PROJECT SUMMARY/ABSTRACT

Insulin resistance (IR) is a consistent but under-recognized finding that independently contributes to coronary arterial disease (CAD), the leading cause of mortality in type 1 diabetes (T1DM). Although the endothelial dysfunction that ultimately leads to CAD is operative at an early stage in the natural history of the disease, a greater understanding of the pathophysiologic mechanisms underpinning IR in T1DM is needed and the relationship between IR and endothelial dysfunction must be defined. While other investigators have concluded hyperglycemia is the key factor triggering IR and endothelial dysfunction, I posit that iatrogenic hyperinsulinemia resulting from peripheral insulin delivery is the principal driver of T1DM IR and endothelial dysfunction. The proposal will test the hypothesis that IR in T1DM: 1) is driven primarily by iatrogenic peripheral hyperinsulinemia, 2) occurs in tissues exposed to chronic hyperinsulinemia (muscle, fat, but not the liver), and 3) correlates tightly with endothelial dysfunction. The hyperinsulinemic, euglycemic clamp and isotopic glucose tracer techniques will be used to determine whether iatrogenic hyperinsulinemia or hyperglycemia is the primary contributor to T1DM IR at whole-body (Aim 1) and tissue-specific (Aim 2) levels. In Aim 3, an intervention to lower iatrogenic hyperinsulinemia (the SGLT2-inhibitor empagliflozin) will be used to determine the extent to which a decrease hyperinsulinemia-mediated IR lessens endothelial dysfunction as quantified by flow mediated dilation. The proposed research will provide information on whether novel therapeutic strategies to lessen iatrogenic hyperinsulinemia by restoring the physiologic portal to peripheral insulin distribution (e.g. hepatopreferential insulin analogs, intraperitoneal insulin pumps) can normalize insulin sensitivity and atherosclerotic risk in T1DM.

The proposed studies provide a focus for my mentored research training plan to become an independent, leading investigator of metabolic dysregulation. Along with my mentors, I have formed a comprehensive training program to expand expertise in glucose metabolism and physiology (Aims 1-2), transition from my background canine physiology research into translational human subjects research (Aims 1-3), and develop proficiency applying advanced cardiovascular research techniques to study preclinical vascular dysfunction (Aim 3).