Oxidative Stress Contributes to Microvascular Endothelial Dysfunction in Women with a History of Gestational Diabetes

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Abstract #: 25

Introduction

- Women who have had gestational diabetes (GDM) are 7x more likely to develop type II diabetes (T2DM) [1] and 2x more likely to develop cardiovascular disease (CVD) [2].
- GDM is associated with endothelial dysfunction and elevated oxidative stress during pregnancy, and vascular dysfunction postpartum. However, the mechanism(s) mediating this postpartum dysfunction are unknown.
- Using the cutaneous circulation as a model, we examined if oxidative stress contributes to microvascular dysfunction in healthy women with a history of GDM (GDM) and control women who had a history of uncomplicated pregnancy (HC).
- We hypothesized that:
  1. Endothelium-dependent dilation would be attenuated in women with a history of GDM compared to women with a history of normal glucose tolerance during pregnancy
  2. Attenuated vasodilation following GDM would be mediated by a reduction in NO-dependent dilation.
  3. Local administration of a nonspecific antioxidant (L-ascorbate) would augment endothelium-dependent dilation in the microvasculature of women with a history of GDM.

1. Lacet. 2009 May 23;373(9677):1773-9
2. Diabetologia. (2019) 62, 905-914

Subjects

We recruited healthy women who had been pregnant within the last 5 years. HC (n=10) had a history of uncomplicated pregnancy. GDM (n=10) had a self-reported history of gestational diabetes during pregnancy. Potential participants were excluded if they had metabolic or cardiovascular disease, a history of gestational hypertension or preeclampsia, a history of diabetes before pregnancy, and if they used cardiovascular medications or tobacco products.

Subject Characteristics	HC (n=10)	GDM (n=10)	p-value
Age (years)	35 ± 1	34 ± 1	0.37
Time post-partum (months)	18 ± 4	22 ± 5	0.43
MAP (mmHg)	87 ± 5	87 ± 3	0.99
SBP (mmHg)	117 ± 5	119 ± 4	0.80
DBP (mmHg)	72 ± 5	71 ± 2	0.88
BMI ($kg \cdot m^{-2}$)	28 ± 2	32 ± 3	0.34
Total cholesterol ($mg \cdot dl^{-1}$)	179 ± 8	177 ± 10	0.86
HDL ($mg \cdot dl^{-1}$)	61 ± 5	50 ± 5	0.13
LDL ($mg \cdot dl^{-1}$)	103 ± 5	104 ± 10	0.93
Triglycerides ($mg \cdot dl^{-1}$)	75 ± 15	114 ± 18	0.11
BUN ($mg \cdot dl^{-1}$)	12 ± 1	12 ± 1	0.94
Creatinine ($mg \cdot dl^{-1}$)	0.8 ± 0.0	0.8 ± 0.0	0.80
BUN/creatinine ratio	14.9 ± 1.4	15.2 ± 1.0	0.86
Fasting Glucose ($mg \cdot dl^{-1}$)	78 ± 4	87 ± 4	0.06
Fasting Insulin ($uU \cdot ml^{-1}$)	8.6 ± 2.4	16.1 ± 3.1	0.07
HOMA-IR	1.7 ± 0.5	3.6 ± 0.7	0.04
HbA1c (%)	5.2 ± 0.1	5.3 ± 0.2	0.62
ACR (mg/g)	3.0 ± 1.5	15.7 ± 6.5	0.06

Table 1. Subject Characteristics HC, women who had an uncomplicated pregnancy; GDM, women who had gestational diabetes; MAP, mean arterial pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body max index; HDL, high-density lipoprotein; LDL, low-density lipoprotein; BUN, blood urea nitrogen; ACR, albumin:creatinine ratio.

Approach

- ***In Vivo* Microvascular Function**: We assessed cutaneous microvascular responses to a standard local heating protocol (42°C; 0.1°C·s^{-1}). Two intradermal microdialysis fibers (Figure 1) were placed in the ventral forearm for local delivery of lactated Ringer's (control) or 5mM ascorbate. After full expression of the local heating response, 15mM N^G-nitro-L-arginine methyl ester (L-NAME; NO synthase-inhibition) was perfused. Red cell flux was measured continuously by laser-Doppler flowmetry, and cutaneous vascular conductance (CVC=flux·MAP^{-1}) was standardized to maximum (%max; infusion of sodium nitroprusside, local heat 43°C). % NO-dependent dilation was calculated within-site as the difference between the endothelium-dependent plateau and post L-NAME plateau.

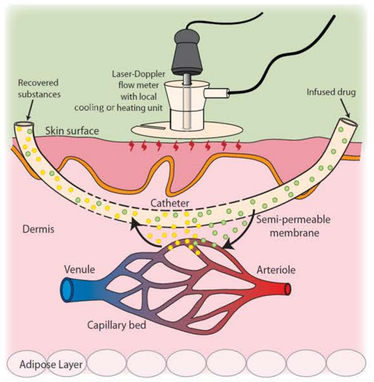

Figure 1. Schematic representation of intradermal microdialysis

Results

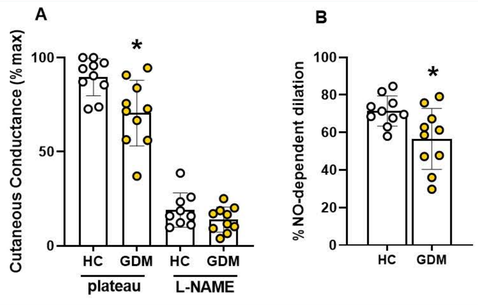

Figure 2. Mean ± SD vasodilation (cutaneous vascular conductance, %max) response to local heating protocol at the initial plateau and post-L-NAME plateau (panel A) and the NO-dependent dilation (panel B) in the control microdialysis site of women who had a healthy pregnancy (HC) and women who had gestational diabetes (GDM). GDM had attenuated endothelium-dependent (GDM: 67±7 vs. HC: 90±4%CVCmax; * p<0.001) and NO-dependent dilation (GDM: 54±7 vs. HC: 71±3%; * p=0.002). There were no group differences in the post-L-NAME plateau.

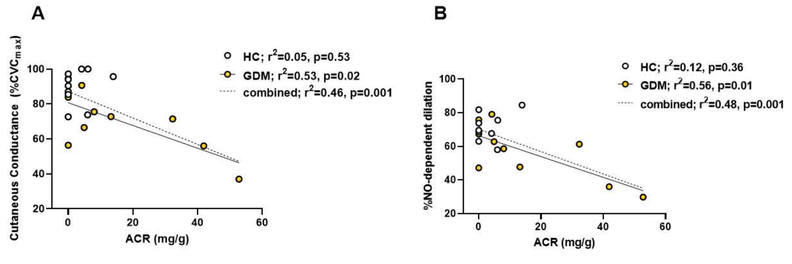

Figure 3. Relation between urine albumin:creatinine ratio (ACR, $mg \cdot g^{-1}$) and vasodilation (cutaneous vascular conductance, %max; panel A) and %NO-dependent dilation (panel B) in women with a history of healthy pregnancy (HC) and those with a history of gestational diabetes (GDM). Endothelium-dependent (r^2=0.53, p=0.02) and NO-dependent (r^2=0.56, p=0.01) dilation were related to urine ACR in GDM.

Results

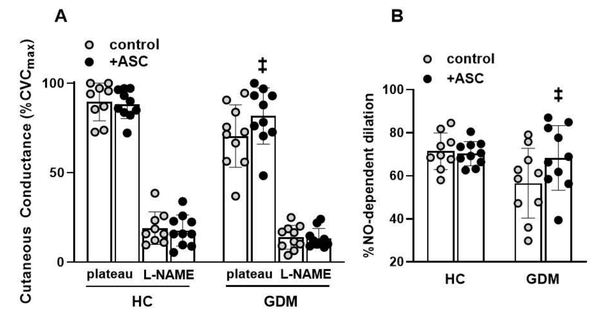

Figure 4. (A) Mean ± SD vasodilation (cutaneous vascular conductance, %max; panel A) and %NO-dependent dilation (panel B) response to local heating at the control and ascorbate treated (+ASC) microdialysis sites. HC, women with a history of healthy pregnancy; GDM, women with a history of gestational diabetes. Local ascorbate perfusion improved endothelium-dependent (82±5%CVCmax; ‡p=0.03 vs. control) and NO-dependent (68±5%; ‡p=0.02 vs. control) dilation in GDM but had no effect in HC (p>0.05).

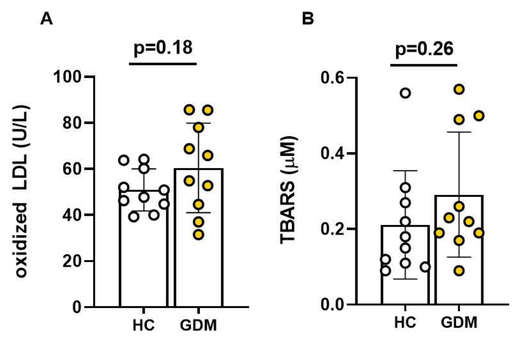

Figure 5. Mean± SD (A) oxidized LDL (U/L) and (B) Thiobarbituric acid reactive substances (TBARS, μM) in women who had a healthy pregnancy (HC) and those who had gestational diabetes (GDM). There were no differences in plasma oxidized LDL (GDM 60.5 vs. HC 50.9 U/L) or TBARS (GDM 0.3 vs. HC 0.2 μM) concentrations between groups.

Summary and Conclusions

- Women with a history of gestational diabetes had an attenuated endothelium-dependent response to local heating compared to women with a history of healthy pregnancy.
- Endothelium- and NO-dependent dilation assessed in the cutaneous microvasculature was related to urine ACR in women with a history of gestational diabetes.
- Local perfusion of ascorbate improved endothelium- and NO-dependent dilation in women with a history of gestational diabetes.
- These data suggest that oxidative stress contributes to microvascular endothelial dysfunction in women with a history of gestational diabetes.

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