

Originals

Current therapeutic management of diabetic nephropathy

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Abstract. Roughly 40% of all patients with insulin-dependent diabetes mellitus (IDDM) develop diabetic nephropathy with proteinuria, hypertension and a decrease in glomerular filtration rate 10 to 20 years after the onset of the disease, and 5 years later most patients suffer from end-stage renal disease. Microalbuminuria, defined as an urinary albumin excretion rate (UAER) between 30 and 300 mg/day, strongly predicts the development of nephropathy in IDDM. Nearly all patients with IDDM, a decreasing glomerular filtration rate and a UAER > 300 mg/day have coexisting hypertensive disease additionally worsening renal function. We review the results of recent long-term studies of the current therapeutic management in diabetic patients by means of better blood pressure control, low-protein diet and near-normal blood glucose control in the early microalbuminuric phase as well as in the later phases of the disease characterized by diabetic nephropathy with a UAER > 300 mg/day. Since the large majority of studies have been performed on IDDM, our conclusions with regard to therapy are only valid in this subgroup of diabetic patients.

Key words: Diabetic nephropathy – ACE inhibitor – Protein restriction – Microalbuminuria

Introduction

Diabetic nephropathy, characterized by proteinuria, hypertension and a decrease in glomerular filtration rate (GFR), occurs in approximately 40% of insulin-dependent diabetes mellitus (IDDM) patients 10–20 years after the onset of IDDM [1, 2]. Microalbuminuria strongly predicts the development of diabetic nephropathy [3, 4, 5]. Very often patients with IDDM, a decreasing GFR and a urinary albumin excretion rate (UAER) > 300 mg/

day have coexisting hypertensive disease additionally worsening renal function [6]. Diabetic nephropathy is one of the leading causes of end-stage renal disease [7]. Therefore therapeutic regimens to delay or even prevent the development of end-stage renal disease are of great importance. We discuss three different therapeutic approaches to diabetic nephropathy in the microalbuminuric and macroalbuminuric phases of the disease. First, the influence of blood glucose levels on the progression of the disease is considered. Second, the effects of low-protein diets on GFR and micro- and macroalbuminuria are evaluated. Finally, the role of antihypertensive therapy in normotensive or hypertensive patients with either micro- or macroalbuminuria is discussed.

Blood glucose control

Blood glucose control in microalbuminuria and diabetes mellitus

Recently a number of long-term studies investigating whether the development of diabetic nephropathy may be prevented or slowed by strict glycaemic control, measured by HbA_{1c} levels, have been published. The Kroc Collaborative Study Group demonstrated a decrease in UAE in patients with a HbA_{1c} level of 8.1% over a period of 8 months. Feldt-Rasmussen et al. studied patients with a HbA_{1c} level of 7.2% over 2 years and also noted a decrease in albumin excretion. In both studies the group of patients with HbA_{1c} levels of 8.1% or 7.2%, respectively, were treated with continuous subcutaneous insulin infusion (CSII). None of the patients in the control group receiving conventional insulin treatment (CIT) showed a significant or sustained improvement in the degree of metabolic control [8, 9, 10]. The Kroc Collaborative Study Group found a decrease in UAER in microalbuminuric patients on CSII with HbA_{1c} levels of 8.1% [8, 9]. In contrast, Feldt-Rasmussen et al. did not observe a decrease in UAER in subjects on CSII, and indeed the rate was unchanged after 2 years of treatment (170 vs

160 mg/min). On the other hand, microalbuminuric patients on CIT experienced no change in HbA_{1c} and a significant rise in UAER (160 vs 360 mg/min) [10]. Good blood glucose control with HbA_{1c} levels of 8.1% or 7.2% was achieved with CSII (Table 1) [8, 9, 10]. Reichard et al. treated 44 patients with intensified insulin treatment (IIT) for 3 years. The measured HbA_{1c} levels were 7.4% compared with 9.0% in the control patients who received regular insulin treatment. The improved blood glucose control of the 44 patients being treated with IIT delayed the development of diabetic nephropathy compared with the control patients receiving regular treatment [11]. In the Steno 1 and Steno 2 studies [12] a total of 51 patients with IDDM and microalbuminuric were followed for 8 and 5 years. In the conventional treatment group an increase in UAER, a decline in GFR and a rise in blood pressure were found only in patients with high microalbuminuria (100–300 mg/day), whereas in the same subgroup of patients treatment with CSII resulted in a stable UAER and GFR. Analysing the 19 patients with a UAER of 100–300 mg/day, 2 out of 9 in the CSII group progressed to diabetic nephropathy, compared with 10 out of 10 patients in the regular treatment group. Only 1 patient out of 32 with microalbuminuria in the range of 30–99 mg/day developed diabetic nephropathy. Intensive blood glucose control in the Diabetes Control and Complications Trial (DCCT) was associated with a 39% reduction in the occurrence of microalbuminuria (≥ 40 mg/day) and a 54% reduction in the occurrence of diabetic nephropathy (≥ 300 mg/day). In this study 1441 IDDM patients were followed for a median of 6.5 years after random allocation to intensive therapy (external insulin pump or ≥ 3 daily insulin injections) or to conventional therapy (≤ 2 daily insulin injections) [13].

Blood glucose control with near-normal UAER in diabetes mellitus

In the 7-year Oslo study [14], 8 out of 10 patients with IDDM and HbA_{1c} levels of 8.5% showed a decrease in UAER, while 4 out of 14 patients with HbA_{1c} levels

greater than 10% developed significant increases in UAER to > 200 mg/day. Blood glucose control was achieved by CSII in 10 patients, by IIT in 33 patients and by CIT in 2 patients. All patients participating in the Oslo study had a mean UAER in the upper normal range during the 2 months prior to enrolment in the study (Table 1). Thus, near-normoglycaemic blood glucose levels with HbA_{1c} levels below 8% delay the onset of diabetic nephropathy in patients with microalbuminuria and UAER in the upper normal range. It remains unproved whether good glycemic control prevents worsening of renal function in manifest diabetic nephropathy.

Protein restriction

Effect of protein restriction in diabetic nephropathy

Low-protein diets improve the haemodynamic situation in the glomerulus and reduce proteinuria in rats with streptozocin (STZ)-induced diabetes. The degree of histological change in diabetic nephropathy is also improved by a low-protein diet [15, 16]. Walker et al. [17] and Zeller et al. [18] examined the effects of a low-protein diet (0.6–0.7 g protein/kg per day) in 19 and 20 patients, respectively, with diabetic nephropathy. The study by Walker et al. had a case-control design. In the study by Zeller et al., 15 patients received a control diet containing at least 1 g protein/kg per day. The follow-up periods were 33 and 37 months, respectively, for the two studies. The patients with a restricted protein intake had a decrease in proteinuria and a reduced decline in GFR (Fig. 1). In another study Brouhard and LaGrone also demonstrated a beneficial effect of a reduced protein intake on GFR and on albuminuria [19]. Evanoff et al. [20] observed eight patients with IDDM, proteinuria (protein excretion > 0.5 g/day) and renal insufficiency for 12 months before and 12 months after the introduction of dietary protein restriction to 40 g high biological value protein/day. The creatinine clearance before starting the protein-restricted diet (55 ± 27) ml/min was not significantly different from that after 12 months of the diet (56 ± 25 ml/min). The mean daily urinary protein excretion

Table 1. Blood glucose control and its effect on UAER and GFR in diabetes mellitus

	Kroc Collaborative		Feldt-Rasmussen		Steno 1 and 2 [12]		Oslo study [14]		
Insulin regimen	CIT	CSII	CIT	CSII	CIT	CSII	CIT, CSII or IIT		
Number of patients	10	10	18	18	10	9	45		
Follow-up	8 months		24 months		5–8 years		7 years		
HbA _{1c} (%)							HbA _{1c}	HbA _{1c}	HbA _{1c}
End of study	10.3	8.0	8.6	7.2	9.4	7.7	< 9.0	9.1–10	> 10
UAER (mg/day)									
Beginning of study	70.4	70.4	88.7	95.2	181	163	20	17	26
End of study	nsd	2.3*	100	78**	713	167**	25	25	91*
GFR (ml/min)									
Beginning of study	–	–	116	109	110	113	115	114	118
End of study	–	–	114	99	87	100	108	107	114

CIT, Conventional insulin treatment; CSII, continuous subcutaneous insulin infusion; IIT, intensified insulin treatment; nsd, no significant decline

* Significant difference between beginning and end of study ($P \leq 0.02$)

** Significant difference between CIT and CSII at end of study ($P \leq 0.002$)

fell from 2.11 ± 1.36 g/day before dietary protein restriction was started to 0.14 ± 0.16 g/day after 12 months of the diet. In a later study [21], Evanoff et al. followed 11 IDDM patients suffering from proteinuria (> 0.5 g/day) and renal insufficiency on a diet containing 0.6 g/kg per day high biological value protein for 2 years. In a similar manner to the earlier 12-month study, creatinine clearances at 12 and 24 months of protein restriction were not significantly different from those obtained at the beginning of the low-protein diet. Urinary protein excretion again decreased after the initial 12 months to 0.57 ± 0.40 g/day compared with 2.27 ± 0.49 g/day at the beginning of the study. However, after 24 months of the low-protein diet urinary protein excretion increased to 1.43 ± 0.63 g/day. According to the authors, one reason for this phenomenon might have been non-compliance with the dietary regimen, expressed as higher urea nitrogen concentrations in urine samples.

Effect of protein restriction on GFR and microalbuminuria

In a crossover study lasting only 3 weeks, Cohen et al. observed a decrease in UAER to 22 mg/day in eight nor-

motensive patients with IDDM and microalbuminuria who received a low-protein diet of 38–57 g protein/day. A protein intake of 55–117 g/day resulted in UAER of 33 mg/day [22]. The results of this study imply that a low-protein diet causes a reduction in UAER even in the microalbuminuric phase of the disease. Long-term studies with a larger number of patients are required to determine the stage of disease (microalbuminuria versus nephropathy) at which protein restriction should be started.

Role of antihypertensive therapy

Normotension and microalbuminuria in diabetes mellitus

In a randomized, placebo-controlled, double-blind study of 20 patients, of whom 10 suffered from NIDDM, microalbuminuria and normotension and the other 10 from IDDM, microalbuminuria and normotension, Marre et al. demonstrated that the ACE inhibitor enalapril 20 mg/day induced a significant decrease in UAER during the first 6 months of treatment. None of the diabetics in the treatment group developed diabetic nephropathy, whereas three patients in the placebo group progressed to diabetic nephropathy during the complete follow-up of 1 year [23, 24]. However, the mean arterial pressure was reduced by enalapril administration (Table 2). It is not clear whether the decrease in mean arterial pressure or the vasodilating effect of the ACE inhibitor at the vas efferens was responsible for the noted decrease in microalbuminuria [23, 24]. The Melbourne Study Group followed 43 diabetic patients for 1 year, of whom 30 were normotensive and 13 hypertensive, and 19 suffered from IDDM and 24 from NIDDM [25]. In the subgroup of patients with IDDM or NIDDM, microalbuminuria and normotension there was no significant change in UAER under treatment with either perindopril or nifedipine. None of these patients progressed to diabetic nephropathy. In the 13 hypertensive subjects also suffering from

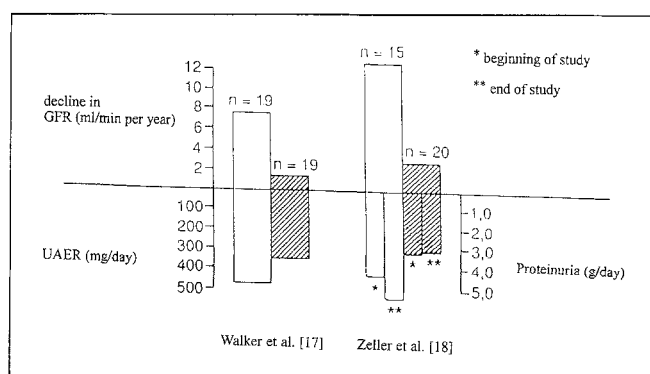


Fig. 1. Decline in UAER and diminished loss of GFR with low-protein diet (0.6–0.7 g/kg per day). Open bar, control group; filled bar, treatment group

Table 2. Normotension and microalbuminuria in diabetes mellitus

	Melbourne Study Group [25]		Mathiesen et al. [28]		Marre et al. [23, 24]	
	Perindopril (2–8 mg/day)	Nifedipine (20–80 mg/day)	Captopril (25–100 mg/day)	Control	Enalapril (20 mg/day)	Control
Number of patients	30	30	21	23	10	10
Follow-up	12 months		4 years		12 months	
Mean RR (mmHg)						
Beginning of study	99	99	103	101	90	97
End of study	93	93	98	100	86	102
UAER (mg/day)						
Beginning of study	49	45	82	105	—	—
End of study	36	48	57	166*	—	—
GFR (mg/min)						
Beginning of study	—	—	126	129	131	129*
End of study	—	—	120	127	124	109**

* Significant difference between two treatment groups at end of study ($P < 0.05$)

** Significant difference between beginning and end of study ($P < 0.05$)

IDDM or NIDDM and microalbuminuria, both treatments reduced UAER significantly (Table 2). Cook et al. found a significant decrease in UAER during 3 months of ACE inhibitor therapy with captopril in 12 normotensive adolescents [26]. Another short-term study lasting 6 weeks [27] showed a 40% decrease in UAER during captopril treatment compared with a 40% increase during nifedipine treatment and no change in UAER in the placebo group. The study population comprised microalbuminuric patients with IDDM randomly assigned to one of the two treatment groups or to the placebo group. In a 4-year prospective randomized, controlled study of 44 normotensive patients with microalbuminuria and IDDM [28], captopril 25–100 mg/day with the addition of bendrofluazide 2.5 mg/day after 30 months resulted in a decrease in UAER. During this long-term study none of the patients in the treatment group progressed to diabetic nephropathy, whereas seven patients in the placebo group developed diabetic nephropathy with a UAER of > 300 mg/day (Table 2). The above-mentioned results suggest a positive effect of ACE inhibition on renal function in patients with microalbuminuria and normotension.

Hypertension and microalbuminuria in diabetes mellitus

Patients with diabetes mellitus and microalbuminuria often suffer from high blood pressure in the further course of their disease. Christensen and Mogensen observed a correlation between the duration of the disease and the degree of microalbuminuria, as well as between the elevation of diastolic blood pressure and the worsening of microalbuminuria [29]. Gambardella et al. treated ten patients with NIDDM, hypertension and microalbuminuria with indapamide 2.5 mg/day for 2 years [30]. Microalbuminuria significantly decreased. Two studies have compared the effects of an ACE inhibitor and a calcium antagonist in hypertensive patients with diabetes mellitus and microalbuminuria: 2–8 mg/day perindopril vs 20–80 mg/day nifedipine in 13 IDDM and NIDDM patients for 12 months [25]; 10–20 mg/day enalapril vs 60–120 mg/day nicardipine in seven IDDM patients for 4 weeks [31]. No significant differences in terms of lowering of blood pressure, decrease in microalbuminuria and GFR could be shown between the two types of agents [25, 31]. In contrast, Pedersen et al. observed a further decline in UAER after adding an ACE inhibitor to the antihypertensive regimen in ten patients with IDDM [32]. Antihypertensive treatment is valuable in patients with microalbuminuria and hypertension. In animal studies ACE inhibitors have been shown to be superior to other antihypertensive agents, but as far as we know, long-term studies proving superiority of ACE inhibitors over conventional antihypertensive therapy in humans are lacking, although as stated above short-term studies demonstrate that the addition of an ACE inhibitor to antihypertensive therapy has a favourable effect on UAER.

Normotension and diabetic nephropathy

Parving et al. [33] found that 15 normotensive IDDM patients with nephropathy treated with an ACE inhibitor

(captopril 25–100 mg/day) for 12 months showed a decrease in mean arterial pressure of 3 mm Hg, in UAER of 11% and in GFR of 3 ml/min per 1.73 m², while the 17 untreated control patients showed an increase in mean arterial pressure of 6 mmHg, an increase in UAER of 55% and a decrease in GFR of 6 ml/min per 1.73 m². Although the rate of decline in GFR was not statistically significant in this study, the results suggest that treatment of patients with still-normal blood pressure and diabetic nephropathy with an ACE inhibitor might reduce the rate of or prevent the decline in GFR.

Hypertension and diabetic nephropathy

Diabetic patients with nephropathy have a 50–70% risk of developing hypertension, often resulting in a further decline in renal function [1]. In the first long-term study of a small group of patients with IDDM, proteinuria and high blood pressure treated with propranolol and later with metoprolol (100–200 mg/day), a diminished loss of GFR and a decrease in proteinuria was found in treated patients. Three and four, respectively, of the six patients were additionally treated with 40 mg/day frusemide and 100–200 mg/day hydralazine [34]. Good blood pressure control achieved with metoprolol, hydralazine and frusemide was shown to slow the decline in GFR and reduce proteinuria in 11 patients with IDDM, nephropathy and high blood pressure. This study lasted for 6 years [35], and a follow-up to a total of 9.7 years confirmed the results in the same 11 patients [36]. The rate of the decline in GFR decreased from 10.7 ml/min per year before treatment to 2.5 ml/min per year during antihypertensive therapy. UAER fell from 1.5 g/day to 0.8 g/day [36]. In another study, Parving et al. treated 18 hypertensive patients with nephropathy with the ACE inhibitor captopril and a diuretic frusemide or bendrofluazide. During the 2.5 years of follow-up UAER decreased and a reduced decline in GFR was noted (Fig. 2) [37]. Björk et al. used an antihypertensive therapy combining an ACE inhibitor (captopril), a diuretic, a beta-blocker and a calcium antagonist [38]. Mean arterial blood pressure was lowered by 5 mmHg and the decline in renal function was slowed in all 14 patients (Fig. 2). Björk et al. thus confirmed the beneficial impact of ACE inhibition on UAER and GFR. In a 2-year follow-up, 22 of 40 IDDM patients with diabetic nephropathy were treated with 5–20 mg/day enalapril and the other 18 patients received up to 200 mg/day metoprolol [39]. A diuretic was added to the treatment of both groups. The rate of decline in GFR was 2.0 ml/min per year in the enalapril group and 5.6 ml/min per year, a surprisingly high value, in the metoprolol group. UAER was 60% lower in the enalapril group. The supine diastolic blood pressure was 6 mmHg lower in the enalapril group, whereas the standing mean arterial pressure did not differ significantly between the two treatment groups. In the group treated with enalapril one patient had a rise in serum creatinine and was withdrawn from the study. However, a superior effect on GFR of an ACE inhibitor compared with a beta-blocking agent could not be confirmed in a study by Grönhagen-Riska

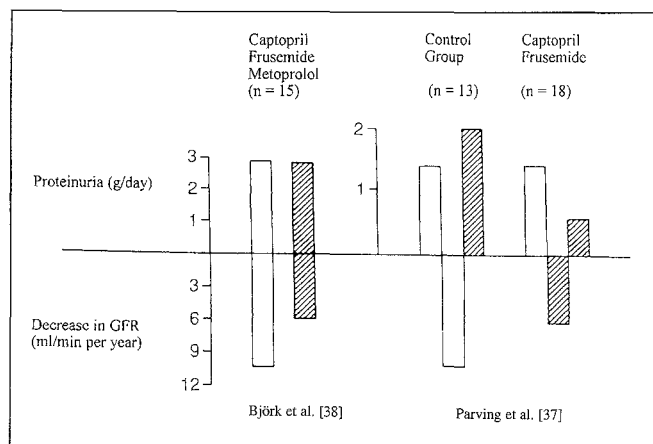


Fig. 2. Effects of antihypertensive treatment on proteinuria and GFR in patients with diabetic nephropathy. *Open bar*, before therapy; *filled bar*, after therapy

et al. [40]. In a recent study by Lewis et al., 409 IDDM patients were followed up for a median of 3 years in a randomized controlled trial. 207 patients (155 hypertensive) received 3 · 25 mg/day of captopril and 202 patients (153 hypertensive) received placebo. Doubling of serum creatinine and the combined endpoints of death, dialysis and transplantation were significantly higher in the placebo group. However blood pressure control was better, GFR as baseline higher and protein excretion lower in the captopril group [41]. Therapy to normalize blood pressure slows the progression of renal disease in manifest diabetic nephropathy, but study results so far have not demonstrated a clear superiority of any one class of antihypertensive agents (e.g. ACE inhibitors).

Future trends and perspectives in treating diabetic nephropathy

In animal models thromboxane (TX) A₂ seems to be of relevance in the pathogenesis of diabetic nephropathy. In a controlled study the effects of the dietary administration of the TX synthetase inhibitor OKY-046 on urinary protein excretion and serum BUN were evaluated in 20 STZ-induced diabetic rats [42]. The treated group developed a urinary protein excretion of 64.1 mg/day compared with 85.6 mg/day in the control group. The treated rats also showed a reduced thickening of the glomerular basement membrane, lower serum glucose levels and normalization of enhanced platelet aggregation, but no significant differences in the serum BUN levels of the treated and control groups were found. Unfortunately the GFR was not studied. No side effects of OKY-046 have been reported. It might therefore be a promising therapy in humans as well, but further evaluation is clearly needed.

In experimental diabetes using STZ diabetic rats, the administration of indomethacin an inhibitor of prostaglandin synthesis, leads to an increase in the afferent arteriolar hydraulic resistance and a moderate increase in the efferent resistance causing a reduction in the hydraulic pressure in the glomerular capillaries [43]. In a

small randomized double-blind trial the effects of 150 mg/day indomethacin for 3 days were studied in 8 patients with IDDM and microalbuminuria, who were compared with a placebo group of 9 normoalbuminuric IDDM patients and 11 healthy controls [44]. Indomethacin caused a significant reduction in UAER (from 207 to 87 mg/day) and in prostaglandin E₂ urinary excretion (from 317 to 103 pg/ml), which was elevated compared with two control groups not suffering from microalbuminuria. GFR remained stable. In a more recent study the beneficial effect of indomethacin on exercise-induced UAER in IDDM with microalbuminuria was confirmed [45]. Of the 14 patients with IDDM studied, 9 suffered from microalbuminuria at rest and 5 were normoalbuminuric. The patients were treated in a randomized cross-over design with a single oral dose of indomethacin, metoprolol or placebo shortly before exercising. The rise in UAER in the microalbuminuric patients receiving indomethacin was lower than in those receiving placebo or metoprolol (7, 29 and 18 µg/min). Although the results of animal studies and short-term evaluations in small groups of patients are promising, the long-term influence of prostaglandin synthesis inhibitors on diabetic nephropathy is not yet known.

Some investigators have suggested the polyol-sorbitol pathway to be of major importance in the development of diabetic nephropathy. Oates et al. demonstrated a dose-dependent reduction in UAER in STZ-induced diabetic rats being treated with zopolrestat, an aldose-reductase inhibitor [46]. With a dose of 100 mg/kg the elevated UAER was reduced by 77%. In a short-term double-blind, cross-over study aldose reductase inhibition with 600 mg/day polanrestat given for 3 months to 28 microalbuminuric IDDM patients decreased UAER significantly compared with placebo (37 mg/day decrease vs 16.5 mg/day increase) [47].

Although, as mentioned above, ACE inhibitors so far have not been proven to be superior to other antihypertensive agents in delaying the decline in renal function in patients with microalbuminuria in long-term studies, the treatment of diabetic uninephrectomized rats before microalbuminuria was present with the ACE inhibitor, fosinopril, markedly limited the development of progressive albuminuria after 8 months of diabetes, compared with control groups receiving either nifedipine or no antihypertensive agent. The value for UAER in the ACE inhibitor group was 32 mg/day, for the nifedipine group 136 mg/day and 113 mg/day for the group without antihypertensive therapy [48]. The positive effect of ACE inhibition on the development of microalbuminuria has also been confirmed in another animal study [49]. Based on these animal trials it could be the case that patients with IDDM may profit from the administration of an ACE inhibitor even before microalbuminuria has developed.

A positive effect of dipyridamole on the UAER of patients suffering from diabetes mellitus has been reported [50]. In 27 patients suffering from NIDDM an increase in the U_{alb}/U_{creat} ratio of 0.80 per month was found over an observation period of 10.8 months. After the observation period 11 patients with a U_{alb}/U_{creat} ratio of

> 1.0 were treated with 50 mg dipyridamole three times daily for 4.2 months. A decrease in the U_{alb}/U_{creat} ratio of 0.36 per month was found. Four of the patients were on insulin, the others were taking oral antidiabetics. Another 15 patients without a prior observation period and a U_{alb}/U_{creat} ratio > 1.0 received the same amount of dipyridamole for 9 months, resulting in a decrease in the U_{alb}/U_{creat} ratio of 0.43 per month. Unfortunately the authors did not record the daily albumin excretion to demonstrate the effect of dipyridamole on UAER. Furthermore, untimed urine samples were taken. It is therefore difficult to compare the above results with those of other study regimens, and further, more standardized evaluations of dipyridamole in diabetic nephropathy are needed.

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