Published in final edited form as:

Diabet Med. 2017 November ; 34(11): 1532–1540. doi:10.1111/dme.13430.

Predictors of early renal function decline in adults with Type 1 diabetes: the Coronary Artery Calcification in Type 1 Diabetes and the Pittsburgh Epidemiology of Diabetes Complications studies

P. Bjornstad^{1,2}, T. Costacou³, R. G. Miller³, D. M. Maahs⁴, M. J. Rewers^{1,2}, T. J. Orchard³, and J. K. Snell-Bergeon²

¹Department of Pediatric Endocrinology, University of Colorado School of Medicine, Aurora, CO

²Barbara Davis Center for Diabetes, University of Colorado Denver, Aurora, CO

³Department of Epidemiology, University of Pittsburgh, Pittsburgh, PA

⁴Department of Pediatric Endocrinology, Stanford University School of Medicine, Palo Alto, CA, USA

Abstract

Aim—Diabetic kidney disease is one of the leading complications of Type 1 diabetes, but its prediction remains a challenge. We examined predictors of rapid decline in estimated GFR (eGFR) in two Type 1 diabetes cohorts: the Coronary Artery Calcification in Type 1 Diabetes (CACTI) and the Pittsburgh Epidemiology of Diabetes Complications (EDC).

Methods—A select subset of participants (CACTI: $n = 210$ and EDC: $n = 98$) diagnosed before 17 years of age with Type 1 diabetes duration ≥ 7 years, and follow-up data on eGFR by CKD-EPI creatinine for up to 8 years were included in the analyses. Early renal function decline was defined as annual decline in eGFR ≥ 3 ml/min/1.73 m², and normal age-related decline as eGFR ≤ 1 ml/min/1.73 m². Parallel logistic regression models were constructed in the two cohorts.

Results—Early renal function decline incidence was 36% in CACTI and 41% in EDC. In both cohorts, greater baseline eGFR (CACTI: OR 3.12, 95% CI 1.97–5.05; EDC: OR 1.92, 95% CI

Correspondence to: Petter Bjornstad. Petter.Bjornstad@childrenscolorado.org.
DR PETTER BJORNSTAD (Orcid ID : 0000-0002-5160-2947)

Competing interests

None declared.

Author contributions

PB researched, wrote, contributed to discussion, and reviewed/edited the manuscript; TJO designed the EDC Study, researched, contributed to the discussion and reviewed/edited the manuscript; RGM contributed to discussion, and reviewed/edited the manuscript; DMM researched, contributed to discussion, and reviewed/edited the manuscript; MR designed the CACTI Study, researched, contributed to the discussion and reviewed/edited the manuscript; TC researched, contributed to the discussion, reviewed/edited the manuscript; JKSB researched, contributed to the discussion, reviewed/edited the manuscript.

Supporting information

Additional Supporting Information may be found in the online version of this article.

Table S1. Baseline characteristics in sub-cohort and entire CACTI cohort.

Table S2. Baseline characteristics in sub-cohort and entire EDC cohort.

Table S3. Correlation between independent variables and annual change in eGFR.

1.17–3.15 per 10 ml/min/1.73 m²) and log albumin-to-creatinine (ACR) (CACTI: OR 3.24, 95% CI 1.80–5.83; EDC: OR 1.87, 95% CI 1.18–2.96 per 1 unit) predicted greater odds of early renal function decline in fully adjusted models. Conversely, ACE inhibition predicted lower odds of early renal function decline in women in CACTI, but similar relationships were not observed in women in EDC.

Conclusions—A substantial proportion of people with Type 1 diabetes in the EDC and CACTI cohorts experienced early renal function decline over time. ACE inhibition appeared to be protective only in women in CACTI where the prevalence of its use was twofold higher compared with the EDC.

Introduction

The public health burden of Type 1 diabetes, a disease affecting ~ 30 million globally, is progressively increasing largely due to the prevalence of the associated vascular complications [1–3]. Diabetic kidney disease remains the leading cause of end-stage renal disease (ESRD) and dialysis in the USA [4].

The appearance of albuminuria is usually the earliest clinical sign of diabetic kidney disease, but the paradigm of early diabetic kidney disease has evolved over the past decade based on the demonstration that microalbuminuria does not necessarily imply progressive decline in GFR in Type 1 diabetes [5–7]. The Diabetes Control and Complications Trial–Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) reported incident GFR < 60 ml/min/1.73 m² in 24% of people without prior microalbuminuria [8]. Therefore, rapid decline in GFR may be the most clinically relevant measure of diabetic kidney disease in Type 1 diabetes. Early renal function decline is defined as an annual loss ≥ 3 ml/min/1.73 m², which represents a magnitude of change three times the rate of that expected in normal physiology (1 ml/min/1.73 m²/year), and corresponded to 25% of the cohort of the Cardiovascular Health Study, an observational study of risk factors for cardiovascular disease in adults 65 years or older, with the largest decline in GFR [9,10]. We have previously demonstrated that early renal function decline is associated with both hyperfiltration and incident eGFR < 60 ml/min/1.73 m² [11]. The determinants of early renal function decline remain unclear in Type 1 diabetes. We thus conducted parallel analyses in two large Type 1 diabetes cohorts, the Coronary Artery Calcification in Type 1 diabetes (CACTI) and the Pittsburgh Epidemiology of Diabetes Complications (EDC) studies, to examine predictors of early renal function decline.

Materials and Methods

CACTI

The CACTI study enrolled 1416 participants, aged 19–56 years old; 652 with and 764 without Type 1 diabetes, who were asymptomatic for cardiovascular disease (CVD) at the baseline visit in 2000–2002 and were re-examined 6.2 ± 0.5 years later ($n = 1173$), as described previously [12]. Only CACTI participants diagnosed between 1965 and 1980, before 17 years of age and who had Type 1 diabetes for at least 7 years at the baseline assessment with serum creatinine <2 mg/dl at baseline visit were included in the parallel

analyses. To distinguish between early renal function decline and physiological age-related GFR decline, we excluded participants who had an annual GFR decline between 1 and 3 ml/min/1.73 m², which gave a total of 142 participants with longitudinal data (Fig. 1). The study was approved by the Colorado Multiple Institutional Review Board and all participants provided informed consent.

We measured height and weight, and calculated BMI in kg/m². Resting systolic blood pressure (SBP) and fifth-phase diastolic blood pressure (DBP) were measured three times while the patient was seated, and the second and third measurements were averaged for subsequent analysis. After an overnight fast, blood was collected, centrifuged and separated. Plasma was stored at 4 °C until assayed. Total plasma cholesterol and triglyceride levels were measured using standard enzymatic methods; HDL cholesterol was separated using dextran sulphate, and LDL cholesterol was calculated using the Friedewald formula. High-performance liquid chromatography was used to measure HbA_{1c} (HPLC, BioRad variant).

Two timed overnight urine samples were collected in duplicate and urine creatinine and albumin were measured (RIA, Diagnostic Products) and averaged. At both visits, urinary albumin excretion rate (AER) and albumin-to-creatinine ratio (ACR) were measured. GFR (ml/min/1.73 m²) was determined using the CKD-EPI creatinine equation [13]. Serum creatinine was measured according to package insert instructions using a Roche Mira Plus II analyser until 2006 and then an Olympus AU400e ($r = 0.9999$ between methodologies) traceable to the National Institutes of Standards and Technology Standard Reference Material in the University of Colorado Clinical Translational Research (CTRC) Lab [14].

EDC

The EDC cohort is a historical, prospective cohort based on incident cases of childhood-onset Type 1 diabetes (< 17 years) diagnosed, or seen within 1 year of diagnosis, at Children's Hospital of Pittsburgh (1950–1980). Baseline examinations were performed between 1986 and 1988 ($n = 658$, mean age 28 years; duration 19 years) followed by biennial examinations or surveys for up to 25 years. A subgroup comparable with the CACTI cohort, i.e. diagnosed between 1965 and 1980 who attended the 1996–1998 and 2004–2007 follow-up assessments (8.5 ± 0.5 years) and had a serum creatinine < 2 mg/dl (< 176.8 μmol/L) during the 1996–1998 examination, was selected for the present study. Similar to CACTI, analyses were restricted to participants who exhibited an annual GFR decline ≥ 3 or ≥ 1 ml/min/1.73 m². For the purposes of these analyses, data from the 1996–1998 clinical assessment were considered baseline. This participant selection gave 198 participants with longitudinal data (Fig. 1).

Before attending each cycle of examinations, information was collected by questionnaire concerning demographic characteristics, medical history and healthcare behaviours, as described previously [15]. At each cycle, both a standardized medical history and clinical examination were performed to document complications of diabetes. Blood pressure was measured by a random-zero sphygmomanometer according to a standardized protocol [16] after a 5-min rest period. Blood pressure was analysed, using the mean of the second and third readings. Participants on blood pressure medication or with a blood pressure > 140/90 mm Hg were classified as hypertensive.

Fasting blood samples were assayed for lipids, lipoproteins and HbA_{1c}. HDL cholesterol was determined by a heparin and manganese procedure, a modification of the Lipid Research Clinics method [15]. Cholesterol was measured enzymatically, as were triglycerides, as described previously [15]. LDL cholesterol levels were calculated from measurements of the levels of total cholesterol, triglycerides and HDL cholesterol [17]. Automated HPLC (Diamat; BioRad, Hercules, CA, USA) was performed for the determination of HbA₁. HbA₁ values were converted to DCCT-aligned HbA_{1c} values using a regression equation derived from duplicate assays ($\text{DCCT HbA}_{1c} = 0.14 + 0.83 [\text{EDC HbA}_1]$).

Albuminuria determined by urine AER from at least two of three timed urine collections (24-h, overnight, random timed post clinic). Urinary albumin was determined immunonephelometrically [15], and creatinine was assayed using an Ectachem 400 analyser (Eastman Kodak, Rochester, NY, USA). GFR (ml/min/1.73 m²) was determined using CKD-EPI creatinine equation [13].

Diabetic kidney disease

Albuminuria was defined as AER ≥ 20 $\mu\text{g}/\text{min}$ if timed urine samples were obtained, or ACR ≥ 30 mg/g (3.4 mg/mmol) for spot samples if AER was unavailable. Macroalbuminuria was defined as AER ≥ 200 $\mu\text{g}/\text{min}$ or ACR ≥ 300 mg/g (34 mg/mmol) for spot samples if AER was unavailable. For the parallel analyses, we used eGFR data at baseline and follow-up and calculated the difference in eGFR between the two visits (Δ eGFR). The annual change in eGFR was calculated by dividing Δ eGFR by the time (years) between the two visits. Early renal function decline was defined as an annual GFR loss ≥ 3 ml/min/1.73 m² vs. the expected age-related decline of ≤ 1 ml/min/1.73 m²/year [11,18]. Chronic kidney disease (CKD) was defined as eGFR < 60 ml/min/1.73 m². End-stage renal disease (ESRD) was defined as kidney transplantation, needing dialysis or GFR < 15 ml/min/1.73 m².

Statistical analysis

Parallel analyses were performed in EDC and CACTI. Analyses were performed in SAS (v. 9.4 for Windows; SAS Institute, Cary, NC, USA). Differences between participants with and without early renal function decline were assessed using the chi-squared or Fisher's exact test, as appropriate, for categorical variables and the *t*-test for continuous variables. Positively skewed variables (ACR) were natural log transformed. Univariable and multivariable logistic regression models were built to examine the associations between variables at baseline and the development of early renal function decline. Variables considered for inclusion in the multivariable models were based on *a priori* criteria: significance in previous work, significant contribution to the model ($P < 0.1$), or confounding between the main variable of interest and the outcome by $> 10\%$. The following models were built: model 1 (eGFR, log ACR, sex), model 2 (model 1 + HbA_{1c}, duration and BMI) and model 3 (model 2 + hypertension, ACEi use and LDL-C). Finally, model 3 (without sex as a covariate) was re-run stratifying by sex to examine sex-specific determinants of early renal function decline, due to a significant interaction between sex and ACEi in CACTI ($P = 0.04$). Because we sought to identify risk factors of early renal function decline, an intermediate phenotype of diabetic kidney disease, we excluded participants with

CKD at baseline (eGFR < 60 ml/min/1.73 m²). Odds ratios (OR) and the associated 95% confidence intervals (CI) represent the odds of developing early renal function decline for every 10 ml/min/1.73 m² increase in baseline eGFR, every 1 unit increase in log ACR, every 1% increase in HbA_{1c}, every 2-year increase in duration, every 1 kg/m² increase in BMI and every 0.26 mmol/L (10 mg/dl) increase in LDL-C, and for presence or absence of the dichotomous outcomes (sex, hypertension and ACEi). Significance was based on an α -level of 0.05.

Results

Baseline characteristics

Baseline characteristics for this parallel analysis in CACTI and EDC are shown in Table 1. Although participants of the two cohorts were similar in regards to age at diagnosis, duration, BMI and blood pressure, there was a higher percentage of males in EDC. On average, EDC participants had worse lipid profiles, glycaemic control and a lower use of ACE inhibition (Table 1).

Tables S1 and S2 show baseline characteristics of participants in the subcohorts of CACTI and EDC used for the parallel analyses compared to the entire cohort.

Diabetic kidney disease

The prevalence of microalbuminuria or greater at baseline was 17% in CACTI and 57% in EDC. Similarly, the prevalence of macroalbuminuria was 4% in CACTI and 22% in EDC. The incidence of microalbuminuria or greater was 3% in CACTI and 12% in EDC, and the incidence for macroalbuminuria was 1% in CACTI and 5% in EDC. The incidence of impaired GFR was 4% in CACTI and 10% in EDC. Only one participant in EDC developed ESRD. Conversely, no participants in CACTI had incident ESRD. The incidence of early renal function decline was 36% in CACTI and 41% in EDC.

Early renal function decline in CACTI and EDC

Participants who experienced early renal function decline in CACTI had greater eGFR at baseline (118 ± 18 vs. 93 ± 21 ml/min/1.73 m², $P < 0.0001$) and a higher prevalence of macroalbuminuria at baseline (11.1% vs. 0.0%, $P = 0.005$). No difference was observed for sex, ethnicity, age at diagnosis, glycaemic control, BMI or lipid profiles (Table 2).

Participants who experienced early renal function decline in EDC had worse glycaemic control (9.1 ± 1.4 vs. 8.0 ± 1.0 %, $P < 0.0001$), higher total cholesterol (5.2 ± 1.1 vs. 4.7 ± 1.0 mmol/l, $P = 0.03$) and triglyceride concentrations (1.2 ± 0.2 vs. 0.9 ± 0.2 mmol/l, $P = 0.006$), and greater eGFR at baseline (107 ± 21 vs. 94 ± 22 ml/min/1.73 m², $P = 0.004$) than those who did not experience early renal function decline. No difference was observed for sex, ethnicity, age at diagnosis, BMI, LDL-C or HDL-C (Table 2).

Predictors of early renal function decline in CACTI and EDC

As shown in the Table 3, baseline eGFR and ACR were positively related to greater odds of early renal function decline in both CACTI (eGFR: 3.15, 95% CI 1.97–5.05; ACR: 3.24,

95% CI 1.80–5.83) and EDC (eGFR: 1.92, 95% CI 1.17–3.15; ACR: 1.87, 95% CI 1.18–2.96) in multivariable models. Use of ACE inhibitor treatment (OR 0.05, 95% CI 0.004–0.59) conferred lower odds of early renal function decline in women in CACTI cohort (Table 4). Because of the concern for over-adjustment in the smaller EDC cohort, we performed stepwise logistic regression as a sensitivity analyses where all covariates were considered for inclusion. The final model included baseline eGFR (1.89, 95% CI 1.24–2.87), log ACR (1.90, 95% CI 1.27–2.83) and HbA_{1c} (1.73, 95% CI 1.02–2.94). The association between baseline eGFR and early renal function decline was not limited to participants with elevated baseline eGFR, as similar relationships were obtained when only including participants with baseline eGFR between 60 and 110 ml/min/1.73 m² (data not shown).

Table S3 demonstrate the correlations between the independent variables and annual change in eGFR. Stratifying participants into quartiles of glycaemic control (CACTI: < 6.90%, 6.90 to < 7.65%, 7.65 to < 8.48%, 8.48%; EDC: < 7.4%, 7.4 to < 8.4, 8.4 to < 9.1, 9.1), there was a trend towards greater incidence of early renal function decline across the HbA_{1c} categories for EDC ($P < 0.0001$), but not CACTI ($P = 0.57$) (Fig. 2).

Discussion

Although participants of CACTI and EDC were similar in terms of age at diagnosis, diabetes duration and race/ethnicity distribution, participants of the CACTI study had better glycaemic control and were more likely to use ACE inhibitors and hypertension medications than EDC participants. Despite these differences the incidence of early renal function decline was similar; 36% in CACTI and 41% in EDC, and baseline eGFR and ACR were strong predictors of early renal function decline in both cohorts. Use of ACE inhibitor treatment inversely predicted early renal function decline in women with Type 1 diabetes in the CACTI cohort. Finally, in stepwise selection models in EDC, HbA_{1c} was also associated with greater odds of early renal function decline.

Early renal function decline is increasingly recognized as an early intermediate phenotype of diabetic kidney disease. GFR is hypothesized to fall progressively after renal hyperfiltration and may lead, in the long run, to ESRD [19]. GFR declines with age and an annual loss of ~ 1 ml/min/1.73 m² is described in studies of normal aging [20]. The cut-off for annual GFR of ~ 3 ml/min/1.73 m² distinguishes early renal function decline from slow changes in GFR associated with aging or changes in hydration status, and is beyond the range of measurement noise expected in estimating GFR [9]. We have previously demonstrated in CACTI that early renal function decline is associated with both hyperfiltration and incident eGFR < 60 ml/min/1.73 m² [11], but have not previously examined baseline predictors of early renal function decline in CACTI and EDC. Early renal function decline has also been shown to predict ESRD and cardiovascular outcomes in other cohorts [21,22].

The mechanisms that initiate renal GFR decline in Type 1 diabetes remain controversial, but likely include both renal arteriolar and glomerular functional and structural defects due to hyperglycaemia, hypertension, dyslipidaemia and smoking. Also uncertain is whether those initial mechanisms remain operative as renal function decline progresses through advanced CKD stages. It is possible that early renal function decline (in the range of normal renal

function) is related to functional changes, and that the late early renal function decline (CKD stage 3–5) is due to morphological injuries. However, data from the Joslin Kidney Study demonstrated similar rates of GFR loss during early and late phases of early renal function decline [23], which may suggest similar underlying mechanisms.

In both CACTI and EDC, for every 10 ml/min/1.73 m² increase in baseline eGFR we observed a several fold increase in the odds of developing early renal function decline over time, which is consistent with our previous report demonstrating a relationship between hyperfiltration and early renal function decline [11]. Albuminuria at baseline was also associated with increased odds of early renal function decline in both cohorts. Early renal function decline is thought to be an intermediate high-risk phenotype of diabetic kidney disease, which may succeed hyperfiltration and albuminuria. Early renal function decline has also been shown to precede the onset of albuminuria in Type 1 diabetes [23]. HbA_{1c} at baseline was associated with early renal function decline in EDC in stepwise regression models, but not in CACTI, probably reflecting CACTI participants being in better glycaemic control. Beyond the known effects of ACE inhibition on hyperfiltration [24], this study also demonstrated that ACE inhibition was associated with lower odds of early renal function decline in women in CACTI. This relationship was not evident in the EDC cohort, perhaps due to the low proportion of participants taking ACE inhibitors. It is recognized that compared with men, women have greater humoral, renal and systemic responsiveness of renin–angiotensin–aldosterone system (RAAS) inhibition [25]. Furthermore, experimental data have also recently demonstrated that women with hyperfiltration have relatively higher efferent arteriolar resistance and lower renal blood flow compared with men with Type 1 diabetes and hyperfiltration [24]. Because RAAS inhibition acts primarily on the efferent arteriole, this could explain the greater RAAS inhibition response in women [26].

There are important limitations to this study, including the observational design and the absence of a direct measurement of GFR. A direct measure of GFR would have been too cumbersome for use in a large-scale clinical study like CACTI and EDC, and improved methods to detect early kidney changes are needed [27]. We employed the state-of-the-art CKD-EPI equations [13], recently used by studies such as the DCCT-EDIC [28], but it is established that eGFR at higher levels is associated with greater variability, which could lead to misclassification of hyperfiltration and normofiltration, and bias our study results to the null. We adjusted for a variety of important confounding variables, but cannot rule out the presence of unknown risk factors that may have biased or confounded the analyses. These subcohorts were created *a priori* to allow meaningful parallel analyses between CACTI and EDC. Therefore, results from these analyses may not be generalizable to people with Type 1 diabetes who deviate significantly from the eligibility criteria (Fig. 1). Furthermore, while we attempted to make the subcohorts as similar as possible we cannot rule out unobserved confounding between the two cohorts. The strength of the study is the parallel analyses in two contemporary Type 1 diabetes cohorts with longitudinal data.

In summary, we report strong associations between baseline eGFR, albuminuria and early renal function decline in adults with Type 1 diabetes in CACTI and EDC cohorts. Despite differences in glycaemic control, the incidence of early renal function decline did not differ between the EDC and CACTI cohorts. Glycaemia was only related to early renal function

decline incidence in EDC where glycaemic control was poorer ($8.5 \pm 1.3\%$ vs. $7.7 \pm 1.1\%$). Conversely, ACE use appeared to be protective only in women in CACTI where the prevalence of use was twofold higher compared with the EDC. Understanding the mechanisms underlying the rapid GFR decline associated with early renal function decline will help in stratifying people according to risk of diabetic kidney disease progression and the direct development of therapies to prevent or delay rapid GFR loss. Further longitudinal studies are needed to elucidate the pathophysiological mechanisms underlying the early renal function decline, and clinical trials to determine whether halting early renal function decline will prevent progression of diabetic kidney disease.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Drs Petter Bjornstad, Tina Costacou and Janet K. Snell-Bergeon are guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis

Funding sources

Support for this study was provided by NHLBI grant R01 HL61753, HL79611, and HL113029, DK34818, T32 DK063687, JDRF grant 17-2013-313, and DERC Clinical Investigation Core P30 DK57516, and the Rossi Memorial Fund. The study was performed at the Adult CTSC at UCD support by NIH-M01-RR00051, at the Barbara Davis Center for Childhood Diabetes and at Colorado Heart Imaging Center in Denver, CO. Dr Snell-Bergeon by an American Diabetes Association Junior Faculty Award (1-10-JF-50).

References

1. Stark Casagrande S, Fradkin JE, Saydah SH, Rust KF, Cowie CC. The prevalence of meeting A1C, blood pressure, and LDL goals among people with diabetes, 1988–2010. *Diabetes Care*. 2013; 36:2271–2279. [PubMed: 23418368]
2. Libby P, Nathan DM, Abraham K, Brunzell JD, Fradkin JE, Haffner SM, et al. Report of the National Heart, Lung, and Blood Institute–National Institute of Diabetes and Digestive and Kidney Diseases working group on cardiovascular complications of type 1 diabetes mellitus. *Circulation*. 2005; 111:3489–3493. [PubMed: 15983263]
3. de Ferranti SD, de Boer IH, Fonseca V, Fox CS, Golden SH, Lavie CJ, et al. Type 1 diabetes mellitus and cardiovascular disease: a scientific statement from the American Heart Association and American Diabetes Association. *Circulation*. 2014; 130:1110–1130. [PubMed: 25114208]
4. Collins AJ, Foley RN, Herzog C, Chavers B, Gilbertson D, Ishani A, et al. US Renal Data System 2010 Annual Data Report. *Am J Kidney Dis*. 2011; 57(1 Suppl 1):A8, e1–e526. [PubMed: 21184928]
5. Gross JL, de Azevedo MJ, Silveiro SP, Canani LH, Caramori ML, Zelmanovitz T. Diabetic nephropathy: diagnosis, prevention, and treatment. *Diabetes Care*. 2005; 28:164–176. [PubMed: 15616252]
6. Perkins BA, Ficociello LH, Silva KH, Finkelstein DM, Warram JH, Krolewski AS. Regression of microalbuminuria in type 1 diabetes. *N Engl J Med*. 2003; 348:2285–2293. [PubMed: 12788992]
7. Costacou T, Ellis D, Fried L, Orchard TJ. Sequence of progression of albuminuria and decreased GFR in persons with type 1 diabetes: a cohort study. *Am J Kidney Dis*. 2007; 50:721–732. [PubMed: 17954285]
8. Molitch ME, Steffes M, Sun W, Rutledge B, Cleary P, de Boer IH, et al. Development and progression of renal insufficiency with and without albuminuria in adults with type 1 diabetes in the

diabetes control and complications trial and the epidemiology of diabetes interventions and complications study. *Diabetes Care*. 2010; 33:1536–1543. [PubMed: 20413518]

9. Rifkin DE, Shlipak MG, Katz R, Fried LF, Siscovick D, Chonchol M, et al. Rapid kidney function decline and mortality risk in older adults. *Arch Intern Med*. 2008; 168:2212–2218. [PubMed: 19001197]
10. Shlipak MG, Katz R, Kestenbaum B, Siscovick D, Fried L, Newman A, et al. Rapid decline of kidney function increases cardiovascular risk in the elderly. *J Am Soc Nephrol*. 2009; 20:2625–2630. [PubMed: 19892934]
11. Bjornstad P, Cherney DZ, Snell-Bergeon JK, Pyle L, Rewers M, Johnson RJ, et al. Rapid GFR decline is associated with renal hyperfiltration and impaired GFR in adults with Type 1 diabetes. *Nephrol Dial Transplant*. 2015; 30:1706–1711. [PubMed: 26050268]
12. Maahs DM, Kinney GL, Wadwa P, Snell-Bergeon JK, Dabelea D, Hokanson J, et al. Hypertension prevalence, awareness, treatment, and control in an adult type 1 diabetes population and a comparable general population. *Diabetes Care*. 2005; 28:301–306. [PubMed: 15677783]
13. Inker LA, Schmid CH, Tighiouart H, Eckfeldt JH, Feldman HI, Greene T, et al. Estimating glomerular filtration rate from serum creatinine and cystatin C. *N Engl J Med*. 2012; 367:20–29. [PubMed: 22762315]
14. Maahs DM, Jalal D, McFann K, Rewers M, Snell-Bergeon JK. Systematic shifts in cystatin C between 2006 and 2010. *Clin J Am Soc Nephrol*. 2011; 6:1952–1955. [PubMed: 21784814]
15. Orchard TJ, Chang YF, Ferrell RE, Petro N, Ellis DE. Nephropathy in type 1 diabetes: a manifestation of insulin resistance and multiple genetic susceptibilities? Further evidence from the Pittsburgh Epidemiology of Diabetes Complication Study. *Kidney Int*. 2002; 62:963–970. [PubMed: 12164879]
16. The hypertension detection and follow-up program: hypertension detection and follow-up program cooperative group. *Prev Med*. 1976; 5:207–215. [PubMed: 935073]
17. Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. *Clin Chem*. 1972; 18:499–502. [PubMed: 4337382]
18. Bjornstad P, Snell-Bergeon JK, Rewers M, Jalal D, Chonchol MB, Johnson RJ, et al. Early diabetic nephropathy: a complication of reduced insulin sensitivity in type 1 diabetes. *Diabetes Care*. 2013; 36:3678–3683. [PubMed: 24026551]
19. Ruggenti P, Porrini EL, Gaspari F, Motterlini N, Cannata A, Carrara F, et al. Glomerular hyperfiltration and renal disease progression in type 2 diabetes. *Diabetes Care*. 2012; 35:2061–2068. [PubMed: 22773704]
20. Lindeman RD, Tobin J, Shock NW. Longitudinal studies on the rate of decline in renal function with age. *J Am Geriatr Soc*. 1985; 33:278–285. [PubMed: 3989190]
21. Orchard TJ, Secrest AM, Miller RG, Costacou T. In the absence of renal disease, 20 year mortality risk in type 1 diabetes is comparable to that of the general population: a report from the Pittsburgh Epidemiology of Diabetes Complications Study. *Diabetologia*. 2010; 53:2312–2319. [PubMed: 20665208]
22. Groop PH, Thomas MC, Moran JL, Waden J, Thorn LM, Makinen VP, et al. The presence and severity of chronic kidney disease predicts all-cause mortality in type 1 diabetes. *Diabetes*. 2009; 58:1651–1658. [PubMed: 19401416]
23. Krolewski AS, Niewczas MA, Skupien J, Gohda T, Smiles A, Eckfeldt JH, et al. Early progressive renal decline precedes the onset of microalbuminuria and its progression to macroalbuminuria. *Diabetes Care*. 2013; 37:226–234. [PubMed: 23939543]
24. Sochett EB, Cherney DZ, Curtis JR, Dekker MG, Scholey JW, Miller JA. Impact of renin angiotensin system modulation on the hyperfiltration state in type 1 diabetes. *J Am Soc Nephrol*. 2006; 17:1703–1709. [PubMed: 16672313]
25. Miller JA, Cherney DZ, Duncan JA, Lai V, Burns KD, Kennedy CR, et al. Gender differences in the renal response to renin–angiotensin system blockade. *J Am Soc Nephrol*. 2006; 17:2554–2560. [PubMed: 16914541]

26. Skrtic M, Lytvyn Y, Bjornstad P, Reich HN, Scholey JW, Yip PM, et al. The influence of sex on hyperfiltration in patients with uncomplicated type 1 diabetes. *Am J Physiol Renal Physiol*. 2017; 312:F599–F606. [PubMed: 28031170]
27. Maahs DM, Bushman L, Kerr B, Ellis SL, Pyle L, McFann K, et al. A practical method to measure GFR in people with type 1 diabetes. *J Diabetes Complicat*. 2014; 28:667–673. [PubMed: 25027389]
28. de Boer IH, Sun W, Cleary PA, Lachin JM, Molitch ME, Steffes MW, et al. Intensive diabetes therapy and glomerular filtration rate in type 1 diabetes. *N Engl J Med*. 2011; 365:2366–2376. [PubMed: 22077236]

What's new?

- Early renal function decline is increasingly recognized as an intermediate phenotype of diabetic kidney disease.
- In this parallel analysis in the Coronary Artery Calcification in Type 1 Diabetes (CACTI) and Pittsburgh Epidemiology of Diabetes Complications (EDC) studies, baseline estimated GFR and albuminuria were the strongest predictors of early renal function decline.

FIGURE 1.
Participant selection diagram for parallel analyses

A. CACTI

B. EDC Study

FIGURE 2.

Early renal function decline incidence by HbA_{1c} categories. (A) Incidence of early renal function decline by HbA_{1c} quartiles in CACTI (< 6.9%, 6.9 to < 7.65%, 7.65 to < 8.48% and 8.48%. *P*-value for difference in incidence of early renal function decline across tertiles 0.64 (*P*-trend = 0.57). (B) Incidence of early renal function decline by HbA_{1c} quartiles in EDC (< 7.4%, 7.4 to < 8.4%, 8.4 to < 9.1% and ≥ 9.1%. *P*-value for difference in incidence of early renal function decline across tertiles 0.001 (*P*-trend < 0.0001).

Table 1

Baseline characteristics in CACTI and EDC

	CACTI (<i>n</i> = 142)	EDC (<i>n</i> = 98)
Age at diagnosis (years)	8.8 (3.7)	8.6 (4.0)
Duration (years)	27.0 (4.8)	24.5 (4.3)
% Female	57.8	45.9
Non-Hispanic white (%)	93.7	96.9
HbA _{1c} (mmol/mol)	61 (12)	69 (14)
HbA _{1c} (%)	7.7 (1.1)	8.5 (1.3)
SBP (mmHg)	116 (13)	112 (12)
DBP (mmHg)	77 (8)	71 (9)
Total cholesterol (mmol/L)	4.5 (0.9)	4.9 (1.1)
LDL-cholesterol (mmol/L)	2.6 (0.8)	3.0 (1.0)
HDL-cholesterol (mmol/L)	1.5 (0.4)	1.4 (0.4)
Triglycerides (mmol/L)	1.0 (0.7)	1.2 (0.6)
% current smoker	10.2	12.6
BMI (kg/m ²)	25.9 (3.6)	25.2 (3.8)
Waist circumference (cm)	85 (10)	85 (11)
Hypertension medication (% yes)	33.8	12.5
ACE inhibitors (% yes)	27.5	17.3
Angiotensin receptor blocker (% yes)	3.5	1.0
Urinary ACR (mg/mmol [*])	1.1 (0.5)	2.6 (0.8)
Serum creatinine (μmol/L)	74.3 (22.1)	80.4 (21.2)
eGFR at baseline (ml/min/1.73 m ²)	102 (23)	99 (22)
eGFR at follow-up (ml/min/1.73 m ²)	97 (21)	81.9 (24.5)
Change in eGFR (ml/min/1.73 m ² /year) [†]	0.1 (−1.6–3.8)	6.7 (4.8–30.2)
ACR 3.4 mg/mmol (%)	16.9	57.1
ACR 340 mg/mmol (%)	4.0	22.4
eGFR < 60 ml/min/1.73m ² (%)	4.2	8.2
Incident ACR 3.4 mg/mmol (<i>n</i>)	3 of 194 (1.5)	5 of 42 (12)
Incident ACR 340 mg/mmol (<i>n</i>)	1 of 94 (1)	4 of 75 (5)
Incident ESRD (<i>n</i>)	0 of 142 (0)	1 of 91 (1)
Incident early renal function decline (<i>n</i>)	51 of 142 (36)	40 of 98 (41)
Incident eGFR < 60 ml/min/1.73 m ² (<i>n</i>)	5 of 131 (4)	9 of 90 (10)
Incident hard coronary artery disease (<i>n</i>)	10 of 142 (7)	6 of 95 (6)

Values in parentheses are percentages.

^{*} Geometric mean and SD of the geometric mean reported.[†] Median, P25–75.

Table 2

Participant characteristics stratified by early renal function decline status

	CACTI cohort			EDC cohort		
	No early renal function decline (n = 91)	Early renal function decline (n = 51)	P-value	No early renal function decline (n = 58)	Early renal function decline (n = 40)	P-value
Age at diagnosis (years)	9.2 (3.3)	8.3 (4.4)	0.15	8.1 (4.1)	9.4 (3.7)	0.11
Duration (years)	27.1 (5.2)	27.0 (4.0)	0.93	25.0 (4.1)	23.7 (4.5)	0.15
% Female	56.0	60.8	0.58	60.3	45.0	0.13
Non-Hispanic white (%)	94.5	92.2	0.72 [‡]	96.6	97.5	1.00 [‡]
HbA _{1c} (mmol/mol)	61 (12)	60 (12)	0.38	64 (11)	76 (15)	<0.0001
HbA _{1c} (%)	7.7 (1.1)	7.6 (1.1)	0.38	8.0 (1.0)	9.1 (1.4)	<0.0001
SBP (mmHg)	115 (13)	116 (12)	0.70	112 (12)	113 (12)	0.50
DBP (mmHg)	76 (8)	79 (9)	0.05	71 (9)	71 (9)	0.70
Total cholesterol (mmol/L)	4.6 (0.9)	4.5 (0.9)	0.80	4.7 (1.0)	5.2 (1.1)	0.03
LDL-cholesterol (mmol/L)	2.6 (0.8)	2.6 (0.6)	0.65	2.9 (0.9)	3.1 (1.0)	0.23
HDL-cholesterol (mmol/L)	1.4 (0.4)	1.5 (0.4)	0.40	1.4 (0.4)	1.4 (0.3)	0.88
Triglycerides (mmol/L) *	1.1 (0.7)	1.0 (0.7)	0.41	0.9 (0.2)	1.2 (0.2)	0.006
% current smoker	10.2	10.2	1.00	10.5	15.8	0.53
BMI (kg/m ²)	25.9 (3.4)	25.8 (3.8)	0.77	25.8 (4.2)	24.4 (3.1)	0.05
Waist circumference (cm)	85 (10)	83 (10)	0.27	85 (12)	86 (8)	0.50
Hypertension medications (% yes)	38.5	25.5	0.12	8.8	17.9	0.22 [‡]
ACE inhibitors (% yes)	31.9	19.6	0.12	13.8	22.5	0.26 [‡]
Angiotensin receptor blocker (% yes)	5.5	0	0.16 [‡]	0.0	2.5	0.41 [‡]
Urinary ACR (mg/mmol) *	0.9 (0.3)	1.6 (0.6)	0.08	1.6 (0.5)	5.4 (1.0)	0.002
Serum creatinine (μmol/L)	82.2 (21.2)	60.1 (17.7)	<0.0001	84.0 (21.2)	76.0 (20.3)	0.05
eGFR (ml/min/1.73 m ²)	93 (21)	118 (18)	<0.0001	94 (22)	107 (21)	0.004
eGFR (ml/min/1.73 m ²) at follow-up	102 (19)	88 (21)	<0.0001	92 (20)	68 (24)	<0.0001
Change in eGFR (ml/min/1.73 m ² /year)	1.4 (1.8)	-4.8 (1.7)	<0.0001	-0.23 (0.86)	-4.6 (2.1)	<0.0001
Microalbuminuria (%)	16.5	17.8	0.85	51.7	65.0	0.19

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

	CACTI cohort			EDC cohort		
	No early renal function decline (n = 91)	Early renal function decline (n = 51)	P-value	No early renal function decline (n = 58)	Early renal function decline (n = 40)	P-value
Macroalbuminuria (%)	0.0	11.1	0.005 [‡]	17.2	30.0	0.14
eGFR <60 ml/min/1.73 m ² (%)	6.6	0.0	0.09 [‡]	10.3	5.0	0.47 [‡]
Incident eGFR < 60ml/min/1.73 m ² (%)	1.2	7.8	0.07 [‡]	0	23.7	0.0002 [‡]

Values in parentheses are percentages.

^{*} Geometric mean and SD of the geometric mean reported.

[‡] Fisher's exact test P-value.

Table 3

Multivariable Logistic Regression Models

	CACTI (n=118)		EDC (n=81)	
	OR, 95% CI	P-value	OR, 95% CI	P-value
Model 1				
eGFR (per 10ml/min/1.73m ²)	2.62 (1.79–3.82)	< 0.0001	2.16 (1.43–3.27)	0.0003
Log ACR (per 1 unit)	2.21 (1.43–3.42)	0.0003	2.16 (1.45–3.23)	0.0002
Sex (female)	0.98 (0.37–2.57)	0.96	0.53 (0.18–1.57)	0.25
Model 2				
eGFR (per 10ml/min/1.73m ²)	3.12 (2.00–4.97)	< 0.0001	1.96 (1.21–3.18)	0.006
Log ACR (per 1 unit)	2.87 (1.69–4.91)	0.0001	2.00 (1.27–3.14)	0.003
Sex (female)	1.16 (0.97–1.62)	0.78	0.64 (0.20–2.04)	0.45
HbA1c (per 1%)	0.71 (0.43–1.18)	0.19	1.61 (0.94–2.78)	0.08
Duration (per 2 years)	1.26 (0.97–1.62)	0.08	1.01 (0.88–1.16)	0.88
BMI (per 1 kg/m ²)	1.00 (0.86–1.15)	0.94	0.89 (0.76–1.05)	0.16
Model 3				
eGFR (per 10ml/min/1.73m ²)	3.15 (1.97–5.05)	< 0.0001	1.92 (1.17–3.15)	0.01
Log ACR (per 1 unit)	3.24 (1.80–5.83)	< 0.0001	1.87 (1.18–2.96)	0.008
Sex (female)	1.14 (0.40–3.29)	0.81	0.65 (0.19–2.28)	0.50
HbA1c (per 1%)	0.64 (0.36–1.13)	0.12	1.57 (0.91–2.70)	0.11
Duration (per 2 years)	1.28 (0.99–1.68)	0.06	0.99 (0.85–1.15)	0.91
BMI (per 1 kg/m ²)	0.99 (0.85–1.14)	0.86	0.88 (0.74–1.04)	0.12
Hypertension (yes)	1.31 (0.14–12.10)	0.81	0.97 (0.10–9.52)	0.98
ACEi (yes)	0.31 (0.08–1.23)	0.10	2.10 (0.38–11.71)	0.40
LDL-C (per 0.26 mmol/L)	1.03 (0.84–1.26)	0.78	1.12 (0.92–1.35)	0.25

* For CACTI only 118 of 142 had available data for all covariates. Participants with eGFR <60ml/min/1.73m² at baseline were excluded

Data are presented as OR and 95% CI. OR represent the increase in odds of early renal function decline for every unit increase in the independent continuous variable (e.g. HbA1c) or the presence of an independent categorical variable (e.g. sex or hypertension).

Table 4

Multivariable Logistic Regression Models Stratified by Sex

	CACTI (n=118)		EDC (n=81)	
	OR, 95% CI	P-value	OR, 95% CI	P-value
Model 3 in women (CACTI n=66; EDC n=37)				
eGFR (per 10ml/min/1.73m ²)	3.47 (1.76–6.84)	0.0003	1.99 (0.93–4.28)	0.08
Log ACR (per 1 unit)	3.87 (1.69–8.86)	0.001	1.92 (0.95–3.85)	0.07
HbA1c (per 1%)	0.82 (0.36–1.86)	0.61	1.92 (0.87–4.24)	0.11
Duration (per 2 years)	1.19 (0.79–1.81)	0.41	0.84 (0.65–1.08)	0.17
BMI (per 1 kg/m ²)	0.90 (0.74–1.09)	0.28	0.83 (0.62–1.06)	0.14
Hypertension (yes)	0.17 (0.02–1.95)	0.15	0.00 (0.00–999.99)	0.99
ACEi (yes)	0.05 (0.004–0.59)	0.02	3.17 (0.18–55.19)	0.43
LDL-C (per 0.26 mmol/L)	0.96 (0.73–1.27)	0.77	1.19 (0.91–1.56)	0.21
Model 3 in men (CACTI n=52; EDC n=44)				
eGFR (per 10ml/min/1.73m ²)	7.04 (1.83–27.10)	0.005	3.12 (1.11–8.72)	0.03
Log ACR (per 1 unit)	5.38 (1.30–22.22)	0.02	1.70 (0.91–3.19)	0.10
HbA1c (per 1%)	0.47 (0.17–1.30)	0.15	2.92 (0.81–10.63)	0.10
Duration (per 2 years)	1.48 (0.88–2.49)	0.14	1.33 (0.94–1.87)	0.10
BMI (per 1 kg/m ²)	1.14 (0.80–1.64)	0.46	0.92 (0.69–1.23)	0.57
Hypertension (yes)	100.23 (0.73–999.99)	0.07	4.78 (0.14–158.32)	0.38
ACEi (yes)	0.68 (0.04–12.33)	0.80	0.60 (0.04–8.75)	0.71
LDL-C (per 0.26 mmol/L)	1.06 (0.72–1.55)	0.78	1.02 (0.72–1.43)	0.93

* For CACTI only 118 of 142 had available data for all covariates. Participants with eGFR <60ml/min/1.73m² at baseline were excluded

Data are presented as OR and 95% CI. OR represent the increase in odds of early renal function decline for every unit increase in the independent continuous variable (e.g. HbA1c) or the presence of an independent categorical variable (e.g. sex or hypertension)."