Glomerular hyperfiltration in prediabetes and prehypertension

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Abstract

Background. This study aimed to investigate the associations of hyperfiltration and hypofiltration with prediabetes and prehypertension.

Methods. The study subjects included 99,140 people aged 20–89 years who underwent health checkups in Aichi Prefecture, Japan. The prevalence of hyperfiltration [estimated glomerular filtration rate (eGFR) above the age-/sex-specific 95th percentile] and hypofiltration (eGFR below the age-/sex-specific 5th percentile) was compared among stages of prediabetes (fasting plasma glucose <100, 100–109, 110–125 and ≥126 mg/dL for no prediabetes, Stage 1 prediabetes, Stage 2 prediabetes and diabetes, respectively) and prehypertension [blood pressure (BP) <120/80, 120–129/80–84, 130–139/85–89 and ≥140/90 mmHg for no prehypertension, Stage 1 prehypertension, Stage 2 prehypertension and hypertension, respectively].

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Results. The prevalence of hyperfiltration increased with increasing stage of prediabetes [odds ratios (ORs): 1.29, 1.58 and 2.47 for Stage 1 prediabetes, Stage 2 prediabetes and diabetes, respectively] and prehypertension (ORs: 1.10, 1.33 and 1.52 for Stage 1 prehypertension, Stage 2 prehypertension and hypertension, respectively). Hypofiltration was not associated with prediabetes or prehypertension.

Conclusions. The prevalence of glomerular hyperfiltration increased with increasing stages of prediabetes and prehypertension. Therefore, kidney function should be monitored in subjects with prediabetes or prehypertension. In subjects with hyperfiltration, earlier treatment of hyperglycemia and high BP may be necessary to prevent the development of kidney damage.

Keywords: glomerular hyperfiltration; prediabetes; prehypertension

Introduction

Glomerular hyperfiltration is well-recognized as an early renal alteration in subjects with diabetes and hypertension [1, 2], and it may be a marker for subsequent kidney damage characteristic of hyperfiltration in chronic kidney disease (CKD) and end-stage renal disease (ESRD) [3–7]. However, it is unclear whether hyperfiltration occurs in the early stages of hyperglycemia and high blood pressure (BP), such as in prediabetes and prehypertension [8, 9]. Because hyperfiltration is considered to represent an early and reversible stage of kidney damage [7], identifying subjects at increased risk for CKD/ESRD among those with prediabetes/prehypertension by identifying individuals with hyperfiltration may be an important and effective preventative strategy.

However, so far, there are no widely accepted definitions for hyperfiltration [10]. Using fixed reference values, many young subjects are defined as having hyperfiltration, reflecting the decline in glomerular filtration rate (GFR) with age. The same problem occurs for hypofiltration because many subjects are defined as having CKD, even though their risk for this disease may not be high [11]. Thus, age- and sex-specific reference values for hyperfiltration and hypofiltration are needed.

Therefore, the objectives of this study were to (i) determine reference values for hyperfiltration and hypofiltration according to age and sex in subjects without prediabetes or prehypertension and (ii) investigate the associations of hyperfiltration and hypofiltration with prediabetes and prehypertension.

Materials and methods

Study population

The Aichi CKD Epidemiology Conference was initiated in 2008 with the support of the Aichi Kidney Foundation for the purpose of surveying the prevalence of CKD in Aichi prefecture, Japan. Four large-scale community- or bureau-based health-check centers in Okazaki, Hiekan and Kasugai Cities and Chita County in Aichi prefecture were invited to enroll in this study. The centers provided data for participants who enrolled in their health checkup programs conducted between April 2006 and March 2008. The latest data for each participant were used. Subjects aged 20–89 years with complete data for the following characteristics were included in this study: serum creatinine, age, sex, systolic/diastolic BP and fasting plasma glucose (FPG). This study was approved by the Ethics Committee of Nagoya University Graduate School of Medicine.

Estimation of the GFR

Serum creatinine (SCr) was measured in all participants using an enzymatic method. The method used to measure SCr was initially calibrated at the Central Laboratory in Aichi prefecture for all four centers, and their precision and accuracy were authorized by the Japanese Association of Medical Technologists. The GFR of each participant was estimated from the SCr value, using the modified Modification of Diet in Renal Disease (MDRD) equation (adapted for Japanese by the Japanese Society of Nephrology [12]), as follows:

\[
\text{Estimated GFR (eGFR) (mL/min/1.73m²)} = 194 \times \frac{\text{SCr}^{-1.094} \text{[mg/dL]} \times \text{age}^{-0.287} \text{[years]} \times 0.739 \text{ if female}}{72}
\]

Definition of hyperfiltration and hypofiltration in healthy subjects

The distributions of eGFR in subjects without prediabetes (FPG < 100 mg/dL) and prehypertension (BP < 120/80 mmHg) were divided into 10-year age groups. Subjects being treated for diabetes, hypertension, kidney diseases and cancer and those with proteinuria (urinary protein \( \geq 1 \) on dipstick test) were excluded. The number of subjects aged \( \geq 80 \) years was too small to derive reference values, so they were combined with those aged \( \geq 70 \) years. Hyperfiltration was defined as eGFR above the age- and sex-specific 95th percentile for healthy subjects, while hypofiltration was defined as eGFR below the 5th percentile.

Prevalence of hyperfiltration and hypofiltration according to the stages of prediabetes and prehypertension

Using the reference values determined as above, all of the participants were divided according to their eGFR as showing hyperfiltration, normal filtration and hypofiltration. The characteristics of the subjects were compared between those with hyperfiltration/hypofiltration and normal filtration. The prevalence of hyperfiltration and hypofiltration was also compared according to the stages of prediabetes and prehypertension [8, 9]. Subjects were categorized as having normal fasting glucose (i.e. no prediabetes; FPG < 100 mg/dL), Stage 1 prediabetes (FPG 100–109 mg/dL), Stage 2 prediabetes (FPG 110–125 mg/dL) or diabetes (FPG \( \geq 126 \) mg/dL or under treatment for diabetes). Subjects were also categorized as having normal BP (i.e. no prehypertension; BP < 120/80 mmHg), Stage 1 prehypertension (BP 120–129/80–84 mmHg), Stage 2 prehypertension (BP 130–139/85–89 mmHg) or hypertension (BP \( \geq 140/90 \) mmHg or under treatment for hypertension).

Statistical analysis

Odds ratios (ORs) and 95% confidence intervals were estimated for hyperfiltration and hypofiltration using unconditional logistic regression analysis adjusted for age and sex (adjusted ORs) and for age, sex, body mass index, high-density lipoprotein cholesterol (HDL-C), lipid-lowering medication use, uric acid and smoking status. The analyses of stages of prediabetes were also adjusted for systolic BP and anti-hypertensive medication use, while analyses of stages of prehypertension were also adjusted for FPG and glucose-lowering medication use as the stages of prediabetes and prehypertension were confounding (fully adjusted ORs). Proteinuria was not adjusted in the analysis because proteinuria is not just a confounder to be adjusted but the outcome (kidney damage) itself. The P-values for trends were calculated using a score variable assigning 0, 1, 2 and 3 for no prediabetes, Stage 1 diabetes, Stage 2 diabetes and diabetes (or for no prehypertension, Stage 1 prehypertension, Stage 2 prehypertension and hypertension). P < 0.05 was considered statistically significant. All analyses were carried out using STATA version 9 software (StataCorp, College Station, TX).

Results

A total of 99,140 people (54,547 males and 44,593 females) aged 20–89 years participated in this study. The distribution of eGFR and the reference values for hyperfiltration/
hyperfiltration in subjects without prediabetes or prehypertension (n = 30,426) for each 10-year age group are shown in Figure 1. Among those aged 50–59 years, the reference values for hyperfiltration and hypofiltration were ~100 and 60 mL/min/1.73m², respectively, for both sexes.

The characteristics of subjects according to filtration status are shown in Table 1. We found no clinically important differences between subjects with hyperfiltration and those with normal filtration except for fasting blood glucose level, while more of the subjects with hypofiltration were older males with higher uric acid, dyslipidemia and proteinuria, as compared with subjects with normal filtration.

Table 2 shows the prevalence of hyperfiltration and hypofiltration according to the stages of prediabetes and prehypertension. The prevalence of hyperfiltration increased with increasing stage of prediabetes (ORs: 1.29, 1.58 and 2.47 for Stage 1 prediabetes, Stage 2 prediabetes and diabetes, respectively; P for trend: <0.001) and stage of prehypertension (ORs: 1.10, 1.33 and 1.52 for Stage 1 prehypertension, Stage 2 prehypertension and hypertension, respectively; P for trend: <0.001). We found no association between hypofiltration and prediabetes or prehypertension, as the age- and sex-adjusted ORs were almost 1.00. Furthermore, hypofiltration was only weakly associated with diabetes and hypertension.

**Discussion**

We found that the prevalence of hyperfiltration increased with increasing stages (i.e. worsening) of prediabetes and prehypertension. This suggests that renal function should be monitored in people with prediabetes or prehypertension to identify those with hyperfiltration who might be at increased risk for subsequent kidney damage.

Glomerular hyperfiltration is a well-recognized early renal change in subjects with diabetes and hypertension [1, 2], partly because of inappropriate afferent arteriole dilatation in diabetes [13] or elevated glomerular hydraulic pressure in hypertension [5]. GFR was reported to decrease significantly faster in subjects with hyperfiltration [1], and long-standing hyperfiltration may contribute to the development of kidney damage [3, 4]. Kidney failure may occur in people having had hyperfiltration for 30 years [5] because of progressive glomerular sclerosis that occurs as a result of prolonged glomerular hyperfiltration [6]. Preventing glomerular hyperfiltration can reduce glomerular injury [7].

New designations for prediabetes (impaired fasting glucose or impaired glucose tolerance) and prehypertension

![Fig. 1. Distribution of eGFR in subjects without prediabetes or prehypertension by sex and age (n = 30,426). The 95th and 5th percentiles are shown in 10-year age groups. Subjects with prediabetes (FPG ≥ 100 mg/dL), prehypertension (BP ≥ 120/80 mmHg), confirmed proteinuria (urinary protein ≥ 1+ on dipstick test) or being treated for diabetes, hypertension, renal diseases or cancer were excluded from this analysis. Hyperfiltration was defined as an eGFR over the age- and sex-specific 95th percentile and hypofiltration was defined as an eGFR below the 5th percentile.](image-url)

| Table 1. Characteristics of subjects with hyperfiltration/hypofiltration compared with subjects with normal filtration (N = 99,140) |
|---------------------------------------------------------------|---------------------------------|---------------------------------|
| Normal filtration (n = 87,251)                                | Hyperfiltration (n = 55,484)      | Hypofiltration (n = 63,41)      |
| Age (years)                                                   | 50.5 ± 15.1                      | 51.4 ± 14.8                     | 55.0 ± 16.0                     |
| Female                                                        | 39.455 (45.2%)                   | 2531 (45.6%)                    | 2607 (41.1%)                    |
| Body mass index                                               | 22.63 ± 3.28                     | 22.41 ± 3.65                    | 23.28 ± 3.32                    |
| FPG (mg/dL)                                                   | 94.7 ± 15.6                      | 100.9 ± 30.6                    | 95.2 ± 15.1                     |
| HbA1c (%)                                                     | 5.17 ± 0.47                      | 5.30 ± 0.92                     | 5.22 ± 0.44                     |
| Glucose-lowering medication                                  | 3116 (3.6%)                      | 400 (7.2%)                      | 416 (6.6%)                      |
| Systolic BP (mmHg)                                            | 122.1 ± 15.9                     | 123.8 ± 16.6                    | 123.2 ± 17.0                    |
| Diastolic BP (mmHg)                                           | 74.4 ± 10.4                      | 74.5 ± 10.7                     | 75.5 ± 11.0                     |
| Anti-hypertensive medication                                 | 11.698 (13.4%)                   | 830 (15.0%)                     | 1667 (26.3%)                    |
| HDL-C (mg/dL)                                                 | 67.4 ± 17.8                      | 67.7 ± 17.9                     | 64.8 ± 18.4                     |
| Triglycerides (g/dL)                                          | 88 (61–129)                      | 87 (61–128)                     | 100 (69–145)                    |
| Lipid-lowering medication                                    | 5841 (7.7%)                      | 337 (6.6%)                      | 730 (12.7%)                     |
| Uric acid (mg/dL)                                             | 5.29 ± 1.37                      | 4.77 ± 1.33                     | 6.15 ± 1.53                     |
| Proteinuria                                                   | 3367 (3.9%)                      | 270 (4.9%)                      | 812 (12.9%)                     |
| Ever smokers                                                  | 34,843 (39.9%)                   | 2360 (42.5%)                    | 2354 (37.1%)                    |

aSubjects taking glucose-lowering medication are excluded.

bSubjects taking anti-hypertensive medication are excluded.

Subjects taking lipid-lowering medication are excluded. Data are mean ± SD, number (%) or median (interquartile range) for triglycerides. Hyperfiltration was defined as an eGFR over the age- and sex-specific 95th percentile and hypofiltration was defined as an eGFR below the 5th percentile as shown in Figure 1.
Stages of prehypertension 

<table>
<thead>
<tr>
<th>No prehypertension (BP &lt;120/80 mmHg)</th>
<th>64 566</th>
<th>3525 (4.9%)</th>
<th>1 (reference)</th>
<th>1 (reference)</th>
<th>1 (reference)</th>
<th>4384</th>
<th>1 (reference)</th>
<th>1 (reference)</th>
<th>0.813</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 1 prehypertension (BP 120-129/80-84 mmHg)</td>
<td>12 024</td>
<td>787 (5.7%)</td>
<td>1.22 (1.12–1.32)</td>
<td>1.29 (1.17–1.41)</td>
<td>0.96 (0.94–1.09)</td>
<td>0.89</td>
<td></td>
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</tr>
<tr>
<td>Stage 2 prehypertension (BP 130-139/85-89 mmHg)</td>
<td>4938</td>
<td>408 (7.1%)</td>
<td>1.53 (1.37–1.71)</td>
<td>1.58 (1.38–1.80)</td>
<td>0.95 (0.85–1.06)</td>
<td>0.77</td>
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</tr>
<tr>
<td>Hypertension (BP ≥140/90 mmHg or under treatment)</td>
<td>5723</td>
<td>828 (11.6%)</td>
<td>2.81 (2.58–3.06)</td>
<td>2.47 (2.22–2.75)</td>
<td>0.95 (0.85–1.06)</td>
<td>0.88</td>
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</table>

Stages of prediabetes 

<table>
<thead>
<tr>
<th>No prediabetes (FPG &lt;100 mg/dL)</th>
<th>64 566</th>
<th>3525 (4.9%)</th>
<th>1 (reference)</th>
<th>1 (reference)</th>
<th>1 (reference)</th>
<th>4384</th>
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<td>Stage 1 prediabetes (FPG 100-109 mg/dL)</td>
<td>12 024</td>
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<td>0.96 (0.94–1.09)</td>
<td>0.89</td>
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<td></td>
</tr>
<tr>
<td>Stage 2 prediabetes (FPG 110-125 mg/dL)</td>
<td>4938</td>
<td>408 (7.1%)</td>
<td>1.53 (1.37–1.71)</td>
<td>1.58 (1.38–1.80)</td>
<td>0.95 (0.85–1.06)</td>
<td>0.77</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes (FPG ≥126 mg/dL or under treatment)</td>
<td>5723</td>
<td>828 (11.6%)</td>
<td>2.81 (2.58–3.06)</td>
<td>2.47 (2.22–2.75)</td>
<td>0.95 (0.85–1.06)</td>
<td>0.88</td>
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</tbody>
</table>

Table 2. Prevalence of hyperfiltration/hypofiltration according to the stages of prediabetes and prehypertension in all the subjects (N = 99 140) 

<table>
<thead>
<tr>
<th>Normal filtration (n = 87 251)</th>
<th>Hyperfiltration (n = 5548)</th>
<th>Fully adjusted OR (95% CI)</th>
<th>P for trend</th>
<th>Hypofiltration (n = 6341)</th>
<th>Fully adjusted OR (95% CI)</th>
<th>P for trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (%)</td>
<td>Adjusted OR (95% CI)</td>
<td>n (%)</td>
<td>Adjusted OR (95% CI)</td>
<td>n (%)</td>
<td>Adjusted OR (95% CI)</td>
<td>n (%)</td>
</tr>
</tbody>
</table>

aAdjusted for age and sex.

bAdjusted for age, sex, body mass index, high-density lipoprotein (HDL-C), lipid-lowering medication use, uric acid and smoking status. 

were recently introduced [8, 9]. Subjects with prediabetes and prehypertension are at increased risk for the development of CKD [14, 15] and ESRD [16, 17]. As a large proportion of the population has prediabetes and prehypertension (20 and 37% in our study), identifying subjects at increased risk for CKD/ESRD among those with prediabetes or prehypertension by finding those with hyperfiltration may represent a beneficial and effective preventative strategy.

We found significant associations between hyperfiltration and prediabetes or prehypertension in a large population of subjects. To our knowledge, the only other study to have shown an association between hyperfiltration and prediabetes contained a small number of subjects with prediabetes (n = 24) [18]. On the other hand, we are aware of no studies describing an association between hyperfiltration and prehypertension. Thus, this study is the largest study to date to show associations of hyperfiltration with prediabetes and prehypertension.

Interestingly, we found no association between hypofiltration and prediabetes or prehypertension. It is possible that prediabetes and prehypertension are associated with earlier stages of kidney damage (i.e. glomerular hyperfiltration), while long-term diabetes and hypertension are associated with hypofiltration and CKD. The finding that
Hyperfiltration in prediabetes and prehypertension

prehypertension was higher in our subjects. Thus, eGFR reference values for each sex and age group should be established for clinical use, particularly for older subjects. Hyperfiltration was prevalent in younger subjects followed by a higher prevalence of hypofiltration at an older age in diabetic subjects (23 and 0% in age 20s, and 7 and 13% in age 70s for prevalence of hyperfiltration and hypofiltration, respectively). This distribution is in accordance with the hyperfiltration hypothesis [5]. The Japanese eGFR equation can be used to identify people with hyperfiltration because the Japanese eGFR equation is more accurate than the MDRD Study equation, particularly for hyperfiltration [12, 21].

One limitation of our study is that we lack information on microalbuminuria and glucose tolerance following an oral glucose challenge. Thus, only impaired fasting glucose, but not impaired glucose tolerance, was used as a criterion for prediabetes. Microalbuminuria is another marker of early kidney damage, although glomerular hyperfiltration precedes the development of microalbuminuria [22]. Another limitation is that among diabetic subjects with normal filtration, subjects with renal damage who have already undergone hyperfiltration stage might be included in accordance with the hyperfiltration hypothesis [5], though this mixture does not affect the association between prediabetes and hyperfiltration. Since these results were obtained in a Japanese population, confirmation in other ethnic groups is needed.

Our findings should be considered descriptive rather than pathogenetic because we lack longitudinal data on GFR and information on microalbuminuria. Though we believe treating hyperglycemia and high BP from an early and reversible stage as hyperfiltration is important to prevent kidney damage, further confirmation by longitudinal studies is needed. Also, whether age-specific reference values reflect the risk of ESRD, cardiovascular disease or mortality should be proved by prospective studies.

In conclusion, we found that the prevalence of hyperfiltration increased with increasing stage (i.e. worsening) of prediabetes and prehypertension. Kidney function should be monitored in subjects with prediabetes or prehypertension. In people with hyperfiltration, we suggest that hyperglycemia and high BP should be treated as early as possible to prevent the development of kidney damage.

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Conflict of interest statement. None declared.


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