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Early Nephropathy in Type 1 Diabetes: The Importance of Early Renal Function Decline

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Abstract

Purpose of review—The results of recent clinical trials in early diabetic nephropathy demonstrate that current therapies designed to suppress microalbuminuria do not prevent renal function decline. However, recent observational studies refined the traditional model of early nephropathy in type 1 diabetes and may inform more effective therapies for the prevention of advanced stage of chronic kidney disease.

Recent findings—A contemporary model of early nephropathy in type 1 diabetes has emerged in which initiation of renal function decline occurs soon after the onset of microalbuminuria and is not conditional on progression to proteinuria. Early renal function decline can be diagnosed using serial measurement of serum cystatin C, a valid marker of GFR even when in the normal or elevated range. Abnormal levels of specific markers of protein glycation, uric acid metabolism, and chronic inflammation appear to represent mechanisms unique to early renal function decline and distinct from those involved in microalbuminuria.

Summary—Recent findings refine the existing paradigm of early nephropathy in type 1 diabetes and have significant implications for research on the mechanisms underlying early diabetic nephropathy. Clinical tests – such as an algorithm for the serial determination of serum cystatin C – should be developed for monitoring early renal function decline (ERFD) so clinical trials can be carried out to test new therapies to prevent or delay it.

1. Introduction

According to the traditional model of diabetic nephropathy in type 1 diabetes, the development of microalbuminuria alone is seen as the fundamental predictor of eventual advanced stage kidney disease. For that reason and because of efficacy in late-stage nephropathy, blockade of the renin angiotensin aldosterone system (RAAS) to suppress microalbuminuria was assumed to represent the effective strategy for early prevention of relevant clinical outcomes such as the advanced stages of chronic kidney disease (generally representing GFR < 60 ml/min) and death. To the contrary, results of recent large-scale clinical trials are in direct opposition to this traditional view and thus force a critical review of the model and the therapies that arise from it [1–3].

Specifically this review will place into context the evidence for a second fundamental phenotype of early nephropathy – termed *early renal function decline (ERFD)*– that, together with microalbuminuria can further refine risk prediction of advanced stage kidney disease and

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possibly serve as a better proxy for diabetic kidney disease progression. Based on knowledge ascertained about the predictors of early renal function decline in the past year, speculation on more effective therapies for prevention of advanced stage kidney disease in type 1 diabetes will be made. Although there is limited knowledge about the natural history of ERFD in type 2 diabetes, we postulate the conclusions inferred for type 1 diabetes may also apply to type 2 diabetes.

2. The Contemporary Model of Nephropathy in Type 1 Diabetes

Microalbuminuria has become firmly entrenched as the primary predictive marker of risk for the advanced stages of chronic kidney disease. In effect, the origins of this model can be traced to three follow-up studies published in the 1980's [4–6]. Patients with microalbuminuria, defined by persistent urinary albumin excretion approximately in the range of 30–300 micrograms per minute, were followed for 7 to 14 years, and advanced nephropathy developed in 60–90% of them. In retrospect, interpretation of the evidence could have been more cautious. Collectively the three studies included only thirty subjects and the outcome was based on a surrogate marker, the progression of microalbuminuria to proteinuria (frequently referred to as 'macroalbuminuria'). The presumed association of renal function impairment with proteinuria gave plausibility to a simple model of diabetic nephropathy comprising three sequential stages: Microalbuminuria heralds proteinuria, which in turn initiates the process of renal function loss to end stage renal disease[7].

As an extension of this traditional model, therapy in patients with microalbuminuria became focused on the prevention of proteinuria through blockade of the RAAS [8,9]. However, that the progression of microalbuminuria to proteinuria was seen as the proxy for declining renal function was a premature conclusion. Contrary to the three early studies that viewed microalbuminuria as the committed step toward advanced stage kidney disease, it came to be seen as a dynamic process that was more likely to remit to normoalbuminuria than to progress to proteinuria [10–13]. Reinforced by more recent results from the Oxford Regional Prospective Study in which the majority (52%) of subjects with microalbuminuria had a dynamic process described as "intermittent microalbuminuria", [14] the 6-year cumulative incidence of remission is now accepted to be approximately 50% [10–12]. This risk of remission far outweighs the risk of progression to proteinuria observed in epidemiological study (15–25%) or clinical trials [10–12,14–17].

Early Renal Function Decline (ERFD) Forms the Basis of a New Model of Early Nephropathy

Although microalbuminuria is of fundamental importance to the model of early diabetic nephropathy, in view of the frequent occurrence of microalbuminuria remission and low risk of progression to proteinuria, it can no longer be seen as the independent predictive marker for advanced stage of chronic kidney disease in the contemporary model. The past year of the early nephropathy literature has provided major insight into the early natural history of diabetic nephropathy in type 1 diabetes and has identified a new phenotype – *early renal function decline (ERFD)* [19–22].

To better understand what is meant by ERFD, one must recall that the assessment of a patient's renal function may be used for two different purposes. One is to diagnose impaired renal function, while the other is to detect the presence of a progressive loss of GFR over time even if it remains in the normal range (early renal function decline)[23]. The first is a cross-sectional assessment at a particular moment, and thus the identification of impaired renal function (typically considered to be less than 60 ml/min/1.73m²) serves only to recognize disease at a late stage [24]. The second, and most clinically relevant for disease prevention, is a longitudinal assessment to detect systematic decreases in GFR and requires repeated measurements over

time. The most important result is whether a downward trend (slope) is present, regardless of the initial GFR value [23,25].

Consistent with earlier reports,[26,27] a recent report from the Pittsburgh Epidemiology of Diabetes Complications Study demonstrated that nearly 10% of cases with incident microalbuminuria already had frankly impaired renal function at the time of microalbuminuria onset, indicating that this process of renal function decline might precede even the onset of microalbuminuria [28]. Although this report emphasized that all subjects with endstage renal disease had previously developed proteinuria, it did not address the issue of timing of the process of initiation of renal function loss relative to microalbuminuria. To explore this relationship, a specific kind of cohort is needed – one in which renal status is evaluated at the onset of microalbuminuria, as absence of this evidence would compromise the assessment of renal function changes after the onset of microalbuminuria. A collection of prevalent cases detected by a single screening examination would not only lack this information but would be biased by the under-representation of patients with rapidly progressive urinary albumin excretion.

Guided by these methodologic considerations, a cohort of patients with type 1 diabetes and normoalbuminuria was monitored for the onset of microalbuminuria through the 1st Joslin Kidney Study on the Natural History of Microalbuminuria in Type 1 Diabetes. Seventy-nine participants who developed microalbuminuria during the first four years of follow-up were subsequently monitored for 12 years to characterize the longitudinal changes of albumin excretion and of renal function [29]. The 12-year risk of advanced stage kidney disease -- corresponding to Stage 3–5 chronic kidney disease ($GFR_{MDRD} < 60\text{ml/min}$) -- was exceedingly high (29%). However, nearly half of cases never developed proteinuria and, in those cases that did, the vast majority began to lose renal function years prior to the development of proteinuria independent of such factors as the use of angiotensin converting enzyme inhibitor agents. That renal function appeared to begin its decline as early as the onset of microalbuminuria in a substantial subset of patients necessitated a systematic study of GFR using a method that would be simple enough for epidemiological study, yet not hindered by the inaccuracy inherent in creatinine-based techniques when GFR is normal or elevated as it is in type 1 diabetes patients with early nephropathy.

Cystatin C as a Marker of GFR

Cystatin C is an endogenously-produced non-glycosylated protease inhibitor that has characteristics that make it a desirable marker for renal function [30–34]. The accuracy of serum cystatin C for detecting the slope of GFR over time in patients with normal or elevated GFR has been well validated [34,35]. Two very important aspects of the performance of serum cystatin C were demonstrated in these studies. First, they confirmed cross-sectional correlation of cystatin C with iothalamate clearance across the full range of GFR values. Second, and of greater importance, they demonstrated the validity of serial measures of cystatin C for measuring the slope of GFR over time – the correlation between the slopes of GFR change per year as estimated by cystatin C and iothalamate clearance are very high, whereas they are poor for the creatinine-based estimates including the Cockcroft-Gault and the MDRD equations [34]. To illustrate the performance of cystatin C, a representative example is shown in Figure 1 from a study conducted in the Diabetic Renal Disease Study [34,36].

Microalbuminuria and the risk of early progressive renal function decline in type 1 diabetes

To determine the precise timing of renal function decline relative to the onset of microalbuminuria – and specifically if it could begin in patients with longstanding normoalbuminuria or in patients with microalbuminuria – the Joslin investigators measured serial determinations of GFR estimated by serum cystatin C ($GFR_{cystatin\ C}$) in 301 subjects

with microalbuminuria (a mixed population of prevalent and incident cases) and compared with a control population of 268 subjects with longstanding normoalbuminuria [18]. It was first observed that the trends in $\text{GFR}_{\text{cystatin C}}$ were linear, regardless of whether renal function appeared to be stable or rapidly declining. Figure 2 demonstrates the fundamental finding from the study. It plots the distribution of the annual percent change in $\text{GFR}_{\text{cystatin C}}$ for each individual according to the two groups studied: subjects with longstanding normoalbuminuria (the distribution shown on the left side of the plot) compared to subjects with microalbuminuria (shown on the right side of the plot). The horizontal line represents the threshold ($-3.3\%/year$) beyond which the annual percent loss in GFR is predicted to be abnormally rapid. As the reference distribution for evaluating whether a negative slope or trend in renal function qualified as an abnormal rate of decline, the longitudinal data available from the Baltimore Aging Study was used [37]. Using the weighted mean and variances for the participants aged 30 to 59.9 years, the range that included 95% of the distribution (-3.3 to $+2.8\%/year$) was determined and the 2.5th percentile (the lower limit) was selected as the threshold to define cases of early renal function decline [37]. Although 9% of those with longstanding normoalbuminuria had ERFD by this definition, the magnitude of decline was small. In contrast – and contrary to the old model of nephropathy in which renal function was believed to decline only after exposure to proteinuria – one third (31%) of those with microalbuminuria had ERFD and many had dramatic rates of decline approaching 25%/year [18].

Taken together with the data on microalbuminuria, a new model for diabetic nephropathy emerges: First, the onset of microalbuminuria is a dynamic process in which remission to normoalbuminuria is the most common course after onset. Second, even as early as the onset of microalbuminuria, ERFD is initiated in a third of patients with new onset microalbuminuria. This ERFD is a progressive, linear process that leads to impaired renal function in a subset regardless of the course of urinary albumin excretion. Although it is not clear if the onset of microalbuminuria causes ERFD, the initiation of the process certainly does not depend on proteinuria as previously thought. These new observations on the natural history of early nephropathy raise the possibility that urinary albumin excretion and ERFD may represent parallel phenotypes that only share in part the same etiologic mechanisms.

3. Interpretation of Recent Clinical Trial Results In the Context of the Contemporary Model

Of fundamental importance in assessing the validity of the new model of diabetic nephropathy is the evaluation of its consistency with the results of clinical trials. First, the notion that remission of microalbuminuria requires 4 years to observe the natural history of its non-linear rise and fall indicates that clinical trials evaluating change in urinary albumin excretion need to be of at least this duration. Studies that are of this sufficient duration are uncommon, and demonstrate much less suppression of urinary albumin excretion compared to those that are of shorter duration [8]. Secondly, recent clinical trial evidence strongly suggests that agents that inhibit the RAAS, while they may suppress urinary albumin excretion in the relative short-term, may not prevent renal function decline and the development of advanced stage kidney disease. For example, a meta-analysis of 9 studies (with 23 study groups) derived from randomized, blinded clinical trials of type 1 diabetes patients with microalbuminuria fail to demonstrate a beneficial effect on the annual percent change in GFR despite significant suppression of microalbuminuria by way of agents that inhibit the RAAS (Figure 4) [2]. In addition, the results of the landmark Renin Angiotensin Study were recently presented in a late-breaking clinical trials session[1]. In this multicenter randomized controlled trial, 285 normoalbuminuric type 1 diabetes subjects underwent renal biopsy before and after randomization to placebo, angiotensin converting enzyme inhibitor therapy, or angiotensin receptor blockade for 5 years. The primary outcome of change in the glomerular mesangial

fractional volume (the strongest predictor of renal function loss) was similar in all groups, indicating that in this patient population RAAS inhibition does not influence the gold standard morphological measures of early nephropathy despite suppression of urinary albumin excretion. Finally, although by analogy in type 2 diabetes, the results of the ONTARGET study disagree entirely with the traditional model in which augmented RAAS inhibition should equate to improved clinical outcomes [3]. In this 4.5-year study examining as predefined primary renal outcomes the combination of dialysis, doubling of creatinine, and death, 25,620 high vascular risk participants (of which 9612 had diabetes) were randomized to angiotensin converting enzyme inhibitor therapy, or angiotensin receptor blockade, or both. A statistically significant increase in the primary renal outcome was observed on combination therapy (hazard ratio 1.09, 1.01–1.18; $p=0.037$ versus angiotensin converting enzyme inhibitor) [3].

The traditional model of early diabetic nephropathy cannot reconcile these consistent discrepancies between suppression of urinary albumin excretion and improvements in either morphological or renal function measures. Rather, they highlight the messages inherent in the new model of diabetic nephropathy that views ERFD as a fundamental phenotype. Although ERFD is initiated at the onset of microalbuminuria and is only moderately correlated with the course of albumin excretion, it appears to represent pathological mechanisms that are distinct to those that promote progression or regression of urinary albumin excretion.

4. Future Directions: Therapy to Prevent and Treat Early Renal Function Decline

That the course of microalbuminuria occurs in parallel with ERFD without strong evidence for a causal relationship implies that therapies designed to reduce urinary albumin excretion may not have the same beneficial effect on renal function at this early stage of nephropathy. Furthermore, despite the short-term reduction in albumin excretion from RAAS inhibition, this therapy does not appear to attenuate ERFD as it does in late-stage nephropathy. These observations highlight the need to evaluate the effect of current and emerging therapies on ERFD instead of its impact only on the legacy marker, reduction of urinary albumin excretion. Knowledge of the determinants of ERFD may inform therapies to prevent loss of renal function regardless of effect on urinary albumin excretion. To date, determinants with potential etiologic implications for ERFD include: 1) markers of protein glycation; 2) uric acid metabolism; and 3) low-grade chronic inflammation.

Although protein glycation damage, such as the formation of advanced glycation end-products, has long been recognized as a fundamental mechanism of cellular injury in diabetes [38], knowledge of the relative contribution of specific glycation damage mechanisms on microalbuminuria versus ERFD has not been recognized until recently. In a study comprising participants from the 1st Joslin Kidney Study with new onset microalbuminuria and normoalbuminuria, the urines and plasma ultrafiltrate was examined for adducts of oxidative, nitrative, and glycation protein damage by an advanced liquid chromatography-tandem mass spectrometry technique [39]. The fractional urinary excretion of two specific glycation adducts [Pentosidine, a fluorophore, and N_ω-Carboxymethylarginine(CMA), a hydroimidazolone advanced glycation endproduct] were elevated in subjects prior to development of ERFD as compared to those whose renal function was stable over 10-year follow-up. This association was observed to be independent of HbA1c, the level of albumin excretion, and the levels of the other ten adducts studied [39]. Although the precise etiological roles of pentosidine and CMA are not understood, the main implication of this finding is that increased urinary fractional excretion of these protein glycation adducts may represent a pathogenic mechanism unique to ERFD, distinct from those mechanisms involved in abnormal urinary albumin excretion.

Serum uric acid, the main byproduct of purine metabolism, has received renewed attention as having a potential causal role in renal function impairment, possibly owing to its pro-oxidant, complement system activation, RAAS upregulation, and nitric oxide inhibitory mechanisms rather than its role as a marker of renal function itself [40–43]. In the 2nd Joslin Kidney Study on the Natural History of Microalbuminuria in Type 1 Diabetes, a cohort of 675 patients with normoalbuminuria or microalbuminuria and estimated GFR generally above 90 ml/min, serum uric acid was the variable most strongly associated with the level of GFR, independent of its association with urinary albumin excretion, age, sex, HbA1c, and antihypertensive medication use [20]. Uric acid levels in this study were not in the hyperuricemic range – rather, even high normal levels were found to relate to GFR reductions. As observed with markers of protein glycation, the independent association of subtle change in uric acid with the cross-sectional level of GFR within the normal range provides even further support for the existence of mechanisms for microalbuminuria and ERFD that may be distinct from one another [20,21].

Recent publications have strongly supported the role of chronic inflammation and apoptosis in the pathogenesis of progressive urinary albumin excretion in diabetic nephropathy [45–48]. The association of inflammatory markers with renal function, however, was also recently reported in both longitudinal and cross-sectional studies. In an analysis of baseline urine samples from participants in the longitudinal 1st Joslin Kidney Study, three study groups were investigated: those with microalbuminuria and ERFD, those with microalbuminuria only, and those with neither [19]. The urinary levels of five inflammatory markers measured at baseline were significantly higher for those with future ERFD: IL-6, IL-8, monocyte chemoattractant protein-1, interferon-gamma-inducible protein (IP-10), and macrophage inflammatory protein-1 δ . Multivariate analysis revealed that those with more than two elevated markers were more than five times as likely to have subsequent ERFD. Additionally, cross-sectional analyses of the level of GFR and serum concentrations of inflammatory markers were investigated in the 2nd Joslin Kidney Study. In these analyses, two classes of soluble markers of the TNF α pathway – TNF receptors and the soluble form of Fas – had association with the level of GFR within its normal range, independent of age and the level of urinary albumin excretion [22].

Although requiring further study, collectively this data suggests that therapy designed to modify processes of protein glycation, uric acid metabolism, and chronic inflammation may be found to impact changes in early renal function rather than the specific pathogenic mechanisms involved in preventing abnormalities in urinary albumin excretion. As an example, the use of drugs such as allopurinol or probenecid for modification of serum uric acid may hold promise as therapy for the prevention of ERFD in early nephropathy [20,44]. This will require confirmation in prospective studies that measure ERFD with the use of a valid marker of renal function when in the normal or elevated ranges, such as the serial measurement of serum cystatin C.

5. Conclusions

A contemporary model of early nephropathy has emerged from studies in type 1 diabetes in which the onset of microalbuminuria is characterized by frequent remission to normoalbuminuria. During this time, regardless of the course of albumin excretion, a subset of approximately a third of individuals will initiate a process of ERFD to advanced stages of chronic kidney disease. The existence of pathogenic mechanisms for the two independent early phenotypes – microalbuminuria and ERFD – are further supported by the findings of recent clinical trials that imply that therapy that successfully suppresses urinary albumin excretion may not have impact on ERFD. In view of the recent observational studies and clinical trial results summarized in this review, progressive urinary albumin excretion on its own may no longer be accepted as a proxy for the risk of advanced kidney disease. Furthermore, given the independence of the microalbuminuria and ERFD phenotypes, therapies that have failed to

demonstrate consistent efficacy in clinical studies of progressive urinary albumin excretion – such as glycosaminoglycans [49] or inhibitors of protein kinase C β [50] - should be considered for their effect on early renal function decline (ERFD) using an outcome measure such as serial determinations of serum cystatin C.

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FIGURE 1. Serial Determinations of Glomerular Filtration Rate by Measurement of Iothalamate Clearance, 100/Cystatin C, and the MDRD Equation from a Representative Example in the Diabetic Renal Disease Study [36]

This representative example demonstrates the findings in systematic studies that compare longitudinal determinations in change in $GFR_{CYSTATIN\ C}$ to gold standard methods of GFR determination. The creatinine-based estimates (in this example, the Modification of Diet in Renal Disease equation), were accurate only when GFR was abnormally low; however, cystatin C overcame this limitation by approximating the reference standard (iothalamate clearance) even when GFR was normal or elevated.

FIGURE 2. Distribution of Glomerular Filtration Rate Slopes over Time (in %/year) According to the Presence of Microalbuminuria in the 1st Joslin Kidney Study [18]

Open circles represent individuals with stable renal function, while black circles represent cases of early progressive renal function decline, and open triangles represent cases with clinical end-stage renal disease (15 individuals required hemodialysis or renal transplantation) by the end of follow-up.

In subjects with normoalbuminuria, who had mean baseline $GFR_{CYSTATIN\ C}$ 155 ± 22 ml/min, 9 percent had early progressive renal function decline. In the subjects with microalbuminuria, however, for whom mean baseline $GFR_{CYSTATIN\ C}$ was 143 ± 26 , 31 percent had early progressive renal function decline.

$GFR_{CYSTATIN\ C}$, glomerular filtration rate estimated by $100/\text{serum cystatin C (in mg/L)}$.

FIGURE 3. Frequency (in percent) of Early Progressive Renal Function Decline in Patients With Normoalbuminuria and Microalbuminuria Divided according to the 4-year Course of Microalbuminuria in the 1st Joslin Kidney Study [18]

Regression is defined as a halving (decrease by 50% or more) of the urinary albumin excretion rate (in $\mu\text{g}/\text{min}$) (N=100).

Stable is defined as no change greater than a halving or doubling of the urinary albumin excretion rate (N=121).

Progression is defined as a doubling (increase by 100% or more) of the urinary albumin excretion rate (N=58).

Twenty-two subjects had insufficient urine samples in the second follow-up interval to determine the course of their microalbuminuria.

FIGURE 4. Relationship Between Initial Change in Albumin Excretion Rate and Overall Change in GFR per Year from Studies in Early Nephropathy(a) and Late Nephropathy (b) in Type 1 Diabetes [2]

Reproduced with permission from Jerums et al.[2] The data for early nephropathy in (a) are derived from 23 study groups in 9 studies of type 1 diabetes. The data for late nephropathy (b) are derived from 10 study groups in 5 studies of type 1 diabetes.