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Subclinical cardiovascular disease is associated with a high glomerular filtration rate in the nondiabetic general population

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A reduced glomerular filtration rate (GFR) in chronic kidney disease is a risk factor for cardiovascular disease. However, evidence indicates that a high GFR may also be a cardiovascular risk factor. This issue remains unresolved due to a lack of longitudinal studies of manifest cardiovascular disease with precise GFR measurements. Here, we performed a cross-sectional study of the relationship between high GFR measured as iohexol clearance and subclinical cardiovascular disease in the Renal Iohexol Clearance Survey in Tromsø 6 (RENIS-T6), a representative sample of the middle-aged general population. A total of 1521 persons without cardiovascular disease, chronic kidney disease, diabetes, or micro- or macroalbuminuria were examined with carotid ultrasonography and electrocardiography. The GFR in the highest quartile was associated with an increased odds ratio of having total carotid plaque area greater than the median of non-zero values (odds ratio 1.56, 95% confidence interval 1.02–2.39) or electrocardiographic signs of left ventricular hypertrophy (odds ratio 1.62, 95% confidence interval 1.10–2.38) compared to the lowest quartile. The analyses were adjusted for cardiovascular risk factors, urinary albumin excretion, and fasting serum glucose. Thus, high GFR is associated with carotid atherosclerosis and left ventricular hypertrophy and should be investigated as a possible risk factor for manifest cardiovascular disease in longitudinal studies.

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Low glomerular filtration rate (GFR) is a risk factor for cardiovascular disease (CVD).[1] Although high GFR has been regarded as normal, evidence suggests that it may also confer increased risk. In a pooled analysis of over two million subjects, Nitsch *et al.*[2] found an increased cardiovascular mortality for nonproteinuric men with high GFR, whereas a lower increase for women did not reach statistical significance. These analyses were adjusted for the presence of diabetes. Another study found an increased risk of coronary heart disease with high GFR in individuals without prevalent CVD, diabetes, or chronic kidney disease.[3] As these studies used serum creatinine to estimate GFR, it has been assumed that these and similar findings can be explained by an association between chronic disease and low muscle mass that would result in overestimated GFR. However, this assumption has not been investigated.

Because precise GFR measurements are costly and cumbersome, there are, to our knowledge, no longitudinal population-based studies of measured GFR and CVD. GFR estimates based on creatinine or cystatin C are known to be inaccurate in the upper range.[4] In addition, creatinine and cystatin C are influenced by non-GFR factors, including cardiovascular risk factors, that may cause confounding.[5–7] Accordingly, whether high GFR is a CVD risk factor remains unresolved.

However, the hypothesis implies that subclinical CVD may be cross-sectionally associated with high GFR. We investigated this issue in the Renal Iohexol Clearance Survey in Tromsø 6 (RENIS-T6) that has the largest population-based cohort with GFR measurements. The cohort consists of a representative sample of the middle-aged general population without manifest CVD, diabetes, or chronic kidney disease, and who underwent carotid ultrasonography and electrocardiography (ECG). Carotid atherosclerosis and left ventricular hypertrophy (LVH) are signs of subclinical CVD that predict manifest CVD.[8–10] Our aim was to investigate whether

there is a cross-sectional association between subclinical CVD and high GFR in apparently healthy individuals.

RESULTS

Of the 1627 subjects included in the RENIS-T6, individuals with GFR <60 ml/min per 1.73 m^2 ($n=34$), micro- or macroalbuminuria ($n=44$), or diabetes ($n=33$) were excluded. Three individuals had both diabetes and microalbuminuria; two had both diabetes and GFR <60 ml/min per 1.73 m^2. Accordingly, 106 subjects were excluded, leaving 1521 for the present analyses (Figure 1).

There were differences across the GFR quartiles with regard to age; gender; height; body weight; current smoking; ambulatory systolic blood pressure (BP), diastolic BP, mean arterial pressure, and pulse pressure; antihypertensive drug use; high-density lipoprotein cholesterol and fasting glucose ($P<0.05$) (Table 1). These findings have been discussed in previous publications.[5,11,12]

In unadjusted analyses, higher GFR quartile was associated with greater carotid mean intima media thickness (IMT), a higher number of carotid plaques, greater total plaque area (TPA), greater Sokolow and Multi-Ethnic Study of Atherosclerosis (MESA) voltage, and a higher percentage of LVH detected by the MESA voltage criterion ($P<0.05$ for linear trend; Table 2). There was an opposite trend for the Cornell product (Table 2). In the calculation of the Cornell product, a factor of 0.8 is added for women, who have a lower GFR than men, which explains this finding. Quadratic trends were not statistically significant for any of the variables in Table 2. More information about the relationships between covariates and the outcomes can be found in Supplementary Tables S4 to S6 online.

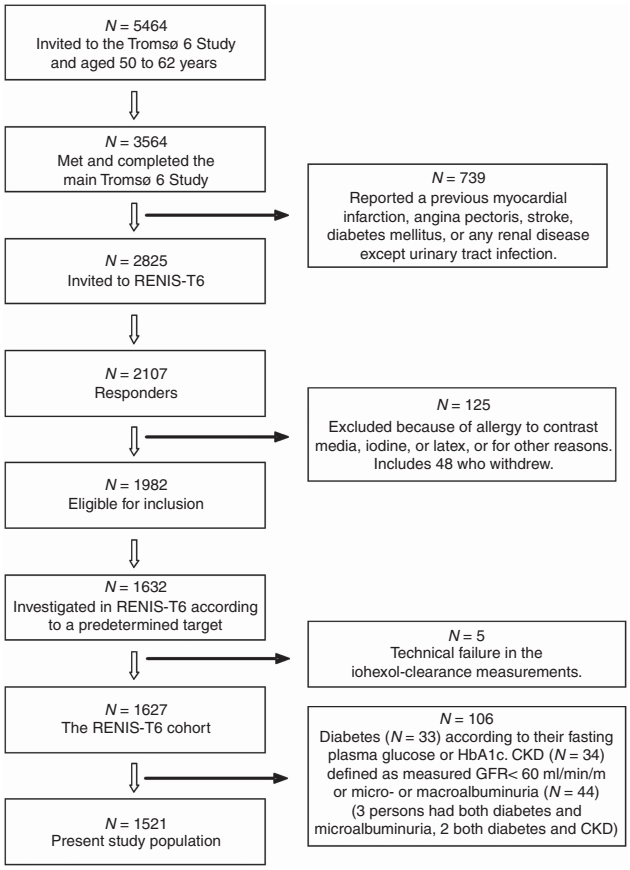

Figure 1 | Study population derived from RENIS-T6, an ancillary investigation of the sixth Tromsø Study. CKD, chronic kidney disease; GFR, glomerular filtration rate; RENIS-T6, Renal Iohexol Clearance Survey in Tromsø 6.

In the adjusted models (Table 3), the odds ratios (ORs) for the dichotomous IMT and TPA variables increased with increasing quartile of GFR ($P<0.05$). The ORs for the highest quartile compared with the lowest quartile were 1.49 for IMT and 1.56 for TPA in the fully adjusted models (model 4; $P<0.05$). Both IMT and TPA were also associated with GFR as a continuous variable ($P<0.05$).

In the adjusted models, LVH was judged to be present when detected by either the Sokolow or MESA voltage criterion, or the Cornell product criterion. In all the adjusted models (Table 3), the OR for LVH was elevated for the highest compared with the lowest GFR quartile ($P<0.05$). For the fully adjusted model, the OR was 1.62. When LVH by each criterion was analyzed separately, OR was increased in the highest GFR quartile in all the adjusted models for the Cornell product criterion ($P<0.05$), and there was a linear trend for increasing OR with increasing GFR for the MESA voltage in the fully adjusted model ($P<0.05$)(Supplementary Table S2 online). LVH as detected by the Sokolow voltage criterion was not associated with GFR. There were positive associations between both the Sokolow voltage and MESA voltage analyzed as continuous variables and GFR ($P<0.05$), but there was no association with the Cornell product (Supplementary Table S3 online).

None of the interactions between sex and GFR in any of the fully adjusted models in Table 3 were statistically significant.

When analyzing fractional polynomial models with the same dependent variables as in Table 3 and the same independent variables as in the fully adjusted models (model 4), no nonlinear effects of GFR were found ($P\geqslant0.05$).

To explore possible confounding by body size, all the multiple regression analyses were repeated with GFR standardized to a total body water of 40 l (GFR40) as the dependent variable instead of GFR standardized to body surface area. The results of these analyses were similar, as were also the results of analyses using absolute GFR in ml/min (not shown).

DISCUSSION

To our knowledge, this investigation is the first to find an independent association between high normal GFR and subclinical CVD manifested as carotid atherosclerosis and LVH in the healthy general population.

The cross-sectional relationship between GFR and carotid atherosclerosis has been examined previously. Several studies have found no statistically significant association between GFR and IMT,[13,14] whereas two studies found an association