Metabolic syndrome but not obesity measures are risk factors for accelerated age-related glomerular filtration rate decline in the general population

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Rapid age-related glomerular filtration rate (GFR) decline increases the risk of end-stage renal disease, and a low GFR increases the risk of mortality and cardiovascular disease. High body mass index and the metabolic syndrome are well-known risk factors for patients with advanced chronic kidney disease, but their role in accelerating age-related GFR decline independent of cardiovascular disease, hypertension and diabetes is not adequately understood. We studied body mass index, waist circumference, waist-hip ratio and metabolic syndrome as risk factors for accelerated GFR decline in 1261 middle-aged people representative of the general population without diabetes, cardiovascular disease or kidney disease. GFR was measured as iohexol clearance at baseline and repeated after a median of 5.6 years. Metabolic syndrome was defined as fulfilling three out of five criteria, based on waist circumference, blood pressure, glucose, high-density lipoprotein cholesterol and triglycerides. The mean GFR decline rate was 0.95 ml/min/year. Neither the body mass index, waist circumference nor waist-hip ratio predicted statistically significant changes in age-related GFR decline, but individuals with baseline metabolic syndrome had a significant mean of 0.30 ml/min/year faster decline than individuals without metabolic syndrome in a multivariable adjusted linear regression model. This association was mainly driven by the triglyceride criterion of metabolic syndrome, which was associated with a significant 0.36 ml/min/year faster decline when analyzed separately. Results differed significantly when GFR was estimated using creatinine and/or cystatin C. Thus, metabolic syndrome, but not the body mass index, waist circumference or waist-hip ratio, is an independent risk factor for accelerated age-related GFR decline in the general population.

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Age-related kidney function decline is an integral part of aging.[1] Consequently, the prevalence of chronic kidney disease (CKD), defined as glomerular filtration rate (GFR) < 60 ml/min per 1.73 m^2, increases with age and reaches almost 50% at 70 years.[2] Additionally, the prevalence of the most severe form of CKD, end-stage renal disease, increases almost exponentially with age and leads to an impaired quality of life, high mortality, and high health care costs.[3–5]

Obesity, the unhealthy accumulation of excess fat mass usually assessed with anthropometric measurements such as body mass index (BMI), waist circumference (WC), or the waist-hip ratio (WHR), is an established risk factor for CKD and end-stage renal disease.[6,7] The rising prevalence of obesity worldwide is alarming,[8] but this prevalence also offers potential for prevention. A high BMI increases the CKD risk mainly due to the associated risk of diabetes, cardiovascular disease (CVD), and hypertension.[7,9] Whether increased BMI also increases the CKD risk by accelerating age-related GFR decline independent of these conditions is less clear. Several studies have attempted to identify whether BMI or WC affects the rate of GFR decline in people without preexisting CKD, but these studies have not reached a firm conclusion.[10–16]

The most important reason for these divergent results may be that they used estimated instead of measured GFR. Estimated GFR (eGFR) based on serum cystatin C or creatinine is imprecise for normal and high levels of GFR and is biased by non-GFR-related factors.[17–20]

Another obstacle may be that obesity is a heterogeneous condition. Recent reports have studied people with so-called metabolically healthy obesity, defined as a BMI ≥ 30 kg/m^2 without the metabolic syndrome (MS), and compared their risk of kidney disease with the risk in metabolically unhealthy obese people (obesity with MS), but the results of these studies have also been divergent.[21–24] Furthermore, the normalization to body surface area incorporated in eGFR has been criticized and is especially problematic in studies of obesity.[25,26]

Obesity and the components of MS are potentially modifiable conditions. Understanding the factors that affect the rate of GFR decline may enable targeted risk factor interventions in susceptible individuals.[27] Therefore, deeper knowledge of the relationship between these risk factors and the GFR decline rate is of great clinical interest.

In the present study, we aimed to investigate whether BMI, WC, or WHR at baseline were associated with changes in the subsequent age-related decline rate of measured GFR (mGFR) using iohexol clearance. We also examined whether MS and its individual components are related to the decline rate.

RESULTS

Population characteristics

This study was a follow-up to the Renal Iohexol-Clearance Survey in Tromsø 6 (RENIS-T6), which included 1627 people representative of the general population without baseline self-reported CKD, CVD or diabetes. One thousand three hundred and twenty-four subjects (81%) had a second GFR measurement after a median (interquartile range [IQR]) observation period of 5.6 (IQR: 5.2–6.0) years. Among those who had 2 measurements, 25 had diabetes at baseline (defined as fasting plasma glucose ≥ 7.0 mmol/l, or glycosylated hemoglobin ≥ 6.5%, or both); 36 had a missing WC measurement; and 2 had missing triglyceride values at baseline. These people were excluded, resulting in a study population of 1261 people (Figure 1). As previously reported, there were only small differences in the characteristics of the included participants compared with the 19% who were lost to follow-up.[28]

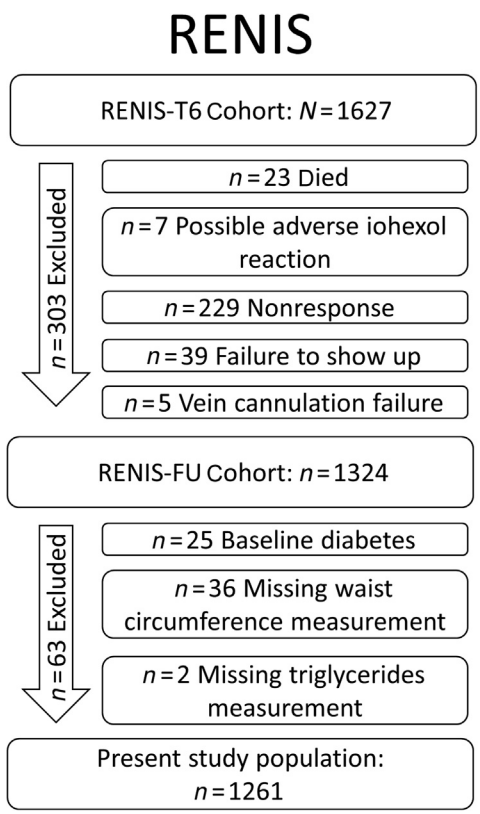

Figure 1 | Flowchart depicting the selection of subjects in the Renal Iohexol-Clearance Survey (RENIS) cohort for the current study. RENIS-FU, Renal Iohexol-Clearance Survey Follow-Up; RENIS-T6, Renal Iohexol-Clearance Survey in Tromsø 6.

The mean ± SD age at baseline was 58.0 ± 3.9 years, mean BMI was 27.1 ± 3.8 kg/m^2, and mean mGFR was 103.6 ± 19.6 ml/min among subjects who had 2 GFR measurements. Three hundred eighty-two subjects (30%) had MS, fulfilling at least 3 of the following 5 criteria: WC > 94 cm in men or > 80 cm in women; fasting plasma glucose ≥ 5.6 mmol/l; systolic blood pressure ≥ 130 mm Hg, diastolic blood pressure ≥ 85 mm Hg, or use of antihypertensive medication, or a combination of these; triglycerides ≥ 1.7 mmol/l or the use of triglyceride-altering drugs; HDL cholesterol levels < 1.03 mmol/l in men or < 1.29 mmol/l in women or the use of HDL-altering drugs.[29] Most of the baseline characteristics differed between the groups when the population was stratified by MS status (Table 1), including the mean baseline mGFR, which was 10.2 ml/min higher in the MS group ($P < 0.001$). Twenty-five subjects had mGFR < 60 ml/min per 1.73 m^2 at baseline, increasing to 33 at follow-up (Supplementary Table S1).

BMI, WC, WHR, and the GFR decline rate

The unadjusted mean ± SD mGFR decline rate was 0.95 ± 2.25 ml/min per year. In separate multivariable adjusted linear regression models analyses, there was no statistically significant linear relationship among the age-related mean mGFR decline rate and BMI, WC, or WHR (Table 2).

In the same models, we examined whether mean mGFR decline was associated with any of the constituent components of MS when analyzed as continuous variables. Higher HDL cholesterol was linearly associated with a 0.58 ml/min/per year faster mean mGFR decline per mmol/l in the fully adjusted model with BMI as an independent variable ($P = 0.002$) (not shown), and there were very similar results in the analyses with WC and WHR. There was no statistically significant linear or nonlinear relationship in generalized additive models among the mean mGFR decline rate and glucose, blood pressure, HDL, or triglycerides.

There was a statistically significant nonlinear relationship between the mean mGFR decline rate and BMI in the fully adjusted model, but the relationship lost its statistical significance when 1 subject with a very high BMI and steep mGFR decline was removed from the dataset. No nonlinear relationship was found among the age-related mean mGFR decline and WC, WHR, or body weight.

The metabolic syndrome

The dichotomous variable MS (yes or no) was included as an independent variable in 3 new models. The new models were based on the previously used models, but they excluded variables that overlapped with the components of MS. In the fully adjusted model, subjects with MS had a mean (95% confidence interval [CI]) 0.30 (95% CI: 0.02–0.58) ml/min per year faster decline ($P = 0.03$) than those without the