the onset of microalbuminuria, urinary transferrin excretion appeared higher in diabetic subjects than in their healthy controls [24-26]. Other investigators also suggest that urinary transferrin is a more sensitive biomarker of glomerular injury in diabetes mellitus [27-29]. The reasons are not far-fetched: for instance, diabetic patients are more likely to present with urinary transferrinuria than with albuminuria, while albumin/transferrin ratio is significantly lower in these patients who present with normoalbuminuria and microalbuminuria than in those who have macroalbuminuria [30]. Furthermore, transferrinuria predicts the development of microalbuminuria in patients with T2DM who have normoalbuminuria [31,32]. Finally, some reports indicate that in diabetic patients with macroalbuminuria or overt DN, urinary transferrin excretion is positively correlated with UAE [33-35]. Nevertheless, urinary transferrin excretion has low specificity for DN as the biomarker is also reportedly excreted in other glomerulopathies [36].

Second, elevated urinary TNF-α and levels in renal interstitial fluid have been observed to precede a significantly increased albuminuria in experimental murine models [37]. In addition, findings from clinical studies indicate a direct and significant relationship between serum TNF-α level and urinary protein excretion in diabetic patients with normal renal function and microalbuminuria, as well as in patients with overt nephropathy and ESRD [38,39]. The prospect of employing this cytokine as a biomarker for predicting DN is strongly supported by these findings: urinary TNF-α levels that are raised in diabetic patients who have increased UAE, and the significant rise of urinary TNF-α excretion which occurs as DN progresses [40]. Despite these unique features, the biomarker is not used in the routine evaluation of DN because dysregulation of its production has also been implicated in other diseases such as Alzheimer's disease [41], cancer [42], psoriasis [43], and inflammatory bowel disease [44]. This observation goes to underscore its low specificity for DN.

Third, a more elevated urinary levels of type IV collagen have been documented in patients with diabetes mellitus in comparison to their controls, and even in subjects with normoalbuminuria [45-48]: highlighting the fact that type IV collagen could be an early predictor of DN. In addition, urinary type IV collagen has also been found to show more sensitivity than albuminuria in the detection of renal damage in patients with T2DM [48], although other investigators have reported that as many as one-third of patients with microalbuminuria do not have increased urinary type IV collagen excretion [49].

Another glomerular biomarker which may serve as a useful biomarker of DN is urinary fibronectin, but its relevance compared to albuminuria needs to be validated by further studies. Nevertheless, urinary excretion of fibronectin has been noted to be higher in diabetic patients compared to their controls, with a significant difference observed only in patients with macroalbuminuria [50,51]. Its possible predictive role in DN is further supported by the findings of its higher excretion in diabetic patients with microalbuminuria than in those with normoalbuminuria [50]; the correlation of its urinary levels with the evolution of biopsy-proven glomerular diffuse lesions [52]; as well as the correlation of its degradation products with UAE [53].

Finally, urinary laminin and urinary NAG have also been reported as potential predictors of DN risk in T2DM [54, 55]. Whereas further studies are required to determine the relevance of urinary laminin as a biomarker of the disease, urinary NAG has been shown to detect DN at an early stage, as its level is elevated before the appearance of microalbuminuria. However, several studies have also shown that urinary laminin excretion is higher in diabetic patients in comparison to their healthy controls, even prior to the onset of microalbuminuria

Table 1: Microalbuminuria versus some glomerular biomarkers: predictive ability for DN risk.

Glomerular biomarker	Type 1 diabetes mellitus	Type 2 diabetes mellitus	Predictive ability
Microalbuminuria	+	+	-Predicts DN risk and progression -Predicts cardiovascular disease risk
Urinary transferrin	+	+	-Predicts DN risk† -Poor specificity for DN
Urinary TNF-α	+	+	-Predicts DN risk and progression†
Urinary type-IV collagen	+	+	-Predicts DN risk†
Urinary fibronectin	+	+	-Predicts DN risk‡
Urinary NAG		+	-Predicts DN risk†
Urinary laminin		+	-Predicts DN risk‡

TNF-α: Tumor Necrosis Factor-α; NAG, N-acetyl β-Glucosaminidase; DN: Diabetic Nephropathy
†: Appears in urine before microalbuminuria; ‡: Needs validation by further studies

[54-57]. To buttress the discriminatory role of urinary laminin in diabetic and nondiabetic kidney disease, it has been reported that patients with T2DM who show evidence of nephropathy present with significantly higher laminin/albumin ratio in comparison to patients with nondiabetic nephropathy [54].

Other glomerular markers worthy of note include nephrin, interleukin 8 (IL-8), interferon gamma-induced protein (IP-10), MCP-1 (monocyte chemoattractant protein 1), granulocyte colony-stimulating factor (G-CSF), eotaxin, and RANTES (regulated on activation, normal T cell expressed and secreted) or CCL-5. Nephrin is a slit diaphragm protein whose expression is reduced in late proteinuric phase of experimental DN, suggesting that reduced nephrin expression may be a determinant of glomerular hyperpermeability in DN [58,59]. Although there are other proteins involved in the structure of the epithelial podocyte and specifically the slit diaphragm, nephrin appears to play a critical role in preventing proteinuria through the glomerular barrier [60]. Thus, an inverse relationship exists between albuminuria and the measured expression of nephrin in a diabetic kidney. IL-18 is a proinflammatory cytokine secreted from mononuclear cells; its serum concentration is thought to be a strong predictor of mortality in patients with cardiovascular diseases because of underlying microinflammation. Serum and urinary IL-18 levels have been reported to correlate positively with albumin excretion rate, while its serum levels also correlates positively with carotid intima-media thickness in patients with T2DM, and thus may be a predictor of DN progression, as well as cardiovascular diseases [61,62]. IP-10 and MCP-1 are other proinflammatory cytokines whose serum levels have been shown to be significantly elevated in subjects with T2DM [62]. Moreover, serum and urinary levels of these two proinflammatory cytokines were found to be positively correlated with albumin excretion rate and intima-media thickness, suggesting thatmicroinflammation, may be a common risk factor for DN and atherosclerosis in T2DM [62]. Serum and urinary G-CSF levels are also reportedly elevated in the early stages of DN [63], while urinary RANTES (or CCL-5) and eotaxin excretion rates were noted to be significantly higher in hyperfiltering than in normofiltering T1DM subjects [64]. Like RANTES which is a chemotactic cytokine, eotaxins are a chemotactic cytokine subfamily of eosinophil chemotactic proteins consisting of eotaxin-1 (CCL-11), eotaxin-2 (CCL-24) and eotaxin-3 (CCL-26) [65]. The high urinary levels of eotaxin and RANTES, from hyperfiltration in the diabetic kidney, are a reflection of high intraglomerular pressure which causes renal inflammation: a component of DN [64].

In summary, microalbuminuria is different from other novel glomerular biomarkers by its ability to predict DN risk and progression in both T1DM and T2DM, as well as to predict cardiovascular disease risk. In contrast, urinary transferrin has the advantage of predicting DN risk earlier than microalbuminuria in both forms of diabetes mellitus but has the disadvantage of poor specificity for DN. Similarly, urinary TNF-α and type-IV collagen not only predict DN risk and progression in T12DM and T2DM but also appear in urine before microalbuminuria. Urinary fibronectin exhibits the same characteristics as urinary TNF-α and type-IV collagen but its predictive ability for DN risk needs further validation. However, urinary NAG and laminin predict DN risk in only T2DM: an ability that also requires confirmation (Table 1).

Conclusion

Despite the role of microalbuminuria as the gold-standard biomarker for predicting DN risk and progression to ESRD in T1DM and T2DM, other glomerular biomarkers are proving to be better predictors because of the limitations of microalbuminuria. For instance, not all diabetics with microalbuminuria will end up with ESRD, while a substantial number of them may actually have normoalbuminuria. Better still, several biomarkers of glomerular dysfunction can precede microalbuminuria which tends to suggest that microalbuminuria can only occur when significant renal damage has occurred. Although several of these novel glomerular markers have been demonstrated as comparatively reliable predictors of DN risk, some of them still require validation by further studies.

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