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Guide

Best Practice for Diabetic Patients on Hemodialysis 2012

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I. GLYCEMIC CONTROL

(1) Targets for glycemic control

Statements

1. Predialysis casual plasma glucose and glycated albumin (GA) levels are recommended as indicators for glycemic control.
2. The hemoglobin A_{1c} (HbA_{1c}) level *might be used only as reference*, because HbA_{1c} level decreases in the presence of anemia or erythropoiesis-stimulating agents (ESAs) and may not accurately represent glycemic control in hemodialysis patients.
3. Tentative targets for glycemic control: predialysis casual plasma glucose levels (or 2-h postprandial plasma glucose levels) <180–200 mg/dL and GA levels <20.0% are recommended for hemodialysis patients. GA levels <24.0% are suggested for hemodialysis patients with a history of cardiovascular events and who have hypoglycemic episodes. Further studies are required to definitively determine target values.
4. In glycemic control, multiple indicators, including predialysis casual plasma glucose and GA levels, should be comprehensively evaluated to reduce the risk of hypoglycemia and improve the prognosis of patients.

Commentary

1. Targets for glycemic control in general diabetic patients

Glycemic control in diabetic patients affects the development and progression of microvascular complications (1–3). A study showed that achieving HbA_{1c} levels <6.9% (National Glycohemoglobin Standardization Program [NGSP] reference value) and 2-h postprandial plasma glucose levels <180 mg/dL prevents the development and progression of diabetic microvascular complications (2). Another study showed that intensive glycemic control with tight regulation of lipid levels and blood pressure decreases the incidence of cardiovascular events and improves the prognosis of diabetic patients (4). Intensive glycemic control at the initial stage of diabetes was also shown to reduce the incidence of cardiovascular events and improve the prognosis of diabetic patients in the following 10 years (5,6). Thus, intensive glycemic control in diabetic patients is considered to prevent the development of not only microvascular but also macrovascular complications and improve their prognosis. Considering recent reports (7,8), the prevention of hypoglycemia is also important.

2. Targets for glycemic control in hemodialysis patients

1) HbA_{1c}

HbA_{1c} level is the most common indicator for glycemic control in diabetic patients and represents a time-weighted mean plasma glucose level during the preceding 1 to 3 months. The life span of red blood cells is approximately 120 days. The plasma glucose level in the preceding 30 days contributes 50% to the HbA_{1c} level, and those in the preceding 30–60 and 60–120 days contribute 25% each to the HbA_{1c} level (9).

For hemodialysis patients, however, the life span of red blood cells is shorter (approximately 60 days), blood loss and hemorrhage may occur during hemodialysis, and the percentage of immature red blood cells is increased by the administration of ESAs as a treatment for renal anemia. Therefore, hemodialysis

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patients tend to show low HbA_{1c} levels for their glycemic control, which may underestimate glycemic control.

2) GA

GA is produced when serum albumin is glycated. The half-life of albumin is approximately 17 days. The GA level represents glycemic control in the preceding 2 to 4 weeks. The plasma glucose level in the 17 days immediately preceding blood sampling contributes 50% to the GA level, and those in the preceding 18–34 days and days before contribute 25% each to the GA level (9).

Several studies showed that GA is not affected by the life span of red blood cells or ESA administration and can be used as a better indicator of glycemic control than HbA_{1c} in hemodialysis patients (10–14). A study of Japanese patients compared hemodialysis patients with diabetes ($n = 538$), hemodialysis patients without diabetes ($n = 828$), and diabetic patients with normal kidney function ($n = 365$). The results showed that the HbA_{1c} and GA levels in the hemodialysis patients with diabetes were significantly and positively correlated with the mean casual plasma glucose levels in the prior 3 months. However, the HbA_{1c} levels in these patients were ~30% lower than those in the diabetic patients with normal kidney function. The correlations between the mean casual plasma glucose levels and GA levels were similar in both groups of patients (12).

Similar results were also found in US reports. A comparative study of diabetic patients without nephropathy (non-dialysis group, $n = 49$) and on hemodialysis (dialysis group, $n = 258$) showed significantly positive correlations between HbA_{1c} and GA levels in both groups but showed a significant difference in the slope of the regression line for the two groups. The slope of the regression line showing the correlation between HbA_{1c} and casual plasma glucose levels also significantly differed between the two groups. In that study, it was concluded that the HbA_{1c} level for a given casual plasma glucose level is lower in the dialysis group than in the non-dialysis group. In contrast, there was no significant difference in the slope of the regression line showing the correlation between GA and casual plasma glucose levels in the two groups (13). Note that the GA level is dependent on factors other than plasma glucose level in the following groups: (i) patients with nephritic syndrome (15); (ii) patients undergoing peritoneal dialysis (16,17); (iii) patients with thyroid dysfunction (18); and (iv) patients with hepatic cirrhosis (19).

3. Targets for glycemic control in hemodialysis patients with diabetes

The majority of dialysis patients with diabetes have already developed microvascular and macrovascular complications, because they start dialysis as therapy for end-stage renal disease caused by diabetic nephropathy and they generally had diabetes for a long period by the time they start dialysis. Intensive glycemic control in such patients is considered to be effective for slowing the progression of not only microvascular complications such as retinopathy and neuropathy but also macrovascular complications and infectious diseases, and for improving the prognosis of these patients (20,21). The prevention of hypoglycemia is also indispensable in dialysis patients with diabetes.

Previous observational studies on the relationship between glycemic control and survival in hemodialysis patients with diabetes showed different results. In some studies, it was concluded that HbA_{1c} level used as the indicator for glycemic control is predictive of survival in such patients (22–28). Others showed no such correlations in these patients (29–36), but their HbA_{1c} levels were generally low. As mentioned above, the HbA_{1c} level in hemodialysis patients underestimates glycemic control and cannot always be used as an accurate indicator of glycemic control. Therefore, the effects of glycemic control on the prognosis of hemodialysis patients should be reexamined using indicators other than HbA_{1c} levels, such as plasma glucose and GA levels.

1) Target predialysis plasma glucose levels

An 11-year follow-up study of 245 new hemodialysis patients with diabetes in a Japanese facility showed that having (2-h postprandial) predialysis plasma glucose levels ≥180 mg/dL (the mean over the total observation period to death or termination of analysis) was associated with significantly shortened patient survival. However, there was no threshold HbA_{1c} level at which survival shortened (20). Recently, a 6-year follow-up observational study of 54 757 hemodialysis patients with diabetes in the USA has shown higher mortality in the group with casual plasma glucose levels ≥200 mg/dL (patients categorized by plasma glucose level at increments of 25 mg/dL using mean casual plasma glucose levels of 150–175 mg/dL as the reference) (21). Moreover, survival was also shorter in the groups with HbA_{1c} levels ≥8.0% and ≤6.9% (patients categorized by HbA_{1c} level at increments of 1.0% using mean HbA_{1c} levels of 7.0–7.9% as the reference). The distribution of the hazard ratio is V-shaped, indicating that HbA_{1c} level is not directly associated with survival.

Based on the above-mentioned studies, (predialysis) casual plasma glucose levels of <180–200 mg/dL are recommended as tentative targets for glycemic control.

2) Target GA levels

Although the GA level is a helpful indicator for glycemic control in hemodialysis patients as mentioned above, there have been a very limited number of reports on the relationship between the GA level and the risk of cardiovascular events or the prognosis of hemodialysis patients. A study of Japanese patients showed that the risk of cardiovascular events was significantly higher in diabetic hemodialysis patients with GA levels ≥23% (35). Another study of Japanese patients also showed that the survival rate of chronic hemodialysis patients with GA levels ≥29% was significantly low (34). In a recent 4-year follow-up study of 170 hemodialysis patients with diabetes in a Japanese facility, the relationship between glycemic control and survival in these patients was examined using the GA level as the indicator for glycemic control at the start of observation. The results showed that survival was longer in the patients who had no history of cardiovascular events as of the start of observation than in the patients with such a history. In addition, a report on the analysis of the patients who had no history of cardiovascular events revealed that survival was significantly longer in the group with GA levels <20.0% than in the groups with GA levels of 20.0–24.5 or >24.5% (37). In this report, however, the threshold GA level at which survival shortens was not found in the diabetic dialysis patients with a history of cardiovascular events as of the start of observation. A US study also showed significant associations of GA level with survival and the number of hospitalizations in hemodialysis patients with diabetes. However, the HbA_{1c} level was not associated with survival or the number of hospitalizations in that study (38).

Based on the above-mentioned studies, GA levels <20.0% are suggested as tentative targets for glycemic control in patients without a history of cardiovascular events. For patients with a history of cardiovascular events, however, GA levels <24.0% are suggested, because the positive effect of achieving GA levels <20.0% on the prognosis is not expected to exceed the negative effect of the increased incidence of hypoglycemia. Further study is required to definitively determine target values.

3) Target HbA_{1c} levels

The HbA_{1c} level has long been used as an indicator in clinical practice and in many studies of glycemic control in dialysis patients with diabetes. However, as mentioned above, HbA_{1c} levels are apparently low in hemodialysis patients and may not accurately represent glycemic control. Therefore, it is difficult to determine target HbA_{1c} levels for glycemic control on the basis of the above studies. We calculated the mean HbA_{1c} level in 195 hemodialysis patients with diabetes and found it to be 6.6% (NGSP reference value) for a predialysis plasma glucose level of 180 mg/dL. This value should be used only as a reference.

Hemodialysis patients are prone to hypoglycemia because of various factors, and they require careful assessment of plasma glucose levels and appropriate management to prevent hypoglycemia. In glycemic control, multiple indicators, including (predialysis) casual plasma glucose and GA levels, should be comprehensively evaluated to reduce the risk of hypoglycemia and improve the prognosis of patients.

Many of the recommendations in overseas guidelines for the treatment of diabetes in hemodialysis patients are based on weak evidence (39). The Japanese Society for Dialysis Therapy (JSDT) guide provides suggestions on the indicators for glycemic control and their tentative targets based on previous reports. Further clinical trials are needed to strengthen the basis of these suggestions.

(2) Frequency of monitoring glycemic control indicators

Statements

1. For patients treated with insulin, pre- and post-dialysis casual plasma glucose levels should be monitored in each hemodialysis session.
2. For patients treated with oral hypoglycemic agents, predialysis casual plasma glucose level should be monitored once a week.
3. For hemodialysis patients having good glycemic control without the above drug therapies, predialysis casual plasma glucose levels should be monitored at least once a month.
4. For all hemodialysis patients with diabetes, the GA level should be monitored once a month.
5. For hemodialysis patients without diabetes, plasma glucose and GA levels should be monitored at least once a year.

Commentary

1. Patients who are treated with insulin

Self-monitoring of blood glucose (SMBG) is useful for maintaining and improving glycemic control in all patients with type 1 diabetes and patients with type 2

diabetes who are treated with insulin (1,2). Therefore, all patients who are treated with insulin, irrespective of diabetes type, are recommended to carry out SMBG. Clinicians should also monitor their pre- and postdialysis plasma glucose levels in each hemodialysis session.

When patients treated with insulin are suspected to have developed various symptoms resulting from hypoglycemia or feel sick, plasma glucose level should be monitored to understand their condition. Some studies showed that the adjustment of insulin dose based on the results of SMBG is indispensable for providing intensive insulin therapy to non-dialysis patients with type 1 diabetes and contributes to improved glycemic control and the prevention of complications (1,2). SMBG is also an essential component of intensive insulin therapy for non-dialysis patients with type 2 diabetes and has similar contributions (2).

2. Non-insulin-treated patients

There has been insufficient evidence on the frequency of monitoring plasma glucose level in non-insulin-treated patients, including non-dialysis patients. However, hemodialysis patients generally visit their medical institution three times per week and have more opportunities to know their plasma glucose levels than non-dialysis patients. This advantage enables a more accurate evaluation of glycemic control in hemodialysis patients. For hemodialysis patients with stable glycemic control who are taking oral hypoglycemic agents, predialysis plasma glucose level should be monitored once a week. For hemodialysis patients who have changed their dose of a hypoglycemic agent or switched to or added another hypoglycemic agent, predialysis plasma glucose level should be monitored more frequently until stable glycemic control is achieved.

For diabetic hemodialysis patients who have achieved good glycemic control without drug therapy, predialysis plasma glucose level should be monitored at least once a month. When hyperglycemia is detected, clinicians are advised to reevaluate glycemic control in their patients.

3. Frequency of GA level monitoring

The GA level represents the mean plasma glucose level in the preceding 2 to 4 weeks, which is relatively shorter than for the HbA_{1c} level. The GA level does not greatly change in 2 weeks when diabetic patients have stable glycemic control. Therefore, once-a-month monitoring of the GA level is recommended for diabetic hemodialysis patients.

4. Continuous glucose monitoring

Currently, continuous glucose monitoring (CGM) systems can be used to continuously monitor the plasma glucose level to understand its dynamic changes. CGM systems are applicable to the evaluation of postprandial changes in plasma glucose level, the levels at nighttime and midnight, and the presence of asymptomatic hypoglycemia. In particular, the use of CGM systems for diabetic hemodialysis patients treated with insulin is attracting attention because circadian changes in plasma glucose level may differ between dialysis and non-dialysis days (40,41).

5. Diabetes screening and diagnosis in dialysis patients

There are few reports on the incidence rate of diabetes mellitus after initiating of dialysis therapy. The American Diabetes Association recommends that regular testing should begin at age ≥45 and should be considered in all adults who have obesity and who have one or more risk factors: physical inactivity, family history of diabetes, women who were diagnosed with gestational diabetes mellitus or who delivered a large baby, hypertension, dyslipidemia, women with polycystic ovary syndrome, other clinical conditions associated with insulin resistance, or history of cardiovascular disease or abnormal glucose tolerance (42). End-stage kidney disease results in increased insulin resistance, which has been reported as a predictor of cardiovascular events (43–45). Therefore, casual plasma glucose and GA levels should be monitored at least once a year in hemodialysis patients without diabetes as a screening for type 2 diabetes.

When a patient is suspected to have diabetes, clinicians should make a diagnosis following the clinical guidelines established by the Japan Diabetes Society (46), which recommend that both plasma glucose and HbA_{1c} levels should be monitored in 1-day blood sampling. Criteria for the diagnosis of diabetes are as follows: fasting plasma glucose ≥126 mg/dL; 2-h plasma glucose ≥200 mg/dL during an oral glucose tolerance test (OGTT) using a glucose load containing the equivalent of 75 g of glucose; or casual plasma glucose levels ≥200 mg/dL; and HbA_{1c} levels ≥6.5% (46). When patients satisfy the criteria for both plasma glucose and HbA_{1c} levels using blood sampled on 1 day, they are diagnosed as having diabetes by only one blood sampling. As mentioned above, the HbA_{1c} level tends to be low in hemodialysis patients and underestimates glycemic control. Thus, some hemodialysis patients who should be diagnosed as having diabetes may have HbA_{1c} levels <6.5% but satisfy the plasma glucose level criterion

for diabetes. Therefore, testing (monitoring of fasting and casual plasma glucose levels and OGTT) should be repeated in the case of diabetes diagnosis of hemodialysis patients.

(3) Glucose levels in dialysis fluid

Statements

1. In insulin-treated diabetic hemodialysis patients with high predialysis plasma glucose levels, plasma glucose levels may rapidly and markedly decrease during hemodialysis, because of a large gap between blood and dialysis fluid glucose levels.
2. A large intradialytic fall in plasma glucose level may induce an increase in plasma glucose level after hemodialysis (hemodialysis-induced hyperglycemia). In order to prevent hemodialysis-induced hyperglycemia, the use of a dialysis fluid with a relatively higher glucose level is suggested to reduce the intradialytic changes in plasma glucose level.

Commentary

1. Plasma glucose levels in hemodialysis patients with diabetes are affected by dialysis fluid, and they change during and after hemodialysis

1) Intradialytic changes in plasma glucose level

As of October 2011, approximately 25 types of dialysis fluid were commercially available from four companies in Japan. Table 1 shows a summary of the composition of each dialysis fluid. The glucose level in the dialysis fluid is 0, 100, 125, or 150 mg/dL. Many dialysis patients with diabetes have already developed hyperglycemia before the initiation of dialysis. Generally, morning hemodialysis starts between 8:30 and 9:00, which is 1 or 2 h after breakfast and when the plasma glucose level reaches the maximum. When hemodialysis is started in patients with such a high plasma glucose level using a dialysis fluid with a glucose level in the range of 100–150 mg/dL, the large difference in glucose level between the blood and the dialysis fluid allows plasma glucose to diffuse into the dialysis fluid, decreasing the plasma glucose level

TABLE 1. *Composition of main dialysis fluid products commercially available in Japan*

Trade name	Manufacturer	Concentration of dilute dialysate (mEq/L)							Glucose level (mg/dL)
		Na	K	Ca	Mg	Cl	Acetate	Bicarbonate	
Kindary AF1	Fuso Pharmaceutical	136	2.5	3.5	1.5	106.5	8†	30	0
Kindary AF1P	Industries, Ltd.	136	2.5	3.5	1.5	106.5	8†	30	–
Kindary AF2P		140	2.0	3.0	1.0	110	8†	30.0	100
Kindary 2D		140	2.0	3.0	1.0	110	8†	30.0	100
Kindary 2E		140	2.0	3.0	1.0	110	8†	30.0	100
Kindary AF4P		140	2.0	2.75	1.0	112.25	8†	27.5	125
Kindary 4D		140	2.0	2.75	1.0	112.25	8†	27.5	125
Kindary 4E		140	2.0	2.75	1.0	112.25	8†	27.5	125
Kindary AF3P		140	2.0	2.5	1.0	114.5‡	8‡	25.0	150
Kindary 3D		140	2.0	2.5	1.0	114.5‡	8†	25.0	150
Kindary 3E		140	2.0	2.5	1.0	114.5‡	8†	25.0	150
HYSORB-D	Ajinomoto Pharmaceuticals	140	2.0	3.0	1.0	111	12§	25.0	100
CARBOSTAR·P	Co., Ltd.	140	2.0	3.0	1.0	111	–	35.0	150
HYSORB-F		143	2.0	2.5	1.0	112	11§	27.5	100
AK-SOLITA·DP		140	2.0	3.0	1.0	113§	10	25.0	100
CARBOSTAR·M		140	2.0	3.0	1.0	111	–	35.0	150
AK-SOLITA·DL		140	2.0	3.0	1.0	113§	10	25.0	100
CARBOSTAR·L (9L)		140	2.0	3.0	1.0	111	–	35.0	150
CARBOSTAR·L (6L)		140	2.0	3.0	1.0	111	–	35.0	150
AK-SOLITA·FP		143	2.0	2.5	1.0	114§	9	27.5	100
AK-SOLITA·FL		143	2.0	2.5	1.0	114§	9	27.5	100
D Dry 2.5S	Nikkiso Co., Ltd.	140	2.0	2.5	1.0	112.5	10†	25.0	100
D Dry 3.0S		140	2.0	3.0	1.0	113.0	10†	25.0	100
LYMPACK 1	Nipro Corporation	138	2.0	2.5	1.0	110	8†	28.0	100
LYMPACK 3		140	2.0	3.0	1.0	113	10.2†	25.0	100
LYMPACK TA1		138	2.0	2.5	1.0	110	8†	28.0	100
LYMPACK TA3		140	2.0	3.0	1.0	113	10.2†	25.0	100

†Including CH_3COO^- of glacial acetic acid (pH regulator); ‡including Cl^- of dilute hydrochloric acid (pH regulator); §including components of pH regulator.

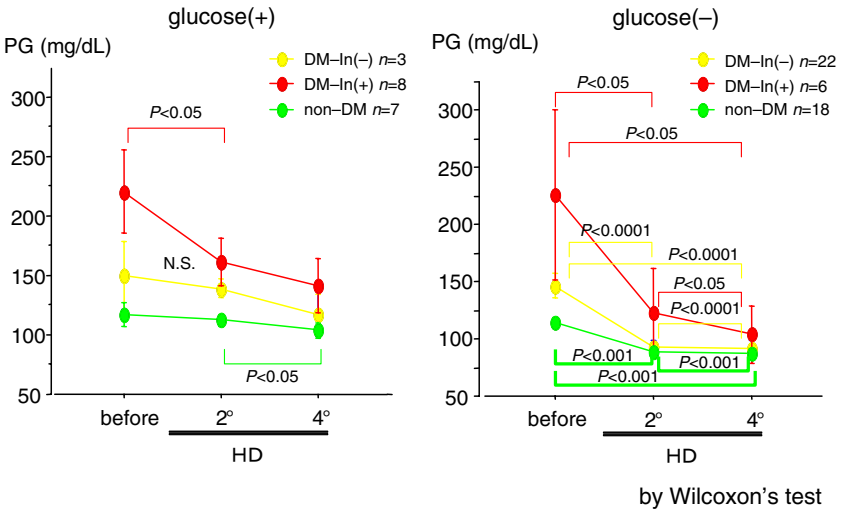

FIG. 1. Changes in plasma glucose level during hemodialysis session using glucose-containing or non-glucose-containing dialysis fluid (48).
DM, diabetes mellitus; glucose(+), glucose-containing dialysate (100 mg/dL); glucose(–), non-glucose-containing dialysate (0 mg/dL); HD, hemodialysis; In, insulin; PG, plasma glucose; N.S., not significant; 2°, 2 h after start of hemodialysis session; 4°, 4 h after start of hemodialysis session.

(47,48). When hemodialysis is performed using a dialysis fluid with a glucose level of 100 mg/dL, the intradialytic decrease in plasma glucose level is greater in insulin-treated patients with higher predialysis plasma glucose levels (Fig. 1) (48). For patients with good glycemic control (i.e. diabetic patients with low predialysis plasma glucose levels), the plasma glucose level tends to decrease but not significantly. The plasma glucose level in dialysis patients without diabetes rarely changes during dialysis. Changes in plasma glucose level are more significant when a dialysis fluid with a plasma glucose level of 0 mg/dL is used. Plasma glucose levels monitored at the inlet and outlet of a dialyzer during hemodialysis similarly decrease at the start of the hemodialysis session and 2 and 4 h after the start. The degree of decrease is large in patients with extremely high predialysis plasma glucose levels. These trends are similarly observed in patients with both good and poor glycemic control. This is because glucose in the blood diffuses into the dialysis fluid in accordance with the predialysis plasma glucose level during hemodialysis.

2) Postdialysis changes in plasma glucose level

The plasma glucose level in diabetic patients changes even after hemodialysis, because of the effect of dialysis fluid (47,48). In patients with markedly decreased plasma glucose levels during a hemodialysis session, their plasma glucose levels are greatly elevated after dialysis or lunch, causing significant hyperglycemia (Fig. 2). In hyperglycemic patients, their plasma glucose levels are not markedly elevated even after lunch on a non-dialysis day, because their plasma glucose levels do not decrease. In diabetic patients who have good glycemic control, their

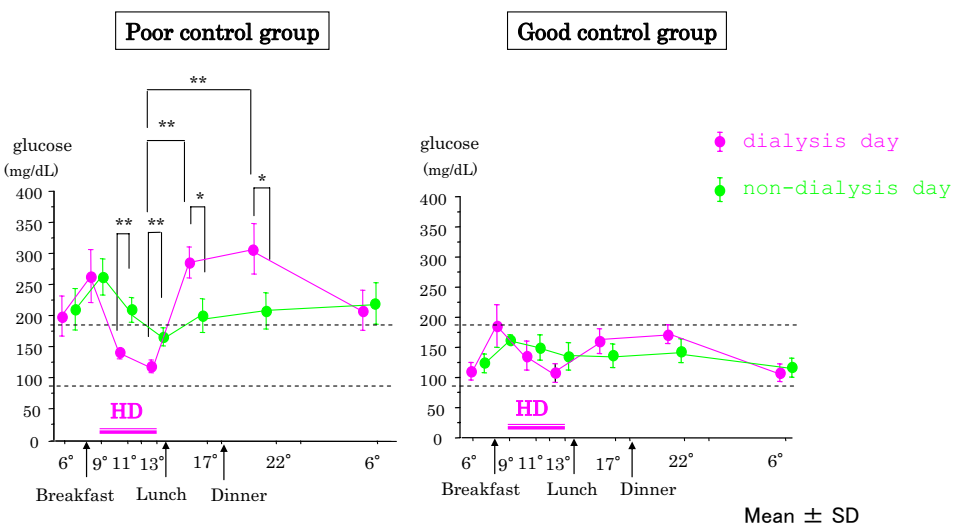

FIG. 2. Circadian changes in plasma glucose level in dialysis patients with diabetes on dialysis and non-dialysis days (48). HD, hemodialysis; SD, standard deviation. $*P < 0.05$, $**P < 0.01$.

plasma glucose levels do not decrease during dialysis and hyperglycemia does not develop after hemodialysis. Hyperglycemia that develops after hemodialysis as a result of the decrease in plasma glucose level during hemodialysis is called hemodialysis-induced hyperglycemia. It is speculated that when the plasma glucose level decreases, insulin secretion decreases, but the secretion of counter-regulatory hormones that elevate plasma glucose levels increases to maintain a stable plasma glucose level. Glucose-level-elevating hormones, such as glucagon, may contribute to the development of hemodialysis-induced hyperglycemia.

2. Factors affecting intradialytic decrease in plasma glucose level in hemodialysis patients with diabetes are insulin, predialysis plasma glucose level, and glucose levels in dialysis fluid

Patients undergoing insulin therapy generally receive insulin before the hemodialysis session. Insulin probably contributes to the intradialytic decrease in plasma glucose level, but this contribution may weaken during hemodialysis, because insulin in the blood is removed by hemodialysis and the blood insulin level decreases to various degrees. However, insulin is still one of the factors affecting the intradialytic decrease in plasma glucose level.

(4) Treatment of hyperglycemic and hypoglycemic episodes before and after hemodialysis

Statements

1) Hyperglycemia at the start of hemodialysis
   1. If marked hyperglycemia ≥500 mg/dL was observed at the start of each dialysis session, subcutaneous injection of a small dose (2–4 units) of ultrafast-acting insulin is suggested. In these cases, levels of plasma glucose should be again monitored in 2 h. The target plasma glucose levels are 100–249 mg/dL. Sudden and excessive decrease in plasma glucose after insulin injection (<100 mg/dL) should be avoided.
   2. When plasma glucose ≥600 mg/dL is detected, urgent measures of blood gas analysis, serum potassium, and if possible, ketone bodies in the blood are recommended, to exclude the diagnosis of diabetic ketoacidosis (DKA). Patients diagnosed as having DKA should be immediately hospitalized.
   3. When hyperglycemia occurs frequently, consultation with a diabetes specialist is strongly recommended to fundamentally revise the current diabetes therapeutic regimen.

Commentary

To the best of our knowledge, there are no reports on the management of hyperglycemic episodes detected at the start of a dialysis session. The plasma glucose level naturally decreases after the start of a hemodialysis session because of the diffusion of glucose into dialysis fluid. Data from a Japanese facility showed that in patients who had predialysis plasma glucose levels <500 mg/dL, their plasma glucose levels decreased to <300 mg/dL in a 3–4-h hemodialysis session without the use of hypoglycemic agents (Table 1). Therefore, hyperglycemic patients with predialysis plasma glucose levels <500 mg/dL do not usually need insulin injection.

However, for significantly hyperglycemic patients with predialysis plasma glucose levels ≥500 mg/dL, subcutaneous injection of a small dose (two to four units) of ultrafast-acting insulin is suggested. In this case, plasma glucose level should be again monitored 2 h. The target plasma glucose levels are suggested to be 100–249 mg/dL.

Changes in the plasma glucose level caused by insulin differ among patients. Even a small dose of insulin, as mentioned above, may markedly decrease the plasma glucose level. Therefore, care should be taken to prevent a sudden or extreme drop in the plasma glucose level (<100 mg/dL).

When hyperglycemia occurs frequently, consultation with a diabetes specialist is strongly recommended to fundamentally review the current diabetes treatment regimen.

Hemodialysis patients are considered to rarely develop DKA. However, several case report of Japanese patients (Table 2) (49–62) showed that DKA patients on hemodialysis had higher plasma glucose levels (all patients, ≥600 mg/dL; average, 1336 ± 369 mg/dL) than those without renal disease and developed an advanced metabolic acidosis and hyperkalemia, which cannot be explained by renal disease alone.

When hyperglycemia with plasma glucose levels ≥600 mg/dL is detected, urgent measures, such as blood gas analysis, serum potassium monitoring, and if possible, monitoring of ketone bodies in the blood, are recommended to rule out DKA. Patients diagnosed as having DKA should be immediately hospitalized.

TABLE 1. *Plasma glucose levels before and after hemodialysis session in dialysis patients with diabetes*

	Predialysis blood glucose level (mg/dL)				Postdialysis blood glucose level (mg/dL)		
No. of patients	Category (mg/dL)	Mean ± SD	Min.	Max.	Mean ± SD	Min.	Max.
874	<200	140 ± 34	33	199	124 ± 31	52	270
228	200–299	229 ± 24	200	292	141 ± 38	55	293
33	300–399	342 ± 27	300	393	161 ± 46	92	244
7	400–	457 ± 27	420	506	132 ± 49	84	216

Patients were divided into four groups according to the predialysis glucose level in blood sampled before hemodialysis using a dialysate with a glucose level of 100 mg/dL. Blood samples were obtained from a dialysis circuit before hemodialysis and 3–4 h after hemodialysis at bedside using a small electrode-type blood glucose meter (ANTSENSE III, HORIBA, Ltd., Kyoto, Japan). SD, standard deviation.

TABLE 2. *Case reports of Japanese hemodialysis patients who developed DKA*

No.	Author(s)	Year	Age of patient (years)	Gender	Diabetes type	Blood glucose level (mg/dL)	Arterial blood pH	Serum K level (mEq/L)
1	Araki et al. (49)	1997	46	M	1	1467	7.09	6.6
2	Fujiwara et al. (50)	2000	63	F	1	1270	6.97	N.I.
3	Kurata et al. (51)	2001	32	F	1	1912	6.76	7.2
4	Yamaguchi et al. (52)	2002	65	F	N.I.	609	7.15	N.I.
5	Shiga et al. (53)	2002	36	F	N.I.	N.I.	N.I.	N.I.
6	Fujikura et al. (54)	2003	65	M	N.I.	N.I.	N.I.	N.I.
7	Tominaga et al. (55)	2004	71	F	2	1645	N.I.	8.6
8	Imanaka (56)	2006	40s	M	1	1365	7.10	8.5
9	Koyama et al. (57)	2006	35	M	1	1686	6.54	N.I.
10	Sakuda et al. (58)	2006	46	M	1	1520	7.10	7.5
11	Hashimoto et al. (59)	2008	58	M	1	1363	6.84	9.6
12	Urahama et al. (60)	2009	45	M	1	1360	N.I.	N.I.
13	Taira et al. (61)	2010	62	M	2	838	7.09	8.3
14	Kato et al. (62)	2012	58	M	N.I.	1001	6.81	N.I.
Mean			52			1336	6.54	8.0
SD			13			369	0.20	1.0

Data were extracted from *Ichushi* published by the Japan Medical Abstracts Society. The mean and standard deviation (SD) were calculated using only available data from 14 patients. DKA, diabetic ketoacidosis; F, female; M, male; N.I., not indicated.

Statements

2) Hypoglycemia before and after hemodialysis
   1. Immediate treatment is required in insulin-treated patients if predialysis plasma glucose levels are <60 mg/dL or hypoglycemic symptoms develop.
   2. If oral intake is possible, 5–10 g of glucose should be taken orally. Otherwise, 20 mL of 50% glucose solution should be injected via the hemodialysis circuit in around 60 s.
   3. Plasma glucose measurements should be repeated every 30 to 60 min thereafter. If plasma glucose levels decrease below 60 mg/dL, the above procedure should be repeated.
   4. If hypoglycemia was detected at the end of dialysis session, the procedure of administration of glucose with the monitoring of plasma glucose should be repeated to obtain stable normoglycemia before the end of the session.
   5. When hypoglycemia occurs frequently, consultation with a diabetes specialist is strongly recommended to fundamentally revise the current diabetes therapeutic regimen.

Commentary

Urgent treatment, as described above, are required for insulin-treated patients with predialysis plasma glucose levels <60 mg/dL or those with significant

hypoglycemic symptoms. Hypoglycemic symptoms are classified into early-onset autonomic symptoms and late-onset central neurological symptoms.

Many hemodialysis patients with diabetes have autonomic neuropathy and decreased activities of counterregulatory hormones such as glucagon (63). In these patients, autonomic symptoms, such as cold sweat, palpitations, and finger tremor, may manifest as the initial symptoms of hypoglycemia, rapidly leading to neuroglycopenia symptoms, such as abnormal behavior, seizure, a reduced level of consciousness, and finally coma (asymptomatic hypoglycemia). Therefore, care should be taken for hemodialysis patients with diabetes.

For patients with frequent hypoglycemic episodes, similarly to patients with frequent hyperglycemic episodes, consultation with a diabetes specialist is strongly recommended to fundamentally review the current diabetes treatment regimen.

(5) Oral hypoglycemic agents

Statements

1. Sulfonylureas (SUs), biguanide, thiazolidinedione, nateglinide (a ultrafast-acting insulin secretagogue), and sitagliptin (a dipeptidyl peptidase-4 [DPP-4] inhibitor) are contraindicated in dialysis patients.
2. The following oral hypoglycemic agents can be used in dialysis patients: mitiglinide and repaglinide (fast-acting insulin secretagogues); acarbose, voglibose, and miglitol (α-glucosidase inhibitors [α-GIs]); and vildagliptin, alogliptin, linagliptin, teneligliptin, and anagliptin (DPP-4 inhibitors).
3. Dose of oral hypoglycemic agents
   1) Fast-acting insulin secretagogues: mitiglinide and repaglinide should be initiated at a low dose with caution.
   2) α-GIs: acarbose and voglibose can be used at up to a regular dose. Miglitol should be used with caution.
   3) DPP-4 inhibitors: vildagliptin should be initiated at a low dose (25 mg/day). Alogliptin (6.25 mg/day) and anagliptin (100 mg/day) should be used with caution. Linagliptin and teneligliptin can be used at a regular dose.

Commentary

1. Use of oral hypoglycemic agents

Insulin is partly degraded in the kidney. Dialysis patients with impaired kidney function are prone to hypoglycemia, because the metabolism and excretion of insulin, as well as drugs, are delayed. Among oral hypoglycemic agents, SUs stimulate insulin secretion and tend to induce prolonged hypoglycemia (once developed, hypoglycemia is prolonged); hence, they are contraindicated in dialysis patients (64–67). If the sole use of a first-choice drug does not improve glycemic control, increasing the dose or adding another hypoglycemic agent with a different action mechanism should be considered. When glycemic control is still poor even with the use of multiple hypoglycemic agents, additional injection of basal insulin or switching to insulin therapy should be considered. It is necessary to avoid continuing the use of hypoglycemic agents if they fail to improve glycemic control.

As shown in Table 1, there are six classes of oral hypoglycemic agents, which are categorized as (i) agents that stimulate insulin secretion (insulin secretagogues); (ii) agents that improve insulin resistance (insulin sensitizers); and (iii) agents that improve postprandial hyperglycemia (postprandial glycemic regulators) (68). Insulin secretagogues include SU, fast-acting insulin secretagogues, and DPP-4 inhibitors. Insulin sensitizers include biguanide and thiazolidine. Postprandial glycemic regulators include fast-acting insulin secretagogues and α-GIs (68). According to Japanese guidelines, SUs, biguanide, and thiazolidinediones are contraindicated in patients with severe renal impairment. α-GIs and DPP-4 inhibitors, as well as mitiglinide and repaglinide (which are fast-acting insulin secretagogues), can be used in dialysis patients. However, there is no clear evidence that determines the best agent among them.

1) SUs

All SUs have a high protein-binding rate and are not removed by dialysis. Although their major metabolic pathway is the liver, SUs easily induce hypoglycemia in dialysis patients through the accumulation of active metabolites that decrease the plasma glucose level (69). Gliclazide is metabolized in the liver and 99% or more of its metabolites are excreted from the kidney (60–70%) and in the feces (10–20%). The use of gliclazide is recommended in the Kidney Disease Outcomes Quality Initiative guidelines because of the very low activity of its metabolites (70). However, it is stated as contraindicated in the explanatory leaflet of SUs in Japan (64).

2) Fast-acting insulin secretagogues

Fast-acting insulin secretagogues stimulate insulin secretion by a mechanism similar to that for SUs. However, they have a faster onset of action, a greater elevation of blood insulin level, and a shorter dura-

TABLE 1. *Metabolic pathway, dialyzability, and dose of oral hypoglycemic agents*

Classification	Drugs		Major metabolic pathway	Dialyzability	Regular dose (mg/day)	Optimal dose for dialysis patients (mg/day)
	Nonproprietary name	Trade name				
Sulfonylureas	Tolbutamide	Rastinon	Liver	–	250–2000	Contraindication
	Acetohexamide	Dimelin	Liver	–	250–1000	Contraindication
	Chlorpropamide	Abemide	Liver (kidney 20%)	–	100–500	Contraindication
	Glyclopyramide	Deamelin S	Kidney (rat)	–	250–500	Contraindication
	Glibenclamide	Euglucon/Daonil	Liver	–	1.25–10	Contraindication
	Gliclazide	Glimicron	Liver	–	40–160	Contraindication
	Glimepiride	Amaryl	Liver	–	0.5–6	Contraindication
Ultrafast-acting insulin secretagogues	Nateglinide	Starsis/Fastic	Liver (kidney 5–16%)	–	270–360	Contraindication
	Mitiglinide	Glufast	Liver	–	30	Careful administration
	Repaglinide	Surepost	Liver	–	0.75–3	Careful administration
Biguanides	Metformin	Glycoran	Kidney 80–100%	+	500–750	Contraindication
		Metgluco	Kidney 80–100%	+	500–2250	Contraindication
	Buformin	Dibetos	Kidney 84.5%	+	50–150	Contraindication
Thiazolidinediones	Pioglitazone	Actos	Liver	–	15–45	Contraindication
α-Glucosidase inhibitors	Acarbose	Glucobay	Feces	NA	150–300	Regular dose
	Voglibose	Basen	Feces	NA	0.6–0.9	Regular dose
	Miglitol	Seibule	Kidney 30%	+	150–225	Careful administration
DPP-4 inhibitors	Sitagliptin	Januvia/Glactiv	Kidney 79–88%	3.5–13.5%	50–100	Contraindication[†]
	Vildagliptin	Equa	Liver (kidney 33%)	3%	50–100	Careful administration
	Alogliptin	Nesina	Kidney	7.2%	25	6.25
	Linagliptin	Trazenta	Bile	–	5	5
	Teneligliptin	Tenelia	Liver (kidney 21%)	15.6%	20–40	Regular dose
	Anagliptin	Suiny	Kidney	–	200–400	100

[†]From August 2013, the permitted dose is 12.5–25 mg/day. DPP-4, dipeptidyl peptidase-4; NA, not applicable.

tion of lowering plasma glucose level (approximately 3 h) than SUs. As a side effect, they increase the risk of hypoglycemia. Although the risk of hypoglycemia posed by fast-acting insulin secretagogues is smaller than that posed by SUs (71), there is insufficient evidence that supports this. Nateglinide is contraindicated in dialysis patients, because its metabolites lower the plasma glucose level and are excreted from the kidney, which increases the risk of hypoglycemia in these patients (72,73). Mitiglinide rarely increases the risk of hypoglycemia even in patients with renal impairment, because its metabolites have no plasma glucose-lowering effect (74). However, the half-life of mitiglinide in the blood is prolonged in patients with renal impairment, including dialysis patients. Therefore, mitiglinide should be initiated at a low dose (7.5–15 mg/day). Some studies showed that the plasma glucose and GA levels in Japanese hemodialysis patients were reduced by mitiglinide at a dose lower than the regular dose (75,76). Repaglinide is excreted in the bile and its metabolites do not decrease plasma glucose level. Although repaglinide has been safely used in patients with renal impairment (77–79), it should be initiated at a low dose and with caution.

3) α-GIs

Among α-GIs, voglibose is not absorbed into the blood and hence it can be used at a regular dose even in dialysis patients (64,80). Only 2% or less of the total dose of acarbose is absorbed into the blood, but its use at a regular dose in dialysis patients is allowed in accordance with Japanese guidelines, because acarbose metabolites have only a weak effect on decreasing the plasma glucose level. Miglitol is absorbed in the upper part of the small intestine but is not metabolized and is excreted from the kidney in its unchanged form. Miglitol in the blood does not decrease plasma glucose level, has a low rate of protein binding (≤3.9%) and a molecular weight of 207 Da, and is removed by hemodialysis. In accordance with the Japanese guidelines, miglitol should be used with caution (64). The sole use of miglitol rarely induces hypoglycemia. Although miglitol can be used with other oral hypoglycemic agents or insulin, care should be taken to prevent hypoglycemia in this case. Its side effects are digestive symptoms such as flatulence, feeling of abdominal fullness, and diarrhea. Intake of glucose, but not sugar, is required for the patient to recover from hypoglycemia.

4) Biguanide

In Europe and the USA, biguanide is used as a first-choice drug on the basis of clear evidence that supports its efficacy in preventing macrovascular complications in diabetic patients with normal kidney function (81–83). However, biguanide may induce severe lactic acidosis as a side effect and is therefore contraindicated in patients with renal impairment, including dialysis patients. Biguanide is not metabolized in the body and excreted unchanged in the urine. It can be removed by hemodialysis because it hardly binds to plasma proteins and its molecular weight is in the range of 165–194 Da. If biguanide-induced lactic acidosis is detected, the patient can be treated by hemodialysis, which removes biguanide and lactate and supplements bicarbonate ions. Thus, hemodialysis is also effective for lactic acidosis (84,85).

5) Thiazolidinedione

Thiazolidinedione acts as a peroxisome proliferator-activated receptor γ agonist and helps improve insulin resistance. There is evidence that supports its efficacy in preventing macrovascular complications in non-dialysis patients with type 2 diabetes (86,87). However, thiazolidinedione is contraindicated in dialysis patients, according to Japanese guidelines. Thiazolidinedione is also contraindicated in patients with a history of cardiac failure, because it has a side effect of fluid retention and may induce edema, anemia, and cardiac failure (88).

6) DPP-4 inhibitors

DPP-4 inhibitors selectively block DPP-4, increase the activity of glucagon-like peptide-1 (GLP-1), stimulate insulin secretion, and inhibit glucagon secretion (89–92). The sole use of a DPP-4 inhibitor is considered to rarely induce hypoglycemia because its plasma glucose-lowering effect is dependent on plasma glucose level. As another characteristic, DPP-4 inhibitors help improve glycemic control without increasing body weight.

It is suggested to start the use of alogliptin and anagliptin at reduced doses and vildagliptin at a low dose (25 mg/day). The dose of alogliptin should be reduced in accordance with the severity of renal impairment and should be 6.25 mg/day for dialysis patients (93,94). Vildagliptin is hydrolytically degradable, has a short half-life in the blood and a small cumulative amount (Ae) of 23% excreted in urine, and can be used in patients with renal impairment (92,95). A study showed that the predialysis postprandial casual plasma glucose and GA levels decreased from 186 to 140 mg/dL and from 24.5 to 20.5%, respectively, in Japanese hemodialysis patients who were administered vildagliptin for 6 months (96). However, vildagliptin is contraindicated

in patients with severe hepatic dysfunction. Linagliptin is a DPP-4 inhibitor excreted via the bile and has an Ae <1%. Therefore, dose adjustment is unnecessary in dialysis patients (92,97). Teneligliptin has a low Ae of ~20% and can be used in patients with renal impairment. Anagliptin is used at a regular dose of 100 mg twice a day, but should be used at the same dose once a day in dialysis patients, because their area under the concentration-time curve ($AUC_{0-\infty}$) is 3.22-fold higher than that for healthy adults.

There have been no long-term outcome studies of dialysis patients that examined the efficacy of any DPP-4 inhibitor against diabetic complications. Further accumulation of clinical data on the safety of long-term administration of DPP-4 inhibitors in dialysis patients is needed.

2. Notes for elderly patients

In general, the use of hypoglycemic agents is effective for treating hyperglycemia in elderly patients (98–100). There are no randomized controlled trials that prove the high incidence of hypoglycemia induced by hypoglycemic agents in elderly patients. However, several observational studies showed that severe hypoglycemia caused by hypoglycemic agents is frequently encountered in elderly patients, in particular those aged ≥75 years, patients taking multiple drugs (excluding diabetes medication), patients who were just discharged from the hospital, patients with renal failure, and patients with reduced food intake (101–103). In Japan, the dialysis patient population is aging. The administration of hypoglycemic agents in elderly patients and their follow-up observation should be carefully carried out. Attention should be paid to impaired awareness of hypoglycemia in elderly patients; many of them may feel anxiety, lack motor coordination, or have nonspecific central neurological symptoms (e.g. dementia- and depression-like symptoms) as hypoglycemic symptoms in addition to typical symptoms (104).

(6) Insulin therapy

Statements

1. Type 1 diabetic patients with impaired insulin secretion must be treated intensively with insulin (three- or four-times-daily injections).
2. Type 2 diabetic patients who cannot achieve good glycemic control even when using single or multiple oral hypoglycemic agents should also be treated with insulin.
3. For type 2 diabetic patients, the type and dose of insulin and the frequency of injections should be determined according to their insulin secretory capacity and actual plasma glucose levels. Many type 2 diabetic patients can achieve good glycemic control with three-times-daily preprandial injections of fast- or ultrafast-acting insulin, twice-daily injections (morning and evening) of premixed insulin, or once-daily injection of intermediate- or long-acting soluble insulin.
4. In insulin-treated dialysis patients with diabetes, their insulin levels may decrease during dialysis.
5. An additional dose of insulin may be required after dialysis to prevent hyperglycemic events caused by the intradialytic drop in plasma insulin level.
6. Insulin-treated patients are strongly recommended to do SMBG.
7. Because plasma glucose and insulin levels are severely affected by hemodialysis, the insulin dose and the timing of injection on non-dialysis days can be changed from those on dialysis days to achieve good glycemic control.

Commentary

1. Adoption of insulin therapy

Patients who must be treated with insulin include type 1 diabetics, patients with diabetic coma, diabetics with severe infectious disease, and those following moderate or major surgery. Patients who should be treated with insulin include patients with significant hyperglycemia (e.g. fasting plasma glucose ≥250 mg/dL and casual plasma glucose ≥350 mg/dL) and patients with ketosis-prone diabetes. Hemodialysis patients with type 2 diabetes should also be treated with insulin when they cannot achieve good glycemic control with optimized dietary therapy, lifestyle intervention, and the use of oral hypoglycemic agents. Insulin therapy is also used to eliminate glucotoxicity due to hyperglycemia. Patients with poor glycemic control should be treated with insulin therapy as early as possible (105) with the aim of shortening the period of poor glycemic control, which contributes to the progression of future complications (5).

2. Characteristics of insulin products (Table 1)

Insulin products are classified into the following groups according to their action duration and mechanism: ultrafast-acting insulin (e.g. lispro, aspart, glulisine), fast-acting insulin, intermediate-acting insulin

TABLE 1. *Types and characteristics of insulin products*

Type	Proprietary name	Time to evident effects	Time to peak effects	Duration of effects	Function
Ultrafast-acting	NovoRapid	10–20 min	1–3 h	3–5 h	Replace additional insulin secretion
	Humalog	<15 min	0.5–3 h	3–5 h	
	Apidra	<15 min	0.5–3 h	3–5 h	
Fast-acting	Novolin R	~30 min	1–3 h	~8 h	
	InnoLet R	~30 min	1–3 h	~8 h	
	Humulin R	0.5–1 h	1–3 h	5–7 h	
Intermediate-acting	Novolin N	~1.5 h	4–12 h	~24 h	Replace basal insulin secretion
	InnoLet N	~1.5 h	4–12 h	~24 h	
	Humalog N	0.5–1 h	2–6 h	18–24 h	
	Humulin N	1–3 h	8–10 h	18–24 h	
Long-acting	Levemir	~1 h	3–14 h	~24 h	
	Lantus	1–2 h	No peak	~24 h	
Premixed	NovoRapid 30 Mix	10–20 min	1–4 h	~24 h	Replace additional and basal insulin secretion
	NovoRapid 50 Mix				
	NovoRapid 70 Mix				
	Novolin 30R, 40R, 50R	~30 min	2–8 h	~24 h	
	InnoLet 30R, 40R, 50R	~30 min	2–8 h	~24 h	
	Humalog Mix25	<15 min	0.5–6 h	18–24 h	
	Humalog Mix50		0.5–4 h		
	Humulin 3/7	0.5–1 h	2–12 h	18–24 h	

(neutral protamine Hagedorn), premixed insulin (a combination of intermediate- and fast-acting insulins at different ratios), and long-acting soluble insulin (e.g. glargine, detemir).

Ultrafast-acting insulin, such as lispro, aspart, and glulisine, is rapidly absorbed and is expected to supply insulin secretion dynamics closer to normal physiology than the other types. This type of insulin decreases postprandial plasma glucose levels more than fast-acting human insulin and can be injected immediately before or after meals, reducing nocturnal hypoglycemic episodes and improving the quality of life of patients (106–109). Long-acting soluble insulin, such as glargine and detemir, is slowly absorbed from the subcutaneous tissue and can maintain a stable blood insulin level over a long period. This type of insulin is used to simulate basal insulin secretion.

3. Standard insulin therapy

A standard insulin therapy regimen for type 1 diabetic patients is the use of three doses of fast- or ultrafast-acting insulin (immediately) before each meal and one dose of intermediate- or long-acting soluble insulin before bedtime, based on the physiology of the insulin secretion pattern. Many type 2 diabetic patients retain some insulin secretory capacity and have various choices of insulin therapy regimens: for example, three doses of fast- or ultrafast-acting insulin (immediately) before each meal, one dose of intermediate- or long-acting soluble insulin before bedtime, one (before dinner) or two (before breakfast and dinner) doses of premixed insulin, and three doses of fast-acting insulin before each meal + one dose of intermediate-acting insulin before bedtime (105).

4. Intradialytic blood insulin dynamics and changes in plasma glucose level

The blood insulin levels of insulin-treated dialysis patients with diabetes decrease during dialysis (47,48). The degree of decrease depends on the dialyzer membrane; it is greatest for polysulfone membranes and smallest for polyester polymer alloy membranes (48,110–111). The cause of the intradialytic drop in blood insulin level is considered to be adsorption of insulin onto the dialyzer membrane (1). The removal of insulin by hemodialysis occurs even when the patient is treated with insulin, and the degree of decrease in blood insulin level is greater for patients with high predialysis blood insulin levels (Fig. 1) (5). Therefore, the blood insulin levels in insulin-treated patients on dialysis tend to decrease during the dialysis session.

However, intradialytic insulin deficiency rarely causes hyperglycemia, because plasma glucose in patients with higher predialysis plasma glucose levels is diffused into the dialysis fluid, thus decreasing its level. However, hyperglycemic patients have a high risk of experiencing a sudden drop in plasma glucose level during dialysis, which induces hyperglycemic events after dialysis because insulin has been

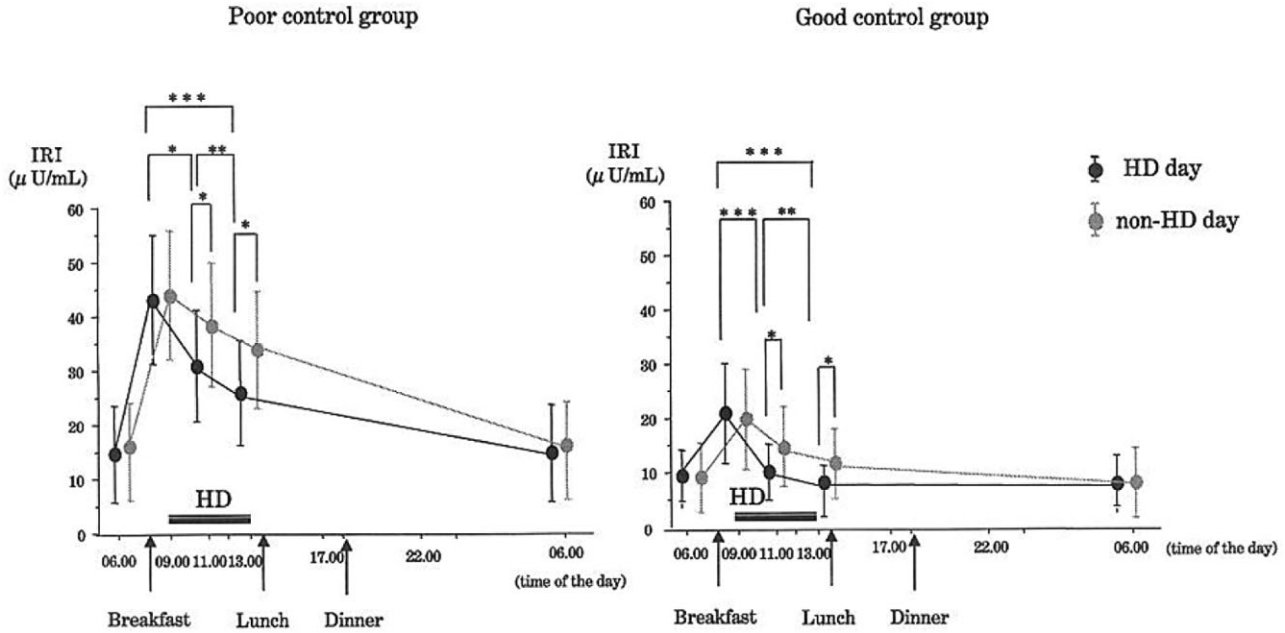

FIG. 1. Intradialytic blood insulin dynamics (50). HD, hemodialysis; IRI, immunoreactive insulin. *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$.

removed by dialysis. A concern is the postdialysis increase in plasma glucose level, caused by intradialytic insulin deficiency and the secretion of glucose-elevating hormones, such as glucagon, growth hormones, and adrenocorticotropic hormone, stimulated by the sudden drop in plasma glucose level (47,48). Insulin-treated outpatients who undergo dialysis in the morning most likely cannot detect the postdialysis increase in their plasma glucose levels because they leave the hospital after lunch. High HbA_{1c} levels in patients with relatively normal predialysis casual plasma glucose levels may be associated with postdialysis hyperglycemia. To prevent this, it is necessary to additionally inject insulin after dialysis to compensate for the postdialysis insulin deficiency or supplement glucose during hemodialysis to prevent the sudden intradialytic drop in plasma glucose level. Therefore, the insulin dose and the timing of injection on non-dialysis days can be changed from those on dialysis days to achieve good glycemic control.

5. Adverse effects of insulin therapy

An adverse effect of insulin therapy is the increased risk of hypoglycemia. A study showed that intensive insulin therapy helped achieve good glycemic control but also increased the risk of severe hypoglycemia (1). To prevent this, appropriate management of hypoglycemia with SMBG should be provided to patients. Moreover, rapid improvement in glycemic control through intensive insulin therapy may worsen retinopathy and neuropathy (112,113).

6. Sick day and its rule for insulin-treated patients

If insulin-treated patients are feeling too sick to eat because of infectious disease or other reasons (sick days), their plasma glucose levels tend to be elevated by insulin antagonistic hormones despite a reduced food intake. Therefore, insulin therapy should not be omitted but continued at adjusted doses. As a sick day rule, carbohydrates in a form easy to take are recommended to supplement energy (105).

(7) Injection of drugs other than insulin: GLP-1 receptor agonists

Statements

1. Liraglutide should be used with caution in dialysis patients.
2. Exenatide is contraindicated in dialysis patients.

Commentary

As an injection drug, liraglutide can be used in dialysis patients. It is a GLP-1 analog product and acts as a GLP-1 receptor agonist. Liraglutide is resistant to degradation and inactivation by DPP-4 (Table 1) (114) and is slowly metabolized in the blood by DPP-4. Regardless of the presence of obesity, the use of liraglutide helps improve glycemic control without weight gain. The sole use of liraglutide rarely increases the risk of hypoglycemia. As a side effect, patients may suffer from digestive symptoms (114). Liraglutide should be used with caution,

TABLE 1. *Metabolic pathway, dialyzability, and dose of GLP-1 receptor agonists (as of May 2012)*

Classification	Drugs: Nonproprietary name	Drugs: Trade name	Major metabolic pathway	Dialyzability	Regular dose (mg/day)	Optimal dose for dialysis patients
GLP-1 receptor agonists	Liraglutide	Victoza	Not kidney	–	0.3–0.9	Regular dose
	Exenatide	Byetta	Kidney	–	10–20	Contraindication

GLP-1, glucagon-like peptide-1.

because there is insufficient data to support its use in patients with renal impairment, including those on dialysis. GLP-1 receptor agonists are contraindicated in type 1 diabetic patients. Exenatide is contraindicated in dialysis patients (115,116).

II. DIETARY ENERGY INTAKE

Statements

1. The estimated energy requirement is in the range of 25–35 kcal/kg/day for the majority of hemodialysis patients, but it should be set for individual patients considering their gender, age, and physical activity level.
2. For obese patients who need to lose weight, the estimated energy requirement should be set lower than the above-mentioned level. For malnourished and emaciated patients who need to gain weight, the estimated energy requirement should be set higher.
3. Dietary prescription should be assessed and optimized over time by monitoring the changes in the body weight of the patients.

Commentary

1. Concept of estimated energy requirement

An imbalance between energy intake and energy expenditure changes the body weight of individuals. Continuous intake of too much energy leads to obesity, whereas continuous low energy intake leads to malnourishment and emaciation. The estimated energy requirement is defined as the average dietary energy intake per day that is predicted to maintain energy balance in a healthy adult with the highest probability (117). That is, the true energy intake of a healthy adult has a fifty-fifty chance of being higher or lower than the estimated energy requirement.

2. Assessment and calculation of estimated energy requirement (117)

The estimated energy requirement is calculated from basal metabolic rate and physical activity coefficient (Table 1) as follows:

$$\text{Estimated energy requirement (kcal/day)} = \text{basal metabolic rate (kcal/day)} \times \text{physical activity coefficient.}$$

Ideally, a measured basal metabolic rate should be used. However, basal metabolic rate is difficult to measure and also varies even within a person. Hence, it is practical in clinical settings to calculate basal metabolic rate from a reference basal metabolic rate (Table 2) and a reference body weight (calculated assuming a body mass index of 22 kg/m^2) as follows:

$$\text{Basal metabolic rate (kcal/day)} = \text{reference basal metabolic rate (kcal/kg/day)} \times \text{reference body weight (kg).}$$

Table 3 shows the estimated energy requirement with respect to reference body weight calculated using the above equations according to age, gender, and physical activity level.

TABLE 1. *Physical activity level and coefficient (cited from Ministry of Health, Labour and Welfare (117) and revised)*

Physical activity coefficient	
2.0	Doing physical work and vigorous physical activity habitually (Level III)
1.75	4 h of standing or walking and 1 h of moderate to heavy physical activity (Level II)
1.5	Mostly sedentary with 3–5 h of standing, walking, or light physical activity (Level I)
1.25	Sedentary with about 1 h of standing or walking (Level 0)
1.2	Using wheelchair
1.1	Bedridden with autokinetic motion
1.0	Bedridden without autokinetic motion (vegetative state)

TABLE 2. *Reference basal metabolic rate (kcal/kg/day) (117)*

Age (years)	Male	Female
>70	21.5	20.7
50~69	21.5	20.7
30~49	22.3	21.7
18~29	24.0	22.1

TABLE 3. *Estimated energy requirement with respect to reference body weight according to age, gender, and physical activity level (based on Dietary Reference Intakes of Japanese provided by the Ministry of Health, Labour and Welfare) (117)*

	(With respect to reference body weight)					
	Male			Female		
Age	Physical activity level			Physical activity level		
(years)	Level 0	Level I	Level II	Level 0	Level I	Level II
>70	26	31	37	25	30	35
50–69	27	32	38	26	31	36

Note 1: Estimated energy requirement = estimated energy requirement per reference body weight (shown in the table) × reference body weight. The reference body weight is calculated as (height [m])^2 × 22 (kg/m^2). Note 2: For obese patients who need to lose weight, the estimated energy requirement should be set lower than those based on the values in the table. For emaciated and malnourished patients who need to gain weight, the estimated energy requirement should be set higher. Dietary prescription should be assessed and optimized over time by monitoring the changes in the body weight of the patients. Note 3: The recommended fat intake is in the range of 20–25% of the total energy intake.

3. Assessment of estimated energy requirement for dialysis patients

Previous reports showed different tendencies of the resting energy expenditure of patients with chronic renal failure undergoing maintenance dialysis. Some showed that the resting energy expenditure of hemodialysis patients was equal to that of healthy people, but others showed that it was higher or lower, or that it depended on the clinical state of complications (118–128). Even among healthy people, the resting energy expenditure varies from person to person. To the best of our knowledge, there have been no reports on the energy expenditure or diet-induced thermogenesis of maintenance hemodialysis patients with chronic renal failure considering their physical activity level. In addition, recording the dietary intake of patients is the only method to estimate their total energy intake. Therefore, the reliability of the assessment of the energy intake greatly depends on the dietitian's skill of accurately assessing the content of the patients' diet and the patients' ability to accurately record the content of their diet. In many cases, the assessment of energy intake includes errors.

From the above, a practical measure for hemodialysis patients in clinical settings is as follows. First, prescribe dietary therapy on the basis of the dietary energy intake recommended for healthy people. Then, monitor the changes in the body weight of the patients to assess and optimize the prescription over time.

4. Intakes of other nutrients

For diabetic patients undergoing hemodialysis three times a week, the recommended protein intake per reference body weight is in the range of 0.9–1.2 g/kg/day (up to 60 g/day for men and 50 g/day for women), similar to nondiabetic dialysis patients. The recommended fat intake is in the range of 20–25% of the total energy intake. The recommended intakes of salt, water, potassium, and phosphorus are the same as the recommended intakes for nondiabetic hemodialysis patients.

III. CONTROL OF COMPLICATIONS

(1) Diabetic retinopathy

Statements

1. As diabetic retinopathy may progress even after the initiation of dialysis, regular ophthalmologic checkup is recommended.
2. Nafamostat mesilate or low-molecular weight heparin is recommended instead of regular heparin as an anticoagulant in hemodialysis immediately after severe vitreous hemorrhage or perioperative period of vitrectomy.

Commentary

1. Epidemiology and stage classification

Both diabetic nephropathy and diabetic retinopathy are microangiopathies attributed to chronic hyperglycemia and they generally progress in parallel. Conventionally, diabetic retinopathy is roughly classified into nonproliferative retinopathy or proliferative retinopathy. In particular, the stage of nonproliferative retinopathy with soft exudates and intraretinal microvascular abnormalities is classified as preproliferative retinopathy (revised Davis' classification, Table 1).

In ophthalmology in Japan, Fukuda's classification (Table 2) is widely used (129). This classification indicates the course of treatment in addition to the severity of retinopathy, which is easy to understand for physicians. Stages A1 and A2 are background retinopathy, and stage B1 is preproliferative retinopathy in which soft exudates are developed. Stages B2–B5 are proliferative retinopathy; stages B2 and B3 are characterized by neovascularization, stage B4 is characterized by vitreous hemorrhage, and stage B5 is characterized by vitreous tissue proliferation. Stages A3–A5 are interrupted proliferative retinopathy in which the above conditions have been treated by photocoagulation or vitrectomy and are benign.

TABLE 1. *Revised Davis' classification of diabetic retinopathy*

Stage	Symptoms	Ocular fundus findings
Without retinopathy	Normal	None
Background retinopathy	Vascular hyperpermeability	Capillary aneurysm Dot, blot, or linear retinal hemorrhage Hard exudates Retinal edema
Preproliferative retinopathy	Vascular occlusion	Soft exudates Venous abnormality Intraretinal microvascular abnormality
Proliferative retinopathy	Neovascularization	Retinal and optic-disk neovascularization Preretinal and vitreous hemorrhage Fibrovascular membrane Traction retinal detachment

2. Treatment

Glycemic control is essential as a preventive measure against retinopathy. For patients with chronic kidney disease (CKD), risk factors for worsening retinopathy include hypertension, coagulation–fibrinolysis abnormalities, hypoproteinemia, the presence of uremic toxins, and anemia (130). Preventive medical therapies against these factors are also important.

Direct ophthalmologic therapies include photocoagulation and vitrectomy. Recently, vitrectomy has been safely applied even to hemodialysis patients (131,132).

3. Occurrence and progression of diabetic retinopathy at and after initiation of hemodialysis

Diabetic patients who started dialysis for nephropathy have often developed late-stage retinopathy. Reports from overseas and Japan showed that 37–85% of diabetic patients who started dialysis had already developed proliferative retinopathy and that 47–54% of these patients had severe visual impairment (20/200 vision or less) (133–137). The Diabetes Center, Tokyo Women's Medical University School of Medicine examined 652 diabetic patients who had started hemodialysis between 1978 and 2000, investigating a total of 1304 eyes (138). The results showed that 69% of these patients had proliferative retinopathy (stages B2–B5 in Fukuda's classification) or interrupted proliferative retinopathy (stages A3–A5), which was in agreement with previous results.

Among new hemodialysis patients, the percentage of patients with proliferative retinopathy has recently decreased and that of patients with severe vision impairment has accordingly decreased. This may be because such patients have undergone photocoagulation or vitrectomy to treat their visual impairment before the initiation of dialysis (138).

TABLE 2. *Fukuda's classification of diabetic retinopathy*

Stage		Ocular fundus findings
Benign retinopathy (A)	A1: Mild background retinopathy	Capillary aneurysm, dot retinal hemorrhage
	A2: Severe background retinopathy	Blot hemorrhage, hard exudates, small amount of soft exudates
	A3: Mild nonproliferative retinopathy	Obsolete neovascularization
	A4: Moderate nonproliferative retinopathy	Obsolete vitreous hemorrhage
	A5: Severe nonproliferative retinopathy	Obsolete fibrovascular membrane
Malignant retinopathy (B)	B1: Preproliferative retinopathy	Intraretinal microvascular abnormality, soft exudates, retinal edema, linear or flame retinal hemorrhage, phlebectasia
	B2: Early-stage proliferative retinopathy	Neovascularization elsewhere
	B3: Mid-stage proliferative retinopathy	Neovascularization of the disk
	B4: End-stage proliferative retinopathy	Vitreous and preretinal hemorrhage
	B5: End-stage proliferative retinopathy	Vitreous fibrovascular membrane
Complications	Macula lutea (M), traction retinal detachment (D), rubeotic glaucoma (G), ischemic optic neuropathy (N), photocoagulation (P), vitrectomy (V)	

Takeda et al. (135) reported that the symptoms of retinopathy improved ≥6 months after the initiation of dialysis. Tokuyama et al. (137) reported that 50% of new hemodialysis patients had preproliferative or proliferative retinopathy and that this decreased to nearly half within 1 year after the initiation of hemodialysis, showing that retinopathy in patients undergoing hemodialysis tended to improve with time. Ichikawa (139) reported that maculopathy disappeared several months after the initiation of hemodialysis and that many patients had inactive burnout retinopathy 2 years after the initiation of dialysis.

However, an observational study of many patients conducted by Ishii et al. (138) showed that retinopathy worsened in approximately 10% of hemodialysis patients within 1 year after the initiation of hemodialysis and in an additional 10% within 3 years after the initiation of hemodialysis. Thus, not a few patients showed worsening of their retinopathy after the initiation of dialysis, requiring close and continuous consultation with an ophthalmologist. The JSDT guidelines strongly recommend that patients have regular eye examinations.

4. Strategy of diabetic retinopathy in hemodialysis patients

There have been few reports on the effect of glycemic control in diabetic patients who started hemodialysis. A report from a hemodialysis facility showed that the rate of progression of nonproliferative retinopathy significantly increased in patients with poor glycemic control, as determined from their HbA_{1c} level, whereas the rate of progression of proliferative retinopathy after the initiation of dialysis was not affected by glycemic control. These findings suggest the need for glycemic control even in diabetic patients who have started hemodialysis.

In the management of retinopathy in diabetic patients on hemodialysis, care must be taken in the selection of an anticoagulant during hemodialysis session immediately after severe vitreous hemorrhage or before and after vitrectomy. To the best of our knowledge, the comparison between heparin and nafamostat mesilate or low-molecular weight heparin as an anticoagulant used in these periods has not been reported overseas or in Japan. For safety, the JSDT guidelines recommend that nafamostat mesilate or low-molecular weight heparin should be used as an anticoagulant in hemodialysis immediately after severe vitreous hemorrhage or before and after vitrectomy. Note that this is level 2 evidence and requires further verification.

(2) Orthostatic hypotension

Statements

1. Diabetic patients undergoing dialysis may have severe orthostatic hypotension upon standing at the end of hemodialysis session in these patients; therefore, attention should be paid to dizziness and loss of consciousness.
2. In patients with frequent orthostatic hypotension, monitoring of blood pressure upon standing after dialysis session is recommended.
3. In these patients, the following treatments are recommended as opinions by the committee: (i) keeping the patients in a sitting position for a certain time after the dialysis session and slowly raising the patient; (ii) revising the adequate dry weight; (iii) minimization of intradialytic weight gain by restricting daily salt and water intake; and (iv) modifying the dialysis regimen (in combination with the extracorporeal ultrafiltration method [ECUM] or change to hemodiafiltration) or extending the dialysis duration.
4. For patients using antihypertensive drugs, reducing their dose, withdrawal, or change to weaker ones on the day of hemodialysis session should be considered.

Commentary

According to the JSDT Clinical Guidelines for the Evaluation and Treatment of Cardiovascular Complications in Hemodialysis Patients (140), hemodialysis-related hypotension collectively refers to hypotension in hemodialysis patients and is classified into intradialytic hypotension (sudden drops in blood pressure during hemodialysis session), orthostatic hypotension, or chronic sustained hypotension. Among them, orthostatic hypotension is of particular concern for hemodialysis patients with diabetes and is focused on here. For the other two, readers should refer to the above-mentioned JSDT clinical guidelines.

Physiologically, when the volume of circulating blood decreases as a result of water removal by hemodialysis, compensatory autonomic reflex occurs to constrict blood vessels, preventing the drop in blood pressure (140). For patients with diabetic autonomic neuropathy, this impaired reflex is the main cause of orthostatic hypotension at the end of a hemodialysis session. When orthostatic hypotension is present, patients may develop dizziness upon standing up, and in rare cases, suddenly lose consciousness (syncope).

The following treatments are recommended as opinions by the committee: (i) keeping the patient in

a sitting position for a certain time after the hemodialysis session and slowly raising the patient; (ii) setting an appropriate dry weight of the patient; (iii) minimizing the interdialysis weight gain by regulating the intake of table salt and water; and (iv) removing moderate amounts of water by modifying the hemodialysis regimen (in combination with the ECUM or change to hemodiafiltration) or extending the hemodialysis duration. For patients using antihypertensive drugs, reducing the frequency of hemodialysis sessions or even stopping dialysis therapy should be examined. The above measures have been actually taken in clinical settings for hemodialysis patients and often found helpful.

(3) Atherosclerosis

Statements

1. Severe atherosclerosis and vascular calcification after the initiation of hemodialysis are more common in hemodialysis patients with diabetes than in those without diabetes.
2. Atherosclerosis may be diagnosed by plain radiography to estimate macrovascular and peripheral vascular calcification as well as B-mode ultrasonography to measure intima-media thickness (IMT) and pulse wave velocity (PWV).
3. The prevalence of peripheral arterial disease (PAD) in hemodialysis patients with diabetes is approximately fourfold higher than that in hemodialysis patients without diabetes. Clinicians should regularly palpate the pulses of feet including dorsalis pedis artery at least once every 6 months and provide an appropriate treatment regimen when abnormalities are detected.
4. There are no target levels for blood pressure control specific to hemodialysis patients with diabetes. The efficacy of statin for dyslipidemia has been shown in hemodialysis patients with type 2 diabetes. Presently, the target levels recommended in the 2011 JSDT Clinical Guidelines for the Evaluation and Treatment of Cardiovascular Complications in Hemodialysis Patients should be followed.

Commentary

1. Epidemiology

Diabetic nephropathy is the most common causative disease for hemodialysis in Japanese patients. The progression of atherosclerosis in patients with diabetic nephropathy in the predialysis phase increases their cardiovascular mortality to worsen their prognosis (141–143), as coexistence of two major risk factors for atherosclerosis, CKD (144,145) and diabetes, is present in these patients during predialysis stage. Consecutive coronary angiography of even asymptomatic patients at the time of hemodialysis initiation (146,147) showed that significant coronary artery stenosis was observed in as high as 83.3% of diabetic patients, whereas it was observed in only 33.3% of nondiabetic patients.

Stricter target levels for the control of hypertension (148) and dyslipidemia (149) have been proposed for diabetic patients with normal renal function than for nondiabetic counterparts. However, there is no evidence to support the rationality of strict glycemic control for diabetic hemodialysis patients than for nondiabetic hemodialysis patients. Rather, severe glycemic control may lead to poor prognosis of patients because of more frequent occurrence of hypoglycemic episodes, particularly in those with hypotension or hypolipidemia because of malnutrition-inflammation-atherosclerosis syndrome (150). Therefore, the improvement of nutritional status should be prioritized.

Vascular calcification is frequently observed in hemodialysis patients, which is independently associated with a poor prognosis (151–153). Furthermore, either medial calcification or aortic calcification occurs significantly more in hemodialysis patients with diabetes than in those without diabetes. The mechanism for higher occurrence in diabetic patients particularly focused on includes sustained hyperglycemia (154) and low bone turnover (155–157) by itself and the resultant impaired fibroblast growth factor (FGF)-23 secretion from osteocyte/osteoblast dysfunction.

2. Factors contributing to progression of atherosclerosis in hemodialysis patients with diabetes

Atherosclerosis significantly progresses in hemodialysis patients with diabetes because of the coexistence of two major independent risk factors for atherosclerosis, CKD and diabetes. In addition, the progression of atherosclerosis is associated with risk factors for vascular disease, such as dyslipidemia and hypertension, which frequently develop in diabetic patients. Diabetic patients with renal failure have already developed atherosclerosis at the initiation of hemodialysis, because atherosclerosis in such patients significantly progresses during the predialysis phase. In clinical settings, measurements of IMT (a measure of arterial wall thickness) and PWV (a measure of arterial stiffness) showed that significant

progression of atherosclerosis is observed more frequently in patients with diabetic nephropathy during the predialysis phase than in nondiabetic patients. The frequency of significant stenosis of coronary arteries at the initiation of hemodialysis is significantly higher, which is the main factor determining the incidence of cardiovascular events and mortality after the initiation of hemodialysis (158).

Hemodialysis patients have specific risk factors for atherosclerosis, such as anemia, malnutrition, and mineral metabolism abnormalities, in addition to the risk factors commonly encountered in non-dialysis patients, such as hypertension, dyslipidemia, diabetes, and smoking (140). These hemodialysis-specific risk factors are frequently observed in diabetic patients on hemodialysis and may contribute to the progression of atherosclerosis.

3. Diagnosis

Studies of cardiovascular mortality showed that noninvasive measurements of IMT and PWV are effective for the diagnosis of atherosclerosis in hemodialysis patients (159,160). Plain radiography of macrovascular calcification and peripheral vascular calcification in the hands (151,152), as well as X-ray computed tomography for determining the aortic calcification score, were also shown to be effective on the basis of the association with cardiovascular events and mortality (161). In addition, a decrease in the ankle brachial pressure index (ABI) can be used as a predictor of PAD. However, when arterial calcification in lower extremities is present, vascular collapse does not occur under pressurization and the ABI may be paradoxically elevated. Therefore, both a decrease and an extreme increase in ABI can be recognized as predictors of PAD (162). In the case of ABI > 1.3, measurement of the toe-brachial pressure index (TBI) is effective for the diagnosis of PAD associated with arterial calcification in lower extremities. When TBI ≤ 0.6, vascular disease, such as arterial stenosis, should be suspected (163).

4. Therapy for atherosclerosis and its risk factors in dialysis patients with diabetes

Good glycemic control in diabetic patients on hemodialysis leads to a better prognosis and particularly decreases cardiovascular mortality (28). Therefore, improved glycemic control is an initial therapeutic goal for such patients. In addition, risk factors for atherosclerosis commonly associated with diabetes, such as abnormal blood pressure, dyslipidemia, and bone metabolism abnormalities, should be appropriately controlled. Considering the high prevalence of lower-extremity ulcer associated with diabetic neuropathy, clinicians should be careful of foot care for hemodialysis patients with diabetes and regularly check their legs.

1) Management of blood pressure

Strict control of blood pressure has been proposed for diabetic patients with normal kidney function to reduce the risk of atherosclerosis associated with diabetes. For diabetic patients on hemodialysis, however, there is no evidence to support the rationality of strict control of blood pressure. Therefore, the target blood pressure just before a hemodialysis session at the beginning of each week for stable patients undergoing maintenance hemodialysis should be lower than 140/90 mm Hg, as recommended in the JSDT Clinical Guidelines for the Evaluation and Treatment of Cardiovascular Complications in Hemodialysis Patients (140). The percentage of patients showing low predialysis blood pressure before a hemodialysis session is higher among hemodialysis patients with diabetes than those without diabetes, and such patients have a poor prognosis (reverse epidemiology). Malnutrition and severe chronic cardiac failure may contribute to the poor prognosis of patients with low blood pressure and should be treated for improvement of nutritional state with high priority.

2) Dyslipidemia

High levels of low-density lipoprotein cholesterol (LDL-C), low levels of high-density lipoprotein cholesterol (HDL-C), and high levels of triglycerides are significant predictors of myocardial infarction (164). A high non-HDL-C (= total cholesterol [TC] minus HDL-C) level is also a predictor of cardiovascular events (140). The Die Deutsche Diabetes Dialyse Studie (4D Study) of 1255 patients with type 2 diabetes undergoing hemodialysis, in which the effects of 20 mg/day atorvastatin and placebo (165) were compared, showed that the risks for the composite primary endpoints of cardiovascular death, nonfatal myocardial infarction, and cerebrovascular disease did not differ significantly between the two treatment groups. However, a subsequent sub-analysis of the 4D Study (166), which restricted the patients analyzed to those whose LDL-C levels ≥145 mg/dL, indicated that cardiovascular events, cardiovascular mortality, and all-cause mortality were significantly lower in patients with type 2 diabetes who were kept on atorvastatin. Currently, there are no reports on the setting of the target levels for the control of dyslipidemia specifically for diabetic hemodialysis patients. Therefore, for hemodialysis patients, regardless of the presence/absence of diabetes, the JSDT guidelines

should be followed similarly in diabetic patients to the case of nondiabetic hemodialysis patients, that is, LDL-C levels of <120 mg/dL or non-HDL-C levels of <150 mg/dL for primary prevention, and LDL-C levels of <100 mg/dL or non-HDL-C levels of <130 mg/dL for secondary prevention (140). Statin is recommended as the first-choice drug on the basis of evidence.

However, a high percentage of diabetic patients on hemodialysis have a low TC level. Such patients have malnutrition as a dominant factor and have a high risk of all-cause mortality and cardiovascular death (reverse epidemiology). Therefore, nutritional improvement is first of all recommended as the primary therapy.

3) PAD

PAD has some risk factors common to coronary artery disease. The prevalence of PAD in hemodialysis patients with diabetes is approximately fourfold higher than that in hemodialysis patients without diabetes (167). Many patients with PAD do not show any signs, but their PAD rapidly progresses, and it may be detected in later stages, causing refractory and severe limb ischemia. Clinicians should palpate the feet and the pulses of dorsalis pedis artery at least once every 6 months and provide an appropriate treatment regimen as soon as abnormalities are detected. The increased frequency of lower extremity amputation in the Japanese hemodialysis patient population (168) indicates that the prevalence of PAD becomes more popular. The prognosis of diabetic hemodialysis patients who have undergone lower extremity amputation is much poorer than expected for nondiabetic hemodialysis patients or diabetic non-CKD patients (169). The diagnosis and treatment methods for PAD specific to diabetic patients have not yet been established. At present, recommendations stated in the JSDT Clinical Guidelines for the Evaluation and Treatment of Cardiovascular Complications in Hemodialysis Patients should be followed (140).

(4) Bone disease

Statements

1. Hemodialysis patients with diabetes have higher risks of low bone turnover, adynamic bone disease, and fractures than those without diabetes.
2. Patients with severely suppressed bone turnover are at risk of developing atherosclerotic changes, such as vascular calcification, when the levels of serum calcium and phosphate are elevated.
3. There is no evidence for effective treatment of bone disease specific to dialysis patients with diabetes. At present, the JSDT Clinical Practice Guideline for Chronic Kidney Disease—Mineral and Bone Disorder 2012 Edition should be followed.

Commentary

1. Mineral and bone disorder in association with diabetes

Hemodialysis patients with diabetes are prone to low bone turnover-induced osteoporosis (170) with low rates of bone resorption and bone formation as a result of decreased parathyroid hormone (PTH) secretion (155,171) and PTH sensitivity of the bone (172). This leads to bone mass retention in many such patients.

2. Increased frequency of bone fracture

Bone turnover rate decreases even in diabetic patients with normal kidney function (173–175). Along with this, minor damage to bones accumulates, secondary calcification occurs, and oxidation stress increases, increasing the accumulation of collagen cross-linking by advanced glycation end-products, which might increase bone fragility, which in turn increases the frequency of bone mass-independent and bone quality-related fragile fracture (176). Decreased PTH secretion and markers of bone metabolism, as well as the increased frequency of bone mass-independent vertebral fracture, were also observed in diabetic patients on hemodialysis (177).

3. Effect of low bone turnover rate on blood vessels

Excess calcium and phosphate in the blood are adsorbed into bones. However, patients with low bone turnover rate show markedly reduced adsorption of calcium and phosphate into bones (156) and are prone to ectopic calcification, such as vascular calcification (157). Therefore, the low bone turnover rate in hemodialysis patients with diabetes should be monitored using bone alkaline phosphatase or tartrate-resistant acid phosphatase-5b (178,179), which are bone markers whose levels do not apparently increase upon the deterioration of kidney function, in contrast with bone markers related to collagen metabolism. Alternatively, calcium and phosphate loading should be avoided to reduce the risk of low bone turnover rate and the resultant ectopic calcification, including vessels. Therefore, hemodialysis patients with diabetes should use non-

calcium-based phosphate binders and avoid excessive intake of vitamin D to reduce calcium and phosphate overload.

Conflict of interest: The JSDT has been making the best effort to avoid any actual and potential conflicts of interest for there to be a neutral and fair process of guideline development. In 2010, the JSDT developed a new system for working group members to declare any potential conflicts of interest. All members of JSDT guideline development groups are now required to provide signed declaration forms to state any actual or potential conflicts of interest. These forms are updated yearly, or sooner if an individual member's status changes. Further information is available at: http://www.jsdt.or.jp/jsdt/1236.html (Japanese).

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APPENDIX I

Members of the guideline working group

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