

Title: Effect of Metformin on Vascular and Mitochondrial Function in Type 1 Diabetes

Short Title: Metformin and Cardiovascular Function in T1D

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ABSTRACT:

Introduction: Cardiovascular (CV) disease remains the leading cause of mortality in type 1 diabetes (T1D) despite advances in glycemic control and to a greater extent than predicted by traditional CV risk factors. Metformin is generally thought to have vascular benefit in T2D and other insulin resistant states, though conclusive data for CV outcomes is lacking. In T1D metformin has been studied for glycemic control, but little attention has been paid to CV effects. We hypothesized that metformin would improve insulin sensitivity (IS), vascular function and compliance, and mitochondrial function in T1D.

Materials and Methods: T1D participants (n=17) underwent a placebo-controlled, double-blind, random order, cross-over design intervention with 6 weeks of metformin vs placebo. Glycemic control (CGM), cardiac function (echocardiography), vascular stiffness (Sphygmocor and Dynapulse), autonomic function, IS (hyperinsulinemic euglycemic clamp with glucose tracer), and mitochondrial function in vivo (³¹P MRS) and ex vivo (muscle biopsy with high resolution respirometry) were measured after each phase.

Results: Glucose control and IS by clamp were not improved with metformin. Oxidative phosphorylation was increased in vivo, but ex vivo mitochondrial function was not improved. Cardiac contractility and output, arterial stiffness, systemic vascular resistance, and possibly autonomic function, were improved with metformin.

Conclusions: Metformin may provide CV benefit in T1D through improvements in vascular resistance and mitochondrial efficiency.