Diabetic Complications Consortium

Application Title: Dolphin-T1D Study: Define Renal Oxygenation Levels and Perfusion in Hyperfiltration in Adolescents with Type 1 Diabetes

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1. Project Accomplishments:

- October 2019: IRB approval
- October 2020: Completed enrollment
- November 2020: Completed all study visits
  - Measured cortical and medullary oxygenation, and cortical perfusion of left and right kidneys in 50 adolescents with type 1 diabetes.
  - DiaComp P&F award funded BOLD and pCASL MRI scans in 30 of the 50 participants, and JDRF funds leveraged for the additional 20 scans.
- December 2020: Finished preliminary MRI analysis for abstracts

2. Specific Aims:

Aim 1: To compare renal oxygenation and perfusion in youth with T1D with hyperfiltration vs. youth with T1D with normofiltration.

Aim 2: To define the relationship between renal perfusion and renal oxygenation, intrarenal hemodynamic function, mitochondrial dysfunction and IR in youth with T1D.

Results of Aim 1 and 2: Data from 50 participants (mean±SD age 16±3 years; 50% female; 5.7±2.6 years diabetes duration; HbA1c 8.6±1.4%) were analyzed. Mean GFR was 183±28 ml/min/1.73m^2, ERPF was 826±124 ml/min/1.73m^2, FF 22.9±4.5% and RVR 0.066±0.019 mm Hg/L/min. Average cortical R2* was 20.9±2.5s^{-1} and medullary R2* was 26.9±3.1s^{-1}. Cortical oxygenation (R2*) positively correlated with FF (r: 0.41, p=0.02), ERPF (r: 0.45, p=0.007), and RVR (r: 0.47, p=0.006), and these relationships remained significant after adjusting for age, sex and HbA1c. GFR (r=0.45, p=0.007) and FF (r=0.45, p=0.008) positively correlated with furosemide-suppressible oxygen consumption, and these relationships remained significant after adjusting for age, sex and HbA1c.

Of note, samples have been sent to measure biomarkers needed to estimate insulin sensitivity and mitochondrial function (mitochondrial metabolites by metabolomics). Anticipate receiving results early to mid-January 2020.

3. Publications:

- Preliminary MRI data will be submitted as abstracts to European Diabetic Nephropathy Study Group meeting in Glasgow in May 2020 and American Diabetes Association Scientific Sessions in June 2020.
- Abstract draft included on page 2:

Renal hemodynamic dysfunction is associated with reduced cortical oxygenation in adolescents with type 1 diabetes

The kidneys are highly metabolically active and are second only to the heart with respect to oxygen consumption per tissue mass. Animal models suggest that renal hemodynamic dysfunction in diabetes upregulates oxygen consumption and predisposes to renal hypoxia and early diabetic kidney disease (DKD). However, these relationships have not yet been defined in people with type 1 diabetes (T1D). The objective of this study was to detail the relationship between renal hemodynamics, renal oxygenation and furosemide-suppressible oxygen consumption by renal functional MRI (fMRI) in adolescents with T1D, who are known to have a high prevalence of glomerular hyperfiltration.

A cross-sectional study in 50 adolescents [NCT03618420] (ages 12-21 years) with T1D (1-10 years of disease duration) who underwent fasting blood oxygen level dependent (BOLD) MRI on 3T Siemens scanner (MAGNETOM Skyra, Siemens Medical Solutions, Erlangen, Germany) before and after IV furosemide (0.5mg/kg) at 7 am to quantify cortical and medullary oxygenation (R2*) and furosemide-suppressible oxygen consumption (ΔR2*). Images were analyzed with the twelve-layer concentric objects method. A high R2* corresponds to low oxygenation. Ninety minutes after the MRI, participants underwent iohexol and *p*-aminohippurate clearance to measure glomerular filtration rate (GFR) and effective renal plasma flow (ERPF) during clamped glycemia and a DXA to quantify lean and fat mass at our Clinical Translational Research Center. Participants were provided with diet and physical activity instructions prior to their study visit to limit the impact of nutrients and exercise on renal function. Filtration fraction (FF=GFR/ERPF), renal blood flow (RBF=ERPF/1-hematocrit) and renal vascular resistance (RVR=mean arterial pressure/renal blood flow) were calculated. All renal hemodynamic parameters were normalized for body surface area (BSA). Correlation and multivariable linear regression models were built to define the relationships between renal hemodynamic parameters and renal oxygenation.

Data from 50 participants (mean±SD age 16±3 years; 50% female; 5.7±2.6 years diabetes duration; HbA1c 8.6±1.4%) were analyzed. Mean GFR was 183±28 ml/min/1.73m^2, ERPF was 826±124 ml/min/1.73m^2, FF 22.9±4.5% and RVR 0.066±0.019 mm Hg/L/min. Average cortical R2* was 20.9±2.5s^{-1} and medullary R2* was 26.9±3.1s^{-1}. Cortical oxygenation (R2*) positively correlated with FF (r: 0.41, p=0.02), ERPF (r: 0.45, p=0.007), and RVR (r: 0.47, p=0.006), and these relationships remained significant after adjusting for age, sex and HbA1c. GFR (r=0.45, p=0.007) and FF (r=0.45, p=0.008) positively correlated with furosemide-suppressible oxygen consumption, and these relationships remained significant after adjusting for age, sex and HbA1c.
For the first time, we demonstrate that renal hemodynamic dysfunction, including increased GFR, ERPF, FF, and RVR, is associated with lower renal cortical oxygenation and increased oxygen consumption by renal fMRI in adolescents with T1D. These data may suggest a potential role of decreased renal oxygenation in early DKD.