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Original Investigation

Prediabetes and Risk of Glomerular Hyperfiltration and Albuminuria in the General Nondiabetic Population: A Prospective Cohort Study

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Background: The role of prediabetes as a risk factor for hyperfiltration and albuminuria in persons who do not develop diabetes is unclear. The lack of evidence is mainly due to the difficulty of accurately assessing the glomerular filtration rate (GFR) in the near-normal range of GFR. We investigated whether prediabetes is an independent risk factor for glomerular hyperfiltration and high-normal urinary albumin-creatinine ratio (ACR) using measured GFR (mGFR) rather than estimated GFR.

Study Design: Prospective cohort study based on the Renal Iohexol Clearance Survey in Tromsø 6 (RENIS-T6) and the RENIS Follow-Up Study. Median observation time was 5.6 years.

Setting & Participants: A representative sample of 1,261 persons without diabetes mellitus (DM) from the general population aged 50 to 62 years.

Predictor: Prediabetes defined by fasting glucose and hemoglobin A_{1c} according to levels suggested by the American Diabetes Association ($preDM_{ADA}$) and the International Expert Committee of 2009 ($preDM_{IEC}$).

Outcomes: Change in mGFR; hyperfiltration defined as mGFR > 90th percentile adjusted for age, sex, weight, and height; and high-normal ACR (>10 mg/g) at follow-up.

Measurements: GFR was measured with iohexol clearance.

Results: Baseline fasting glucose, hemoglobin A_{1c}, and both definitions of prediabetes were predictors of higher mGFR at follow-up and lower annual mGFR decline in multivariable-adjusted regression analyses. Participants with $preDM_{IEC}$ had an OR for hyperfiltration of 1.95 (95% CI, 1.20-3.17) and for high-normal ACR of 1.83 (95% CI, 1.04-3.22) at follow-up. We adjusted for cardiovascular risk factors including ambulatory blood pressure at baseline and change in use of antihypertensive medication between baseline and follow-up.

Limitations: Only middle-aged white patients participated. There is no consensus on how to define glomerular hyperfiltration.

Conclusions: Our findings imply an independent role of prediabetes in the development of glomerular hyperfiltration and albuminuria. Prediabetes might be a target for early treatment to prevent chronic kidney disease in chronic hyperglycemia.

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INDEX WORDS: Prediabetes; hyperfiltration; glomerular filtration rate (GFR); albuminuria; iohexol clearance; measured GFR; estimated GFR; fasting glucose; HbA_{1c}; albumin-creatinine ratio (ACR); chronic hyperglycemia; renal disease; modifiable risk factor; Tromsø study.

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Diabetes-related kidney disease accounts for almost 50% of patients with end-stage renal disease in the United States.[1] Even with optimal treatment of new-onset diabetes, a large percentage of patients will develop chronic kidney disease (CKD). Prediabetes is approximately twice as common as diabetes, affecting 20% to 35% of adults, and it progresses to diabetes in 45% to 50% of individuals after 10 years.[2,3] Prediabetes has been associated with CKD in cross-sectional studies,[4,5] but whether prediabetes predicts CKD in persons who do not develop diabetes is unclear. Longitudinal studies did not find prediabetes to be an independent risk factor for albuminuria or incident CKD, defined as estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m^2.[6-11] If prediabetes is a causal factor in the development of kidney disease, this condition would represent a window of opportunity to treat kidney damage at an early and reversible stage.

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Recently, we reported that prediabetes, defined as elevated fasting glucose level, was associated with an abnormally high GFR, or glomerular hyperfiltration, in a cross-sectional study of the general population.[12] Glomerular hyperfiltration has been established as an early manifestation of diabetic nephropathy and has been shown to predict albuminuria and GFR decline in diabetes.[13,14] Hyperfiltration is also a possible common causal pathway for other causes of CKD; however, the longitudinal association between prediabetes and hyperfiltration remains to be established. Previous longitudinal studies assessing the association between prediabetes and kidney function used eGFR to assess changes in GFR. However, eGFR has low precision, particularly in the higher range of GFRs,[15] and is expected to have low sensitivity for detecting hyperfiltration and GFR changes in the normal range. Also, eGFR is biased by non−GFR-related factors such as obesity, smoking, hyperglycemia, and nontraditional cardiovascular risk factors.[16-18]

We hypothesized that prediabetes is a risk factor for glomerular hyperfiltration and high-normal albumin-creatinine ratio (ACR) during an intermediate follow-up time point. To overcome the limitations of using eGFR, we measured GFR by iohexol clearance at baseline in 2007 to 2009 and at follow-up in 2013 to 2015 in a general-population cohort without self-reported diabetes, cardiovascular disease, or kidney disease at baseline. To study the independent role of prediabetes, we excluded persons with diabetes diagnosed at baseline and at follow-up.

METHODS

Study Participants

The Renal Iohexol Clearance Survey in Tromsø 6 (RENIS-T6) was conducted in October 2007 to September 2009 as a substudy of the population-based sixth Tromsø study (Tromsø 6) in the municipality of Tromsø, northern Norway.[19] The RENIS-T6 included a representative sample of 1,627 persons aged 50 to 62 years from the general population without self-reported kidney disease, myocardial infarction, stroke, or diabetes. A description of study participants and enrollment in the RENIS-T6 is shown in Fig 1 and has been previously published in detail.[19]

The RENIS Follow-up Study (RENIS-FU) was conducted in September 2013 to January 2015. Seven persons had a possible adverse reaction to iohexol in RENIS-T6, and 23 persons died during the follow-up period. The other 1,597 participants were invited to RENIS-FU and 1,368 (86%) gave a positive response, but 39 did not make their appointments and 5 could not be examined because the antecubital vein could not be cannulated. Accordingly, a total of 1,324 (83%) patients were examined in RENIS-FU (Fig 1). In the present investigation, an additional 25 persons with diabetes (fasting glucose ≥ 126 mg/dL [≥7.0 mmol/L] and/or glycosylated hemoglobin (hemoglobin A_{1c} [HbA_{1c}]) ≥ 6.5%) at baseline were excluded. The study was approved by the Norwegian Data Inspectorate and the Regional Ethics Committee of Northern Norway (2012/122/REK nord). All participants provided written informed consent.

Data Collection and Measurements

Both RENIS-T6 and RENIS-FU were conducted at the Clinical Research Unit at the University Hospital of Northern Norway with a standardized procedure and the same staff responsible for all measurements. Participants met during 8:00 AM to 10:00 AM after an overnight fast, including abstinence from tobacco.

Iohexol Clearance

GFR was measured at baseline and follow-up using single-sample plasma iohexol clearance. Participants were instructed to avoid large meals with meat and nonsteroidal anti-inflammatory drugs during the 2 days prior to the investigation. A Teflon catheter was placed in an antecubital vein. Five milliliters of iohexol (Omnipaque, 300 mg/mL; Amersham Health) was injected, and the syringe was weighed before and after injection. The venous catheter was flushed with 30 mL of isotonic saline solution. After a calculated time based on each person's eGFR, the iohexol blood sample was drawn from the same catheter. Serum iohexol was measured by high-performance liquid chromatography, as described by Nilsson-Ehle.[20] Analytical coefficients of variation during the study periods were 3% in RENIS-T6 and 3.1% in RENIS-FU. To explore the possibility of a drift in the method between baseline and follow-up, we reanalyzed iohexol and recalculated measured GFR (mGFR) in a random sample of 105 serum samples frozen at −80°C at baseline. There was a mean difference of 2.28 mL/min/1.73 m^2 between the original baseline measurement and the repeated baseline measurement taken from the thawed sample. An adjustment was made by adding this difference to the baseline measurements. mGFR was calculated as described by Jacobsson.[21] Details regarding iohexol clearance measurements are published elsewhere.[19]

Other Measurements Including ACR

Serum creatinine analyses were performed using a standardized enzymatic assay, and cystatin C was measured by particle-enhanced turbidimetric immunoassay as previously described.[18] GFR was estimated from creatinine or cystatin C level using the CKD-EPI (CKD Epidemiology Collaboration) equations (ie, $eGFR_{cr}$ and $eGFR_{cys}$, respectively).[15,22]

Three samples of first-void morning spot urine were collected on separate days at baseline and follow-up. Urinary albumin and urinary creatinine excretion were measured with commercial kits as described previously.[23] ACR was calculated in milligrams per millimole for each urine specimen, and the mean ACR was used in the analyses. High-normal ACR was defined as ACR > 10 mg/g (>1.13 mg/mmol) as suggested by the CKD Prognosis Consortium because this level has been associated with increased risks for cardiovascular disease, CKD, and death.[24,25]

HbA_{1c} was measured using liquid chromatography (Variant II instrument; Bio-Rad Laboratories), and fasting serum glucose was measured on the Modular model P800 (Roche Diagnostics). Insulin samples were measured with an enzyme-linked immunosorbent assay kit (DRG Instruments) as previously reported.[12]

Ambulatory blood pressure (BP) recordings were started after the baseline iohexol clearance measurement (RENIS-T6) and continued for 24 hours. The method is described in a previous publication.[26]

Definition of Prediabetes and Hyperfiltration

We defined prediabetes according to fasting glucose and HbA_{1c} levels to capture both fasting hyperglycemia and part of nonfasting hyperglycemia, both of which may represent distinct pathophysiologic abnormalities.[2] Prediabetes was defined as fasting glucose level of 110 to 125 mg/dL (6.1-6.9 mmol/L) and/or HbA_{1c} level of 6.0% to 6.4% according to the classification of "high risk state of developing diabetes" by the International Expert Committee of 2009 ($preDM_{IEC}$) or as fasting glucose level of 100 to 125 mg/dL (5.6-6.9 mmol/L) and/or HbA_{1c} level of 5.7% to 6.4% according to the American Diabetes Association criteria ($preDM_{ADA}$).[27,28] In addition we made a separate group for those with $preDM_{ADA}$ and not $preDM_{IEC}$ ($preDM_{ADAnotIEC}$: fasting glucose, 100-109 mg/dL