Results The study was completed by 47 (84%) of 56 participants in the low-protein diet group and 41 (73%) of 56 participants in the normal-diet group. During the study period, the difference in mean annual change in estimated GFR between the low-protein diet and the normal-protein diet groups was −0.3 ml min^{-1} 1.73 m^{-2} (95% CI −3.9, 4.4; p=0.93). The difference in mean annual change in creatinine clearance between the low-protein diet and the normal-protein diet groups was −0.006 ml s^{-1} 1.73 m^{-2} (95% CI −0.089, 0.112; p=0.80). A doubling of serum creatinine was reached in 16 patients of the low-protein group (34.0%), compared with 15 in the normal-protein group (36.6%), the difference between groups being −2.6% (95% CI −22.6, 17.5; p=0.80). The time to doubling of serum creatinine was similar in both groups (p=0.66).
Conclusions/interpretation It is extremely difficult to get patients to follow a long-term low-protein diet. Although in the low-protein group overall protein intake was slightly (but not significantly) lower, it did not confer renoprotection.

Clinical trial registration: ClinicalTrials.gov NCT 00448526
Funding: Research grant from the Ministry of Health, Labour and Welfare of Japan

Keywords Albuminuria · Diabetic nephropathy · eGFR · Low-protein diet · Proteinuria

Abbreviations

ACE-I	ACE inhibitors
ARBs	Angiotensin II receptor blockers
eGFR	Estimated GFR
ESRD	End-stage renal disease
MDRD	Modification of Diet in Renal Disease study

Introduction

Diabetic nephropathy develops in 40% of patients with diabetes and, in spite of progress in new treatment for diabetes and anti-hypertensive drugs, is the leading cause of end-stage renal disease (ESRD) worldwide [1–3]. Diabetic nephropathy is also closely associated with higher cardiovascular mortality rates [4]. Therefore, additional efforts are needed to arrest the progression of diabetic nephropathy.

A low-protein diet slows the progression of renal disease and improves survival in patients with various glomerulopathies, including diabetic kidney disease [5]. Clinically, a meta-analysis suggested that low-protein diet lowers the incidence of ESRD or death in patients with non-diabetic nephropathies [6]. Another meta-analysis of 108 patients with type 1 diabetes in five studies (mean follow-up 4.5–35 months) showed the benefit of low-protein diet in slowing the progression of diabetic nephropathy [7]. Indeed, a low-protein diet is recommended as nutritional management of diabetic nephropathy [8], although there is insufficient evidence to suggest that such a diet improves renal dysfunction [9, 10]. The landmark study of non-diabetic kidney disease, the Modification of diet in renal disease study (MDRD), also failed to reach a conclusion regarding the benefits of a low-protein diet in reducing risk of ESRD or death [11, 12]. Furthermore, extended follow-up after the MDRD trial also failed to show a significant benefit of low-protein diet in slowing the development of ESRD and all-cause mortality [13].

To explore the uncertainties on effectiveness of low-protein diet, we conducted a randomised controlled trial to determine the effect of low-protein diet on the progression of renal dysfunction and albuminuria in type 2 diabetic patients with overt nephropathy.

Methods

Study design This was a multi-site randomised controlled trial for prevention of diabetic nephropathy progression among 112 type 2 diabetic patients, who were aged 30 to 70 years and had overt nephropathy. The trial was conducted from 1 December 1997 to 30 April 2006. After a baseline run-in period (3 months), the patients were monitored for 5 years. The protocol was approved by the institutional review boards of each centre. All participating patients provided written, informed consent. Before the present study, 41 diabetic patients with overt nephropathy had been randomly assigned to normal protein intake (n=21) and low protein intake (n=20) groups. This 1 year feasibility trial was completed by 34 patients. Daily protein intake in the feasibility study was 1.22±0.25 g $kg^{-1}day^{-1}$ (normal) and 0.92±0.43 g $kg^{-1}day^{-1}$ (low protein) and the difference was statistically significant (p<0.05). Based on these data, sample size for the present study was calculated. To achieve 90% power with a 5% significance level, we found that least 31 participants per group would be necessary. To account for drop-out due to trial duration, a 100 participants (50 per group) were planned for analysis.

Participants The participants were Japanese men and women, aged 30 to 70 years. All had type 2 diabetes (defined according to World Health Organization criteria) of at least 5 years duration and were being treated by diet or by diet plus oral hypoglycaemic agents or insulin injection. Other inclusion criteria were: (1) urinary protein excretion more than 1 g/day but less than 10 g/day; (2) urinary albumin excretion rate of more than 200 μg/min at least twice in a 1 year period; (3) serum creatinine below

176 μmol/l; (4) at least simple diabetic retinopathy; and (5) on normal-protein diet (1.2 g kg^{-1} day^{-1}). Potential participants were excluded if they had: type 1 diabetes; other renal diseases; body weight less than 80% of ideal body weight; clinically significant illness such as congestive heart failure, hepatic disease, recent myocardial infarction and stroke, and urinary tract infection; or if they were being treated with a low-protein diet (0.8 g $kg^{-1}day^{-1}$) and/or ACE inhibitors (ACE-I) or angiotensin II receptor blockers (ARBs). Hypertension was defined as blood pressure ≥140/90 mmHg or use of anti-hypertensive drugs.

Randomisation and intervention During the 3 month screening period, the participants continued to take a normal-protein diet (1.2 g $kg^{-1}day^{-1}$) and their usual medications. They were then randomly assigned at a central location to follow either a low-protein diet (0.8 g $kg^{-1}day^{-1}$) or a normal-protein diet (1.2 g $kg^{-1}day^{-1}$) with the appropriate energy intake for each participant without masking.

The methods of minimisation for allocation were applied according to age, sex, serum creatinine, estimated GFR (eGFR), and urinary albumin and protein levels during the screening period. Both groups were instructed to meet the registered dietitian for 30 min every 3 months to assess and counsel dietary issues. After randomisation we followed the participants for approximately 3.5 years (1–5 years). Every 3 months, all participants completed a 3 day food record to assess daily protein, energy and sodium intake. For this purpose, we used the fourth revised and enlarged edition of *Standard tables of food composition in Japan* [14]. The dietary protein intake was also assessed by urinary urea nitrogen excretion during 24 h urine collection every 3 months, using the formula of Maroni et al. [15]. To achieve dietary protein goals, dietary regimens were modified every 3 months or more as needed. The estimated protein intake during the study represents the mean of all measurements after randomisation.

Laboratory tests Blood and urine samples were brought to the central laboratory (SRL, Tokyo, Japan) and each clinical parameter was measured using the Hitachi 7170 analyzer (Hitachi High-Technologies, Tokyo, Japan) unless otherwise specified. GFR was estimated using the following modified MDRD formula for Japanese participants [16]: eGFR (ml $min^{-1}1.73\ m^{-2}$)=175×[serum creatinine (μmol/l)/88.4]$^{-1.154}$×[age (years)]$^{-0.203}$×0.741×(0.742 if female), where serum creatinine estimated by an enzymatic method was calibrated. Creatinine clearance from a 24 h timed urine collection was calculated and corrected to a body surface area of 1.73 m^2. Urinary excretion of protein and albumin was measured every 3 months in 24 h timed urine samples using an immunoturbidity assay and a pyrogallol red–molybdate complex (LX60000; Eiken Chemical Co., Tokyo, Japan), respectively. Urinary nitrogen was measured by an enzymatic ultraviolet method every 3 months. Blood samples were obtained every 3 months to measure: renal function (blood urea nitrogen, creatinine, Na, K, Cl, uric acid) by an autoanalyser; lipids (total cholesterol, triacylglycerol, HDL-cholesterol) by an enzymatic colorimetric method and a direct inhibition method, respectively; transferrin by an immunoturbidity assay (BN-II; Dade Boehring, Marbug, Germany); serum glucose by a glucose oxidase method; and HbA_{1c} by ion exchange HPLC (ADAMS A1c HA-8160; Aarkray, Kyoto, Japan).

Outcomes The primary outcomes were: (1) the annual change in eGFR and creatinine clearance; (2) the incidence of doubling of serum creatinine; and (3) the time to doubling of baseline serum creatinine. The secondary outcomes included the proportion of patients with ESRD requiring haemodialysis and the annual changes in urinary protein and albumin excretion. Quality of life was assessed annually using the SF-36 [17].

The secondary analysis, which was not based on a direct comparison of randomised groups, was performed to assess the biological dose–response relationship between actual protein intake and progression of type 2 diabetic nephropathy.

Statistical analysis An independent data and safety monitoring board monitored the study. The Lan–DeMets alpha spending-function method was used to adjust for interim analyses once a year. Four formal interim analyses were performed during the study period. The p value for one interim analyses was set at p=0.01. Data handling and trial management were coordinated centrally by EPS (Tokyo, Japan).

The mean dietary protein intake between the low- and normal-protein diet groups was analysed using Wilcoxon's rank sum test. Dietary protein intake in the low- and normal-protein diet groups during the study was analysed by repeated measures ANOVA.

Analyses of the primary and secondary outcomes were performed according to the intention-to-treat principle; we included data from all randomised patients with the exception of the 24 participants lost or excluded between randomisation and study termination (Fig. 1). For continuous variables, the mean and standard deviation were calculated. Because of the skewed deviation, values for albuminuria and proteinuria are given as medians and interquartile ranges. In calculating the slopes of the rates of change of eGFR and creatinine clearance, linear regression analysis was used and included the data of patients who reached an endpoint. A minimum of 1 year follow-up with at least two measurements of serum and urinary creatinine

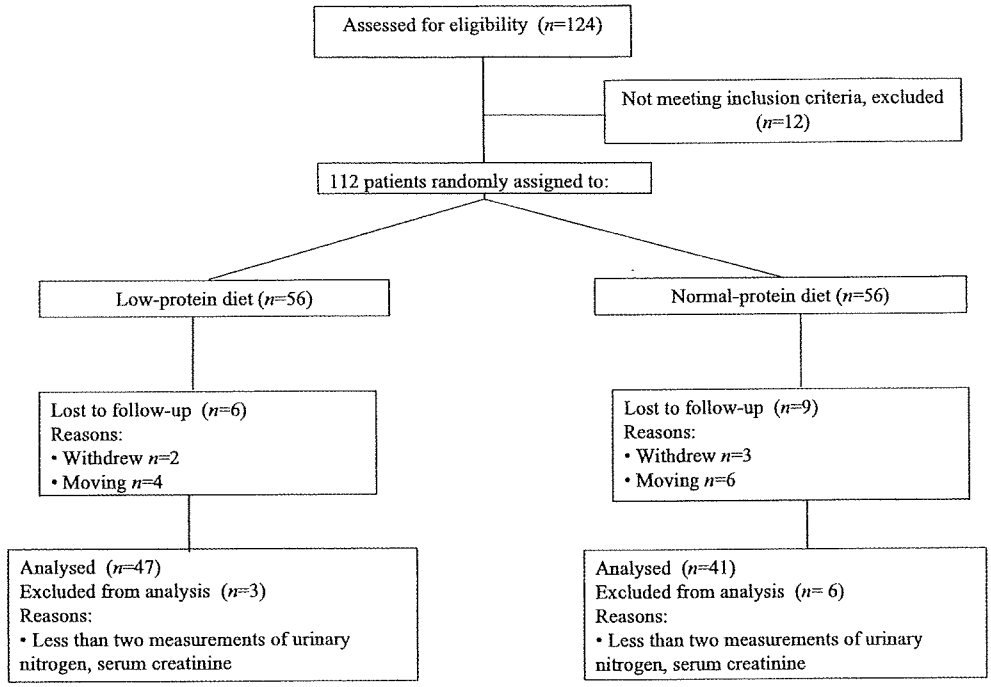


Fig. 1 Design of the trial. Fifteen patients were lost during follow-up because they moved away or withdrew informed consent within 1 year of follow-up. Nine patients were excluded from analysis because they had less than two measurements of urinary nitrogen excretion and serum creatinine

during the study period were aggregated in the slope analysis. Primary outcome values between groups were assessed by an analysis of covariance model, with low-protein diet as a factor and baseline urinary protein, serum creatinine, HbA_{1c}, systolic blood pressure and daily protein intake, in addition to age and sex, as covariates. The incidence of doubling of serum creatinine was compared with the χ^2 test. The times to doubling of baseline serum creatinine and its components were compared by Kaplan–Meier survival curves and the log-rank test. Baseline serum creatinine was adjusted using Cox proportional hazards models with terms for the diet assignment. Secondary outcomes were compared with the χ^2 test (for non-parametric data) or repeated measures ANOVA (for continuous data).

In secondary analysis, the differences between achieved protein intake and renal functions were determined using Pearson's correlation coefficient and Spearman's rank/correlation coefficient. To identify the factors associated with the doubling of serum creatinine, the potential risk factors such as systolic blood pressure, protein intake, sodium intake, HbA_{1c} and total cholesterol were included in the Cox proportional hazards model, adjusting for sex, age, urinary albumin excretion and serum creatinine.

All statistical tests were two-sided. For the final analysis of the primary endpoints and all other endpoints, a p value of 0.05 or less was considered to indicate significance. Data were analysed using SAS 8.2 (Statistical Analysis System, Cary, NC, USA).

Results

Participants The baseline characteristics of the 112 type 2 diabetic participants with nephropathy who underwent randomisation were similar between low-protein diet and normal-protein diet groups (Table 1). The study was completed by 47 of the 56 (84%) participants in the low-protein diet group and by 41 of the 56 (73%) participants in the normal-protein diet group (Fig. 1). In both groups, the reasons for dropping out were: loss of follow-up due to moving (ten participants); withdrawal of informed consent (five participants); and less than two measurements of dietary protein intake and of serum and urinary creatinine during the study period (nine participants).

Dietary assessment At randomisation, there was no difference in mean dietary protein intake between the two diet groups as assessed by a 3 day food record and a dietitian (low-protein 1.0±0.3 vs normal-protein 1.1±0.2 g $kg^{-1}day^{-1}$) and by estimates using 24 h urinary nitrogen excretion (1.0±0.2 vs 1.0±0.2 g $kg^{-1}day^{-1}$, respectively). During the study, the mean protein intake from the food record was significantly different between low- and normal-protein intake group (0.9±0.2 vs 1.1±0.2 g $kg^{-1}day^{-1}$, respectively, $p<0.0001$), while the protein intake derived from 24 h urinary nitrogen excretion was similar between the two group (1.0±0.2 vs 1.0±0.2 g $kg^{-1}day^{-1}$, respectively, $p=0.16$). The mean protein intake estimated by urinary nitrogen excretion in the low-protein diet group was lower than that in the normal-protein group during the study period, but the difference was

Table 1 Baseline characteristics of the participants

Variable	Low-protein diet (n=56)	Normal-protein diet (n=56)
Age (years)	57.5±7.8	56.3±8.7
Male sex, n (%)	33 (58.9)	33 (57.1)
Height (cm)	160.4±8.5	160.7±7.8
Weight (kg)	63.8±10.7	62.9±10.5
Systolic blood pressure (mmHg)	138±21	137±16
Diastolic blood pressure (mmHg)	77±11	77±12
Serum creatinine (μmol/l)	91.9±50.4	98.1±45.1
eGFR (ml min^{-1} 1.73 m^{-2})	63.5±26.9	61.1±23.7
Urinary albumin (μg/min)	488 (214–1,359)	527 (325–1,364)
Urinary protein (g/day)	1.1 (0.4–3.2)	1.2 (0.5–2.9)
HbA_{1c} (%)	7.8±1.5	7.5±1.7
Total cholesterol (mmol/l)	5.7±1.1	5.8±1.3
Triacylglycerol (mmol/l)	1.8±0.9	1.8±0.9
With hypertension (%)	63.0	68.6

Unless otherwise stated, values are mean±SD or medians (interquartile range)

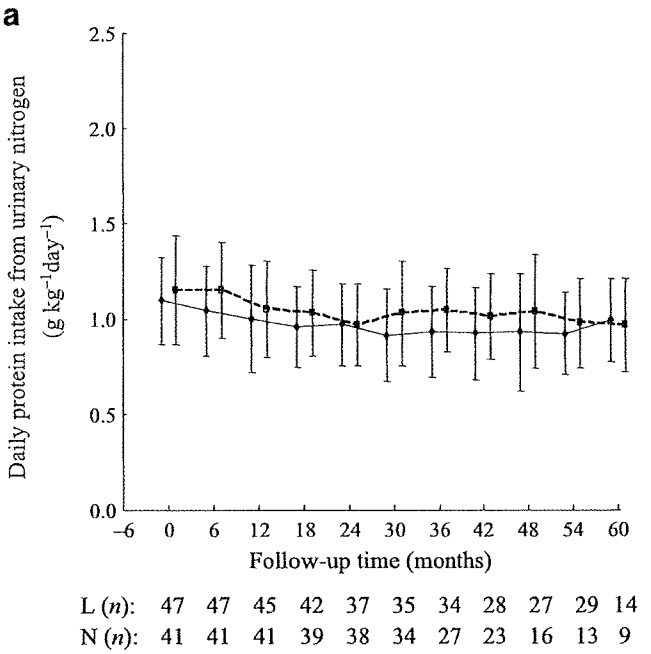
not significant (p=0.14) (Fig. 2a). This was in contrast to the significant difference between the two groups based on food record (p<0.0001) (Fig. 2b).

Primary outcomes The mean annual change in eGFR was −6.1±6.5 ml min^{-1} 1.73 m^{-2} for the low-protein diet group, compared with −5.8±5.7 ml min^{-1} 1.73 m^{-2} for the normal-protein diet group; the difference between the two groups was −0.3 ml min^{-1} 1.73 m^{-2} and not significant (95% CI −3.9, 4.4; p=0.93). The mean annual change in creatinine clearance was −0.163±0.159 ml s^{-1} 1.73 m^{-2} for the low-protein diet group, compared with −0.157± 0.125 ml s^{-1} 1.73 m^{-2} for the normal-protein diet group; the difference between the two groups was −0.006 ml s^{-1} 1.73 m^{-2} and also not significant (95% CI −0.089, 0.112; p=0.80). A doubling of serum creatinine was reached in 16 patients of the low-protein diet group (34.0%), as compared with 15 in the normal-protein diet group (36.6%), with a difference between the two groups of −2.6% (95% CI −22.6, 17.5; p=0.80). The time to doubling of serum creatinine was similar in both groups (p=0.66) (Fig. 3). The hazard ratio for the doubling of serum creatinine by Cox regression was 0.42 (95% CI 0.042, 4.22) for the low-protein diet group.

Secondary outcomes The proportion of patients with ESRD was 6.4% in the low-protein diet group, compared with 7.3% in the normal-protein diet group, with a difference between the two groups of −0.9% (95% CI −0.11, 0.10; p= 0.86). During the study period, the level of albuminuria in the low-protein diet group was not different from that in the normal-protein diet group (Fig. 4a). The level of proteinuria was also similar (Fig. 4b).

Associations of achieved protein intake with eGFR and creatinine clearance The secondary analysis, which was not based on a direct comparison of randomised groups, was performed to assess the biological dose–response relationship between actual protein intake and the progression of diabetic nephropathy in type 2 diabetes, without adjustment for other covariates. The lower protein intake, which was calculated by urinary nitrogen excretion (Fig. 5a) and the 3 day food record (Fig. 5b), was not associated with a slower deterioration of GFR. The correlational analysis using the annual change in creatinine clearance was also not conclusive with regard to the efficiency of low-protein diet, as measured by urea nitrogen excretion (p=0.22) (Fig. 5c) and dietary record (p=0.71) (Fig. 5d). In the multivariate model, adjusted for systolic blood pressure, protein and sodium intake, HbA_{1c} and serum total cholesterol during the study, systolic blood pressure was independently associated with the doubling of serum creatinine (Table 2).

Adverse events and quality of life During the study, one participant of the low-protein diet group died due to tuberculosis-linked sepsis and one participant of the normal-protein diet group died due to acute myocardial infarction. The difference in body weight between baseline and end of follow-up was 0.9 kg in the low-protein diet group and 0.2 kg in the normal-diet group, which was not significantly different between the two groups. During the study period, there was also no significant difference between the two groups in total energy (108.8±18.4 vs 113.8±15.9 kJ $kg^{-1}day^{-1}$) and sodium intake (7.7±2.1 vs 7.9±2.0 g/day) as determined from the 3 day food record. Furthermore, the level of transferrin was not significantly



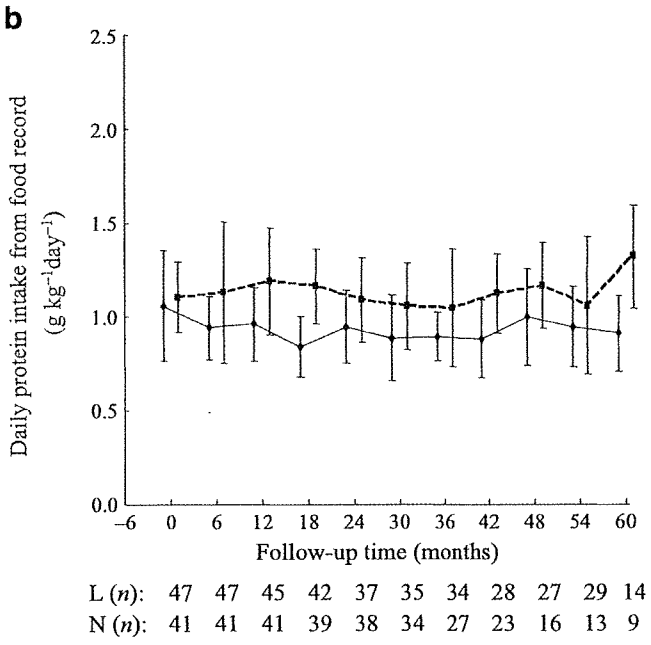


Fig. 2 Dietary protein intake in the low-protein diet (continuous lines) and normal-protein diet (dashed lines) groups estimated (**a**) from urinary nitrogen excretion and (**b**) from 3 day food record during the study. L (*n*), low-protein diet group (*n* participants); N (*n*), normal-protein diet group (*n* participants). Data are mean±SD

different between the two groups during the study period (p=0.83). There were no significant differences in health-related quality of life between the two groups during the study period, as measured by several SF-36 subscales (physical function, social function, physical role, emotional role, mental health, energy, pain and general health perceptions; p>0.1).

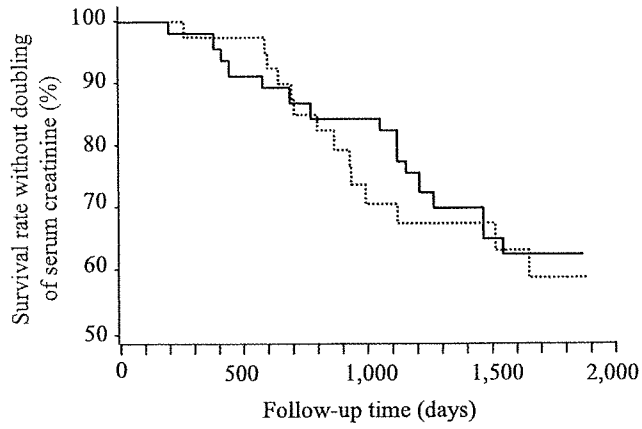


Fig. 3 Kaplan–Meier estimates of the primary endpoints from the study entry to time of doubling of baseline serum creatinine. The time to doubling was similar in both low-protein diet (continuous line) and normal-protein diet (dashed line). p=0.66 by logrank test

Discussion

We found that the low-protein diet was not associated with a better renal outcome than a normal-protein diet in patients with type 2 diabetes. Low-protein diet did not slow the rate of progression of nephropathy as estimated not only by the incidence of doubling of serum creatinine, but also by the time to doubling of serum creatinine concentration, compared with the normal-protein diet group. The mean annual change in eGFR and creatinine clearance was also similar between the two groups. The secondary analysis, which assessed the association between the rate of progression of diabetic nephropathy and the achieved protein intake, also failed to find a beneficial effect. Based on the time-dependent Cox proportional hazards model, no renal benefit of low-protein diet was observed, although systolic blood pressure significantly influenced the progression of diabetic nephropathy. We thus interpret these results to indicate that a low-protein diet is probably not renoprotective in patients with type 2 diabetic nephropathy.

In a long-term study similar to ours, Pijls et al. reported that protein restriction is neither feasible nor efficacious [18], although they had recruited type 2 diabetic patients with microalbuminuria (30–300 mg/day) and relatively high albuminuria within the normo-albuminuric range (albuminuria >20 mg/day or detectable urinary albumin, i.e. albumin concentration >6.5 mg/l). In contrast, Hansen et al. performed a 4 year prospective, controlled trial with concealed randomisation to compare the decline in GFR and development of ESRD or death in type 1 diabetes patients with advanced diabetic nephropathy comparable to our participants [19]. Their usual-protein diet group consumed 1.02 g kg^{-1}day^{-1} as compared with 0.89 (range

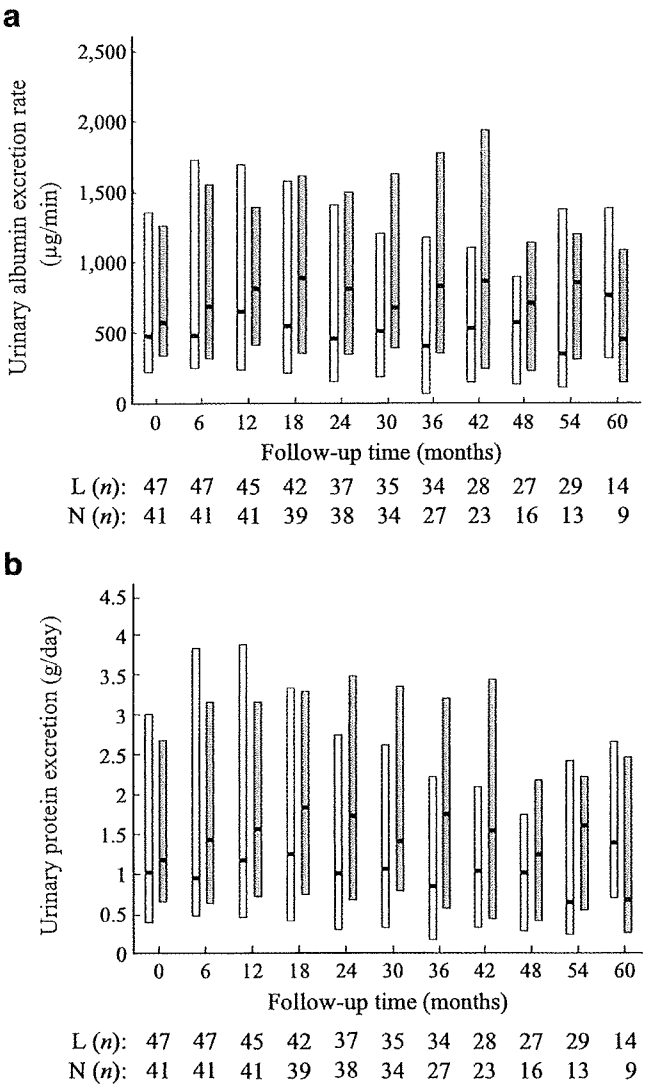


Fig. 4 The effect of low-protein diet (white columns) and normal protein intake (grey columns) on albuminuria (**a**) and proteinuria (**b**). Boxes indicate 25th and 75th percentiles of albuminuria or proteinuria. Horizontal lines indicate median. L (*n*), low-protein diet group (*n* participants); N (*n*), normal-protein diet group (*n* participants)

0.83–0.95) g $kg^{-1}day^{-1}$ in the low-protein diet group, a protein intake similar to our groups. However, in contrast to our findings, Hansen et al found that type 1 diabetic patients suffering from progressive diabetic nephropathy experienced a beneficial effect of moderately restricted dietary protein on the development of ESRD or mortality rates. The discrepancy might be due to the different types of diabetes and/or use of antihypertensive drugs, with almost 90% of patients in their study taking ACE-I. In our study, patients were instructed not to take ACE-I and/or ARBs, as these had not been approved for the treatment of diabetic nephropathy in Japan when this study was completed.

The prescribed protein intake in the low-protein group in our study (approximately 0.8 g $kg^{-1}day^{-1}$) resulted in a mean achieved protein intake of about 1.0 g $kg^{-1}day^{-1}$, as estimated by urinary nitrogen excretion, which was not statistically different from protein intake in the normal-protein diet. Since diabetic patients have to accept other restrictions to their diet regimen [4, 8, 20], compliance to an additional low-protein diet could be reduced. The achieved level of long-term dietary protein restriction may reflect everyday life in an outpatient clinic set-up. Therefore, we cannot directly address the issue of whether the effects of lower protein intake such as 0.8 g $kg^{-1}day^{-1}$, the amount recommended in a nutritional statement by the American Diabetes Association (2008) [8], would be beneficial for type 2 diabetic patients with nephropathy. Non-adherence to the prescribed low-protein diet would result in underestimation of the true beneficial effect of the low-protein diet in the present study. However, it is not reasonable to assume that a lower protein intake equal to or less than 0.8 g $kg^{-1}day^{-1}$ would reduce the risk of progression of diabetic nephropathy, because the relationship between achieved protein intake (0.55–1.6 g $kg^{-1}day^{-1}$) and annual rate of eGFR decline as well as creatinine clearance decline also failed to produce any benefits for low-protein diet in our study. The MDRD, moreover, also failed to reach a conclusion on this issue [11–13]. Indeed, the recent long-term follow-up of the MDRD provides evidence that even very low protein diet, supplemented with keto acids and amino acids, increased the risk of death without the benefit of delaying progression of kidney diseases [21].

In the present study, we found that systolic blood pressure, rather than other variables such as blood glucose control, daily protein intake and sodium intake, played a major role in accelerating the progression of diabetic nephropathy during the follow-up period. Our results suggest that blood pressure control results in inhibition of progression of diabetic nephropathy [4, 22]. Furthermore, coexisistence of hypertension and type 2 diabetes is well known to accelerate the risk not only of development and progression of diabetic nephropathy, but also of cardiovascular disease outcome [22–25], meaning that control of high blood pressure is a major protective strategy against renal and cardiovascular outcomes in patients with diabetic nephropathy. Indeed, recent guidelines recommend treating type 2 diabetic patients with antihypertensive drugs, if their blood pressure is in the high-normal (previously normal) range (130–139/85–90 mmHg), and sometimes even if blood pressure is in the normal and/or low prehypertensive range (120–129/80–85 mmHg) [26, 27].

Although previous experimental data suggested that the effects of low-protein diet, similar to treatment with an ACE-I or ARBs, are mediated through blockade of the renal renin–angiotensin system [28, 29], dietary protein

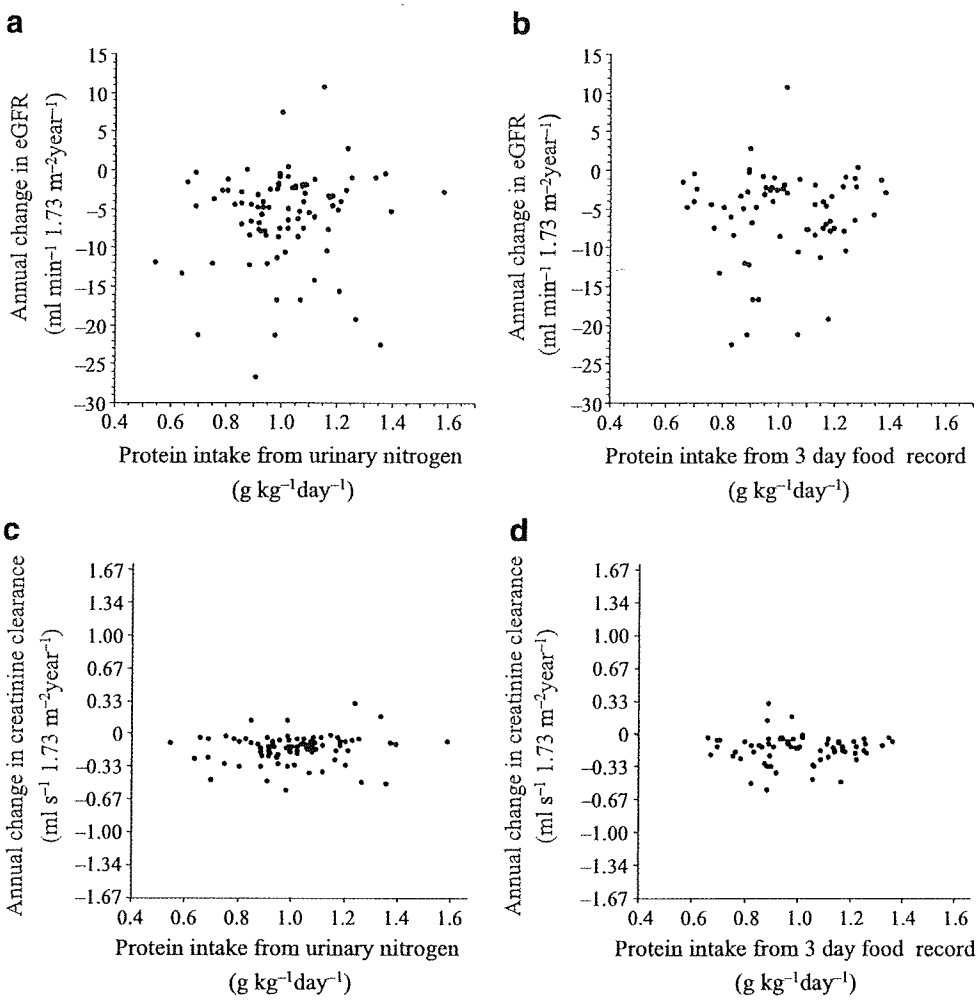


Fig. 5 Correlation between achieved protein intake estimated (**a**) from urinary nitrogen excretion and the annual change in eGFR, and (**b**) from 3 day food record and the annual change in eGFR. **c** Correlation between achieved protein intake, estimated from urinary nitrogen excretion and (**d**) from from 3 day food record, and the annual change in creatinine clearance. The p value was calculated using Spearman's rank correlation coefficient

restriction in the present study, where patients were not on ACE-I or ARBs, did not seem to act through the renin–angiotensin system. At present, adding ACE-I or ARB to multifactorial intervention could reduce the progression of diabetic nephropathy, as reported in several studies [30–35]. Interestingly, a recent report by Parving et al. showed that without restriction of dietary salt or protein, the use of the renin inhibitor, aliskiren, in combination with an ARB efficiently reduces urinary albuminuria in diabetic patients with overt proteinuria [36].

In summary, it is extremely difficult to get patients to follow a long-term low-protein diet, and although overall protein intake was slightly (but not significantly) lower, it did not confer renoprotection. Our data may shed the light on the dietary management of diabetic nephropathy. One possible result is that protein restriction may not remain a main nutritional recommendation in clinical practice, because we now have a most valuable therapeutic strategy for reducing progression of diabetic nephropathy as well as cardiovascular events and mortality rates by using intensive multifactorial interventions such as lifestyle management, ACE-I or ARBs, and lipid-lowering drugs, as reported in the Steno-2 study [32, 33]. Without additional data, we must continue to base decisions on the current balance of evidence for and against the efficacy and safety of dietary protein restriction.

Table 2 Hazard ratios of factors associated with the doubling of serum creatinine

Variable	Hazard ratio (95% CI)[a]	p value
Systolic blood pressure (mmHg)	1.1 (1.02–1.14)	0.012
Protein intake (g kg^{-1}day^{-1})	1.8 (0.07–44.64)	0.73
Sodium intake (g/day)	0.9 (0.72–1.14)	0.41
HbA_{1c} (%)	0.9 (0.59–1.23)	0.49
Total cholesterol (mmol/l)	1.0 (1.0–1.01)	0.49

[a] The multivariate model was adjusted for the following baseline variables: sex, age, urinary albumin excretion and serum creatinine

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Duality of interest The authors declare that there is no duality of interest associated with this manuscript.

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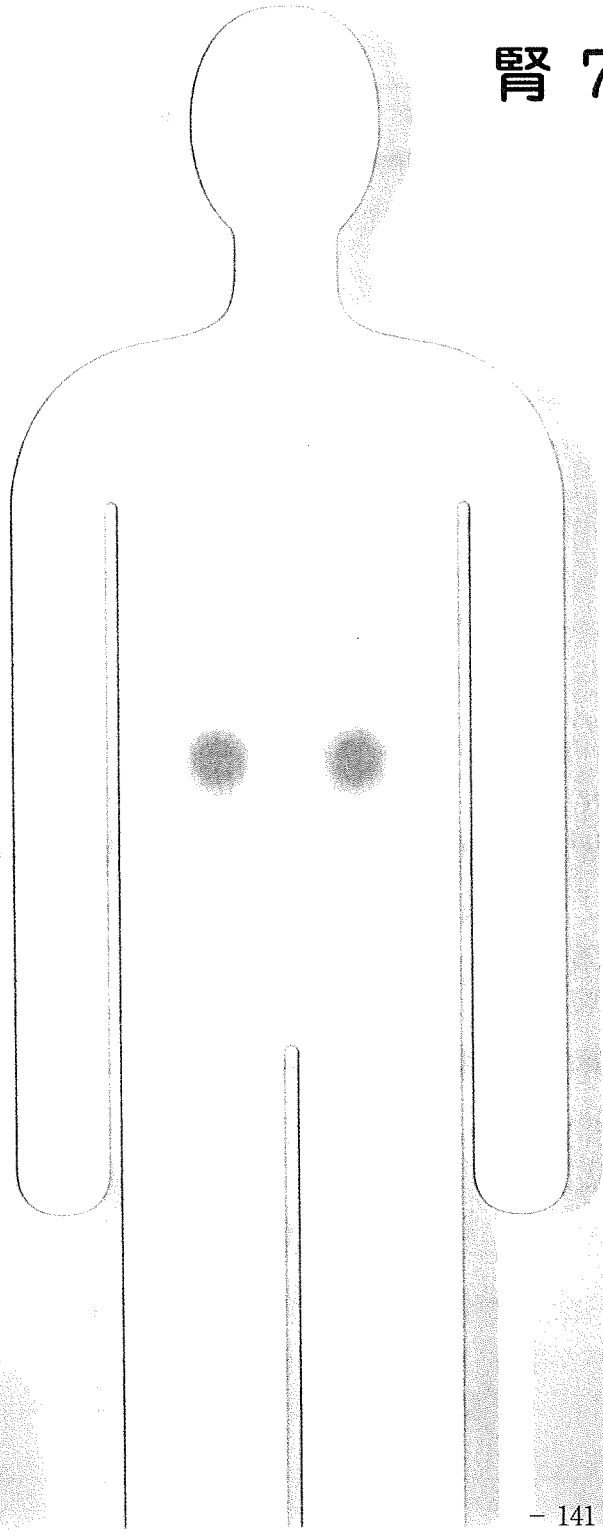
最新医学別冊
新しい診断と治療のABC 61

糖尿病性腎症

腎 7



編集 槇野博史

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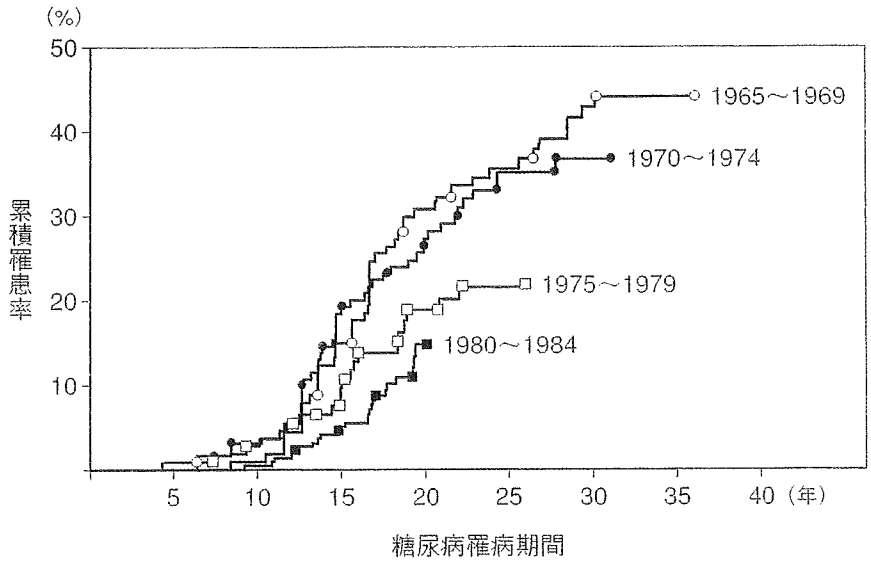
図1　1型糖尿病の発症年代による腎症の累積罹患率（文献[3]より引用）



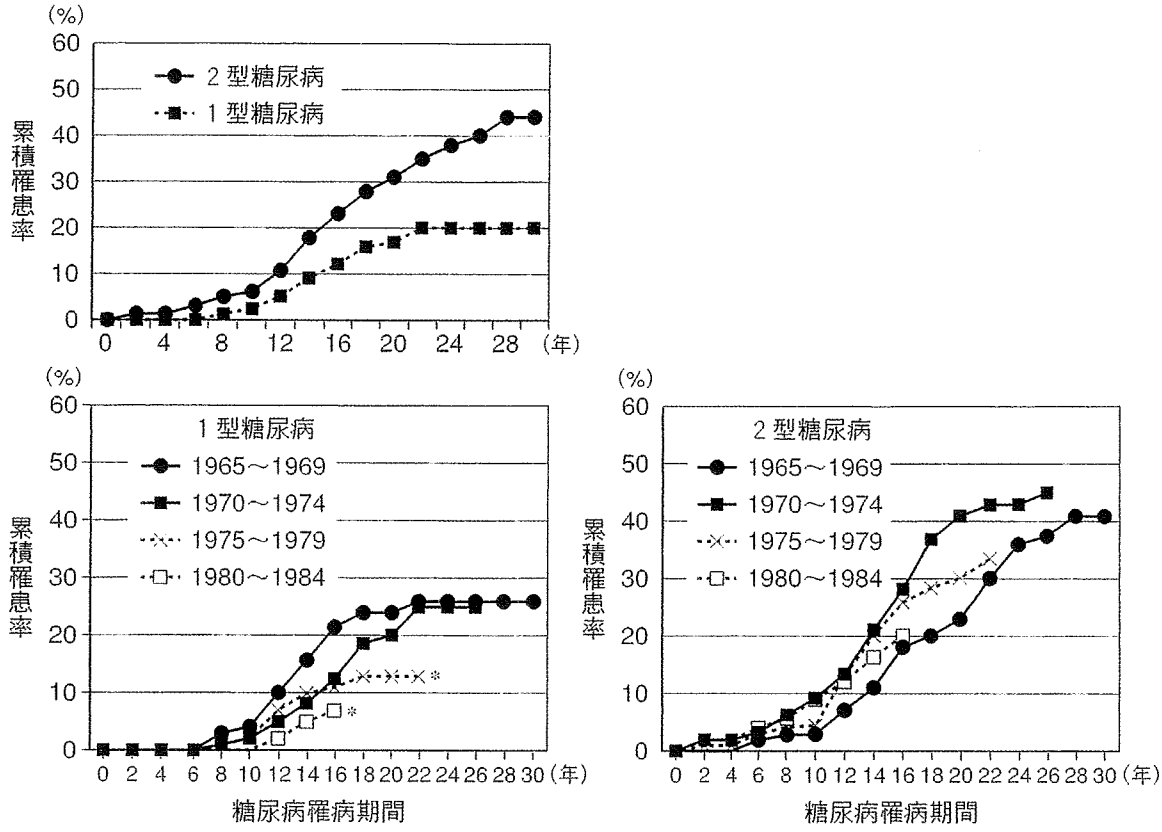
1．1型糖尿病における腎症の頻度

1型糖尿病はその発症と経過が厳密に評価できるので，腎症の疫学は1型糖尿病における報告が多く，また信頼性も高い．

Andersen ら[1]は，907 人の1型糖尿病の観察結果により，腎症（タンパク尿）の有病率は糖尿病罹病期間とともに増加するが，20 年で 21％ になった後は減少し 40 年で 10％ になること，罹患率も糖尿病罹病期間とともに増加するが，16 年で3％になった後は減少すること，累積罹患率は 40 年で 45％ になることを報告した．

糖尿病の発症年代の比較から，腎症の罹患率は次第に減少していることが，特に北欧から相次いで報告された．Hovind ら[2]は，1965～1984 年に発症した 600 人の1型糖尿病を5年ごとに区分した観察結果により，年代ごとの腎症の累積罹患率が減少することを報告した（図1）．同様に Finne ら[3]は，腎症による ESRD の罹患率も年代ごとに減少することを報告した．これらは calender effect とも呼ばれるが，インスリン療法や腎症治療の進歩の結果と考えられている．しかし，米国では，Pambianco ら[4]が 1950～1980 年に発症した 906 人の1型糖尿病の 30 年間の観察結果により，腎症の罹患率は増加し続けていることを報告した．以上より，人種や国別の統計により，腎症の頻度が異なる．

図2　1型と2型糖尿病，および発症年代による腎症の累積罹患率（文献[9]より引用）



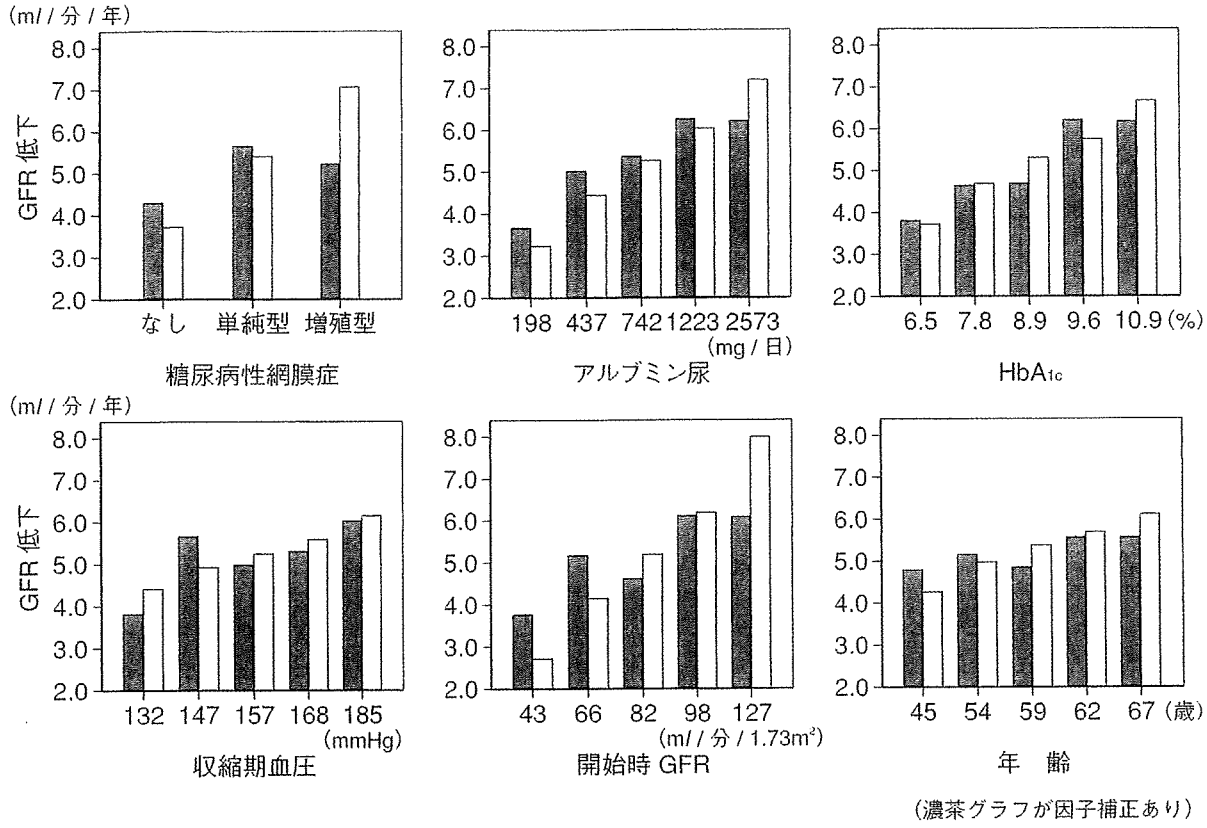
*P＜0.05（1965～1969との比較）

は上記のいずれかの方法で評価するが，独特な病態が明らかになりつつある．

1．Early progressive renal function decline（EPRFD）

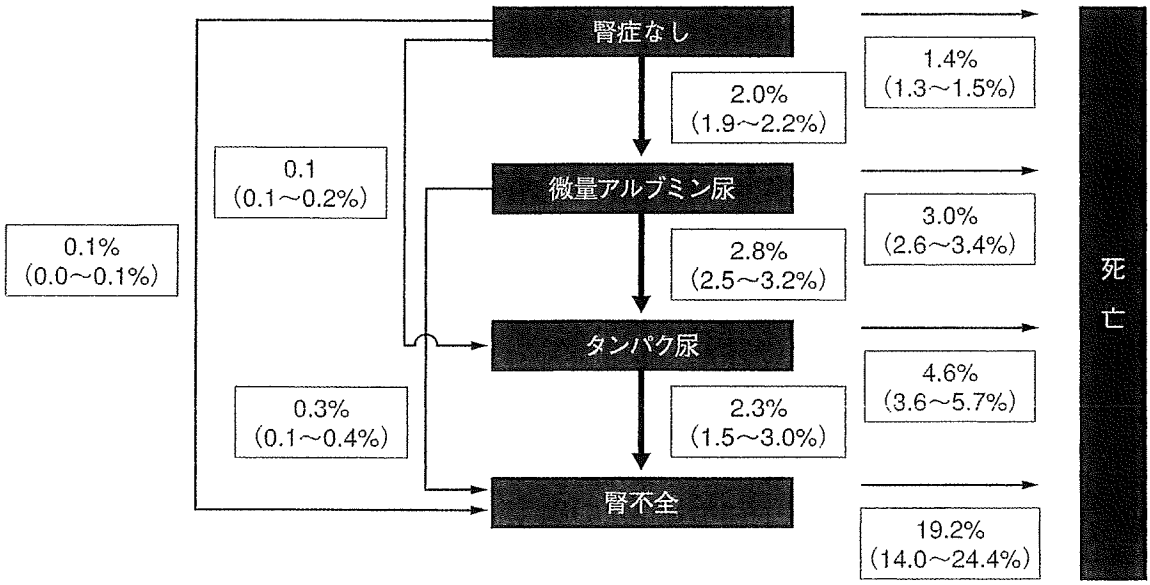
Perkins ら[9]は，早期に進行性にGFRが低下（EPRFD）する一群が，1型糖尿病にあることを報告した．EPRFDの定義は，cystatin Cで評価した健常者のGFR低下率が3.3％毎年であることから，それ以上の低下を示す場合としている．その出現頻度は，正常アルブミン尿で9％，微量アルブミン尿で31％と高頻度であることが判明した（図3）．EPRFDに関連する因子は，年齢（35歳以上），HbA_{1c}（9％以上）で，糖尿病罹病期間，喫煙，血圧，アンジオテンシン変換酵素（ACE）阻害薬の使用などは有意な関連因子ではなかった．腎症の経過が一様でないことは明らかであるが，進行する症例および関連する因子を特定することは，治療戦略のうえで極めて重要である．また，この現象の2型糖尿病，特に本邦における病態の解明が必要で

図4　2型糖尿病における糸球体濾過量（GFR）低下率と関連する因子との関連（文献[10]より引用）



2型糖尿病では，Chaiken ら[13]は，194 人の African-American で，^{125}I-iothalamate による GFR が 140 以上を HF とした場合，糖尿病罹病期間が1年未満の 42 人中 15 人（36％）に HF があること，しかし HF を示す症例の腎機能は最長 15 年後まで明確な低下を示さなかったことから，腎機能低下の予測因子としては否定的な報告をした．Premaratne ら[14]は，662 人の2型糖尿病で，^{99m}Tc-DTPA による GFR が 130 以上を HF とした場合，加齢による GFR の低下を是正するために年齢補正をすると，40 歳以上では HF の頻度が上昇するが，40 歳未満では年齢補正をしなくても，50％と高率であることを報告した．すなわち，HF の頻度は決して低いものではなく，臨床的意義も明確ではないことから，本邦でも正確に評価された GFR で，頻度と意義を再検討する必要がある．

図6　腎症の病期の進行率と死亡率（文献[20]より引用）



あったが，白人と比較してアジア人とヒスパニックで，微量アルブミンと顕性タンパク尿の頻度の高いことを報告した．Wu ら[19]は，アジア人の 5,549 人の 2 型糖尿病で同様に検討したところ，全体では微量アルブミン尿は 39.8％，顕性タンパク尿は 18.8％ とアジア人で高いこと，特にインドネシア，シンガポール，台湾で高いことを報告した．いずれの検討にも日本人は含まれていないが，アジア人で ESRD がさらに増加する可能性がある．本邦でも糖尿病データベース構築による前向き研究である Japan Diabetes Complication Prospective study などが開始されたが，日本人での正確な頻度の解明と，それを踏まえた ESRD の対策が必要である．

尿中アルブミン（タンパク）と心血管病との関係

Adler ら[20]は，UKPDS のサブ解析において，尿中アルブミンの進展と各腎症病期における死亡率との関係を検討し，腎症の病期によっては腎症の進展率よりも死亡率のほうが高いことを報告した（図6）．その他の多くの報告から，微量アルブミン尿あるいは顕性タンパク尿は，ESRD への進行因子だけでなく，心血管病や死亡のリスクであることが判明している．

ていると考えられる．また，国際間で生存率が異なることには，腎移植を含めた RRT の選択方法，透析療法の質，腎以外の主要臓器の障害の程度などが関与していると考えられる．

おわりに

腎症の頻度や臨床経過はその治療の影響を受けるために，疫学的な成績は治療の進歩とともに変遷する．現在は，微量アルブミン尿の remission や regression が可能な時代となったが，疫学には未知の部分が多く，それを明らかにすることは，腎症の治療戦略あるいは克服のために重要である．

鈴木芳樹・山本佳子

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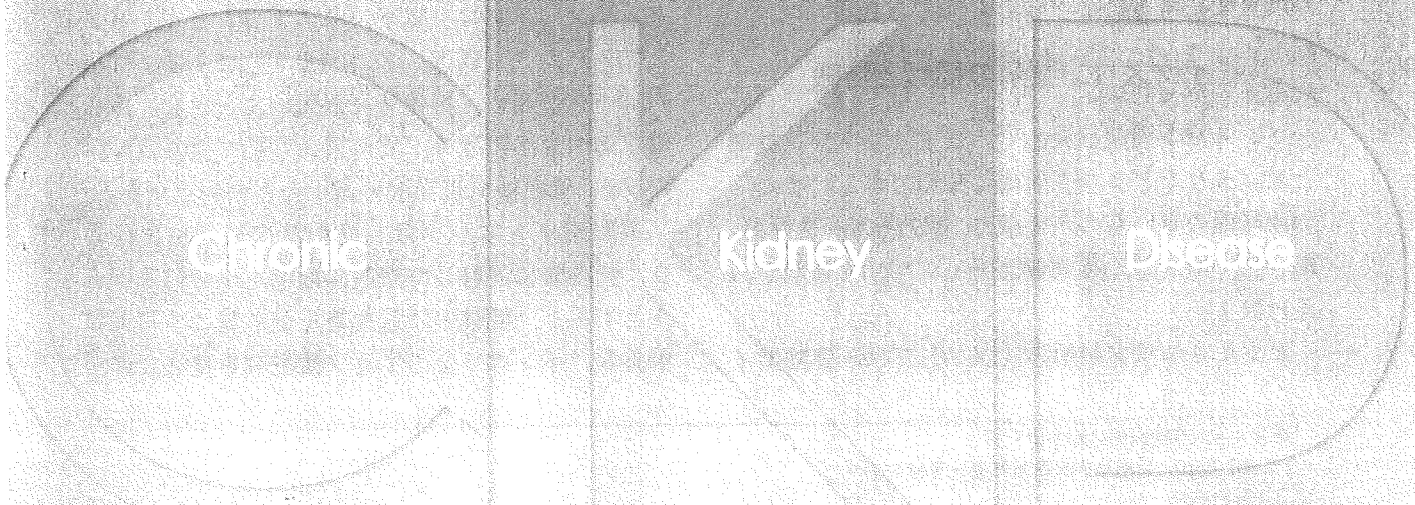
CKDのすべて

編集＝『腎と透析』編集委員会



東京医学社

インスリン製剤の注意点と処方例

Insulin therapy in patients with CKD

悴田亮平*1,2　鈴木芳樹*3

Key words　CKD，インスリン製剤，BOT（basal supported oral therapy），従来インスリン療法，強化インスリン療法

はじめに

糖尿病性腎症は，慢性腎臓病（CKD）の主要な疾患の一つである。また，CKDに糖尿病が併発する頻度も高いことから，CKDを診療するには糖尿病診療にも精通する必要がある。1型糖尿病ではインスリン療法を継続するが，2型糖尿病でも食事と運動療法に加えて経口血糖降下薬（OHA）の効果が乏しい場合に，インスリン療法が必要となる。2型糖尿病では，患者側も医療側もインスリン療法には消極的な傾向が強く，最終手段としてやむを得ず導入する場合が多い。

CKDでは，腎機能の低下により，OHAからインスリン療法への変更を余儀なくされる場合がある。しかし，最近では新しい負担の少ない方法を用いて，早期からインスリン療法に導入し，腎症あるいはその他の糖尿病細小血管合併症の発症と進展を阻止することが求められている。

I　インスリン製剤の種類と特徴

インスリン製剤は大きく，ヒトインスリン製剤とインスリンアナログ製剤に分類できる。また，作用時間の短いものから順に，超速効型，速効型，混合型，中間型，持効型溶解インスリン製剤がある（**表1**）。

ヒトインスリン製剤の代表としては，速効型インスリンと中間型インスリン（NPH）がある。速効型インスリンは効果発現が速く持続時間が短いため，主に食後高血糖を抑制するための追加分泌の補充に用いられる。中間型インスリンは，効果発現が遅くほぼ1日持続するため，主に基礎分泌の補充に用いられる。混合型ヒトインスリン製剤は，速効型と中間型を種々の割合で混ぜたもので，速効型の割合が10～50%の5種類の製剤があり，30%のものが広く用いられている。

しかし，速効型インスリンは，作用のピークを生理的なインスリン分泌と一致させるために，食前30分前の注射が必要である。また，食後血糖を十分に下げようとすると，次の食前まで効果が持続し，低血糖を引き起こす可能性がある。このため，インスリンのアミノ酸配列を変えて，皮下注射後に速やかに効果を発現するように改良したものが，超速効型インスリンアナログ製剤であるインスリンリスプロ（以下，リスプロ）とインスリンアスパルト（以下，アスパルト）である。作用のピークが速く，持続時間が短いことから，生理的な追加分泌に近く，食直前の注射で食後高血糖の改善，低血糖発現頻度の減少などの利点がある。

中間型インスリンは，血中濃度にピークがあり，就寝前に注射して空腹時血糖を十分に下げようとすると，就寝中に低血糖を引き起こす可能性がある。インスリンのアミノ酸配列を変えて徐々

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表1 インスリン製剤の分類（文献9）より引用，一部改変）

分類			発現時間	最大作用時間	持続時間
インスリンアナログ製剤	超速効型	リスプロ	15分未満	30～90分	3～5時間
		アスパルト	10～20分	1～3時間	3～5時間
	混合型	25%リスプロ	15分未満	30分～6時間	18～24時間
		30%アスパルト	10～20分	1～4時間	約24時間
	持効型溶解	グラルギン	1～2時間	ピークなし	約24時間
		デテミル	約1時間	3～14時間	約24時間
ヒトインスリン製剤	速効型		約30分	約1～3時間	約5～8時間
	混合型	30%レギュラー	約30分	約2～8時間	約24時間
	中間型		約90分	約4～12時間	約24時間

注）ヒトインスリン製剤では，発現時間，最大作用時間，持続時間は製品によって異なる

に効果を発現するようにしたものが，持効型溶解インスリンアナログ製剤のインスリングラルギン（以下，グラルギン）とインスリンデテミルである。これらは，1日1回の注射でピークがなく安定して効果が持続するため，夜間の低血糖が少なく暁現象が抑制できる利点がある。

なお，超速効型インスリンアナログと中間型インスリンを混合したものが，混合型インスリンアナログ製剤である。

II インスリン療法の目的と方法

血糖コントロールを厳格に行うためには，インスリンの分泌動態を健常者に近い状態にすることが必要である。インスリン療法は，血糖自己測定の結果を参考にして基礎分泌と追加分泌を適正に補充することが求められる。

1日の注射回数が1～2回を従来インスリン療法，3～4回を強化インスリン療法ということが多い（図）。

従来インスリン療法は，0.2～0.3単位/体重kg/日で開始し，血糖値の経過により2～4単位ずつ増減し，2回注射が必要な場合は朝：夕を2：1に配分するとよい。

強化インスリン療法は，中間型インスリンあるいは持効型溶解インスリンアナログにより基礎分泌量を，速効型インスリンあるいは超速効型インスリンアナログにより追加分泌量を補充するBBT（basal bolus therapy）が主流である。追加分泌の補充量は，各食前の血糖値によるスライディングスケールに従う（**表2**）。また，混合型ヒトインスリンもしくは混合型インスリンアナログを用いて，基礎分泌量と追加分泌量を食事毎に補うPPT（prandial premixed therapy）も用いられる。

なお，ケトアシドーシス，外科手術，ステロイドの使用，シックデイなどの場合は，よりきめ細かな調整が必要である。

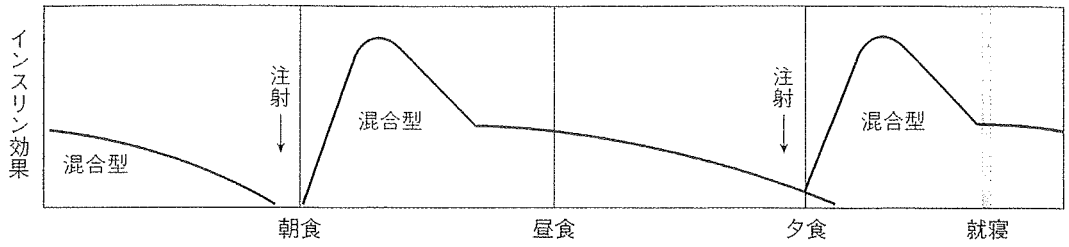
III 1型糖尿病のインスリン療法

1型糖尿病では内因性のインスリンがほとんどないため，強化インスリン療法かCSII（continuous subcutaneous insulin infusion）を行うことが通常である。使用するヒトインスリン製剤とインスリンアナログ製剤の優劣については，以下のような報告がある。

1．強化インスリン療法

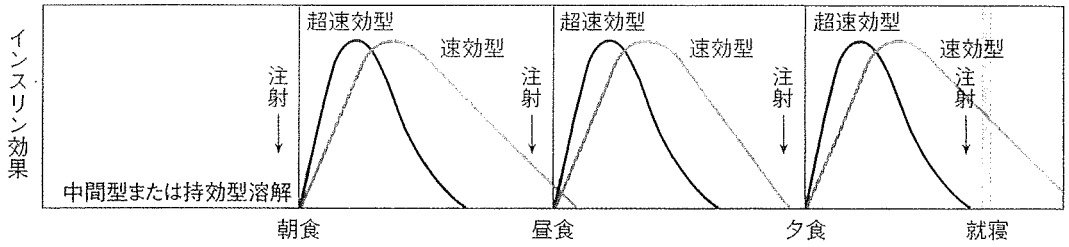
Rossettiら[1]は，リスプロとNPHを各食前およびNPHの就寝前と，リスプロ各食前およびグラルギン夕食時1回とを比較したところ，3カ月後のHbA_{1c}は前者で変化はなかったが，後者で6.8±

1. 従来インスリン療法の例



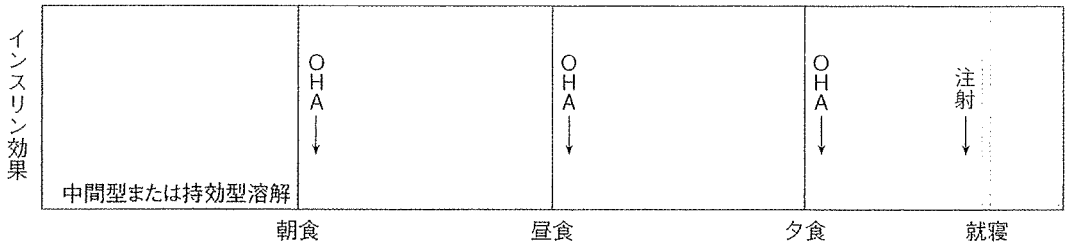
混合型インスリンを1日2回注射

2. 強化インスリン療法の例



速効型または超速効型インスリンを各食前，就寝前に中間型または持効型溶解インスリンを注射

3. BOTの例



OHAを内服しながら就寝前に中間型または持効型溶解インスリンを注射

図 インスリン療法の例（文献9）より引用，一部改変）

表2 スライディングスケールの例

血糖値 (mg/dL)	速効型・超速効型インスリン製剤 (単位)
70未満	なし
70～150未満	4
150～200未満	6
200～250未満	8
250～300未満	10
300以上	12

0.2%から6.4±0.1%に改善し，さらに低血糖の頻度も少なかったと報告した。このことから，NPHを用いたPPTと比較して，グラルギンを用いたBBTの方が，低血糖の頻度は少なく，良好な血糖コントロールが得られると考えられる。

Ashwellら[2]は，速効型インスリン各食前およびNPHを1日1～2回と，リスプロ各食前およびグラルギン就寝前とを比較したところ，16週後でHbA_{1c}はそれぞれ8.0%，7.5%と差があることを報告した。このことから，基礎分泌も追加分泌も，ヒトインスリン製剤と比較してインスリンアナログ製剤を用いた方が，良好な血糖コントロールが得られると考えられる。

2. CSII

速効型インスリン製剤もしくは超速効型インスリンアナログ製剤を使用し，携帯型ポンプを用いて生理的に近い形でインスリン注射を行う方法である。

Hanaire-Broutinら[3]は，リスプロを用いたmultiple daily injection（以下MDI）とCSIIを比

較したところ，HbA_{1c}はそれぞれ8.24±0.77%，7.89±0.77%で，さらにCSIIでは血糖値の変動とインスリン使用量が少ないことを報告した。このことから，MDIと比較してCSIIでは，さらに良好な血糖コントロールが得られると考えられる。一方で，CSIIでは専用の機器や管理が必要であり，症例の選択には十分な検討が必要である。

Ⅳ 2型糖尿病におけるインスリン療法

1. BOT（basal supported oral therapy）

OHAで血糖コントロールが不十分な場合に，OHAを使用しながら基礎分泌量のインスリンを補充する方法である（図）。1日1回のインスリン注射で，インスリン導入にあたり患者の負担が少ないこと，血糖が確実に改善することから，近年注目されている。

Jankaら[4]は，グラルギンを1日1回併用するBOT群と，OHAを中止し混合型ヒトインスリン製剤を1日2回する群で比較したところ，HbA_{1c}の変化率は後者では−1.31%であるのに対し，BOT群では−1.64%と有意に改善することを報告した。また，低血糖の発現頻度もBOT群で少なかったことから，BOTは低血糖の少ないリスクで，より良好な血糖コントロールの達成が可能であると考えられる。

これらの成績から，米国糖尿病学会と欧州糖尿病学会による2型糖尿病のための治療アルゴリズム[5]は，OHAで効果不十分の場合に，就寝前のNPHあるいは朝か就寝前の持効型溶解インスリンアナログを併用するBOTを推奨している。しかし，BOTでも血糖コントロールが不良の場合は，各食前のインスリンを追加補充することが必要である。

2. 従来インスリン療法

Qayyumら[6]は，混合型インスリンアナログ製剤と混合型ヒトインスリン製剤および持効型溶解インスリンアナログ製剤とを比較したシステマティック・レビューで，混合型インスリンアナログ製剤は，混合型ヒトインスリン製剤とは空腹時血糖，HbA_{1c}の低下は同等で，持効型溶解インスリンアナログ製剤とは食後血糖は−27.9 mg/dL，HbA_{1c}は−0.39%低下することを報告した。このことから，従来インスリン療法では，混合型インスリンアナログ製剤で，より良好な血糖コントロールが得られると考えられる。

3. 強化インスリン療法

Rosenstockら[7]は，リスプロ混合製剤の各食前1日3回のPPTと，リスプロ各食前およびグラルギン就寝前のBBTとを比較した。その結果，BBTのHbA_{1c}の低下率は，PPTのそれより0.22%低かったことから，BBTの方が望ましいと考えられる。

Ⅴ CKDにおけるインスリン療法

1. CKDステージ1〜2

インスリン療法については，CKDのない糖尿病の場合と大きく相違する点はない。

2. CKDステージ3〜5

腎機能が低下しているために，OHAの使用には慎重を要するか禁忌となる場合がある。使用禁忌は，軽度の腎機能障害に該当するビグアナイド薬はステージ3から，重篤な腎機能障害に該当するスルホニル尿素薬とインスリン抵抗性改善薬はステージ4から，透析を必要とする腎機能障害に該当する速効型インスリン分泌促進薬はステージ5から相当する。その場合は中止して，他剤かインスリン療法に変更する必要がある。なお，α-グルコシダーゼ阻害薬は透析患者まで使用できる[8]。

また，腎機能の低下に伴って，インスリンクリアランスの低下，尿毒素物質による摂取熱量の低下により，インスリン使用量が減少することに注意する必要がある。

3. CKDステージ5（血液透析）

多くのOHAが禁忌であり，インスリン療法が基本である。血液透析導入後の血糖管理を良好に保つことは，血管合併症の進行阻止と感染症の予防により生命予後を改善するために必要である。透析により食事が不規則になることや透析液中のブドウ糖濃度により，透析中は低血糖になりやすい。そのため，透析日と非透析日でインスリン量

を検討することが必要である。

4. CKDステージ5（腹膜透析）

血液透析と同様に，インスリン療法が基本である。ブドウ糖を使用している腹膜透析液では，ブドウ糖負荷によるインスリン量の調整が必要である。インスリンの腹腔内注射は生理的と考えられるが，腹膜炎が発生しやすいこと，チューブやバッグにインスリンが吸着されること，肝皮膜下の脂肪壊死の報告例があることなどから，インスリンを皮下注射で行うことが多い。

おわりに

インスリンアナログ製剤の登場により，インスリン療法は多様化している。多種類のインスリン製剤の組み合わせによる強化インスリン療法，BOTなどの新しいインスリンの導入方法などがそのよい例である。腎機能の低下，すなわちCKDステージによって，糖尿病の治療法の選択や変更の検討が必要であるが，良好な血糖コントロールの目的のためには，インスリン療法の導入に躊躇があってはならない。

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