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Insulin Sensitivity and Diabetic Kidney Disease in Children and Adolescents With Type 2 Diabetes: An Observational Analysis of Data From the TODAY Clinical Trial

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Abstract

Background—Diabetic kidney disease (DKD) is a major cause of premature mortality in type 2 diabetes mellitus (T2DM). Worsening insulin sensitivity (IS) independent of glycemic control may contribute to the development of DKD. We investigated the longitudinal association of IS with hyperfiltration and increased albumin excretion in adolescents with T2D.

Study Design—Observational, prospective cohort study.

Setting & Participants—532 TODAY (Treatment Options for Type 2 Diabetes in Adolescents and Youth) participants ages 12–17 years with T2D duration <2-years at baseline. The TODAY study was a multicenter, randomized clinical trial that examined the efficacy of three treatment regimens (metformin monotherapy, metformin plus rosiglitazone, or metformin plus an intensive lifestyle intervention program) to achieve durable glycemic control.

Predictors—Natural log-transformed estimated insulin sensitivity [reciprocal of fasting insulin (eIS)], HbA1c, age, race-ethnicity, treatment group, BMI, loss of glycemic control and hypertension.

Outcomes—Hyperfiltration was defined as 99th percentile of estimated glomerular filtration rate [eGFR ≥ 140 mL/min/1.73m²] when referenced to healthy adolescents (NHANES 1999–2002) and albumin-creatinine ratio (ACR) ≥ 30 µg/mg at 3 consecutive annual visits.

Results—Hyperfiltration was observed in 7.0% of participants at baseline and in 13.3% by 5-years, with a cumulative incidence of 5.0% over 5-years. The prevalence of increased albumin excretion was 6% at baseline and 18% by 5-years, with a cumulative incidence of 13.4%. There was an 8% increase in risk of hyperfiltration per 10% lower eIS in unadjusted and adjusted models ($p=0.01$). Increased albumin excretion was associated with HbA1c, but not eIS.

Limitations—Longer follow-up is needed to capture the transition from hyperfiltration to rapid GFR decline in youth onset type 2 diabetes.

Conclusions—Lower eIS was associated with risk for hyperfiltration over time, whereas increased albumin excretion was associated with hyperglycemia in youth-onset T2D.

Keywords

type 2 diabetes mellitus (T2DM); insulin sensitivity; increased albumin excretion; hyperfiltration; Cystatin C; creatinine; estimated glomerular filtration rate (eGFR); Diabetic kidney disease (DKD); Albumin-creatinine ratio (ACR); children; adolescents; disease progression; renal function; youth-onset T2DM

Introduction

Diabetic kidney disease (DKD) remains the leading cause of end-stage renal disease (ESRD) (1). Early DKD, including hyperfiltration and increased albumin excretion, is common in youth with type 2 diabetes mellitus (T2DM) and progresses at an alarming rate. A prevalence of 24% for hyperfiltration and 34% for increased albumin excretion has been reported in a small cohort of 46 adolescents with T2D (2). We previously examined longitudinal data from the Treatment Options for Type 2 Diabetes in Adolescents and Youth (TODAY) study, showing that the prevalence of increased albumin excretion rose from 6.3% of participants at baseline to 16.6% by the end of the study period (3). However, at the time of that publication, average time of follow-up was only 3.9 years, and laboratory data needed to assess hyperfiltration was not available.

Youth-onset T2D appears to carry a particularly high risk of progressive DKD, significantly greater than in youth-onset type 1 diabetes or in adult-onset T2D of similar disease duration (3–10). The early stages of DKD are clinically silent for many years, yet renal parenchymal damage progresses during this time (11). Hyperfiltration is an early indicator of DKD, often preceding increased albumin excretion and kidney function decline (12,13). Therefore, identification of clinical phenotypes that are associated with hyperfiltration and predictive of DKD progression is needed to improve outcomes in adolescents with T2D. Specifically, reduced insulin sensitivity (IS) is associated with the development of future kidney disease in adults with and without T2D (14,15). While the mechanisms underlying the relationship between reduced IS and DKD remain unclear, experimental evidence suggests that the energy profile of T2D cannot accommodate the renal hypermetabolism of DKD (16–18). Associations between insulin resistance and hyperfiltration have been reported in a small cross-sectional cohort of adolescents with T2D (2), but data on hyperfiltration are lacking in larger cohorts as are longitudinal hyperfiltration data in adolescents with T2D. Cross-sectional relationships between insulin resistance and increased albumin excretion were previously reported in adolescents with T2D in the SEARCH for Diabetes in Youth Study (19) but longitudinal data on these relationships are also lacking. To our knowledge, there are no longitudinal data on the relationship between IS and hyperfiltration or increased albumin excretion in adolescents with T2D.

Our aim was to add to our previous work by describing the prevalence and incidence of hyperfiltration (defined as estimated glomerular filtration rate (eGFR) 99th percentile for healthy controls) in the TODAY study of youth-onset T2D at baseline and over 5 years, as well as extending the albumin excretion data previously reported out to 5 years. Moreover,

we sought to investigate the longitudinal relationship between estimated IS (eIS) and renal outcomes over the 5 years of study. Considering our previous cross-sectional data, we hypothesized that lower eIS in adolescents with T2D would be associated with DKD, reflected by increased risk of hyperfiltration and increased albumin excretion.

Methods

Study population and design

The TODAY study (ClinicalTrials.gov identifier NCT00081328) was a multicenter, randomized clinical trial designed to evaluate three treatment therapies in children and adolescents with TDM. Beginning in July 2004 and ending in February 2009, 699 participants were randomly assigned to metformin monotherapy, metformin plus rosiglitazone, or metformin plus an intensive lifestyle intervention program (materials developed and used for the TODAY standard diabetes education program and the intensive lifestyle intervention program are available to the public at <https://today.bsc.gwu.edu>). Eligibility criteria included youth 10–17 years of age with type 2 diabetes according to American Diabetes Association criteria with diabetes duration <2 years, body mass index (BMI) 85th percentile, negative testing for diabetes-associated autoantibodies, fasting C-peptide >0.6 ng/mL, and an adult caregiver willing to support study participation. Participants were excluded for refractory hypertension, defined as blood pressure (BP) 150/95 mmHg despite appropriate medical therapy, or a calculated Cockcroft-Gault creatinine clearance <70 mL/min (21). The primary objective of the parent study was to compare the three treatment arms in terms of time to treatment failure, classified as a loss of glycemic control (defined as HbA1c ≥8% for 6 months or sustained metabolic decompensation requiring insulin). Half the cohort reached the primary endpoint and results demonstrated that adding rosiglitazone to metformin was associated with more durable glycemic control after an average follow-up of 3.86 years (22). Insulin was initiated at the time of primary outcome. The protocol was approved by the institutional review boards of all participating institutions, and appropriate informed consent and assent was obtained.

This study is a secondary analysis using observational data from the parent TODAY clinical trial. Of the 699 TODAY participants, 137 were excluded who did not have baseline eIS and/or eGFR data, leaving a final cohort of 532 subjects. Excluded participants did not differ significantly on any demographic or baseline characteristic (sex, race-ethnicity, age, BMI or HbA1c) from the 699 in the original cohort. Analyses included data available on TODAY participants at each annual visit time points up to 60 months of follow-up.

Data collection and laboratory analysis

The methods of the TODAY trial, including laboratory analyses, study definitions, and data collection protocols, have been previously reported in detail (20). Briefly, samples were obtained at baseline and annually and processed immediately according to standardized procedures and shipped on dry ice for analysis at the TODAY central biochemical laboratory (20). Estimated insulin sensitivity (eIS) was calculated annually as the reciprocal of fasting insulin (in units of mL/μU), which correlates strongly with hyperinsulinemic-euglycemic clamp-derived in vivo IS in obese youth with or without type 2 diabetes (23).

Concentrations of creatinine in serum and urine were determined by using the Creatinine Plus enzymatic Roche reagent on a Modular P analyzer (Roche Diagnostics, Inc., Indianapolis, IN), which is traceable to the IDMS reference standard. Concentration of cystatin C in serum was measured immunochemically by using Siemens reagents (Siemens Healthcare Diagnostics, Inc, Newark, DE) on a Siemens nephelometer autoanalyzer (BNII). This method is standardized against the IFCC/ERM DA-471 Reference Material (RT Corp, Laramie WY).

Measurements and definitions of study outcomes

eGFR was calculated using the Zappitelli combined creatinine and cystatin C equation ($\text{eGFR} = 25.38 * (1/\text{serum cystatin C})^{0.331} * (1/\text{serum creatinine})^{0.602} * (1.88^{\text{height}})$) which has demonstrated strong agreement with measured GFR in adolescents (25,26). Due to the large variability of eGFRs over time in the cohort, a conservative approach was used in the present study to define presence of hyperfiltration. First, elevated GFR was defined as an eGFR $\geq 99^{\text{th}}$ percentile [$\geq 140 \text{ mL/min/1.73m}^2$] when referenced to a nationwide sample of healthy adolescent controls (NHANES 1999–2002 (26)). Second, a participant was classified as having hyperfiltration only if the eGFR was elevated on 3 consecutive annual visits. While this approach may underestimate the number of participants with hyperfiltration in our analyses, it ensures the stability and persistence of elevated values over time.

Urine albumin excretion (albumin-creatinine ratio [ACR]) was measured at baseline and annually thereafter. Spot urine samples were obtained after a 10–14hr overnight fast. Increased albumin excretion (referred to as albuminuria in previous TODAY publications) was defined as an ACR of $\geq 30 \mu\text{g/mg}$ on two of three urine samples collected over a 3-month minimal period (21). Severely increased albumin excretion (previously termed macroalbuminuria) was defined as ACR $\geq 300\mu\text{g/mg}$.

Statistical analysis

Analyses were performed using SAS (version 9.4 for Windows; SAS Institute, Cary, NC). To account for multiple observations per participant, generalized estimating equations models were used to evaluate the longitudinal changes over discrete-time for eIS, eGFR and ACR. Analyses employed the natural log-transformed ACR and eIS to better approximate a normal distribution and are presented as the geometric mean and the 95% asymmetric confidence limits. The assumption of missing completely at random was used for missing data. Average annual change was obtained from similar models with time entered as a continuous measure. We include unadjusted models and models adjusted for sex, race-ethnicity, treatment group, baseline BMI, HbA1c, age, treatment failure status (loss of glycemic control yes/no), and hypertension diagnosis. Sensitivity analyses were conducted using only data from participants while still in glycemic control to assure reported results were not biased as insulin therapy was started after failure to maintain glycemic control and could interfere with the measurement of eIS.

The cumulative incidence of events over time was estimated using a Kaplan-Meier estimate and Cox proportional hazard models were used to examine the relationships between eIS

and incident increased albumin excretion and hyperfiltration. Participants with existing hyperfiltration or increased albumin excretion at baseline were excluded from all time-to-event analyses. Univariate and multivariable Cox proportional hazard models were evaluated using eIS as a time-dependent variable, while adjusting for sex, race-ethnicity, and treatment group (as fixed covariates) and age, BMI, HbA1c, hypertension diagnosis, and primary outcome status (loss of glycemic control) as time-dependent covariates. In sensitivity analyses, we adjusted for ACE-I/angiotensin II receptor blocker (ARB) use rather than hypertension diagnosis. Similar Cox models were used to examine the relationships between eGFR with incident increased albumin excretion, and between ACR with incident hyperfiltration. The proportional hazards assumption in the Cox model was assessed with graphical methods and with models including time-by-covariate interactions; all covariates tested met the assumption. All analyses were considered exploratory and $P<0.05$ was the cut-off used to determine statistical significance.

Results

Longitudinal changes in eGFR, ACR and eIS

Table 1 shows participant characteristics at baseline for the 532 participants included in the analysis. Figure 1 presents eGFR, ACR and eIS annually during the 5-year study period. There was an annual increase in eGFR by a mean of 2.45 ± 0.28 (standard error) mL/min/ 1.73m^2 ($p<0.001$), an average increase in ACR of 5.5% per year ($p=0.002$), and an average decrease in eIS of 5.4% per year ($p<0.001$). These linear trends remained significant for eGFR in fully adjusted models (Figure 1, Table S1). At baseline, 1.5% of the participants had severely increased albumin excretion, with no significant increase over time. When examined only in participants who remained in glycemic control, eGFR still increased ($p=0.003$) and eIS still decreased over time ($p=0.01$), while at a lower but still significant rate, and the trends remained significant in fully adjusted models (Table S2).

Hyperfiltration and increased albumin excretion

At baseline, 12.8% of the participants had an elevated eGFR [≥ 140 mL/min/ 1.73m^2] and 26.8% had elevated eGFR at year 5 (Table S1). Presence of hyperfiltration (based on first of 3 consecutive annual elevated eGFR values) was observed in 7.0% of participants at baseline and 13.3% at 5 years (Table S1), with a cumulative incidence of 5.0% over 5 years (Figure 2). The prevalence of increased albumin excretion was 6.0% at baseline and 18.0% at 5 years (Table S1), with a cumulative incidence of 13.4% over 5 years. The cumulative incidence of increased albumin excretion has been previously reported (3).

At baseline, 0.8% of participants had both hyperfiltration and increased albumin excretion, and 4.0% had both at year 5. Baseline eGFR was not associated with development of increased albumin excretion, nor was baseline $\ln(\text{ACR})$ associated with risk of hyperfiltration.

In contrast to what was observed in the entire cohort (Table S1), when examined only in participants who remained in glycemic control, prevalence of hyperfiltration and elevated albumin excretion did not significantly increase over time (Table S2).

Associations between eIS and development of hyperfiltration

Lower log eIS was associated with a 2.1-fold increased risk of hyperfiltration in a univariate model (Table 2), corresponding to an 8% increase in risk of hyperfiltration per 10% lower eIS. This association remained significant in the adjusted model (Table 3). HbA1c, BMI, age, loss of glycemic control, development of hypertension, nor treatment group were associated with increased risk of developing hyperfiltration in the adjusted model. However, male sex was associated with decreased risk of developing hyperfiltration ($p=0.03$, Table 3). In sensitivity analyses, we adjusted for ACE-I/ARB use instead of development of hypertension in the multivariable model, and the association between eIS and incident hyperfiltration remained statistically significant (HR, 2.05; 95% CI, 1.11–3.79; $p=0.02$). Due to concerns of collinearity between HbA1c and loss of glycemic control, we also reran the multivariable model without HbA1c, and loss of glycemic control conferred greater risk of hyperfiltration (HR, 3.49; 95% CI, 1.43–8.47; $p=0.006$).

Associations between change in eIS and development of hyperfiltration

A 10% worsening of eIS relative to baseline was associated with a 7% percent increase in hyperfiltration in unadjusted (Table 2) and adjusted models (Table 4). Neither change in HbA1c nor change in BMI from baseline was associated with increased risk of developing hyperfiltration. When we adjusted for ACE-I/ARB use instead of hypertension diagnosis in the multivariable model, the relationship between change in eIS and incident hyperfiltration was of borderline statistical significance (HR, 1.54; 95% CI, 1.00–2.35; $p=0.05$).

Associations between eIS and development of increased albumin excretion

Neither log eIS, BMI, age, loss of glycemic control, development of hypertension nor treatment group were associated with increased risk of developing increased albumin excretion in univariate (Table 2) or multivariable (Table 3) models. However as previously reported (3), 1% greater HbA1c was associated with increased risk of incident increased albumin excretion in adjusted models (HR, 1.36; 95% CI, 1.18–1.57; $p<0.001$) (Table 3).

Associations between change in eIS and development of increased albumin excretion

Neither change in log eIS (Table 2) nor change in BMI from baseline to the time of increased albumin excretion were associated with increased risk of developing increased albumin excretion in unadjusted or adjusted models (Table 4). However, change in HbA1c from baseline and hypertension diagnosis were associated with increased risk of increased albumin excretion (Table 4).

Discussion

Adolescents with T2D in the TODAY study overall demonstrated a rise in eGFR, increased albumin excretion, and a decline in eIS over time. Lower eIS and female sex were clearly associated with incident hyperfiltration over the study period, independent of other risk factors. Conversely, increased albumin excretion was not associated with eIS over time, but *was* related to glycemic control and hypertension. These findings suggest that worsening insulin resistance confers increased risk for hyperfiltration in youth-onset T2D, and that

hyperfiltration and increased albumin excretion may be associated with discrete risk factors reflecting their underlying pathophysiology.

Adolescents with T2D are at especially high risk of developing kidney disease, with up to 45% progressing to kidney failure as adults, which is significantly greater than youth with type 1 diabetes and adults with adult-onset T2D (14,15). The natural history of DKD features an extended silent period during which overt clinical signs or symptoms of kidney disease are absent. For this reason, a substantial challenge in efforts to prevent DKD is how difficult it is to accurately identify high-risk patients with pre-clinical disease. Therefore, American Diabetes Association now recommends assessing eGFR in adolescents with T2D annually (27) to screen for DKD. There is a shortage of longitudinal eGFR data in youth-onset T2D. The reports on eGFR and hyperfiltration in this study provide clinicians with reference data from a large national study of youth with T2D. To our knowledge, this report is also one of the first to demonstrate a longitudinal relationship between eIS and hyperfiltration in adolescents with T2D; it also shows a longitudinal relationship between HbA1c and increased albumin excretion in this population. Moreover, IS was more predictive of hyperfiltration than conventional risk factors for the development of kidney disease, including glycemic control, BMI, and hypertension. These observations are similar to the previous cross-sectional report by Bjornstad, et al (2) demonstrating an independent association of IS and GFR in adolescents with T2D.

Hyperfiltration is a distinct, preclinical phenotype of DKD that is predictive of subsequent development of increased albumin excretion and progression of diabetic nephropathy (28,29). Hyperfiltration is proposed to reflect an underlying increase in intraglomerular pressure, leading to structural changes (mesangial expansion and glomerular basement membrane thickening) over time (30). The mechanisms believed to underlie these pathological changes are complex, involving growth factors, neurohormonal activation, and alterations in renal tubuloglomerular feedback (31). Accumulating evidence has shown that insulin resistance is associated with an increase in glomerular hydrostatic pressure, leading to increased renal vascular permeability and eventually glomerular hyperfiltration (32–36).

The association between insulin resistance and progression of increased albumin excretion in adults with T2D is increasingly accepted. Parvanova et al (37) reported a significant cross-sectional association between measured insulin resistance and increased albumin excretion in adults, while De Cosmo et al (38) found that adult men with HOMA-IR values in the highest quartile were more likely to have increased albumin excretion than those in the lowest quartile. Other researchers have demonstrated a longitudinal relationship between insulin resistance and incident increased albumin excretion over 5 years in adults (33). While we observed strong longitudinal relationships between IS and hyperfiltration, similar relationships were not demonstrated with increased albumin excretion. Conventional understanding is that hyperfiltration is a maladaptive glomerular response that precedes increased albumin excretion and subsequent decline of kidney function in diabetic nephropathy (39). Compared to adults, DKD in our adolescent cohort with short diabetes duration may be in its earliest stage of disease progression, and therefore before an association between insulin resistance and increased albumin excretion becomes apparent. Others have more recently proposed that hyperfiltration and increased albumin excretion, are

in fact, distinct phenotypes of DKD (12), each with their own discrete pathogenic mechanisms. This hypothesis would be consistent with the observation that increased albumin excretion does not necessarily reflect progressive nephropathy and that increased albumin excretion may revert to normal albumin excretion in T2D (40), a fact that confounds longitudinal analyses. Data from SEARCH for Diabetes in Youth Study demonstrated a cross-sectional relationship between ACR and IS calculated by an equation consisting of waist circumference, triglycerides, and HbA1c in youth with T2D (19). Because HbA1c was incorporated into the equation used to calculate IS, HbA1c was not included in their multivariable models, and it is possible that the association demonstrated between calculated IS and ACR in SEARCH was driven by HbA1c rather than insulin resistance, consistent with the relationship we observed between HbA1c and elevated albumin excretion. Another explanation for the discrepancy is longer duration of diabetes in the SEARCH population.

Since IS can be modified by changes in lifestyle (such as diet and exercise) and medications (e.g. metformin), IS may be a promising therapeutic target to reduce DKD in adolescents with T2D. In adults with coronary artery disease and T2D (41), BARI-2D (Bypass Angioplasty Revascularization Investigation in Type 2 Diabetes) insulin-sensitizing therapy had no benefit on progression of DKD. However, this study population was significantly different than the TODAY cohort, with a mean participant age of 62 years and most participants already having hypertension and hyperlipidemia at baseline (42). The kidney injury in longstanding DKD may be less responsive to changes in IS than the early alterations in kidney function observed in adolescents with T2D, arguing for separate studies in youth. Moreover, since signs of DKD are already detectable in youth with T2D, early interventions are likely needed to prevent further progression of DKD. Our supplemental data also suggest a lower prevalence of DKD in those participants who did not experience progressive β -cell failure and remained in glycemic control.

Our study does have limitations, including the use of calculated GFR (eGFR) and estimated IS (eIS). Although gold standard measurements are preferable, these would have presented an unreasonable burden to an already challenged group of TODAY study subjects. Moreover, the reciprocal of fasting insulin has demonstrated strong agreement with IS measured by hyperinsulinemic euglycemic clamp studies (43,44). While there are several pediatric eGFR equations, none have been validated against measured GFR in obese adolescents with T2D. We decided to calculate eGFR by the Zappitelli combined creatinine and cystatin C equation as it has shown accuracy in estimating GFR in adolescents with GFR in the normal to elevated range (45). Because our definition of hyperfiltration required elevated GFR at three consecutive annual visits, participants who had eGFR $\geq 140\text{ mL/min/1.73m}^2$ at year 4 and 5, or only year 5 were not categorized as having hyperfiltration as data beyond year 5 were not available for these analyses. This conservative definition of hyperfiltration may underestimate the number of participants with hyperfiltration in our analyses and therefore may bias the results towards the null hypotheses. Our definition of hyperfiltration is based on NHANES (National Health and Nutrition Examination Survey)²⁶ rather than a supraphysiological rise in each participant baseline GFR before the onset of T2D, which would have been ideal. Furthermore, longer follow-up is likely required to capture the transition from hyperfiltration to rapid GFR decline. Even though basic and clinical research studies imply that IS has direct effects on kidney health, underlying

common risk factors that are responsible for both worsening IS and renal pathology could be an alternative explanation. The strengths of our study include the large number of participants and the availability of longitudinal data at several time points not only for eIS and eGFR, but also for other important covariates (e.g., HbA1c, and BMI and hypertension), which allowed us to examine the independent relationship between eIS and incident hyperfiltration.

In summary, the high rates of increased albumin excretion and hyperfiltration in youth with T2D forecast early renal morbidity and mortality. Improved understanding of the determinants of DKD risk and progression over longer periods of follow-up is essential to improve outcomes in youth with T2D. We found that insulin resistance rather than adiposity, blood pressure, or glycemic control was associated with greater risk of hyperfiltration over the 5-year study period in adolescents with T2D. Worsening IS may therefore represent an early risk factor for future progression of DKD in adolescents with T2D.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. Annual longitudinal changes for (A) mean eGFR, (B) median ACR and (C) median eIS (along with 95% CI error bars) across the 5 years in the TODAY study*

*The arithmetic mean and 95% CI error bars is shown for eGFR (A) values over time. The geometric mean and 95% CI error bars is shown for ACR (B) and eIS (C) due to skewed distributions. The geometric mean is a good approximation of the median as the log-transformed data is approximately symmetric. Data shown in figures from all participants, irrespective of whether participants lost glycemic control.

[†]P-value from an unadjusted model testing for linear trend over time, and from adjusted model including sex, race-ethnicity, treatment group, baseline BMI, baseline HbA1c, age at

baseline, treatment failure status (loss of glycemic control yes/no), and hypertension diagnosis.

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Figure 2. Cumulative incidence curves for time to hyperfiltration by Zappitelli combined creatinine and cystatin C equation during TODAY*

*Participants with hyperfiltration at baseline are excluded. Time to hyperfiltration defined at the first of three consecutive annual visits with eGFR $\geq 99^{\text{th}}$ percentile for NHANES controls (i.e., eGFR $\geq 140 \text{ mL/min/1.73m}^2$); Data shown in figure from all participants, irrespective of whether participants lost glycemic control.

Table 1

Demographic and baseline characteristics of the sample

Characteristic	Value
Female (%)	340 (63.9%)
Age (y)	13.9 $\pm$ 2.0
Diabetes duration (m)	7.9 $\pm$ 5.9
Race/ethnicity	
Black non-Hispanic	179 (33.6%)
Hispanic	229 (43.0%)
White non-Hispanic	107 (20.1%)
Other	17 (3.2%)
BMI (kg/m ²)	35 $\pm$ 8
Blood pressure (mm Hg)	
Systolic	113 $\pm$ 11
Diastolic	66 $\pm$ 8
ACE inhibitor/ARB use	25 (4.7%)
Hypertension diagnosis	100 (18.8%)
Serum creatinine (mg/dL)	0.61 $\pm$ 0.13
Serum cystatin C (mg/L)	0.75 $\pm$ 0.12
HbA1c (%)	6.0 $\pm$ 0.7

N = 532. Values are shown as mean mean $\pm$ SD or count (percentage).

Univariate Cox Proportional Hazards Model predicting hyperfiltration or increased albumin excretion

Table 2

Variable	Hyperfiltration		Increased albumin excretion		
	HR (95% CI)	P	HR	95% CI	P
In(estimated insulin sensitivity), per 1-U lower	2.12 (1.22–3.68)	0.008	1.25	0.86–1.82	0.2
in ln(estimated insulin sensitivity), per 1-U decrease	1.87	1.19–2.94	0.82	0.57–1.17	0.3
Male sex	0.32	0.11–0.91	1.12	0.68–1.86	0.6
Baseline age, per 1-y higher	0.89	0.73–1.09	1.07	0.95–1.22	0.3
Hispanic race-ethnicity *	1.79	0.80–3.97	1.29	0.79–2.11	0.3
Non-Hispanic black race-ethnicity *	0.49	0.18–1.31	0.84	0.49–1.44	0.5
Other race-ethnicity	2.48	0.57–10.9	0.46	0.06–3.42	0.4
Metformin+rosiglitazone **	1.19	0.52–2.71	1.26	0.76–2.09	0.4
Metformin+intensive lifestyle **	0.93	0.40–2.18	0.65	0.38–1.13	0.1
BMI, per 1 kg/m ² higher	0.98	0.93–1.03	1.02	0.99–1.04	0.3
in BMI, per 1 kg/m ² increase	0.96	0.83–1.10	0.98	0.91–1.07	0.7
HbA1c, per 1% lower	1.21	1.05–1.39	1.38	1.36–1.51	<0.001
in HbA1c, per 1% decrease	1.23	1.05–1.43	1.41	1.29–1.55	<0.001
Loss of glycemic control	3.31	1.47–7.43	4.37	2.57–7.43	<0.001
Hypertension diagnosis	1.56	0.70–3.48	2.02	1.22–3.35	0.006

HR: hazard ratio; CI: confidence interval; : change from baseline.

* Referent group: Non-Hispanic White.

** referent group: metformin only.

Table 3
Multivariate Cox Proportional Hazards Model predicting hyperfiltration or increased albumin excretion

Variable	Hyperfiltration			Increased albumin excretion		
	HR	95% CI	P-value	HR	95% CI	P-value
ln ln(estimated insulin sensitivity), per 1-U decrease	2.13	1.16–4.00	0.01	1.01	0.68–1.49	0.9
Male	0.32	0.11–0.91	0.03	0.88	0.50–1.56	0.7
Baseline age, per 1-y higher	0.93	0.75–1.17	0.5	1.00	0.87–1.15	0.9
Hispanic race-ethnicity [*]	1.38	0.43–4.42	0.6	1.00	0.48–2.09	0.9
Non-Hispanic black race-ethnicity [*]	0.51	0.13–2.06	0.3	0.55	0.24–1.25	0.1
Other race-ethnicity	2.14	0.36–12.9	0.4	0.70	0.09–5.65	0.7
Metformin+rosiglitazone ^{**}	1.47	0.54–4.04	0.4	1.20	0.65–2.22	0.5
Metformin+intensive lifestyle ^{**}	1.14	0.41–3.22	0.8	0.66	0.33–1.31	0.2
BMI, per 1 kg/m ² higher	0.95	0.89–1.02	0.1	1.01	0.98–1.05	0.4
HbA1c, per 1% lower	1.05	0.82–1.34	0.7	1.36	1.18–1.57	<0.001
Loss of glycemic control	2.92	0.80–10.7	0.1	1.47	0.64–3.40	0.4
Hypertension diagnosis	1.93	0.80–4.66	0.1	1.70	0.95–3.05	0.07

HR: hazard ratio; CI: confidence interval.

^{*} Referent group: Non-Hispanic White.

^{**} referent group: metformin only.

Table 4
Multivariate Cox Proportional Hazards Model predicting hyperfiltration or increased albumin excretion

Variable	Hyperfiltration			Increased albumin excretion		
	HR	95% CI	P-value	HR	95% CI	P-value
in ln(estimated insulin sensitivity), per 1-U decrease	1.59	1.04–2.44	0.03	0.83	0.58–1.18	0.3
Male	0.30	0.11–0.87	0.03	0.87	0.49–1.54	0.6
Baseline age, per 1-y higher	0.88	0.72–1.09	0.2	1.03	0.90–1.18	0.7
Hispanic race-ethnicity [*]	1.34	0.42–4.26	0.6	1.01	0.48–2.11	0.9
Non-Hispanic black race-ethnicity [*]	0.54	0.14–2.10	0.4	0.56	0.25–1.28	0.2
Other race-ethnicity	2.23	0.37–13.5	0.4	0.66	0.08–5.33	0.7
Metformin+rosiglitazone ^{**}	1.34	0.49–3.67	0.6	1.14	0.62–2.12	0.7
Metformin+intensive lifestyle ^{**}	0.96	0.34–2.71	0.9	0.64	0.32–1.27	0.2
in BMI, per 1 kg/m ² increase	0.94	0.80–1.10	0.4	1.08	0.99–1.18	0.1
in HbA1c, per 1% decrease	1.12	0.88–1.41	0.3	1.39	1.20–1.60	<0.001
Loss of glycemic control	2.42	0.75–7.82	0.1	1.95	0.90–4.24	0.09
Hypertension diagnosis	1.95	0.83–4.57	0.1	1.89	1.08–3.31	0.03

HR: hazard ratio; CI: confidence interval.

^{*} Referent group: Non-Hispanic White.

^{**} referent group: metformin only.