Association between glomerular filtration rate and endothelial function in an elderly community cohort

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Background: Endothelial dysfunction is prevalent among individuals with chronic kidney disease. However, the association between glomerular filtration rate and endothelial function in the community is unclear and needs to be investigated in the general population.

Methods: In the community-based Prospective Investigation of the Vasculature of Uppsala Seniors study (PIVUS, n = 952, mean age 70, women 49.3%), we investigated cross-sectional associations between estimated cystatin C-based glomerular filtration rate (eGFR), and 3 measures representing different aspects of endothelial function (endothelial-dependent vasodilatation [EDV], endothelial independent vasodilatation [EIDV], and flow-mediated dilatation [FMD]). We also performed pre-specified sub-group analyses in participants with normal eGFR (>60 ml/min/1.73 m²).

Results: In the whole cohort, 10 ml/min/1.73 m² higher eGFR was associated with 3% higher EDV (p = 0.001) and 2% higher EIDV (p = 0.007), adjusted for age and sex. The associations were attenuated and no longer statistically significant after adjusting for established cardiovascular risk factors. In participants with eGFR >60 ml/min/1.73 m², 10 ml higher eGFR was associated with 2% higher EDV (p = 0.04) after adjusting for sex and age. eGFR was not associated to FMD in any model or sub-sample.

Conclusion: This community-based study suggests that eGFR is associated with endothelial function also in persons with normal kidney function, but that this association is largely explained by confounding by established cardiovascular risk factors. Thus, our data do not support the notion of a direct causal interplay between renal and vascular function prior to the development of CKD.

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1. Introduction

Chronic kidney disease (CKD) is recognized as a global public health problem [1]. Patients with severe chronic kidney disease are at substantially higher risk of developing cardiovascular disease (CVD) [2] but an increased cardiovascular risk is also evident in individuals with only mild signs of kidney damage in the community [3]. The increased risk of CVD in patients with CKD, has been attributed to the clustering of cardiovascular risk factors [4–7], but also to endothelial dysfunction, which is prevalent in patients with CKD stages 3–5 (GFR<60 ml/min/1.73 m²) [8–11]. Whether glomerular filtration rate (GFR) is associated with endothelial dysfunction in the community is less studied.

Four previous community-based studies have studied the association between decreased GFR and endothelial dysfunction. These studies have measured endothelial function by indirect markers or flow-mediated dilatation (FMD) and the studies indicate divergent results [10,12–14]. No previous community-based studies have investigated the association of GFR with endothelial function assessed by the gold standard invasive method (endothelium-dependent vasodilatation – EDV), as a response to acetylcholine in the brachial artery.

We hypothesized that eGFR is associated with impaired endothelial function in the general population. Accordingly, we investigated the cross-sectional associations between serum cystatin C-based GFR (eGFR) and direct measures of endothelial function (FMD and EDV) in

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a community-based sample of elderly men and women. We also investigated the association between eGFR and endothelium-independent vasodilation (EIDV). In addition, we investigated a prespecified subgroup of the cohort with eGFR >60 ml/min/1.73 m².

2. Materials and methods

2.1. Subjects

All 70-year-old residents of Uppsala County (Sweden), between April 2001 and June 2004, were invited to participate in the Prospective Investigation of the Vasculature of Uppsala Seniors (PIVUS), described in detail elsewhere [15] (http://www.medsci.uu.se/pivus/pivus.htm). Of 2025 subjects invited, 1016 were examined within 1 month of their 70th birthday. For the present study, we excluded 64 participants for missing data on eGFR or covariates. After these exclusions, 952 individuals aged 70 (49.3% women) were eligible and constituted the study sample. Measurements of FMD, EDV and EIDV were available on 952, 835 and 852 of these participants, respectively. The Ethics Committee of Uppsala University approved the study, and all participants provided written informed consent.

2.2. Clinical and biochemical evaluation at baseline

The subjects underwent a physical examination including anthropometrical measurements and blood pressure, and answered a questionnaire regarding medical history, smoking habits, and medication. Body mass index (BMI) was calculated as the ratio between weight and height squared (kg/m²). Blood pressure was measured three times after at least 30 min of rest by use of a calibrated mercury sphygmomanometer, and the mean was used for analyses. Blood were collected in the morning after an overnight fast, during which medication and smoking were disallowed.

Estimated GFR was derived from serum cystatin C (Gentian, Moss, Norway), by the formula eGFR = 79.901 × CystC⁻¹.4389 [16].

High sensitivity CRP was measured in human serum by an ultra-sensitive particle enhanced immunoturbidimetric assay (Orion Diagnostica, Espoo, Finland) on a Konelab 20 autoanalyser (Thermo Clinical Labsystems, Espoo, Finland). The inter-assay coefficient of variation was 3.2%. Diabetes mellitus was defined as fasting blood glucose ≥6.1 mmol/L (≥110 mg/dL), corresponding to plasma glucose ≥7.0 mmol/L (≥126 mg/dL), or self reported diagnosis of diabetes. Hypertension was defined as use of antihypertensive medication or having a systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg.

2.3. The brachial artery ultrasound technique

The brachial artery was assessed by external B-mode ultrasound imaging 2–3 cm above the elbow (Acuson XP128 with a 10 MHz linear transducer, Acuson Mountain View, CA, USA), according to the International Brachial Artery Reactivity Task Force [17]. A cuff was placed below the elbow and inflated to a pressure of at least 50 mmHg above systolic blood pressure for 5 min. FMD was defined as the maximal brachial artery diameter recorded between 30 and 90 s following cuff release minus diameter at rest divided by the diameter at rest, using electronic calipers for measurements. FMD was successfully evaluated in 97% of the participants. The reproducibility (CV) was 3% for baseline brachial artery diameter and 29% for FMD [18].

2.4. The invasive forearm technique

Forearm blood flow (FFB) was measured by venous occlusion plethysmography (Elektromedicin, Kullavik, Sweden). Venous occlusion was achieved by a blood pressure cuff applied proximal to the elbow and inflated to 50 mmHg by a rapid cuff inflator. Evaluations of FBF were made by calculations of the mean of at least five consecutive recordings. An arterial cannula was placed in the brachial artery. Resting FBF was measured 30 min after cannula insertion. After evaluation of resting FBF, local intra-arterial drug infusions were given during 5 min for each dose, with a 20 min washout period between the drugs. The infused dosages were 25 and 50 μg/min for acetylcholine (Clin-Alpha, Laufelfingen, Switzerland) to evaluate EDV and 5 and 10 μg/min for sodium nitroprusside (SNP; Nitropress; Abbott Pharmaceutical, Abbott Park, IL, USA) to evaluate EIDV. EDV was defined as FBF during infusion of 50 μg/min of acetylcholine minus resting FBF divided by resting FBF. EIDV was defined as FBF during the infusion of 10 μg/min of SNP minus resting FBF divided by resting FBF. The CV of the ultrasound assessments when repeating the measurements was 8% for EDV and 10% for EIDV [19].

2.5. Statistical analysis

Logarithmic transformation was performed to obtain a normal distribution of EDV, EIDV, serum triglycerides, fasting glucose and CRP. All other variables were normally distributed. We defined renal dysfunction at <60 ml/min/1.73 m² [20].

Linear regression analyses were used to assess the cross-sectional associations of eGFR (independent variable) with FMD, EDV or EIDV (dependent variables in separate models).

The following models were investigated:

Model A: adjusted for age (continuous) and sex (binary).

Model B: adjusted for established CVD risk factors; model A + systolic and diastolic blood pressure (continuous), anti-hypertensive medication (binary), BMI (continuous), LDL-cholesterol, HDL-cholesterol and triglycerides (continuous), lipid-lowering medication (binary), smoking (binary), fasting glucose (continuous), antidiabetic medication (binary) and CRP (continuous).

We also performed the above analyses in a subgroup with eGFR >60 ml/min/1.73 m². Two-tailed significance values were given, with p = 0.05 regarded as significant.

In order to evaluate the individual effect of different CVD risk factors on the association between eGFR and endothelial function we also performed separate exploratory models adjusted for variables reflecting blood pressure, dyslipidemia, impaired glucose metabolism, adiposity, inflammation or smoking.

To gain additional insights into the potential nonlinearity of the associations, we examined the regression models using penalized splines.

Additionally, we performed tests for effect modification by gender by including a multiplicative interaction term in multivariable model B.

The statistical software package STATA 11.0 (Stata Corporation, College Station, TX) was used for all analyses.

3. Results

Table 1 shows the characteristics of the whole study population and a subsample with eGFR >60 ml/min/1.73 m².

3.1. Relationship between renal function and flow-mediated dilatation

eGFR was not significantly associated with FMD in the whole cohort or in individuals with eGFR >60 ml/min/1.73 m² (n = 888) in either age- and sex-, or multivariable-adjusted models (Table 2).
3. Relationship between renal function and endothelium-dependent vasodilatation (EDV)

In the whole cohort, a 10 ml/min/1.73 m² higher eGFR was associated with 3% higher EDV, adjusting for age and sex (model A, Table 2). The association was attenuated after adjusting for established cardiovascular risk factors (model B, Table 2). In a sub-sample with eGFR >60 ml/min/1.73 m², n = 778, the association between eGFR and EDV was similar but with wider confidence interval (model A, Table 2). No significant association was observed after further adjustment for cardiovascular risk factors, (model B, Table 2).

3.3. Relationship between renal function and endothelium-dependent vasodilatation (EIDV)

In the whole cohort, a positive association between eGFR and EIDV was observed. A 10 ml/min/1.73 m² higher eGFR was significantly associated with 2% higher EIDV in age and sex adjusted model (Table 2). No association was observed after adjusting for cardiovascular risk factors. Furthermore, no association between eGFR and EIDV was observed in the sample with eGFR >60 ml/min/1.73 m², n = 796 (Table 2).

3.4. Secondary analyses

No evidence of effect modification by gender on the association between eGFR and any vascular function was observed. Examination of regression splines suggests no obvious deviation from linearity in the association between eGFR and the different indices of vascular function (FMD, EDV and EIDV, data not shown).

4. Discussion

In a community-based study of elderly men and women, eGFR was associated with directly measured endothelium-dependent vasodilatation (EDV) and endothelium independent vasodilatation in resistance arteries (EIDV) but not in conduit arteries (FMD). However, after adjustment for cardiovascular risk factors the associations were attenuated and no longer statistically significant. After further exclusion of participants with impaired eGFR (<60 ml/min/1.73 m²), eGFR was associated with EDV adjusted for sex and age suggesting that lower eGFR is associated with impaired endothelial function also in persons with normal kidney function. Again, this association was mainly explained by confounding by established cardiovascular risk factors.

Clinical studies have indicated that impaired endothelial function is observed among individuals with moderate to severe kidney function compared to healthy controls using biomarkers of endothelial function [21,22] and brachial measures of endothelial function [11,23,24]. However, previous community-based data is scarce and inconsistent. A report from the Hoorn study, show an inverse association between eGFR and different indirect biomarkers of endothelial function, (von Willenbrand factor, vascular cell adhesion molecule-1, urinary albumin excretion) [10]. In a community-based study (Study of Health in Pomerania [SHIP]) indicated that endothelial dysfunction measured with FMD was associated with mild reduction in renal function in females [14]. In contrast, the Framingham Heart Study [12] and the Multi-Ethnic Study of Atherosclerosis (MESA) [13], indicated that endothelial dysfunction measured with FMD was not a major correlate of moderate CKD. Our data is in line with previous studies suggesting no association between eGFR and endothelial function assessed by FMD. It is
possible that the some of the inconsistencies between previous studies is due to the different methods used to estimate endothelial function as well as age- and gender differences between the study samples. To our knowledge, our study is the first to report the association between GFR and endothelial function as assessed by the invasive forearm technique.

The potential underlying mechanisms of the interplay between renal dysfunction and endothelial dysfunction in arteries is incompletely understood. Evidence from animal experiments has shown that systemic administration of nitric oxide synthase inhibitor induces renal vasoconstriction and injury that is characterized by glomerulosclerosis and interstitial fibrosis [25,26]. But the opposite chain of events is also possible; clinical studies have showed that renal dysfunction is known to increase oxidative stress and inflammation [7,21], that in turn, may cause endothelial dysfunction and atherosclerosis in the systemic vasculature [27].

In the present study, the association between renal function and endothelial function was attenuated after adjustment for cardiovascular risk factors which could indicate that these factors are deleterious for both the vasculature and the kidney. BMI and lipid status appeared particularly important in that respect. Consequently, the present results do not support the notion of a direct causal interplay between kidney dysfunction and endothelial dysfunction in the community-based setting.

We could not find any correlation between eGFR and FMD, which may be due to several reasons. First, FMD has been questioned as measure of endothelium-dependent vasodilatation in elderly, because FMD is much dependent on arterial compliance which is impaired in healthy elderly subjects [28]. Second, FMD has a higher variability than EDV which may explain some divergence in the results. Third, the different techniques reflect diverse mechanisms, FMD uses shear stress as stimulus for vasodilatation and it reflects the conduit artery, whereas the invasive forearm technique is induced by pharmacologically receptor agonists and reflects vasodilatation in resistance arteries.

The strengths of our study include the large homogeneous community-based sample with comprehensive measures of non-invasive and invasive arterial measurement of endothelial function. Also all participants are well characterized with regards to cardiovascular risk factors which allowed adjustment for many potential confounders. Some limitations are also worth noting. This study was a cross-sectional study, thus we cannot assess causality. The present sample consisted of individuals of Northern European descent and 70 years of age, so generalizability to other ethnic and age groups is uncertain. The present study had a moderate participation rate. However, an analysis of non-participants showed the present sample to be fairly representative of the total population in terms of most cardiovascular disorders and medication [15]. A large number of participants in the present cohort regularly used cardiovascular drugs. Although no drugs were taken on the day of the investigation, differential effects of certain drugs on the risk factors and measures of endothelial vasodilatory function may exist that may have weakened the observed relations. Microalbuminuria is not only considered to be markers of kidney damage but have also been suggested to reflect endothelial dysfunction [29]. Unfortunately, no urine samples were collected in the present study, which makes it impossible to determine the influence of albuminuria levels on the present associations. Moreover, we have not used the gold standard method to measure GFR (isotope clearance measurements). This may be important as estimated GFR, have been suggested to be less reliable in individuals with GFR > 60 ml/min [30]. Yet, isotope clearance measurements are seldom used in epidemiological research as it is a very time-consuming and costly procedure. In the present study we used cystatin C-based GFR which have been shown to be closely correlated with GFR assessed by isotope clearance measurements also in the normal range of GFR [16]. Importantly, any bias introduced by limitations in the estimation of GFR would most likely conservatively bias our regression estimates.

5. Conclusions

This community-based study show that eGFR is associated with endothelial function also in persons with normal kidney function, but that this association is largely explained by confounding by established cardiovascular risk factors. Thus, our data do not support the notion of a direct causal interplay between renal and vascular function prior to the development of CKD.

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Appendix A. Supplementary material

Supplementary data related to this article can be found online at http://dx.doi.org/10.1016/j.atherosclerosis.2012.07.008.

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