Low Plasma Renin Activity in Diabetes
Relation to Urine Prostaglandin Excretion

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SUMMARY

Renal functional abnormalities, occurring before overt renal disease and possibly due to abnormal vascular control mechanisms, have been described in diabetes mellitus. We used intravenous (i.v.) furosemide, which stimulates renal prostaglandin (PG) synthesis and renin release, to compare these vasoactive systems in 14 diabetic and 23 normal control subjects. Using urine thromboxane B_2 (TXB_2) as an index of renal synthesis of the vasoconstrictor prostanoid TXA_2, and urine 6keto-$PGF_{1\alpha}$ for the vasodilator PGI_2, we found evidence of increased renal TXA_2 synthesis in diabetic subjects in response to furosemide. The increased TXA_2 synthesis did not occur at the expense of PGI_2 synthesis, as urine 6keto-$PGF_{1\alpha}$ was not reduced. Increased TXB_2 excretion in diabetic subjects was particularly marked in the first 10 min after i.v. furosemide. During this time, diabetic males excreted 31 ± 6 ng of TXB_2 compared with 10 ± 1 ng for normal males ($P < 0.05$), while diabetic females excreted 15 ± 3 ng compared with 7 ± 1 ng for normal females ($P < 0.05$). Also, 6keto-$PGF_{1\alpha}$ excretion at 10 min was increased in diabetic subjects: males, 29 ± 3 ng versus 19 ± 3 ($P < 0.05$); females, 33 ± 8 versus 16 ± 3 ($P < 0.05$). The ratio of TXB_2 to 6keto-$PGF_{1\alpha}$ tended to be higher in diabetic males. Plasma renin activity 10 min after i.v. furosemide was lower in diabetic males: 0.9 ± 0.2 $ng \cdot ml^{-1} \cdot h^{-1}$ versus 3.5 ± 0.4 ($P < 0.05$) and tended to be lower in diabetic females: 1.5 ± 0.3 versus 2.0 ± 0.3. There was a significant negative correlation between the TXB_2/6keto-$PGF_{1\alpha}$ ratio and PRA at this time ($r = -0.392$, $P < 0.05$), suggesting that the relatively increased TXA_2 could be a factor in the reduced early increment in plasma renin activity after i.v. furosemide.

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Renal disease is a well-recognized and characterized late complication of diabetes mellitus.[1-3] Once clinically significant proteinuria occurs, the appearance of hypertension, azotemia, and eventual renal failure is likely. However, before the onset of proteinuria, renal functional abnormalities are less well described and there is less agreement as to their prevalence or significance. Thus, an increase in glomerular filtration rate, increased excretion of albumin, but not of $beta_2$ microglobulin, and abnormalities of the ratio of glomerular filtration rate to renal blood flow[4,5] have been reported. These abnormalities are generally rapidly reversible with control of the blood sugar, implying that they are due to a change in renal vascular tone. Of the factors known to affect renal vascular tone, the renin-angiotensin system and the renal prostaglandins (PG) figure prominently. Furthermore, the two systems are interrelated: angiotensin II increases the synthesis of renal vasodilator PG,[6] while PGI_2, a potent vasodilator, is a stimulus to renin release.[7]

There are reported abnormalities in both the renin-angiotensin system and the PG system in diabetes. Plasma renin activity (PRA) is reduced in diabetic subjects with neuropathy but without obvious nephropathy.[8] Indeed, there is a poor correlation between the occurrence of low plasma renin activity and histologic severity of diabetic nephropathy,[9] suggesting that factors other than destruction of renin-producing cells reduce renin release.

We hypothesized that one such factor could be a change in the production or action of renal prostaglandins. Various tissues in the kidney produce PGI_2, PGE_2, PGF_2, PGD_2, and thromboxane A_2 (TXA_2) all from a common precursor, PGH_2, in turn produced by the enzyme cyclooxygenase from arachidonic acid. Changes in renal PG synthesis can affect renin release, renal blood flow, and salt and water excretion.[10] PGI_2 appears to be the more potent vasodilator and renin releaser,[11] while TXA_2 can vasoconstrict renal vessels[12] and may reduce renin release.[13] Reduction of PGI_2 formation by

various vascular tissues has been reported in human diabetic subjects[14,15] and in animal models of diabetes.[16,17] On the other hand, platelets from diabetic patients produce more TXA_2 in response to standard stimuli.[18,19]

We compared renal PGI_2 and TXA_2 synthesis in diabetic and normal volunteers by measuring the excretion rates of their nonenzymatic hydrolysis products: 6keto-$PGF_{1\alpha}$ and TXB_2, respectively. While the origin of urinary 6keto-$PGF_{1\alpha}$ and TXB_2 is not known with certainty, their excretion rates appear to reflect renal synthesis of the parent compounds.[20] In support of this, Rosenkranz et al.[21] found that only about 15% of a fairly large dose of PGI_2 (enough to lower the blood pressure) appeared in the urine as 6keto-$PGF_{1\alpha}$. Patrono et al. found that infusion of hypotensive doses of PGI_2 did not change the excretion of 6keto-$PGF_{1\alpha}$.[22] Thromboxane A_2 cannot be injected intravenously (i.v.) because of platelet activation, but labeled TXB_2 has been infused into a monkey. Only 3.5% of a large dose (1.25 mg) appeared in urine as TXB_2.[23] It seems likely, therefore, that the bulk of 6keto-$PGF_{1\alpha}$ and TXB_2 in urine arises from the kidney.

We used the drug furosemide, which, when given i.v., releases the PG precursor arachidonic acid from renal sites,[24] thereby increasing the synthesis of many PGs, including PGI_2 and TXA_2.[13,25,26] The early 10-min increment in PRA seen after i.v. furosemide appears to be due to increased renal synthesis of PGI_2, which in turn releases renin.[26] We sought to determine whether this early increment in PRA was abnormal in diabetes and whether any abnormality could be attributed to changes in renal prostaglandin synthesis. Diabetic subjects without overt renal or neurologic disease and without markedly increased blood sugars were studied to avoid possible effects of these variables on PRA.

MATERIALS AND METHODS

Subjects. Twenty-three normal volunteers (14 male, 9 female) ranging in age from 19 to 49 yr participated. Diabetic subjects included 5 males and 9 females aged 20–69 yr. All were healthy and ambulant. The diagnosis of diabetes had been made 2–29 yr previously, usually on the basis of increased fasting and postprandial plasma glucose levels. None had more than 30 mg/dl protein on routine urinalysis or a serum creatinine >150 μmol and none had been diagnosed as hypertensive. There was no history of lightheadedness on standing or bowel or bladder dysfunction. The systolic blood pressure decrease with 3 min of standing was <12 mm Hg. Of the males, one had been diagnosed before age 20 yr and had had ketonuria in the past. All were within 20% of ideal weight for height and build. Of female diabetic subjects, five had been diagnosed before age 20 yr and three of them had had ketonuria. Two female diabetic subjects were obese: 33% and 41% above ideal weight, respectively. In subjects who took insulin (see Table 1), the prescribed dose had been unchanged for 6 wk or more before the study.

None of the subjects took any prescription or nonprescription drug (other than insulin) and all avoided aspirin and other nonsteroidal anti-inflammatory agents for 2 wk before, and during the study. No alcohol was permitted 2 days before, or during the study. Three normal volunteers smoked up to 10 cigarettes daily, but no diabetic subject smoked. Table 1 shows some subject characteristics.

All signed a consent form and the protocol was approved by the University of Saskatchewan President's Advisory Committee on Ethics in Human Experimentation.

Protocol. Subjects were studied on two mornings 1 wk apart. They reported to the laboratory at 0800 h having fasted 8 h. Diabetic subjects omitted crystalline zinc or semilente insulin on study days, but took their usual dose of intermediate-acting insulin at 0700–0730 h.

After emptying the bladder, subjects rested 10 min before sitting heart rate and blood pressure (mean of three readings) were recorded along with weight and height. Fluids, 20 ml/kg, consisting of equal parts water and 7-Up were given orally, after which initial blood samples were taken. Furosemide (Lasix, Hoechst Canada) 0.5 mg/kg or saline for injection 0.05 ml/kg was then injected i.v. Blood (collected in seated position) and urine samples were obtained at 10, 30, and 240 min. Urine volume was approximated and replaced with equal parts water and 7-Up. Heart rate and blood pressure were recorded after each sample, while

TABLE 1
Subject characteristics

	Normal		Diabetic	
	Male	Female	Male	Female
N	14	9	5	9
Age (yr)	34.1 ± 2.9	35.1 ± 4.0	56.2 ± 2.7*	39.7 ± 5.8
Weight (kg)	65.5 ± 9.0	6.1 ± 3.3	70.4 ± 2.6	72.0 ± 4.1
Height (cm)	176.2 ± 1.8	167.9 ± 1.9	172.2 ± 1.3	163.7 ± 1.7
Duration (yr)	—	—	12.6 ± 4.7	8.1 ± 2.6
Insulin (no.)	—	—	4	7
SBP	108.7 ± 2.3	109.1 ± 2.8	133.4 ± 9.7	118.0 ± 7.3
DBP	71.5 ± 1.7	70.6 ± 1.4	83.8 ± 5.0	77.3 ± 2.8
HR	71.1 ± 2.1	72.9 ± 2.7	76.0 ± 3.2	81.4 ± 3.1
HbA_{1c}	—	—	10.2 ± 0.8	9.8 ± 1.5
SCr (μmol)	89.7 ± 3.7	81.4 ± 4.4	98.0 ± 6.3	74.6 ± 3.6
SNa (mmol)	141.6 ± 0.3	141.3 ± 0.7	144.0 ± 1.8	142.2 ± 0.4
SK (mmol)	4.0 ± 0.1	4.0 ± 0.1	3.8 ± 0.2	4.0 ± 0.2

Abbreviations: SBP and DBP, systolic and diastolic blood pressure; HR, heart rate; HbA_{1c}, hemoglobin A_{1c} (%) (normal range 4.5–6.5); SCr, serum creatinine; SNa, serum sodium; and SK, serum potassium.
*$P < 0.05$ (diabetic males versus normal males).

TABLE 2
Responses to placebo (0–240 min)

	Normal		Diabetic	
	Males (N = 9)	Females (N = 4)	Males (N = 5)	Females (N = 9)
Intake (ml)	967 ± 116	900 ± 140	1050 ± 42	1086 ± 57
Volume (ml)	518 ± 54	569 ± 137	638 ± 58	904 ± 71
UNaV (mmol)	19 ± 4	12 ± 5	30 ± 6	26 ± 5
UKV (mmol)	14 ± 2	12 ± 0.7	14 ± 2	14 ± 2
UCrV (mmol)	3.0 ± 0.1	1.9 ± 0.2	3.0 ± 0.3	2.0 ± 0.1
U6kV (ng)	132 ± 14	86 ± 13	129 ± 23	119 ± 16
UTXV (ng)	48 ± 7	31.3 ± 3.6	102 ± 23	66 ± 10
ΔW (kg)	0.2 ± 0.2	0.1 ± 0.1	0.3 ± 0.2	0.07 ± 0.1

Abbreviations: UNaV, UKV, UCrV, U6kV, and UTXV: urinary excretion rates (per 240 min) of sodium, potassium, creatinine, 6keto-$PGF_{1\alpha}$, and TXB_2; ΔW: final weight minus initial weight.

weight was noted after the final sample. The protocol was repeated the following week except that the alternate solution was injected. Furosemide and saline were given in random order.

Analyses. Sodium, potassium, and creatinine were measured in urine and plasma by autoanalyzer. PRA was taken as the generation rate of angiotension I, measured by radioimmunoassay, by the method of Stockigt.[27]

Aliquots of each urine sample were analyzed for 6keto-$PGF_{1\alpha}$ and TXB_2 using our previously validated methods.[28] Briefly, 6 keto-$PGF_{1\alpha}$ was extracted from acidified urine (10 ml) with an octadecyl reversed-phase column, purified over Sephadex LH-20, and subjected, in duplicate, to radioimmunoassay. Interassay variability averaged 10–15% (coefficient of variation). We corrected for losses during the extraction and purification procedures by quantitating the recovery of a tracer amount (1000 dpm or 20 pg) of ^{3}H-6keto-$PGF_{1\alpha}$ (New England Nuclear, Boston, Massachusetts). TXB_2 was extracted from acidified urine using chloroform and subjected to Sephadex LH-20 purification. Losses were corrected for by using tracer amounts of ^{3}H-TXB_2 (New England Nuclear). Radioimmunoassay of duplicate aliquots was carried out using standard techniques. The coefficient of variation between assays was 8–13%.

The excretion rates of all substances in urine were calculated by multiplying the concentration in the urine sample by the total sample volume and summing the results for each time period.

Statistical analysis. Data are presented as mean ± SEM. Differences between groups were assessed with a two-way analysis of variance (using the BMDP program) in which interactions between diagnosis (i.e., normal or diabetic) and sex could be measured. For PRA, the values for diabetic subjects were compared with normals using a one-way analysis of variance. When PRA values at a single point of time were compared, the nonparametric Mann-Whitney test was used. Correlations among parameters were assessed with the Pearson product-moment correlation. A P-value of 0.05 or less was deemed statistically significant.

RESULTS

As shown in Table 1, diabetic males were older (56.2 yr) than normal males (34.1 yr). There were no differences in weight, height, systolic or diastolic blood pressure, heart rate, serum creatinine, sodium, or potassium between diabetic and normal subjects.

All diabetic subjects completed the protocol and all normal volunteers received furosemide. Ten normal volunteers (5 female, 5 male) were not studied with placebo. No untoward events occurred. There were no significant changes in heart rate or blood pressure during the study, although both systolic and diastolic blood pressure tended to rise 10–30 min after furosemide in both groups ($0.05 < P < 0.1$, not shown). Fasting blood sugar values in normals were: males, 5.7 ± 0.4 mmol; females, 5.1 ± 0.4 mmol. The results before placebo and furosemide were averaged as there was no difference

TABLE 3
Responses to furosemide (0–240 min)

	Normal		Diabetic	
	Males (N = 14)	Females (N = 9)	Males (N = 5)	Females (N = 9)
Intake (ml)	1221 ± 116	1150 ± 115	1140 ± 81	1067 ± 64
Volume (ml)	1784 ± 122	1563 ± 110	1560 ± 222	1755 ± 72
UNaV (mmol)	164 ± 10	127 ± 9	147 ± 22	149 ± 13
UKV (mmol)	26 ± 3	21 ± 2	27 ± 4	26 ± 2
UCrV (mmol)	2.7 ± 0.2	1.8 ± 0.1	3.0 ± 0.3	2.0 ± 0.1
U6kV (ng)	119 ± 12	76 ± 10	152 ± 20	147 ± 18
UTXV (ng)	62 ± 6	34 ± 3	149 ± 66*	91 ± 17*
ΔW (kg)	−0.8 ± 0.1	−0.8 ± 0.1	−0.8 ± 0.3	−1.0 ± 0.1

Abbreviations are as in Table 2.
*$P < 0.05$ compared with normal subjects (both sexes).

TABLE 4
Values at 10 min after i.v. furosemide

	Normal		Diabetic	
	Males (N = 14)	Females (N = 9)	Males (N = 5)	Females (N = 9)
Volume (ml)	172 ± 22	184 ± 38	109 ± 13	143 ± 13
UCrV (mmol)	0.38 ± 0.05	0.34 ± 0.04	0.64 ± 0.14	0.35 ± 0.09
U6kV (ng)	19 ± 3	16 ± 3	29 ± 3†	33 ± 8†
UTXV (ng)	10 ± 1	7 ± 1	31 ± 6†	15 ± 3†
PRA	3.5 ± 0.4	2.0 ± 0.3*	0.9 ± 0.2†	1.5 ± 0.3
TX/6k	0.68 ± 0.14	0.39 ± 0.11	1.06 ± 0.19	0.53 ± 0.14

Abbreviations: TX/6k, ratio of TXB_2 to 6keto-$PGF_{1\alpha}$; PRA, plasma renin activity ($ng^{-1} \cdot ml^{-1} \cdot hr^{-1}$). Other abbreviations are as in Table 2.
*$P < 0.05$ males versus females.
†$P < 0.05$ diabetic versus normal subjects.

between them. For diabetic males, the values before placebo were 7.4 ± 0.7 mmol while before furosemide the blood sugar was 6.5 ± 2.1. For diabetic females, the values before placebo and furosemide were 7.9 ± 1.8 mmol and 9.0 ± 1.0 mmol, respectively.

Table 2 shows responses to placebo. Urinary excretion values represent the total in 240 min. Although diabetic males showed a tendency to excrete more TXB_2 ($0.05 < P < 0.1$), there were no significant differences among the groups for any variable.

The responses to furosemide over 240 min are shown in Table 3. Diabetic subjects of both sexes excreted more TXB_2 ($P < 0.05$, both sexes) after furosemide than did normals. While the mean values for 6keto-$PGF_{1\alpha}$ excretion were somewhat higher in both male and female diabetic subjects, the differences did not reach statistical significance ($0.05 < P < 0.1$). In addition, there were no differences between diabetic and normal volunteers in excretion of urine, sodium, potassium, or creatinine.

During the first 10 min after furosemide, both groups appeared to have an increase in PG excretion rate over the basal rate after placebo (not shown). Diabetic subjects excreted more TXB_2 and 6keto-$PGF_{1\alpha}$ in this period (Table 4, Figure 1). The ratio of TXB_2 to 6keto-$PGF_{1\alpha}$ tended to be higher in diabetic males than in normal males (1.06 ± 0.19 versus 0.68 ± 0.14, $0.05 < P < 0.1$, Table 4). Diabetic males also produced less urine during this time (Table 4). There was no correlation between urine volume and excretion of TXB_2 or 6keto-$PGF_{1\alpha}$ in any group or the subjects as a whole.

Figure 2 shows changes in PRA after furosemide. While there were no differences in PRA before furosemide, normal males and females showed a brisk increase by 10 min. The increment at 10 min was reduced in diabetic subjects of both sexes (Table 4). There was no correlation between urine volume and PRA, or 6keto-$PGF_{1\alpha}$ and PRA. In contrast, there was a weak negative correlation between the TXB_2/6keto-$PGF_{1\alpha}$ ratio and PRA 10 min after furosemide ($r = -0.392$, $P < 0.05$) for all subjects ($N = 37$).

At 30 and 240 min, differences in PRA were less marked although values in diabetic subjects tended to be lower throughout the study. These modest differences in PRA at 30 and 240 min, when taken as a group, were significant. Also, although PRA values were no different at any one time point after placebo among the groups, diabetic subjects tended to have lower values throughout (not shown). When all PRA values after placebo in diabetic and normal subjects were compared, diabetic subjects had significantly lower values ($F = 34.4$, $P < 0.001$, one-way ANOVA). Similarly, when all values after furosemide were compared, diabetic subjects showed lower PRA ($F = 12.6$, $P < 0.001$).

There was no correlation between age and PRA at any time point including the 10-min value. Also, we could find no correlation between age and TXB_2 or 6keto-$PGF_{1\alpha}$ excretion or their ratio at any time after placebo or furosemide in any single group. When all subjects were included, there was a weak correlation between age and TXB_2 excretion ($r = 0.366$, $N = 37$, $P < 0.05$).

DISCUSSION

We have demonstrated differences in some, but not all, responses to furosemide in diabetes. The most striking difference was the increase in excretion (at 10 min) of both 6keto-$PGF_{1\alpha}$ and TXB_2, presumably reflecting increased fu-

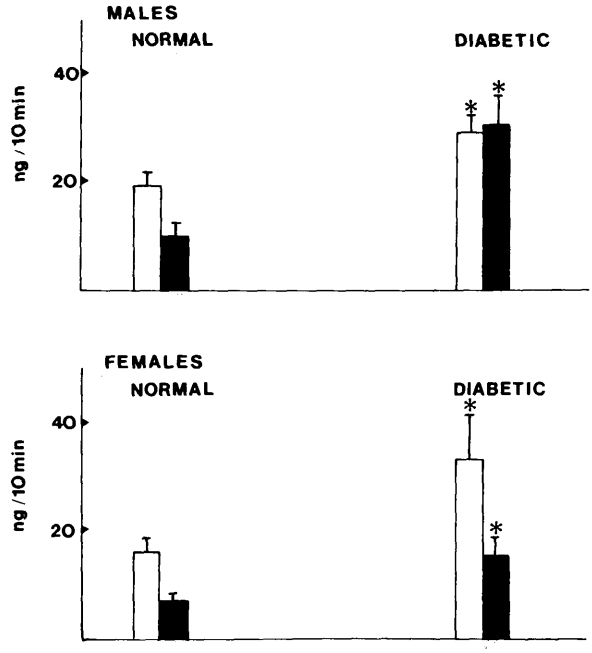

FIGURE 1. 6keto-$PGF_{1\alpha}$ (open bars) and TXB_2 (solid bars) excretion at 10 min after furosemide 0.5 mg/kg, i.v. Means ± SEM. *$P < 0.05$ (normal versus diabetic).

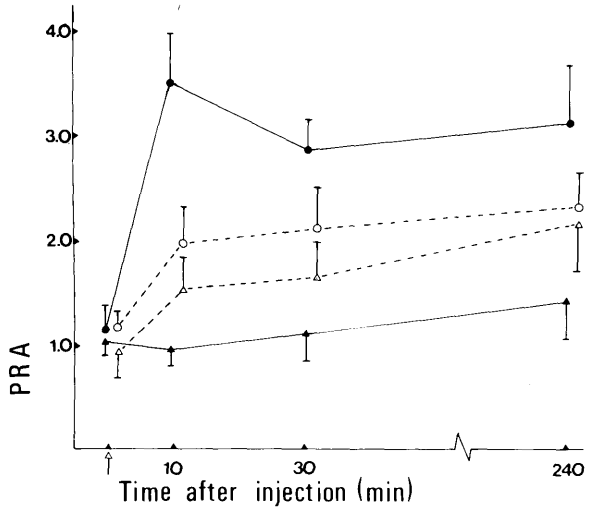

FIGURE 2. Plasma renin activity (PRA, ng · ml^{-1} · h^{-1}) after furosemide. Means ± SEM for normal males (●), normal females (○), diabetic males (▲), and diabetic females (△).

rosemide-induced release of the parent compounds within the kidney. As these are potent substances, one might expect to find differences in other responses to furosemide. Although there was no significant difference in the overall diuretic response in 4 h (Table 3), the initial diuretic response at 10 min was reduced in diabetic males and tended to be lower in diabetic females (Table 4). The diuretic and natriuretic responses to furosemide are a function of the concentration and residence time of the drug at its active site on the luminal surface of the nephron.[29] Determinants of these include furosemide concentration in plasma water, glomerular filtration rate, renal blood flow, and activity of the process secreting furosemide into the tubule. The factor or factors reducing the initial diuretic response in our male diabetic subjects cannot be discerned from the data. It is possible, however, that the initial transient increase in renal blood flow, known to occur with i.v. furosemide[26] was reduced in these subjects, reducing the delivery of the drug to both the glomerulus and the tubular secreting site. In an earlier study, we showed that the renal vasodilating response to furosemide is due to the release of vasodilator PG, namely PGI_2.[26] In the present study, renal PGI_2 formation (as reflected by urine 6keto-$PGF_{1\alpha}$) was not lower in diabetic compared with normal subjects. There was a difference in the excretion of TXB_2 and a tendency for the ratio of TXB_2/6keto-$PGF_{1\alpha}$ to be higher in male diabetic subjects. Because furosemide increases the availability of the common precursor of PGI_2 and TXA_2 (arachidonic acid), one might speculate that the ratio of TXA_2 to PGI_2 determines the overall vasodilation response to the drug. If more TXA_2, relative to PGI_2, were formed, the vasodilator response to furosemide should be reduced. This, in turn, could decrease the diuretic response.

We have also shown[26] that the early increment (7.5 min) in PRA after furosemide correlates with the increase in urine 6keto-$PGF_{1\alpha}$ in dogs. We might, therefore, expect a relatively greater increase in PRA in diabetic subjects. In fact, the PRA response was reduced in the diabetic group as a whole, particularly so in males. We speculate that this paradox may be due to a renin release-inhibiting effect of TXA_2. Because PGI_2 increases, while TXA_2 decreases, cyclic adenosine monophosphate (cAMP) production[30,31] and because cAMP increases renin release,[32] one might expect less renin release when the TXA_2/PGI_2 ratio is increased. Indeed, there was a significant negative correlation between the urine TXB_2/6keto-$PGF_{1\alpha}$ ratio and PRA at 10 min after furosemide (see RESULTS). However, it should be noted that this correlation is weak ($r = -0.392$) so that factors other than the ratio of prostanoids probably affect PRA. For example, insulin therapy itself, an abnormality of adrenergic stimulation, or a defect in the conversion of pro-renin to renin could conceivably alter the PRA at 10 min. Furthermore, to our knowledge, there are no data on the direct effect of TXA_2 on renin release or cAMP formation within the juxtaglomerular cell. Finally, the juxtaglomerular cell itself is devoid of cyclooxygenase so that one must postulate effects of PGs produced at distant sites.

Could these differences between our study groups be due to factors other than diabetes mellitus? Our diabetic subjects, particularly males, were older than the control subjects. PGI_2 formation decreases with age,[33] but to our knowledge there are no data concerning TXA_2 formation and age. We could find no correlation between the urinary excretion of either prostanoid or age for normal or diabetic subjects. For the subjects as a whole, there was a weak correlation between age and TXB_2 excretion ($r = 0.366$, $P < 0.05$), but this could be accounted for by the older age of our diabetic males. Our diabetic females also produced more TXB_2 than did normals, while their ages were no different. We, therefore, feel it unlikely that our findings could be accounted for by age differences alone.

The mechanism by which furosemide-induced TXA_2 and PGI_2 synthesis in the kidney is increased in diabetic subjects is unknown. Our finding of increased TXB_2 excretion in the face of normal or elevated 6keto-$PGF_{1\alpha}$ excretion mitigates against the hypothesis that TXA_2 is preferentially formed from PGH_2 at the expense of PGI_2. Rather, it appears likely that PGH_2 formation itself is increased, perhaps by an increase of cyclooxygenase activity or phospholipase A_2 activity. There is evidence that both of these enzymes may be more active in diabetes.[34,35] Finally, it is possible that the fatty acid precursor pool differs in size or composition in diabetic subjects and that this in turn leads to greater production of all of the "2" series of prostanoids.

Our results do not support the notion that prostacyclin synthesis is reduced in diabetes. Harrison[16] and Carreras[17] showed that aortic PGI_2 production was decreased in rats made diabetic with streptozocin, and preliminary results suggested that arterial PGI_2 production was reduced in diabetic humans.[14] Other investigators, however, could find no differences in vascular PGI_2 synthesis[36] or plasma concentrations[37] of 6keto-$PGF_{1\alpha}$ between diabetic subjects and normal controls. The finding that vascular PGI_2 production is reduced only at very high ambient glucose levels (606 mg/dl [33.7 mmol]) may reconcile these observations.[38] None of our diabetic subjects had blood sugars in this range at the time of testing, and hemoglobin A_{1c} concentrations were only moderately elevated. It may be that, at higher plasma glucose concentrations in man, PGI_2 synthesis is reduced.

In summary, we have shown that urine TXB_2 and 6keto-$PGF_{1\alpha}$ excretions are increased immediately (within 10 min)

in diabetic humans compared with normals in response to furosemide. We feel this represents increased renal synthesis of TXA_2 and PGI_2. Other cells, notably platelets, show a similar increased production of TXB_2. However, this does not appear to be a generalized cellular abnormality, because polymorphonuclear leukocytes of diabetic subjects produce decreased amounts of TXB_2 on stimulation.[39] The abnormal renal prostanoid synthesis may be responsible for differences in renin release and vascular tone in diabetic subjects. The significance of these as a marker for future renal dysfunction and hypertension awaits clarification.

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