Pioglitazone Reduces Urinary Protein and Urinary Transforming Growth Factor-β Excretion in Patients with Type 2 Diabetes and Overt Nephropathy

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Objective: *Increased urinary excretion of protein and transforming growth factor-β (TGF-β) are associated with progression of diabetic nephropathy (DN). Thiazolidinediones (TZD) could reduce urinary protein excretion in patients with microalbuminuric DN. There is little data of patients with macroalbuminuric DN. Also, there are no available clinical data regarding the effect of TZD on TGF-β and type IV collagen in clinical DN. The present study was carried out to evaluate the effect of pioglitazone (PGZ), a member of TZD, on urinary protein, urinary TGF-β, and urinary type IV collagen excretion in type 2 diabetic patients with macroalbuminuric DN.*

Material and Method: *Forty patients with type 2 diabetes and overt nephropathy, proteinuria more than 500 mg/day, were randomly assigned to receive PGZ (30 mg/day, n = 24) or placebo (control group, n = 16), for 12 weeks. Blood pressure, plasma glucose, glycated hemoglobin, lipid profile, 24-hour proteinuria, urinary TGF-β, and urinary type IV collagen were determined and compared.*

Results: *Glycemic control and blood pressure in both groups were not significant different. At baseline, the levels of proteinuria, urinary TGF-β, and type IV collagen were not significant different between both groups. The geometric mean of urinary protein excretion in the PGZ group was progressively reduced from 1.64 to 0.98 gram/day (g/d), or 40.1% decrease which was significantly different ($p < 0.05$) from the 4.3% increase (from 1.72 to 1.80 g/d) in the control group. Urinary TGF-β excretion in the PGZ group was decreased by 47.8% which significantly differed from the 59.7% increase in the control group ($p < 0.05$). Urinary type IV collagen levels in the PGZ group were decreased by 35% which was slightly, but not significantly, different from the 51.6% elevation in the control group ($p = 0.06$).*

Conclusion: *Besides the effectiveness in blood sugar control, pioglitazone could salutarily reduce proteinuria and synthesis of TGF-β as well as type IV collagen. These beneficial effects of pioglitazone on diabetic nephropathy are comparable to angiotensin converting enzyme inhibitors and angiotensin receptor blockers*

Keywords: *Pioglitazone, Diabetic nephropathy, Overt proteinuria, Urinary TGF-β*

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Diabetic nephropathy (DN) is one of the most common causes of end stage renal disease (ESRD) worldwide[1]. Thus, treatment modalities that could prevent or retard the progression of DN to ESRD are crucial and have a major contributory role in diabetic patient care. Current therapeutic strategies, including optimal glycemic as well as blood pressure control and inhibition of renin-angiotensin-aldosterone system (RAAS) can slow the rate of progression but cannot absolutely prevent DN. As such, newer methods of therapy are crucially required. Current evidences has suggested that treatment, which could reduce transforming growth factor-β (TGF-β), the principal pathogenetic factor in DN, would retard or abrogate the progression of DN[2,3].

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Several *in vitro* and animal studies related with DN have demonstrated that thiazolidinediones (TZD) could reduce the amount of proteinuria, could lessen the synthesis of TGF-β and type IV collagen, a marker of extracellular matrix, and could attenuate pathological changes of the kidney[4-7]. In clinical studies, TZD could decrease the amount of microalbuminuria in type 2 diabetic patients[8-12]. There is little data regarding the effect of TZD in DN with overt nephropathy. Moreover, whether the proteinuria reducing ability of TZD in diabetic patients is related to TGF-β has not been established.

The present study was conducted to examine the effect and the basic mechanism of pioglitazone (PGZ), a member of TZD, in type 2 diabetic patients with overt nephropathy.

Material and Method

Patients

The effect of TZD on progression of DN was examined in 40 type 2 diabetic patients with overt nephropathy. The present study was approved by the Ethical Committee, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand. Each participating patient gave informed consent. Inclusion criteria were type 2 diabetic patients who had proteinuria more than 500 mg/day and serum creatinine below 3 mg/dL. Exclusion criteria comprised patients who 1) had received TZD during the last 3 months, 2) had hepatitis or the levels of serum SGPT more than 3 times of normal, 3) had severe congestive heart failure with class III-IV New York Heart Association, 4) had acute renal failure, and 5) had urinary tract infection.

Method

The present study was a single-blinded randomized controlled trial. Forty type 2 diabetic patients were randomly allocated into pioglitazone (PGZ) and control groups. In the PGZ group (n = 24), the patients received once daily PGZ, contained in medication capsule, at the dose of 30 mg/day, in combination with other oral hypoglycemic agents and/or insulin for optimal glycemic control. In the control group (n = 16), the patients obtained only oral hypoglycemic drugs and/or insulin to normalize blood sugar. A medication capsule containing placebo was also administered once daily to each control subject. The patients did not know whether they received PGZ or placebo. Fasting plasma glucose (FPG) as well as hypoglycemic and hyperglycemic symptoms was evaluated in every visit which occurred every two weeks in the first four weeks and then every four weeks thereafter. The doses of other oral hypoglycemic agents and/or insulin were adjusted accordingly for the optimal glycemic control. The compliance of the patients was monitored by the remaining drug count.

The values of the following laboratory parameters were determined at baseline and after 12-week treatment: FPG, hemoglobin A1c (HbA1c), blood urea nitrogen (BUN), serum creatinine, creatinine clearance, cholesterol, triglyceride, high density lipoprotein (HDL), 24-hour urinary protein excretion, urinary TGF-β, and urinary collagen type IV. BUN, serum creatinine, creatinine clearance, and 24-hour urinary protein excretion were also determined after 4-week and after 8-week treatment.

Creatinine clearance was calculated from serum creatinine and 24-hour urine collection. Urinary protein excretion was calculated from 24-hour urine collection. Urinary TGF-β1 was basically measured by sandwich enzyme immunoassay (Quantikine; R&D systems, Minneapolis, US) as described by Ellis et al[13]. The intraassay and interassay coefficients of variation were below 10%. Urinary collagen type IV was determined by sandwich enzyme immunoassay (Biotrin; Biotrin International, Dublin, Ireland) according to the manufacturer's instruction. The intraassay and interassay coefficients of variation were less than 10%. The values of all other parameters were obtained by routine standard measurements.

Statistical analysis

Data with normal distribution were expressed in mean $\pm$ standard error. Data with skewed distribution were logarithmically transformed before statistical analysis and were expressed as geometric mean (95% confidence interval). Paired t-tests were used for comparison between the values of all parameters at baseline and after 12-week treatment. Unpaired t-tests were performed to compare between the PGZ and control groups. Correlations of the change in FPG and HbA1c to the change in urinary protein excretion and urinary TGF-β1 were assessed by Pearson's correlation. Statis-tical significance was attained when $p < 0.05$.

Results

As demonstrated in Table 1 and 2, both control and PGZ groups were comparable in all baseline parameters. The doses of all drugs other than oral hypoglycemic drugs and insulin were kept constant during the study period. In the PGZ group, serum

Table 1. Baseline parameters

	Control	Pioglitazone
Number	16	24
Age (years)	62.3±2.6	61.4±2.1
Gender (male/female)	8/8	6/8
Duration of diabetes (years)	13.8±1.8	13.6±1.4
Treatment (Insulin/ACEI-ARB/Statins)	10/9/14	9/8/7
BMI (kg/m^2)	29.2±1.4	28.5±1.1
Fasting plasma glucose (mg/dL)	135.7 (115.3-159.7)	137.3 (114.7-164.4)
HbA1c (%)	8.3±0.5	8.6±0.4
Systolic BP (mmHg)	143.1±4.7	142.1±4.3
Diastolic BP (mmHg)	82.3±2.1	77.9±2.8
Creatinine clearance (mL/min)	58.6±7.01	57.1±6.6

Data are number (percent) or mean ± SE or geometric mean (95% confidence interval)
Abbreviations: ACEI-ARB = angiotensin converting enzyme inhibitors and/or angiotensin receptor blockers, BMI = body mass index, Hb = hemoglobin, BP = blood pressure

Table 2. Blood pressure and metabolic parameters

	Control (n = 16)			Pioglitazone (n = 24)		
	Baseline	12 weeks	Change	Baseline	12 weeks	Change
Systolic BP (mmHg)	143.3±5.0	136.9±4.3	-6.4±3.2	142.1±4.3	142.4±4.2	+0.3±3.5
Diastolic BP (mmHg)	82.3±2.1	81.6±2.4	-0.7±2.2	77.9±2.8	78.6±3.1	+0.7±3.0
FPG (mg/dL)	135.7 (115.3-159.7)	149.7 (121.9-183.9)	+10.3% (-14.6 to +42.5)	137.3 (114.7-164.4)	117.7 (102.7-135.0)	-14.3% (-30.5 to +5.6)
HbA1c(%)	8.34±0.47	8.53±0.48	+0.19±0.44	8.62±0.41	8.26±0.46	-0.35±0.19
Cholesterol (mg/dL)	219.9±13.2	201.7±10.5	-18.2±13.1	206.8±9.5	201.2±8.7	-5.6±10.9
Triglyceride (mg/dL)	190.4 (151.2-239.8)	183.9 (143.2-236.2)	-3.4% (-21.4 to +18.7)	225.0 (156.8-322.7)	166.6* (117.2-236.9)	-25.9% (-41.2 to -6.8)
HDL-C (mg/dL)	49.0±3.2	43.4±2.1*	-5.6±1.94	56.7±5.9	55.0±4.8	-1.7±4.0

Data are mean ± SE or geometric mean (95% confidence interval)
Abbreviations: FPG = fasting plasma glucose, Hb = hemoglobin, BP = blood pressure, HDL-C = high density lipoprotein - cholesterol
*$p < 0.05$ when compared with baseline

triglyceride levels at 12 week were significantly lower than baseline ($p < 0.05$) while the values of other parameters were not different between the two periods (Table 2). In the control group, only the values of HDL-C at 12 week were significantly less than baseline ($p < 0.05$). Following 12-weeks of treatment, there were no significant differences in all parameters between the PGZ and control groups (Table 2).

Table 3. 24-hr urine protein, urinary TGF-β1 urinary collagen type IV and creatinine clearance at baseline and 12 weeks after treatment

	Control (n = 16)			Pioglitazone (n = 24)		
	Baseline	12 weeks	Change	Baseline	12 weeks	Change
24-hr Urine protein (g/day)	1.7 (1.2-2.5)	1.8 (1.14-2.82)	+5.9% (-20.9 to +37.6)	1.64 (1.16-2.31)	0.98* (0.55-1.77)	-40.2% (-57.2 to -16.1)
Urinary TGF-β1 (ng/gCr)	92.1 (47.7-177.9)	147.1 (90.0-240.4)	+59.7% (-12.0 to +190.0)	184.3 (107.7-315.4)	96.3 (54.5-170.3)	-47.8% (-70.2 to -8.5)
Urinary collagen IV (μg/gCr)	4.5 (1.7-12.0)	6.8 (4.5-10.1)	+51.6% (-35.4 to +255.8)	7.2 (4.6-11.2)	4.7 (3.2-6.8)	-35.0% (-58.1 to +0.9)
Creatinine clearance (ml/min)	58.6±7.0	51.6±5.2	-7.0±6.3	57.1±6.6	54.2±4.5	-2.9±3.6

Data are geometric mean (95% confidence interval) or mean ± SE
* $p < 0.01$ when compared with baseline; $p < 0.05$ when compared with baseline; $p < 0.05$ when compared with control
$p = 0.06$ when compared with control

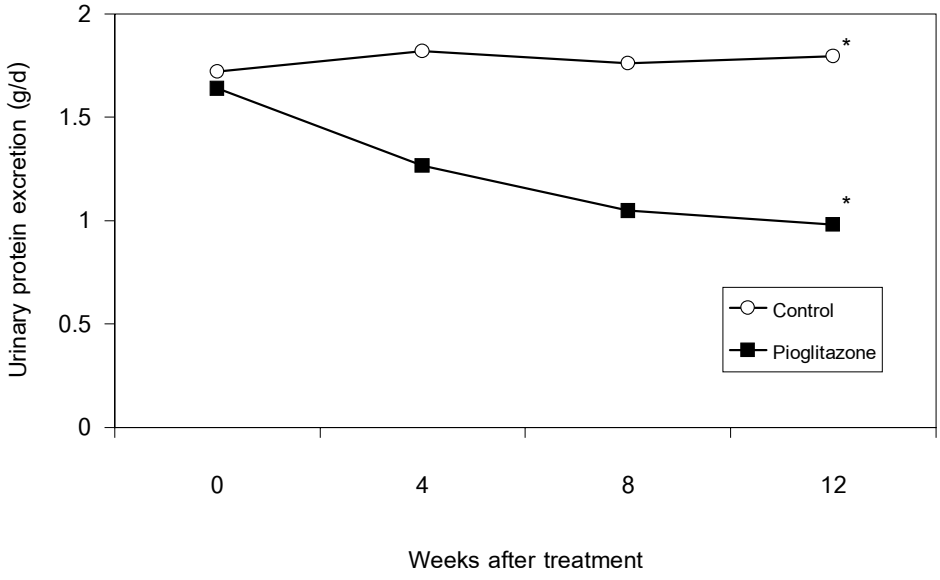

Fig. 1 Urinary protein excretion during 12 weeks of treatment in control (white bar) and pioglitazone group (black bar)
* $p < 0.05$, pioglitazone compared with control

Urinary protein excretion

At baseline, there were no statistical significances in the values of urinary protein excretion between both groups. As shown in Table 3 and Fig. 1, the geometric mean of urinary protein excretion in the PGZ group was progressively decreased and was significantly reduced by 40.1% from 1.64 to 0.98 g/day after 12-week treatment ($p = 0.009$). In the control group, urinary protein excretion was not significantly increased, from 1.72 to 1.80 g/day or 4.3% (Table 3 and Fig. 1, 2). The magnitude of urinary protein excretion change in the PGZ group, 40.1% reduction, was significantly different from the control group, 4.3% increase ($p = 0.016$) (Fig. 2).

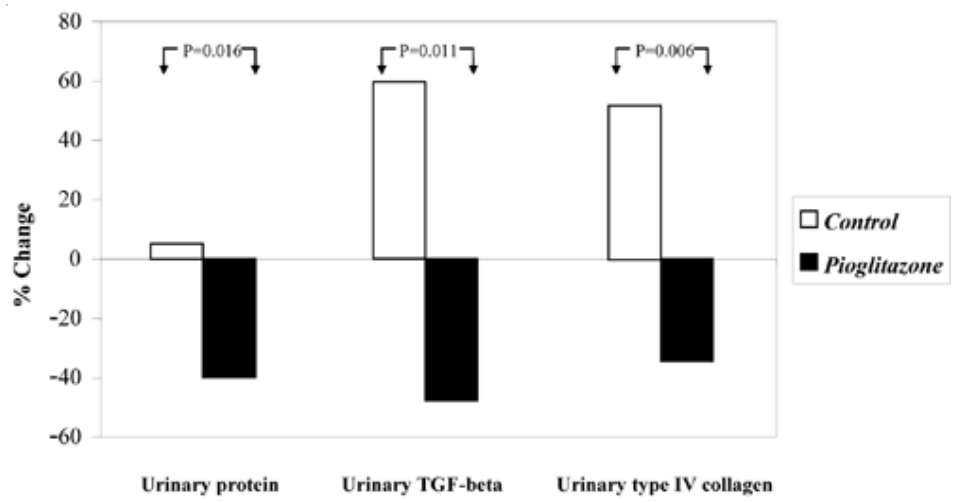

Fig. 2 Percent change of urinary protein excretion and urinary TGF-β excretion at baseline and 12 weeks after treatment in control (white bar) and pioglitazone group (black bar)

Urinary TGF-β1 excretion

At baseline, the value of urinary TGF-β1 in the PGZ group was not different from the control group. In the PGZ group, urinary TGF-β1 excretion was significantly decreased by 47.8%, from 184.3 to 96.3 nanogram per gram of creatinine ($p<0.05$), while, in the control group it was slightly, but not significantly, elevated, from 92.1 to 147.1 nanogram per gram of creatinine or 59.7% (Table 3 and Fig. 2). The magnitude of urinary TGF-β1 excretion change was significantly different between the two groups (Fig. 2; 47.8% decrease in the PGZ group vs 59.7% increase in the control group, $p < 0.05$).

Correlations of the change in FPG and HbA1c to the change in urinary protein and urinary TGF-β1 excretion

The change in urinary protein excretion was not correlated with the change in FPG or HbA1c (correlation coefficient: $r = 0.24$ and 0.26 respectively). Also, the change in urinary TGF-β1 was not correlated with the change in FPG or HbA1c ($r = 0.07$ and 0.25 respectively).

Urinary type IV collagen excretion

At baseline, the values of urinary type IV collagen in the PGZ group were not different from the control group. As shown in Table 3, urinary type IV collagen excretion was decreased in the PGZ group (35% decrease) while it was increased in the control group (51.6% increase). The statistical significances, however, were close but not attained ($p = 0.06$).

Creatinine clearance

There were no significant differences among the values of creatinine clearance at baseline (Table 3), after 4-weeks (data not shown), 8-weeks (data not shown), and 12-weeks (Table 3) treatment in both groups.

Adverse effects

None of the PGZ-treated patients developed congestive heart failure or hepatitis. Four patients in the PGZ group and one patient in the control group had mild hypoglycemic symptoms. Patients in the PGZ group had a significant weight gain of 1.93 kg in 12 weeks ($p < 0.001$) while the patients in the control group had stable weight.

Discussion

At present, DN is the most common cause of ESRD. In diabetes, several metabolic and hemodynamic factors could enhance TGF-β levels which would promote renal cell hypertrophy and stimulate extracellular matrix deposition, a marker of which is type IV collagen[2,3]. Proteinuria and progressive renal injury would eventually develop.

Recent studies demonstrated possible beneficial effect of thiazolidinedione (TZD) in diabetic nephropathy[4-7]. Few studies have demonstrated that TZD including pioglitazone (PGZ), troglitazone (TGZ), and rosiglitazone (RSG) could reduce microalbuminuria in type 2 diabetic patients[8-12]. However, there was only one limited report of 8 type 2 diabetic patients with macroalbuminuria which showed that administration

of TGZ at the dose of 400 mg/day for 12 months could not lessen the magnitude of macroalbuminuria[10].

In the present study, PGZ 30 mg/day could effectively reduce urinary protein in type 2 diabetic patients with macroalbuminuria (Table 3, Fig. 1, 2). The disparity between the two studies might be caused by the larger number of participants in the present study (n = 40 vs 16) and the difference in the TZD drugs used (PGZ vs TGZ). In this regard, TGZ has been withdrawn from the market since 2002 because of the serious hepatotoxicity of the drug.

The approximately 40% reduction in urinary protein excretion by PGZ in the present study are comparable to the values of 26 to 55% reduction from angiotensin converting enzyme inhibitors and angiotensin receptor blockers in previously reported studies in type 2 diabetic patients with overt nephropathy[14-16].

At present, there are no available data regarding the effect of TZD on TGF-β in diabetic patients. Previous studies have shown that urinary rather than blood levels of TGF-β are correlated with the activity of DN[17,18]. The present study demonstrated that, in type 2 diabetic patients with overt nephropathy, PGZ could lessen urinary TGF-β excretion by 48%. This magnitude of reduction is, of interest, greater than the figures of 23 to 39% decrease by angiotensin II receptor blocker in recent studies in type 2 diabetic patients with overt nephropathy[19] and in proteinuric renal diseases[20].

The pathologic hallmark of DN is increased extracellular matrix in glomerular basement membrane and mesangium, resulting in microalbuminuria and proteinuria[2]. TGF-β appears to play a central role in this process. In agreement with previous works[13,21,22], the present study has demonstrated that urinary type IV collagen excretion is increased in DN. The effect of PGZ on type IV collagen, however, has never been determined in diabetes. In the present study, PGZ could reduce the amount of urinary type IVcollagen by 35% while the levels were increased by 51% in the control group. The statistical significance, however, was nearly but not attained. This might be caused by the small number of subjects. The magnitude of urinary type IV collagen reducing the ability of PGZ, however, is still impressive. Taken together, in type 2 diabetes with macroalbuminuria, PGZ could reduce the synthesis of TGF-β and type IV collagen, leading to improved renal pathology and, consequently, decreased proteinuria.

Although glycemic control in the PGZ group seemed to be better than the control group, it did not reach statistical significance. Moreover, there were no correlations between the difference in glycemic control and the change in urinary protein excretion or urinary TGF-β excretion. Thus, the significant reduction in urinary protein excretion as well as urinary TGF-β excretion by PGZ in the present study was unlikely mediated via better glycemic control.

Since proteinuria and increased urinary TGF-β are associated with progression of DN, pioglitazone, which could effectively reduce proteinuria and urinary TGF-β, may have the therapeutic role in retarding the progression of DN. Larger and longer follow-up randomized controlled trials are needed before the definite role of TZD in DN is clear. Data from the present study in diabetic macroalburic patients and from previous studies in microalbuminuric patients[8-12] would privilege this class of oral hypoglycemic agents, and TZD would be considered as one of the most preferable antidiabetic drugs which could provide beneficial effect on the kidney.

In conclusion, besides the effectiveness in blood sugar control, pioglitazone could salutarily reduce proteinuria and synthesis of TGF-β as well as type IV collagen. These beneficial effects of pioglitazone on diabetic nephropathy are comparable to angiotensin converting enzyme inhibitor and angiotensin receptor blocker.

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ไพโอกลิทาโซนลดปริมาณโปรตีนและทรานส์ฟอร์มมิ่งโกร้ทแฟคเตอร์-เบตาในปัสสาวะในผู้ป่วยเบาหวานชนิดที่ 2 ในระยะโอเวอร์ทเนฟโฟรพาที่

พิสุทธิ์ กตเวทิน, สมชาย เอี่ยมอ่อง, สมพงษ์ สุวรรณวลัยกร

วัตถุประสงค์: *เพื่อศึกษาผลของไพโอกลิทาโซนต่อปริมาณโปรตีนและทรานส์ฟอร์มมิ่งโกร้ทแฟคเตอร์-เบตา ในปัสสาวะในผู้ป่วยเบาหวานชนิดที่ 2 ในระยะโอเวอร์ทเนฟโฟรพาที่*

วัสดุและวิธีการ: *ทำการศึกษาเป็นระยะเวลา 12 สัปดาห์ในผู้ป่วยเบาหวานที่มีปริมาณโปรตีนในปัสสาวะสูงกว่า 500 มก./วัน แบ่งผู้ป่วยเป็น 2 กลุ่ม กลุ่มที่ 1(24ราย) ได้รับไพโอกลิทาโซน (30 มก./วัน) กลุ่มที่ 2 (16 ราย) เป็นกลุ่มควบคุม*

ผลการวิจัย: *ตลอดการศึกษาไม่พบความแตกต่างกันในการควบคุมระดับน้ำตาลและความดันโลหิต ก่อนเริ่มศึกษาไม่มีความแตกต่างของค่าต่าง ๆ ที่ทำการตรวจปริมาณโปรตีนในปัสสาวะในกลุ่มไพโอกลิทาโซนลดลง 40.1 $\pm$ 3% (จาก 16 $\pm$ 0.2 เป็น 0.9 $\pm$ 0.1 กรัม/วัน) ซึ่งมีความแตกต่างอย่างมีนัยสำคัญกับค่า 4.3$\pm$0.1% ที่เพิ่มขึ้นในกลุ่มควบคุม (จาก 1.7 $\pm$ 0.2 เป็น 1.8 $\pm$ 0.2 กรัม/วัน) ปริมาณทรานส์ฟอร์มมิ่งโกร้ทแฟคเตอร์-เบตาในกลุ่มไพโอกลิทาโซนลดลง 47.8% เปรียบเทียบกับ 59.7% เพิ่มขึ้นในกลุ่มควบคุม ($p < 0.05$) ปริมาณคอลลาเจนชนิดที่ 4 ในปัสสาวะในกลุ่มไพโอกลิทาโซนลดลง 35% เปรียบเทียบกับ 51.6% เพิ่มขึ้นในกลุ่มควบคุม ($p = 0.06$)*

สรุป: *นอกจากประสิทธิภาพในการควบคุมระดับน้ำตาลแล้ว ไพโอกลิทาโซนสามารถลดปริมาณของโปรตีนทรานส์ฟอร์มมิ่งโกร้ทแฟคเตอร์-เบตาและคอลลาเจนในปัสสาวะ*