Published in final edited form as:

Curr Diab Rep. ; 18(5): 22. doi:10.1007/s11892-018-0996-2.

Renal Hyperfiltration in Adolescents with Type 2 Diabetes: Physiology, Sex Differences, and Implications for Diabetic Kidney Disease

Petter Bjornstad, M.D.¹ and David Z. Cherney, M.D., Ph.D.²

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

²Department of Medicine, Division of Nephrology, Toronto General Hospital, University of Toronto, Ontario, Canada

Abstract

Purpose of the review: Compared to adult-onset type 2 diabetes (T2D), youth with T2D have a more aggressive phenotype with greater insulin resistance (IR), more rapid β -cell decline, and higher prevalence of diabetic kidney disease (DKD).

Recent findings: Hyperfiltration is common in youth with T2D and predicts progressive DKD. Hyperfiltration is a consequence of early changes in intrarenal hemodynamic function, including increased renal plasma flow (RPF) and glomerular pressure. Girls with T2D are disproportionately affected by DKD, with a 3-fold greater risk of developing hyperfiltration over 5 years compared to boys. Despite the high prevalence and gravity of DKD in youth-onset T2D, widely effective therapeutic options are lacking.

Summary

In this review, we focus on pathophysiology underlying early DKD in T2D and sex differences and summarize promising novel medical therapies and bariatric surgery.

Keywords

Type 2 diabetes; hyperfiltration; sex differences; bariatric surgery; intrarenal hemodynamic function

Address all correspondence to: Petter Bjornstad, M.D., Pediatric Endocrinology, University of Colorado School of Medicine, 13123 East 16th Ave, Box B265, Aurora, CO 80045, Phone: (720) 777-4659, Fax: (720) 777-7301, petter.bjornstad@childrenscolorado.org.

Author Contributions:

PB and DZC wrote, contributed to discussion, and reviewed/edited the manuscript.

Conflict of Interest

P.B. has no conflict of interest to disclose. D.Z.I.C. receives operating funding from Boehringer Ingelheim, Janssen, AstraZeneca, Merck. D.Z.I.C. has received consulting fees and/or speaking honoraria from Boehringer Ingelheim, Janssen, AstraZeneca, Merck, Mitsubishi-Tanabe, Sanofi and Abbvie.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

Introduction

In the United States, almost half of patients with end-stage renal disease (ESRD) have diabetic kidney disease, and over 80% of these have type 2 diabetes (T2D) (1). T2D in youth has a female predominance and is increasing in prevalence (1–3). Further, girls with T2D are also disproportionally impacted by DKD, with a 3-fold greater risk of developing DKD (4). Elevated albumin excretion is present in up to one-third of adolescents with T2D (5). Since elevated albumin excretion, the traditional measure of renal injury in T2D, does not reliably reflect progressive DKD and commonly regresses to normal albumin excretion (6), it is important to directly examine early changes in renal function that are associated with future DKD risk, such as hyperfiltration. Hyperfiltration impacts between 24–50% of youth with T2D as assessed by estimated GFR (eGFR) using creatinine and cystatin-C equations (4, 5), which is likely an underestimation of GFR, especially with increasing GFR values in the hyperfiltration range (7).

Hyperfiltration is a consequence of early changes in intrarenal hemodynamic function, including increased renal plasma flow (RPF) and glomerular pressure (8–10). Our preliminary data have suggested that insulin resistance, rather than traditional risk factors, including blood pressure, glycemic control and dyslipidemia, is the strongest determinant for hyperfiltration in youth-onset T2D (5). The pathophysiology underlying the early changes in intrarenal hemodynamic function, as well as the relationship between insulin resistance the role of hyperfiltration on GFR decline and renal injury remain unclear. Furthermore, it is unknown why girls have a greater propensity for hyperfiltration compared to boys with T2D, which may contribute to their future risk of clinical DKD.

Despite the high prevalence and gravity of DKD in youth-onset T2D, the availability of effective therapeutic options is lacking. Bariatric surgery is an emerging approach that offers remission of T2D in the vast majority of adults, along with improvement in weight, as well as changes in IR and DKD risk markers that may be weight-independent (11, 12). While there are no studies to date investigating the effects of bariatric surgery or SGLT2 inhibition on intrarenal hemodynamic function and hyperfiltration in youth-onset T2D, bariatric surgery does reduce hyperfiltration in obese adults (13). On the medical side, SGLT2 inhibition attenuates hyperfiltration in adults with T1D (10) and is associated with renal and cardiovascular protective effects in adults with T2D at high cardiovascular risk (14–16). In addition, SGLT2 inhibition improves insulin sensitivity in adults (17). Amongst newer antihyperglycemic agents, attenuation of hyperfiltration and improvement in intrarenal hemodynamic function appears to be unique to SGLT2 inhibitors, and has not been observed with glucagon-like peptide (GLP)1 receptor agonists or dipeptidyl peptidase-4 inhibitors in adults with T2D (18–20). A better understanding of the mechanisms contributing to hyperfiltration and its relationship with IR and progression of DKD in youth-onset T2D is critical to inform medical decision making and improve the renal health and mortality of children with T2D. In this review, we focus on the potential pathophysiology underlying early DKD in T2D and summarize risk factors and potential novel therapeutic approaches for this condition.

The risk of DKD in youth-onset T2D

Youth with T2D are at an increased risk for DKD, with up to 45% of these patients subsequently progressing to ESRD. This risk is significantly higher compared to youth with type 1 diabetes and compared to adults with adult-onset T2D (21–23). We previously reported a prevalence of 24% for hyperfiltration and 35% for elevated albumin excretion in a small cohort of youth with T2D (mean age of 15 ± 2 years) (2). In a separate analysis of longitudinal data from the Treatment Options for Type 2 Diabetes in Adolescents and Youth (TODAY) study, the prevalence of increased albumin excretion rose from 6.3% of participants at baseline to 16.6% at 3.9 years follow-up (3) and 18.0% at 5 years follow-up (4). In the SEARCH study, the age-adjusted prevalence of DKD in youth with T2D was 20%, which was significantly greater than DKD in youth with T1D (6%, $p < 0.001$) (24). Moreover, after multivariable adjustment for established risk factors measured over time, youth with T2D vs. those with T1D had over 2-fold greater odds DKD (OR: 2.58; 95% CI, 1.39, 4.81; $p = 0.003$) (24).

Pathophysiology of Hyperfiltration

The kidneys are metabolically active and have a high energy requirement to sustain filtration, intrarenal hemodynamic function and tubular reabsorption (25). Diabetes is associated with an increase in energy and hence O_2 consumption, in part due to the greater filtered load of glucose and the associated rise in GFR (26, 27) into the hyperfiltration range (28). However, in T2D, emerging animal data suggest that the kidneys are not able to sufficiently compensate for the increased O_2 consumption due to the effects of diabetes on O_2 utilization, leading to a relative state of hypoxia and ischemia (29–31). In addition to increased O_2 consumption, renal hypoxia may be worsened by insulin resistance (IR)-associated AMP-activated protein kinase inhibition, resulting in ATP depletion (25, 29–34). Hyperglycemia and IR are also associated with mitochondrial dysfunction (35), leading to impaired electrolyte transport (28). Accordingly, changes in fuel substrate utilization and energy efficiency, in conjunction with increase metabolic demands from hyperfiltration in the setting of T2D appears to contribute to a state of renal hypoxia and DKD progression (Figure 1).

This paradigm is supported by the observation that IR and hyperfiltration are strongly correlated in youth with T2D who participated in the RESISTANT and TODAY studies (4, 5). In the RESISTANT cohort, adolescents with T2D exhibited significantly lower peripheral insulin sensitivity measured by hyperinsulinemic-euglycemic clamp, and higher eGFR compared to obese or lean controls (5). Stratifying eGFR into tertiles, adolescents with T2D in the highest tertile of eGFR were more IR than those in the mid and low tertiles, even after adjusting for age, sex, pubertal stage, BMI and HbA1c (5). Furthermore, IR, but not HbA1c, LDL-C or BP, was also inversely associated with eGFR after adjusting for sex and pubertal stage (5). In the TODAY study, there was an annual increase in eGFR, and decrease in eIS over 5 years, and IR independently conferred a 2.1-fold increased risk of hyperfiltration, even after adjusting for other established risk factors (HR: 2.15, $p = 0.01$) (4). Importantly, IR, rather than traditional risk factors, was the strongest determinant of renal health (4, 5).

Sex-Related Differences and Early DKD

In TODAY, girls with T2D had higher estimated GFR levels at baseline compared to boys (123 ± 19 vs. 108 ± 17 ml/min/1.73m², $p < 0.0001$ [n=532]), and a 3-fold greater risk of developing hyperfiltration over 5 years, even after adjustment for age, ethnicity, treatment group, BMI, HbA1c, hypertension, loss of glycemic control and estimated insulin sensitivity (Figure 2) (4). These sex-related findings do not appear to be unique to T2D. In an analysis in youth with T1D, we found that adolescent girls with T1D had a 4-fold increase in prevalence of hyperfiltration compared to boys of similar age and glycemic control, with a similar difference observed for elevated albumin excretion (36).

Despite these observations from observational studies, the mechanisms responsible for the increased risk of hyperfiltration in girls vs. boys remain poorly understood. In our previous work, we have reported distinct intrarenal hemodynamic differences in women vs. men with T1D, whereby hyperfiltration in women is characterized by an increase in efferent arteriolar resistance (37) (Figure 3). While there are no such data in youth with DKD, we theorize that this sex-specific intrarenal hemodynamic dysfunction may explain the greater prevalence and incidence of hyperfiltration observed in adolescent girls with T1D and T2D, possibly due to sex-related effects on the renin-angiotensin-aldosterone system (RAAS) or on nitric oxide bioactivity, leading to efferent arteriolar vasoconstriction (38–41). For example, experimental models suggest that estradiol may upregulate expression of renal angiotensin II receptor type 1 (AT1R) in the setting of high angiotensin II concentrations (42). Hyperglycemia is associated with RAAS activation and higher concentrations of angiotensin II. Therefore, it is plausible that the greater efferent arteriolar resistance observed in women with T1D may be ascribed to upregulation of AT1R in the setting of RAAS activation. Dedicated renal physiology studies are therefore now needed in youth with T1D and T2D to elucidate sex differences in intrarenal hemodynamic dysfunction.

Potential Novel Therapies for Hyperfiltration

i. Metabolic Surgery

Bariatric surgery is a new approach that offers remission of T2D in the vast majority of adults, along with improvement in weight, as well as changes in IR and DKD risk markers that may be weight-independent (11, 12). In the Teen-LABS study, bariatric surgery in nondiabetic youth resulted in reduction in weight (BMI decline of 38%), improvement in IR at 3 months and normalization (increased by 300%) by 1 year after surgery (11). In the small subset of youth with T2D studied, remission of T2D was seen in 95% of participants at 3 years of follow-up (12). In a parallel analysis in youth-onset T2D who underwent bariatric surgery (Teen-LABS) vs. medical management (TODAY), the proportion of participants in Teen-LABS with elevated albumin excretion decreased from 26% to 5% over 2 yrs. Conversely, the prevalence of elevated albumin excretion did not change over time in TODAY (43). No data exist on the effect of bariatric surgery on hyperfiltration, intrarenal hemodynamic function, or renal O₂ in youth-onset T2D (Figure 4). A better understanding of the effects of bariatric surgery on intrarenal hemodynamic function and renal O₂ is critical to help define mechanisms of surgical benefits and identify potential novel future non-surgical approaches to DKD.

ii. Antihyperglycemic and Natriuretic Agents

Experimental models of diabetes have suggested that the process of early DKD starts with hyperfiltration and glucosuria, which enhanced sodium/glucose reabsorption through SGLT2. The resultant increased proximal tubular intracellular sodium concentration and activation of basolateral Na^+/K^+ ATPase lead to net increased renal O_2 consumption compared to non-diabetic models (25, 29–31). With increased renal O_2 consumption in DKD, energy efficient fuel is required to meet the increased demand and prevent renal hypoxia. Emerging animal data show that organs prone to complications are unable to compensate for the effects of diabetes on fuel generation (29–31).

SGLT2 inhibitors reduce blood pressure, weight and hyperglycemia in adults with T2D. Furthermore, in the EMPA-REG OUTCOME trial, a 38% reduction in cardiovascular death, and a 39% reduction in incident or worsening nephropathy has been demonstrated with the selective SGLT2 inhibitor, empagliflozin, in adults with T2D (15, 44). The CANVAS study, reported similar results with the selective SGLT2 inhibitor, canagliflozin, in adults with T2D (45). It appears that SGLT2 inhibitors reduce hyperfiltration in adults with T1D by increasing natriuresis, resulting in afferent vasoconstriction and declines in intraglomerular hypertension (10). In adults with T2D, the reduction in intraglomerular hypertension was reflected by a mean reduction in eGFR of 2–4 ml/min/1.73m² after treatment initiation, followed by a stabilisation of eGFR decline compared to placebo during long-term treatment (15). Therefore, the initial decline in eGFR likely reflects attenuation of single-nephron hyperfiltration, which is associated with subsequent long-term renal function preservation (46). It is not known whether these renal hemodynamic effects occur in youth-onset T2D, as there are no published studies to date examining the effect of SGLT2 inhibitors on intrarenal hemodynamic function in this patient population.

GLP-1 receptor agonists also affect proximal tubular reabsorption resulting in increased natriuresis, at least initially, (47) and have shown to reduce incident or worsening nephropathy in adults with T2D in the LEADER (48) and SUSTAIN6 trials (49). However, the beneficial intrarenal hemodynamic function responses observed with SGLT2 inhibitors have not been demonstrated with GLP-1 agonists (50). The reduction of DKD with GLP-1 receptor agonists may instead relate to non-hemodynamic, anti-inflammatory effects. Similarly, dipeptidyl peptidase-4 (DPP-4) inhibitors do not appear to affect intrarenal hemodynamic function (50). Longer term cardio-renal protection with DPP4 inhibitors are being examined in the ongoing CARMELINA (NCT01897532) and CAROLINA (NCT01243424) trials in adults with T2D.

Current Unmet Needs: DKD and Youth Onset T2D

To date there are no DKD specific clinical trials in youth-onset T2D. Some of reasons include: 1) youth-onset T2D remains a relatively rare disease (albeit increasing in prevalence); 2) youth-onset T2D patients represent a cohort that is difficult to recruit for research; 3) the need for long follow-up to capture hard end-points (ESRD and dialysis) is challenging due to the long natural history of the disease; 4) prohibitive costs to perform large clinical trials with long follow-up. Accordingly, there is an impetus for smaller, cost-effective mechanistic trials with gold-standard methods to quantify early changes in renal

function, including trials with measures of intrarenal hemodynamic function, which have until now focused primarily on adults with T1D and adult-onset T2D (51–53). These studies have established that intrarenal hemodynamic dysfunction is common (8, 52, 54, 55), and may be reversed with therapeutic agents early in the course of the disease (10, 50). Yet no such data are available for youth-onset T2D, a disease that carries a significantly high risk of progressive DKD (22–24, 56–63). Knowledge gaps and specific research priorities to prevent or delay the development of DKD in youth with T2D are listed in Table 1.

Conclusion

With the current pediatric obesity epidemic and the rising incidence of youth-onset T2D (63, 64), a greater understanding around the pathophysiology underlying the initiation and progression of hyperfiltration and its relationship with progressive DKD is urgently needed. Carefully designed mechanistic human studies are required to advance our understanding of the intrarenal hemodynamic dysfunction of youth-onset T2D, the role of renal oxygenation and metabolism, and the impact of metabolic surgery and novel anti-hyperglycemic therapies on these parameters. Such research endeavors have the potential to improve the renal health and mortality of obese children worldwide.

Acknowledgments

Duality of Interest:

P.B. receives salary support by NIH (T32-DK063687, K23 DK116720–01), in addition to research support by Thrasher Foundation, Juvenile Diabetes Research Foundation (JDRF), International Society of Pediatric and Adolescent Diabetes (ISPAD) and Center for Women's Health Research at University of Colorado. D.Z.I.C. receives support from the Canadian Institutes of Health Research, as well as Diabetes Action Canada, a Strategy for Patient-Oriented Research initiative supported by the Canadian Institutes for Health Research. D.Z.I.C. also receives operating funding from the Heart and Stroke Richard Lewar Centre of Excellence in Cardiovascular Research and Banting and Best Diabetes Centre, University of Toronto. D.Z.I.C. is the recipient of a University of Toronto, Department of Medicine Merit Award. The authors were fully responsible for all content and editorial decisions, were involved at all stages of manuscript development and have approved the final version.

References:

Papers of particular interest, published recently, have been highlighted as:

• Of importance

9: Thorough review of hyperfiltration as a phenotype of DKD

51: Review of the application and promise of Gomez' equations in DKD research

53: Demonstrate sex differences in intrarenal hemodynamic function

•• Of major importance:

1: Report the prevalence and incidence of ESRD due to DKD

4: Demonstrate strong relationships between insulin sensitivity and hyperfiltration over time in youth-onset T2D

12: Demonstrate benefits of bariatric surgery in obese youth.

24: Report differences in DKD between youth with T1D and youth with T2D.

44: Demonstrate benefit of SGLT2 inhibition of DKD in adults with T2D.

45: Demonstrate benefit of SGLT2 inhibition of DKD in adults with T2D.

1. Saran R, Li Y, Robinson B, Abbott KC, Agodoa LY, Ayanian J, et al. US Renal Data System 2015 Annual Data Report: Epidemiology of Kidney Disease in the United States. *American journal of kidney diseases : the official journal of the National Kidney Foundation*. 2016;67(3 Suppl 1):Svii, S1–305.
2. Bjornstad P, Cherney DZ, Maahs DM, Nadeau KJ. Diabetic Kidney Disease in Adolescents With Type 2 Diabetes: New Insights and Potential Therapies. *Current diabetes reports*. 2016;16(2):11. [PubMed: 26803647]
3. Nadeau KJ, Anderson BJ, Berg EG, Chiang JL, Chou H, Copeland KC, et al. Youth-Onset Type 2 Diabetes Consensus Report: Current Status, Challenges, and Priorities. *Diabetes Care*. 2016;39(9):1635–42. [PubMed: 27486237]
4. Bjornstad P, Nehus E, El Ghormli L, Bacha F, Libman IM, McKay S, et al. Insulin Sensitivity and Diabetic Kidney Disease in Children and Adolescents With Type 2 Diabetes: An Observational Analysis of Data From the TODAY Clinical Trial. *Am J Kidney Dis*. 2018;71(1):65–74. [PubMed: 29157731]
5. Bjornstad P, Maahs DM, Cherney DZ, Cree-Green M, West A, Pyle L, et al. Insulin sensitivity is an important determinant of renal health in adolescents with type 2 diabetes. *Diabetes Care*. 2014;37(11):3033–9. [PubMed: 25071077]
6. Yamada T, Komatsu M, Komiya I, Miyahara Y, Shima Y, Matsuzaki M, et al. Development, progression, and regression of microalbuminuria in Japanese patients with type 2 diabetes under tight glycemic and blood pressure control: the Kashiwa study. *Diabetes Care*. 2005;28(11):2733–8. [PubMed: 16249548]
7. Gaspari F, Ruggenti P, Porrini E, Motterlini N, Cannata A, Carrara F, et al. The GFR and GFR decline cannot be accurately estimated in type 2 diabetics. *Kidney Int*. 2013;84(1):164–73. [PubMed: 23447062]
8. Tonneijck L, Muskiet MH, Smits MM, van Bommel EJ, Heerspink HJ, van Raalte DH, et al. Glomerular Hyperfiltration in Diabetes: Mechanisms, Clinical Significance, and Treatment. *J Am Soc Nephrol*. 2017.
9. Tonneijck L, Smits MM, van Raalte DH, Muskiet MH. Incretin-based drugs and renoprotection-is hyperfiltration key? *Kidney Int*. 2015;87(3):660–1.
10. Cherney DZ, Perkins BA, Soleymanlou N, Maione M, Lai V, Lee A, et al. Renal hemodynamic effect of sodium-glucose cotransporter 2 inhibition in patients with type 1 diabetes mellitus. *Circulation*. 2014;129(5):587–97. [PubMed: 24334175]
11. Inge TH, Prigeon RL, Elder DA, Jenkins TM, Cohen RM, Xanthakos SA, et al. Insulin Sensitivity and beta-Cell Function Improve after Gastric Bypass in Severely Obese Adolescents. *J Pediatr*. 2015;167(5):1042–8 e1. [PubMed: 26363548]
12. Inge TH, Courcoulas AP, Jenkins TM, Michalsky MP, Helmrath MA, Brandt ML, et al. Weight Loss and Health Status 3 Years after Bariatric Surgery in Adolescents. *N Engl J Med*. 2016;374(2):113–23. [PubMed: 26544725]
13. Chagnac A, Weinstein T, Herman M, Hirsh J, Gafer U, Ori Y. The effects of weight loss on renal function in patients with severe obesity. *J Am Soc Nephrol*. 2003;14(6):1480–6. [PubMed: 12761248]
14. Neal B, Perkovic V, Mahaffey KW, de Zeeuw D, Fulcher G, Erondou N, et al. Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes. *N Engl J Med*. 2017.
15. Wanner C, Inzucchi SE, Lachin JM, Fitchett D, von Eynatten M, Mattheus M, et al. Empagliflozin and Progression of Kidney Disease in Type 2 Diabetes. *N Engl J Med*. 2016;375(4):323–34. [PubMed: 27299675]
16. Wanner C, Lachin JM, Inzucchi SE, Fitchett D, Mattheus M, George J, et al. Empagliflozin and Clinical Outcomes in Patients With Type 2 Diabetes Mellitus, Established Cardiovascular Disease, and Chronic Kidney Disease. *Circulation*. 2017;137(2):119–29. [PubMed: 28904068]

17. Merovci A, Solis-Herrera C, Daniele G, Eldor R, Fiorentino TV, Tripathy D, et al. Dapagliflozin improves muscle insulin sensitivity but enhances endogenous glucose production. *J Clin Invest*. 2014;124(2):509–14. [PubMed: 24463448]
18. Tonneijck L, Smits MM, Muskiet MHA, Hoekstra T, Kramer MHH, Danser AHJ, et al. Acute renal effects of the GLP-1 receptor agonist exenatide in overweight type 2 diabetes patients: a randomised, double-blind, placebo-controlled trial. *Diabetologia*. 2016;59(7):1412–21. [PubMed: 27038451]
19. Lovshin J, Cherney D. GLP-1R Agonists and Endothelial Dysfunction: More Than Just Glucose Lowering? *Diabetes*. 2015;64(7):2319–21. [PubMed: 26106189]
20. Lovshin JA, Rajasekaran H, Lytvyn Y, Lovblom LE, Khan S, Alemu R, et al. Dipeptidyl Peptidase-4 Inhibition Stimulates Distal Tubular Natriuresis and Increases in Circulating SDF-1 α 1–67 in Patients With Type 2 Diabetes. *Diabetes Care*. 2017.
21. Group TS. Rapid rise in hypertension and nephropathy in youth with type 2 diabetes: the TODAY clinical trial. *Diabetes Care*. 2013;36(6):1735–41. [PubMed: 23704672]
22. Kiess W, Bottner A, Bluher S, Raile K, Galler A, Kapellen TM. Type 2 diabetes mellitus in children and adolescents--the beginning of a renal catastrophe? *Nephrol Dial Transplant*. 2004;19(11):2693–6. [PubMed: 15385634]
23. Eppens MC, Craig ME, Cusumano J, Hing S, Chan AK, Howard NJ, et al. Prevalence of diabetes complications in adolescents with type 2 compared with type 1 diabetes. *Diabetes Care*. 2006;29(6):1300–6. [PubMed: 16732012]
24. Dabelea D, Stafford JM, Mayer-Davis EJ, D'Agostino R, Jr., Dolan L, Imperatore G, et al. Association of Type 1 Diabetes vs Type 2 Diabetes Diagnosed During Childhood and Adolescence With Complications During Teenage Years and Young Adulthood. *JAMA*. 2017;317(8):825–35. [PubMed: 28245334]
25. Mudaliar S, Alloju S, Henry RR. Can a Shift in Fuel Energetics Explain the Beneficial Cardiorenal Outcomes in the EMPA-REG OUTCOME Study? A Unifying Hypothesis. *Diabetes Care*. 2016;39(7):1115–22. [PubMed: 27289124]
26. O'Neill J, Fasching A, Pihl L, Patinha D, Franzen S, Palm F. Acute SGLT inhibition normalizes O₂ tension in the renal cortex but causes hypoxia in the renal medulla in anaesthetized control and diabetic rats. *Am J Physiol Renal Physiol*. 2015;309(3):F227–34. [PubMed: 26041448]
27. Vallon V, Thomson SC. Targeting renal glucose reabsorption to treat hyperglycaemia: the pleiotropic effects of SGLT2 inhibition. *Diabetologia*. 60(2):215–25. [PubMed: 27878313]
28. Friederich M, Fasching A, Hansell P, Nordquist L, Palm F. Diabetes-induced up-regulation of uncoupling protein-2 results in increased mitochondrial uncoupling in kidney proximal tubular cells. *Biochim Biophys Acta*. 2008;1777(7–8):935–40. [PubMed: 18439413]
29. Nangaku M. Chronic hypoxia and tubulointerstitial injury: a final common pathway to end-stage renal failure. *J Am Soc Nephrol*. 2006;17(1):17–25. [PubMed: 16291837]
30. Haase VH. The VHL/HIF oxygen-sensing pathway and its relevance to kidney disease. *Kidney Int*. 2006;69(8):1302–7. [PubMed: 16531988]
31. Singh DK, Winocour P, Farrington K. Mechanisms of disease: the hypoxic tubular hypothesis of diabetic nephropathy. *Nat Clin Pract Nephrol*. 2008;4(4):216–26. [PubMed: 18268525]
32. Schrier RW, Harris DC, Chan L, Shapiro JJ, Caramelo C. Tubular hypermetabolism as a factor in the progression of chronic renal failure. *Am J Kidney Dis*. 1988;12(3):243–9. [PubMed: 3046343]
33. Li H, Satriano J, Thomas JL, Miyamoto S, Sharma K, Pastor-Soler NM, et al. Interactions between HIF-1 α and AMPK in the regulation of cellular hypoxia adaptation in chronic kidney disease. *Am J Physiol Renal Physiol*. 2015;309(5):F414–28. [PubMed: 26136559]
34. Miyamoto S, Hsu CC, Hamm G, Darshi M, Diamond-Stanic M, Decleves AE, et al. Mass Spectrometry Imaging Reveals Elevated Glomerular ATP/AMP in Diabetes/obesity and Identifies Sphingomyelin as a Possible Mediator. *EBioMedicine*. 2016;7:121–34. [PubMed: 27322466]
35. Cree-Green M, Gupta A, Coe GV, Baumgartner AD, Pyle L, Reusch JE, et al. Insulin resistance in type 2 diabetes youth relates to serum free fatty acids and muscle mitochondrial dysfunction. *Journal of diabetes and its complications*. 2017;31(1):141–8. [PubMed: 27839922]

36. Lovshin JA, Skrtic M, Bjornstad P, Moineddin R, Daneman D, Dunger D, et al. Hyperfiltration, urinary albumin excretion, and ambulatory blood pressure in adolescents with type 1 diabetes mellitus. *Am J Physiol Renal Physiol*. 2017.
37. Skrtic M, Lytvyn Y, Bjornstad P, Reich HN, Scholey JW, Yip P, et al. Influence of sex on hyperfiltration in patients with uncomplicated type 1 diabetes. *Am J Physiol Renal Physiol*. 2017;312(4):F599–F606. [PubMed: 28031170]
38. Cherney DZ, Scholey JW, Sochett EB. Sex differences in renal responses to hyperglycemia, L-arginine, and L-NMMA in humans with uncomplicated type 1 diabetes. *Diabetes Care*. 2013;36(5):1290–6. [PubMed: 23250800]
39. Cherney D, Montanari A. The effect of gender on arterial stiffness responses to hyperglycemia in type 1 diabetes mellitus. *Clinical and Experimental Hypertension* 2013;
40. 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(9):2554–60. [PubMed: 16914541]
41. Cherney DZ, Sochett EB, Miller JA. Gender differences in renal responses to hyperglycemia and angiotensin-converting enzyme inhibition in diabetes. *Kidney Int*. 2005;68(4):1722–8. [PubMed: 16164648]
42. de Gasparo M, Levens NR. Pharmacology of angiotensin II receptors in the kidney. *Kidney Int*. 1994;46(6):1486–91. [PubMed: 7699986]
43. Inge TH, Laffel L, Jenkins T, Marcus MD, Leibel NI, Brandt ML, et al. Surgical Therapy is More Effective than Medical Therapy for Type 2 diabetes in Severely Obese Adolescents. *JAMA Pediatr* (In Press). 2017.
44. Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, et al. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. *N Engl J Med*. 2015;373(22):2117–28. [PubMed: 26378978]
45. Neal B, Perkovic V, Mahaffey KW, de Zeeuw D, Fulcher G, Erondur N, et al. Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes. *N Engl J Med*. 2017;377(7):644–57. [PubMed: 28605608]
46. Denic A, Mathew J, Lerman LO, Lieske JC, Larson JJ, Alexander MP, et al. Single-Nephron Glomerular Filtration Rate in Healthy Adults. *N Engl J Med*. 2017;376(24):2349–57. [PubMed: 28614683]
47. Muskiet MH, Tonneijck L, Smits MM, Kramer MH, Heerspink HJ, van Raalte DH. Pleiotropic effects of type 2 diabetes management strategies on renal risk factors. *Lancet Diabetes Endocrinol*. 2015;3(5):367–81. [PubMed: 25943756]
48. Marso SP, Daniels GH, Brown-Frandsen K, Kristensen P, Mann JF, Nauck MA, et al. Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes. *N Engl J Med*. 2016;375(4):311–22. [PubMed: 27295427]
49. Marso SP, Bain SC, Consoli A, Eliaschewitz FG, Jodar E, Leiter LA, et al. Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes. *N Engl J Med*. 2016;375(19):1834–44. [PubMed: 27633186]
50. Tonneijck L, Smits MM, Muskiet MH, Hoekstra T, Kramer MH, Danser AH, et al. Renal Effects of DPP-4 Inhibitor Sitagliptin or GLP-1 Receptor Agonist Liraglutide in Overweight Patients With Type 2 Diabetes: A 12-Week, Randomized, Double-Blind, Placebo-Controlled Trial. *Diabetes Care*. 2016;39(11):2042–50. [PubMed: 27585605]
51. Bjornstad P, Skrtic M, Lytvyn Y, Maahs DM, Johnson RJ, Cherney DZ. The Gomez' equations and renal hemodynamic function in kidney disease research. *Am J Physiol Renal Physiol*. 2016;
52. Lytvyn Y, Skrtic M, Yang GK, Lai V, Scholey JW, Yip PM, et al. Plasma uric acid effects on glomerular haemodynamic profile of patients with uncomplicated Type 1 diabetes mellitus. *Diabet Med*. 2016;33(8):1102–11. [PubMed: 26670339]
53. 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*. 2016;
54. Tonneijck L, Smits MM, Muskiet MH, Hoekstra T, Kramer MH, Danser AH, et al. Acute renal effects of the GLP-1 receptor agonist exenatide in overweight type 2 diabetes patients: a

- randomised, double-blind, placebo-controlled trial. *Diabetologia*. 2016;59(7):1412–21. [PubMed: 27038451]
55. Smits MM, Tonneijck L, Muskiet MH, Hoekstra T, Kramer MH, Diamant M, et al. The effects of GLP-1 based therapies on postprandial haemodynamics: Two randomised, placebo-controlled trials in overweight type 2 diabetes patients. *Diabetes Res Clin Pract*. 2017;124:1–10. [PubMed: 28086201]
 56. Alleyn CR, Volkening LK, Wolfson J, Rodriguez-Ventura A, Wood JR, Laffel LM. Occurrence of microalbuminuria in young people with Type 1 diabetes: importance of age and diabetes duration. *Diabet Med*. 2010;27(5):532–7. [PubMed: 20536948]
 57. Epidemiology of Diabetes Interventions and Complications (EDIC). Design, implementation, and preliminary results of a long-term follow-up of the Diabetes Control and Complications Trial cohort. *Diabetes Care*. 1999;22(1):99–111. [PubMed: 10333910]
 58. Rapid rise in hypertension and nephropathy in youth with type 2 diabetes: the TODAY clinical trial. *Diabetes Care*. 2013;36(6):1735–41. [PubMed: 23704672]
 59. Yokoyama H, Okudaira M, Otani T, Takaike H, Miura J, Saeki A, et al. Existence of early-onset NIDDM Japanese demonstrating severe diabetic complications. *Diabetes Care*. 1997;20(5):844–7. [PubMed: 9135953]
 60. Yokoyama H, Okudaira M, Otani T, Watanabe C, Takaike H, Miura J, et al. High incidence of diabetic nephropathy in early-onset Japanese NIDDM patients. Risk analysis. *Diabetes Care*. 1998;21(7):1080–5. [PubMed: 9653599]
 61. Rodriguez BL, Dabelea D, Liese AD, Fujimoto W, Waitzfelder B, Liu L, et al. Prevalence and correlates of elevated blood pressure in youth with diabetes mellitus: the SEARCH for diabetes in youth study. *J Pediatr*. 2010;157(2):245–51 e1. [PubMed: 20394942]
 62. Maahs DM, Snively BM, Bell RA, Dolan L, Hirsch I, Imperatore G, et al. Higher prevalence of elevated albumin excretion in youth with type 2 than type 1 diabetes: the SEARCH for Diabetes in Youth study. *Diabetes Care*. 2007;30(10):2593–8. [PubMed: 17630264]
 63. Al-Saeed AH, Constantino MI, Molyneaux L, D'Souza M, Limacher-Gisler F, Luo C, et al. An Inverse Relationship Between Age of Type 2 Diabetes Onset and Complication Risk and Mortality: The Impact of Youth-Onset Type 2 Diabetes. *Diabetes Care*. 2016;39(5):823–9. [PubMed: 27006511]
 64. Dabelea D, Mayer-Davis EJ, Saydah S, Imperatore G, Linder B, Divers J, et al. Prevalence of type 1 and type 2 diabetes among children and adolescents from 2001 to 2009. *JAMA*. 2014;311(17):1778–86. [PubMed: 24794371]

Figure 1. The Progression of DKD from Hyperfiltration to ESRD

Nephrons are depicted as steam factories, and the height of the smoke stacks represents how hard the nephrons are working (their GFR). Supraphysiologic GFR (hyperfiltration) leads to vascular changes, inflammation, fibrosis and nephron loss over time

Figure 2. Greater risk of hyperfiltration in girls vs. boys with T2D

Adjusted for estimated insulin sensitivity, age, ethnicity, treatment group, BMI, HbA1c, hypertension and loss of glycemic control (primary outcome).

Figure 3. Greater efferent arteriolar resistance in women vs. men, with resultant increased glomerular pressure and GFR

Figure 4. Proposed Mechanism of Bariatric Surgery on Hyperfiltration

Youth-onset T2D is characterized by IR, central obesity and hyperfiltration, due to afferent arteriolar vasodilation (a) with increased renal blood flow (RBF) and glomerular pressure. We theorize that the improvement in IR and central adiposity and remission of T2D will normalize the afferent arteriolar tone (b) and attenuate hyperfiltration, with resultant normalization of the O₂ consumption / utilization mismatch.

Table 1

What progress do we need to make in the next 5–10 years?

Areas of Research Priority	Knowledge Gaps
Studies defining intrarenal hemodynamic function in early DKD in youth-onset T2D	Why does youth-onset T2D carry a greater risk for DKD than youth with T1D and adult-onset T2D?
Improved understanding of sex-related differences in the pathogenesis of early DKD in youth-onset T2D	What are the mechanisms explaining the disproportionate impact of DKD in girls with youth-onset T2D?
Non-invasive methods to quantify number nephrons to better quantify single-nephron GFR (e.g. cattonized ferritin (CF)–enhanced MRI (CFE-MRI))	How does single nephron-GFR relate to the progression of DKD in youth-onset T2D?
Improved functional and structural evaluation of renal function and metabolism by non-invasive MRI methods	T1D and T2D specific risk factor targets based on clinical trial data
Mechanistic clinical trials with gold-standard intrarenal hemodynamic function as outcomes	What is the impact of novel therapies (e.g. SGLT2 inhibitors) on intrarenal hemodynamic function in youth with T2D?
Better understanding of the impact of bariatric surgery on intrarenal hemodynamic function in youth-onset T2D, and the development of non-surgical approaches	What are the effects of metabolic surgery on the pathogenesis driving early DKD in youth with T2D, and can these effects be accomplished non-surgically?