Relationship of diabetes with renal dysfunction in hypertensive adults

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Abstract

We aimed to examine the relationship of diabetes with the estimated glomerular filtration rate (eGFR)-based renal function in the Chinese hypertensive adults.

This cross-sectional analysis included a total of 18,641 hypertensive adults aged 45 to 75 years. The relationship of diabetes (a fasting glucose ≥7.0 mmol/L or self-reported use of hypoglycemic agents or physician diagnosed diabetes) with glomerular hyperfiltration (an absolute eGFR >90th percentile after adjusting for sex, age), hypofiltration (an eGFR <10th percentile and ≥60 mL/min/1.73 m²), and reduced eGFR (an eGFR <60 mL/min/1.73 m²) were estimated by multiple logistic regressions.

Both the cut-points for hyperfiltration and hypofiltration decreased with age increased, ranging from 115 to 91 mL/min/1.73 m² and 91 to 67 mL/min/1.73 m², respectively. In the multiple logistic models, diabetes was positively associated with glomerular hyperfiltration (odds ratio [OR]: 2.19, 95% confidence interval [CI]: 1.93–2.47), hypofiltration (1.24, 1.05–1.46), and reduced eGFR (2.88, 2.21–3.76). Furthermore, the stronger association between diabetes and hyperfiltration was found in those with younger age (P for interaction <.001), or higher total cholesterol (TC) levels (P for interaction =.008). Consistently, significant association between diabetes and hypofiltration was only observed in participants with younger age (P for interaction =.043). And detrimentally interaction between diabetes and higher TC levels was also found (P for interaction <.001) on the risk of reduced eGFR.

Diabetes was significantly associated with the impairment of renal function, particularly in those with younger age or with higher TC levels. Fasting glucose should be monitored as a marker to identify those with early renal dysfunction.

Abbreviations: BMI = body mass index, BP = blood pressure, CI = confidence interval, CKD = chronic kidney disease, DBP = diastolic blood pressure, eGFR = estimated glomerular filtration rate, ESRD = end-stage renal disease, OGTT = oral glucose tolerance test, ORs = odds ratios, SBP = systolic blood pressure, TC = total cholesterol.

Keywords: diabetes, fasting glucose, hyperfiltration, hypofiltration, reduced eGFR

1. Introduction

Chronic kidney disease (CKD) affected exceeds 10% of the population in worldwide,[1,2] and is associated with a substantial burden of mortality, morbidity, and health care costs.[3] Diabetes and hypertension, which remain the main reasons of CKD, have increased rapidly in the past 15 to 20 years and often coexisted in China.[4] However, no previous studies have examined the association of diabetes with hyperfiltration and hypofiltration, the early and reversible stages of kidney damage,[5,6] in a hypertensive sample. Furthermore, the possible modifiers for the relation of diabetes with kidney function had not been fully elucidated.

In addition, no consensus definition for hyperfiltration or hypofiltration existed.[7,8] As we know, the number of nephrons varies significantly among individuals. The whole-kidney glomerular filtration rate (GFR) will reflect variation in nephron number as well as in single-nephron GFR. Moreover, GFR and nephron number both decrease with age and are lower in women than in men.[9] Generally, using fixed reference cut-points may lead to misclassified: healthy young subjects may be defined as having hyperfiltration and healthy elders were likely to have hypofiltration, as GFR decreased 1 mL/min/1.73 m² per year of age.[10] Furthermore, men tended to have GFR decline faster than women.[11] Thus, age- and sex-adjusted threshold values for hyperfiltration and hypofiltration may be more reasonable.[12]

Therefore, in the present study, we aimed to examine the relationship of diabetes with the age- and sex-specific glomerular...
hyperfiltration, hypofiltration, and reduced eGFR in a Chinese hypertensive population.

2. Methods

2.1. Study population

In the current study, we included subjects from Lianyungang who participated in the screening phase of the China Stroke Primary Prevention Trial (CSPT),\(^{13}\) whose methods have been previously reported.\(^{14}\) The study was initiated in May 2008 with the support by Chinese governmental research grants and was approved by the Institutional Review Boards from the Institute of Biomedicine in the Anhui Medical University. Written informed consent was obtained from each participant before data collection.

Briefly we conducted a community-based screening in 20 townships within 2 counties (Ganyu, which is coastal, and Donghai, which is inland) in Lianyungang of Jiangsu province, East China.\(^{14}\) The inclusion criteria were as follows: aged 45 to 75 years; and seated systolic blood pressure (SBP) ≥140 mm Hg and/or seated diastolic blood pressure (DBP) ≥90 mm Hg in both of 2 screening visits (with at least 24 h between visits) or currently under antihypertension treatment. Participants were excluded if they reported a history of myocardial infarction, stroke, heart failure, cancer, and/or serious mental disorders; or if they were unwilling to participate in the survey.

2.2. Data collection procedures

Baseline data collection was conducted by trained research staff according to the standard operating procedure. Each participant was interviewed using a standardized questionnaire designed specifically for this study. Anthropometric measurements, including height, weight, and waist circumference, were taken using the standard operating procedure. Height was measured without shoes to the nearest 0.1 cm on a portable stadiometer. Weight was measured in light indoor clothing without shoes to the nearest 0.1 kg. Body mass index (BMI) was calculated as weight (kilograms)/height (meters) squared. Seated blood pressure (BP) measurements were obtained by trained research staff after subjects had been seated for 10 min using a mercury manometer with the standard method of calibration and appropriately sized cuffs, according to the standard operating procedure. Triplicate measurements on the same arm were taken, with at least 2 min between readings. Each patient’s systolic and diastolic BP was calculated as the mean of the 3 independent measures.

2.3. Laboratory assays

Serum creatinine, lipids, and glucose were measured using automatic clinical analyzers (Beckman Coulter, CA) at the core laboratory of the National Clinical Research Center for Kidney Disease (Nanfang Hospital, Guangzhou). Specifically, serum creatinine was measured using an enzymatic assay that has been calibrated to be isotope dilution mass spectrometry traceable. The measurement imprecisions, expressed as coefficients of variation, were 1.4%, 2.0%, and 1.5%, respectively, for serum creatinine, glucose, and total cholesterol (TC).

2.4. Definitions

Estimated glomerular filtration rate (eGFR) was calculated using the following equation derived from the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI)\(^{15}\):

\[
\text{eGFR} = 141 \times \min \left( \frac{\text{Scr}}{k} \right)^a \times \text{max} \left( \frac{\text{Scr}}{k} \right)^b \times 0.993^{\text{age}} \times 1.018^{\text{if female}}
\]

Where Scr is serum creatinine [mg/dL], \(k\) is 0.7 for females and 0.9 for males, \(a\) is \(-0.329\) for females and \(-0.411\) for males, min indicates the minimum of \(\frac{\text{Scr}}{k}\) or 1, and max indicates the maximum of \(\frac{\text{Scr}}{k}\) or 1.

Renal hyperfiltration was defined as an absolute eGFR >90th percentile after adjusting for sex, age. This was done by selecting subjects without diabetes >90th percentile in the distribution of residuals from a multiple linear regression analysis where we used the eGFR as a dependent variable and age, sex as independent variables, while hypofiltration was defined as an eGFR <10th percentile and 260 mL/min/1.73 m\(^2\). Reduced eGFR was defined as an eGFR <60 mL/min/1.73 m\(^2\).

Diabetes was defined as a fasting serum glucose ≥7.0 mmol/L or self-reported use of hypoglycemic agents or insulin or physician diagnosed diabetes.

2.5. Statistical analysis

Means and proportions were calculated appropriately for population characteristics according to glomerular filtration status, that is, normal filtration, hyperfiltration, hypofiltration, and reduced eGFR. The adjusted odds ratios (ORs) and 95% confidence interval (CI) of glomerular hyperfiltration, hypofiltration, and reduced eGFR were determined from multivariable logistic-regression models which included age, sex, BMI, systolic BP, diastolic BP, TC, uric acid levels, cigarette smoking status, use of antihypertensive drugs, and glucose lowering drugs. We also perform the subgroup analyses stratified by the potential confounding factors, which were significantly associated with kidney function (hyperfiltration, hypofiltration, or reduced eGFR), including age (45-55, 55-65, 65-75 years), sex, BMI (<28, ≥28 kg/m\(^2\)), for 28 is the threshold value of obesity in China), BP (grade 1: SBP <160 and DBP <100 mm Hg, grade 2: SBP 160-180 and/or DBP 100-110 mm Hg, grade 3: SBP ≥180 and/or DBP ≥110 mm Hg), and TC (<5.2, ≥5.2 mmol/L). Two-tailed \(P<0.05\) was considered to be statistically significant in all analyses. R software, version 3.0 (http://www.R-project.org/), was used to perform all statistical analyses.

3. Results

Overall, 20,192 subjects aged 45 to 75 years with hypertension were screened. We excluded participants subjects with missing data for age (n=242), BP (n=9), height (n=19), smoking status (n=237), fasting glucose (n=987), serum creatinine (n=3), TC (n=1), and subjects with age <45 or >75 years (n=53), resulting in a final sample of 18,641 (6825 males and 11,816 females).

3.1. Distribution of eGFR overall

The cut-points for the age- and sex-adjusted hyperfiltration or hypofiltration were shown in Figure 1. With age increased, both of the cut-points for hyperfiltration and hypofiltration decreased, ranging from 115 to 91 mL/min/1.73 m\(^2\) and 91 to 67 mL/min/1.73 m\(^2\), respectively. And normal filtration was defined as a range between hyperfiltration and hypofiltration (Fig. 1).

The prevalence of hyperfiltration, hypofiltration, reduced eGFR, and diabetes was 11.7%, 8.5%, 2.1%, and 13.9%, respectively.

3.2. Subject characteristics

The characteristics of subjects according to glomerular filtration status were shown in Table 1. Subjects with hyperfiltration were
more likely to be older, males, taking glucose-lowering drugs, with higher triglycerides and fasting glucose levels, lower level of DBP, high-density lipoprotein and uric acid, less likely smoking, or taking anti-hypertension drug. Although hypertension subjects were more likely to be females, smokers have higher DBP, uric acid, TC, and fasting glucose levels, but lower triglycerides levels. And reduced eGFR subjects were more likely to be old, males, smokers, and taking anti-hypertension drugs, have higher SBP, uric acid, TC, fasting glucose, when compared with normal filtration subjects.

3.3. Relationship of fasting glucose and diabetes with hyperfiltration, hypofiltration, and reduced eGFR

The log2-transformed fasting glucose levels were significantly associated with the hyperfiltration (OR: 2.32, 95% CI: 2.04–2.64) and reduced eGFR (3.10, 2.26–4.24). Consistently, diabetes were positively associated with hyperfiltration, hypofiltration, and reduced eGFR, with ORs of 2.18 (1.93–2.47), 1.24 (1.05–1.46), and 2.88 (2.21–3.76), respectively (Table 2).

3.4. Relationship of diabetes with hyperfiltration, hypofiltration, and reduced eGFR in subgroups

Furthermore, the strongest association between diabetes and hyperfiltration was found in those with younger age (45–55 years old: 3.14, 2.49–3.96, 55–65 years old: 2.18, 1.82–2.61 vs 65–75 years old group: 1.46, 1.15–1.86, P for interaction <.001), and higher TC levels (2.32, 2.02–2.68 in TC ≥ 5.2 mmol/L vs 1.77, 1.39–2.25 in TC < 5.2 mmol/L, P for interaction = .008). Consistently, significant association between diabetes and hypofiltration was only observed in participants with younger age (45–55 years old: 1.63, 1.21–2.19 vs 55–65 years old: 1.25, 0.98–1.59 and 65–75 years old: 0.91, 0.65–1.26, P for interaction = .043). And detrimentally interaction between diabetes and higher TC levels was also found (TC ≥ 5.2 mmol/L-3.93, 2.93–5.26 vs TC < 5.2 mmol/L: 1.54, 0.81–2.91, P for interaction <.001) on the risk of reduced eGFR. Furthermore, the relation of diabetes with glomerular hyperfiltration was stronger

Table 1 Baseline characteristics of subjects by glomerular filtration status.

|                   | Normal filtration | Hyperfiltration | Hypofiltration | Reduced eGFR |
|-------------------|-------------------|----------------|----------------|--------------|
| N                 | 14,609            | 2066           | 1579           | 387          |
| Age, y            | 59.4 ± 7.5        | 60.2 ± 7.6***  | 59.2 ± 7.7     | 64.5 ± 7.4***|
| BMI, kg/m²        | 25.7 ± 3.6        | 25.6 ± 3.7     | 26.0 ± 3.5***  | 25.0 ± 3.5***|
| Systolic blood pressure, mm Hg | 168.0 ± 20.7      | 168.4 ± 20.5   | 168.8 ± 22.7   | 173.6 ± 24.4***|
| Diastolic blood pressure, mm Hg | 95.2 ± 11.8       | 93.9 ± 11.6*** | 96.9 ± 12.4*** | 95.4 ± 14.4   |
| Uric acid, mmol/L | 290.1 ± 74.7      | 273.4 ± 80.1***| 329.7 ± 80.4***| 391.3 ± 114.1***|
| Total cholesterol, mmol/L | 5.72 ± 1.15       | 5.67 ± 1.24    | 5.92 ± 1.22    | 6.25 ± 1.97***|
| HDL-C, mmol/L     | 1.35 ± 0.37       | 1.26 ± 0.35*** | 1.36 ± 0.35    | 1.38 ± 0.42***|
| Triglyceride, mmol/L | 1.65 ± 1.18       | 2.33 ± 1.44*** | 1.53 ± 0.73*** | 1.63 ± 0.68***|
| eGFR, mL/min/1.73 m² | 95.3 ± 8.7       | 107.7 ± 8.0*** | 73.6 ± 7.3***  | 47.5 ± 12.1***|
| Fasting glucose, mmol/L | 6.0 ± 1.6        | 6.7 ± 2.0***   | 6.0 ± 1.3      | 6.7 ± 2.5***  |
| Categorical variables, no. (%) | 9340 (63.9)       | 1205 (58.3)*** | 1057 (66.9)*** | 214 (55.3)***|
| Never             | 10,462 (71.6)     | 1418 (68.6)*** | 1157 (73.3)    | 245 (63.3)***|
| Diabetes, no. (%) | 1751 (12.0)       | 492 (23.8)***  | 233 (14.8)***  | 112 (28.9)***|
| Smoking status, no. (%) | 987 (6.8)         | 171 (8.3)      | 107 (6.8)      | 40 (10.3)     |
| Former            | 3160 (21.6)       | 477 (23.1)     | 315 (19.8)     | 102 (26.4)    |
| Anti-hypertensive drugs | 8149 (55.8%)      | 1249 (60.5%)***| 704 (44.6%)*** | 165 (42.6%)***|
| ACE/ARBs          | 1312 (9.0%)       | 152 (7.4%)     | 177 (11.2%)    | 53 (13.7%)    |
| Drugs other than ACE/ARBs | 5148 (35.2%)    | 665 (32.2%)    | 698 (44.2%)    | 169 (43.7%)   |
| Glucose-lowering drugs | 193 (1.3%)       | 58 (2.8%)***   | 50 (1.9%)      | 11 (2.8%)     |

ACE = angiotensin converting enzyme inhibitors; ARB = angiotensin II type I receptor blockers; BMI = body mass index; eGFR = estimated glomerular filtration rate; HDL-C = high-density lipoprotein-cholesterol.

1 For continuous variables, values are presented as mean ± SD.
2 Hypertension was defined as absolute eGFR >90th percentile after adjusting for sex, age. Hypofiltration was defined as an eGFR < 10th percentile and ≥60 mL/min/1.73 m². Reduced eGFR was defined as an eGFR <60 mL/min/1.73 m². Diabetes was defined as a fasting glucose ≥7.0 mmol/L or self-reported use of hypoglycemic agents or physician diagnosed diabetes.

***P < .001; ** P < .01; * P < .05, compared with those with normal filtration.
in females than in males (females: 2.24, 1.91–2.61 vs males: 2.08, 1.70–2.54; P for interaction = .012) (Table 3).

Similar results were observed when we divided subjects into 3 groups by age (every 10 years a group) and defined hyperfiltration as eGFR above the age- and sex-specific 90th percentile and hyperfiltration as below the 10th percentile[16] (data are not shown).

4. Discussion

Both glomerular hyperfiltration and hypofiltration are precursors of consequent progressive GFR decline due to CKD and end-stage renal disease (ESRD) or cardiovascular mortality. CKD, rather than an inevitable outcome, can be prevented at the status of hyperfiltration or hypofiltration.[19] The future burden of CKD and its associated complications might be alleviated by further exploring the changeable risk factors of renal hyperfiltration or hypofiltration, which helps with early detection and prevention.

Diabetes in all stages affects the kidney. In early diabetes, the pathogenesis of glomerular hyperfiltration, which is a well-recognized maladaptive response that initiates and perpetuates the progression of kidney damage as diabetes develops, is mostly attributed to the joint action of hemodynamic, vasoactive, metabolic, tubular, and progrowth actors.[19] The cause at the glomerular level is an elevation of plasma flow rate and hydraulic pressure in glomerular capillaries, which in turn are attributed to the changes in systemic arterial pressure and efferent/afferent arteriolar resistance. It is hypothesized that hyperfiltration in diabetic patients would irreversibly injure some glomeruli, which alters the blood flow to the rest functioning nephrons, even accelerating the filtration rates in the rest glomeruli, which aggravates nephron loss, hypofiltration, and ESRD.[6] Consistently, our current analysis first shows that diabetes is significantly associated with the hyperfiltration, hypofiltration, or eGFR reduction in hypertensive Chinese adults. Furthermore, the major modifiers are age and TC level.

A cross-sectional study involving 662 type-2 diabetic patients shows that hyperfiltration tendency to attack the youth. The possible reason is that the manifestations with age are arterial stiffening, renovascular disease, and systolic hypertension, which were recognized to be negatively associated with both GFR and renal plasma flow.[7,20] Also, ageing kidneys, particularly in deeper juxtaglomerular glomeruli, have been identified with an elevation of filtration fraction, which is an adaption for renal function protection.[21,22] The present study consistently shows a stronger association between diabetes and hyperfiltration in younger patients.

Most interestingly, younger age also has an interaction on the relationship between diabetes and hyperfiltration. In consistency with our results, a study involving over 2 illion US veterans shows that lower eGFR is significantly more associated with the risk of mortality in the younger than older adults.[23] Another study from the United Kingdom shows that the standardized mortality ratio is higher in the younger patients with elevated serum creatinine (≥1.7 mg/dL for at least 6 months).[24] Nevertheless, our results and the underlying mechanisms should be confirmed by further studies.

In addition, the interaction between diabetes and hypercholesterolemia (TC ≥5.2 vs <5.2 mmol/L) was detrimental to the prevalence of hyperfiltration and eGFR reduction. Hypercholesterolemia is suggested to be critical in the development of renal dysfunction, either through the toxic effects of lipids on mesangial cells or by quickening the atherosclerosis of kidney arteries.[25] We hypothesize that the hypercholesterolemia status may aggravate the glycemic-induced renal damages. Nevertheless, the relationships among cholesterol, diabetes, and kidney dysfunction should be confirmed by future studies.

Despite the slight difference (females: 2.24, 1.91–2.61 vs males: 2.08, 1.70–2.54; P for interaction = .012), the relationship between diabetes and glomerular hyperfiltration is stronger in females versus males. This sex difference may be attributed to the between-sex difference in the renal hemodynamic function in response to hyperglycemia. Female diabetic patients experienced loss of afferent arteriolar tone,[26] which is associated with an increased renal vascular resistance and consequent hyperfiltration and hyperperfusion injury.[24] In comparison, the renal hemodynamic response to hyperglycemia changed little in men diabetic patients. This sex difference is potentially attributed to the between-sex differences in glomerular structure, changes in the production and activity of local cytokines hormones, or the direct impacts of sex hormones on kidney cells.[23] Nevertheless, our results should be supported by more studies. Further understanding the sex differences would provide new CKD control strategies.

Our study has some limitations. First, our study population was selected from a rural cohort and unrepresentative of the general Chinese population, so its generalizability to other populations, ethnicities, or subjects with CKD should be taken...
Table 3: Relationship of diabetes with hyperfiltration, hypofiltration, and reduced eGFR in subgroups∗

| Variables                  | Hyperfiltration (% of subgroup) | P for interaction | Hypofiltration (% of subgroup) | P for interaction | Reduced eGFR (% of subgroup) | P for interaction |
|----------------------------|--------------------------------|------------------|--------------------------------|------------------|-------------------------------|------------------|
| Age, y                     |                                |                  |                                |                  |                               |                  |
| <65                        | 416 (9.2)                      | 0.001            | 143 (25.3)                     | 3.14 (2.49–3.96) | 421 (9.3)                    | 1.00             |
| 65–75                      | 671 (10.7)                     | 1.00             | 229 (21.9)                     | 2.18 (1.82–2.61) | 562 (9.2)                    | 1.00             |
| ≥75                        | 487 (13.3)                     | 1.00             | 120 (19.0)                     | 1.47 (1.16–1.87) | 363 (10.3)                   | 1.00             |
| Gender                     |                                |                  |                                |                  |                               |                  |
| Male                       | 689 (12.9)                     | 1.00             | 172 (22.4)                     | 2.08 (1.70–2.62) | 129 (2.7)                   | 1.00             |
| Female                     | 885 (9.8)                      | 1.00             | 320 (21.7)                     | 2.24 (1.92–2.62) | 893 (9.8)                   | 1.00             |
| Blood pressure, mm Hg      |                                |                  |                                |                  |                               |                  |
| Grade 1                    | 466 (11.2)                     | 1.00             | 145 (23.3)                     | 2.59 (2.07–3.24) | 389 (9.6)                   | 1.00             |
| Grade 2                    | 607 (10.4)                     | 1.00             | 206 (22.8)                     | 2.45 (2.02–3.86) | 471 (10.7)                   | 1.00             |
| Total cholesterol, mmol/L  |                                |                  |                                |                  |                               |                  |
| <5.0                      | 419 (8.2)                      | 0.003            | 132 (20.8)                     | 2.90 (2.25–3.79) | 387 (8.6)                   | 1.00             |
| 5.1–7.0                   | 667 (9.7)                      | 1.00             | 225 (21.7)                     | 2.14 (1.70–2.70) | 542 (9.6)                   | 1.00             |
| ≥7.1                      | 467 (11.2)                     | 1.00             | 137 (23.3)                     | 2.52 (1.96–3.26) | 330 (9.6)                   | 1.00             |

* Hypertension was defined as absolute eGFR >90th percentile after adjusting for sex, age. Hypofiltration was defined as an eGFR <160 and DBP 110 mm Hg, grade 3: SBP ≥180 and/or DBP ≥100 mm Hg. Diabetes was defined as a fasting glucose ≥7.8 mmol/L. Reduced eGFR was defined as an eGFR <60 mL/min per 1.73 m². Diabetes was defined as an OGTT, HbA1-c, microalbuminuria, and Cystatin-C were not measured, which might underestimate the prevalence of diabetes and extent of kidney dysfunction, as Cystatin-C-based eGFR is more precise than serum creatinine-based eGFR. However, it is difficult and expensive to perform such a large-scale epidemiological survey, particularly in rural China.

Diabetes is significantly associated with the impairment of renal function, particularly in those with younger age or higher TC levels. Fasting glucose should be monitored as a marker to identify those with early renal dysfunction.

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