Hyperglycemia Is the Main Mediator of Prediabetes- and Type 2 Diabetes–Associated Impairment of Microvascular Function: The Maastricht Study

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Prediabetes and type 2 diabetes (T2D) are associated with microvascular dysfunction (1), which may explain their increased risk of microvascular complications. However, mechanisms remain poorly understood. We investigated to what extent prediabetes- and T2D-associated microvascular dysfunction is potentially attributable to (composite indices of) hyperglycemia, insulin resistance, blood pressure, arterial stiffness, lipid profile, and/or low-grade inflammation.

In the Maastricht Study (2), a T2D-enriched population-based cohort study (n = 1,791, 49% women, aged 60 ± 8 years), we determined flicker light–induced retinal arteriolar %-dilation (1) using the Dynamic Vessel Analyzer, heat-induced skin %-hyperemia (1) using laser Doppler flowmetry, and diabetes status using the oral glucose tolerance test (normal glucose metabolism [NGM] [n = 1,040], prediabetes [n = 276], or T2D [n = 475]) (Table 1). Mediating effects of composite indices on prediabetes- and T2D-associated microvascular dysfunction were estimated by linear regression.

Age- and sex-adjusted analyses showed lower retinal arteriolar %-dilation in prediabetes (B = −0.16 [95% CI –0.53; 0.21]), with further deterioration in T2D (B = −0.83 [–1.15; –0.51]) versus NGM; P for trend <0.001. Skin %-hyperemia was lower in prediabetes (B = −80 [–198; 38]), with further deterioration in T2D (B = −210 [–309; –112]) versus NGM; P for trend <0.001. T2D-associated differences in retinal and skin microvascular function were explained mainly by hyperglycemia (mediating effect [bootstrapped 95% CI] 55.3% [20.4%; 91.3%] and 64.8% [6.2%; 122.4%], respectively). In contrast, insulin resistance, blood pressure, lipid profile, and low-grade inflammation did not significantly contribute. Patterns of mediation were qualitatively similar for prediabetes-associated microvascular dysfunction, with mediation effects of hyperglycemia of 69.2% [25.3%; 119.5%] and 47.5% [5.0%; 91.2%], respectively. Qualitatively similar patterns of mediation were found in additional analyses (available on request) in which we additionally adjusted for smoking, BMI, and (micro)vascular complications, used absolute retinal arteriolar diameter and skin blood flow as outcomes, investigated arterial stiffness as a potential mediator, or used a composite index of long-term hyperglycemic measures (glycated hemoglobin A_{1c} and skin autofluorescence).

These findings suggest that hyperglycemia itself, rather than the cardiovascular risk context associated with prediabetes and T2D, is the main contributor to both prediabetes- and T2D-associated retinal and skin microvascular dysfunction. This supports an early detrimental effect of hyperglycemia on the retinal and skin microvascular responses. Impairments in both these responses reflect decreased availability of nitric oxide and are likely a reflection of microvascular endothelial dysfunction, possibly in conjunction with neuronal dysfunction (3,4).

Our study had some limitations. First, data were cross-sectional; therefore, we cannot exclude reverse causality. Second, inflammatory markers drawn from venous plasma, compared with local

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Table 1—General characteristics and retinal and skin measures for the retinal study population according to glucose metabolism status

Characteristics	NGM (n = 1,040)	Prediabetes (n = 276)	T2D (n = 475)
Age (years)	58.0 ± 8.2	61.5 ± 7.2	62.9 ± 7.6
Women	596 (57.3)	130 (47.1)	147 (30.9)
Diabetes duration (years)*	—	—	6.0 (3.0–12.0)
Diabetes medication use			
Any type	—	—	359 (75.6)
Insulin	—	—	86 (18.1)
Oral glucose-lowering medication	—	—	338 (71.2)
BMI (kg/m^2)	25.5 ± 3.4	27.5 ± 4.0	29.5 ± 4.5
Waist circumference (cm)			
Men	96.3 ± 9.1	101.6 ± 9.4	106.7 ± 11.6
Women	85.6 ± 9.7	92.7 ± 12.1	100.9 ± 13.6
Smoking			
Never/former/current, *n*	409/502/116	75/161/33	136/264/62
Never/former/current, %	39.8/48.9/11.3	27.9/59.9/12.3	29.4/57.1/13.4
History of cardiovascular disease	116 (11.4)	30 (11.2)	118 (25.8)
eGFR (mL/min/1.73 m^2)	89.9 ± 13.0	87.2 ± 14.0	85.3 ± 17.2
eGFR <60 mL/min/1.73 m^2	18 (1.7)	10 (3.6)	45 (9.5)
(Micro)albuminuria†	47 (4.6)	15 (5.4)	77 (16.2)
Retinopathy	1 (0.1)	1 (0.4)	18 (3.9)
Composite indices of potential mediators‡			
Markers of hyperglycemia			
HbA_{1c} (%)‡	5.4 ± 0.4	5.7 ± 0.4	6.8 ± 0.9
HbA_{1c} (mmol/mol)	35.8 ± 3.7	38.4 ± 4.5	50.6 ± 9.9
Fasting glucose (mmol/L)‡	5.2 ± 0.4	5.9 ± 0.6	7.7 ± 1.7
2-h postload glucose (mmol/L)‡§	5.4 ± 1.1	8.2 ± 1.7	14.2 ± 3.9
Skin autofluorescence (AU)‡	2.3 ± 0.5	2.4 ± 0.5	2.6 ± 0.6
Markers of blood pressure			
Ambulatory 24-h SBP (mmHg)‡	117.3 ± 11.1	120.1 ± 11.9	122.4 ± 11.7
Ambulatory 24-h DBP (mmHg)‡	73.6 ± 7.2	74.5 ± 7.3	73.0 ± 7.0
Antihypertensive medication use‡	226 (21.7)	113 (40.9)	333 (70.1)
Markers of lipid profile			
Total-to-HDL cholesterol ratio	3.5 ± 1.1	3.9 ± 1.3	3.7 ± 1.1
LDL cholesterol (mmol/L)	3.3 ± 0.9	3.3 ± 1.1	2.4 ± 0.9
Total cholesterol (mmol/L)‡	5.6 ± 1.0	5.5 ± 1.2	4.4 ± 1.1
HDL cholesterol (mmol/L)‡	1.7 ± 0.5	1.5 ± 0.4	1.3 ± 0.4
Triglycerides (mmol/L)‡	1.2 ± 0.6	1.6 ± 1.0	1.8 ± 0.9
Lipid-modifying medication use‡	178 (17.1)	93 (33.7)	350 (73.7)
Markers of insulin resistance			
HOMA2-$IR_{Insulin}$ (AU)‡	1.3 ± 0.7	1.9 ± 1.1	2.4 ± 1.4
HOMA2-$IR_{C\text{-}peptide}$ (AU)‡	1.3 ± 0.5	1.7 ± 0.7	2.1 ± 0.9
Markers of low-grade inflammation			
hs-CRP (mg/L)‡	1.1 (0.6–2.2)	1.8 (0.8–3.5)	1.5 (0.7–3.3)
Serum amyloid A (mg/L)‡	3.0 (1.9–5.0)	3.6 (2.3–5.7)	3.5 (2.2–6.0)
Soluble ICAM-1 (ng/mL)‡	338.6 ± 80.2	365.8 ± 103.2	383.8 ± 115.9
Interleukin-6 (pg/mL)‡	0.5 (0.4–0.8)	0.6 (0.4–0.9)	0.8 (0.6–1.1)
Interleukin-8 (pg/mL)‡	3.7 (3.0–4.6)	4.3 (3.3–5.3)	4.8 (4.0–6.1)
Tumor necrosis factor-α (pg/mL)‡	2.1 (1.8–2.4)	2.2 (1.9–2.6)	2.5 (2.1–2.9)
Markers of arterial stiffness			
Carotid-femoral pulse wave velocity (m/s)‡	8.4 ± 1.7	9.2 ± 2.1	9.9 ± 2.3
Carotid distensibility coefficient (10^3/kPa)‡	15.1 ± 5.2	13.7 ± 4.8	13.3 ± 4.9
Microvascular outcomes			
Baseline arteriolar diameter (MU)	115.3 ± 15.3	114.8 ± 15.9	116.0 ± 15.9
Arteriolar average dilation (%)			
Mean ± SD	3.4 ± 2.8	3.1 ± 2.8	2.4 ± 2.7
Median [interquartile range]	3.0 (1.1–5.3)	2.8 (0.8–5.0)	1.6 (0.4–3.9)
Baseline skin blood flow (PU)‖	10.8 ± 6.4	11.7 ± 7.2	11.0 ± 5.7
Skin hyperemic response (%)‖			
Mean ± SD	1,252.6 ± 813.4	1,107.4 ± 710.8	941.7 ± 701.1
Median [interquartile range]	1,104.0 (668.7–1,656.9)	1,006.9 (604.9–1,536.9)	821.2 (479.0–1,209.8)

Data are reported as mean ± SD, median [interquartile range], or number (%) as appropriate. AU, arbitrary units; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HOMA2-IR, HOMA of insulin resistance; ICAM, intercellular adhesion molecule; MU, measurement units; PU, perfusion units; SBP, systolic blood pressure. *Available in 313 individuals with type 2 diabetes. †(Micro)albuminuria was defined as a urinary albumin excretion of >30 mg per 24 h. ‡Indicates that the individual marker is part of the corresponding composite index. §Available in 389 individuals with T2D, as the oral glucose tolerance test was not performed in individuals who were on insulin treatment. ‖Heat-induced skin hyperemia measures were available in a different subset of n = 1,281.

measurement, may have underestimated the mediation effect of the inflammation index (5). Last, generalizability of the results should be interpreted with caution, as in our cohort individuals with T2D were generally well controlled for their diabetes and cardiovascular risk factors. Hence, our population may be representative for a population with access to quality diabetes care. As a consequence, we cannot exclude the possibility that mediation effects of the other composite indices exist in populations with greater differences in cardiovascular risk profile between individuals without and with diabetes.

We conclude that hyperglycemia is the main contributor to prediabetes- and T2D-associated retinal and skin microvascular dysfunction. Longitudinal studies should assess whether hyperglycemia, via retinal and skin microvascular (endothelial) dysfunction, contributes to the development of microvascular complications in prediabetes and T2D.

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