Renal hemodynamic effect of cyclooxygenase 2 inhibition in young men and women with uncomplicated type 1 diabetes mellitus

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1Division of Nephrology, Toronto General Hospital, Divisions of 2Endocrinology and 3Cardiology, Hospital for Sick Children, University of Toronto, Toronto; and 4Department of Cellular and Molecular Medicine, Kidney Research Centre, Faculty of Medicine, University of Ottawa, Ottawa, Ontario, Canada

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Cherney DZ, Scholey JW, Nasrallah R, Dekker MG, Slorach C, Bradley TJ, Hébert RL, Sochett EB, Miller JA. Renal hemodynamic effect of cyclooxygenase 2 inhibition in young men and women with uncomplicated type 1 diabetes mellitus. Am J Physiol Renal Physiol 294: F1336–F1341, 2008. First published January 9, 2008; doi:10.1152/ajprenal.00574.2007.—In experimental studies, cyclooxygenase 2 (COX2)-derived vasodilatory prostaglandins play a more prominent role in arterial vasoregulation in females. The gender-dependent effect of COX2 modulation in humans with type 1 diabetes mellitus (DM) is unknown. Accordingly, we examined the renal hemodynamic role of prostaglandins by assessing the response to COX2 inhibition in young men and women with type 1 DM. We also used a graded ANG II infusion to determine whether gender-based differences were mediated by effects of COX2 inhibition on the renin angiotensin system (RAS). We hypothesized that COX2 inhibition would be associated with preferential vasoconstriction in women and would augment their response to ANG II. Baseline renal function and the response to an ANG II infusion were assessed during clamped euglycemia, and again after COX2 inhibition (200 mg celecoxib daily for 14 days) in 12 men and 9 women after 1 wk on a controlled protein and sodium diet. COX2 inhibition was associated with increases in filtration fraction (P = 0.045) and renal vascular resistance and a decline in renal blood flow (P = 0.04) in women compared with men. Before COX2 inhibition, women exhibited a decline in glomerular filtration rate in response to ANG II. COX2 inhibition abolished this effect, whereas the response was not altered in men. In summary, COX2 inhibition was associated with hemodynamic effects that differed based on gender. The ANG II response suggests that with uncomplicated type 1 DM, prostaglandins may contribute to RAS-mediated gender differences. Our results are consistent with experimental data suggesting augmented female prostanoid dependence.

RENAL HEMODYNAMIC ABNORMALITIES associated with diabetes mellitus (DM) (26, 30) include increased intraglomerular capillary pressure and hyperfiltration (2, 10, 12). The cyclooxygenase 2 (COX2) pathway has been implicated in the pathogenesis of these abnormalities. In experimental models of DM, renal COX2 expression is augmented in the presence of hyperglycemia, leading to the increased production of vasodilatory prostaglandins. The possible role of COX2 in the mediation of the characteristic renal hemodynamic abnormalities is underscored by the finding that COX2 inhibition resulted in an amelioration of the hyperfiltration state (21) and an alleviation of proteinuria (34, 40) in animal models of DM. We also recently demonstrated that, in the same cohort of subjects with type 1 DM (8), COX2 inhibition reduces, but does not correct, hyperfiltration in subjects whose baseline glomerular filtration rate (GFR) is ≥135 ml·min⁻¹·1.73 m⁻². COX2 inhibition also mediates important hemodynamic effects through blockade of the intrarenal renin angiotensin system (RAS) (5, 7, 39, 42). COX2-RAS interactions are of particular importance in the context of DM, since both of these pathways may be activated in this condition (2, 15, 21).

In experimental studies, COX2-derived vasodilatory prostaglandins play a more prominent role in arterial vasoregulation in females that female animals exhibit higher plasma prostanoid levels and are more sensitive to their inhibition compared with males (3, 13, 33), an effect that may be estrogen mediated (3, 13, 18, 36). Whether or not this augmented dependence exists in women with type 1 DM is currently not known. Previous studies from this laboratory (9, 27, 28) have defined gender differences in RAS function. Accordingly, our goals for the current study were to determine if there are gender differences in the renal and peripheral hemodynamic response to COX2 inhibition, and in intrarenal COX2-RAS interactions.

We therefore compared the renal hemodynamic responses to COX2 inhibition during clamped euglycemic conditions in men and women with uncomplicated type 1 DM. We used an ANG II infusion to probe the intrarenal RAS before and after COX2 inhibition. Based on previous observations in animal models (3, 33), we hypothesized that women would experience an exaggerated renal hemodynamic response to COX2 inhibition compared with men, suggesting a greater dependence on COX2 for the maintenance of normal renal function. We further hypothesized that COX2 inhibition would augment the effect of ANG II in women (27) because of increased dependence on vasodilatory prostaglandins. We studied subjects without clinical evidence of diabetic nephropathy during clamped euglycemia to remove any confounding effect of proteinuria, renal functional impairment, or hyperglycemia (9).

MATERIALS AND METHODS

Subjects. Participants who fulfilled the following inclusion criteria were asked to participate: duration of type 1 DM >5 yr, age ≥16 yr, Tanner Stage 4–5 puberty, normal albuminuria [albumin excretion rate (AER) <20 μg/min on 2/3 overnight urine collections obtained during the month before study], normal clinic blood pressure, no albuminuria (34, 40) in animal models of DM. We also recently demonstrated that, in the same cohort of subjects with type 1 DM (8), COX2 inhibition reduces, but does not correct, hyperfiltration in subjects whose baseline glomerular filtration rate (GFR) is ≥135 ml·min⁻¹·1.73 m⁻². COX2 inhibition also mediates important hemodynamic effects through blockade of the intrarenal renin angiotensin system (RAS) (5, 7, 39, 42). COX2-RAS interactions are of particular importance in the context of DM, since both of these pathways may be activated in this condition (2, 15, 21).

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DIABETES, GENDER, RENAL HEMODYNAMICS, CYCLOOXYGENASE 2 INHIBITION

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microvascular disease, and absence of chronic illness other than treated hypothyroidism or mild asthma. The Research Ethics Board at the Hospital for Sick Children (Toronto, Canada) approved the protocol. All patients and/or their parents gave informed consent. Twenty-one adolescents and young adults with type 1 DM were eligible to participate.

Protocol and evaluations. The pre-study dietary preparation of our subjects has been published previously (8). Females were studied during the low-estrogen follicular phase of the menstrual cycle (8). Ambulatory blood pressure monitoring (ABPM) was performed in all subjects 1 day before admission to the hospital, as previously described in other studies from this laboratory (29). ABPM was performed one time before COX2 inhibition and again after 14 days of COX2 inhibition before readmission to the hospital.

Euglycemic (blood glucose 4–6 mmol/l) conditions were maintained for ~10 h preceding and during all investigations by a modified glucose clamp technique, as described previously (29). After their baseline study was complete, subjects were prescribed COX2 inhibition (200 mg celecoxib orally/day) for 14 days and were then similarly studied.

Subjects were admitted to the Clinical Investigation Unit at the Hospital for Sick Children the evening before each day of the study, and the renal hemodynamic function studies were performed the following morning, as described previously (8, 29). In brief, after blood for inulin and paraaminohippurate (PAH) blank was collected, a priming infusion containing 25% inulin (60 mg/kg) and 20% PAH (8 mg/kg) was administered. Thereafter, inulin and PAH were infused continuously at a rate calculated to maintain their respective plasma concentrations constant at 20 and 1.5 mg/dl. Subjects remained supine at all times. After a 90-min equilibration period, blood was collected for inulin, PAH, and hemocrit (Hct). Blood was further collected every 30 min for 60 min, and GFR and effective renal plasma flow (ERPF) were estimated by steady-state infusion of inulin and PAH according to the calculation method described by Schnurr et al. (35).

A solution of ANG II (51.2 μg/vial; Clinalfa, Laufenlingen, Switzerland) was prepared by dissolving the diluent in normal saline to produce a concentration of 100 μg/ml. Normal saline (22 ml) was then added to 0.22 ml ANG II solution to produce a concentration of 400 ng/ml. ANG II was infused at two doses, 1 and 3 ng/kg·min⁻¹, for 30 min each. Subjects remained supine at all times. Blood was collected one time during each ANG II infusion period for Hct, inulin, and PAH. Mean arterial pressure (MAP) was measured at the midpoint of each infusion. A further collection of blood was obtained at the end of the ANG II infusion, after a 30-min recovery period. The graded ANG II infusion was performed before and again after 14 days of COX2 inhibition.

Sample collection and analytical methods. Blood samples collected for inulin and PAH determinations were immediately centrifuged at 3,000 revolutions/min for 10 min at 4°C. Plasma was separated, placed on ice, and then stored at −70°C before the assay. Inulin and PAH were measured in serum by colorimetric assays using anthrone and N-(1-naphthyl)ethylenediamine, respectively. The mean of two baseline clearance periods represent GFR and ERPF, expressed per 1.73 m². Filtration fraction (FF) was determined as the ratio of GFR to ERPF. Renal blood flow (RBF) was calculated by dividing the ERPF by (1 − Hct). Renal vascular resistance (RVR) was derived by dividing the MAP by the RBF. All renal hemodynamic measurements were adjusted for body surface area. We measured circulating ANG II, renin, and aldosterone and urinary prostanooids as described previously (8).

Urineary AER was determined from three timed overnight urine collections. Urinary albumin concentration was determined by immunoturbidimetry (44). HbA1C was measured by high-performance liquid chromatography.

Statistical analysis. The data were analyzed on the basis of gender. Results are presented as means ± SE. Between-group comparisons of all parameters at baseline were made using parametric methods (unpaired t-test). Within-subject and between-group differences in the response to COX2 inhibition and ANG II were determined by repeated-measures ANOVA. All statistical analyses were performed using the statistical package SPSS (SPSS for graduate students, version 14.0).

RESULTS

Baseline characteristics. Twelve male and nine female subjects fulfilled the criteria for the study. At baseline, the two groups were similar in age, DM duration, body mass index, body surface area, AER, and HbA1C (Table 1). Age ranges were 16.2−23.3 yr in men and 16.2−21.8 yr in women. No differences in renal hemodynamic parameters or humoral RAS mediators (Table 2) were present at baseline. In men, ABPM revealed daytime, nighttime, and 24-h systolic blood pressures of 124 ± 3 114 ± 2, and 120 ± 2, respectively. In women, these values were lower (114 ± 2, 106 ± 2, and 112 ± 2 mmHg, P < 0.05). Diastolic daytime, nighttime, and 24-h blood pressures in men (69 ± 2, 60 ± 1, and 66 ± 1 mmHg, respectively) were similar to those in women (69 ± 2, 62 ± 1, and 67 ± 2 mmHg, respectively). Baseline renal hemodynamic function was similar in men and women (Table 2).

Response to COX2 inhibition. After COX2 inhibition, daytime systolic pressure in women rose from 114 ± 1 to 121 ± 4 mmHg (P < 0.05), whereas ABPM diastolic blood pressures did not change in either group and systolic pressures remained stable in men (data not shown). Nighttime and 24-h blood pressure also rose in women (106 ± 2 to 111 ± 4 and 112 ± 2 to 114 ± 2 mmHg), but these changes were not significant.

Women exhibited a rise in FF after COX2 inhibition (P = 0.045) (Table 2, Fig. 1), a result that was not seen in men (between-group FF difference, P = 0.019). The between-group changes in ERPF (P = 0.023) and RBF (P = 0.025) were also significantly different, with a fall in these parameters in women compared with men (Table 2).

Response to ANG II before and after COX2 inhibition. Before COX2 inhibition, women exhibited a decline in GFR that was significantly different compared with men at the 1 ng·kg⁻¹·min⁻¹ infusion level (P = 0.002) and the 3 ng·kg⁻¹·min⁻¹ level (P = 0.006) (Figs. 2 and 3 and Tables 3 and 4). The ANG II-induced rise in RVR was also significantly greater in women compared with men (P = 0.018). COX2 inhibition abolished the gender-based differences in the renal response to ANG II so that GFR was maintained during the ANG II infusion in women after COX2 inhibition. Men exhibited no significant change in GFR in response to ANG II before or after COX2 inhibition.

Table 1. Baseline characteristics by gender

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Men (n = 12)</th>
<th>Women (n = 9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperfilterers/normofilterers</td>
<td>6/6</td>
<td>3/6</td>
</tr>
<tr>
<td>Age, yr</td>
<td>20±1</td>
<td>19±1</td>
</tr>
<tr>
<td>Body surface area, kg/m²</td>
<td>1.98±0.04</td>
<td>1.83±0.07</td>
</tr>
<tr>
<td>Hemoglobin A1C</td>
<td>0.084±0.004</td>
<td>0.084±0.006</td>
</tr>
<tr>
<td>Diabetes duration, yr</td>
<td>15±3</td>
<td>15±3</td>
</tr>
<tr>
<td>Albumin excretion rate, mg/day</td>
<td>5.1±1.0</td>
<td>4.2±1.0</td>
</tr>
<tr>
<td>Sodium intake, mmol/24 h</td>
<td>220±17</td>
<td>174±12</td>
</tr>
<tr>
<td>Protein intake, g/kg</td>
<td>1.1±0.2</td>
<td>0.9±0.3</td>
</tr>
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</table>

Values are means ± SE; n, no. of subjects.
levels in men. In women, COX2 inhibition was associated with significant declines in PGE (0.06 for PGD and PGI). ERPF, effective renal plasma flow (ml·min⁻¹·1.73 m⁻²); FF, filtration fraction; RBF, renal blood flow (ml·min⁻¹·1.73 m⁻²); RVR, renal vascular resistance (mmHg·min⁻¹·l⁻¹). *The change in ERPF, FF, and RBF in response to COX-2 inhibition in women vs. men, P < 0.025. †The change in FF and RBF in women in response to COX-2 inhibition, P = 0.045.

Impact of COX2 inhibition on humoral RAS mediators and prostaglandin metabolites. COX2 inhibition was associated with numerical reductions in RAS mediators in both groups, although these changes were not statistically significant (Tables 3 and 4). By enzyme-linked immunosorbent assay, COX2 inhibition was associated with significant decreases in PGE [1.9 ± 0.3 decrease to 1.3 ± 0.3 pg/l, P = not significant (NS)] and PGI (0.8 ± 0.1 decrease to 0.6 ± 0.1 pg/l, P = NS) and thromboxane B2 (TXB2) metabolites (0.8 ± 0.1 decrease to 0.4 ± 0.2 pg/l, P = NS). With the use of mass spectrometry, at baseline, PGE levels were higher in men than women (Table 5), whereas levels of other prostanoids were similar. COX2 inhibition was associated with significant declines in PGE levels in men. In women, COX2 inhibition was associated with numerical, nonsignificant declines in PGE, PGD, and PGI (P = 0.06 for PGD and PGI).

DISCUSSION

Experimental models have suggested that females are more dependent on vasodilatory prostaglandins to maintain normal renal hemodynamic function and blood pressure, and to avoid vasoconstriction compared with males (3, 13, 33). This increased effect of vasodilatory prostaglandins in women may be estrogen mediated (3, 13, 18, 36). Whether this augmented effect of selective COX2 inhibition on renal hemodynamic function exists in women with type 1 DM is unknown. Accordingly, we studied the hemodynamic response to COX2 inhibition in a well-characterized cohort of young women with uncomplicated type 1 DM compared with a similar group of young men (4, 11, 17, 23, 31, 32). In a second set of experiments, we probed the effect of COX2 inhibition on intrarenal RAS activity with an ANG II infusion. Our major findings were that: 1) COX2 inhibition resulted in a significant increase in FF and declines in ERPF and RBF in women compared with men. 2) COX2 inhibition abolished the ANG II-mediated decline in GFR in women, resulting in a pattern similar to the response in men.

COX2 is constitutively expressed in the kidney and undergoes inducible expression in inflammatory states (16, 25). In animal models of DM, augmented COX2 activity has been associated with renal hyperfiltration (21, 22). Conversely, COX2 inhibition diminishes intraglomerular hypertension in experimental models through the blockade of vasodilatory prostaglandins, thereby reducing hyperfiltration (21), protein...

Table 2. Mean systemic and renal hemodynamic responses to COX2 inhibition by gender

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Post-COX-2 Inhibition</td>
</tr>
<tr>
<td>Renin</td>
<td>0.24±0.05</td>
<td>0.11±0.03</td>
</tr>
<tr>
<td>Aldosterone</td>
<td>162±39</td>
<td>97±31</td>
</tr>
<tr>
<td>ANG II</td>
<td>3.5±1.0</td>
<td>2.1±0.6</td>
</tr>
<tr>
<td>MAP</td>
<td>75±3</td>
<td>75±2</td>
</tr>
<tr>
<td>ERPF</td>
<td>663±20</td>
<td>679±28</td>
</tr>
<tr>
<td>GFR</td>
<td>137±7</td>
<td>141±5</td>
</tr>
<tr>
<td>FF</td>
<td>0.21±0.01</td>
<td>0.21±0.01</td>
</tr>
<tr>
<td>RBF</td>
<td>1.132±47</td>
<td>1.189±65</td>
</tr>
<tr>
<td>RVR</td>
<td>70±3</td>
<td>69±4</td>
</tr>
</tbody>
</table>

Values are mean ± SE. COX-2, cyclooxygenase 2; MAP, mean arterial pressure (mmHg); GFR, glomerular filtration rate (ml·min⁻¹·1.73 m⁻²); ERPF, effective renal plasma flow (ml·min⁻¹·1.73 m⁻²); FF, filtration fraction; RBF, renal blood flow (ml·min⁻¹·1.73 m⁻²); RVR, renal vascular resistance (mmHg·min⁻¹·l⁻¹). *The change in ERPF, FF, and RBF in response to COX-2 inhibition in women vs. men, P < 0.025. †The change in FF and RBF in women in response to COX-2 inhibition, P = 0.045.

Fig. 1. Effect of cyclooxygenase 2 (COX2) inhibition on filtration fraction (FF) in men and women with type 1 diabetes mellitus (DM) (means ± SE). *P ≤ 0.05 vs. baseline. §P ≤ 0.05 vs. response in men.

Fig. 2. Change in glomerular filtration rate (GFR; ml·min⁻¹·1.73 m⁻²) in response to ANG II in men with type 1 DM (means ± SE).

Fig. 3. Change in GFR (ml·min⁻¹·1.73 m⁻²) in response to ANG II in women with type 1 DM (means ± SE). *P ≤ 0.05 vs. baseline. §P ≤ 0.05 vs. response pre-COX2 inhibition.
sensitive rats exhibit a greater systemic hypertensive effect dependent on these prostaglandins to maintain vasodilatation (36), some investigators have suggested that females are more...}

 referred to nitric oxide-cGMP, prostacyclin-cAMP, and hyperpolarization-related pathways (33). Moreover, endothelium-independent effects of sex hormones may act through the inhibition of the signaling mechanisms of vascular smooth muscle contraction such as intracellular calcium and protein kinase C (33).

reported that females derive greater cardiovascular protection from prostaglandins through the interaction of estrogen with cytosolic/nuclear receptors that trigger long-term genomic effects (33), such as the inhibition of smooth muscle proliferation and the stimulation of endothelium-dependent mechanisms of vascular relaxation. These include but are not limited to nitric oxide-cGMP, prostacyclin-cAMP, and hyperpolarization-related pathways (33). Moreover, endothelium-independent effects of sex hormones may act through the inhibition of the signaling mechanisms of vascular smooth muscle contraction such as intracellular calcium and protein kinase C (33).

Based on these observations, women may therefore depend on prostaglandins for the maintenance of normal vascular tone and blood pressure.

Our first major finding was that, in response to COX2 inhibition, women exhibited a significant renal hyperfiltration response, reflected by a rise in FF after COX2 inhibition. The rise in FF, with the associated numerical decreases in RBF and ERPF, suggest a COX2 inhibition-mediated postglomerular vasoconstrictive effect in women. This may have been due to either celecoxib-mediated inhibition of vasodilators (such as prostacyclin) or the activation of vasoconstrictors such as thromboxanes or ANG II. Activation of thromboxanes seems unlikely, since previous animal studies have demonstrated significant reductions, not increases, in constrictor response to thromboxane levels using selective COX2 inhibition (20, 21), which is consistent with the numerical reductions that we observed.

Although the effect of COX2 inhibition on thromboxane production is controversial in human studies (6, 24, 25), our findings are consistent with a loss of glomerular vasodilators, since we observed numerical reductions in PGE, PGD, and PGI metabolite levels and a numerical fall in thromboxane production. Loss of glomerular vasodilators may therefore underlie the postglomerular vasoconstrictive effect that we observed after COX2 inhibition in women. As further supportive evidence for augmented sensitivity to COX2 inhibition in women, we observed an increase in daytime systolic blood pressure on ABPM in this group. One possible explanation for this is a systemic reduction in vasodilators, leading to a hypertensive response, which has been observed in experimental models (3, 13, 18, 36).

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of GFR in women, consistent with equivalent vasoconstrictive activity in the pre- and postglomerular vascular compartments. One explanation for the renal effect of ANG II before COX2 inhibition in women is based on the concept of the greater baseline prostaglandin activity in this group, which is typically preglomerular. Under these circumstances, COX2-derived vasodilators are maximally active and cannot mitigate the vasoconstrictive action of ANG II, leading to a predominant preglomerular vasoconstrictive effect and a decline in GFR. After COX2 inhibition, however, COX2-derived vasodilators are relatively depleted (3, 13, 33). This may eliminate the glomerular polarity in the activity of vasodilators, resulting in a more even distribution of ANG II-mediated arteriolar vasoconstriction throughout the renal microcirculation and the maintenance of GFR. An alternative speculative explanation that could explain the response to ANG II in women is that COX2 inhibition may have blocked intrarenal RAS mediators (7, 37, 42), leading to glomerular ANG II type 1 receptor upregulation and greater ANG II sensitivity.

This study has important limitations. The sample size was small, which may have limited our ability to detect significant differences in some parameters such as changes in prostaglandin levels after COX2 blockade. This was of particular importance in women, in whom the P value failed to reach significance, likely in part due to the small sample size. We attempted to minimize the effect of the small sample size by utilizing homogeneous study groups and by careful presudy dietary preparation. We attempted to minimize the effect of variations in estrogen on renal hemodynamic and RAS function in female subjects by only studying those who were nonusers of oral contraceptive medications, and only during the follicular (low estrogen) phase of the menstrual cycle. We also decreased variability by using a study design that allowed each subject to act as his/her own control. Finally, because of ethical considerations at our institution, we were not permitted to study a healthy control group of adolescents. Our results therefore only pertain to humans with type 1 DM.

In summary, our results demonstrate that women with type 1 DM have a greater dependence on vasodilatory prostaglandins to maintain normal renal and peripheral blood vessel function compared with men. Furthermore, COX2-dependent factors may counteract the effect of ANG II in the renal microcirculation to a greater degree in women than in men with uncomplicated type 1 DM, so that COX2 inhibition eliminates gender-based differences in the response to ANG II that we have observed previously.

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