Glomerular hyperfiltration is a predictor of adverse cardiovascular outcomes

Gianpaolo Reboldi[1], Paolo Verdecchia[2], Gioia Fiorucci[1], Lawrence J. Beilin[3], Kazuo Eguchi[4], Yutaka Imai[5], Kazuomi Kario[4], Takayoshi Ohkubo[5,6], Sante D. Pierdomenico[7], Joseph E. Schwartz[8,9], Lindon Wing[10], Francesca Saladini[11] and Paolo Palatini[11]

[1]University of Perugia, Perugia, Italy; [2]Hospital of Assisi, Assisi, Italy; [3]University of Western Australia, Perth, Western Australia, Australia; [4]Jichi University, Tochigi, Japan; [5]Tohoku University, Sendai, Japan; [6]Shiga University of Medical Science, Otsu, Japan; [7]University of Chieti, Chieti, Italy; [8]Columbia University, New York, New York, USA; [9]Stony Brook University, Stony Brook, New York, USA; [10]Flinders University, Adelaide, South Australia; Australia; and [11]University of Padua, Padua, Italy

The association between glomerular hyperfiltration and cardiovascular events is not well known. To investigate whether glomerular hyperfiltration is independently associated with risk of adverse outcome we analyzed 8794 participants, average age 52 years enrolled in 8 prospective studies. Of these, 89% had hypertension. Using the 5th and 95th percentiles of the age- and sex-specific quintiles of CKD-EPI-calculated estimated glomerular filtration rate (eGFR), we identified three participant groups with low, high and normal eGFR. The ambulatory pulse pressure interval was wider and nighttime blood pressure fall was smaller in both the low and high than in the normal eGFR participants. During a mean follow-up of 6.2 years, there were 722 cardiovascular events. Crude event rates were significantly higher for both high (1.8 per 100-person-year) and low eGFR groups (2.1 per 100 person-year) as compared with group with normal eGFR (1.2 per 100 person-year). In multivariable Cox models including age, sex, average 24-hour blood pressure, smoking, diabetes, and cholesterol, both high eGFR (hazard ratio 1.5 (95% confidence interval 1.2-2.1) and low eGFR (2.0 [1.5-2.6]) participants had a significantly higher risk of cardiovascular events as compared to those with normal eGFR. Addition of body mass index to the multivariable survival model did not change the magnitude of hazard estimates. Thus, glomerular hyperfiltration is a strong and independent predictor of cardiovascular events in a large multiethnic population of predominantly hypertensive individuals. Our findings support a U-shaped relationship between eGFR and adverse outcome.

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Correspondence: *Paolo Palatini, Department of Medicine, University of Padua, Via Giustiniani 2, 35128 Padua, Italy. E-mail: palatini@unipd.it*

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Chronic kidney disease (CKD) is recognized as a global public health problem affecting a large portion of the population.[1] It is well established that a lower than normal glomerular filtration rate (GFR) is a strong and independent predictor of both end-stage renal disease and cardiovascular morbidity and mortality.[2–4] However, the association between an abnormally elevated GFR, a clinical condition called glomerular hyperfiltration (GHF),[5] and the risk of cardiovascular events (CVEs) remains uncertain. It has been postulated that GHF represents an early stage of CKD,[5,6] and a number of studies suggest that GHF is associated with clinical conditions such as hypertension,[2,7] diabetes,[3,8] obesity,[9,10] prehypertension, and prediabetes.[11] In patients with diabetes, GHF can contribute to renal function loss and nephropathy onset or progression,[12,13] but recent evidence emphasizes the importance of systemic blood pressure (BP) as a modulator of GHF and its association with subclinical cardiovascular damage.[14–17] In a pooled analysis of general population and CKD cohorts, Nitsch *et al.*[18] found increased cardiovascular mortality for nonproteinuric men with GHF. However, the independent prognostic significance of GHF in the risk of CVE in patients with hypertension remains largely unexplored. In the Ambulatory Blood Pressure in referred Hypertensive Subjects: An International Database (ABP-International) study,[19] we initially measured the estimated GFR (eGFR) in 8 well-characterized international cohorts of middle-aged participants mainly referred for hypertension. Therefore, we designed the current study to investigate whether GHF is independently associated with the risk of CVE in the large multiethnic population of the ABP-International study.[19]

RESULTS

Of 11,235 participants, after the exclusion of those with an unavailable baseline eGFR measurement ($N = 2411$) and incomplete follow-up information ($N = 30$), 8794 remained available for the analysis. More information on excluded participants is provided in the Supplementary Material (Supplementary Table S1). The study cohort consisted of 3959 women (45%) and 4835 men (55%). Of these, 7596 were Caucasians, 1141 were Asians, and 57 were black. At enrollment, 7805 participants (89%) had hypertension, 1768 (20%) were current smokers, and 666 (8%) were diabetic.

Mean ± SD age was 52.3 ± 15.7 years, office systolic BP was 152.8 ± 18.3 mm Hg, diastolic BP was 93.4 ± 10.4 mm Hg, body mass index (BMI) was 26.1 ± 3.9 kg/m^2, and median (interquartile range) eGFR was 81.4 ml/min per 1.73 m^2 (68.1–96.8 ml/min per 1.73 m^2). According to the age- and sex-specific 5th and 95th percentiles of eGFR distributions, we categorized patients as having low filtration (LF) ($N = 433$, 4.9%), normal filtration (NF) ($N = 7935$, 90.3%), and high filtration (HF) ($N = 426$, 4.8%). Their main characteristics are shown in Table 1. Compared with LF and NF participants, HF participants were younger, mostly male, more frequently of white race, and with a lower prevalence of diabetes. Neither the prevalence of hypertension nor the level of office BP or average 24-hour ambulatory BP showed significant differences among groups. The distribution of eGFR and the reference values for NF, LF, and HF for each age quintile by sex are shown in Figure 1. Thresholds for HF varied with age, ranging between 141 and 88 ml/min per /1.73 m^2 and 151 and 102 ml/min per 1.73 m^2 for female and male subjects, respectively. A similar age-related trend was observed for LF thresholds, with levels ranging between 77 and 38 ml/min per 1.73 m^2 and 87 and 43 ml/min per 1.73 m^2 for female and male subjects, respectively.

Ambulatory pulse pressure and nocturnal dip

In both LF and HF groups, age- and sex-adjusted 24-hour pulse pressure, daytime pulse pressure, and nighttime pulse pressure were higher than in NF participants (Table 2). The highest values were found in the HF group. In addition, in LF and HF groups, there was a blunted nighttime diastolic BP decrease compared with the NF group (Table 2). The nocturnal decrease in systolic BP was smaller in the HF than the NF participants.

Outcome events

During a mean follow-up period of 6.2 years, a first CVE developed in 722 participants. There were 137 cardiovascular deaths, 162 patients had a nonfatal myocardial infarction, 232 had a nonfatal stroke, 97 underwent coronary revascularization, 42 experience heart failure leading to hospitalization, 39 had peripheral occlusive disease, and 13 patients started dialysis. The unadjusted CVE rates were higher for both HF (1.8 per 100 person-years) and LF (2.1 per 100 person-years) participants compared with NF participants (1.2 per 100 patient-years; log-rank $\chi^2 = 15.6$; $P < 0.001$). Kaplan-Meier estimates for the 3 GFR groups are presented in Figure 2. The unadjusted hazard ratios (HRs) for CVE are shown in Table 3. In multivariable Cox models stratified by center (Table 3), including age, sex, average 24-hour systolic BP, smoking, diabetes, and cholesterol, both HF (HR, 1.5; 95% CI 1.2–2.1; $P = 0.006$) and LF (HR, 2.0; 95% CI 1.5–2.6; $P < 0.001$) participants had a higher risk of CVE compared with NF participants. Adding BMI to the multivariable survival model did not materially change the magnitude and the significance of both GHF (HR, 1.527; 95% CI 1.128–2.067; $P = 0.006$ and LF (HR, 1.957; 95% CI 1.473–2.601; $P < 0.001$) hazard estimates. The HR per BMI unit was 1.01 (95% CI 0.99–1.03, $P = 0.28$), and no interaction was found between BMI and eGFR group ($P = 0.68$). Similar results were obtained when BMI was used as a categorical variable. For participants with a BMI ≥25 kg/m^2, the HR was 1.05 (95% CI 0.87–1.26, $P = 0.61$), and no statistical evidence of an interaction was found in the eGFR group ($P = 0.87$).

To better characterize the shape of the relationship between eGFR and CVE, we grouped the study population by age- and sex-adjusted deciles of the eGFR distribution. We used the 7th decile as the reference, being the one with the lowest CVE rate (1.1, 95% CI 0.8–1.4 per 100 person-years). In fully adjusted models including the same covariables as above (Table 4), both patients in the lowermost (median eGFR 54 ml/min per 1.73 m^2) and uppermost (median eGFR 108 ml/min per 1.73 m^2) eGFR decile exhibited a significant increase in the risk of CVE (HR, 1.89; 95% CI 1.32–2.71; $P < 0.001$ and HR, 1.61; 95% CI 1.13–2.30; $P = 0.008$ for the

Table 1 | Baseline characteristics of study participants grouped by eGFR class

Variable	Low eGFR	Normal eGFR	High eGFR	*P* value
N	433	7935	426	
Age, yr	55.3 (15.4)	52.3 (15.7)	48.6 (16.4)	<0.001
Sex, male, %	33.7	54.7	81.7	<0.001
Race, white, %	76.8	85.0	98.5	<0.001
Hypertension, %	89.6	88.7	88.3	0.81
Diabetes, %	13.4	8.1	6.3	<0.001
BMI, kg/m^2	25.8 (4.1)	26.1 (3.9)	26.3 (3.9)	0.12
Office SBP, mm Hg	155.2 (21.0)	152.7 (18.2)	151.5 (15.8)	0.008
Office DBP, mm Hg	93.6 (11.9)	93.3 (10.3)	94.0 (9.0)	0.35
24-hr SBP, mm Hg	137.2 (17.5)	136.0 (14.8)	136.5 (13.5)	0.21
24-hr DBP, mm Hg	83.7 (10.9)	83.4 (9.6)	83.8 (9.4)	0.58
Total cholesterol, mg/dl	215.7 (42.8)	209.4 (39.8)	202.5 (43.7)	<0.001
Serum creatinine, mg/dl	1.4 (0.4)	0.9 (0.2)	0.7 (0.1)	<0.001
eGFR (CKD-EPI), ml/min per 1.73 m^2	48.2 (38.1–58.7)	81.4 (69.6–95.8)	111.2 (99.1–126.7)	<0.001
eGFR (Cockroft-Gault formula), ml/min per 1.73 m^2	52.8 (37.9–68.1)	87.3 (66.4–110.3)	140.3 (109.7–170.2)	<0.001

BMI, body mass index; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration equation; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; SBP, systolic blood pressure.
Continuous variables are presented as mean and (SD). eGFR was calculated using the CKD-EPI creatinine equation with further adjustment for Japanese ethnicity. Values are median and interquartile range, using the Cockroft-Gault formula with further adjustment for Japanese ethnicity.