Published in final edited form as:

Curr Opin Endocrinol Diabetes Obes. 2014 August ; 21(4): 279–286. doi:10.1097/MED.0000000000000074.

Early Diabetic Nephropathy in Type 1 Diabetes – New Insights

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Abstract

Purpose of review—Despite improvements in glycemic and blood pressure control in patients with T1D, diabetic nephropathy (DN) remains the most common cause of chronic kidney disease worldwide. A major challenge in preventing DN is the inability to identify high-risk patients at an early stage, emphasizing the importance of discovering new therapeutic targets and implementation of clinical trials to reduce DN risk.

Recent findings—Limitations of managing patients with DN with renin angiotensin aldosterone system (RAAS) blockade have been identified in recent clinical trials, including the failure of primary prevention studies in T1D and the demonstration of harm with dual RAAS blockade. Fortunately, several new targets, including serum uric acid, insulin sensitivity, vasopressin and sodium-glucose cotransporter-2 inhibition are promising in the prevention and treatment of DN.

Summary—DN is characterized by a long clinically silent period without signs or symptoms of disease. There is an urgent need for improved methods of detecting early mediators of renal injury, to ultimately prevent initiation and progression of DN. In this review, we will focus on early DN and summarize potential new therapeutic targets.

Keywords

Early diabetic nephropathy; glomerular filtration rate; serum uric acid; insulin sensitivity; sodium-glucose cotransporter-2

INTRODUCTION

Diabetic nephropathy (DN) is the leading cause of mortality in type 1 diabetes (T1D) (1–3). Microalbuminuria, generally recognized as the earliest clinical phenotype of DN, has a cumulative life-time incidence of approximately 50% in T1D, and develops at a rate of

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No conflicts of interest

around 2 – 3 % annually (4). A quarter of T1D patients with DN progress to ESRD (5). In fact, the 2011 US Renal Data System showed that DN accounted for 44.5% of all cases of ESRD in the United States in 2009, making it the most common cause of ESRD (6). DN is also an important risk factor for coronary artery disease (CAD) (7–9) and overall mortality (7, 10). The natural history of DN is characterized by a long silent period without overt clinical signs and symptoms of nephropathy. This is further complicated by under-treatment in adolescents with T1D, as recently shown by data from the T1D Exchange registry which reported that only a third of subjects <20 years with a clinical diagnosis of microalbuminuria received ACE inhibitors (ACEi)/angiotensin-receptor blockers (ARB) (11).

By the time $GFR < 60 mL/min/1.73m^2$ manifest, approximately 50% of renal function is lost, renal structural changes are well established and are usually refractory to therapeutic strategies including improved blood pressure and glycemic control (12, 13). Current therapeutic strategies may slow but do not prevent the progression of DN (4, 14). Earlier identification of GFR decline would allow interventions to decrease the rate of GFR loss and prolong the time to development of end stage renal disease (ESRD) (Figure 1).

Although there is strong evidence showing benefit of glycemic and blood pressure control in preventing microvascular complications in T1D (1, 15, 16), optimal control does not abolish the risk. In fact, DN outcomes have not changed significantly and continue to be a major concern for endocrinologists and nephrologists caring for patients with T1D (1, 2).

Managing DN in patients with T1D has been further complicated by disappointing results of renin-angiotensin-aldosterone system (RAAS) inhibitor trials, including the failure of primary prevention studies (The Renin Angiotensin System Study [RASS]) (17) and the demonstration of harm with dual RAAS blockade (18). Furthermore, once promising renoprotective strategies for DN including protein kinase C- β antagonists, selective endothelin receptor-A antagonists, and the Nrf2 modulator bardoxolone have resulted in disappointing clinical trial results (19–21).

It is therefore important to identify novel and modifiable risk factors that contribute to the development and progression of early DN (22). Understanding these risk factors may enable us to identify subjects at high risk of early DN and intervene at a time when the renal lesions might be responsive to therapy. Accordingly, in this review, we examine the current evidence addressing novel mediators and therapeutic targets in T1D to prevent DN (Table 1).

Early diabetic nephropathy

In the conventional paradigm of DN, progressive pathological changes develop over a long silent period without evidence of proteinuria, hypertension or impaired GFR (34). In this paradigm, during the clinically silent phase, a significant proportion of patients exhibit renal hyperfiltration secondary to elevated intraglomerular pressure resulting in a glomerular injury, followed by microalbuminuria and progressive GFR decline, eventually resulting in ESRD (35). Renal hyperfiltration is the earliest hemodynamic abnormality seen in diabetes, and has been linked with an increased risk of DN in many, but not all, studies, reflected by microalbuminuria and declining GFR (35). In addition to controversy around hyperfiltration

in the pathogenesis of DN, hyperfiltration remains difficult to detect clinically with current GFR estimating equations. The appearance of microalbuminuria is usually the earliest clinical sign of DN, but the paradigm of early DN in T1D has been further questioned over the past few years after the demonstration that microalbuminuria does not necessarily imply progressive nephropathy, and may in fact regress to normoalbuminuria (Figure 2) (36, 37). Early progressive renal decline defined as an annual eGFR decline greater than 3.3% (38) or 3mL/min/1.73m² (39, 40) has been shown to occur prior to the onset of microalbuminuria (38), and thought to be more predictive of progression to impaired renal function and eventual ESRD than microalbuminuria (38, 41). Unfortunately, current understanding of determinants implicated in early GFR loss is limited (41). Recently identified modifiable biomarkers, including serum uric acid (23, 24) and insulin sensitivity (26), may provide insight into the design of more effective programs for preventing DN in T1D, reflected either by microalbuminuria and/or early GFR decline.

Current methods of identifying early DN

The American Diabetes Association and International Society of Nephrology recommend annual screening for albuminuria and also measurement of estimated glomerular filtration rate (eGFR) to identify and monitor DN (42, 43). Microalbuminuria is defined as albumin excretion rate (AER) 20ug/min or albumin creatinine ratio (ACR) 30mg/g, and have both been shown to be associated with expansion of the glomerular basement membrane in T1D (44). The most state-of-the-art equations to estimate GFR for adults are the three recently published CKD-EPI equations: CKD-EPI Creatinine, CKD-EPI Cystatin C and CKD-EPI Creatinine and Cystatin C (45), and for children and adolescents are the CKiD Creatinine and Cystatin C equations (46). However, when eGFR is >90mL/min/1.73m², concordance between CKD-EPI cystatin C eGFR and CKD-EPI creatinine eGFR has been reported to be as low as 56% (47, 48). These results echo the discordance between eGFR by CKD-EPI creatinine and CKD-EPI cystatin C reported by Inker et al in subjects with normal-to-high eGFR (45).

Overall, CKD-EPI cystatin C eGFR is considered to be less biased by age and weight compared to creatinine-based measurements, and correlates more closely with direct measures of GFR over a wide spectrum of plasma glucose levels compared to creatinine based measures in experimental studies (40, 49). These observations suggest that cystatin C more accurately reflects measured GFR in subjects with T1D, favoring its use as an estimate of GFR in this population. Moreover, GFR estimated by cystatin C appears to better predict micro- and macrovascular complications in subjects with T1D compared to creatinine-based equations (9, 26, 50, 51). Cystatin C more accurately detected rapid GFR decline than creatinine-based measurements in T1D subjects with normal renal function (51). Rapid GFR decline estimated by cystatin C is also associated with a higher risk for cardiovascular complications and mortality than creatinine based GFR estimated (39, 47). Furthermore, Skupien et al demonstrated that GFR staging with eGFR_{CYSTATIN C} is superior for predicting ESRD and mortality compared to eGFR_{BOTH}, which might suggest that serum creatinine counters the predictive effect of serum cystatin C (52). Finally, Shlipak et al demonstrated that the use of cystatin C compared to creatinine strengthens the association between eGFR and risk of death and ESRD in 11 diverse general-population studies (53).

Despite the possible superiority of cystatin C vs. creatinine, estimates of GFR by both serum creatinine and cystatin C, like measurements of urinary albumin excretion, remain imperfect (9, 54, 55). The CKD-EPI eGFR equation has not been validated in people with eGFR >80 mL/min/1.73m², and it is associated with greater variability when eGFR >60 mL/min/1.73m² (45). However, by the time eGFR is <60 mL/min/1.73m² almost half of renal function has already been lost (56) (Figure 3).

Improved methods to easily and accurately measure GFR as well as changes in renal function in the normal and hyperfiltration range are therefore needed. Gold-standard measures of GFR with iohalamate, iothexol or inulin clearance in people with T1D are impractical and not routinely performed in clinical practice. Recently, a practical method of measuring GFR by iothexol clearance using dried capillary blood spots has been developed in non-diabetics (57, 58), which is ideally suited for people with T1D (59) in whom early detection of DN is imperative to prevent early morbidity and mortality (2, 60), which may hopefully allow the early identification of subjects at increased risk of early DN. Simultaneous hyperglycemia has an effect on renal hemodynamics and a difference of 4–6 mmol/L versus 9–11 mmol/L is associated with a 15–18 mL/min/1.73m² difference in GFR measured by inulin (49). Furthermore, we've demonstrated that simultaneous blood glucose has an independent positive effect on eGFR by cystatin C, which could bias the accurate detection of early diabetic nephropathy (48, 61). Accounting for ambient blood glucose could improve intra-individual precision in GFR change over time in people with T1D.

Another promising method of identifying early DN is through the use of urinary proteomic techniques. Since many urinary proteomic markers remain stable for long enough to perform reliable polypeptide analysis, the emerging field of proteomics has given some recent insight into the development of practical and non-invasive novel biomarkers (62). The association between urinary proteomics and DN is well recognized (63–65, 32, 66). Both acute hyperglycemia and renal hyperfiltration are associated with increased urinary excretion of inflammatory cytokines/chemokines (e.g. IL-6, IL-8, IP-10, MCP-1) in T1D which may contribute to DN (67, 68), and in particular progressive renal decline (32, 33). In previous studies, we have also identified urinary biomarker panels for DN and coronary artery disease (CAD) in subjects with T1D in CACTI (66).

Novel targets for the prevention of DN

Inhibition of the renin-angiotensin-aldosterone system (RAAS) has been the mainstay therapy for the prevention and treatment of DN. However, the renoprotective role of ACEi/ARBs has recently been challenged by data from the Renin Angiotensin System Study (RASS) which demonstrated that early, primary prevention with ACE inhibition or angiotensin receptor blockade does not modify DN progression in adults with T1D (17). Moreover, large clinical trials including ONTARGET, ALTITUDE and VA-NEPHRON-D, have failed to demonstrate improved renal outcomes in diabetic subjects with dual RAAS inhibition using combined ACEi and ARB or using direct renin inhibitor-related regimens (18). Other classes of agents including protein kinase C-beta antagonists, selective endothelin receptor (A) antagonists and anti-oxidants such as bardoxolone have been associated with disappointing clinical trial results (19, 20).

There is therefore a need for novel methods of identifying and treating patients at high risk of developing DN at an early stage to prevent progression. Multiple studies have linked serum uric acid (SUA) levels to DN development and accumulating data have suggested that lowering SUA prevents renal function loss in animal models of diabetes and in patients with type 2 diabetes (23, 69, 70). To determine the role of SUA lowering in patients with T1D, the multi-center double-blind randomized clinical trial “Preventing Early Renal Function Loss - PERL”, will test the hypothesis that lowering SUA with allopurinol will prevent GFR decline measured by iohexol (24) (Table 1). An additional study design innovation in PERL is the use of GFR (measured by iohexol) as the study end point allowing for assessment of therapy earlier in the pathophysiologic pathway.

A second potential therapeutic target relates to insulin sensitivity. Reduced insulin sensitivity is well documented in both adolescents and adults with T1D, and is thought to contribute both to the initiation and progression of macro- and microvascular complications (71). We have previously demonstrated that insulin sensitivity predicts development of microalbuminuria and rapid eGFR decline by cystatin C over 6 years in patients with T1D (26), similar to data in the Epidemiology of Diabetes Complications study (72). Various hypotheses exist to explain reduced insulin sensitivity in T1D (73, 74), but we have shown that only 6% of the variance of insulin sensitivity is explained by SUA in adults with T1D, in contrast to 39% in non-diabetic adults (75). The absence of a clinically significant association between SUA and reduced insulin sensitivity in T1D may suggest that SUA and reduced insulin sensitivity are independent mediators of vascular pathology in T1D. Despite the findings from the BARI-2D study (76) which showed no benefit of insulin sensitizing strategy on DN in subjects with type 2 diabetes, modification of insulin sensitivity holds promise as a therapeutic target to reduce vascular complications in T1D, since both life style changes (diet and exercise) and drugs such as metformin can improve insulin sensitivity. The Metformin Vascular Adverse Lesions in Type 1 Diabetes (REMOVAL) trial was therefore designed to improve insulin sensitivity in T1D (NCT01483560) (Table 1).

Sodium glucose co-transporter 2 (SGLT2) inhibitors also hold promise as a therapeutic target to prevent progression of DN in T1D, after it was shown that SGLT2 inhibition with empagliflozin reduces HbA1c and significantly attenuates renal hyperfiltration to near normal GFR levels in patients with uncomplicated T1D (28) (Figure 4). Patients with T1D exhibited significant weight loss, HbA1c reductions and a decline in blood pressure (77–79, 29). In *post-hoc* analyses of clinical trials, this class of agents acutely reduces eGFR over 3–4 weeks, followed by preservation of renal function over 2 years, and also reduces albuminuria, suggesting a protective decline in intraglomerular pressure (29), similar to data from GFR inulin studies (28).

Emerging evidence also suggests that acute glycemic excursions may significantly contribute to microvascular end-organ injury in patients with diabetes, independent of long-term glycemic control (80). Although the mechanisms responsible for end-organ injury with increased glycemic variability are unclear, it has been demonstrated that acute hyperglycemia increases urinary excretion of inflammatory cytokines/chemokines in subjects with T1D (67). Acute hyperglycemia may also contribute to kidney injury via RAAS activation, as it has been demonstrated that acute clamped hyperglycemia activates

the RAAS, which subsequently increases the urinary excretion of inflammatory cytokines/chemokines (81). Furthermore, the increased urinary excretion of inflammatory cytokines/chemokines in response to acute hyperglycemia is blunted by RAAS blockade by direct renin inhibitor in subjects with T1D (81).

Arginine vasopressin (AVP) plays an essential role in the regulation of volume status, and exerts important renal and cardiovascular effects. AVP modulates tubular cell growth thereby causing vasoconstriction of the renal microcirculation and in particular in the efferent arteriole (82, 83). Furthermore, AVP infusion induces hypertension, glomerular hyperfiltration and albuminuria (84, 85) and lowering the AVP concentration provides renal protection (86). There is also evidence linking increased fluid intake with decreased risk for developing CKD (87). Copeptin is a more stable peptide derived from the same precursor molecule as AVP, and appears to be a useful surrogate marker for AVP in the assessment of fluid and osmosis status in various diseases. Recently Boertien et al demonstrated copeptin predicts the estimated glomerular filtration rate decline in subjects with type 2 diabetes, however there is little if any data on its ability to predict DN in subjects with T1D (30). With the availability of AVP receptor antagonists (e.g. vaptans), AVP might also become a promising therapeutic target for DN in the future.

Conclusion

A major challenge in preventing DN relates to the accurate identification of high risk patients at an early stage. Identifying risk factors and biomarkers specifically associated with early DN will help us understand the mechanisms underlying the development and progression of DN. In this review we present novel methods of detecting early change in renal function in T1D, and also several promising new modifiable targets (insulin sensitivity, SUA, SGLT-2 and copeptin) to slow progression of early DN. The translation of these potential methods and therapies into clinical practice now requires investment in adequately powered clinical trials that will capture important renal and cardiovascular long-term outcomes.

Acknowledgments

NIH funded

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Key Points

1. Diabetic nephropathy remains the most common cause of CKD worldwide
2. There is a need for improved methods of detecting early diabetic nephropathy
3. Novel targets to prevent diabetic nephropathy include; serum uric acid, insulin sensitivity, vasopressin and sodium-glucose cotransporter-2

Figure 1. Intervening early in the course of diabetic nephropathy

Adapted from a figure by Alessandro Doria M.D., Ph.D.

Doria A, Niewczas MA, Fiorina P. *Can existing drugs approved for other indications retard renal function decline in patients with type 1 diabetes and nephropathy?* *Semin Nephrol.* 2012 Sep;32(5):437–44. doi: 10.1016/j.semnephrol.2012.07.006.

Figure 2. Progression of diabetic nephropathy

Adapted from a figure by Amy K. Mottl M.D., M.P.H. (not previously published)

“Stages” in Development of Diabetic Kidney Disease

Figure 3. Stages in Development of DN

Adapted from David Maahs M.D., Ph.D. *Early Detection of Kidney Disease in Type 1 Diabetes: What Do We Really Know? Diabetes Technology and Therapeutic*. 2012. Vol 14. doi: 10.1089/dia.2012.0089 (Reprinted with permission from DIABETES TECHNOLOGY & THERAPEUTICS 14/7, 2012, published by Mary Ann Liebert, Inc., New Rochelle, NY)

Figure 4. Tubuloglomerular feedback and SGLT-2 in DN

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Table 1

Promising markers and therapeutic targets of DN

Biomarker:	Important studies:	Randomized control trials:
Serum uric acid	(23, 24, 25)	The preventing early renal function loss (PERL) allopurinol study (NCT01575379)
Insulin sensitivity	(8, 26, 27)	Metformin Vascular Adverse Lesions in Type 1 Diabetes (REMOVAL) trial (NCT01483560) Effects of Metformin On Cardiovascular Function In Adolescents with Type 1 Diabetes (EMERALD) study (NCT01808690) Metformin Therapy for Overweight Adolescents With Type 1 Diabetes (NCT01881828)
Sodium glucose co-transporter 2	(28, 29)	Safety and Efficacy of Empagliflozin (BI 10773) in Type 1 Diabetes Mellitus Patients With or Without Renal Hyperfiltration (NCT01392560)
Copeptin	(30, 31)	--
Serum and urinary inflammatory markers	(32, 33)	--