

# Influence of Blood Pressure Level on the Suppression of Proteinuria by Dipyridamole in Diabetic Patients with Nephropathy

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**Summary.** To study the influence of blood pressure on the anti-proteinuric effect of dipyridamole, 14 diabetic patients with proteinuria were divided into two groups: Group A (n=7) in which the mean blood pressure was always >100 mmHg, and Group B (n=7) in which the mean blood pressure might be >100 mmHg. During the observation period, protein excretions and serum creatinine (Cr) were examined every six months. In Group A, the urinary protein excretion increased during the control period and decreased during dipyridamole therapy. In Group B, the urinary protein excretion increased both during the control period and dipyridamole therapy.  $\Delta 1/\text{Cr}$  was lowered in Group A, but changed rather dramatically in Group B by dipyridamole therapy. We conclude that the anti-proteinuric effect of dipyridamole was achieved in patients with a mean blood pressure of < 100 mmHg.

**Key words**—diabetic nephropathy, proteinuria, dipyridamole, anti-hypertensive therapy.

## INTRODUCTION

Dipyridamole has been shown to be effective in reducing urinary protein in patients with diabetic nephropathy.<sup>1-3)</sup> However, the response to this therapy seems variable and affected by blood pressure. As far as we know, the effect of the control of blood pressure on the anti-proteinuric effect of dipyridamole has not been studied. We therefore conducted this study to investigate whether the anti-

proteinuric and renal function-preserving effects of dipyridamole are affected by blood pressure levels.

## MATERIALS AND METHODS

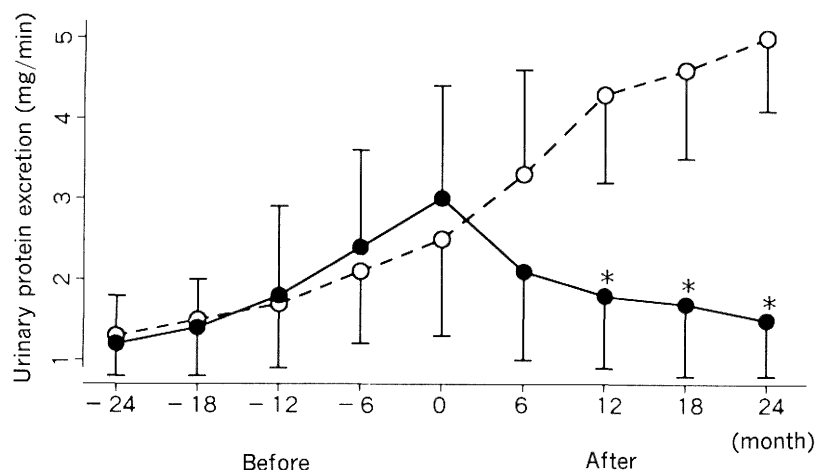
This study included fourteen Type 2 diabetic patients who were treated in our out-patient department. The inclusion criteria were: urinary protein excretion > 1.0 g/day and serum creatinine (Cr) < 180 mmol/l. The clinical profile of the patients is shown in Table 1.

Blood pressure was measured once a month. Depending on blood pressure, the patients were divided into two groups: Group A (n=7) in which the mean blood pressure (diastolic blood pressure + pulse pressure/3) was always < 100 mmHg without anti-hypertensive therapy, and Group B (n=7) in which the mean blood pressure was always >100 mmHg (Fig. 1). Three patients of Group B were treated with antihypertensive drugs: a calcium-channel blocker in two and beta-blocker in one. In Group A, had three patients with a family history of hypertension, with six in Group B.

Urine samples timed overnight (22:00-8:00) were collected and the urinary concentrations of protein were measured every six months for 24 months by the CBB pigment binding method. The serum Cr and  $1/\text{Cr}$  was calculated every six months and the slope of  $1/\text{Cr}$  ( $\Delta 1/\text{Cr}$ ) vs. time was determined by the least square method. The level of glycosylated hemoglobin (HbA1c) was measured every month. Dipyridamole 300 mg/day was administered for 12 months.

Values are expressed as mean  $\pm$  S.D. Statistical analysis was performed by the Wilcoxon's method or paired t-test.

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**Fig. 1.** Changes in urinary protein excretion before and after treatment with dipyridamole. Urinary protein excretion decreased after treatment with dipyridamole in Group A (—). In Group B (---), urinary protein excretion increased before and after treatment with dipyridamole. \* $p < 0.05$  vs. Group B.

**Table 1.** Clinical profile of diabetic patients

	Group A	Group B
Male/Female	3/4	4/3
Age (years)	48.3 ± 11.8	45.9 ± 11.9
Duration of diabetes (years)	8.9 ± 3.4	9.2 ± 4.8
HbA1c (%)	6.8 ± 1.2	6.7 ± 1.4
Treatment*	1 / 3 / 3	1 / 3 / 3
Retinopathy**	0 / 3 / 4	0 / 2 / 5

\*diet alone/oral hypoglycemic agent/insulin

\*\*background/pre-proliferative/proliferative

## RESULTS

### Urinary protein

In Group A, urinary protein excretion increased during the control period ( $p < 0.05$ ), but was reduced by dipyridamole at the end of 24 months of therapy ( $p < 0.05$ ). In Group B, the urinary protein excretion increased during the control period ( $p < 0.05$ ), and increased during the 24 months of therapy with dipyridamole ( $p < 0.05$ ).

### Renal function

$\Delta 1/\text{Cr}$  was  $1.6 \times 10^{-3}$  (mmol/l) $^{-1}$ /year in Groups A and B before dipyridamole administration, and declined less rapidly in Group A ( $-0.5 \times 10^{-3}$  (mmol/l) $^{-1}$ /year). In Group B, it declined more rapidly ( $-3.2 \times$

$10^{-3}$  (mmol/l) $^{-1}$ /year) during dipyridamole therapy (Fig. 2).

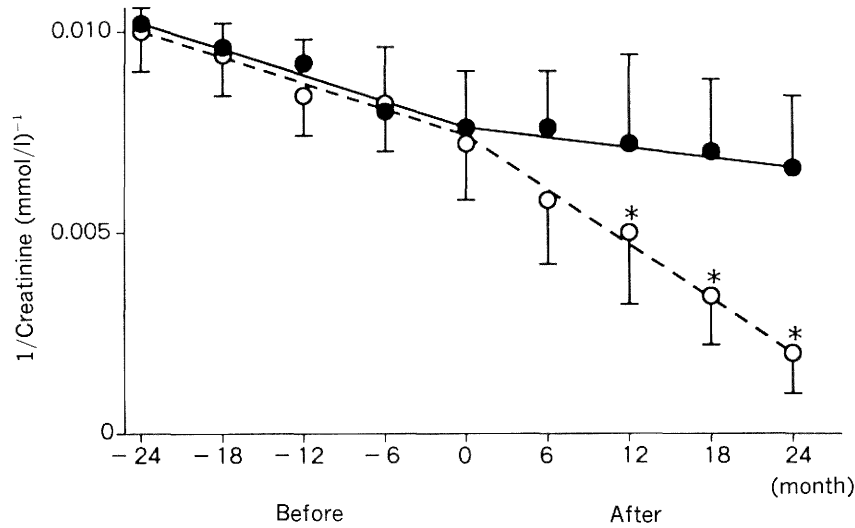
The level of HbA1c did not change in Groups A and B, as there were no significant differences between the two groups (Table 3).

## DISCUSSION

The anti-proteinuric effect of dipyridamole has already been reported in patients with diabetic nephropathy,<sup>1-3</sup> but inconsistent responses might have been observed. The present study demonstrated that the anti-proteinuric effect of dipyridamole was achieved in patients with a mean blood pressure of  $< 100$  mmHg.

The mechanisms of protein leakage into the urine in diabetic nephropathy include: (a) loss of negative charge on the basement membrane of renal glomeruli,<sup>4</sup> (b) increased intra-glomerular pressure,<sup>5</sup> (c) an impaired size barrier in the glomerulus,<sup>4</sup> and (d) higher permeability of the wall of glomerular loops due to an accelerated platelet aggregation ability.<sup>6</sup> It has been reported that the control of blood pressure is effective in suppressing diabetic nephropathy.<sup>7</sup> Dipyridamole is reported to improve (a) and (d) abnormalities.<sup>2,8</sup> Since controlling blood pressure improves (b), the combination of dipyridamole and well-controlled blood pressure would correspond to two therapies with different action mechanisms, with a result of the further improvement of proteinuria.

In the present study, anti-proteinuric and renal function preserving effects of dipyridamole were



**Fig. 2.** Changes in renal function (1/Cr) before and after treatment with dipyridamole. Before the administration of dipyridamole, 1/Cr was  $-0.0016$  (mmol/l)<sup>-1</sup>/year in both groups. After treatment with dipyridamole,  $\Delta 1/Cr$  was  $-0.0005$  (mmol/l)<sup>-1</sup>/year in Group A (—), and  $\Delta 1/Cr$  in Group B (---) was  $-0.0032$  (mmol/l)<sup>-1</sup>/year after treatment with dipyridamole.

**Table 2.** Mean blood pressure before and after treatment with dipyridamole

Group	Before					After			
	-24	-18	-12	-6	0	6	12	18	24 (month)
A	94.2 ±5.6	96.1 ±6.9	95.7 ±4.1	95.9 ±6.0	96.1 ±7.4	94.3 ±5.8	94.9 ±5.5	93.7 ±5.0	96.6 ±6.5
B	104.4* ±6.3	105.0* ±7.2	104.2* ±5.5	106.3* ±6.1	107.9* ±4.9	105.8* ±7.7	106.0* ±6.6	105.9* ±5.5	107.8* ±4.8

Values are expressed as mean±S.D. in mean blood pressure (mmHg).  
\*p<0.05 vs. Group A.

**Table 3.** Glycosilated hemoglobin before and after treatment with dipyridamole

Group	Before					After			
	-24	-18	-12	-6	0	6	12	18	24 (month)
A	6.8±1.2	6.7±1.3	7.0±1.1	6.9±1.0	7.1±1.1	7.2±1.3	6.9±1.2	6.7±1.0	6.6±1.2
B	6.7±1.4	7.0±1.5	7.1±1.5	7.3±1.3	6.9±1.4	6.8±1.5	7.0±1.3	6.9±1.5	6.8±1.6

Values are expressed as mean±S.D. in HbA1c (%).

observed in patients with the mean blood pressure always at < 100 mmHg; however, the changes in renal function and proteinuria were not compared between patients with well-controlled blood pressure with or without dipyridamole therapy. This point has

to be further studied.

Furthermore, we did not perform histological studies and were not able to relate the effect of dipyridamole to some specific lesion, this being another point to be studied.

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