Published in final edited form as:

J Diabetes Complications. 2017 February ; 31(2): 369–374. doi:10.1016/j.jdiacomp.2016.06.012.

Adiponectin is associated with early diabetic kidney disease in adults with type 1 diabetes: A Coronary Artery Calcification in Type 1 Diabetes (CACTI) Study

Petter Bjornstad^{a,b,*}, Laura Pyle^{a,c}, Gregory L. Kinney^{b,d}, Marian Rewers^{a,b}, Richard J. Johnson^e, David M. Maahs^{a,b,e}, and Janet K. Snell-Bergeon^{a,b}

^aDepartment of Pediatric Endocrinology, University of Colorado School of Medicine, Aurora, CO, United States

^bBarbara Davis Center for Diabetes, University of Colorado School of Medicine, Aurora, CO, United States

^cDepartment of Biostatistics and Informatics, Colorado School of Public Health, Aurora, CO

^dDepartment of Epidemiology, Colorado School of Public Health, Aurora, CO

^eDepartment of Medicine, Division of Nephrology, University of Colorado School of Medicine, Aurora, CO, United States

Abstract

Objective—The associations between elevated adiponectin and end-stage renal disease are well recognized and thought to be at least partially explained by reduced renal clearance. Conversely, the relationship between adiponectin and early diabetic kidney disease (DKD) with preserved glomerular filtration rate (GFR), including rapid GFR decline and incident chronic kidney disease (CKD) is unclear. We hypothesized that elevated adiponectin would be associated with early DKD in adults with type 1 diabetes.

Methods—Adults with type 1 diabetes (n = 646 at baseline, n = 525 at 6 years) had adiponectin and renal function by estimated GFR (eGFR) by CKD-EPI creatinine and albumin-excretion rate (AER) evaluated at baseline and 6 years. Linear and logistic models evaluated the associations of baseline adiponectin with AER, macroalbuminuria (AER ≥ 200 µg/min), eGFR, CKD (<60 mL/min/1.73 m²) and rapid GFR decline (>3 mL/min/1.73 m²/year). Models adjusted for age, sex, duration, HbA1c, SBP, LDL-C and current smoking.

Results—Compared to non-diabetics, adults with type 1 diabetes had significantly higher adiponectin, and the difference remained significant after adjusting for AER and/or eGFR (p < 0.0001). Adiponectin at baseline was positively associated with rapid GFR decline (OR: 1.24, 95% CI 1.00–1.53), incident CKD (OR: 1.75, 1.14–2.70), and persistent macroalbuminuria and CKD

*Corresponding author at: Barbara Davis Center for Childhood Diabetes, University of Colorado, Denver, 1775 Aurora Court, Aurora, CO 80045. Tel.: +1 720 777 4659; fax: +1 720 777 7301. Petter.Bjornstad@childrenscolorado.org (P. Bjornstad).

Drs. Bjornstad, Pyle, Kinney, Snell-Bergeon, Rewers and Maahs have no conflict of interest to disclose.

Duality of interest: Drs. Bjornstad and Pyle are the 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.

(OR: 1.61, 1.10–2.36) over 6 years in adjusted models. The associations also remained significant after further adjustments for CRP, estimated insulin sensitivity and ACEi/ARB therapy.

Conclusions—Adults with type 1 diabetes have higher adiponectin than their non-diabetic peers, and elevated adiponectin at baseline is independently associated with greater odds of developing early DKD over 6 years.

Keywords

Adiponectin; Glomerular filtration rate (GFR); Diabetic nephropathy; CKD-EPI creatinine; Type 1 diabetes

1. Introduction

Diabetic kidney disease (DKD) remains the single most important cause of end stage renal disease (ESRD) in the Western world (Bjornstad, Cherney, & Maahs, 2014; Maahs & Rewers, 2006; Orchard, Secrest, Miller, & Costacou, 2010), and early detection of risk factors for DKD remain a major goal to improve risk stratification and prevention. Circulating adiponectin, an adipokine with anti-inflammatory and insulin-sensitizing properties (Berg & Scherer, 2005; Giannessi, Maltinti, & Del Ry, 2007; Hopkins, Ouchi, Shibata, & Walsh, 2007), is elevated in individuals with type 1 diabetes. Furthermore, lower adiponectin concentrations are associated with cardiovascular disease among people with type 1 diabetes (Berg & Scherer, 2005; Giannessi et al., 2007; Hopkins et al., 2007; West et al., 2009). Therefore, the increased concentrations of adiponectin observed in type 1 diabetes, a disease characterized by insulin resistance, inflammation and increased risk of cardiovascular disease (CVD)(Hecht Baldauff et al., 2015; Pereira et al., 2012), are unexpected and paradoxical.

Several theories have been proposed to explain the increased concentrations of adiponectin observed in people with type 1 diabetes, but the underlying mechanisms remain elusive. While recent data suggest that adiponectin levels increase acutely with insulin therapy (Combs et al., 2015), adiponectin is positively associated with insulin sensitivity in type 1 diabetes, although the association is similar but at higher concentrations of adiponectin in people with type 1 diabetes than in non-diabetics (Costacou & Orchard, 2008). Furthermore, dissociation between adiponectin and suppressor of glucose from autophagy (SOGA) was recently reported in type 1 diabetes, which raises the possibility of adiponectin resistance in type 1 diabetes (Panduru et al., 2015). It has been proposed that elevated adiponectin counteracts increased inflammation in type 1 diabetes, and that an inadequate adiponectin response to stress and inflammation leads to progression of DKD (Saraheimo et al., 2008).

Equally unexpected were the reported associations between elevated adiponectin and advanced stages of CKD and ESRD in type 1 diabetes, when elevated adiponectin has been associated with decreased risk for CVD outcomes in the same patient population (Inker et al., 2012; Maahs et al., 2005). The kidneys possibly play an important role in the biodegradation and/or elimination of adiponectin, but altered clearance rates are not likely to fully account for the increase in circulating adiponectin in DKD (Saraheimo et al., 2008). Furthermore, while the associations between adiponectin and advanced stages of DKD,

including ESRD are well recognized, the relationship between adiponectin and early DKD with preserved glomerular filtration (rate), including rapid GFR decline and incident chronic kidney disease (CKD) is unclear.

Given these uncertainties, we decided to examine the association between adiponectin at baseline and development of CKD (<60 mL/min/1.73 m²) and rapid GFR decline (>3 mL/min/1.73 m²/year) in a prospective cohort of adults with type 1 diabetes (the Coronary Artery Calcification in Type 1 diabetes [CACTI] cohort).

2. Materials and methods

2.1. Cohort and methods

The CACTI Study enrolled subjects 19–56 years old, with and without type 1 diabetes, who were asymptomatic for cardiovascular disease (CVD) at the baseline visit in 2000–2002 and then were re-examined 6 years later, as previously described (Schauer et al., 2011). Subjects with serum creatinine >2 mg/dL were excluded at baseline, unless they were participants in the pilot study. Participants with ($n = 646$ at baseline, $n = 525$ at 6 years) and without type 1 diabetes ($n = 761$ at baseline, $n = 604$ at 6 years) and who had data to calculate eGFR by CKD-EPI creatinine at baseline were eligible for inclusion in the present analyses. The study was approved by the Colorado Multiple Institutional Review Board and all participants provided informed consent.

After an overnight fast, blood was collected, centrifuged, and separated. Adiponectin was measured using the radioimmunoassay (RIA) methodology (Millipore, Billerica MA) on the frozen baseline samples just before the 6-year visit, and the 6-year visit samples were measured on a real-time basis. For that reason, the baseline and 6-year samples were measured at approximately the same time which reduces the risk of assay drift. Blood glucose was measured using standard enzymatic methods and high performance liquid chromatography was used to measure HbA1c (HPLC, BioRad variant). Total plasma cholesterol and triglyceride (TG) levels were measured using standard enzymatic methods, HDL-C was separated using dextran sulfate and LDL-C was calculated using the Friedewald formula. Commercially available ELISA kits (R&D Systems, Alpco Diagnostics) were used to measure high sensitivity CRP.

GFR was determined using the CKD-EPI creatinine equation published by the CKD-EPI Investigators Group (Bjornstad et al., 2013). Rapid GFR decline was defined as an annual eGFR loss >3 mL/min/1.73 m², and incident CKD was defined as the development of eGFR <60 mL/min/1.73 m² at 6-year follow-up without prior documented impaired GFR (i.e. participants with eGFR <60 mL/min/1.73 m² were excluded from the analyses [$n = 49$]). Persistent DKD was defined as persistent macroalbuminuria (albumin excretion rate [AER] 200 µg/min or albumin to creatinine [ACR] 300 mg/g for those with missing AER data) and/or CKD at baseline and 6-year follow-up.

Estimated insulin sensitivity (eIS) was calculated using an equation developed in a subset of the study cohort who underwent a hyperinsulinemic–euglycemic clamp study to measure insulin sensitivity, as previously described in detail (Palanivel, Ganguly, Turdi, Xu, &

Sweeney, 2014). The model included waist circumference, daily insulin dose per kg body weight, triglycerides and diastolic blood pressure (DBP): $\exp(4.1075 - 0.01299 * \text{waist (cm)} - 1.05819 * \text{insulin dose (daily units per kg)} - 0.00354 * \text{triglycerides (mg/dl)} - 0.00802 * \text{diastolic blood pressure (mm Hg)})$ (Pischon et al., 2004).

2.2. Statistical analysis

Analyses were performed in SAS (version 9.4 for Windows; SAS Institute, Cary, NC). Variables were checked for the distributional assumption of normality using normal plots, in addition to Kolmogorov–Smirnov and Shapiro–Wilks tests. Variables that were positively skewed (e.g. AER and CRP) were natural log-transformed for the analyses. For Tables 1–4, we stratified our participants by diabetes status, gender, persistence of DKD and rapid GFR decline, respectively. Differences in continuous normally-distributed and transformed variables were examined with the *t*-test and in dichotomous variables with the chi-squared test.

To examine the relationships between adiponectin, eGFR and AER in adults with type 1 diabetes we used univariable and multivariable linear regression models. Univariable and multivariable logistic regression models were applied to evaluate the association between adiponectin, rapid GFR decline, incident CKD and persistent DKD. Variables considered for inclusion in the multivariable models were based on *a priori* criteria: significance in previous work, significant contribution to the model (*p*-value of <0.1), or confounding between the main variable of interest and the outcome by >10%. The following variables were included in the adjusted model: HbA1c, SBP, LDL-C, diabetes duration, age, sex and current smoking. In sensitivity analyses, we also adjusted for ACEi/ARB therapy, in addition to eIS and CRP respectively which did not significantly attenuate any of the measures of associations. Age is part of the CKD-EPI equations, for which reason we evaluated it for collinearity by examining the variance inflation factor before including age in our multivariable model. Linear and logistic regression analyses were limited to adults with type 1 diabetes. A *P*-value < 0.05 was considered statistically significant.

3. Results

3.1. Participants with and without type 1 diabetes

Adiponectin concentrations were higher in adults with type 1 diabetes compared to their non-diabetic counterparts both at baseline (15.8 ± 9.0 vs. 10.5 ± 6.4 $\mu\text{g/ml}$, $p < 0.0001$) and 6-year follow-up (15.3 ± 9.2 vs. 9.8 ± 6.0 $\mu\text{g/ml}$, $p < 0.0001$), and the difference remained significant after adjusting for AER and/or eGFR ($p < 0.0001$).

3.2. Participants with type 1 diabetes stratified by gender

Characteristics for participants with type 1 diabetes stratified by gender are presented in Table 1. Women with type 1 diabetes had higher adiponectin concentrations compared to men with type 1 diabetes at both baseline (18.6 ± 9.4 vs. 12.5 ± 7.2 , $p < 0.0001$) and 6-year follow-up (18.0 ± 9.4 vs. 12.0 ± 7.9 , $p < 0.0001$). A greater number of women also developed rapid GFR decline over time compared to men, and a greater proportion had persistent DKD (Table 1).

3.3. Participants with type 1 diabetes with and without DKD

Participant characteristics stratified by the presence or absence of persistent DKD are presented in Table 2, and participant characteristics stratified by rapid GFR decline are presented in Table 3. Participants with persistent DKD and rapid GFR decline over 6 years had higher adiponectin concentrations at baseline than participants without persistent DKD or rapid GFR decline respectively (Tables 2 and 3). Adiponectin remained higher at 6-year follow-up for those with compared to those without persistent DKD (Table 2), but did not reach statistical significance for those who experienced rapid GFR decline (Table 3).

3.4. The relationship between adiponectin and DKD in participants with type 1 diabetes

Adiponectin was negatively associated with eGFR ($\beta \pm \text{SE}$: -0.41 ± 0.11 , $p = 0.0004$) and positively associated with AER ($\beta \pm \text{SE}$: 0.02 ± 0.01 , $p = 0.006$) at baseline in adjusted models. One standard deviation (SD) increase in adiponectin was associated with greater odds of developing rapid GFR decline, incident CKD over 6 years and persistent DKD (Table 4) in unadjusted and adjusted models. Further adjustment for ACEi/ARB therapy, in addition to eIS and CRP in separate multivariable models did not attenuate the significance of the measures of associations (Table 4).

4. Discussion

Adults with type 1 diabetes have significantly higher adiponectin concentrations than their non-diabetic counterparts, and women with type 1 diabetes have higher adiponectin concentrations compared to men with type 1 diabetes. Adiponectin was associated with increased odds of developing early as well as overt DKD in adults with type 1 diabetes, independent of conventional risk factors. This is to our knowledge the first observation of an independent relationship between adiponectin and early DKD in adults with type 1 diabetes.

Human adiponectin is a 244-amino acid adipokine protein that is reported to be cardioprotective (Schulze et al., 2005), and studies also suggest that low adiponectin levels may contribute to the development of insulin resistance and inflammation in adults (Hopkins et al., 2007). High plasma adiponectin levels are associated both with a lower risk of myocardial infarction in men (Kopf et al., 2014) and a moderately decreased risk for coronary heart disease in diabetes (de Boer et al., 2011). Paradoxically, elevated serum and urine adiponectin has been linked to renal function decline progression through advanced CKD stages (Inker et al., 2012; Maahs et al., 2005). Saraheimo et al. demonstrated that increased serum adiponectin concentrations predicted progression from macroalbuminuria to ESRD in type 1 diabetic patients in the Finnish Diabetic Nephropathy Study (Inker et al., 2012). While the same group did not observe any differences in serum adiponectin concentrations in patients with normoalbuminuria or microalbuminuria irrespective of progression to ESRD (Inker et al., 2012), they did not examine the relationships between adiponectin, rapid GFR decline and incident CKD. Recent reports also showed that urinary adiponectin excretion predicted progression of DKD in diabetic patients (de Boer, 2014), and that urinary adiponectin was associated with progression of advanced stages of DKD (from macroalbuminuria to ESRD) (Maahs et al., 2005). To our knowledge, data on the relationships between adiponectin and earlier stages DKD in type 1 diabetes are scarce.

In this study, in addition to reporting a relationship between adiponectin and persistent overt DKD, we also demonstrated that adiponectin predicted the development of rapid GFR decline and incident CKD over 6 years in adults with type 1 diabetes. DKD continues to cause major morbidity and mortality in type 1 diabetes (de Boer et al., 2011; Maahs & Rewers, 2006). Treatment exists to prevent or slow decline in renal function, including intensive glucose (Anonymous, 2014; Rifkin et al., 2008) and blood pressure control (Saraheimo et al., 2008; Maahs et al., 2005); however, improved prognostic methods are needed to better identify who is at risk to lose renal function at an early stage (Shlipak et al., 2009). Rapid GFR decline, defined as an annual GFR loss greater than 3 mL/min/1.73 m², represents a magnitude of change 3 times the rate expected in normal physiology (Groop et al., 2009; Krolewski et al., 2013). The cut-off is important to distinguish it from slow changes in GFR associated with aging, and beyond the range of noise expected when estimating GFR (Krolewski et al., 2013). Rapid GFR decline has been shown to precede the onset of microalbuminuria in type 1 diabetes (Bjornstad, Snell-Bergeon, Nadeau, & Maahs, 2015), and predict end-stage renal disease and cardiovascular outcomes (Maahs et al., 2014; Orchard et al., 2010). The mechanisms that initiate renal GFR decline in type 1 diabetes remain controversial, but likely include both renal arteriolar and glomerular functional and structural effects due to hyperglycemia, hypertension, dyslipidemia and smoking. Also uncertain is whether those initial mechanisms remain operative as renal function decline progresses through advanced CKD stages. In our cohort, adiponectin at baseline was associated with both early and more advanced DKD.

Several theories have been proposed to explain (i) the increased circulating concentrations of adiponectin in people with type 1 diabetes, and (ii) the increased risk of DKD with elevated levels of adiponectin in type 1 diabetes, but the mechanisms remain elusive.

Supraphysiologic concentrations of exogenous insulin have been proposed to partially mediate the reduced insulin sensitivity observed in type 1 diabetes (Pereira et al., 2012). In type 1 diabetes, the adiponectin concentration has also been shown to acutely rise with insulin therapy (Combs et al., 2015), but adiponectin is positively associated with insulin sensitivity and not insulin resistance in type 1 diabetes (Costacou & Orchard, 2008). Participants with type 1 diabetes are known to have decreased insulin sensitivity compared to non-diabetic controls at every level of adiponectin, suggesting an important adaptive change of the adiponectin set point (Costacou & Orchard, 2008). While greater adiponectin is associated with greater insulin sensitivity, insulin sensitivity, in contrast to adiponectin, is associated with lower odds of early DKD (Pischon et al., 2004), suggesting that the relationship between adiponectin and DKD is independent of insulin sensitivity in type 1 diabetes. Consistent with these observations, the associations in our participants with type 1 diabetes between adiponectin and DKD were independent of insulin sensitivity.

While the kidneys possibly also play an important role in the biodegradation and/or elimination of adiponectin, altered clearance rates of adiponectin are not likely to fully account for the increase in circulating adiponectin in DKD (Saraheimo et al., 2008). In fact, participants with type 1 diabetes have higher concentrations of adiponectin compared to their non-diabetic counterparts after adjusting for eGFR and AER. A study in adults with type 2 diabetes and DKD, demonstrated that increased production of adiponectin was a stronger determinant of serum concentration of adiponectin than the reduction in clearance

of adiponectin by the kidneys. The increased production of adiponectin has been proposed to counteract the increased inflammation in type 1 diabetes, and an inadequate adiponectin response to stress and inflammation could lead to disease progression (Saraheimo et al., 2008). The Epidemiology of Diabetes Interventions and Complications (EDIC) Study of type 1 diabetes performed an analysis on a subset of their participants ($n = 108$), and demonstrated a concordant increase in adiponectin and TNF- α with declining estimated GFR (eGFR), and a decreasing adiponectin-to-TNF- α ratio with declining eGFR (Saraheimo et al., 2008). However, in CACTI, adjustments for CRP did not significantly attenuate any of the measures of associations in the multivariable models with adiponectin and DKD. Finally, whereas the difference in adiponectin was significant between participants with and without type 1 diabetes, the difference in CRP was much more modest.

Recently, the dissociation between adiponectin and suppressor of glucose from autophagy (SOGA) was reported in type 1 diabetes, which raises the possibility of adiponectin resistance in type 1 diabetes (Panduru et al., 2015). This mechanism is particularly promising as therapeutic interventions that can target the adiponectin signaling deficiency in type 1 diabetes could improve insulin-mediated suppression of excessive hepatic gluconeogenesis. Understanding the mechanisms underlying the development and progression of early DKD will help in stratifying patients according to risk, and direct development of therapies to prevent or delay renal function decline.

There are important limitations to the present study worth mentioning, including the observational design and the absence of a direct measurement of GFR. A direct measure of GFR with current methods would have been too cumbersome for use in a large-scale clinical study like CACTI and improved methods to detect early kidney changes are needed (32). We employed the state-of-the-art CKD-EPI equation (Bjornstad et al., 2013), recently used by studies such as the DCCT-EDIC (Rifkin et al., 2008), but it is established that eGFR at higher levels is associated with greater variability, which could lead to misclassification of normofiltration, and bias our study to not find an effect.

In summary, we report associations between adiponectin, rapid GFR decline, incident CKD and persistent overt DKD over 6 years in adults with type 1 diabetes independent of measures of inflammation and insulin sensitivity, in addition to other important risk factors. These epidemiologic observations support an association between adiponectin in early DKD as well as more advanced stages of DKD in adults with type 1 diabetes. Further studies are needed to elucidate the pathophysiologic mechanisms underlying the associations between adiponectin and DKD in type 1 diabetes. Understanding these mechanisms may direct development of therapies to prevent or delay renal function decline.

Acknowledgments

Support for this study was provided by NHLBI grant R01 HL61753, HL79611, HL 113029, DERC Clinical Investigation Core P30 DK57516 and JDRF grant 17-2013-313. The study was performed at the Adult CTRC at UCD supported by NIH M01-RR00051, at the Barbara Davis Center for Childhood Diabetes and at Colorado Heart Imaging Center in Denver, CO. Dr. Snell-Bergeon was supported by an American Diabetes Association Career Development Award (7-13-CD-10).

References

- Standards of medical care in diabetes—2014. *Diabetes Care*. 2014; 37(Suppl. 1):S14–S80. (Epub 2013/12/21). [PubMed: 24357209]
- Berg AH, Scherer PE. Adipose tissue, inflammation, and cardiovascular disease. *Circulation Research*. 2005; 96(9):939–949. (Epub 2005/05/14). [PubMed: 15890981]
- Bjornstad P, Cherney D, Maahs DM. Early diabetic nephropathy in type 1 diabetes: New insights. *Current Opinion in Endocrinology, Diabetes, and Obesity*. 2014; 21(4):279–286. (Epub 2014/07/02).
- Bjornstad P, Snell-Bergeon JK, Nadeau KJ, Maahs DM. Insulin sensitivity and complications in type 1 diabetes: New insights. *World Journal of Diabetes*. 2015; 6(1):8–16. (Epub 2015/02/17). [PubMed: 25685274]
- 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(11):3678–3683. (Epub 2013/09/13). [PubMed: 24026551]
- Combs TP, Snell-Bergeon JK, Maahs DM, Bergman BC, Lamarche M, Iberkleid L, et al. Adiponectin–SOGA dissociation in type 1 diabetes. *The Journal of Clinical Endocrinology and Metabolism*. 2015; 100(8):E1065–E1073. (Epub 2015/06/09). [PubMed: 26052615]
- Costacou T, Orchard TJ. Adiponectin: Good, bad, or just plain ugly? *Kidney International*. 2008; 74(5):549–551. (Epub 2008/08/19). [PubMed: 18709022]
- de Boer IH. Kidney disease and related findings in the diabetes control and complications trial/epidemiology of diabetes interventions and complications study. *Diabetes Care*. 2014; 37(1):24–30. (Epub 2013/12/21). [PubMed: 24356594]
- de Boer IH, Rue TC, Hall YN, Heagerty PJ, Weiss NS, Himmelfarb J. Temporal trends in the prevalence of diabetic kidney disease in the United States. *JAMA*. 2011; 305(24):2532–2539. (Epub 2011/06/23). [PubMed: 21693741]
- 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. *The New England Journal of Medicine*. 2011; 365(25):2366–2376. (Epub 2011/11/15). [PubMed: 22077236]
- Giannessi D, Maltinti M, Del Ry S. Adiponectin circulating levels: A new emerging biomarker of cardiovascular risk. *Pharmacological Research*. 2007; 56(6):459–467. (Epub 2007/11/22). [PubMed: 18029194]
- 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(7):1651–1658. (Epub 2009/04/30). [PubMed: 19401416]
- Hecht Baldauff N, Tfayli H, Dong W, Arena VC, Gurtunca N, Pietropaolo M, et al. Relationship of adiponectin and leptin with autoimmunity in children with new-onset type 1 diabetes: A pilot study. *Pediatric Diabetes*. 2015 (Epub 2015/03/110).
- Hopkins TA, Ouchi N, Shibata R, Walsh K. Adiponectin actions in the cardiovascular system. *Cardiovascular Research*. 2007; 74(1):11–18. (Epub 2006/12/05). [PubMed: 17140553]
- Inker LA, Schmid CH, Tighiouart H, Eckfeldt JH, Feldman HI, Greene T, et al. Estimating glomerular filtration rate from serum creatinine and cystatin C. *The New England Journal of Medicine*. 2012; 367(1):20–29. (Epub 2012/07/06). [PubMed: 22762315]
- Kopf S, Oikonomou D, von Eynatten M, Kieser M, Zdunek D, Hess G, et al. Urinary excretion of high molecular weight adiponectin is an independent predictor of decline of renal function in type 2 diabetes. *Acta Diabetologica*. 2014; 51(3):479–489. (Epub 2013/12/25). [PubMed: 24366425]
- 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 (Epub 2013/08/14).
- 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. *Journal of Diabetes and its Complications*. 2014; 28(5):667–673. (Epub 2014/07/17). [PubMed: 25027389]
- 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(2):301–306. (Epub 2005/01/29). [PubMed: 15677783]

Maahs DM, Rewers M. Editorial: Mortality and renal disease in type 1 diabetes mellitus—Progress made, more to be done. *The Journal of Clinical Endocrinology and Metabolism*. 2006; 91(10): 3757–3759. (Epub 2006/10/10). [PubMed: 17028289]

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(11):2312–2319. (Epub 2010/07/29). [PubMed: 20665208]

Palanivel R, Ganguly R, Turdi S, Xu A, Sweeney G. Adiponectin stimulates Rho-mediated actin cytoskeleton remodeling and glucose uptake via APPL1 in primary cardiomyocytes. *Metabolism, Clinical and Experimental*. 2014; 63(10):1363–1373. (Epub 2014/08/12). [PubMed: 25108566]

Panduru NM, Saraheimo M, Forsblom C, Thorn LM, Gordin D, Waden J, et al. Urinary adiponectin is an independent predictor of progression to end-stage renal disease in patients with type 1 diabetes and diabetic nephropathy. *Diabetes Care*. 2015; 38(5):883–890. (Epub 2015/02/28). [PubMed: 25720601]

Pereira RI, Snell-Bergeon JK, Erickson C, Schauer IE, Bergman BC, Rewers M, et al. Adiponectin dysregulation and insulin resistance in type 1 diabetes. *The Journal of Clinical Endocrinology and Metabolism*. 2012; 97(4):E642–E647. (Epub 2012/01/27). [PubMed: 22278421]

Pischon T, Gorman CJ, Hotamisligil GS, Rifai N, Hu FB, Rimm EB. Plasma adiponectin levels and risk of myocardial infarction in men. *JAMA*. 2004; 291(14):1730–1737. (Epub 2004/04/15). [PubMed: 15082700]

Rifkin DE, Shlipak MG, Katz R, Fried LF, Siscovick D, Chonchol M, et al. Rapid kidney function decline and mortality risk in older adults. *Archives of Internal Medicine*. 2008; 168(20):2212–2218. (Epub 2008/11/13). [PubMed: 19001197]

Saraheimo M, Forsblom C, Thorn L, Waden J, Rosengard-Barlund M, Heikkila O, et al. Serum adiponectin and progression of diabetic nephropathy in patients with type 1 diabetes. *Diabetes Care*. 2008; 31(6):1165–1169. (Epub 2008/03/19). [PubMed: 18346990]

Schauer IE, Snell-Bergeon JK, Bergman BC, Maahs DM, Kretowski A, Eckel RH, et al. Insulin resistance, defective insulin-mediated fatty acid suppression, and coronary artery calcification in subjects with and without type 1 diabetes. *Diabetes*. 2011; 60(1):306–314. [PubMed: 20978091]

Schulze MB, Shai I, Rimm EB, Li T, Rifai N, Hu FB. Adiponectin and future coronary heart disease events among men with type 2 diabetes. *Diabetes*. 2005; 54(2):534–539. (Epub 2005/01/29). [PubMed: 15677512]

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. *Journal of the American Society of Nephrology : JASN*. 2009; 20(12):2625–2630. (Epub 2009/11/07). [PubMed: 19892934]

West NA, Hamman RF, Mayer-Davis EJ, D'Agostino RB Jr. Marcovina SM, Liese AD, et al. Cardiovascular risk factors among youth with and without type 2 diabetes: Differences and possible mechanisms. *Diabetes Care*. 2009; 32(1):175–180. (Epub 2008/10/24). [PubMed: 18945923]

Table 1

Characteristics of participants with type 1 diabetes stratified by gender.

Variables	Adults with type 1 diabetes		p-values
	Men (n = 298)	Women (n = 354)	
Age (years)	37 ± 9	36 ± 9	0.07
Duration (years)	24 ± 9	23 ± 9	0.29
HbA1c (%)	8.0 ± 1.2	8.0 ± 1.3	0.90
HbA1c (mmol/mol)	64 ± 13	64 ± 14	0.90
BMI (kg/m ²)	27 ± 4	26 ± 5	0.09
Adiponectin at baseline (µg/ml)	12.5 ± 7.2	18.6 ± 9.4	<0.0001
Adiponectin at 6-year follow-up (µg/ml)	12.0 ± 7.9	18.0 ± 9.4	<0.0001
CRP* at baseline (mg/l)	2.36 (2.26–2.46)	2.85 (2.69–3.02)	<0.0001
eIS (mg/kg/min)	3.79 ± 1.39	4.78 ± 1.62	<0.0001
DBP (mm Hg)	121 ± 14	114 ± 14	<0.0001
DBP (mm Hg)	80 ± 9	75 ± 8	<0.0001
ACEi/ARB (yes, %)	38 (112)	32 (112)	0.11
LDL-C (mg/dL)	104 ± 30	98 ± 28	0.007
Current smoking (%)	13% (36)	12% (42)	0.87
AER* at baseline (µg/min)	14 (11–17)	8 (7–10)	<0.0001
AER* at 6-year follow-up (µg/min)	11 (9–13)	7 (6–8)	0.0003
ACR* at baseline (mg/g)	12 (10–15)	10 (9–12)	0.15
ACR* at 6-year follow-up (mg/g)	9 (7–11)	7 (8–9)	0.27
eGFR by CKD-EPI creatinine (mL/min/1.73 m ²)	100 ± 27	105 ± 28	0.02
eGFR by CKD-EPI creatinine at 6-year follow-up (mL/min/1.73 m ²)	97 ± 22	99 ± 21	0.43
Rapid GFR decline >3 mL/min/1.73 m ² over 6-years (%) [n = 144]	22% (52)	32% (92)	0.009
Incident eGFR <60 mL/min/1.73 m ² at 6-year follow-up (%) [n = 15]	2% (5)	4% (10)	0.35
Persistent DKD (%) [n = 27]	9% (16)	5% (11)	0.16

Data presented as mean ± standard deviation, unless otherwise specified.

* Geometric means ± 95% confidence interval.

Table 2

Participant characteristics stratified by the presence of overt diabetic kidney disease.

Variables	Persistent macroalbuminuria and/or persistent CKD (<60 mL/min/1.73 m ²) over 6 years		p-values
	No (n = 399)	Yes (n = 27)	
Age (years)	37 ± 9	41 ± 9	0.03
Duration (years)	24 ± 9	23 ± 9	0.29
HbA1c (%)	7.8 ± 1.2	8.3 ± 1.0	0.047
HbA1c (mmol/mol)	62 ± 13	67 ± 11	0.047
BMI (kg/m ²)	26 ± 4	27 ± 5	0.40
ACEi/ARB (yes, %)	31 (124)	78 (21)	<0.0001
Adiponectin at baseline (µg/ml)	14.9 ± 8.4	19.5 ± 10.8	0.01
Adiponectin at 6-year follow-up (µg/ml)	14.9 ± 8.9	18.9 ± 11.2	0.03
CRP* at baseline (mg/l)	2.6 (2.4–2.7)	2.7 (2.2–3.3)	0.56
AER* at baseline (µg/min)	7 (6–7)	140 (56–347)	<0.0001
AER* at 6-year follow-up (µg/min)	6 (6–7)	116 (46–288)	<0.0001
ACR* at baseline (mg/g)	8 (7–9)	156 (36–332)	<0.0001
ACR* at 6-year follow-up (mg/g)	7 (6–8)	115 (48–276)	<0.0001
eGFR by CKD-EPI creatinine (mL/min/1.73 m ²)	107 ± 22	55 ± 33	<0.0001
eGFR by CKD-EPI creatinine at 6-year follow-up (mL/min/1.73 m ²)	100 ± 16	48 ± 26	<0.0001

Data shown are for participants with complete eGFR and/or AER and/or ACR data at baseline and follow-up.

* Geometric means ± 95% confidence interval.

Table 3

Participant characteristics stratified by the presence of early diabetic kidney disease.

Variables	Rapid GFR decline (>3 mL/min/1.73 m ² /year)		p-values
	No (n = 375)	Yes (n = 144)	
Age (years)	37 ± 9	34 ± 9	<0.0001
Duration (years)	24 ± 9	21 ± 8	0.003
HbA1c (%)	7.9 ± 1.1	8.0 ± 1.5	0.58
HbA1c (mmol/mol)	63 ± 12	64 ± 16	0.58
BMI (kg/m ²)	26 ± 4	26 ± 5	0.69
ACEi/ARB (yes, %)	35 (133)	22 (32)	0.004
Adiponectin at baseline (µg/ml)	14.7 ± 7.9	17.0 ± 10.3	0.02
Adiponectin at 6-year follow-up (µg/ml)	14.9 ± 8.9	16.2 ± 10.8	0.15
CRP* at baseline (mg/l)	2.5 (2.4–2.6)	2.7 (2.5–3.0)	0.10
AER* at baseline (µg/min)	9 (8–11)	10 (8–13)	0.44
AER* at 6-year follow-up (µg/min)	8 (7–9)	10 (7–13)	0.24
ACR* at baseline (mg/g)	9 (8–10)	11 (9–15)	0.08
ACR* at 6-year follow-up (mg/g)	8 (7–9)	10 (8–13)	0.07
eGFR by CKD-EPI creatinine (mL/min/1.73 m ²)	98 ± 25	121 ± 20	<0.0001
eGFR by CKD-EPI creatinine at 6-year follow-up (mL/min/1.73 m ²)	101 ± 21	91 ± 22	<0.0001

* Includes only participants with complete eGFR at baseline and follow-up.

* Geometric means ± 95% confidence interval.

Table 4

Multivariable models predicting rapid GFR decline, incident CKD and persistent DKD over 6 years.

Exposure variables	Outcome variables		
	Rapid GFR decline (>3 mL/min/year) [N = 144]	Incident CKD (<60 mL/min/ 1.73 m ²) [N = 15]	Persistent macroalbuminuria and/or CKD [n = 27]
	OR (95% CI)	OR (95% CI)	OR (95% CI)
Adiponectin (per 1 SD [8.56 µg/ml]) *	1.24 (1.00–1.53) p = 0.049	1.75 (1.14–2.70) p = 0.01	1.57 (1.08–2.30) p = 0.02
Adiponectin (per 1 SD [8.56 µg/ml]) **	1.29 (1.03–1.61) p = 0.03	2.14 (1.26–3.64) p = 0.005	2.00 (1.29–3.08) p = 0.002
Adiponectin (per 1 SD [8.56 µg/ml]) ***	1.24 (1.00–1.54) p = 0.047	2.15 (1.35–3.44) p = 0.001	2.04 (1.30–3.20) p = 0.002

Data are presented as OR and 95% CI. OR represents the increase in odds of rapid GFR decline, incident CKD or persistent overt DKD per 1 standard deviation (SD) [8.56 µg/ml] increase in adiponectin concentration.

* Adjusted for age, sex, duration, SBP, LDL-C and current smoking.

** Adjusted for age, sex, duration, LDL-C, current smoking, ACEi/ARB therapy and eIS (not SBP, as eIS includes DBP).

*** Adjusted for age, sex, duration, SBP, LDL-C, current smoking, ACEi/ARB therapy and log CRP.