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Metformin improves cardiac function, peripheral vascular resistance, and mitochondrial efficiency, but does not lower insulin resistance or increase mitochondrial capacity or content in type 1 diabetes

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Abstract

BACKGROUND: 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.

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 and resistance (Sphygmacor and Dynapulse), autonomic function, IS (hyperinsulinemic euglycemic clamp), 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 were not improved with MF. Stage 3 ex vivo mitochondrial function with either carbohydrate or lipid substrates and mitochondrial content also did not change significantly with MF. However, ex vivo mitochondrial efficiency appeared to improve. In addition, despite the smaller subset, MRS measurement of in vivo mitochondrial function demonstrated increased oxidative phosphorylation and suggested faster recovery of ATP after exercise, increased maximal mitochondrial capacity, improved mitochondrial efficiency, and decreased anaerobic metabolism of glucose after MF treatment. Systemic vascular resistance and brachial artery resistance decreased indicating improved arterial stiffness. However, PWV and augmentation index did not improve. Cardiac output and cardiac index were increased by MF due, at least in part, to a significant increase in heart rate. These results suggest that MF in T1D may improve mitochondrial function in vivo through indirect effects on cardiovascular function that improve oxygen delivery to muscle tissue and possibly mitochondrial efficiency, rather than through direct effects on mitochondrial content or innate mitochondrial capacity.

CONCLUSIONS: Metformin may provide cardiovascular protection in T1D through improved vascular function and stiffness and mitochondrial efficiency, but does not appear to improve glucose control, insulin sensitivity, or mitochondrial content or maximum capacity.

Background

- **Increase in prevalence of type 1 diabetes (T1D)**
- **CVD risk and mortality have a 2-4 x increase in T1D and CVD is a major cause of morbidity and mortality**
- **T1D is associated with impaired mitochondrial function, decreased vascular compliance, and increased insulin resistance**
- **Metformin has been shown to improve mitochondrial function, insulin action, vascular compliance, and glucose control in Type 2 Diabetes (T2D)**
- **Evidence supports benefit for metformin in CVD risk reduction in T2D.**

Hypothesis

Metformin will improve insulin sensitivity (IS), vascular function and compliance, and mitochondrial function in T1D.

Study Design and Methods

- Subjects: Men and women with T1D (n=17), ages 23-61, A1c 6.2-9.0, excluded for: comorbid conditions, smoking, or diabetes-related complications.
- Placebo-controlled, double-blind, random order, cross-over design intervention: 6 weeks of metformin vs placebo with 2-8 weeks washout between stages.
- Study procedures performed after each 6 week period:
  - CGM throughout, blinded for 3 days before study visit
  - 3 day standardized diet
  - 2-stage hyperinsulinemic euglycemic clamp (8 and 40mU/m^2/min) with glucose tracer
  - Cardiovascular measures: Endothelial function (flow-mediated brachial artery dilation), arterial stiffness (Sphygmacor), heart rate variability, and echocardiography
  - Muscle biopsy for ex vivo mitochondrial function (Oroboros high resolution respirometry of permeabilized muscle fibers) and mitochondrial content (citrate synthase activity and immunoblot analyses)
  - ^{31}P MRS for in vivo mitochondrial function in a subset of subjects (n=9)

Results

Baseline characteristics

Gender	8M 9F
Age (years)	43.3 ± 12
BMI (kg/m^2)	27.7 ± 2.8
Percent body fat	31.4 ± 7.8
HbA1c (%)	7.25 ± 0.91

Glucose control

	Placebo	Metformin	P-value
7day mean glucose (mg/dl)	162 ± 26	162 ± 35	NS
SD	68 ± 20	64 ± 14	NS
% <50	3 ± 3	5 ± 8	NS
%<70	8 ± 7	8 ± 10	NS
% target (70-150)	41 ± 14	39 ± 15	NS
%>150	51 ± 15	52 ± 19	NS
%>250	10 ± 10	13 ± 13	NS

Insulin sensitivity

		Placebo	Metformin	P-value
Overnight preclamp:	**Mean Glucose**	143 ± 25	132 ± 23	NS
	Total insulin infused	12.3 ± 3.6	11.3 ± 4.2	NS
Preclamp:	**Glucose**	124 ± 46	135 ± 45	NS (0.1)
	Insulin	49 ± 57	34 ± 34	0.03
	NEFA	446 ± 185	531 ± 174	NS (0.1)
Stage 1:	**Glucose**	96 ± 8	94 ± 13	NS
	Insulin	40 ± 43	36 ± 36	NS (0.06)
	Lactate	0.52 ± 0.08	0.87 ± 0.38	0.014
	GIR	0.68 ± 0.49	0.80 ± 0.41	NS
Stage 2:	**Glucose**	92.0 ± 7.3	93.3 ± 4.7	0.05
	Insulin	93 ± 37	91 ± 43	0.06
	Lactate	0.73 ± 0.24	1.11 ± 0.39	0.0002
	GIR	3.5 ± 2.2	3.3 ± 1.5	NS

Vascular stiffness, cardiac/autonomic function

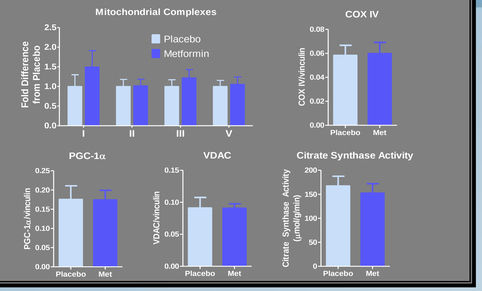
		Placebo	Metformin	P-value
Sphygmacor:	**Augmentation Index**	21.2 ± 12.2	19.0 ± 9.6	**NS**
	AI HR-corrected	15.4 ± 12.2	16.0 ± 9.0	NS
	PWV	8.6 ± 2.9	8.6 ± 2.8	NS
Dynapulse	**Cardiac output**	4.92 ± 0.62	5.52 ± 0.76	**<0.0001**
	Cardiac index	2.53 ± 0.25	2.82 ± 0.33	**<0.0001**
	LV contractility	14.8 ± 1.1	15.4 ± 1.4	**0.012**
	Systemic vascular Res	1445 ± 180	1293 ± 177	**0.0002**
	Brachial artery Res	233 ± 92	205 ± 84	**0.023**
Echocardio-graphy	**Heart rate**	62 ± 8	71 ± 11	**0.0001**
	LV Cardiac output	4.52 ± 1.40	5.52 ± 1.8	**0.003**
	LVOT mean PG	2.13 ± 1.95	2.79 ± 2.22	**0.001**
	LVOT max PG	4.20 ± 2.65	5.56 ± 3.7	**0.008**
Heart rate variability:	**Mean Tachy**	70 ± 6	76 ± 8	**0.001**
	Mean Brady	56 ± 9	62 ± 11	**0.001**
	Difference	15 ± 8	14 ± 7	NS
	Valsalva tachy	90 ± 11	98 ± 10	**0.01**
	Valsalva brady	64 ± 9	65 ± 11	NS
	Tachy:brady ratio	1.42 ± 0.18	1.55 ± 0.34	NS (0.06)
	Supine HR	63 ± 9	71 ± 8	**0.003**
	Standing HR	83 ± 13	90 ± 13	NS (0.06)
	Difference	21 ± 11	19 ± 15	NS

Ex Vivo Mitochondrial function

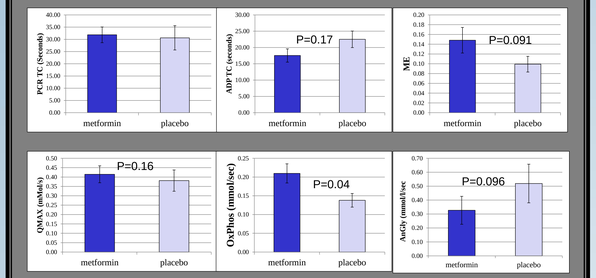
Metformin vs. placebo: ex vivo respirometry in permeabilized fibers			
	Placebo	**Metformin**	**P-value†**
PMG state 3 O_2 flux (pmoles/mg/s)	28.6 ± 10.7	27.8 ± 7.2	NS
PMGS state 3 O_2 flux	39.8 ± 15.5	44.5 ± 17.8	NS
Succinate contribution to state 3	11.1 ± 5.2	12.4 ± 4.4	NS (0.07)
PMGS state 4 leak (+oligomycin)	13.8 ± 6.5	14.5 ± 8.6	NS
PMGS uncoupled max	76.8 ± 22.0	74.3 ± 27.0	NS
RCR (PMGS3/PMGS4)	3.0 ± 0.6	3.3 ± 0.7	0.03
P/E PMGS	0.52 ± 0.12	0.60 ± 0.11	**0.002**

PMGS=pyruvate/malate/glutamate/succinate; Data are mean ± SD. † paired t-test

Mitochondrial content



In Vivo Mitochondrial function



ME=Mitochondrial efficiency; PCr TC=Phosphocreatine recovery time; ADP TC=ADP recovery time; AnGly=anaerobic glycolysis; All are mean ± SE

Summary

- **Metformin did not improve glucose control or insulin sensitivity**
- **Metformin increased cardiac output through increased heart rate and decreased peripheral vascular resistance.**
- **Metformin increased in vivo mitochondrial oxidative phosphorylation and possibly other measures of in vivo mitochondrial function (reflecting possible contributions from both mitochondrial and vascular function).**
- **Ex vivo mitochondrial carbohydrate metabolism exhibited improved efficiency without measurable changes in mitochondrial content or complex 1 activity and largely driven by increased complex 3 flux.Statistical significance was largely driven by participants randomized to the placebo-metformin order suggesting that MF may have prolonged effects and require longer wash-out.**

Conclusion

Metformin has potential to provide cardiovascular protection in T1D through improved vascular function and stiffness and mitochondrial efficiency.