Elevated blood pressure is not associated with accelerated glomerular filtration rate decline in the general non-diabetic middle-aged population

Bjørn O. Eriksen[1,2], Vidar T.N. Stefansson[1], Trond G. Jenssen[1,3], Ulla D. Mathisen[1,2], Jørgen Schei[1], Marit D. Solbu[1,2], Tom Wilsgaard[4] and Toralf Melsom[1,2]

[1]Metabolic and Renal Research Group, UiT The Arctic University of Norway, Tromsø, Norway; [2]Section of Nephrology, University Hospital of North Norway, Tromsø, Norway; [3]Oslo University Hospital, Oslo, Norway; and [4]Department of Community Medicine, Faculty of Health Sciences, UiT The Arctic University of Norway, Tromsø, Norway

Although hypertension is a risk factor for end-stage renal disease, this complication develops in only a minority of hypertensive patients. Whether non-malignant hypertension itself is sufficient to cause reduced glomerular filtration rate (GFR) is unclear. Therefore, we investigated whether elevated blood pressure (BP) was associated with accelerated GFR decline in the general population. The study was based on the Renal Iohexol Clearance Survey in Tromsø 6 (RENIS-T6), which included a representative sample of 1594 individuals aged 50 to 62 years from the general population without baseline diabetes or kidney or cardiovascular disease. GFR was measured as iohexol clearance at baseline and follow-up after a median observation time of 5.6 years. BP was measured according to a standardized procedure. The mean (SD) GFR decline rate was 0.95 (2.23) ml/min/yr. In multivariable adjusted linear mixed regressions with either baseline systolic or diastolic BP as the independent variable, there were no statistically significant associations with GFR decline. Thus, elevated BP is not associated with accelerated mean GFR decline in the general middle-aged population. Hence, additional genetic and environmental factors are probably necessary for elevated BP to develop manifest chronic kidney disease in some individuals.

Kidney International (2016) ■, ■–■; http://dx.doi.org/10.1016/j.kint.2016.03.021

KEYWORDS: cardiovascular disease; chronic kidney disease; hyperfiltration; obesity

Correspondence: *Bjørn Odvar Eriksen, Section of Nephrology, Clinic of Internal Medicine, University Hospital of North Norway, 9038 Tromsø, Norway. E-mail: bjorn.odvar.eriksen@unn.no*

Received 2 December 2015; revised 7 March 2016; accepted 10 March 2016

Hypertension is a risk factor for end-stage renal disease (ESRD)[1–4] and is the second most important cause of ESRD in the United States.[5] However, the incidence of ESRD is low relative to the high prevalence of hypertension. This indicates that hypertensive individuals may have a different susceptibility for developing kidney failure. In people without baseline chronic kidney disease or diabetes, randomized controlled trials have not shown an effect of antihypertensive treatments on renal outcomes.[6–8]

These observations have led some investigators to question whether non-malignant hypertension is indeed a sufficient cause of chronic kidney disease, which would entail an association between elevated BP and accelerated GFR decline at the population level.[9,10] The results of studies of the relationship between BP and the rate of GFR decline in the general population have not been consistent. Although several studies have found that higher BP accelerated GFR decline,[11–17] some have found that hypertension was associated with elevated GFR or hyperfiltration.[18–23] The difficulty of measuring GFR in the near-normal range with sufficient precision is probably the most important explanation for the lack of evidence in this field.[24] Estimates of GFR based on creatinine or cystatin C are both inaccurate in the near-normal range and known to be confounded by non-GFR factors.[25–27]

Iohexol clearance is recognized as a precise method for measuring GFR.[28] We have previously measured GFR as iohexol clearance in a representative sample of the general middle-aged population in the Renal Iohexol Clearance Survey in Tromsø 6 (RENIS-T6). To our knowledge, this study has been the largest population-based cohort with GFR measurements.[29] These measurements have now been repeated in the same cohort as a part of the RENIS Follow-Up Study (RENIS-FU). The aim of this longitudinal study was to investigate whether there was an association between elevated baseline BP and accelerated decline in GFR between baseline and follow-up.

RESULTS

In the present investigation, 1299 (81%) of the 1594 participants in the baseline cohort had a follow-up GFR measurement after a median (interquartile range) observation time of

5.63 years (5.23–6.03) (Figure 1). A total of 87 subjects had a repeated follow-up measurement of GFR. The mean coefficient of variation (95% confidence interval) for the intra-individual GFR variation was 4.2% (3.4%–4.9%).

Except for body weight, fasting triglycerides, mean arterial pressure (MAP), and the use of "other antihypertensives," all of the characteristics changed between the baseline and follow-up investigations ($P < 0.05$) (Table 1). The most important changes were increases in the percentages of subjects receiving antihypertensives (from 17.5% to 31.2%) or lipid-lowering treatments (from 6.1% to 17.0%). Comparisons of the baseline characteristics of those included in the follow-up study and those lost to follow-up are shown in Supplementary Table S1 (online). The differences were small, except for the percentage of current smokers (18% vs. 28%, $P < 0.001$).

The unadjusted mean (SD) rate of change in the study period was –0.95 (2.23) ml/min/yr for the absolute GFR and –0.84 (2.00) ml/min/1.73 m^2/yr for the GFR standardized to body surface area. A negative change signifies a decline in GFR. The unadjusted change rates according to change in MAP (lower or unchanged vs. higher) and change in antihypertensive medication (yes/no) are shown in Table 2. Subjects with an increase in MAP from baseline to follow-up had a slower unadjusted decline in GFR ($P = 0.007$). The unadjusted GFR decline was steeper in participants using antihypertensive treatments both at baseline and at follow-up than in participants who had never used antihypertensive medication ($P = 0.006$) (Table 2). Subjects with lower or unchanged MAP had a mean (SD) body weight loss of 1.1 (4.8) kg between baseline and follow-up (from a mean body weight of 81.2 to 80.1 kg), whereas those with an increase in MAP had a mean weight gain of 0.8 (4.2) kg (from a mean body weight of 77.5 to 78.4 kg) ($P < 0.001$ for the difference in weight change between the MAP groups).

When the GFR change rate was assessed in the linear mixed model using baseline values of BP and the adjustment variables, none of the BP components was associated with GFR decline (Table 3). There were no statistically significant non-linear relationships between the BP components and GFR rate of change when fractional polynomial transformations were tested in the fully adjusted models.

Subgroup analyses were performed for subjects with hypertension at baseline, follow-up, or both, with normotension at both baseline and follow-up, without self-reported heart disease, without albuminuria (albumin–creatinine ratio less than 1.92 mg/mmol for men and 2.83 mg/mmol for women), or with GFR greater than 60 ml/min per 1.73 m^2 (Supplementary Results and Supplementary Tables S2 and S3). The results were essentially the same as shown in model 2 in Table 3; that is, there was no statistically significant association between BP components and GFR decline in any of these subgroups.

The relationships between baseline BP components and GFR decline assessed by body surface–adjusted measured GFR (GFR_{BSA}), estimated GFR based on creatinine ($eGFR_{crea}$), and estimated GFR based on cystatin C ($eGFR_{cys}$) are shown in Supplementary Table S4. The same models and adjustments as in Table 3 were used. In the fully adjusted models, there were statistically significant negative relationships between baseline systolic BP (SBP), diastolic BP (DBP), and MAP and change in $eGFR_{crea}$, but not $eGFR_{cys}$ or GFR_{BSA}.

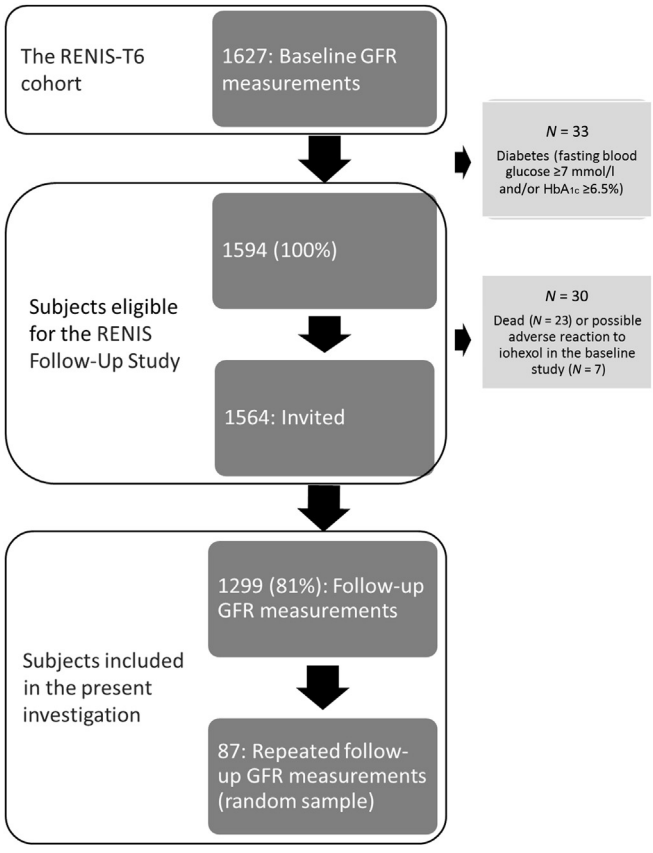

Figure 1 | Inclusion of subjects in the RENIS Follow-Up Study. Subjects had from 1 to 3 glomerular filtration rate (GFR) measurements as follows: at baseline, at follow-up, at a repeated follow-up investigation, or at some combination of these.

DISCUSSION

We did not find an association between accelerated GFR decline and elevated baseline BP (Table 3). To our knowledge, the present study is the first investigation of the association between BP and the GFR change rate in the general population using actual measurements of GFR. However, several investigators have studied changes in serum creatinine, eGFR, or creatinine clearance.[11–17,30] The results across these trials have not been consistent. Most of them have found a faster GFR decline with higher BP, but there has been considerable variation in which BP components have been reported.[11–17] In fully adjusted models, the present study also found statistically significant negative associations between baseline BP components and the $eGFR_{crea}$ change rate, which were not confirmed when change rates were calculated from $eGFR_{cys}$ or iohexol clearance (Supplementary Table S4). Few previous