奈医誌. (J. Nara Med. Ass.) **46**, 551～556, 1995

EFFECT OF DIETARY PROTEIN RESTRICTION AND NUTRITIONAL ASSESSMENT ON EARLY-STAGE DIABETIC NEPHROPATHY

MASAO KANAUCHI, YOSHIHIRO FUJII, TOSHIO HASHIMOTO and KAZUHIRO DOHI
First Department of Internal Medicine, Nara Medical University
Received October 12, 1995

Abstract : We evaluated the effects of a protein-limited diet on renal function, urinary albumin excretion and nutritional status of 16 patients with non-insulin dependent diabetes mellitus (11 males and 5 females, mean age 60.5 years) had a urinary albumin excretion rate of between 15 and 200 μg/min and were classified into two groups : group I patients were placed on a protein-limited diet (0.77 g/kg/day), and group II followed a conventional diabetic diet (1.33 g/kg/day). After six months, the value of creatinine clearance was significantly reduced in group I, but urinary albumin excretion did not change in either group. Anthropometric measurements revealed no significant change in body weight, body mass index, arm circumference or triceps skinfold thickness in either group during the study period, but the arm muscle circumference significantly increased in group I. No significant differences were observed in either group with regard to serum level of protein, including total protein, albumin, prealbumin or transferrin, In conclusion, a protein-limited diet was useful for prevention of diabetic nephropathy in patients with early-stage diabetic nephropathy.

Index Terms

anthropometric measurement, diabetic nephropathy, nutritional status, protein-limited diet, urinary albumin

INTRODUCTION

Dietary protein restriction retards the progression of chronic renal failure[1-4]. Such beneficial effects have also been reported in patients with advanced diabetic nephropathy[5-14]. A strict restriction of protein intake (0.6 g/kg of body weight) significantly reduced urinary albumin excretion[5-7,9-11,14] and decreased the rate of renal deterioration[6-10,12,13]. The usefulness of a low-protein diet in patients with early-stage diabetic nephropathy has not been established[15-17], and controversy exists over whether dietary therapy can directly influence nutritional status. The Committee on Food and Nutrition of the American Diabetes Association[18] reported in 1986 that the recommended dietary protein allowance for nutritional management of patients with incipient renal disease is 0.8 g/kg of body weight. This moderate restriction of protein intake, or "protein-limited diet", may produce beneficial results in diabetic patients and should be considered as dietary therapy even for patients with early-stage diabetic nephropathy[19]. To confirm this hypothesis, we investigated the effects of a protein-limited diet on the nutritional status of diabetic patients with microalbuminuria.

PATIENTS AND METHODS

We studied 16 microalbuminuric patients with non-insulin dependent diabetes mellitus (NIDDM), 11 males and 5 females aged 49 to 69 years (mean 60.5 years). They were selected because their urinary albumin excretion rate in 24 hour urine collection was 15~200 μg/min. Informed consent was obtained after description of the protocol, then patients were randomly allocated to following a protein-limited diet or their usual diet for 6 months. Group I consisted of 8 patients receiving the protein-limited diet (0.77±0.18 g/kg protein daily), and group II contained 8 patients who followed their usual diet (1.33±0.34 g/kg protein daily). The clinical features of these groups are summarized in Table 1. All patients attended the outpatient clinic every month, and they were permitted to maintain their daily exercise during the study period. Blood urea nitrogen (BUN), serum creatinine, serum β_2-microglobulin (β_2MG), HbA$_1$c, urinary albumin excretion and creatinine clearance were determined at the beginning of the study and at the end of the 6-month period. Nutritional status was assessed by anthropometric measurements and biochemical parameters. Calculated anthropometric measurements included body weight (BW), body mass index (BMI), arm circumference (AC), triceps skinfold thickness (TSF), and arm muscle circumference (AMC)[20,21]. Biochemical parameters of visceral proteins, including serum total protein, serum albumin, serum prealbumin and serum transferrin, were also measured[22]. Compliance with dietary prescriptions was estimated using Maroni's formulas to calculate urinary output of urea nitrogen plus non-urea nitrogen[23]. Patients' dietary records were also evaluated to establish compliance. Patients recorded their own prospective 5-day food-intake diaries twice during the study (at 2 and 4 months after the start of the study), from which estimates of the average daily nutrient composition were determined for calories and protein.

Table 1. Clinical features

Items	Protein-limited diet (group I)	Conventional diet (group II)
Gender (M/f)	4/4	7/1
Age (year)	60.0±6.9	60.9±6.2
Duration of diabetes (year)	11.5±10.3	9.0±5.0
Treatment (D/A/I)	2/3/3	3/4/1
HbA$_1$c (%)	7.7±1.6	7.5±1.4
Protein intake (g/kg/day)	0.77±0.18	1.33±0.34[a]
Total energy (Cal/day)	1,576±293	1,500±367

Treatment modalities are : (D) dietary therapy ; (A) oral anti-hyperglycemic agent ; (I) insulin therapy.
a ; $p<0.05$ vs group I

Table 2. Renal function and urinary albumin excretion before and 6-months after dietary therapy

Items	Protein-limited diet (group I)	Conventional diet (group II)
BUN (mg/dl)	20.3±4.7 22.0±4.6	22.3±6.6 20.1±3.7
Serum creatinine (mg/dl)	0.60±0.14 0.63±0.13	0.85±0.49 0.81±0.30
Serum β_2MG (mg/l)	1.34±0.24 1.39±0.32	1.73±0.83 1.66±0.80
Ccr (ml/min)	91±33 ┐* 81±35 ┘	104±43 112±46[a]
Urinary albumin (μg/min)	50.8±32.5 54.9±41.9	53.3±21.0 76.2±45.9

In each block of the table, the upper column indicates the data at the start of the study, and the lower column the data at the end point.
Abbreviations are : BUN, blood urea nitrogen ; β_2MG, β_2-microglobulin ; Ccr, creatinine clearance.
The asterisk indicates significant difference ($p<0.05$).
a ; $p<0.05$ vs group I

Table 3. Anthropometric measurements before and 6-months after dietary therapy

Items	Protein-limited diet (group I)	Conventional diet (group II)
BW (kg)	60.5±8.9	60.6±8.2
	61.5±9.0	60.9±8.5
BMI (kg/m²)	23.3±3.6	23.7±2.3
	23.7±3.4	23.9±2.5
AC (cm)	25.6±2.1	25.9±1.5
	26.1±1.8	25.9±1.8
TSF (mm)	12.0±5.5	9.9±2.9
	10.9±4.3	7.6±2.0
AMC (cm)	21.8±2.4 *	22.8±1.6
	22.6±1.9 *	23.5±1.9

In each block of the table, the upper column indicates the data at the start of the study, and the lower column the data at the end point.
Abbreviations are : BW, body weight ; BMI, body mass index ; AC, arm circumference ; TSF, triceps skinfold thickness ; AMC, arm muscle circumference.
The asterisk indicates significant difference ($p<0.05$).

Table 4. Biochemical nutritional parameters before and 6-months after dietary therapy

Serum protein concentrations	Protein-limited diet (group I)	Conventional diet (group II)
Total protein	7.28±0.43	7.11±0.40
(g/dl)	7.15±0.29	7.11±0.24
Albumin	4.44±0.23	4.39±0.24
(g/dl)	4.39±0.23	4.41±0.22
Prealbumin	28.7±7.1	30.5±4.8
(mg/dl)	28.1±7.8	28.6±4.1
Trastferrin	293±74	275±40
(mg/dl)	271±62	273±43

In each block of the table, the upper column indicates the data at the start of the study, and the lower column the data at the end point.

Statistical analysis

Results are expressed as mean±SD. Significance of the differences between groups was evaluated by using Student's t-test for paired data. A value of $p<0.05$ was considered statistically significant.

RESULTS

Renal function and urinary albumin excretion

There was no significant difference in any measurement of renal function between the two groups at baseline. No significant change in BUN, serum creatinine, and serum β_2MG was noted in either group during the study. The Ccr significantly decreased in group I from 91±33 to 81±35 ml/min($p<0.05$), whereas no significant change occurred in group II 104±43 to 112±46 ml/min). Urinary albumin excretion did not change significantly in either group during the study (Table 2).

Anthropometric measurements

There was no significant difference in any measurement of anthropometric indices between the two groups at baseline. No significant change in BW, BMI, AC or TSF was observed in either group during the study period. AMC significantly increased in group I from 21.8±2.4 to 22.6±1.9 cm($p<0.05$), whereas no change was seen in group II (Table 3).

Biochemical nutritional indices reflecting the status of visceral proteins

No significant change was observed in total serum protein, serum albumin, serum prealbumin or serum transferrin in either group during the study (Table 4).

DISCUSSION

Dietary protein influences the progression of renal failure in patients with various renal diseases[24]. The strict restriction of dietary protein has a profound effect on patients with advanced diabetic nephropathy by preventing a decline in glomerular filtration rate (GFR) and by reducing proteinuria[5-14]. However, there is little information on the role of a low protein diet in paients with early-stage diabetic nephropathy[15-17]. Cohen et al.[15] reported that a low protein diet (0.63 g/kg/day) effectively reduced the urinary excretion of albumin in 8 IDDM patients with microalbuminuria. The median GFR, measured by the clearance of edetic acid labelled with chromium-51, fell from 109 to 100 ml/min after a 3-week study. Wiseman et al.[16] also reported decreased albuminuria and reduced GFR in 12 IDDM patients with microalbuminuria after a 3-week period on a low protein diet (0.64 g/kg/day). GFR decreased from 130±21 to 117±21 ml/min, but there was no difference in renal plasma flow (RPF) between the patients on low protein diet vs conventional diet (1.46 g/kg/day) ; filtration fraction (FF) fell significantly on the low protein diet. Brouhard et al.[17] reported a significant reduction in urinary albumin excretion and preservation of renal function in 8 IDDM patients after a 12-month protein restricted diet (0.6 g/kg/day), compared with data obtained for patients with normal dietary protein intake (1.0 g/kg/day). These studies suggest that, even in early-stage diabetic nephropathy, the reduction of dietary protein induces modifications in intraglomerular hemodynamics, which may prevent or slow down the progression of diabetic renal disease.

We observed that protein-limited diet administered for 6-months significantly decreased the Ccr in 8 NIDDM patients with microalbuminuria. No significant change in urinary albumin excretion was observed. The initial Ccr in these patients (91±33 ml/min in group I, and 104 ±43 ml/min in group II) may represent hyperfiltration, compared with the mean value of Ccr in the non-diabetic elderly patients with atherosclerotic vascular complications (80±24 ml/min) who had participated in our previous study[25]. Dietary intake of protein has been implicated as an important determinant of glomerular blood flow and hydrostatic pressure[26]. The fall in GFR that occurs with protein-restricted diets is not accompanied by a change in RPF, but there is a significant reduction of FF[16]. This reduction in FF is therefore consistent with a decrease in transglomerular hydraulic pressure. In the present study, the correction of the abnormal glomerular hemodynamics may have been caused by the protein-limited diet. Strict glycemic control also has been shown to reduce GFR in diabetic patients with microalbuminuria[27,28]. However, HbA_1c values remained unchanged throughout the study and could not account for the reduction in GFR (Ccr). On the other hand, in a previous study, reduced urinary albumin excretion was achieved by a strict restriction of protein intake (0.6 g/kg/day) for 3 weeks in IDDM patients[8]. The discrepancy between Bending's findings and ours may be explained by the difference in the amount of protein intake. A 6-month diet limiting protein intake to 0.77 g/kg/day may be insufficient to affect urinary albumin excretion.

A deterioration of nutritional status and malnutrition may be caused by a strict protein-restricted diet. Kaysen et al.[29] reported a decrease in urinary protein excretion and an increase in serum albumin levels in nephrotic patients whose protein intake was reduced from 1.6 to 0.8 g/kg/day. Barsotti et al.[7] reported an extremely slow rate of decline in Ccr in 8 IDDM patients with advanced nephropathy who received a low protein diet (0.25～0.6 g/kg/day) for 17 months, and documented a stable nutritional status. In that study, the serum albumin levels improved and the anthropometric measurements did not change. Levine et al.[11] also reported that a 0.6 g/kg/day protein diet for 15 weeks did not produce protein depletion in 7 IDDM patients with advanced nephropathy ; despite dietary protein restriction, stable nutritional status was assessed by BW, TSF and AMC. Serum albumin and serum transferrin concentrations did not change significantly at baseline or after 15 weeks. No adverse effects were indicated by anthropometric measurements or by serum levels of proteins such as total protein, albumin, prealbumin and transferrin. Our results are consistent with those of the aforementioned studies. Thus, such protein-limited diets do not adversely affect nutritional status even over the long term.

In conclusion, the beneficial effects of a protein-limited diet demonstrated in patients with early-stage diabetic nephropathy indicate that such a dietary regimen will help in the overall prevention of diabetic nephropathy.

ACKNOWLEDGMENT

We wish to thank Dr. Sanko Sawada, Professor of Nutrition at Nara Bunka Women's Junior College, for her advice on dietary therapy. Part of this work was presented at the Symposium of the 23 rd Western Meeting of the Japanese Society of Nephrology in Wakayama, June 1993.

REFERENCES

1) **Maschio, G., Oldrizzi, L., Tessitore, N., D'Angelo, A., Valvo, L., Lupo, A., Loschiavo, C., Fabris, A., Gammaro, L., Rugio, C.** and **Panzetta, G.**: Effects of dietary protein and phosphorus restriction on the progression of early renal failure. Kidney Int. **22** : 371-376, 1982.

2) **Rosman, J. B., Meijer, S., Sluiter, W. J., Ter-Wee, P. M., Piers-Becht, T. P.** and **Donker, A. J. M.**: Prospective randomised trial of early dietary protein restriction in chronic renal failure. Lancet **2** : 1291-1295, 1984.

3) **Ihle, B. U., Becker, G. J., Whitworth, J. A., Charlwood, R. A.** and **Kinkaid-Smith, P. S.**: The effect of protein restriction on the progression of renal insufficiency. N. Engl. J. Med. **321** : 1773-1777, 1989.

4) **Mitch, W. E.**: Dietary protein restriction in patients with chronic renal failure. Kidney Int. **40** : 326-341, 1991.

5) **Evanoff, G. V., Thompson, C. S., Brown, J.** and **Weinman, E. J.**: The effect of dietary protein restriction on the progression of diabetic nephropathy. Arch. Intern. Med. **147** : 492-495, 1987.

6) **Ciaverella, A., diMizio, G., Stefoni, S., Bornino, L. C.** and **Vannini, P.**: Reduced albuminuria after dietary protein restriction in insulin-dependent diabetic patients with clinical nephropathy. Diabetes Care **10** : 407-413, 1987.

7) **Barsotti, G., Ciardella, F., Morelli, E., Cupisti, A., Mantovanelli, A.** and **Giovannetti, S.**: Nutritional treatment of renal failure in type 1 diabetic nephropathy. Clin. Nephrol. **29** : 280-287, 1988.

8) **Bending, J. J., Dodds, R. A., Keen, H.** and **Viberti, G. C.**: Renal response to restricted protein intake in diabetic nephropathy. Diabetes **37** : 1641-1646, 1988.

9) **Walker, J. D., Bending, J. J., Dodds, R. A., Mattock, M. B., Murrells, T. J., Keen, H.** and **Viberti, G. C.**: Restriction of dietary protein and progression of renal failure in diabetic nephropathy. Lancet **2** : 1411-1414, 1989.

10) **Evanoff, G., Thompson, C., Brown, J.** and **Weinman, E.**: Prolonged dietary protein restriction in diabetic nephropathy. Arch. Intern. Med. **149** : 1129-1133, 1989.

11) **Levine, S. E., D'Elia, J. A., Bistrian, B., Smith-Ossma, S., Gleason, R., Mitch, W. E.** and **Miller, D. G.**: Protein-restricted diets in diabetic nephropathy. Nephron **52** : 55-61, 1989.

12) **Zeller, K., Whittaker, E., Sullivan, L., Raskin, P.** and **Jacobson, H. R.**: Effect of restricting dietary protein on the progression of renal failure in patients with insulin-dependent diabetes mellitus. N. Engl. J.

Med. **324** : 78-84, 1991.

13) **Shichiri, M., Nishio, Y., Ogura, M.** and **Marumo, F.** : Effect of low-protein, very-low-phosphorus diet on diabetic renal insufficiency with proteinuria. Am. J. Kidney Dis. **18** : 26-32, 1991.

14) **Sugimoto, T., Kikkawa, R., Haneda, M.** and **Shigeta, Y.** : Effect of dietary protein restriction on proteinuria in non-insulin-dependent diabetic patients with nephropathy. J. Nurt. Sci. Vitaminol. **37** : S87-S92, 1991.

15) **Cohen, D., Dodds, R.** and **Viberti, G. C.** : Effect of protein restriction in insulin dependent diabetics at risk of nephropathy. Br. Med. J. **294** : 795-798, 1987.

16) **Wiseman, M. J., Bognetti, E., Dodds, R., Keen, H.** and **Viberti, G. C.** : Changes in renal function in response to protein restricted diet in type 1 diabetic patients. Diabetologia **30** : 154-159, 1987.

17) **Brouhard, B. H.** and **LaGrone, L.** : Effect of dietary protein restriction on functional renal reserve in diabetic nephropathy. Am. J. Med. **89** : 427-431, 1990.

18) **American Diabetes Association** : Nutritional recommendations and principles for individuals with diabetes mellitus ; 1986. Diabetes Care **10** : 126-132, 1987.

19) **Wylie-Rosett, J.** : Evaluation of dietary management of diabetes mellitus. Diabetes Care **11** : 143-148, 1988.

20) **Blumenkrants, M. J., Kopple, J. D., Gutman, R. A., Chan, Y. K., Barbour, G. L., Roberts, C., Shen, F. H., Gandhi, V. C., Tucker, C. T., Curtis, F. K.** and **Coburn, J. W.** : Methods for assessing nutritional status of patients with renal failure. Am. J. Clin. Nutr. **33** : 1567-1585, 1980.

21) **Schoenfeld, P. Y., Henry, R. R., Laird, N. M.** and **Roxe, M.** : Assessment of nutritional status of the National Cooperative Dialysis Study population. Kidney Int. **23** : S80-S88, 1983.

22) **Glassock, R. J.** : Nutrition, immunology and renal disease. Kidney Int. **24** : 194-198, 1983.

23) **Maroni, B. J., Steinmann, T. I.** and **Mitch, W. E.** : A method for estimating nitrogen intake in patients with chronic renal failure. Kidney Int. **27** : 58-65, 1985.

24) **Brenner, B. M., Meyer, T. W.** and **Hostetter, T. H.** : Dietary protein intake and the progressive nature of kidney disease. N. Engl. J. Med. **307** : 652-659, 1982.

25) **Kanauchi, M., Nishioka, H., Akai, M., Kikawa, T., Kawano, T., Nakashima, Y., Hashimoto, T.** and **Dohi, K.** : Urinary excretion of microproteins and atherosclerotic vascular complications. J. Nara Med. Ass. **46** : 181-187, 1995 (*in Japanese*).

26) **Mayer, T. W., Lawrence, W. E.** and **Brenner, B. M.** : Dietary protein and the progression of renal disease. Kidney Int. **24** : S43-S47, 1983.

27) **Kroc Collaborative Study Group** : Blood glucose control and the elevation of diabetic retinopathy and microalbuminuria. N. Engl. J. Med. **311** : 365-372, 1984.

28) **Viberti, G. C., Pickup, J. C., Jarrett, R. J.** and **Keen, H.** : Effect of control of blood glucose on urinary excretion of albumin and β_2-microglobulin in insulin-dependent diabetes. N. Engl. J. Med. **300** : 638-641, 1979.

29) **Kaysen, G. A., Gambertolglio, J., Jimenz, J., Jones, H.** and **Hutchinson, F. N.** : Effect of dietary protein intake on albumin homeostasis in nephrotic patients. Kidney Int. **29** : 572-577, 1986.