Progressive Renal Decline: The New Paradigm of Diabetic Nephropathy in Type 1 Diabetes

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On the basis of extensive studies in Joslin Clinic patients over 25 years, we propose a new model of diabetic nephropathy in type 1 diabetes. In this model, the predominant clinical feature of both early and late stages of diabetic nephropathy is progressive renal decline, not albuminuria. Progressive renal decline (estimated glomerular filtration rate loss >3.5 mL/min/year) is a unidirectional process that develops while patients have normal renal function. It progresses at an almost steady rate until end-stage renal disease is reached, albeit at widely differing rates among individuals. Progressive renal decline precedes the onset of microalbuminuria, and as it continues, it increases the risk of proteinuria. Therefore, study groups ascertained for microalbuminuria/proteinuria are enriched for patients with renal decline (decliners). We found prevalences of decliners in 10%, 32%, and 50% of patients with normoalbuminuria, microalbuminuria, and proteinuria, respectively. Whether the initial lesion of progressive renal decline is in the glomerulus, tubule, interstitium, or vasculature is unknown. Similarly unclear are the initiating mechanism and the driver of progression. No animal model mimics progressive renal decline, so etiological studies must be conducted in humans with diabetes. Prospective studies searching for biomarkers predictive of the onset and rate of progression of renal decline have already yielded positive findings that will help to develop not only accurate methods for early diagnosis but also new therapeutic approaches. Detecting in advance which patients will have rapid, moderate, or minimal rates of progression to end-stage renal disease will be the foundation for developing personalized methods of prevention and treatment of progressive renal decline in type 1 diabetes.

RISK OF END-STAGE RENAL DISEASE IN TYPE 1 DIABETES IS STILL HIGH

Despite almost universal implementation of renoprotective therapies over the past 25 years and attempts to improve glycemic control, the risk of end-stage renal disease (ESRD) in type 1 diabetes (T1D) is not decreasing but increasing (1). ESRD remains the major cause of excess morbidity and premature mortality in patients with T1D. Based on data of the U.S. Renal Data System (http://www.usrds.org/), we plotted in Fig. 1 the number of new cases of ESRD attributed to diabetes in the Caucasian U.S. population aged 20–49 years for years 1990–2006 according to age at onset of ESRD (1). In this age range, T1D is the predominant diabetes type with sufficient duration (at least 15 years) to develop ESRD due to diabetes. The total number of new cases of ESRD attributed to T1D was 3,359 in 1990, 3,972 in 1995, 4,287 in 2000, and 4,600 in 2006—an increase of about 9% per year. The age distribution also changed. While the number aged 20–29 or 30–39 years declined slightly, the number aged 40–49 years almost doubled. This suggests the improved research division of Joslin Diabetes Center and Department of Medicine, Harvard Medical School, Boston, MA

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Recruitment of 1,108 patients into the 2nd Joslin Kidney Study on Natural History of Early Renal Decline in T1D extended from 2003 through 2009, and follow-up is still ongoing (16–19). The Joslin Proteinuria Cohort was assembled from among patients with T1D who developed proteinuria while attending the clinic between 1991 and 2004, and follow-up is still ongoing (1,20–22). For recruitment and follow-up, all relevant data from medical records of the clinic were abstracted. Those data were supplemented with results of special examinations performed at enrollment and biannually afterward. Biobanks of blood and urine were established and specimens are stored at ~85°C. Three phenotypes of diabetic nephropathy have been evaluated in all cohorts at enrollment and monitored during follow-up. These included 1) urinary albumin-to-creatinine ratio (ACR) in spot urine specimens; 2) estimated glomerular filtration rate (eGFR) that was determined based on serum concentration of creatinine, cystatin C, or both using recently developed formulas (3); and 3) onset of new ESRD diagnosed when a patient was placed on dialysis or received a kidney transplant.

In this review, I highlight previously published findings and unpublished data from the Joslin Studies relevant to supporting “progressive renal decline as the new paradigm of diabetic nephropathy in T1D.” As a result, attention to other possibly relevant publications is not exhaustive. This review also incorporates some of our earlier considerations regarding progressive renal decline (23,24).

**OCCURRENCE OF PROGRESSIVE RENAL DECLINE IN T1D**

We refer to renal decline as progressive because, once started, it continues until renal failure develops and dialysis or kidney transplant is required (Figs. 2–5). We distinguish early renal decline that develops when patients have normal renal function from late decline in patients with impaired renal function (eGFR <60 ml/min) not because they differ but because other models have supposed different mechanisms are involved.

**Progressive Renal Decline Develops in Patients With Normoalbuminuria and MA**

We examined in detail the onset of early progressive renal decline in the 2nd
Joslin Kidney Study, comprising 595 patients with T1D with normalalbuminuria (NA) and 513 with MA (19). During 4–10 years follow-up, longitudinal measurements of serum creatinine (cr) and cystatin C (cys) were used to trace individual trajectories of eGFRcys changes over time. The distribution of the annual rate of eGFRcys change was divided into rates consistent with “stable” renal function, eGFRcys loss <3.3% per year (nondecliners), and rates reflecting progressive renal decline, eGFRcys loss ≥3.3% per year (decliners). The frequency of decliners according to baseline eGFR and presence of NA and MA are shown in Table 1. Overall prevalence of decliners was 10% in patients with NA and 32% in those with MA. The frequency of decliners in each group increased with decreasing baseline eGFR. This association most likely resulted from ascertainment bias (i.e., decliners had higher risk of developing urinary albumin abnormalities). Interestingly, the prevalence of decliners in NA and MA in the 2nd Joslin Kidney Study is very similar as in the 1st Joslin Kidney Study (14).

To determine time of initiation/onset of progressive renal decline, we plotted eGFRcys trajectories in decliners with NA in Fig. 2 (19). For clarity, nondecliners are not shown and only patients who were enrolled during the first phase of recruitment (i.e., 2003–2006) are used. Decliners were divided arbitrarily into those with eGFRcys above median (105 mL/min) at entry in panel A and below median in panel B. A striking difference was observed between the panels. Whereas in panel A (above median) almost all decliners had stable eGFRcys (horizontal trajectories) for several years before progressive decline developed, in panel B (below median) almost all decliners had progressively declining eGFRcys trajectories from entry. This unanticipated finding is novel and suggests that in patients with T1D the onset of progressive renal decline (the blue circle) happens suddenly when patients have normal renal function. Once the process begins, renal decline continues at an almost constant rate so the majority of trajectories of eGFRcys in decliners appear linear and can be represented as simple regression slopes. The slopes of decline, however, varied tremendously among patients, ranging from a loss of 21% to 3.3% per year. The fastest decliners will reach ESRD within 5–15 years, while the slowest might need 25–30 years. It is interesting that during follow-up, MA developed in half of the decliners (19). Trajectories of eGFRcys changes in the decliners in the corresponding data from the MA group in the 2nd Joslin Kidney Study are not presented because they are similar to those in the NA group.

To explore the relation of progressive renal decline to changes in urinary albumin excretion, we examined the trajectories of renal function changes in patients as MA developed. In the 1st Joslin Kidney Study, MA developed in the early 1990s in 79 patients who were followed subsequently for 10 years (25). Trajectories of eGFRcys changes for these patients are plotted in Fig. 3. Renal function was stable in the majority (70%), despite the development of MA (Fig. 3A). The remaining trajectories (30%) qualified as progressive renal decline (i.e., eGFRcys loss ≥3.3% per year) (Fig. 3B), which was already established when MA developed and continued during subsequent follow-up. Similar to the decliners with NA in Fig. 2, eGFRcys losses in this group were well represented by simple regression slopes, albeit at rates varying widely among individuals. Within 10 years of follow-up, chronic kidney disease (CKD) stage ≥3 had been reached by half of them and ESRD had developed in five patients. If their trajectories of decline remain linear, CKD stage 3 will be

![Figure 2](image-url)
reached by the rest during the next 10 years.

Early and late progressive renal decline are contrasted in Fig. 3B. The former refers to decline beginning while renal function is normal, a feature of diabetic nephropathy first described by us. The latter is a long-recognized feature of CKD observed by nephrologists when such patients are referred to them for follow-up. Visually striking is the absence of features distinguishing early from late decline except their starting point. Thus early and late decline might be successive segments of a uniform process.

Particularly relevant to the relation between renal decline and urinary albumin excretion is the observation that during the 2-year interval before the onset MA, the distribution of abnormal urinary albumin excretion did not differ between decliners and nondecliners (23). During follow-up one sees further uncoupling of changes in urinary albumin excretion and changes in eGFRcys. At the end of follow-up, and after many years of eGFR loss, proteinuria developed in only half of the decliners. NA was present in three patients and MA in the remainder. In contrast among nondecliners, MA persisted or progressed to proteinuria in half and regressed to NA in the other half. Similar results were obtained when eGFRcr trajectories were analyzed (26).

Not All Patients With Proteinuria Have Progressive Renal Decline

We recently examined the trajectories of renal function changes over time in patients with T1D included in the Joslin Proteinuria Cohort (20). In this cohort, 240 patients entered with eGFRcr above 60 mL/min and were followed for 7–18 years. We used serial measurements of serum creatinine to estimate eGFRcr and to determine trajectories of eGFRcr in this cohort (Fig. 4). For this illustration, we selected examples with the smallest deviations of eGFRcr values around regression lines. The first step in the classification of the trajectories was to distinguish stable versus declining renal function. In this analysis, a decline less steep than 3.5 mL/min/year was considered “stable” (examples in Fig. 4A–C), while a steeper slope was considered clinically significant decline (examples in Fig. 4D–F). For patients with declining renal function, the nonlinearity of a trajectory was considered clinically consequential if the estimated time of reaching an eGFR of 10 mL/min (expected time of ESRD) was more than 1 year from the observed time of ESRD (vertical dotted line). These nonlinear trajectories were further characterized as decelerating (Fig. 4G) or accelerating (Fig. 4H and I). Typically, acceleration interrupted a period of stable renal function (new-onset decline) as in panel H. Panel I illustrates a rare pattern, acceleration from one rate of decline to a faster one. In summary, the frequencies of these different patterns were stable eGFRcr (Fig. 4A–C) in 47% patients, significant linear loss (Fig. 4 D–F) in 37%, decelerating loss (Fig. 4G) in 12%, and accelerating loss (Fig. 4H and I) in only 4%. To gain an appreciation of the distribution of overall slopes of eGFRcr change in the whole group of 240 subjects, we extracted the linear component of each trajectory as a simple slope (Fig. 5). A few individuals had a positive slope (i.e., renal function improved at the end of follow-up), but the majority had negative slopes (i.e., decreased renal function). The median (25th, 75th percentiles) slope was −3 (−7, −1) mL/min/year. Reflecting the long tail of negative values, the 5th percentile was −16 and the minimum −71 mL/min/year (Fig. 4F). The available clinical information for this patient did not indicate any other cause of renal function decline than T1D (20). In summary, 25% of patients can be considered as having rapid progressive renal decline (eGFRcr slope <−7 mL/min/year) and they progressed to ESRD within 2–10 years. Another 25% had moderate progressive renal decline (eGFRcr slope −7 to −3 mL/min/year) and mostly progressed or will progress to ESRD within 10–30 years. The rest (50%) will have slow or no progressive renal decline and few may progress to ESRD during 30 years of follow-up.

PREDICTORS/DETERMINANTS OF PROGRESSIVE RENAL DECLINE

Demonstration of the existence of predictors of progressive renal decline lends credence to it as a disease process and its role as the dominant clinical feature of early and late stages of diabetic nephropathy.

Multiple Systemic Predictors of Early Progressive Renal Decline

We have been searching systemic factors, both clinical characteristics and serum markers, for determinants of early progressive renal decline in patients with NA and MA enrolled into the first phase of the 2nd Joslin Study (19). We
found multiple factors associated with the risk of renal decline, and the associations are similar regardless of whether patients entered the study with NA or MA. This finding supports the conclusion that early progressive renal decline is the primary clinical abnormality of diabetic nephropathy. Therefore, NA and MA were combined for this analysis. Factors associated with the risk of renal decline in multiple regression analysis are shown in Fig. 6. Although the exact mechanisms through which these factors contribute to early progressive renal decline are unknown, we discuss here possible mechanisms with regard to the two serum markers.

We showed that values of serum uric acid in the high normal range increased the risk of early progressive renal decline (17,19). Elevated serum uric acid has proinflammatory properties and may act as either a pro-oxidant or antioxidant molecule, depending on the circumstances (27). In vivo, rats rendered hyperuricemic by means of an uricase inhibitor develop an afferent arteriolopathy that decreases luminal diameter and produces renal ischemia, leading to glomerulosclerosis and tubulointerstitial fibrosis (28). Lowering serum uric acid concentration with allopurinol attenuates these histological and functional changes (29). It is intriguing to postulate that lowering serum uric acid in patients at risk for early progressive renal decline may reduce the risk of
renal decline in T1D. A clinical trial, the Preventing Early Renal Loss in Diabetes (PERL) study, is being implemented to test this hypothesis (30).

Elevated serum concentrations of tumor necrosis factor receptors (TNFR) 1 or 2 are strongly associated with the risk of advanced stages of renal decline such as CKD stage 3 or ESRD (18,21,31). Our most recent study in patients with NA extends that association to include the onset of renal decline itself (19). While we do not know how elevated concentrations of TNFRs initiate renal decline and lead to renal failure, we have excluded some candidate hypotheses. For example, serum TNF-α itself is not involved directly or indirectly through regulation of serum TNFRs in the development of renal decline (18). Furthermore, serum concentrations of several potential downstream effectors of TNFRs (chemokines and circulating adhesion molecules, such as interleukin [IL]-8, IP-10, MCP1, vascular cell adhesion molecule, and intracellular adhesion molecule) are not associated with renal decline either (18). An intriguing finding is the negative interaction between serum uric acid and TNFR1 on the risk of renal decline in both NA and MA, meaning that the risk of renal decline for patients with elevated serum uric acid and serum TNFR1 is less than the sum of their individual risks (19). This suggests that the predisposing effects of serum uric acid and TNFR1 converge on some common pathway that cannot be further activated by one factor if it has already been turned on by the other. The nature of this putative pathway is unknown.

**Urinary Biomarkers and Risk of Early Progressive Renal Decline**

Although glomerulopathy has been assumed to be the major contributor to the pathogenesis of diabetic nephropathy, evidence is growing that tubulointerstitial injury mediated through an inflammation process also contributes to the development of diabetic nephropathy, particularly late progressive renal decline (32,33). For example in kidney biopsy studies, the severity of diabetic nephropathy (measured as GFR) is associated with the presence of specific inflammatory markers (34,35).

To pursue these cross-section findings prospectively, we investigated the role of chemokines in urine in the development of early progressive renal decline in patients with T1D (36)—the same patients whose trajectories of eGFRcys were presented in Fig. 3. In urine specimens obtained at entry into the study, we assayed 23 cytokines/chemokines, but only five (IL-6, IL-8, MCP1, IP-10, and MIP-1β) were detected in a majority of specimens. Urinary concentrations of all five markers were significantly higher in decliners than nondecliners and identical in non-decliners regardless of whether MA or NA was present. The multiplicity of marker elevations distinguished decliners from nondecliners best. In multivariate analysis, elevation of two or more urinary cytokines/chemokines was strongly associated with future risk of early progressive renal decline (odds ratio 5.4 [95% CI 1.9, 15.6]). In contrast, concentration of CRP, IL-8, and MIP-1β in serum did not differ between decliners and nondecliners (36).

In conclusion, our results are consistent with some previous studies in humans that implicated inflammation in the development and progression of renal injury in diabetes (37,38). However, we refined the characterization of its role in humans with T1D by demonstrating that elevated levels of markers of low-level inflammation in urine are not associated with MA per se but are specific for early progressive renal decline (36). The nature of the factors elevating the concentrations of urinary proinflammatory chemokines and cytokine in T1D remains unknown.

**Progressive Renal Decline as the New Paradigm of Diabetic Nephropathy in T1D**

**New Paradigm and Search for Mechanisms**

Having demonstrated unequivocally that progressive renal decline is the primary manifestation of diabetic nephropathy in T1D (Figs. 2–5), we propose that it be the new paradigm of diabetic nephropathy (23,24). As outlined in Fig. 7, progressive renal decline is represented as a one-directional process superimposed upon the natural course of abnormal urinary albumin excretion. The latter can regress, stay the same, or progress while renal decline, once initiated, progresses to ESRD, albeit at
Progressive GFR Loss in Type 1 Diabetes

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in patients with NA (Fig. 2), is estimated.

progressive renal decline that starts

proteinuria enriched even more. In

tained for MA will be enriched with de-

creases the risk of MA in patients with NA

MA, and proteinuria, respectively. It in-

known. To advance our understanding

mechanisms that initiate and sustain progres-

(21, 37) years (1). The putative mecha-

showed in patients with diabetes and

or is protected against ESRD may be de-

formed, should help us understand the

mechanisms responsible for early and

velops eventually develop morphological

interstitium, or vasculature. The risk

physicians face not only the challenge of

progressive renal decline (Fig. 8). De-

in longer postponement of onset of

tive treatment in patients with early

an intervention is either complete preven-

strategies to

960

Third, to what extent does etiologic

heterogeneity account for the wide in-

dividual variation in the rate of eGFR

loss (Fig. 5)? The rates may be grouped

as rapid, moderate, or slow and as

nondecliners. Whether a patient has

rapid loss, moderate or slow decline,
or is protected against ESRD may be de-

termined by genetic factors (41). Alter-

natively, different sets of environmental

factors may be involved. For example,
in a comparison of T1D cohorts with pro-

teinuria from the Joslin Clinic and the

Steno Diabetes Center, rapid decliners

were significantly more frequent in the

Joslin cohort (42).

Lacking an animal model of the pro-

gressive renal decline of human diabetes,

we are left with clinical and epidemiologi-

cal studies to investigate these questions.

Application of new high-throughput tech-

nologies, such as genetics, genomics,

proteomics, and metabolomics platforms,

should help us understand the

mechanisms of progressive renal de-

cline in T1D. Recently we presented

the results of such studies (43,44).

How to Diagnose Progressive Renal

Decline?

An important message conveyed by Fig.

7 is that the majority of patients with

NA and a large proportion of those

with MA and proteinuria will never de-

velop ESRD. On the other hand, among

those at risk for ESRD the rate of eGFR

loss varies widely (Figs. 2–5). Therefore,

physicians face not only the challenge of

identifying patients in whom progressive

renal decline will develop from

those who will be spared but also the

challenge within the affected group of

distinguishing rapid from moderate and

slow decliners for estimating the time to

onset of ESRD (Figs. 4 and 5).

At present, two tests are used to di-

agnose diabetic nephropathy in T1D:

urinary albumin excretion (a measure of

glomerular damage) and serum cre-

atinine concentration (a measure of re-

nal function loss). Positive results of

these tests indicate the presence and

extent of kidney damage at the time of

examination. A recommendation has

been made to use a combination of

these tests in clinical practice to diag-

nose diabetic nephropathy (45), despite

the fact that the results give no informa-

tion about the rate of renal function loss

or allow estimation of the time to ESRD.

Intensive research is under way to

find better predictors. Recently, we

showed in patients with diabetes and

proteinuria that a single determination

of serum cystatin C is superior to a

simultaneous determination of serum

creatinine in stratifying patients accord-

ing to risk of developing ESRD (46). More

recently, we showed that the serum

concentration of TNFR1 or TNFR2 is a

very good predictor of the future devel-

opment of CKD stage ≥3 and ESRD in

patients with T1D (18,21) and is similarly

effective in predicting ESRD in patients

with type 2 diabetes (31). Similar find-

ings were obtained by other authors in

different populations (47,48). Accord-

ingly, we postulate that a suite of deter-

minations, including urinary albumin

excretion and serum concentrations of
creatinine, cystatin C, and TNFR1, may

be sufficient to construct an index for

stratifying patients with T1D according
to their risk of progressive renal decline

and time of onset of ESRD (A.S.K.,

unpublished data).

Progressive Renal Decline and

Interventions

New effective therapies are desperately

needed to reduce the risk of ESRD in T1D

as discussed in a recent issue of Semi-

inars in Nephrology (49). Strategies to

prevent or delay the risk of ESRD are

outlined in Fig. 8. The most desirable

intervention is either complete preven-

tion or postponement of the onset of

early progressive renal decline by

many years. The best example of such

an intervention is the Diabetes Control

and Complications Trial (DCCT) in which

improved glycemic control in healthy

patients with T1D delayed the onset of

early progressive renal decline by 6

years (50). In contrast, treatment of sim-

ilar patients with ACE inhibitors failed to

delay this outcome (51).

The other intervention is treatment to

down the rate of eGFR loss in

patients who already have early or late

progressive renal decline (Fig. 8). De-

signing such interventions can be

helped by taking into account some of

the features of progressive renal decline

discussed in this review.

First, as renal function loss seems to

to be linear, implementation of an effec-

tive treatment in patients with early

progressive renal decline would result in

longer postponement of onset of

ESRD than its implementation in pa-

tients with late renal decline. Second,

the effectiveness of new therapies to

slow progressive renal decline cannot

be evaluated in clinical trials that use
changes in urinary albumin excretion as an outcome. The proper outcome measure is a change in the rate of renal decline as in the ongoing PERL study in which the effectiveness of treatment with allopurinol in reducing the rate of GFR loss in patients with early renal decline is being investigated [28]. The U.S. Food and Drug Administration–recommended outcome measures (a doubling of serum creatinine or significant postponement of the onset of ESRD) for use in the 3–5 year clinical trial may not be sensitive enough to detect effects that are less than dramatic. Furthermore, such trials will not recognize an effective therapy that has a long lag interval before the effect is manifested. Our recent study illustrates precisely that type of delayed effect. In patients with T1D and proteinuria, an extended period of improved glycemic control was required before it decreased the rate of decline and postponed ESRD by many years [22]. Third, the efficiency of clinical trials of new therapies is significantly reduced (and cost significantly increased) if patients who are nondecliners are included (Fig. 5). Recruitment of them is counterproductive despite their having proteinuria, hypertension, or impaired renal function. Finally, the wide variation in rates of renal decline illustrated in Fig. 5 may be determined by heterogeneous mechanisms. Prediction of the rate of renal function loss will allow not only stratification of patients according to risk of ESRD but also selection of different therapeutic strategies according to the urgency of ESRD risk. Rapid decliners (Fig. 5) may be suitable for aggressive interventions that have received little consideration so far. Such personalized approaches are being developed in other diseases and should be tried for progressive renal decline.

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References
1. Rosolowsky ET, Skupien J, Smiles AM, et al. Risk for ESRD in type 1 diabetes remains high despite renoprotection. J Am Soc Nephrol 2011; 22:545–553.
2. Breyer MD, Boettinger E, Brosius FC 3rd, et al.; AMDCC. Mouse models of diabetic nephropathy. J Am Soc Nephrol 2005;16:27–45.
3. Inker LA, Schmid CH, Tighiouart H, et al.; CKD-EPI Investigators. Estimating glomerular filtration rate from serum creatinine and cystatin C. N Engl J Med 2012;367:20–29.
4. Parving HH, Oxenbøll B, Svendsen PA, Christiansen JS, Andersen AR. Early detection of patients at risk of developing diabetic nephropathy. A longitudinal study of urinary albumin excretion. Acta Endocrinol (Copenh) 1982; 100:550–555.
5. Viberti GC, Jarrett RJ, Keen H. Microalbuminuria as prediction of nephropathy in diabetes. Lancet 1982;2:611.
6. Mogensen CE, Christensen CK. Predicting diabetic nephropathy in insulin-dependent patients. N Engl J Med 1984;311:89–93.
7. Parving HH, Mauer M, Ritz E. Diabetic nephropathy. In The Kidney. 7th ed. Brenner BM, Ed. Philadelphia, PA, Elsevier, 2004, p.1777–1818.
8. Caramori ML, Fioretto P, Mauer M, Warram JH. The need for early predictors of diabetic nephropathy risk: is albumin excretion rate sufficient? Diabete 2000;49:1399–1408.
9. Perkins BA, Fiocchi LH, Silva KH, Finkelstein DM, Warram JH, Krolewski AS. Regression of microalbuminuria in type 1 diabetes. N Engl J Med 2003;348:2285–2293.
10. de Boer IH, Rie CE, Cleary PA, et al.; Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Study Research Group. Long-term renal outcomes of patients with type 1 diabetes mellitus and microalbuminuria: a analysis of the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications cohort. Arch Intern Med 2011;171:412–420.
11. Bakris GL, Molitch M. Microalbuminuria as a risk predictor in diabetes: the continuing saga. Diabetes Care 2014;37:867–875.
12. Krolewski AS, Laffel LM, Krolewski M, Quinn M, Warram JH. Glycosylated hemoglobin and the risk of microalbuminuria in patients with insulin-dependent diabetes mellitus. N Engl J Med 1995;332:1251–1255.
13. Scott LJ, Warram JH, Hanna LS, Laffel LM, Ryan L, Krolewski AS. A nonlinear effect of hyperglycemia and current cigarette smoking are major determinants of the onset of microalbuminuria in type 1 diabetes. Diabetes 2001;50: 2842–2849.
14. Perkins BA, Fiocchi LH, Ostrander BE, et al. Microalbuminuria and the risk for early progressive renal function decline in type 1 diabetes. J Am Soc Nephrol 2007;18:1353–1361.
15. Fiocchi LH, Perkins BA, Roshan B, et al. Renal hyperfiltration and the development of microalbuminuria in type 1 diabetes. Diabetes Care 2009;32:889–893.
16. Niewczas MA, Fiocchi LH, Johnson AC, et al. Serum concentrations of markers of TNFalpha...
and Fas-mediated pathways and renal function in nonproteinuric patients with type 1 diabetes. Clin J Am Soc Nephrol 2009;4:62–70.

17. Ficociello LH, Roslosky ET, Niewczas M, et al. High-normal serum uric acid increases risk of early progressive renal function loss in type 1 diabetes: results of 6-year follow-up. Diabetes Care 2010;33:1337–1343.

18. Gohda T, Niewczas MA, Ficociello LH, et al. Circulating TNF receptors 1 and 2 predict stage 3 CKD in type 1 diabetes. J Am Soc Nephrol 2012;23:516–524.

19. Krolewski AS, Niewczas MA, Skupien J, et al. Early progressive renal decline precedes the onset of microalbuminuria and its progression to macroalbuminuria. Diabetes Care 2014;37:226–234.

20. Skupien J, Warram JH, Smiles AM, et al. The early decline in renal function in patients with type 1 diabetes and proteinuria predicts the risk of end-stage renal disease. Kidney Int 2012;82:589–597.

21. Skupien J, Warram JH, Niewczas MA, et al. Synergism between circulating tumor necrosis factor receptor 2 and HbA1c in determining renal decline during 5–18 years of follow-up in patients with type 1 diabetes and proteinuria. Diabetes Care 2014;37:2601–2608.

22. Skupien J, Warram JH, Smiles A, Galecki A, Stanton R, Krolewski AS. Improved glycemic control and risk of ESRD in patients with type 1 diabetes and proteinuria. J Am Soc Nephrol 2014;25:2916–2925.

23. Krolewski AS, Bonventre JV. High risk of ESRD in type 1 diabetes: new strategies are needed to retard progressive renal function decline. Semin Nephrol 2012;32:407–414.

24. Krolewski AS, Gohda T, Niewczas MA. Progressive renal decline as the major feature of diabetic nephropathy in type 1 diabetes. Clin Exp Nephrol 2014;18:571–583.

25. Merchant ML, Perkins BA, Boratyn GM, et al. Urinary peptidome may predict renal function decline in type 1 diabetes and microalbuminuria. J Am Soc Nephrol 2009;20:2065–2074.

26. 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.

27. Yu MA, Sánchez-Lozada LG, Johnson RJ, Kang DH. Oxidative stress with an activation of the renin-angiotensin system in human vascular endothelial cells as a novel mechanism of uric acid-induced endothelial dysfunction. J Hyper tens 2010;28:1234–1242.

28. Mazzali M, Kanellis J, Han L, et al. Hyperuricemia induces a primary renal arteriopathy in rats by a blood pressure-independent mechanism. Am J Physiol Renal Physiol 2002;282:F991–F997.

29. Siu YP, Leung KT, Tong MK, Kwan TH. Use of allopurinol in slowing the progression of renal disease through its ability to lower serum uric acid level. Am J Kidney Dis 2006;47:51–59.

30. Maahs DM, Caramori L, Cherney DZ, et al.; PERL Consortium. Uric acid lowering to prevent kidney function loss in diabetes: the Preventing Early Renal Function Loss (PERL) allopurinol study. Curr Diab Rep 2013;13:550–559.

31. Niewczas MA, Gohda T, Skupien J, et al. Circulating TNF receptors 1 and 2 predict stage 3 CKD in type 2 diabetes. J Am Soc Nephrol 2012;23:507–515.

32. Bohle A, Wehrmann M, Bogenschütz O, Bätz C, Müller CA, Müller GA. The pathogenesis of chronic renal failure in diabetic nephropathy. Investigation of 488 cases of diabetic glomerulosclerosis. Pathol Res Pract 1991;187:251–259.

33. Gilbert RE, Cooper ME. The tubulointerstitial reaction in progressive diabetic kidney disease: more than an aftermath of glomerular injury? Kidney Int 1999;56:1627–1637.

34. Suzuki D, Miyazaki M, Naka R, et al. In situ hybridization of interleukin 6 in diabetic nephropathy. Diabetes 1995;44:1233–1238.

35. Wada T, Furuichi K, Sakai N, et al. Up-regulation of monocyte chemoattractant protein-1 in tubulointerstitial lesions of human diabetic nephropathy. Kidney Int 2000;58:1492–1499.

36. Wolkow PP, Niewczas MA, Perkins B, et al. Association of urinary inflammatory markers and renal decline in microalbuminuric type 1 diabetics. J Am Soc Nephrol 2008;19:789–797.

37. Saitoh A, Sekizuka K, Hayashi T, Kaneko S, Suzuki Y, Tomino Y. Detection of urinary MCP-1 in patients with diabetic nephropathy. Nephron 1998;80:99.

38. Tashiro K, Koyanagi I, Saitoh A, et al. Urinary levels of monocyte chemoattractant protein-1 (MCP-1) and interleukin-8 (IL-8), and renal injuries in patients with type 2 diabetic nephropathy. J Clin Lab Anal 2002;16:1–4.

39. Nowak NZ, Niewczas MA, Walker W, Smiles A, Bonventre JV, Krolewski AS. Plasma KIM-1, a marker of tubular injury, predicts risk of early progressive renal decline in non-proteinuric patients with type 1 diabetes (T1D) [Abstract]. J Am Soc Nephrol 2014;25(Suppl.):F99A–F992A.

40. Humphreys BD, Xu F, Sabbisetti V, et al. Chronic epithelial kidney injury molecule-1 expression causes murine kidney fibrosis. J Clin Invest 2013;123:4023–4035.

41. Pezzolesi MG, Poznik GD, Mychaleckyj JC, et al.; DCCT/EDIC Research Group. Genome-wide association scan for diabetic nephropathy susceptibility genes in type 1 diabetes. Diabetes 2009;58:1403–1410.

42. Rossing P, Lajer M, Smiles AM, Andressdottir G, Skupien J, Krolewski AS. Clinical outcomes of diabetic nephropathy in patients with type 1 diabetes attending the Steno and the Joslin [Abstract]. Diabetes 2014;63(Suppl. 1):A14.

43. Pezzolesi MG, Nikrad M, McDonnell KP, Smiles AM, Nowak N, Krolewski AS. Highly multiplexed proteome analysis identifies novel plasma biomarkers for early progressive renal function decline leading to renal failure in type 1 diabetes [Abstract]. Diabetes 2014;63(Suppl. 1):A139.

44. Niewczas MA, Croall SE, Smiles AM, et al. Early renal decline in type 1 diabetes: metabolic signature of resistors and progressors [Abstract]. Diabetes 2014;63(Suppl. 1):A13.

45. Jerums G, Panagiotopoulos S, Premaratne E, Madsaae R. Integrating albuminuria and GFR in the assessment of diabetic nephropathy. Nat Rev Nephrol 2009;5:397–406.

46. Krolewski AS, Warram JH, Forsblom C, et al. Serum concentration of cystatin C and risk of end-stage renal disease in diabetes. Diabetes Care 2012;35:2311–2316.

47. Forsblom C, Moran J, Harjutsalo V, et al.; FinnDiane Study Group. Added value of soluble tumor necrosis factor-α receptor 1 as a biomarker of ESRD risk in patients with type 1 diabetes. Diabetes Care 2014;37:2334–2342.

48. Pavkov ME, Nelson RG, Knowler WC, Cheng Y, Krolewski AS, Niewczas MA. Evaluation of circulating TNF receptors 1 and 2 increases the risk of end-stage renal disease in American Indians with type 2 diabetes. Kidney Int 2015;87:812–819.

49. Krolewski AS, Bonventre JV. High risk of ESRD in type 1 diabetes: call for action: introduction. Semin Nephrol 2012;32:405–406.

50. de Boer IH, Sun W, Cleary PA, et al.; DCCT/EDIC Research Group. Intensive diabetes therapy and glomerular filtration rate in type 1 diabetes. N Engl J Med 2011;365:2366–2376.

51. Mauer M, Zinman B, Gardiner R, et al. Renal and retinal effects of enalapril and losartan in type 1 diabetes. N Engl J Med 2009;361:40–51.