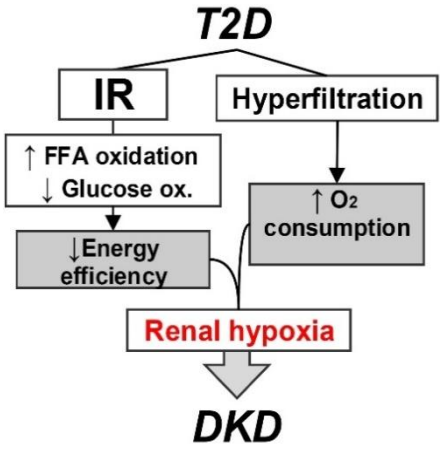
SPECIFIC AIMS:



Type 2 diabetes (T2D) in youth is increasing in prevalence in parallel with the obesity epidemic. In the US, almost half of patients with renal failure have DKD, and ≥80% have T2D. Compared to adult-onset 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), arguing for separate and dedicated studies in youth-onset T2D. Hyperfiltration is common in youth with T2D, and predicts progressive DKD. Hyperfiltration may also be associated with early changes in intrarenal hemodynamic function, including increased renal plasma flow (RPF) and glomerular pressure. Despite the high prevalence and gravity of DKD in youth-onset T2D, widely effective therapeutic options are lacking. Our preliminary data support a strong association between IR and hyperfiltration in youth-onset T2D, but the pathology contributing to this relationship remains unclear. A better understanding of the pathophysiology underlying hyperfiltration and its relationship with IR is critical to inform development of new therapeutics. My overarching hypotheses are that: 1) hyperfiltration in youth-onset T2D is associated with changes in intrarenal hemodynamics, resulting in increased renal oxygen demand, 2) the demand is unmet by the inefficient fuel profile associated with IR (decreased glucose oxidation and increase free fatty acid [FFA] oxidation), resulting in renal hypoxia (**Fig**) and ultimately renal damage. To address these hypotheses, I will measure peripheral insulin sensitivity, adipose insulin sensitivity (FFA suppression), glomerular filtration rate (GFR), RPF, and renal oxygenation in youth with T2D (n=30), obesity (n=20) and in lean (n=20) controls.

Aim 1: To define differences in intrarenal hemodynamic function in adolescents with T2D vs. non-diabetic obese and lean controls, and between T2D youth with and without hyperfiltration.
***Hypothesis 1:* Youth with T2D will have reduced afferent arteriolar resistance, and increased GFR, RPF (volume of plasma delivered per min) and glomerular pressure vs. obese controls and lean controls.**
Rationale: Our preliminary data demonstrate higher GFR and rates of hyperfiltration in youth with T2D compared to non-diabetic controls. Experimental models suggest that hyperfiltration is characterized by reduced afferent arteriolar resistance, and increased glomerular pressure and RPF.
Methods: GFR and RPF will be measured by iohexol and para-aminohippurate (PAH) clearance respectively, and Intrarenal hemodynamics (e.g. glomerular pressure and afferent and efferent arteriolar resistance) calculated by Gomez' equations in T2D, obese and lean adolescents.
Associated training: Experience with GFR and RPF methods and application of Gomez' equations.

Aim 2: To compare renal oxygenation and perfusion in adolescents with T2D vs. non-diabetic obese controls, and between T2D youth with and without hyperfiltration.
***Hypothesis 2:* Youth with T2D will have reduced renal oxygenation and increased renal perfusion (RPF per given mass of tissue) vs. obese and lean controls.**
Rationale: Renal hypoxia is proposed to be a unifying pathway in the development of DKD. The kidneys are highly metabolically active and have a high-energy requirement to sustain their GFR and intrarenal hemodynamic function. We theorize that the kidneys of youth with T2D are unable to sufficiently compensate for the high-energy requirement of hyperfiltration due to the effects of IR on fuel utilization.
Methods: Renal blood-oxygen level dependent (BOLD) and arterial spin labeling (ASL) MRI.
Associated training: Learn MRI techniques to quantify renal oxygenation and perfusion.

Aim 3: To understand the effects of peripheral and adipose insulin sensitivity on intrarenal hemodynamic function and renal oxygenation in obese youth with and without T2D.
***Hypothesis 3:* Peripheral and adipose IR will be inversely associated with afferent arteriolar resistance and renal oxygenation, and positively associated with GFR, glomerular pressure and RPF.**
Rationale: Our preliminary data show strong associations between IR and hyperfiltration in youth with T2D, but it remains unknown whether these associations hold true with gold-standard measured rather than estimated GFR, and how IR relates to intrarenal hemodynamic function and oxygenation.
Methods: Peripheral and adipose Insulin sensitivity by hyperinsulinemic clamp; Aim 1 and 2 methods.
Associated training: Performance, analysis and interpretation of hyperinsulinemic euglycemic clamps

Impact of Aims 1-3: Youth-onset T2D have a lifetime risk for complications. Studies of intrarenal hemodynamic function and oxygenation in youth-onset T2D are lacking. Training in such methodologies is needed to advance DKD research in the pre-clinical stages and direct the development of new therapeutic strategies to improve renal health and mortality for the estimated 422 million people at risk for DKD worldwide.