Renal hyperfiltration and the development of microalbuminuria in type 1 diabetes

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Objective: To examine prospectively whether renal hyperfiltration is associated with the development of microalbuminuria (MA) in patients with type 1 diabetes, after taking into account known risk factors.

Research Design and Methods: The study group is comprised of 426 participants with normoalbuminuria from the First Joslin Kidney Study, followed for 15 years. Glomerular filtration rate was estimated by serum cystatin C and hyperfiltration was defined as exceeding the 97.5th percentile of the sex-specific distribution of a similarly aged, non-diabetic population (134 for men and 149 ml/min/1.73m² for women). The outcome was time to MA development (multiple albumin excretion rate > 30 µg/min). Hazard ratios (HRs) for MA were calculated at 5, 10 and 15 years.

Results: Renal hyperfiltration was present in 24% of the study group and did not increase the risk of developing MA. The unadjusted HR for MA comparing those with and without hyperfiltration at baseline was 0.8 (95% CI: 0.4, 1.7) during the first 5 years, 1.0 (95% CI: 0.6, 1.7) during the first 10 years, and 0.8 (95% CI: 0.5, 1.4) during 15 years of follow-up. The model adjusted for baseline known risk factors including HbA1c, age at diagnosis of diabetes, diabetes duration, and cigarette smoking resulted in similar HRs. In addition, incorporating changes in hyperfiltration status during follow-up had minimal impact on the HRs for MA.

Conclusions: Renal hyperfiltration does not have an impact on the development of MA in type 1 diabetes during 5, 10 or 15 years of follow-up.
The glomerular filtration rate (GFR), the volume of water filtered out of the plasma per unit of time, is indicative of overall kidney function. However, measuring GFR with the gold standard technique is intensive and difficult for both the operator and the participant. Thus, it has not been practical to determine GFR in large epidemiologic studies. Instead, serum creatinine has been widely used to estimate low levels of GFR when loss of kidney function has already occurred. However, serum creatinine is not sensitive enough to detect changes when renal function is normal or abnormally elevated (1). A laboratory test to estimate GFR based on serum cystatin C levels has been recently developed. Cystatin C assays are easy to perform and have been shown to yield accurate estimates even in the normal or elevated ranges of filtration (2,3). This development has created a new opportunity for studying early diabetic renal function abnormalities in large epidemiologic studies.

Hyperfiltration has been suggested as a risk factor for the development of microalbuminuria (MA) (4). The increase in pressure and flow may lead to functional and structural changes in the kidney (5, 6). In several small studies, hyperfiltration was associated with the development of MA in type 1 diabetes, but results have been inconsistent. Some studies were conducted in children beginning at diagnosis or early in the course of diabetes and usually few events of MA were observed (7, 8, 9, 10, 11). Yip et al., found no association between hyperfiltration and MA in a 10-year prospective case control study of 25 adult pairs who had diabetes duration between 1 and 19 years (12). None of these studies adequately addressed confounders. Little subsequent research in large cohorts has been conducted on the role of hyperfiltration, primarily due to difficulties in determining GFR.

Scott et al. studied MA onset in the First Joslin Study on Natural History of Microalbuminuria (First Joslin Kidney Study) during the first four years of follow-up (13). They found younger age at diabetes diagnosis, longer diabetes duration, poorer glycemic control, and cigarette smoking were associated with the development of MA. Serum cystatin C measurements (to estimate GFR) were not available at the time of that work. The current project builds upon this prior study by examining whether hyperfiltration, as measured by cystatin C, is associated with the development of MA during 15 years of follow-up, after taking into account known risk factors.

METHODS

Study Group: The study group is derived from the cohort of the First Joslin Kidney Study on the Natural History of Microalbuminuria. Enrollment was as follows: From January 1991- April 1992, every other Joslin Clinic patient with type 1 diabetes aged 15-44 years who resided in Massachusetts had their urine examined for MA using an albumin-to-creatinine ratio (ACR). Based on the initial screening and additional measurements obtained over a two-year baseline interval, patients (n=1602) were categorized as having normoalbuminuria (n=1080), MA (n=312) or proteinuria (n=210). Men with a median ACR < 17 mg/g or women with a median ACR < 25 mg/g were classified as having normoalbuminuria (n=1080), MA (n=312) or proteinuria (n=210). Men with a median ACR < 17 mg/g or women with a median ACR < 25 mg/g were classified as having normoalbuminuria and men with median ACR between 17 and 250 mg/g and women with median ACR between 25 and 355 mg/g were classified as having MA. Patients with proteinuria were not followed for assessments of albumin excretion rate. All participants with MA and a 50% sample of participants with normoalbuminuria were invited to participate in an entry examination during the first two years of the study. The examined participants...
with normoalbuminuria who still had stored blood samples for measuring cystatin C were the focus of the current investigation.

**Entry examination and measurements of characteristics and exposures:** At the entry examination, a trained study recruiter administered a questionnaire to obtain medical and diabetes history, collected samples of blood and urine, and measured seated blood pressures twice, separated by a 5-minute rest. Chart review supplemented questionnaire information as needed.

Electronic medical record information captured clinical characteristics such as repeated measures of hemoglobin A1c (HbA1c) and ACR. Details of these assays have been published previously (14). The equation for the conversion of ACR to AER was \( \log_{10}(\text{AER}) = 0.44 + (0.85)\log_{10}(\text{ACR}) - (0.13)\text{sex} \), where sex = 1 for women and 0 for men (14). Baseline HbA1c was the mean of all HbA1c measurements over the year before entry examination including HbA1c drawn at the examination. Baseline exposures and characteristics measured for study-specific reasons (such as cystatin C) or related to calendar time (such as age and duration of diabetes) were measurements from the date of entry examination.

Serum cystatin C has been shown to estimate GFR well in diabetes populations with normal or elevated renal function (2, 3, 15). The equation to estimate GFR from cystatin C has been developed by MacIsaac (cC-GFR = (86.7/cystatin C) - 4.2) (3). All serum samples were stored at -85°C Celsius until the day of assay. Samples were thawed, vortexed for 5 seconds, and microcentrifuged at 13,200 rpm for 10 minutes. Samples were then analyzed for cystatin C concentration (Dade Behring Diagnostics) on a BN Prospec™ System nephelometer (Dade Behring Incorporated, Newark, DE, USA). The reported reference interval for cystatin C is 0.53 to 0.95 mg/L for young, healthy individuals. Factory-provided controls are measured on the day of each run for quality control.

We estimated cC-GFR in healthy non-diabetic individuals aged 18-44 years. They were the non-diabetic relatives examined for our family-based study of the genetics of diabetic nephropathy in type 2 diabetes (16). Their serum cystatin C concentrations were determined in the same laboratory by the same method as those for the current study. In these non-diabetic individuals, the distribution of cC-GFR was higher for women than for men (Figure 1). We defined hyperfiltration as a cC-GFR exceeding the sex-specific 97.5th percentile in non-diabetics: >149 and >134 ml/min/1.73m² for women and men, respectively. In previous studies authors used similar definitions (125–140 ml/min/1.73m²), but the definitions were not sex specific (8, 7, 6).

**Follow-up of eligible study group:** Patients were followed for the development of MA over 15 years through routine clinic appointments, home visits by patient recruiters, and mailed urine kits. Of the 502 patients with a study examination, 473 participants qualified by having samples remaining for the measurement of cC-GFR. We excluded participants who developed MA before the first examination and those with less than one year AER follow-up after examination (n=17). Also excluded were 30 participants who did not have HbA1c measurements within a year before the cC-GFR measurement and those who did not have information on smoking status. Thus, 426 participants remained eligible for this study.

**Outcome – Time to onset of microalbuminuria:** The outcome was time to MA development. The onset of MA occurred when two consecutive AER measurements reached the MA range (AER > 30 µg/min). The date of the first AER of the pair was the date of the onset. **Statistical methods:** All statistical analyses were conducted in SAS V
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9.1 (SAS Institute, Cary, NC). Descriptive analyses (mean and standard deviations for continuous variables; percent and counts for categorical variables) compared clinical characteristics among those with and without hyperfiltration during baseline.

The hazard ratio (HR) of developing MA during 5, 10 and 15 years of follow-up and corresponding 95% confidence intervals were calculated using Cox proportional hazards modeling (PROC PHREG). Next, adjusted HRs were calculated comparing participants who were and were not hyperfiltering at baseline. The potential confounders (baseline HbA1c, age at diabetes diagnosis, diabetes duration, and cigarette smoking status) were entered into the multivariate model. To assess effect measure modification, we stratified on gender, baseline HbA1c, age at diabetes diagnosis, and diabetes duration.

Changes in the hyperfiltration status of patients with multiple cC-GFR measures over time were determined. To be eligible for this analysis, patients had at least 2 determinations at least 2 years apart. The median was 3 determinations and median follow-up of cC-GFR was 9 years. Over time, hyperfiltration could have been consistently present, consistently absent or have been inconsistent. These results were incorporated into an analysis that allowed hyperfiltration status to vary over time. Last, as in the analysis of baseline hyperfiltration status, unadjusted and adjusted HR for MA were calculated during 5, 10 and 15 years of follow-up.

RESULTS

Characteristics of study participants with and without renal hyperfiltration at baseline are displayed in Table 1. Renal hyperfiltration was defined as a cC-GFR exceeding 134 for men and 149 ml/min/1.73m² for women, the sex-specific 97.5th percentiles in non-diabetic individuals (Figure 1). There were 24% of patients with renal hyperfiltration in the study group. Those with hyperfiltration were older, more likely to be female, had shorter diabetes duration, later age of onset of diabetes, and slightly higher HbA1c levels. Systolic and diastolic blood pressure, body mass index (BMI), and percentage of current smokers were similar among those with and without hyperfiltration. MA developed in twenty-three percent (74/322) of participants without and nineteen percent (20/104) of those with hyperfiltration at baseline.

HRs for developing MA comparing participants with and without hyperfiltration at baseline are shown in Table 2. Hyperfiltration did not increase the rate of developing MA. The unadjusted HR was 0.8 (95% CI: 0.4, 1.7) during the first 5 years, 1.0 (95% CI: 0.6, 1.7) during the first 10 years, and 0.8 (95% CI: 0.5, 1.4) during 15 years of follow-up. In a model adjusting for known risk factors for MA (HbA1c, age at diabetes diagnosis, diabetes duration, and current cigarette smoking), the HRs were little changed: 0.8 (95% CI: 0.4, 1.7) during the first 5 years, 1.0 (95% CI: 0.5, 1.7) during the first 10 years, and 0.9 (95% CI: 0.6, 1.4) during 15 years of follow-up. There was also no effect measure modification due to gender, baseline HbA1c, age at diabetes diagnosis, and diabetes duration. Results were identical as in Table 2, when we performed a sensitivity analysis using lower (95th percentile) or higher (99th percentile) cutoffs for renal hyperfiltration (data not shown).

There were 243 participants with multiple cC-GFR measures over follow-up. Hyperfiltration was absent throughout follow-up (median 11 years) in sixty-nine percent (167/243). Hyperfiltration was consistently present in four percent (9/243); however, they had shorter follow-up than those whose hyperfiltration status changed. Hyperfiltration status changed in twenty-eight percent (67/243). In the majority of these, baseline hyperfiltration resolved during follow-up.
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(37/67). In a few instances, baseline hyperfiltration resolved only to return (n=9). In the remainder, hyperfiltration developed during follow-up and remained (n=13) or resolved to normal (n=8). Similar to the consistently hyperfiltering group, the group with hyperfiltering that developed during follow-up and remained had shorter follow-up than other groups. This suggests that if follow-up were longer, these participants may have returned to normal filtration levels, albeit this was a small proportion of the total group with follow-up cC-GFR (19/243).

Incorporating changes in hyperfiltration status over follow-up (time-varying analysis) had minimal impact on the HR. The unadjusted HR for MA comparing those with and without hyperfiltration at baseline was 0.6 (95% CI: 0.3, 1.4) during the first 5 years, 1.0 (95% CI: 0.6, 1.7) during the first 10 years, and 1.0 (95% CI: 0.6, 1.7) during 15 years of follow-up. Similar to the analysis of baseline hyperfiltration, there was minimal confounding due to the other risk factors. The adjusted HR during 5, 10, and 15 years of follow-up was 0.7 (95% CI: 0.3, 1.5), 1.0 (95% CI: 0.6, 1.8), 1.1 (95% CI: 0.7, 1.8), respectively.

DISCUSSION

In our 15-year follow-up of AER in a cohort of young adults with type 1 diabetes, neither the presence of hyperfiltration at baseline nor its development subsequently was a risk factor for the development of MA within 5, 10 or 15 years. There was very little confounding by HbA1c, age at diabetes diagnosis, diabetes duration, and current cigarette smoking in the relation between hyperfiltration and MA development. There was also no effect measure modification on the relation between hyperfiltration and MA due to gender, baseline HbA1c, age at diabetes diagnosis, and diabetes duration.

In the subset of the cohort with multiple measurements of cC-GFR during follow-up, we characterized the patterns of change in hyperfiltration status. It did not change in the majority of individuals. Hyperfiltration was never present in 66% and always present in 4%. In the remaining 30% where the status changed, the change was resolution of hyperfiltration in the majority and development of hyperfiltration in a small minority.

Most data on the biologic mechanisms underlying the impact of hyperfiltration on the kidney come from animal models (17). In those models, hyperfiltration increases glomerular pressure and flow, which initiate destructive processes in the kidney (5,6). However, hyperfiltration is benign in some human conditions other than diabetes, so hyperfiltration cannot be the problem by itself (18). Under experimental conditions, induction of hyperglycemia in humans with diabetes increases the GFR in those with hyperfiltration but not in those with normal GFR or in individuals without diabetes (19). In our study, hyperglycemia predicted the onset of MA, but hyperfiltration did not, so the effect of glycemic control is not through an effect on GFR.

Our findings differ with the results of several studies, but the disagreements may be due to methodological limitations in those studies. For instance in Chiarelli et al., hyperfiltration predicted MA over 10-year follow-up in a prospective case-control study of children and young adults aged 9-19 years (7). However, with only 8 cases of MA divided between 23 individuals with hyperfiltration and 23 without, their result has large statistical uncertainty. Moreover, the analysis did not control for confounding by HbA1c. Amin et al. tested the hyperfiltration and MA hypothesis in a 5-year follow-up study of 273 children with five years diabetes duration. MA developed in 30 children (8). After controlling for HbA1c, the estimated HR of 1.02 per unit of GFR was statistically significant. The clinical meaningfulness,
however, of such a small effect is questionable.

On the other hand, our findings are consistent with a number of studies. In the late 1980s, Lervang et al. studied on 29 patients with type 1 diabetes who had been studied 18 years previously when diabetes duration averaged 2 years (range 0 to 9 years) (20). The AER did not differ according to hyperfiltration status at baseline. They suggested that the disagreement with other study findings might have been due to their population’s older age at onset (age 19 on average) (21, 22). Steinke et al. did not find compelling evidence that hyperfiltration predicted MA and suggested that differences among studies may be due to variable definitions of hyperfiltration and AER progression and the inclusion of patients with very short duration of diabetes (11). Levine hypothesized that the duration of hyperfiltration, which is not usually taken into consideration, may be an important factor in kidney damage (17).

One 5-year prospective case-control study of adults with type 1 diabetes and without proteinuria or hypertension found no difference in AER according to hyperfiltration status at baseline (23). However, in this study the rate of renal function decline was faster in those with hyperfiltration than those without. In a study of the same patients at ten years of follow-up, the rate of decline continued to differ according to hyperfiltration status at baseline. However, the absolute GFR remained higher in the hyperfiltration group (12).

The First Joslin Kidney Study has many strengths, including a large, well-characterized cohort followed prospectively over 15 years. The availability of a detailed entry questionnaire and repeated visits that generated laboratory data and stored specimens allowed the examination of novel definitions of exposures and outcomes. Moreover, frequency AER measurements yielded more reliable determinations of renal status than studies based on single measurements, and the sample size enabled us to control for confounders and assess effect measure modification.

One limitation of the current study, however, is that an individual with hyperfiltration occurring and resolving before entry into the study was misclassified. Similarly, we were unable to assess the effect of hyperfiltration occurring and resolving very soon after diabetes onset due to the small number of people studied with less than five years duration. It is possible that renal hyperfiltration has a more immediate impact on the development of MA, and studies started during childhood have captured this information but follow-up was short so outcomes were few.

In conclusion, this study provides evidence that hyperfiltration is not a risk factor for the development of MA in type 1 diabetes. There was little change in the HR at 5, 10 or 15 years when accounting for known risk factors and potential confounders, and there was no effect measure modification by gender, baseline HbA1c, age at diabetes diagnosis, and diabetes duration.

ACKNOWLEDGEMENTS
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REFERENCES


**Table 1.** Selected baseline characteristics of participants according to baseline renal hyperfiltration status.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No hyperfiltration (n=322) Mean (sd) or percent (n)</th>
<th>Hyperfiltration (n=104) Mean (sd) or percent (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women (%)</td>
<td>48%</td>
<td>61%</td>
</tr>
<tr>
<td>Age (years)</td>
<td>29 (8)</td>
<td>31 (7)</td>
</tr>
<tr>
<td>Diabetes Duration (years)</td>
<td>14 (8)</td>
<td>12 (7)</td>
</tr>
<tr>
<td>Age of diabetes diagnosis (years)</td>
<td>15 (8)</td>
<td>19 (8)</td>
</tr>
<tr>
<td>Mean HbA1c (%)</td>
<td>8.1 (1.3)</td>
<td>8.6 (1.7)</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>119 (13)</td>
<td>117 (14)</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>71 (8)</td>
<td>72 (8)</td>
</tr>
<tr>
<td>Current Smoking</td>
<td>17%</td>
<td>18%</td>
</tr>
<tr>
<td>Body Mass Index (Kg/m2)</td>
<td>24.3 (3.0)</td>
<td>23.1 (2.6)</td>
</tr>
<tr>
<td>cC-GFR (ml/min/1.73m²)</td>
<td>122 (13)</td>
<td>155 (13)</td>
</tr>
<tr>
<td>Developed Microalbuminuria* (%)</td>
<td>23%</td>
<td>19%</td>
</tr>
</tbody>
</table>

* Developed confirmed microalbuminuria during 15 year follow-up

( ) Standard deviation

**Table 2.** Unadjusted and adjusted hazard ratios (HR) of developing microalbuminuria (MA) comparing individuals with and without renal hyperfiltration* at baseline.

<table>
<thead>
<tr>
<th></th>
<th>Events of MA</th>
<th>Total Person-Years</th>
<th>Unadjusted HR (95% CI)</th>
<th>Adjusted HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 year HR</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No Hyperfiltration</td>
<td>35</td>
<td>1500</td>
<td>1 (Ref)</td>
<td>1 (Ref)</td>
</tr>
<tr>
<td>Hyperfiltration</td>
<td>9</td>
<td>486</td>
<td>0.8 (0.4, 1.7)</td>
<td>0.8 (0.4, 1.7)</td>
</tr>
<tr>
<td>10 year HR</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No Hyperfiltration</td>
<td>53</td>
<td>2744</td>
<td>1 (Ref)</td>
<td>1 (Ref)</td>
</tr>
<tr>
<td>Hyperfiltration</td>
<td>17</td>
<td>888</td>
<td>1.0 (0.6, 1.7)</td>
<td>1.0 (0.5, 1.7)</td>
</tr>
<tr>
<td>15 year HR</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No Hyperfiltration</td>
<td>74</td>
<td>3574</td>
<td>1 (Ref)</td>
<td>1 (Ref)</td>
</tr>
<tr>
<td>Hyperfiltration</td>
<td>20</td>
<td>1145</td>
<td>0.8 (0.5, 1.4)</td>
<td>0.9 (0.6, 1.4)</td>
</tr>
</tbody>
</table>

* Hyperfiltration defined as exceeding 97.5th percentile of cC-GFR in a non-diabetic, similar aged population. For women this cutoff was 149 ml/min/1.73m² and for men 134 ml/min/1.73m².

† Adjusted by baseline mean HbA1c, age at diabetes diagnosis, diabetes duration, and current cigarette smoking.
Figure 1:
A) Distribution of cC-GFR measurements at baseline in men with (n= 210) and without diabetes (n=127) of similar age (18-44 years).
B) Distribution of cC-GFR measurements at baseline in women with (n= 216) and without diabetes (n=136) of similar age (18-44 years).

Measurements of serum cystatin C concentrations in diabetics and non-diabetics were performed in the same laboratory, according to the same method and the same formula was used to estimate cC-GFR (see methods).