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Black Women Have Evidence Of Cardiometabolic Risk And Damage To The Microvascular Glycocalyx 1 To 10 Years After Uncomplicated Pregnancy

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Introduction

- The endothelium is lined by a specialized layer of proteoglycans and glycoproteins linked to the plasma membrane known as the endothelial glycocalyx (Figure 1A).
- The glycocalyx has important vasoregulatory roles; e.g., growth factor binding, signal transduction, coagulation and permeability (Figure 1B).
- Dysfunction of the microvascular endothelial glycocalyx can disrupt normal microvascular permeability, nitric oxide-mediated vasodilation, and sequestration of proteins with heparan sulfate binding domains etc.

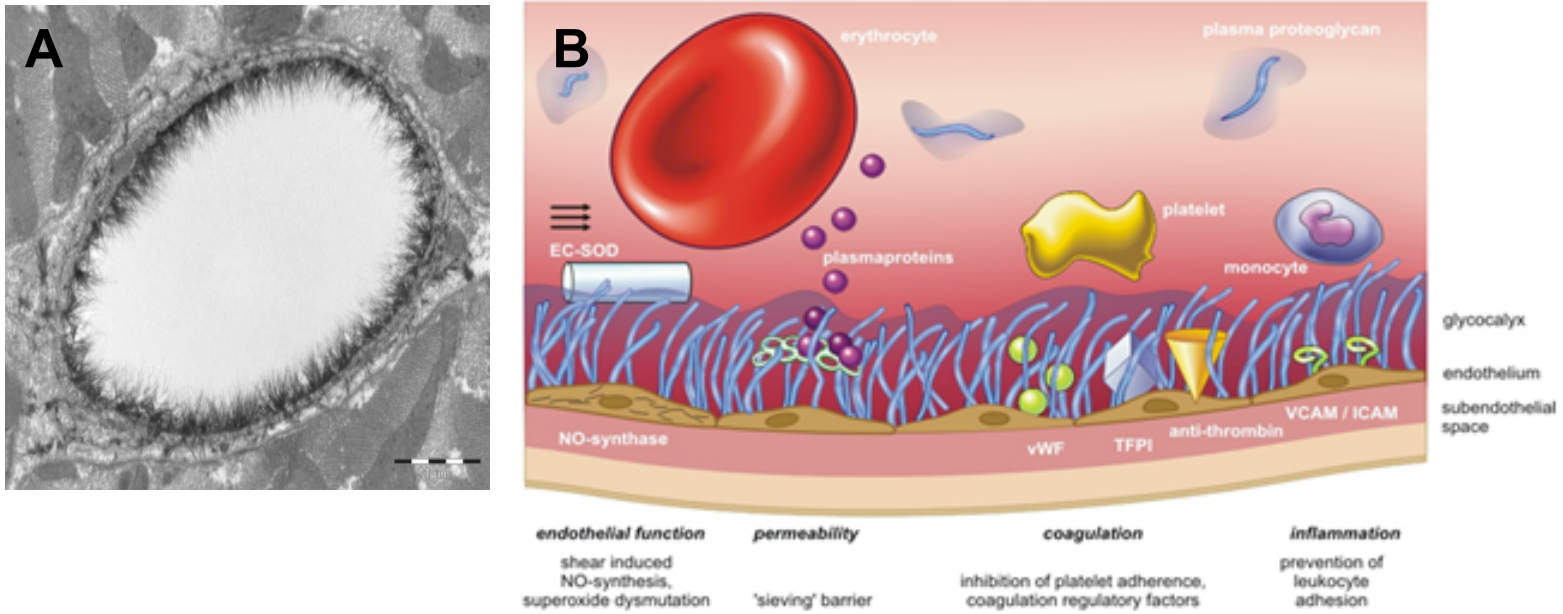


Figure 1: Glycocalyx

In both continuous and fenestrated microvessels, the endothelial glycocalyx (A) provides resistance to the transcapillary escape of water and macromolecules, acting as an integral component of the multilayered barrier provided by the walls of these microvessels (B).

Panel A courtesy of Bernard van den Berg.
Panel B Glycocheck BV.

Objective

Given the excess risk of adverse pregnancy outcomes (APO), chronic hypertension and CVD in black compared to white women, we hypothesized black women would evidence a higher cardiovascular risk profile, including altered structure/function of the microvasculature and its glycocalyx.

The objective of this study was to examine the sublingual microvasculature and glycocalyx and cardiometabolic risk markers in reproductive age black and white women after an uncomplicated index pregnancy

Methods

- 67 Black women and 167 White women recruited into the Strategically Focused Go Red For Women Research Network Study Women's Cardiovascular Health and Microvascular Mechanisms: Novel Insights from Pregnancy clinical project (n=36) and population project (n=198) with no complications (preeclampsia, gestation hypertension, preterm delivery, intrauterine growth restriction or gestational diabetes using their medical record) in the index pregnancy.
- Blood pressure was obtained during the study visit. Insulin and glucose analysis followed a standardized protocol in a core laboratory.
- Sidestream dark-field imaging of the sublingual microcirculation using Glycocheck software at either 1 or 8 years after the index pregnancy. Data generated included:

    1. Microvascular Density (total length of perfused microvessels / mm^2 surface area).
    2. Perfusion (RBC filling %)
    3. Median Diameter of the red cell column (size) of microvessels
    4. Penetration of RBCs into the glycocalyx (perfused boundary region, PBR)

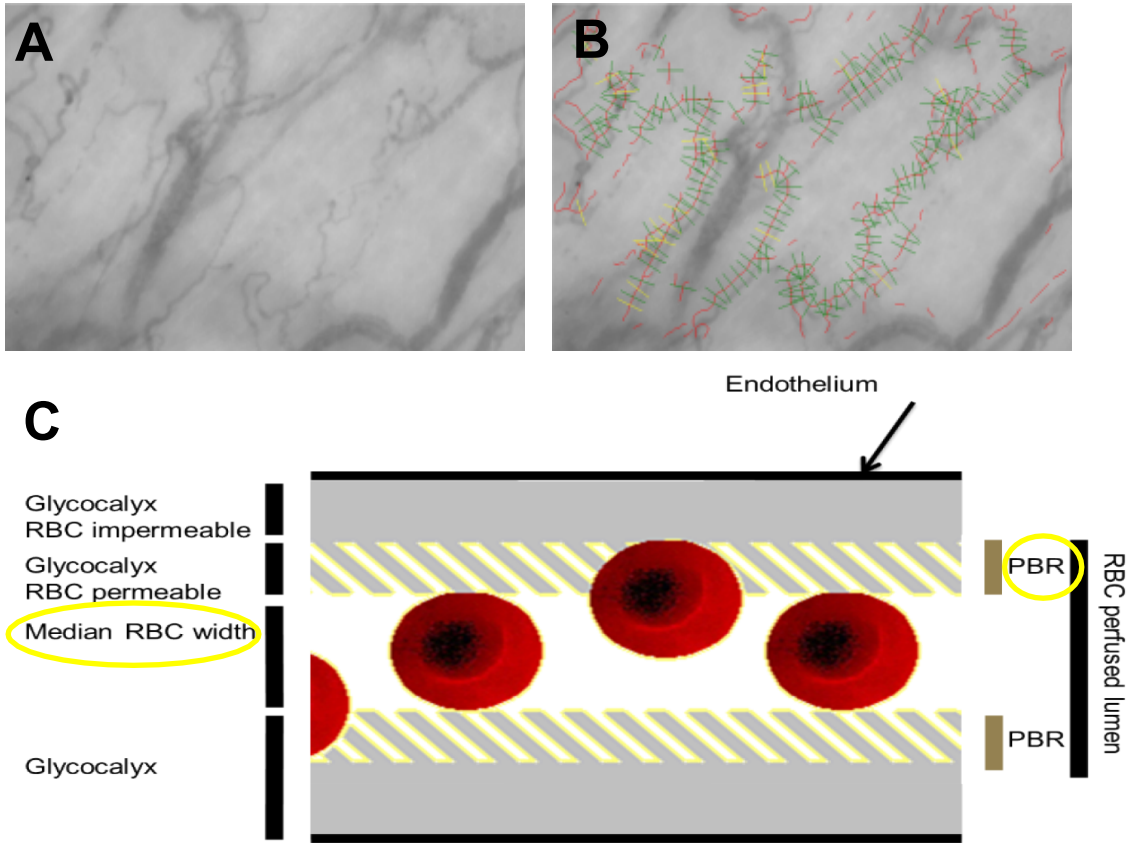


Figure 2. Schematic representation of glycocalyx measurements. Sidestream dark-field video image (**A**) with segments of 5-25 µm blood vessels identified (**B**). Short (10 µm) segments of microvessels are analyzed. Segments with adequate numbers of RBCs present (sufficient contrast) for glycocalyx analyses are indicated in green whereas segments that do not meet criteria for inclusion are marked yellow (B). Glycocalyx variables (median RBC column width and PBR), calculated by GlycoCheck software, are shown in **C**.

Results

Table 1. Clinical Data from Chart Review and Study Visit

Mean ± SD or %	Black N=67	White N=167	P=
Age at delivery of index pregnancy (yrs)	25 ±6	30±5	<0.001
Age at Follow-up (yrs)	34±6	38±6	0.001
Systolic BP study visit (mm Hg)	117±12	112±12	0.002
Diastolic BP study visit (mm Hg)	77±11	72±9	<0.001
Heart Rate study visit	75±9	72±10	0.015
Pre-pregnancy BMI (kg/m^2)	28±7	25±6	0.007
BMI at study visit (kg/m^2)	32±7	27±7	<0.001
Time to follow-up visit (yrs)	8.6±2.3	7.7±3.3	0.021
Time since last pregnancy (yrs)	5.4±3.4	5.0±3.2	0.23
Questionnaire Data at Study Visit			
Cigarette Smoking at Follow-up (%)	28%	14%	0.001*
Regular Cycling at study visit (%)	89%	76%	NS
Vitamin Use at study visit	36%	65%	0.001*
History Hypertension (self-report)	22%	7%	0.002*
History of an APO (self-report)	64%	43%	0.004
History of Asthma (self-report)	19%	8%	0.011*
History Diabetes (self-report)	4%	2%	NS

APO: adverse pregnancy outcome included preeclampsia, gestation hypertension, preterm delivery, intrauterine growth restriction or gestational diabetes.
Statistics were two sample Students t-test or Mann- Whitney on Rank Sums*

Results

Figure 3. Non-invasive Glycocalyx Analysis with Glycocheck

A. Penetration of red blood cells into the sublingual glycocalyx (PBR) is used to assess the barrier integrity of the glycocalyx. **Larger diameter microvessels (size 20-25 µm) have reduced barrier function (greater PBR) in black women compared to white women.**

B. Red blood cell filling percentage (the degree to which sublingual microvascular segments are occupied with RBCs), is a measure of perfusion in the sublingual microvasculature. **Perfusion was reduced in black women compared to white women (71% vs 73%).**

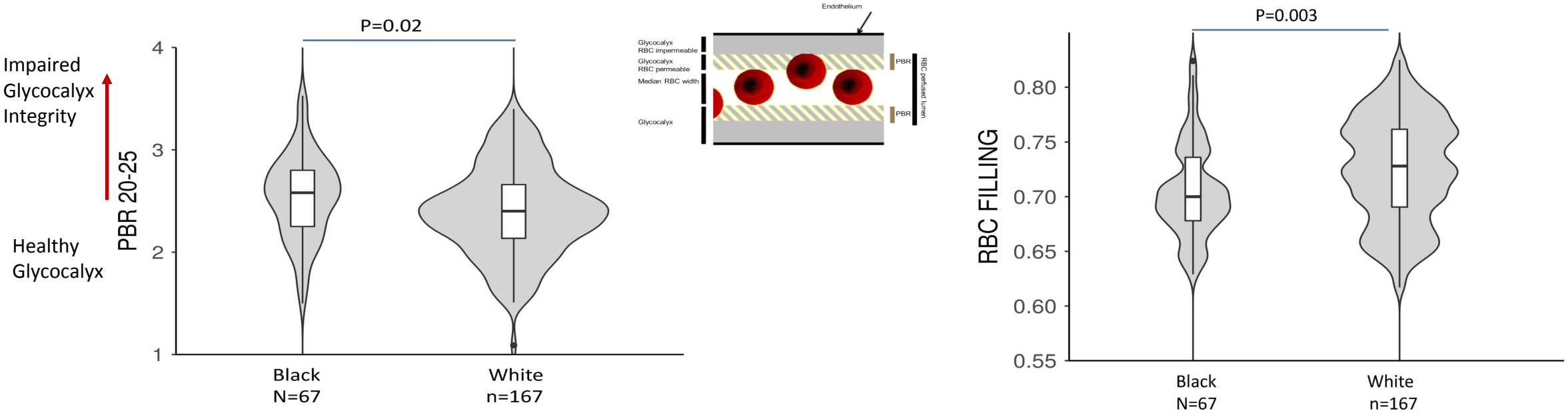
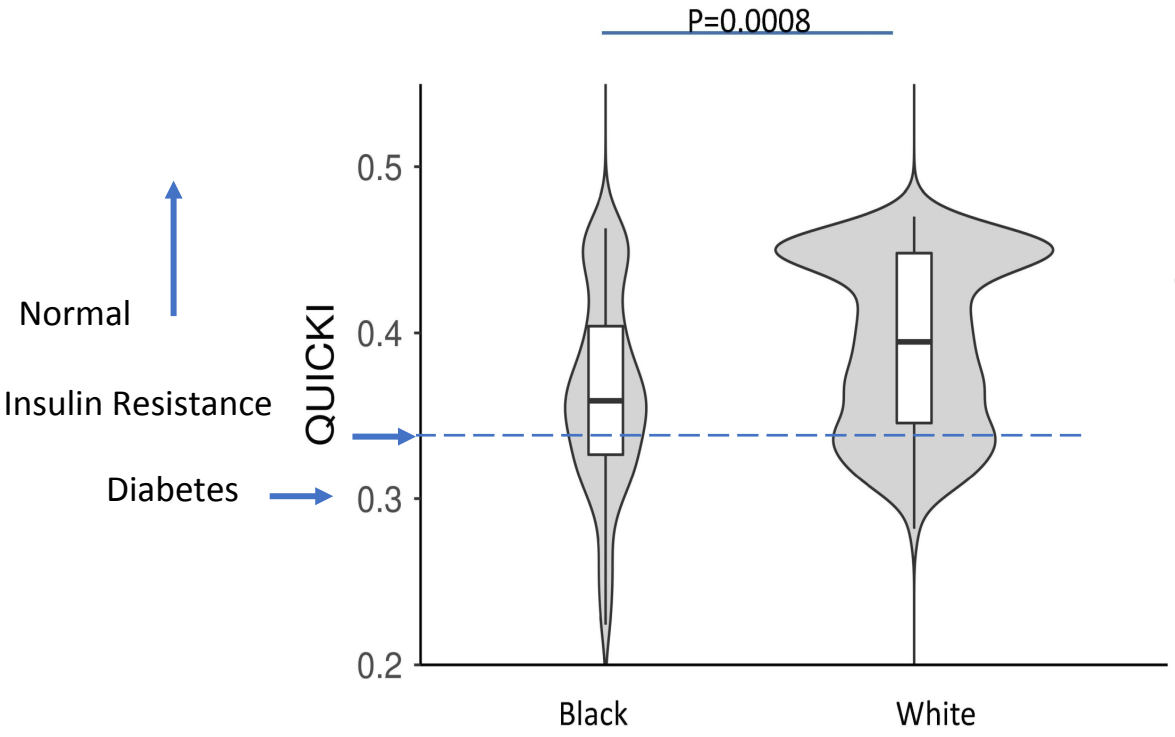


Table 2. GlycoCheck Parameter (Mean ± SD or %)	Black (N=67)	White (N=167)	P=
PBR 5-25 µm (penetration of RBCs into glycocalyx)	2.09±0.21	2.03±0.24	0.07
PBR 5-9 µm	1.12±0.10	1.11±0.01	0.40
PBR 10-19 µm	2.31±0.23	2.27±0.29	0.33
PBR 20-25 µm	2.54±0.41	2.40±0.43	0.02
Red Blood Cell Filling % (percent segments perfused)	70.5±4.2	72.5±4.8	0.003
RBC filling % (subset subjects with no history of APO)	70.7 3.5	72.7 4.7	0.05
Median diameter of segments 5-25 (microns)	9.06±1.25	8.96±0.97	0.51

Statistics were Students t-test

Results

Figure 4. Insulin Sensitivity



QUICKI was calculated from fasting glucose and insulin levels at the study visit.

QUICKI= 1/((log fasting insulin uU/mL)+ (log fasting glucose mg/dL)

≤ 0.34 is Threshold for Insulin Resistance
≤0.3 is associated with Diabetes

Table 3. Insulin Sensitivity Data (Mean ± SD or %)	Black N=67	White N=167	P=
Glucose (mg/dL)	93±27	89±16	0.189
Insulin (uU/mL)	17±36	7±9	0.002
HOMA Insulin Sensitivity	4.3± 10.9	1.4 ± 1.3	0.007
QUICKI Insulin Sensitivity	0.36 ± 0.06	0.39 ± 0.05	0.0008
Met Threshold for QUICKI Insulin Resistance	35%	26%	

Statistics were Students t-test

Results

- Microvascular glycocalyx barrier function and microvascular perfusion are reduced in black compared to white women, years after uncomplicated pregnancy. There was no difference in density or median vessel diameter between groups.

- Black women were significantly younger at index delivery and follow-up study visit; they also had higher BMI both pre-pregnancy and at follow-up study visit and higher fasting insulin and lower QUICKI (an index denoting greater insulin resistance).

- The association between race and glycocalyx measures remained after adjusting for time to follow-up visit, age and BMI, or after removing women with a self-reported history of any adverse pregnancy outcome.

Conclusions

Compared to white women, black women of reproductive age had evidence of microvascular structure/function deficits and insulin resistance, potentially related to cardiometabolic risk.

Informed by these racial differences, we plan to next examine similar data from women with adverse pregnancy outcomes recruited into the Go Red For Women Research Network Study, Women's Cardiovascular Health and Microvascular Mechanisms: Novel Insights from Pregnancy