Early Glomerular Hyperfiltration and Long-Term Kidney Outcomes in Type 1 Diabetes
The DCCT/EDIC Experience

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Abstract
Background and objectives Glomerular hyperfiltration has been considered to be a contributing factor to the development of diabetic kidney disease (DKD). To address this issue, we analyzed GFR follow-up data on participants with type 1 diabetes undergoing 125I-iothalamate clearance on entry into the Diabetes Control and Complications Trial (DCCT)/Epidemiology of Diabetes Interventions and Complications study.

Design, setting, participants, & measurements This was a cohort study of DCCT participants with type 1 diabetes who underwent an 125I-iothalamate clearance (iGFR) at DCCT baseline. Presence of hyperfiltration was defined as iGFR levels ≥140 ml/min per 1.73 m², with secondary thresholds of 130 or 150 ml/min per 1.73 m². Cox proportional hazards models assessed the association between the baseline hyperfiltration status and the subsequent risk of reaching an eGFR <60 ml/min per 1.73 m².

Results Of the 446 participants, 106 (24%) had hyperfiltration (iGFR levels ≥140 ml/min per 1.73 m²) at baseline. Over a median follow-up of 28 (interquartile range, 23, 33) years, 53 developed an eGFR <60 ml/min per 1.73 m². The cumulative incidence of eGFR <60 ml/min per 1.73 m² at 28 years of follow-up was 11.0% among participants with hyperfiltration at baseline, compared with 12.8% among participants with baseline GFR <140 ml/min per 1.73 m². Hyperfiltration was not significantly associated with subsequent risk of an eGFR <60 ml/min per 1.73 m² in an unadjusted Cox proportional hazards model (hazard ratio, 0.83; 95% confidence interval, 0.38 to 1.54). Application of alternate thresholds to define hyperfiltration (130 or 150 ml/min per 1.73 m²) showed similar findings.

Conclusions Early hyperfiltration in patients with type 1 diabetes was not associated with a higher long-term risk of decreased GFR. Although glomerular hypertension may be a mechanism of kidney injury in DKD, higher total GFR does not appear to be a risk factor for advanced DKD.

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Introduction
Glomerular hyperfiltration has long been considered to be a major contributing factor to the development of diabetic kidney disease (DKD) (1–4). Initial studies in various rodent models of DKD demonstrated that partial ablation of kidney mass resulted in the surviving nephrons undergoing adaptations to meet the increased excretory demands, i.e., an increase in single nephron GFR, and ultimately resulted in proteinuria, hypertension, glomerulosclerosis and eventual kidney failure (2). In diabetic rodent models, hyperglycemia induced increases in total and single nephron GFR but proteinuria and glomerulosclerosis did not occur if the increased GFR was prevented by instituting a low protein diet or giving an angiotensin converting enzyme inhibitor, supporting the hypothesis that hyperfiltration rather than hyperglycemia was the pathogenetic factor (5,6).

Early studies in small numbers of patients with type 1 diabetes showed that with diabetes of short duration, the GFR was increased compared with that of nondiabetic controls (7,8). Patients with type 1 diabetes with higher GFRs had an increased risk of developing microalbuminuria in some (9–13), but not all studies (14–18). In larger, more recent studies of patients with type 1 diabetes, those with hyperfiltration had a higher risk of developing microalbuminuria in one study (19), but not in others (20–23). Few studies have been carried out in patients with type 2 diabetes, but results have similarly been conflicting, as one study showed that hyperfiltration was associated with an increased risk of albuminuria (24) whereas others did not show such a risk (25,26).

The impact of hyperfiltration on the long-term development of DKD, defined by low eGFR, is even less clear. Two studies in patients with type 1 diabetes...
have shown that hyperfiltration is associated with a rapid decline in GFR using a diethylene-triamine-penta-acetic acid clearance method (27) or the CKD Epidemiology Collaboration (CKD-EPI) equation (28). However, neither demonstrated an increased risk for the development of a GFR <60 ml/min per 1.73 m² (stage 3 CKD) or more advanced levels of CKD, leaving it uncertain whether these changes represented statistical regression to the mean, a “beneficial” resolution of elevated single nephron GFR to normofiltration, or indeed an abnormal loss of GFR that would persist and result in stage 3 CKD over time. In patients with type 2 diabetes, an increase in the proportion of patients with a rapid decline in GFR was demonstrated in studies using a labeled EDTA clearance method (25), an iohexol clearance method (24), and a Modified Diet in Renal Disease equation method for GFR measurements (29), but again, none demonstrated an increased risk for the development of stage 3 CKD or more advanced stages of CKD.

To address whether early glomerular hyperfiltration results in a subsequent increased risk of developing clinically significant loss of GFR (stage 3 CKD), we have analyzed 30-year GFR follow-up data on patients who underwent 125I-iothalamate clearance (iGFR) on entry into the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) study.

Materials and Methods

Study Population

The Diabetes Control and Complications Trial (DCCT) enrolled 1441 persons with type 1 diabetes from 1983 to 1989 in an international, multicenter study to determine the effects of intensive diabetes therapy on the long-term complications of diabetes (30). Clinicaltrials.gov identification numbers for the study are NCT00360893 and NCT00360815, with a date of registration of August 7, 2006. All participants gave informed, written consent under the individual centers’ institutional review board guidelines, which adhered to the Declaration of Helsinki. The trial included two cohorts. The primary prevention cohort was characterized by diabetes duration 1–5 years, albumin excretion rate (AER) <40 mg/24 h, and no retinopathy by fundus photography. The secondary intervention cohort was characterized by diabetes duration 1–15 years, AER≥200 mg/24 h, and at least one microaneurysm in either eye (but no more than moderate nonproliferative retinopathy). For both cohorts, serum creatinine <1.2 mg/dl and creatinine clearance >100 ml/min per 1.73 m² were required for eligibility.

Participants were randomly assigned to intensive diabetes therapy aimed at lowering glucose levels to as close as safely possible to the nondiabetic range, whereas conventional therapy aimed at preventing symptoms of hyperglycemia and hypoglycemia. In 1994, after completion of the DCCT, 1375 participants (96% of the surviving cohort) agreed to participate in the Epidemiology of Diabetes Interventions and Complications (EDIC) study. All participants were instructed in intensive therapy methods and responsibility for ongoing diabetes care was returned to the participants’ health care provider. Diabetes therapy and glycemic control, as measured by hemoglobin A1c (HbA1c), became similar in the two original DCCT treatment groups, and yearly follow-up is currently ongoing as of 2019 (31).

DCCT enrollment spanned 1983–1989, during which 1441 participants were enrolled. Starting in 1986, after many patients had already been enrolled, iGFR was added to the protocol (32) and was assessed at DCCT baseline in 446 participants. This analysis includes long-term follow-up data on the 446 DCCT/EDIC participants who underwent assessment of kidney function using iothalamate clearance (see below) at the time of entry into the DCCT.

Iothalamate Clearance

The details of the iothalamate clearance methodology and coefficients of variation of this test have been described previously (33). Briefly, GFR was measured as the urinary clearance of 125I-iothalamate after a subcutaneous injection of 35 μCi without epinephrine. After an equilibration period of at least 1 hour, four consecutive urine collections were obtained by voluntary voiding and five serum samples were drawn bracketing the urine collections. The overall GFR was calculated as if the clearance periods were one long period. The median intratest coefficient of variation was 11.7%. All iothalamate clearances were adjusted for body surface area (34).

A review of the pertinent literature showed considerable variability on the level of GFR used for the definition of hyperfiltration: levels (all in ml/min per 1.73 m²) included 120 (24,28,29), 125 (11,13,19,27), 130 (19,22), 135 (17,18,22 in men), 137 (26), 140 (12,23), and 150 (9,22 in women). The primary analysis here utilized an iothalamate clearance of ≥140 ml/min per 1.73 m² to indicate hyperfiltration, as being in the middle of these prior estimates, but sensitivity analyses were also conducted using hyperfiltration cutoff points of ≥130 and ≥150 ml/min per 1.73 m².

Outcomes

Serum creatinine was measured annually throughout the DCCT and EDIC study using a method traceable to isotope dilution mass spectrometry, and was used to determine eGFR (31–35) using the CKD-EPI equation (36). Reduced GFR was defined as an eGFR <60 ml/min per 1.73 m² (stage 3 CKD) and included patients with ESKD. A secondary outcome was sustained reduced GFR, defined as two consecutive visits with eGFR <60 ml/min per 1.73 m², and included participants who had developed ESKD. All reduced GFR events among the 446 participants in this study that occurred up to a median total study follow-up period of 28 years were included in these analyses, whereas participants without an event were censored at last follow-up or at this time. A secondary analysis was also conducted using all the first iGFR values, to include an additional 719 participants with a first iGFR measurement at DCCT year 3/4, and 19 at year 5, for a total of 1184 participants. Other secondary outcomes included the development of macroalbuminuria (AER≥300 mg/24 h or 300 mg/g creatinine) and sustained macroalbuminuria, defined as two consecutive visits with macroalbuminuria.
Covariates
The risk factors considered in these analyses were evaluated at the DCCT baseline visit, which included a medical history, physical examination, and collection of blood and urine biospecimens. HbA1c was measured using high-performance ion-exchange liquid chromatography. BP was measured by trained observers after ≥5 minutes of rest. A seven-point capillary blood glucose profile was collected by the participants and analyzed for glucose as previously described (37).

Statistical Analyses
Discrete variables were summarized using percentages, and continuous variables were summarized using means (±SDs) and medians (first and third quartiles). Event-free (survival) probability curves for onset of stage 3 CKD were obtained using the Kaplan–Meier estimator.

The associations between the iothalamate-determined GFR and eGFR, HbA1c, and seven-point profile blood glucose levels were described using Spearman correlation coefficients. The association between hyperfiltration and the subsequent risk of developing an eGFR <60 ml/min per 1.73 m² was assessed using Cox proportional hazards (PH) models both unadjusted and adjusted for baseline age, systolic and diastolic BP, duration of type 1 diabetes, cohort (primary prevention versus secondary intervention), group (intensive versus conventional), and HbA1c. Additional Cox PH models investigated whether the association between hyperfiltration and risk of stage 3 CKD differed by cohort and treatment group using interaction terms. Separate models were employed for the three cutoffs considered for iothalamate GFR values (i.e., ≥130, ≥140, and ≥150 ml/min per 1.73 m²), and for incident stage 3 CKD and sustained stage 3 CKD. A spline function with three degrees of freedom described the risk gradient of stage 3 CKD as a function of iothalamate-determined GFR values. Sensitivity analyses were conducted using all the first iGFR values (even after baseline).

The association between hyperfiltration and the risk of eGFR <60 ml/min per 1.73 m² in this combined group was assessed using a Cox model stratified by the time of the iGFR measurement (baseline versus DCCT year 3/4 versus DCCT year 5). Because the iGFR values may differ after baseline (i.e., at DCCT year 3/4 and DCCT year 5) between the intensive and the conventional groups, the effect of hyperfiltration was also assessed using an additional model with an interaction term between hyperfiltration (yes/no) and a binary variable, which is 1 for participants in the intensive group first evaluated after DCCT baseline.

Similar to the reduced eGFR analyses, we used Cox PH models to investigate the association between hyperfiltration (yes/no) and the risk of macroalbuminuria (AER≥300 mg/24 h).

Results
The characteristics of the 446 participants who underwent iothalamate GFR assessments on entry into the DCCT, both overall and stratified by iothalamate GFR levels, are shown in Table 1. The participants were young (mean age 28±7 years) and had a short duration of diabetes at just over 4 years. They were normotensive and the mean HbA1c was 8.8%. The characteristics of these 446 participants were similar to the total of 1441 participants in the DCCT (Supplemental Table 1). Overall, 178 participants had iothalamate GFR levels ≥130 ml/min per 1.73 m², 106 had levels ≥140 ml/min per 1.73 m², and 55 had levels ≥150 ml/min per 1.73 m² (Supplemental Figure 1). The proportions of participants with iothalamate clearances of ≥130, 140, and 150 ml/min per 1.73 m² were similar between treatment groups (Supplemental Table 2).

The correlations between the iothalamate GFR levels and the HbA1c and mean seven-point blood glucose profile were 0.07 and 0.09, respectively, and were not statistically significant (Supplemental Figures 2 and 3). A comparison was also carried out of the iothalamate GFR versus the calculated CKD-EPI eGFR on the basis of the serum creatinine levels at baseline (correlation, 0.29; Supplemental Figure 4).

Among the 446 participants in this study, there were 53 (12%) eGFR <60 ml/min per 1.73 m² events over a median follow-up period of 28 (interquartile range, 26, 29) years (rate of 4.69 events per 1000 individuals at risk for 1 year). This is similar to the occurrence in the full cohort, where 13% reached an eGFR <60 ml/min per 1.73 m² (rate of 4.91 events per 1000 person-years). Of the 446 participants who underwent iothalamate studies, 34 experienced sustained eGFR <60 ml/min per 1.73 m² events over a median follow-up time of 28 (14, 24) years (rate of 2.98 sustained events per 1000 individuals at risk for 1 year). Figure 1 depicts the Kaplan–Meier survival curves for developing an eGFR <60 ml/min per 1.73 m² according to their initial filtration status, as determined by the iothalamate GFR using 140 ml/min per 1.73 m² as the cutoff. The proportion maintaining an eGFR ≥60 ml/min per 1.73 m² was not decreased and was actually somewhat greater in the hyperfiltration group (95 out of 106, 89.6% versus 298 out of 340, 87.6%) using the cutoff of 140 ml/min per 1.73 m². The cumulative incidences of developing an eGFR <60 ml/min per 1.73 m² were again similar in the two hyperfiltration groups (≥140 versus <140 ml/min/1.73m²: 41% versus 59%.
after 20 years, 9.7% versus 8.9% after 24 years, and 11% versus 12.8% after 28 years) (Table 2).

Hyperfiltration (iothalamate GFR $\geq 140$ ml/min per 1.73 m$^2$) was not associated with subsequent risk of developing an eGFR $< 60$ ml/min per 1.73 m$^2$ in an unadjusted Cox PH model (hazard ratio [HR], 0.83; 95% confidence interval [95% CI], 0.43 to 1.62) nor in the adjusted model (HR, 0.77; 95% CI, 0.38 to 1.54) (Table 2). Similar results were obtained for the developing of a sustained eGFR $< 60$ ml/min per 1.73 m$^2$ (Supplemental Table 3). Interactions between hyperfiltration, cohort, and group were again not significant. Additional sensitivity analyses were carried out using all the first iGFR values (even after baseline): the 446 participants with iGFR measurements at DCCT baseline were combined with the 719 participants with a first iGFR measurement at DCCT year 3/4 and the 19 participants with a first iGFR measurement at DCCT year 5, for a total of 1184 participants. There were 150 eGFR $< 60$ ml/min per 1.73 m$^2$ events and 89 sustained eGFR $< 60$ ml/min per 1.73 m$^2$ events among the 1184 participants. The results of these analyses are shown in Supplemental Tables 4 and 5.

Sensitivity analyses were performed using hyperfiltration cutoffs of $\geq 130$ and $\geq 150$ ml/min per 1.73 m$^2$. These analyses similarly did not show that hyperfiltration resulted in increased long-term risks of developing an eGFR $< 60$ ml/min per 1.73 m$^2$. Table 2 shows the cumulative incidences and HRs of developing an eGFR $< 60$ ml/min per 1.73 m$^2$ at 20, 24, and 28 years for the cutoffs of $\geq 130$ and $\geq 150$ ml/min per 1.73 m$^2$. Interactions between hyperfiltration, cohort, and group were again not significant. Additional sensitivity analyses were carried out using all the first iGFR values (even after baseline): the 446 participants with iGFR measurements at DCCT baseline were combined with the 719 participants with a first iGFR measurement at DCCT year 3/4 and the 19 participants with a first iGFR measurement at DCCT year 5, for a total of 1184 participants. There were 150 eGFR $< 60$ ml/min per 1.73 m$^2$ events and 89 sustained eGFR $< 60$ ml/min per 1.73 m$^2$ events among the 1184 participants. The results of these analyses are shown in Supplemental Tables 4 and 5.

Briefly, the results for the 140 ml/min per 1.73 m$^2$ and other cutoff values showed no increase in risk of eGFR $< 60$ ml/min per 1.73 m$^2$ (sustained or not) associated with iGFR values above the cutoffs, supporting the main analysis.

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**Table 1. Characteristics of study participants with baseline iothalamate GFR measurements (before randomization in the Diabetes Control and Complications Trial; n=446), both overall and stratified by the iothalamate GFR levels**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Overall, n=446</th>
<th>GFR $&lt; 130^a$, n=268</th>
<th>GFR 130 to $&lt; 140^a$, n=72</th>
<th>GFR 140 to $&lt; 150^a$, n=51</th>
<th>GFR $\geq 150^a$, n=55</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>28 (7)</td>
<td>28 (7)</td>
<td>26 (7)</td>
<td>28 (6)</td>
<td>27 (6)</td>
</tr>
<tr>
<td>Women, %</td>
<td>44</td>
<td>46</td>
<td>36</td>
<td>39</td>
<td>49</td>
</tr>
<tr>
<td>Intensive treatment, %</td>
<td>48</td>
<td>48</td>
<td>47</td>
<td>47</td>
<td>47</td>
</tr>
<tr>
<td>Primary cohort, %</td>
<td>69</td>
<td>72</td>
<td>71</td>
<td>65</td>
<td>60</td>
</tr>
<tr>
<td>Diabetes duration, mo</td>
<td>50 (43)</td>
<td>51 (45)</td>
<td>44 (39)</td>
<td>46 (39)</td>
<td>57 (46.3)</td>
</tr>
<tr>
<td>Hemoglobin A1c (%)</td>
<td>8.8 (1.6)</td>
<td>8.7 (1.5)</td>
<td>8.9 (1.6)</td>
<td>8.8 (1.4)</td>
<td>9.1 (1.9)</td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>114 (11)</td>
<td>113 (11)</td>
<td>116 (10)</td>
<td>115 (12)</td>
<td>117 (13)</td>
</tr>
<tr>
<td>Diastolic BP, mm Hg</td>
<td>73 (8)</td>
<td>73 (8)</td>
<td>72 (8)</td>
<td>72 (7)</td>
<td>72 (9)</td>
</tr>
<tr>
<td>Iothalamate GFR$^a$, mean, IQR</td>
<td>126 (114, 139)</td>
<td>117 (110, 124)</td>
<td>135 (132, 137)</td>
<td>145 (143, 148)</td>
<td>159 (153, 168)</td>
</tr>
</tbody>
</table>

*All GFR units in ml/min per 1.73 m$^2$.  

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Figure 1. Kaplan–Meier survival curves and 95% CIs for developing an eGFR $< 60$ ml/min per 1.73 m$^2$ show no difference for those with hyperfiltration (eGFR $> 140$ ml/min per 1.73 m$^2$) compared to those without hyperfiltration (eGFR $< 140$ ml/min per 1.73 m$^2$).
There were 53 macroalbuminuria events and 35 sustained macroalbuminuria events among the 446 participants with baseline iGFR values. Similar to the eGFR \( < 60 \text{ ml/min per } 1.73 \text{ m}^2 \) analyses, the analyses reported in Supplemental Tables 6 and 7 did not show an increase in the risk of macroalbuminuria associated with iGFR values above versus below the three cutoff values considered.

Figure 2 depicts the risk gradient of developing an eGFR \( < 60 \text{ ml/min per } 1.73 \text{ m}^2 \) as a function of the iothalamate GFR considered as a continuous variable. The risk decreased as the iothalamate GFR increases up to approximately 130 ml/min per 1.73 m\(^2\), and the risk remained approximately flat beyond that value.

### Discussion

Our analyses from the long-term follow-up of participants with type 1 diabetes in the DCCT/EDIC study demonstrated that early hyperfiltration is not associated with an increased risk for the subsequent development of an eGFR \( < 60 \text{ ml/min per } 1.73 \text{ m}^2 \), i.e., stage 3 CKD. The primary analysis used an iothalamate GFR of \( \geq 140 \text{ ml/min per } 1.73 \text{ m}^2 \) to define hyperfiltration and additional analyses using \( \geq 130 \text{ and } \geq 150 \text{ ml/min per } 1.73 \text{ m}^2 \) showed similar findings. Furthermore, similar findings were found when patients were in either the former DCCT conventional or intensive treatment groups. Most prior studies that assessed the effects of hyperfiltration using cutoffs between 120 and 150 ml/min per 1.73 m\(^2\), so the cutoffs used here were similar those used previously. All of the sensitivity analyses, including all participants with a first iGFR evaluation and risk of macroalbuminuria, yielded results similar to the main analysis.

Prior studies that attempted to show an adverse effect of hyperfiltration on DKD outcomes primarily used the development of microalbuminuria as an outcome, but those studies were not uniform in demonstrating this. A concern with these studies is the use of microalbuminuria as a surrogate outcome denoting DKD. The use of microalbuminuria and even macroalbuminuria as a valid surrogate for DKD has been challenged (38,39). Perkins et al. (40) showed that 58% of patients with type 1 diabetes and microalbuminuria had regression of their microalbuminuria to normoalbuminuria on subsequent testing. In a similar study of the DCCT/EDIC cohort of those who developed microalbuminuria, the 10-year cumulative incidence of progression to macroalbuminuria was 28%, progression to impaired GFR \( < 60 \text{ ml/min per } 1.73 \text{ m}^2 \) was only 15%, and progression to ESKD was only 4%, whereas regression to normoalbuminuria was 40% (41). Furthermore, in the DCCT/EDIC cohort, of those who developed macroalbuminuria, the 10-year cumulative incidence of impaired GFR \( < 60 \text{ ml/min per } 1.73 \text{ m}^2 \) was only 32%, progression to ESKD was only 16%, and regression to micro- or normoalbuminuria was 48% (42).

A few studies showed an association of hyperfiltration with an increased rate of decline of eGFR over several years (24,25,27–29), but whether this was a true effect on kidney function or a regression to the mean, in many cases, is not clear. Because GFR can have measurement errors and

### Table 2. Associations of baseline iothalamate GFR with the long-term incidence of eGFR <60 ml/min per 1.73 m\(^2\) in the study

<table>
<thead>
<tr>
<th>Baseline Filtration Status</th>
<th>No. at Risk</th>
<th>No. of Events</th>
<th>Cumulative Incidence in %</th>
<th>Hazard Ratio (95% Confidence Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>At Year 20</td>
<td>At Year 28</td>
<td>Unadjusted</td>
<td>Adjusted a</td>
<td></td>
</tr>
<tr>
<td>Threshold 140 ml/min per 1.73 m(^2)</td>
<td>&lt;140 ml/min per 1.73 m(^2)</td>
<td>340</td>
<td>42</td>
<td>5.9</td>
</tr>
<tr>
<td>(\geq 140 \text{ ml/min per } 1.73 \text{ m}^2)</td>
<td>106</td>
<td>11</td>
<td>4.1</td>
<td>11.0</td>
</tr>
<tr>
<td>Threshold 130 ml/min per 1.73 m(^2)</td>
<td>&lt;130 ml/min per 1.73 m(^2)</td>
<td>268</td>
<td>36</td>
<td>6.4</td>
</tr>
<tr>
<td>(\geq 130 \text{ ml/min per } 1.73 \text{ m}^2)</td>
<td>178</td>
<td>17</td>
<td>4.2</td>
<td>10.1</td>
</tr>
<tr>
<td>Threshold 150 ml/min/1.73 m(^2)</td>
<td>&lt;150 ml/min per 1.73 m(^2)</td>
<td>391</td>
<td>45</td>
<td>5.4</td>
</tr>
<tr>
<td>(\geq 150 \text{ ml/min per } 1.73 \text{ m}^2)</td>
<td>55</td>
<td>8</td>
<td>6.0</td>
<td>14.9</td>
</tr>
</tbody>
</table>

aAdjusted for baseline age, systolic BP, diastolic BP, duration of type 1 diabetes, cohort (primary prevention versus secondary intervention), hemoglobin A1c, and group (intensive versus conventional).

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**Figure 2.** Risk gradient showing the log hazard rate (and 95% pointwise CIs) for the development of an eGFR <60 ml/min per 1.73 m\(^2\) as a function of the iothalamate GFR.
naturally varies within individuals over time, GFR values are likely to regress toward mean values when only those with high initial values are examined. In addition, the implications of short- or medium-term decline of GFR from the elevated back to the normal range is not clear: this could be pathologic or, in fact, a beneficial resolution of potentially damaging elevated single nephron GFR. No prior study has demonstrated that hyperfiltration caused a sustained loss of GFR to levels <60 ml/min per 1.73 m².

The major strength of this study is the large number of participants followed over a very long period of time. Additionally, there was a very high completion rate of tests in this long-term study. The use of an isotope clearance method to define the initial GFR is a major strength, as it is known that calculated eGFRs are less accurate in the normal range (36). Using stage 3 CKD as the primary outcome is also a major strength because it has a much higher correlation with the progression to ESKD than does microalbuminuria. A weakness of this study is that only a small number of participants actually reached ESKD. Another weakness is the fact there was only one measurement per participant for the iothalamate designation of hyperfiltration and glucose concentrations were not closely regulated during the iothalamate clearance procedure.

Finally, we wish to be clear about our interpretation of the term “hyperfiltration.” In the medical literature, this term has been used to describe two phenomena. First, the term has been used to describe an elevation of global GFR, as we have examined in this analysis. However, hyperfiltration is a term that has also been used to describe an elevation in single nephron GFR in response to either adaptation to loss of surrounding nephrons (2,4), or due to tubular mechanisms (such as the sodium reabsorptive effect of sodium glucose linked transporter 2 activation) (43) or neurohormonal mechanisms (such as activation of the renin angiotensin aldosterone system) that independently raise intraglomerular pressure regardless of global GFR (44). Although we could not demonstrate a relationship between global hyperfiltration and the risk of reduced eGFR, we cannot exclude the possibility that single-nephron hyperfiltration is associated with such risk. Global and single nephron GFR may diverge according to the number of functional nephrons each individual possesses.

Hyperfiltration has been attributed to poor glycemic control. However, when we analyzed the relationship of the baseline iothalamate GFR levels to concurrent HbA1c, the initial GFR is a major strength, as it is known that calculated eGFRs are less accurate in the normal range (36). Using stage 3 CKD as the primary outcome is also a major strength because it has a much higher correlation with the progression to ESKD than does microalbuminuria. A weakness of this study is that only a small number of participants actually reached ESKD. Another weakness is the fact there was only one measurement per participant for the iothalamate designation of hyperfiltration and glucose concentrations were not closely regulated during the iothalamate clearance procedure.

In conclusion, we have demonstrated that early hyperfiltration in patients with type 1 diabetes is not associated with any long-term decrease in kidney function. Although it is known with certainty that long-term improved glycemic control reduces the development of microalbuminuria, macroalbuminuria, and stage 3 CKD (30,31,34,35), the notion that early hyperfiltration is a marker of poor long-term kidney outcome is not supported by these robust findings.

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Because Dr. de Boer is a Deputy Editor of the Clinical Journal of the American Society of Nephrology, he was not involved in the peer review process for this manuscript. Another Editor oversaw the peer review and decision-making process for this manuscript.

A complete list of investigators and members of the research group appears in Nathan et al. (45).

Disclosures

Dr. de Boer reports personal fees from Boehringer-Ingelheim, personal fees from Ironwood, nonfinancial support from Medtronic and Abbott, outside the submitted work. Dr. Molitch reports grants and other funding from Novartis, grants from Bayer, grants and other from Novo Nordisk, other from Merck, Pfizer, Janssen, Sanofi, and Senseonics outside the submitted work. Dr. Perkins reports grants and other from Boehringer Ingelheim, personal fees from Medtronic, Abbott, Insulet, Dexcom, Astra Zeneca, Janssen, Neurometrix, and grants and personal fees from Bank of Montreal outside the submitted work. Dr. Bebu, Dr. Gao, Dr. Lachin, Dr. Paterson, Dr. Saenger, and Dr. Steffes have nothing to disclose.

Supplemental Material

This article contains the following supplemental material online at http://cjasn.asnjournals.org/lookup/suppl/doi:10.2215/CJN.14831218/-/DCSupplemental.
Supplemental Table 1. Baseline characteristics of the full DCCT cohort (n=1441) and of the subcohort (n=446) with baseline iothalamate GFR measurements.

Supplemental Table 2. Baseline characteristics and proportion of participants with hyperfiltration by treatment group and overall.

Supplemental Table 3. Number of participants, number of sustained eGFR <60 ml/min per 1.73 m² events, cumulative incidence of sustained eGFR <60 ml/min per 1.73 m², and hazard ratios (95% confidence intervals) for the association between hyperfiltration and the risk of sustained CKD stage 3 separately for different iothalamate GFR cutoff values.

Supplemental Table 4. Associations of first iothalamate GFR measurement with the long-term incidence of eGFR <60 ml/min per 1.73 m².

Supplemental Table 5. Associations of first iothalamate GFR measurement with the long-term incidence of sustained eGFR <60 ml/min per 1.73 m².

Supplemental Table 6. Association between hyperfiltration and the risk of macroalbuminuria (53 events).

Supplemental Table 7. Association between hyperfiltration and sustained macroalbuminuria (35 events).

Supplemental Figure 1. Density of the iothalamate GFR.

Supplemental Figure 2. Iothalamate GFR versus HBAlc (%). (Spearman correlation coefficient =0.07, not statistically significant).

Supplemental Figure 3. Iothalamate GFR versus seven-point blood glucose profile mean (Spearman correlation coefficient =0.09, not statistically significant).

Supplemental Figure 4. Iothalamate GFR versus CKD-EPI eGFR (Spearman correlation coefficient =0.28, P<0.001).

Supplemental Figure 5. Kaplan–Meier event-free (survival) curves stratified by initial DCCT treatment group (intensive versus conventional) comparing the time to development of an eGFR <60 ml/min per 1.73 m² for different iothalamate GFR cutoff values.

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