COMMENTARY

Going in Early: Hypoxia as a Target for Kidney Disease Prevention in Diabetes?

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Diabetic kidney disease (DKD) begins early, which is pertinent to those diagnosed with diabetes during childhood and adolescence. The initiators of DKD are not fully defined, but hypoxia and metabolic abnormalities are important. With growing numbers of young people diagnosed with diabetes and concomitant risk for early mortality, this commentary examines the study by Vinovskis et al. (1) in this issue of *Diabetes*, which highlights renal hypoxia as an early phenomenon in diabetes associated with risk for DKD.

Many diabetologists and nephrologists consider DKD an affliction of late-middle age. Certainly, the proportion of affected individuals with diabetes escalates with age (2), and at least one-third of these will develop DKD, a major risk factor for cardiovascular disease and early mortality (3). Global estimates of people living with diabetes have tripled in the past 20 years (2), topping 463 million individuals, suggesting that 167 million of these already have or will develop DKD.

Perhaps less well known is the growing incidence of diabetes in children and adolescents, which is escalating by 3% each year, and at a higher rate in some ethnic groups (2). Another underappreciated fact is that many children and adolescents with diabetes develop complications in early adulthood, placing significant burden on the individual, the family, and society. Data from the International Diabetes Federation suggest that almost half (46.2%) of deaths associated with diabetes among the 20–79 years age-group are in people under the age of 60 years (2). Hence, because the average age of enrolment in phase 3 studies of diabetes-related mortality is 60 years of age, younger individuals who may have benefited from these interventions were excluded. Therefore, undertaking studies to understand and potentially intervene in early complications of diabetes in a much younger cohort than standard is crucial to potentially improving the outcomes of diabetes in our global population. Vinovskis et al. (1) have undertaken this important step by examining renal metabolic processes in a cohort of young people aged <21 years.

Evidence from a prospective study shows that 88% of future cases of DKD, at least in those with type 1 diabetes, can be predicted in childhood and adolescence, using elevations in urine albumin-to-creatinine ratio during puberty (4). Type 1 diabetes, where there is commonly a known diagnosis date, provides an opportunity to track kidney disease in real time to better understand early determinants of disease. Indeed, in the past, this led to the ascertainment of glomerular mesangial matrix expansion and basement membrane thickening as kidney structural markers of future DKD risk in biopsies (5). Recent clinical studies show that conventional therapies that slow kidney disease progression in adults, targeting dyslipidemia and hypertension, are not as effective in early kidney disease (6,7). This suggests that the factors at play early in DKD development are not well understood, which is hindering the discovery and translation of effective therapeutics for prevention.

The article by Vinovskis et al. (1) presents renal hypoxia, as estimated by blood oxygen–dependent magnetic resonance imaging (BOLD MRI) of renal oxygen availability as a ratio of ioxal measured GFR (RO_2:GFR) in adolescents with type 1 diabetes, that was seen concomitantly with albuminuria, increased renal plasma flow, greater fat mass, and reduced insulin sensitivity measured during hyperglycemic clamps. The anatomical proximity to the heart delivers significant cardiac output to the kidneys ensuring adequate oxygen availability for metabolic processes including synthesis of hormones, amino acids, and glucose and maintenance of fluid balance where ions,

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solutes, and nutrients are reclaimed from the forming urine. The kidneys have disproportionately high oxygen consumption and mitochondrial numbers as compared with many other organs, which facilitates mitochondrial ATP production necessary for normal function (8). A number of pathways regulate stable delivery of renal oxygen, including metabolic control of Na^+ transport and tubuloglomerular feedback, which are coupled to most molecular reabsorption pathways such as for glucose via sodium–glucose cotransporter 2 (SGLT2) and to the glomerular filtration rate (GFR) (9,10). Studies suggest increased metabolic ATP demand, driven by excessive reabsorption of glucose and other molecules, causes the kidneys to increase oxygen demand early in diabetes (11), resulting in hypoxia. Indeed, kidney damage is caused in the absence of diabetes, by phenocopying the excessive oxygen demand required for the reabsorption of high concentrations of glucose and lactate from forming urine via Na^+ K^+ ATPase coupling, as seen in diabetes (12). It is likely that this increased metabolic demand and concomitant insulin insufficiency and diuresis, both seen in the adolescent participants of the study by Vinovskis et al., are also contributing to early renal hypoxia. Insulin insufficiency would not adequately suppress endogenous glucose production and therefore exacerbate hyperglycemia and the glucose load needing to be salvaged from urine thereby increasing renal oxygen consumption. Similarly, diuresis also contributes to hypoxia due to the solute and ion load, which needs to be reabsorbed by the kidney tubules, increasing oxygen consumption while hyperfiltration decreases oxygen tension and therefore delivery (11).

However, other factors that were not studied may also be important such as breathing difficulties apparent in some young people with type 1 diabetes (13), oxidative stress, and decreasing electrolyte transport efficiency (8,11), which could also impact renal hypoxia. The real novelty of the study by Vinovskis et al. (1) lies in the fact that GFR was measured during a mild hyperglycemic clamp (170–190 mg/mL), ensuring that renal glucose reabsorption was fixed and that variations in GFR were not dependent on this factor.

One variable to consider, however, in this study is the population. The cohort comprised primarily female (50% type 1 diabetes, 70% control) participants. These individuals were 12–21 years of age with mean pubertal classification of Tanner stage 5 (4–5), but the age of menarche was not mentioned, which is potentially relevant since women with type 1 diabetes and delayed menarche in the Finnish Diabetic Nephropathy Study (FinnDiane) had a 2.3 times higher risk of DKD (14). Additionally, while excluding from participation those taking oral contraceptives, the investigators do not mention whether they controlled phase of menstrual cycle for the timing of investigations. There is evidence that insulin sensitivity changes across the menstrual cycle (15) as does estimated GFR (16), but less so for renal blood flow (17).

The study by Vinovskis et al. also included predominately White (92% diabetes, 95% control) participants. Data from the U.S. on the incidence of type 1 diabetes shows increases across all ethnic groups, but the annual increase is actually higher in non-White ethnicities including non-Hispanic White 1.2, non-Hispanic Black 2.2, and Hispanic 4.2 increases in cases/100,000 youth/year (18). It would be interesting for future studies to examine these changes in these emerging ethnicities affected by type 1 diabetes.

Overall, the purpose of this study was to increase understanding of DKD development so that it can potentially be prevented. There are already some approaches that target various aspects of hypoxia in clinical development, which are discussed below. The tissue expression of hypoxia inducible factor 1α (HIF-1α) is increased in response to hypoxia and stimulates angiogenesis and erythropoiesis and alters energy metabolism (19). Previous findings show that renal HIF-1α expression is too low to activate compensatory responses to hypoxia in DKD and that stabilizing HIF-1α activity is renoprotective in established DKD (20). Prolyl hydroxylase inhibitors, such as enarodustat (JTZ-951) and roxadustat (FG-4592) (21,22), stabilize HIF-1α and could be tested for their efficacy in primary and secondary prevention of DKD. These therapies are currently undergoing phase 3 clinical trials to determine their utility as activators of erythropoietin production and treatment of anemia in chronic kidney disease (CKD). One concern with this approach is that supraphysiologic doses of these agents can induce renal fibrosis. Thus, such agents need to be carefully evaluated for effects on renal fibrosis, given the presumptive need for chronic administration of these agents for the treatment of anemia in CKD. Indeed, HIF stabilization across the development and progression of DKD may be context and time dependent, which should also be given attention in future studies.

In their article, Vinovskis et al. suggest that SGLT2 inhibition would be a candidate for treatment in this population. While blocking SGLT2 is likely to alleviate some of the metabolic abnormalities including slowing of the oxygen consumed for glucose reabsorption from the forming urine, this may not come without some potential risk. A number of SGLT2 inhibitors have progressed to phase 3 clinical trials for use in type 1 diabetes, and dapagliflozin has been registered for use in Europe (23). There are yet to be formal cardiovascular outcome trials with SGLT2 inhibitors in type 1 diabetes, but early reductions in estimated GFR and urinary albumin excretion have been demonstrated (24). However, all of these trials (23) showed a rate of diabetic ketoacidosis approaching 4%. Clearly the risk–benefit for this group of medications in young people with type 1 diabetes will need careful consideration, given their generally poorer diabetes control and higher risk of DKA. Indeed, groups with poor glycemic control are often excluded from trials/studies, as was seen in the study by Vinovskis et al., which also excluded

potential participants with HbA_{1c} >11% (269 mg/dL), preexisting renal disease, and use of renin-angiotensin system–altering drugs. This limits the potential applicability of the findings to those young people with known renal disease but also to those with the poorest glucose control who are often at greatest risk for DKD.

Overall, it is likely that hypoxia is contributing to early kidney damage in diabetes. Hence, strategies that mitigate this risk should be considered as part of approaches to prevent the onset and progression of DKD and subsequent cardiovascular mortality.

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