Diet and Exercise Therapies for Patients with Diabetic Kidney Disease

AKIO KANAZAWA*

*Department of Metabolism & Endocrinology, Juntendo University Graduate School of Medicine, Tokyo, Japan

Recently, low-carbohydrate diet (LCD) is becoming popular among diabetes patients due to its efficacy in glycemic and body weight control. While LCD might lead to excess intake of protein and lipid, a low-protein diet (LPD) has been recommended to preserve renal function in advanced renal stages. Thus, diabetes patients on LCD are forced to change their diet therapies in accordance with deterioration of renal function. Additionally, the reno-protective effect of LPD on DKD is controversial because several clinical trials regarding efficacy of LPD failed to show conclusive results. This might be associated with the difficulty to adhere to a daily LPD and the insufficiency of clinical data regarding the optimal amount of restricted protein intake. Exercise therapy as well as diet is important for better glycemic control. Mild exercise therapy such as walking in patients with DKD has been recommended. However, intensity of exercise needs to be determined considering the severity of other micro and macrovascular complications.

Key words: low-protein diet (LPD), low-carbohydrate diet (LCD), exercise therapy

Introduction

Aims of diabetes treatment are to maintain a quality of life (QOL) and lifespan which are not different from those of non-diabetes. In order to achieve this goal, prevention of diabetic microvascular complications and atherosclerotic diseases is essential. Among microvascular complications, DKD is the most common primary disease causing the hemodialysis in Japan, and significantly affects the prognosis of diabetes patients. Therefore, management of DKD is very important to maintain QOL and lifespan.

In order to prevent DKD for a long time, adherence to diet guidance is a key issue. However, poor adherence to diet occurs mainly by difficulties in changing eating habits due to non-acceptance of calorie restrictions. Under these circumstances, low-carbohydrate diet becomes popular among obese

and diabetes patients because of free intake of protein and lipids and remarkable body weight reduction. However, if patients have advanced DKD, they need to perform LPD. In LPD, daily intake of carbohydrate and lipid tends to increase instead of restriction of protein intake. Thus, diet plan should be changed in accordance with the severity of diabetic complications.

In this paper, basic approach of diet and exercise for diabetes patients with and without DKD was described. Additionally, two low-carbohydrate diet studies previously performed at Juntendo University were introduced.

Diet therapy for type 2 diabetes patients with and without DKD

To determine appropriate energy intake in patients with type 2 diabetes mellitus, patient's sex,

Akio Kanazawa

Department of Metabolism & Endocrinology, Juntendo University Graduate School of Medicine
2-1-1 Hongo, Bunkyo-ku, Tokyo 113-8421, Japan

TEL: +81-3-5802-1579 FAX: +81-3-3813-5996 E-mail: akana@juntendo.ac.jp

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age, degree of obesity, intensity of physical activity, glycemic control level, and any complications need to be taken into consideration. Usually, men should consume the recommended calorie between 1,600~2,000 kcal/day and women should do between 1,400~1,800 kcal/day. However, it is also necessary to consider the patient's standard body weight and general conditions. Generally, 50~60% of the total energy intake should come from carbohydrate, and protein intake is restricted to 20%. The remaining energy is recommended to consist of lipid. Regarding the method of calculating appropriate energy intake, energy intake (kcal/day) in food = standard body weight $\times$ amount of physical activity. Japan Diabetes Society proposed the following guideline on energy intake (Table-1).

If patients have urinary albumin excretion ≥ 300 mg/g·Cr or continuous proteinuria (≥ 0.5 g/g·Cr), *i.e.*, over nephropathy (stage 3), their protein intake is recommended to restrict to 0.8~1.0 g/kg/day. In renal failure (stage 4), their protein intake is recommended to restrict to 0.6~0.8 g/kg/day. In cases complicated by hypertension, a salt intake of 6 g/day or less is recommended. In particular, the largest energy intake is recommended in the stage 5 (Table-2). Thus, the recommended diet greatly changes in case of advanced DKD.

Table-1 Guidelines on energy intake determined by different degrees of physical activity

Light work (desk workers, housewives, etc.)	25~30
Moderate work (those doing mainly standing work)	30~35
Heavy work (heavy manual workers)	35~

Units: kcal/kg of standard body weight

Efficacy of low-carbohydrate diet (LCD) in patients with type 2 diabetes

According to the guidelines of the Japan Diabetes Society, calorie restricted diet (CRD) is the recommended diet therapy for patients with type 2 diabetes mellitus, who are often educated about such therapy by qualified dietitians. However, even after receiving such education, many patients find it difficult to adhere to CRD. This finding points to the limitation of CRD as a standard diet therapy and calls for alternative therapies. In the United States and Europe, there is extensive debate regarding the value of LCD in the treatment of type 2 diabetes mellitus. However, the usefulness of LCD for Japanese type 2 diabetes mellitus patients has not yet been fully evaluated, apart from one small randomized controlled trial (RCT)¹⁾. Here, we previously evaluated the safety and efficacy of LCD in Japanese patients with poorly controlled type 2 diabetes mellitus who had received repeated education programs on CRD²⁾. This prospective, randomized, open-label, comparative study included 66 type 2 diabetes mellitus patients with HbA1c $>7.5\%$ even after receiving repeated education programs on CRD. They were randomly allocated to either the LCD group (n=33) or CRD group (n=33). Patients received personal nutrition education of CRD or LCD for 30 min at baseline, 1, 2, 4, and 6 months. Patients of the CRD group were advised to maintain the intake of calories and balance of macronutrients (28 x ideal body weight calories per day). Patients of the LCD group were advised to maintain the intake of 130 g/day carbohydrate without other specific restrictions. Several parameters were assessed at baseline and 6 months after each intervention. The primary endpoint was a change in HbA1c level from baseline

Table-2 Guidance of dietary intake for patients with diabetic nephropathy

	Total energy (kcal/kg Body weight/day)	Proteins	Salt (g/day)
Stage 1 (pre-nephropathy)	25~30	$\leq 20\%$ energy	< 6 if also hypertensive
Stage 2 (early nephropathy)	25~30	$\leq 20\%$ energy	< 6 if also hypertensive
Stage 3 (overt nephropathy)	25~30	0.8~1.0 g/kg BW/day	< 6
Stage 4 (renal failure)	25~35	0.6~0.8 g/kg BW/day	< 6
Stage 5 (dialysis)	30~35	0.9~1.2 g/kg BW/day	< 6

to the end of the study. At baseline, median (interquartile range) of body mass index (BMI) and HbA1c were 26.5 (24.6 – 30.1) kg/m² and 8.3 (8.0 – 9.3) % in the CRD group, and 26.7 (25.0 – 30.0) kg/m² and 8.0 (7.6 – 8.9) % in the LCD group, respectively. At the end of the study, HbA1c decreased by –0.65 (–1.53 to –0.10) % in the LCD group, compared with 0.00 (–0.68 to 0.40) % in the CRD group ($p < 0.01$). Also, the decrease in BMI in the LCD group was –0.58 (–1.51 to –0.16) kg/m², which exceeded that in the CRD group [–0.22 (–0.58 to 0.24) kg/m²] ($p = 0.03$). Thus, LCD significantly improved glycemic control and decreased BMI compared to CRD.

Next, we further followed the patients' total calorie intake, dietary composition and clinical data for one year after the end of this intervention. After the end of the RCT, the patients became free to choose their nutrition therapy by themselves, and we could follow 26 patients in the CRD group and 23 patients in the LCD group³⁾. At the end of the one-year follow-up period, HbA1c and BMI decreased by –0.35 (–1.0 to –0.35) % and –0.9 (–1.4 to –0.1) kg/m² in the LCD group, compared with –0.40 (–0.9 to 0.3) % and –0.6 (–1.2 to 0.2) kg/m² in the CRD group from the baseline of the RCT. However, there were no significant differences in HbA1c and BMI between the two groups. Without the intervention, the patients of the LCD group did not continue to take the low amount of carbohydrate. The amount of carbohydrate became 215 (189 – 243) g/day in the CRD group and 214 (176 – 262) g/day in the LCD group at the end of follow-up. Therefore, it was difficult to continue LCD for a long time if no intervention was carried out by dietitians.

Efficacy of low-protein diet (LPD) in diabetes patients with DKD

LPD is utilized in patients with kidney disease including DKD partly to ameliorate glomerular hemodynamics. One possible explanation for the beneficial effects of LPD is linked to the renin-angiotensin system (RAS). Protein overload activates the RAS, and LPD has been shown to inhibit the intrarenal RAS⁴⁾. It is well established that blockade of the RAS with either angiotensin-converting-enzyme inhibitors or angiotensin receptor blockers

slows the progression of kidney disease. In this manner, LPD may exhibit similar protective effects as an RAS blockade. As another mechanism, protein overload increases the excretion of amino acids from the glomerulus⁵⁾. Such increased secretion of amino acid leads to the reabsorption of amino acids via the sodium-amino acid transporter in the proximal tubules. Consequently, such increased reabsorption increases sodium chloride reabsorption as well, resulting in a deficiency of the chloride levels in the juxtaglomerular apparatus⁶⁾. Subsequently, tubular glomerular feedback system, that normalizes the chloride concentration in the tubule is activated. As a result, the glomerular filtration rate is increased by protein overload, contributing to deteriorate glomerular hemodynamics.

In Japan, a long-term effect of LPD on diabetic nephropathy was assessed previously⁷⁾.

This was a multi-site parallel randomized controlled trial for prevention of diabetic nephropathy progression among 112 Japanese type 2 diabetes patients with overt nephropathy. The participants were randomly assigned to either low-protein diet (0.8 g/kg/day) and normal-protein diet (1.2 g/kg/day) and were followed for 5 years. The primary outcomes were the annual change in estimated GFR (glomerular filtration rate) and creatinine clearance, the incidence of doubling of serum creatinine and the time to doubling of baseline serum creatinine. 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/1.73 m² (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/1.73 m² (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 was –2.6% (95% CI –22.6, 17.5; $p = 0.80$). Thus, this study showed no significant differences in the primary outcome. Additionally, the mean protein intake from the food record was significantly different between low- and normal-protein intake group (0.9 ± 0.2 vs $1.1 \pm$

0.2 g/kg/day, respectively, $p < 0.0001$), while the protein intake derived from 24 h urinary nitrogen excretion was comparable between both groups (1.0 ± 0.2 vs 1.0 ± 0.2 g/kg/day, respectively, $p = 0.16$). This discrepancy indicates that an adherence to LPD was reduced, and true beneficial effect of the low-protein diet could not be assessed in this study. Several randomized clinical trials investigating the effects of LPD on the progression DKD have been reported so far. The results related to LPD were inconclusive because both positive^{8) 9)} and negative studies^{10) 11)} were reported. However, as there has been no evidence that high protein diet is safe in DKD, LPD is currently prescribed taking each patient's condition and adherence into consideration.

Exercise therapy

Regular exercise is a cornerstone of diabetes management as well as diet. Beneficial effects of exercise were summarized as follows; 1) An immediate effect of exercise can increase utilization of glucose and fatty acids and lower blood glucose. 2) A long-term exercise brings an improvement in insulin resistance. 3) The improved balance between energy intake and expenditure is effective for the reduction of body weight. 4) Muscle atrophy and osteoporosis caused by aging and insufficient exercise can be prevented. 5) Hypertension and dyslipidemia can be improved. 6) Cardiopulmonary function can be improved. 7) Exercise capacity increases. Thus, exercise can improve QOL in diabetes patients, accompanied by improvement of

various physiological conditions.

Regarding types of exercise, there are two types of exercise, aerobic and resistance (Figure-1). The former consists of exercise whose intensity is proportional to the consumption of oxygen, and which, if performed regularly, increases insulin sensitivity. Exercises such as brisk walking and jogging belong to this category. Conversely, resistance exercise, if performed intensively, is anaerobic exercise against a force or resistance. If patients practiced effectively, this type of exercise can be expected to increase the mass and strength of the muscles. However, the effect of exercise on body weight reduction is limited because much energy is not always consumed by exercise therapy. Patients often have the following misunderstanding, "The amount of energy I used for exercise today makes it possible for me to eat much more today". The main effect of exercise on glucose metabolism is the improvement of insulin sensitivity. This point is important for guidance of exercise therapy.

Regarding the intensity and frequency of exercise, an intermediate-intensity exercise is generally recommended. An intermediate-intensity exercise is defined as an exercise involving a maximum oxygen uptake of 50% more or less, the intensity of which is determined by the heart rate during exercise. The heart rate during exercise is to be maintained within 100 to 120 beats per minute. Most importantly, an intensive exercise should be avoided in DKD, and exercise intensity patients feel to be effortless should be considered. Then, it is recommended that an intermediate-intensity exercise should be done for 50 to 60 min 3 to 5 times a

Figure-1 Type of exercise

week and resistance exercise should be done simultaneously 2 to 3 times a week. In clinical setting, patients are often instructed to spend 15–30 min a day for walking or to walk approximately 10,000 steps in a day.

Interestingly, it has been reported that walking after meals is more effective for lowering postprandial glycemia in type 2 diabetes mellitus than advice that does not specify timing¹²⁾. In this study, two interventions, “one walking for 30 min undertaken at any time of the day” and “post-meal walking for 10 min undertaken after each of the three main meals” were performed in a randomized order. After two weeks intervention, postprandial glycemia during 3 h after a meal using the incremental area under the blood glucose curve (iAUC) was evaluated by continuous glucose monitoring. As a result, overall postprandial glycemia, as measured by the iAUC was 12% lower during the post-meal walking period than a 30-min walk at any time of the day. This difference in postprandial hyperglycemia was largely explained by the highly significant 22% difference in iAUC following the evening meal, when the greatest amount of carbohydrate was consumed. This study shows that short-term walking of 10 min after a big meal is effective for improvement of postprandial hyperglycemia, which might reduce a cardiovascular risk. Then, as another advantage, elderly patients also perform easily this short-term walking.

However, in DKD with the following conditions, exercise should be prohibited or restricted. 1) When metabolic control is extremely poor (fasting blood glucose over 250 mg/dL, or urinary ketone bodies moderately positive), 2) Ischemic heart disease such as unstable angina, 3) severe diabetic neuropathy, 4) severe diabetic retinopathy with fundus hemorrhage. In complicated cases, patients had better consult their physicians in charge.

Conclusions

In order to prevent the onset and progression of DKD, we need to educate patients well so that they

can perform diet and exercise appropriately on their own.

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