

## Early Glomerular Filtration Rate Loss as a Marker of Diabetic Nephropathy

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### Abstract

In the early 1980s, studies in type 1 diabetes suggested that glomerular filtration rate (GFR) loss begins with the onset of macroalbuminuria. However, recent evidence indicates that up to one-quarter of subjects with diabetes reach a GFR of less than 60 ml/min/1.73 m<sup>2</sup> (chronic kidney disease [CKD] stage 3) before developing micro- or macroalbuminuria. Furthermore, the prospective loss of GFR can be detected in early diabetic nephropathy (DN) well before CKD stage 3. Early GFR loss usually reflects DN in type 1 diabetes but, in older patients with type 2 diabetes, the assessment of early GFR loss needs to take into account the effects of ageing. The assessment of GFR is now feasible at clinical level, using formulas based on serum creatinine, age, gender and ethnicity. Overall, the estimation of early GFR loss is more accurate with the Chronic Kidney Disease Epidemiology (CKD-EPI) formula than with the Modification of Diet in Renal Disease (MDRD) study formula, but there is some evidence that the CKD-EPI formula does not exhibit better performance than the MDRD formula for estimating GFR in diabetes. Both formulas underestimate GFR in the hyperfiltration range. Formulas based on the reciprocal of cystatin C can also be used to estimate GFR, but their cost and lack of assay standardisation have delayed their use at clinical level. In summary, early GFR loss is an important marker of DN as well as a potentially reversible target for interventions in DN.

### Keywords

Early glomerular filtration rate loss, hyperfiltration, normoalbuminuric renal insufficiency, Modification of Diet in Renal Disease (MDRD)

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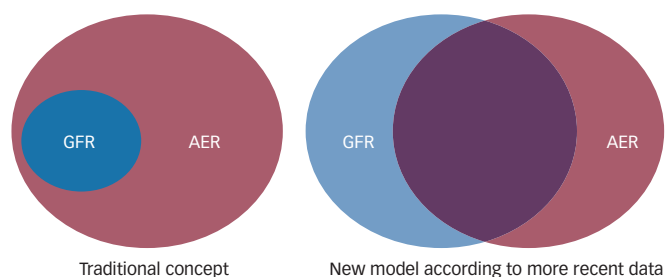
Since the early 1980s, the clinical diagnosis of diabetic nephropathy (DN) has been based on the progression of albuminuria. Albumin excretion rate (AER) was categorised as normo-, micro- or macroalbuminuria based on retrospective studies of AER in type 1 diabetes prior to the introduction of angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs). Microalbuminuria (or dipstick-negative albuminuria) predicted macroalbuminuria (or dipstick-positive albuminuria – i.e., overt nephropathy) in 60–80 % of patients with type 1 diabetes over intervals of 6–14 years. However, recent studies have shown that the predictive value of microalbuminuria is of the order of 30–50 % and spontaneous remission of microalbuminuria occurs in over 50 % of patients.<sup>1,2</sup>

A decline in glomerular filtration rate (GFR) was initially considered to occur only in patients with macroalbuminuria.<sup>3</sup> Subsequent experience has shown that GFR may start to decline in subjects with type 1 diabetes at the stage of microalbuminuria.<sup>4</sup> Furthermore, progressive decline in GFR has also been described in normoalbuminuric subjects with type 1 or type 2 diabetes.<sup>5</sup> Using serial measurements of creatinine clearance, it was shown that approximately one-third of subjects with either type 1 or type 2 diabetes developed a decline in renal function without a corresponding increase in AER. Subsequent studies in type 2 diabetes using isotopic GFR showed that approximately one-quarter of subjects developed non-albuminuric renal insufficiency (GFR <60 ml/min/1.73 m<sup>2</sup>), after exclusion of

patients treated with renin-angiotensin system (RAS) inhibitors.<sup>6</sup> Although these studies have shown that early GFR loss is not confined to macroalbuminuric subjects, the rate of progression of GFR loss is usually more rapid in subjects with macroalbuminuria.

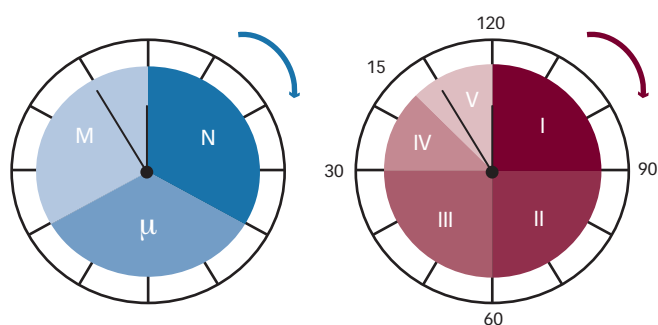
Studies in type 1 diabetes have defined early decline in renal function as a loss of GFR of >3.3 % per year, corresponding to the 97.5th percentile of the decline in creatinine clearance in non-diabetic normotensive Caucasians in the Baltimore Longitudinal Study of Aging.<sup>7</sup> Using this definition, the first Joslin Kidney Study monitored trends in renal function over four years in 279 type 1 diabetes patients with new-onset microalbuminuria.<sup>3</sup> The reciprocal of serum cystatin C was used to compare the annual percentage change in GFR in this cohort (mean baseline GFR 155 ml/min/1.73 m<sup>2</sup>) with a control group of normoalbuminuric patients (mean baseline GFR 143 ml/min/1.73 m<sup>2</sup>). Early renal function decline occurred in 31 % of microalbuminuric and 9 % of normoalbuminuric patients (p<0.001). Furthermore, the frequency of early renal function decline was related to the course of AER over a four-year period. A higher frequency of early GFR loss (67.7 %) occurred in subjects whose AER doubled during the study, compared with subjects who had stable microalbuminuria (32.2 %) and subjects whose microalbuminuria was halved (16.2 %). These findings suggest that early GFR and AER trajectories are separate processes during the early stages, but become more closely coupled during the later stages of DN.<sup>3</sup>

**Figure 1: Albumin Excretion Rate and Glomerular Filtration Rate Concordance and Discordance**



AER = albumin excretion rate; GFR = glomerular filtration rate.

**Figure 2: Albumin Excretion Rate and Glomerular Filtration Rate as Indices of Diabetic Nephropathy**



N = normoalbuminuria; μ = microalbuminuria; M = macroalbuminuria.

The evolution of diabetic nephropathy is shown in the form of two dials: on the left representing stages of albumin excretion rate and on the right representing stages of glomerular filtration rate (GFR) (chronic kidney disease stages I to V, with numbers indicating GFR in ml/min/1.73 m<sup>2</sup>).

In the Diabetes control and complications trial/epidemiology of diabetes interventions and complications cohort (DCCT/EDIC) study, the long-term analysis, performed over 15 years, of subjects with type 1 diabetes showed a persistent decline in estimated GFR (eGFR) to <60 ml/min/1.73 m<sup>2</sup> in 89 of 1,439 subjects, of whom 21 had normoalbuminuria.<sup>8</sup> When expressed per 1,000 person-years, this translated into 36.1 macro-, 1.3 micro- and 1.0 normoalbuminuric subjects progressing to CKD stage 3.

The relationship between early renal function loss and AER has also been studied in type 2 diabetes. In a long-term study of 195 Pima Indians with type 2 diabetes, early renal function decline was defined as a rate of GFR loss of ≥3.3 % per year over four years.<sup>9</sup> In this study, GFR was measured directly by the urinary clearance of iothalamate. The prevalence of early renal function decline during this initial period was 32 % in participants with normal urinary albumin:creatinine ratio at baseline, 42 % in those with microalbuminuria and 74 % in those with macroalbuminuria (p<0.001). Subsequent follow-up showed that the cumulative incidence of end-stage renal disease (ESRD) 10 years after the initial period was 41 % in those with early renal function decline and 15 % in those without.<sup>9</sup> It was concluded that an early decline in GFR often occurs before the onset of macroalbuminuria, but that a decline predictive of ESRD is strongly dependent on the progression to macroalbuminuria.

Studies of eGFR gradients in patients with type 2 diabetes have also shown that the rate of decline in renal function increases progressively from 2 to 8 ml/min/1.73 m<sup>2</sup> per year, adjusted for age and baseline eGFR, as albuminuria increases from <10 to >1,000 mg/g

creatinine.<sup>10</sup> This emphasises that higher levels of albuminuria, even within the normoalbuminuric range, predict a faster decline in eGFR.

In summary, the traditional concept of the natural history of DN that links the transition from micro- to macroalbuminuria as the key to heralding a significant decline in GFR has been challenged. More recent data suggest that AER and GFR are complementary rather than obligatory manifestations of DN (see *Figure 1*). Therefore, according to this new model, both AER and GFR should be measured as markers of DN (see *Figure 2*).

## Effects of Treatment on Assessment of Renal Function in Diabetes

In the 30 years since the description of microalbuminuria as an indicator of early DN, there have been major changes in diabetes management. Instead of being confined to glycaemic control, diabetes care has become multifactorial and now includes aggressive control of blood pressure and dyslipidaemia, as highlighted in the Steno 2 study.<sup>11</sup> This approach has resulted in markedly improved long-term renal outcomes. However, there are short- and long-term treatment effects that complicate the interpretation of renal function tests. For instance, ACE inhibitors and ARBs usually, but not always, decrease AER in micro- or macroalbuminuric patients. In macroalbuminuric patients, a larger initial decrease in AER predicts greater attenuation of the long-term rate of decline of GFR.<sup>12</sup> By contrast, in microalbuminuric patients, the initial decrease in AER during antihypertensive therapy has not been shown to predict attenuation of the subsequent rate of decline of GFR.<sup>13</sup> Post-hoc analyses of several trials have shown that, in microalbuminuric patients, increases in AER are linked to a faster decline in GFR.<sup>14</sup> It follows that decreases in AER induced by RAS inhibitors may create problems in interpreting renal function tests. For instance, 'normoalbuminuria' induced by RAS inhibitors may revert to microalbuminuria after cessation of therapy. Antihypertensive therapy, including RAS inhibitors, may also cause an early decline in GFR, which is reversed on cessation of therapy, indicating a haemodynamic mechanism.<sup>15</sup> In line with early changes in AER, the extent of the early decline in GFR induced by antihypertensive therapy predicts the long-term attenuation of GFR.<sup>16</sup>

Lipid lowering therapy may also influence rates of decline of GFR. In the Collaborative atorvastatin diabetes study (CARDS), atorvastatin reduced the eGFR gradient by 0.38 ml/min/1.73 m<sup>2</sup> per year in subjects with elevated AER.<sup>17</sup> In the Fenofibrate intervention and event lowering in diabetes (FIELD) study, fenofibrate decreased eGFR acutely (but this was reversed on cessation of therapy);<sup>18</sup> it is not yet clear whether this was due to an effect of fenofibrate on renal creatinine handling or to a direct effect of fenofibrate on GFR.

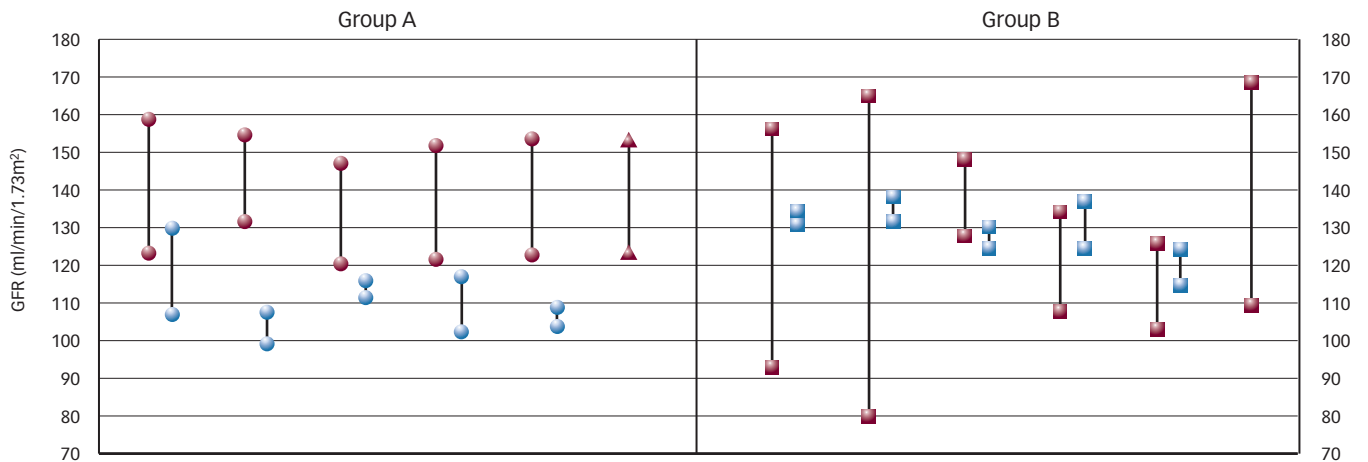
Several studies have evaluated the effects of intensive glucose control on early GFR loss in diabetes. In type 2 diabetes, both the Action in diabetes and vascular disease: PreterAx and Diamicon MR controlled evaluation (ADVANCE) and the Action to control cardiovascular risk in diabetes (ACCORD) studies showed that intensive glucose control reduced the risk of incident microalbuminuria but with no benefit on eGFR.<sup>19-21</sup> A follow-up of the United Kingdom prospective diabetes study (UKPDS) showed no benefit on albuminuria or serum creatinine in the intensive glucose control arm.<sup>22</sup> In type 1 diabetes, the DCCT/EDIC study showed that the intensive glucose control arm had a decreased risk of micro- and macroalbuminuria.<sup>23</sup> On long-term follow-up, the intensive

**Table 1: Comparison of Formulas for Estimating Glomerular Filtration Rate**

	MDRD Study Formula	CKD-EPI Formula	Cystatin C-Based Formula
GFR Parameter	Creatinine*	Creatinine*	Cystatin C
Adjusts for Age, Gender, Race	Yes	Yes	No
Accuracy:			
GFR <60 ml/min/1.73 m <sup>2</sup>	Satisfactory	Accurate	Accurate
GFR >60 ml/min/1.73 m <sup>2</sup>	Underestimates GFR <sup>27</sup>	Generally more accurate than the MDRD formula, except in the elderly or those with extremes of body mass <sup>28</sup> May not exhibit better performance than the MDRD formula in diabetes <sup>30</sup>	More accurate than the MDRD formula
GFR gradient	Underestimates GFR gradient if initial eGFR >90 ml/min/1.73 m <sup>2</sup>	Current evidence suggests that it will underestimate GFR gradient if initial eGFR >90 ml/min/1.73 m <sup>2</sup>	Accurately reflects early iGFR gradients in type 1 diabetes <sup>39</sup> Underestimates GFR in obesity Influenced by extra-renal factors Assays require standardisation

CKD-EPI = Chronic Kidney Disease Epidemiology; GFR = glomerular filtration rate; eGFR = estimated GFR; iGFR = isotopic GFR; MDRD = Modification of Diet in Renal Disease.  
\* eGFR derived from creatinine-based formulas can be influenced by variations in muscle mass, renal tubular creatinine secretion, meat intake and ethnicity.

**Figure 3: Glomerular Filtration Rate Decline in Hyperfiltering and Normofiltering Patients with Type 1 Diabetes**



Mean baseline and final glomerular filtration rate (GFR) in hyperfiltration (red symbols) and normofiltration (blue symbols) subgroups from 12 observational studies of GFR trajectory over 3–18 years in type 1 diabetes patients. Baseline GFR is joined to final GFR by a solid line to form a ‘dumb-bell’ symbol for both hyperfiltration and normofiltration groups. Group A = prospective studies; group B = retrospective studies. The six studies in group B show data categorised retrospectively according to progression or non-progression of albumin excretion rate (AER) to at least microalbuminuria. Note that GFR was not shown to decline below 60 ml/min/1.73 m<sup>2</sup> in any of the studies. Source: reproduced with permission from Jerums et al, 2010.<sup>35</sup> References.<sup>40-50</sup>

glucose control arm showed a lower rate of developing serum creatinine >2.0 mg/dl (0.7 % in the intensive arm versus 2.8 % in the control arm).<sup>24</sup> A more recent study from the DCCT/EDIC research group has shown that the long-term risk of developing an eGFR <60 ml/min/1.73 m<sup>2</sup> over a median follow-up period of 22 years was lower with early intensive glucose control compared with conventional glucose control.<sup>25</sup>

**Glomerular Filtration Rate Slopes in Early Diabetic Nephropathy**

There are two main ways of assessing GFR loss in DN. The first is by assessing the proportion of subjects progressing to a predefined endpoint, such as the doubling of serum creatinine (equivalent to the halving of GFR), or reaching a specific stage, such as eGFR <60 ml/min/1.73 m<sup>2</sup>. While these endpoints are useful in established nephropathy, they focus on fast trackers and do not allow the assessment of early GFR loss in the study group as a whole. By contrast, the assessment of eGFR gradients allows monitoring of GFR profiles in

all participants, and is therefore useful not only in clinical trials but also in individual subjects at a clinical level.

As shown in Table 1, the Modification of Diet in Renal Disease (MDRD) study and the Chronic Kidney Disease Epidemiology (CKD-EPI)<sup>26</sup> formulas both provide satisfactory estimates of GFR at low GFR levels. However, the MDRD formula seriously underestimates GFR in the normal range in subjects with type 2 diabetes.<sup>27,28</sup> It follows that the MDRD formula will underestimate GFR gradients during long-term assessment of individuals with an initial GFR >90 ml/min/1.73 m<sup>2</sup>. Because of the above considerations, the CKD-EPI formula has been proposed as a more sensitive method of assessing early GFR loss in diabetes. However, both formulas underestimate GFR in the hyperfiltration range (>130 ml/min/1.73 m<sup>2</sup>). Furthermore, there is increasing evidence showing that the CKD-EPI equation is less accurate in patients with type 2 diabetes than in healthy individuals, and does not exhibit better performance than the MDRD formula for estimating GFR in diabetes.<sup>29,30</sup>

Formulas for estimating eGFR based on the reciprocal of plasma cystatin C levels have the advantage of accuracy at higher GFR levels. However, cystatin C measurements are more expensive than plasma creatinine measurements. The lack of standardisation of assays is another factor delaying the use of this analyte as a marker of GFR at clinical level.<sup>31,32</sup> Formulas for estimating GFR combining cystatin C and creatinine have been developed, but have not yet been shown to improve the precision of monitoring early GFR decline in diabetics.<sup>33</sup>

Interpreting GFR slopes in subjects with type 2 diabetes is more complex than in younger subjects with type 1 diabetes because of the effect of age-related decline in GFR. The mean rate of age-related GFR decline is approximately 1 ml/min/year after the age of 40 years.<sup>7</sup> It follows that, if a subject aged 60 years with type 2 diabetes has a rate of GFR loss of 2.0 ml/min/year and this is reduced to 1.5 ml/min/year by aggressive antihypertensive therapy, then the diabetes-related component of GFR loss (1.0 versus 0.5 ml/min/year) has been halved.

Competing risks create a further difficulty in assessing GFR loss in type 2 diabetes. For instance, cardiovascular deaths occurred in less than 1 % of type 1 diabetes patients in the DCCT-EDIC study, compared with 25 % of type 2 diabetes patients in the long-term UKPDS follow-up study.<sup>24</sup>

## Hyperfiltration

Hyperfiltration (HF; i.e., GFR >130 ml/min/1.73 m<sup>2</sup>) is a common finding in type 1 diabetes with poor glucose control. In most subjects, it responds to improvement in glucose control. However, in a proportion of subjects, HF persists for several years. A recent meta-analysis of 12 early studies (six prospective, six retrospective) of type 1 diabetes patients with HF concluded that HF predisposes to the development of micro- or macroalbuminuria, with a hazard ratio of 2.3 when compared with a concurrent (normoalbuminuric) control group.<sup>34</sup> However, there is so far no evidence that HF predicts a decline in GFR to subnormal levels (see *Figure 3*).<sup>35</sup> Further long-term studies of GFR gradients are therefore required to establish whether HF ultimately leads to renal impairment, after adjustment for glycaemic control and other confounding factors. In contrast to the meta-analysis mentioned above, a recent single centre study from

the Joslin Clinic found no evidence that HF estimated by cystatin C predisposes to the development of microalbuminuria in type 1 diabetes.<sup>36</sup> The exact reasons for these disparate findings are not known. However, it is possible that a 'calendar' effect may explain the negative findings in the Joslin Clinic study. That is, improvements in the control of glucose, blood pressure and dyslipidaemia over the past 20 years may have diminished the role of HF as a predictor of microalbuminuria. Whether HF results in faster early GFR loss and ultimately leads to impaired GFR awaits further long-term study.

Studies of HF in type 2 diabetes are more difficult to interpret than in type 1 diabetes because of the effects of age and obesity on GFR. A correction for age-related loss of GFR can be made by subtracting 1 ml/min/1.73 m<sup>2</sup> per year after 40 years of age.<sup>37</sup> In obese subjects with type 2 diabetes, there is a continuing debate on whether GFR should be indexed for body surface area.<sup>38</sup>

In the previously mentioned study in Pima Indians with type 2 diabetes with average age below 50 years, early GFR loss ( $\geq 3.3$  % per year) occurred over four years in 88 subjects and renal function remained stable in 107 subjects.<sup>9</sup> Hyperfiltration at baseline, defined as a GFR  $\geq 154$  ml/min, was present in 53 % of subjects with early GFR loss and a similar proportion of subjects with stable renal function (48 %). Therefore, this study does not support the concept that HF predisposes to early GFR decline. However, it should be noted that mean body mass index was over 30 kg/m<sup>2</sup> in both study groups. Therefore, if GFR were expressed per body surface area, most of these subjects would not be classified as having HF.

## Conclusion

Early GFR loss is increasingly recognised as a marker of DN. Loss of GFR commonly occurs before the onset of macroalbuminuria and is even seen in normoalbuminuric subjects. However, early GFR decline and progression to ESRD are still strongly influenced by the progression of albuminuria. The optimal method for accurately estimating an early decline in GFR, from normal to subnormal levels, is yet to be defined. Markers of increased risk for the development of early GFR loss, apart from albuminuria, are currently being investigated. ■

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