Renal Hyperfiltration Is a Determinant of Endothelial Function Responses to Cyclooxygenase 2 Inhibition in Type 1 Diabetes

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OBJECTIVE — Our aim was to examine the effect of cyclooxygenase 2 (COX2) inhibition on endothelial function in subjects with type 1 diabetes analyzed on the basis of renal filtration status.

RESEARCH DESIGN AND METHODS — Flow-mediated dilation (FMD) was determined in type 1 diabetic subjects and hyperfiltration (glomerular filtration rate ≥135 ml/min/1.73 m^2, $n = 13$) or normofiltration (glomerular filtration rate ≥135 ml/min/1.73 m^2, $n = 11$). Studies were performed before and after celecoxib (200 mg daily for 14 days) during euglycemia and hyperglycemia.

RESULTS — Baseline parameters were similar in the two groups. Pretreatment, FMD was augmented in normofiltering versus hyperfiltering subjects during clamped euglycemia (10.2 ± 5.3% vs. 5.9 ± 2.3%, $P = 0.003$). COX2 inhibition suppressed FMD in normofiltering (10.2 ± 5.3% to 5.8 ± 3.4%, $P = 0.006$) versus hyperfiltering subjects (ANOVA interaction, $P = 0.003$).

CONCLUSIONS — Systemic hemodynamic function, including the response to COX2 inhibition, is related to filtration status in diabetic subjects and may reflect general endothelial dysfunction.

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Renal hyperfiltration is associated with an increased risk of progression to diabetic nephropathy in many, but not all, studies (1). Diabetic hyperfiltration may in part be due to cyclooxygenase 2 (COX2) upregulation (2,3). We have previously identified a cohort of subjects with uncomplicated type 1 diabetes who exhibit hyperfiltration (glomerular filtration rate [GFR] ≥135 ml/min/1.73 m^2) or normofiltration (GFR <135 ml/min/1.73 m^2) during clamped euglycemia (4). In hyperfiltering subjects, COX2 inhibition reduces GFR, whereas in subjects with normofiltration, COX2 inhibition is associated with an opposite GFR rise and an exaggerated suppression of vasodilatory prostaglandins (4). Together with previous observations (4–6), these findings suggest that hyperfiltering and normofiltering individuals are physiologically distinct.

Previous studies have suggested that early type 1 diabetes is characterized by a state of generalized vasodilation due to nitric oxide upregulation (7). The role of COX2 in the systemic vasculature in humans with early type 1 diabetes is, however, incompletely understood (8–11). Accordingly, our goal was to study the effect of COX2 inhibition on endothelial function in diabetic subjects with hyperfiltration or normofiltration. Our hypothesis was that renal hemodynamic differences would also be reflected in the systemic circulation.

RESEARCH DESIGN AND METHODS

— Recruitment, study protocols, and renal hemodynamic data from a subset of this cohort have been previously described (supplementary Table A, available in an online appendix at http://care.diabetesjournals.org/cgi/content/full/dc09-2340/DC1) (4). Experiments were carried out on 2 consecutive days before (clamped euglycemia [4–6 mmol/l] and hyperglycemia [9–11 mmol/l]) and repeated after 14 days of COX2 inhibition (celecoxib, 200 mg daily) (4). Circulating insulin levels were measured on each study day (4).

Endothelial function was determined by recording diameter changes in the brachial artery in response to increased blood flow generated during reactive hyperemia (flow-mediated dilation [FMD]) and glyceryl trinitrate-induced dilation (GTN). Longitudinal electrocardiograph-gated end-diastolic images were acquired and the arterial diameter was determined using automatic edge-detection software (Vascular Tools, Coralville, IA). The right brachial artery was scanned 2–5 cm above the antecubital fossa using high-resolution B-mode vascular ultrasound (Vivid 7; GE/Vingmed, Milwaukee, WI). After baseline images were recorded, the blood pressure cuff was inflated around the forearm distal to the elbow to >200 mmHg for 5 min. After deflation, the change in vessel diameter in response to reactive hyperemia (endothelium-dependent dilation) was measured for a further 5 min. GTN (400 μg) was then administered sublingually, and the changes were measured over a further 5 min (endothelium-independent dilation). FMD and

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Table 1—*Effects of COX2 inhibition and hyperglycemia in type 1 diabetes*

	Before COX2 inhibition				After COX2 inhibition			
	Hyperfiltration group		Normofiltration group		Hyperfiltration group		Normofiltration group	
	Euglycemia	Hyperglycemia	Euglycemia	Hyperglycemia	Euglycemia	Hyperglycemia	Euglycemia	Hyperglycemia
Biochemistry								
Plasma insulin (pmol/l)	87 ± 51	101 ± 52	98 ± 99	88 ± 100	103 ± 69	105 ± 74	83 ± 49	77 ± 73
Blood pressure								
Systolic blood pressure	114 ± 10	113 ± 8	117 ± 10	116 ± 13	112 ± 10	116 ± 11	119 ± 9	120 ± 9
Diastolic blood pressure	65 ± 9	62 ± 5	60 ± 5	61 ± 4	62 ± 9	65 ± 7	65 ± 7	66 ± 9
Mean arterial pressure	83 ± 9	79 ± 6	79 ± 7	79 ± 8	79 ± 9	82 ± 8	83 ± 8	84 ± 8
Heart rate (bpm)	70 ± 11	68 ± 11	61 ± 13	61 ± 10	67 ± 12	64 ± 13	62 ± 11	61 ± 12
Endothelial function								
FMD (% change)	5.9 ± 2.3	7.6 ± 2.9	10.2 ± 5.3*	8.3 ± 4.23	8.3 ± 3.9	8.2 ± 2.54	5.8 ± 3.4†‡	8.1 ± 3.2
GTN (% change)	13.0 ± 3.2	14.2 ± 3.1	11.0 ± 3.7	13.7 ± 7.9	12.1 ± 4.2	14.7 ± 4.9	11.1 ± 4.7	13.9 ± 7.0

Data are means ± SD. Clamped euglycemia = 4–6 mmol/l; clamped hyperglycemia = 9–11 mmol/l. *P = 0.003 for FMD during clamped euglycemia in the hyperfiltering group vs. the normofiltering group. †P = 0.006 for the effect of COX2 inhibition on FMD in the normofiltering group during clamped euglycemia. ‡P = 0.003 for the change in FMD in hyperfilterers vs. normofilterers in response to COX2 inhibition during clamped euglycemia.

GTN % changes were defined as the maximal percentage changes in vessel diameter after reactive hyperemia and administration of GTN, respectively, as we have previously described (12). The variability for repeated measurements of arterial diameters at flow-mediated vasodilation was 0.01 ± 0.0.005 mm (absolute diameter) or 0.26 ± 0.01% (% absolute value of brachial artery at FMD), which is similar to previous reports (13,14).

The data were analyzed based on renal filtration status. Between-group baseline comparisons were made using parametric methods (unpaired *t* test). Between-group and within-group differences in hemodynamic responses were determined by repeated-measures ANOVA. All statistical analyses (means ± SD) were performed using SPSS (version 14.0).

RESULTS — Baseline characteristics were similar in the two groups (supplementary Table B). Renal hemodynamic function tests revealed expected differences in GFR. Within-group blood pressure changes were not significant, nor were between-group blood pressure differences (Table 1). Insulin concentrations were similar throughout the study.

Before COX2 inhibition during clamped euglycemia, FMD was higher in normofiltering versus hyperfiltering subjects (P = 0.003, Table 1). In response to COX2 inhibition during clamped euglycemia, FMD declined in normofiltering subjects (P = 0.006; ANOVA interaction term for between-group effect, P = 0.003). Differences were abolished by hyperglycemia. GTN responsiveness was similar in the two groups throughout the study.

CONCLUSIONS — While selective COX2 inhibition reduces hyperfiltration, the effect on FMD in humans with type 1 diabetes was until now unknown. Our first major finding was that during clamped euglycemia, hyperfiltering subjects exhibited evidence of impaired FMD compared with normofilterers. Our results suggest that hyperfiltering type 1 diabetic subjects may be additionally at risk in that they demonstrated an impaired ability to induce arterial vasodilation after an ischemic stimulus compared with individuals with normofiltration.

Our second major observation was that in contrast with hyperfiltering subjects, COX2 inhibition suppressed FMD during clamped euglycemia in normofiltering subjects, without impairing GTN responsiveness. These findings in FMD and GTN responsiveness suggest that the observed differences may have been due to endothelial cell rather than vascular smooth muscle functional effects. While COX2 inhibition may reduce renal hyperfiltration in subjects with GFR ≥135 ml/min/1.73 m^2) (4), we have previously shown in normofiltering subjects an exaggerated suppression of vasodilatory prostaglandins and renal vasoconstriction (4), and in this study, we show impaired FMD.

Our study has limitations. We minimized the effect of the small sample size by using a homogeneous study cohort. Second, although our study offers physiologic insights into diabetic vascular dysfunction, the findings were significant during euglycemia and therefore have limited clinical applications in subjects who are frequently exposed to ambient hyperglycemia.

In conclusion, systemic hemodynamic function, including the response to COX2 inhibition, is related to filtration status in diabetic subjects and may reflect general endothelial dysfunction.

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