Chapter 8

Glycemic Control in Diabetic Patients on Long-Term Maintenance Dialysis

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Additional information is available at the end of the chapter

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1. Introduction

The epidemiology of end-stage renal disease (ESRD) varies considerably worldwide. In Thailand, the incidence of ESRD on renal replacement therapy (RRT) increased from 78.9 per million populations in 1999 to 552.8 per million populations in 2009. The yearly incidence of all RRT modalities increased by an average of 34.8% from 2007 to 2009 [1]. According to the estimation by the International Diabetes Foundation, by the year 2025 the frequency of diabetes is expected to increase threefold worldwide [2]. Diabetic nephropathy is the most common cause of ESRD [3], representing 30-47% of the United States and Asian populations undergoing long-term maintenance hemodialysis [4, 5]. Disparities in the incidence of ESRD due to diabetes among ethnic groups have existed for many years, but the magnitude may be increasing.

In the United States, from 1990 to 1996, the age-adjusted diabetes-related ESRD incidence increased from 299.0 to 343.2 per 100,000 diabetic patients. However, from 1996 to 2006, the age-adjusted diabetes-related ESRD incidence decreased by 3.9% per year from 343.2 to 197.7 per 100,000 diabetic patients [6]. Diabetes-related ESRD incidence in the diabetic population has declined in all age-groups, probably because of a reduction in the prevalence of ESRD risk factors, improved treatment and care, and other factors. An alternative explanation for the decline in diabetes-related ESRD incidence in the diabetic population might be that the patients are not surviving long enough to develop ESRD, which occurs typically between 10 and 15 years after the onset of the disease. Premature mortality among ESRD patients with diabetes as a result of the increasing prevalence of coronary heart disease and stroke by tenfold could reduce the number of people who ultimately develop ESRD [7, 8]. Even though diabetes-related ESRD incidence in the population with diabetes has decreased since 1996, diabetes-related ESRD incidence in the general population and the number of persons initiating

treatment for kidney failure each year who have diabetes listed as a primary cause continue to increase [5, 9]. In Europe, data from the European Renal Association-European Dialysis and Transplant Association (ERA-EDTA) Registry shows an 11.9% annual increase in patients with type 2 diabetes entering RRT [10]. The most recent report of the Thailand RRT Registry shows a prevalence of diabetes among patients with ESRD of 47.6% and an incidence of 47.7%. The majority of patients with ESRD secondary to diabetes (51.0%) are treated by hemodialysis, 45.1% by peritoneal dialysis, and 3.9% have functioning renal transplants [1].

Diabetes-related ESRD is a costly and disabling condition with a high mortality rate. These patients are at a higher risk of mortality, mostly from cardiovascular complications, than other patients with diabetes. Apart from cardiac complications, the patients are subject to a wide range of vascular (e.g., peripheral vascular disease, stroke) and infectious complications. Patients with ESRD due to diabetes challenge the nephrologists because they have the greatest number of comorbid conditions, and the greatest dependency during daily activities. The goal of therapy is to improve quality of life, as well as reduce mortality. Attention to several basic principles helps to guide therapy: control of hypertension, control of hyperglycemia, control of lipid abnormalities, treatment of malnutrition, and attention to the effects of erythropoietin. Current cardio- and renoprotective treatment for diabetic nephropathy without ESRD includes optimization of glycemic control. Early intensive glycemic interventions reduce cardiovascular events as well as nephropathy by about half when compared with a conventional glycemic treatment. However, hypoglycemia is common because of impaired renal gluconeogenesis, malnutrition, chronic inflammation, decrease renal insulin clearance and the increased half-life of hypoglycemic agents [11]. Therefore, data are scarce on how diabetes should best be treated in patients in ESRD. In this chapter, we summarize the current evidence for glucose metabolism and glycemic control in diabetic patients on dialysis.

2. Glucose metabolism in dialysis

Hyperglycemia is an important factor in the progression of diabetic nephropathy. Early functional changes in diabetic nephropathy include glomerular hyperfiltration, glomerular and tubular epithelial hypertrophy, and the development of microalbuminuria, followed by the development of glomerular basement membrane (GBM) thickening, accumulation of mesangial matrix, and overt proteinuria, eventually leading to glomerulosclerosis and ESRD. Hyperglycemia-induced metabolic and hemodynamic pathways are recognized to be mediators of kidney injury [4].

Glucose transport activity is an important modulator of extracellular matrix formation by mesangial cells. Glucose transporter-1 (GLUT-1) regulates glucose entry into renal cells. Glucose and its metabolites subsequently activate metabolic pathways, and these pathways contribute to mesangial expansion and mesangial cell matrix-production, mesangial cell apoptosis and structural changes [12]. This may result from a similar increase in the mesangial cell glucose concentration, since similar changes in mesangial function can be induced in a normal glucose milieu by over-expression of GLUT1 [13]. Multiple biochemical pathways have

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been postulated that explain how hyperglycemia causes tissue damage including: non-enzymatic glycosylation that generates advanced glycosylation end products (AGE); activation of protein kinase C (PKC); and acceleration of the polyol pathway. Oxidative stress also seems to be a common theme. These pathways ultimately lead to increased renal albumin permeability and extracellular matrix accumulation, resulting in increasing proteinuria, glomerulosclerosis and ultimately renal fibrosis.

In ESRD, both uremia and dialysis can complicate blood glucose control by affecting the secretion, clearance, and peripheral tissue sensitivity of insulin. The abnormal glucose homeostasis in patients with dialysis is postulated to be multifactorial issues as Figure 1.

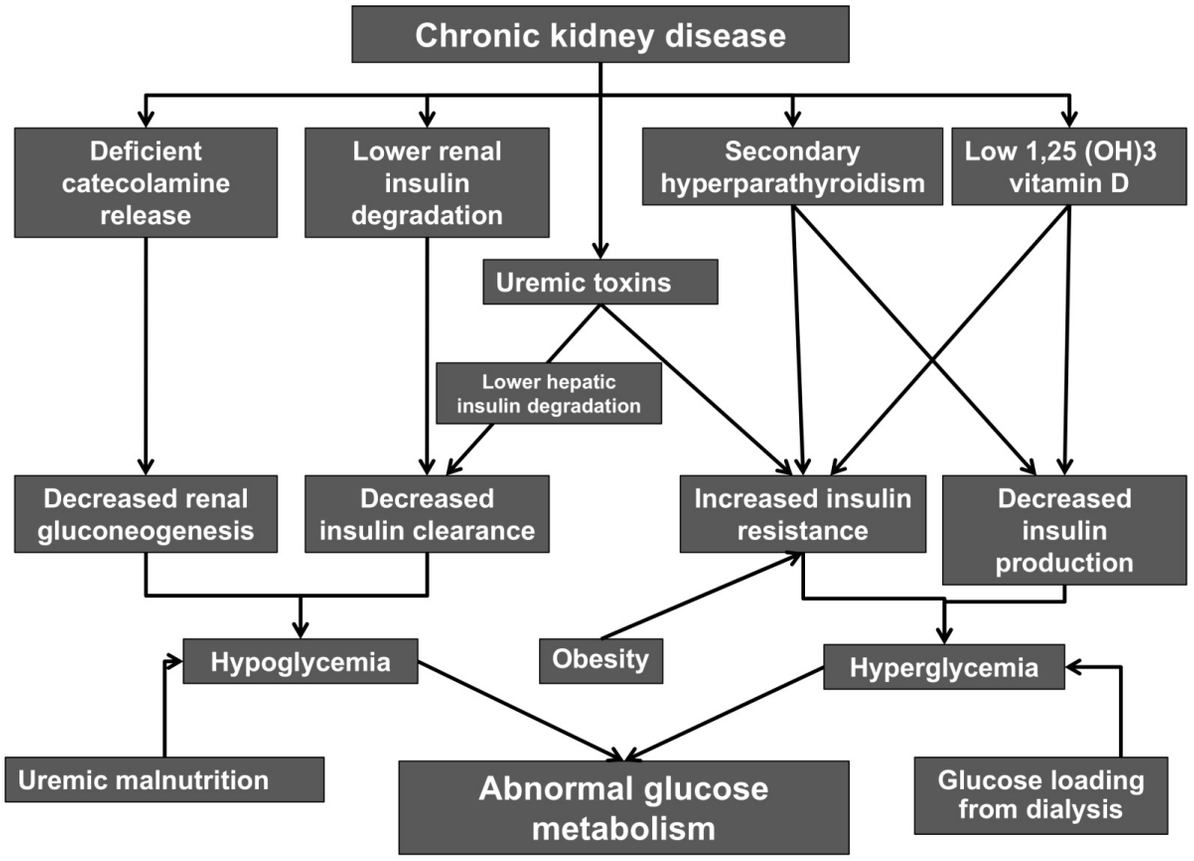

Figure 1. Contribution factors for the abnormal glucose metabolism in dialysis patients.

2.1. Hyperglycemia: Increased insulin resistance and decrease insulin production in dialysis

Advanced-stage chronic kidney disease (CKD) or ESRD can show mild fasting hyperglycemia and abnormal glucose tolerance, suggesting that the uremic state alters glucose homeostasis [14]. Insulin resistance is also frequently recognized in uremic patients and is a predictor of cardiovascular mortality in ESRD patients [15]. Impaired insulin sensitivity in the absence of overt diabetes play a central role in the development of atherosclerotic vascular disease [16]. Several clinical studies have noted impaired tissue sensitivity to insulin in diabetic nephrop-

athy [17], and non-diabetic patients exhibit only mild to moderate reductions in renal function [18-20] and in ESRD [21, 22]. However, impaired insulin sensitivity in both dialysis groups after long-term dialysis was still higher than that of the non-dialysis ESRD group while no significant differences were noted between peritoneal dialysis and hemodialysis treatments [23]. The mechanism of increased insulin resistance in patients with kidney disease is not fully understood. Several factors, including uremic toxins, may increase insulin resistance in ESRD, leading to a blunted ability to suppress hepatic gluconeogenesis and regulate peripheral glucose utilization. In addition, in non-diabetic CKD patients, an independent factor for insulin resistance was the amount of total body fat and body mass index [20]. This change occurs in ESRD because of concomitant metabolic acidosis, deficiency of 1,25 dihydroxy-vitamin D, and secondary hyperparathyroidism. In addition, in uremic patients, previous studies have reported that treatment with hemodialysis, active vitamin D, erythropoietin and angiotensin receptor blocker can improve insulin insensitivity [21, 24-26].

Further complicating the effect of dialysis is the glucose load provided by both dialysis modalities. The dextrose concentration in the dialysate can also affect glucose control. In hemodialysis population, dialysates with lower dextrose concentrations are used and may be associated with hypoglycemia. Conversely, dialysates with higher dextrose concentrations are occasionally used in hypoglycemic patients on hemodialysis and low ultrafiltration patients on peritoneal dialysis (PD), but this can lead to hyperglycemia and insulin resistance [27].

2.2. Hypoglycemia: Decreased insulin clearance and renal gluconeogenesis in dialysis

Decreasing insulin requirements and frequent hypoglycemia also occur in diabetic patients on dialysis. Renal insulin clearance decreases as glomerular filtration rate decreases to less than 15 to 20 mL/min/1.73 m^2 [14]. Hepatic clearance of insulin is also decreased in patients with uremia. In addition, deficient gluconeogenesis along with malnutrition, deficient catecholamine release, and impaired renal insulin degradation and clearance, can contribute to frequent hypoglycemia in patients with CKD [28, 29].

Thus, advanced CKD and ESRD on dialysis exert opposing forces on insulin secretion, action, and metabolism, often creating unpredictable serum glucose values. Some patients who have insulin resistance would need more supplemental insulin. In contrast, the reduced renal gluconeogenesis and insulin clearance seen in ESRD may result in less requirement for insulin treatment. Together, all of these factors contribute to wide fluctuations in plasma glucose levels and increase the risk of both hyperglycemic and hypoglycemic events. Both of these abnormalities are at least partially reversed with the institution of dialysis. As a result, the insulin requirement in any given patient will depend upon the net balance between improving insulin secretion and insulin sensitivity, and restoring normal hepatic insulin metabolism.

3. Glycemic control in dialysis

Glycemic therapy in patients with diabetes has been shown to improve outcomes, especially microvascular complications in patients without kidney disease [30, 31]. The efficacy of

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glycemic control depends in part upon the stage at which it is begun and the degree of normalization of glucose metabolism. Glycemic control can partially reverse the glomerular hypertrophy and hyperfiltration that are thought to be important pathogenic pathways for diabetic nephropathy, and decrease the incidence of new-onset microalbuminuria in retrospective [32] and prospective studies of patients with diabetes [31, 33]. Progression of established overt nephropathy can also be stabilized or retarded through strict glycemic control. However, proving the efficacy of this treatment is difficult, and previous studies examining outcomes of glycemic control in dialysis patients gave conflicting results [34]. The benefit of glucose control on progression in patients with CKD who have advanced kidney disease is less well studied.

Interestingly, benefits of glycemic control after pancreas transplantation in patients with type 1 diabetes were observed: mesangial matrix volume, thickening of glomerular and tubular basement membranes, and nodular glomerular lesions were significantly decreased and/or returned to normal compared to the same measurements at zero and ten years [35, 36].

Effects of intensive glycemic control on prevention of macrovascular complications (e.g., coronary artery disease, peripheral artery disease, cerebrovascular disease) are less certain, particularly in type 2 diabetes. The 10-year follow-up study of patients with type 2 diabetes in the United Kingdom Prospective Diabetes Study (UKPDS) demonstrated risk reduction for myocardial infarction and death from any cause [37]. More recent studies, including the Action to Control Cardiovascular Risk in Diabetes (ACCORD), Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE), and the Veterans Affairs Diabetes Trial (VA-DT) that targeted even lower hemoglobin A_{1c} (HbA_{1c}) goals (<6–6.5%), failed to show cardiovascular disease risk reduction with more intensive glycemic control regimens [38-40].

Several observational studies showed that higher levels of hemoglobin A_{1c} were associated with higher mortality rates in patients with diabetes on long-term dialysis and CKD [41-44]. A previous study demonstrated that a paradoxically lower unadjusted mortality associated with greater hemoglobin A_{1c} levels were found in 23,618 dialysis patients with diabetes. However, after adjusting for markers of malnutrition and inflammation, hemodialysis patients with hemoglobin A_{1c} levels <5% or >7% became associated with greater mortality [45]. The data indicate that competing risk factors related to malnutrition, muscle wasting, and anemia may confound the association between glycemic control and survival in diabetic patients with long-term dialysis. In the study by Williams, hemoglobin A_{1c} levels >11.0% in type 1 diabetes on hemodialysis were required to observe a statistically significant higher mortality risk, but few subjects had hemoglobin A_{1c} levels in this category [46]. In a recent cohort of 54,757 diabetic hemodialysis patients, poor glycemic control (hemoglobin A_{1c} ≥8% or serum glucose ≥200 mg/dL) appears to be associated with high all-cause and cardiovascular death and very low glycemic levels (hemoglobin A_{1c} <7%) are also associated with high mortality risk [47]. In a single interventional study in 83 dialysis patients, patients in the intensive intervention group experienced improved quality of life and a decreased need for amputations and hospitalizations [48]. Larger clinical trials are needed to conclusively prove the concept that better glycemic control is beneficial in patients with advanced CKD. To date, there are no data

available from randomized clinical trials targeting different hemoglobin A_{1c} levels and powered for cardiovascular events or mortality in ESRD populations. Careful evaluation of the relationship of hemoglobin A_{1c} with these outcomes in ESRD patients should be a high priority for future research to determine the risks and benefits of different hemoglobin A_{1c} targets.

The Kidney Disease Outcomes Quality Initiative (KDOQI) foundation state that target hemoglobin A_{1c} for people with diabetes should be <7%, irrespective of presence or absence of CKD. This recommendation is in line with diabetes management in the general population [11]. However, very few studies have addressed the benefits and risks of intensive glycemic control in late stages of CKD and ESRD. Recent evidence from randomized studies has highlighted the potential risks of aggressive glycemic control in non-ESRD diabetic populations [38, 39]. Moreover, because many dialysis patients are wasting, malnourished, and non-ambulatory, they may be less able to respond appropriately to hypoglycemia. Current evidence suggests that aggressive glycemic control cannot be routinely recommended for all diabetic hemodialysis patients on the basis of reducing mortality risk. Physicians are encouraged to individualize glycemic targets based on potential risks and benefits in diabetic ESRD patients.

The guidelines of the 2012 American Diabetes Association recommend lowering hemoglobin A_{1c} to below or around 7% for many adults, and to implement this soon after the diagnosis of diabetes that is associated with long-term reduction in macrovascular disease [49]. Providers might reasonably suggest more stringent hemoglobin A_{1c} goals (such as <6.5%) for selected individual patients, if this can be achieved without significant hypoglycemia or other adverse effects of treatment. Appropriate patients might include those with short duration of diabetes, long life-expectancy, and no significant cardiovascular disease. Less stringent hemoglobin A_{1c} goals (such as <8%) may be appropriate for patients with a history of severe hypoglycemia, limited life- expectancy, advanced microvascular or macrovascular complications, extensive comorbid conditions, and those with longstanding diabetes in whom the general goal is difficult to attain [49]. Therefore, providers should be vigilant in preventing severe hypoglycemia in patients with advanced kidney disease or ESRD and should not aggressively attempt to achieve near-normal hemoglobin A_{1c} levels in patients in whom such a target cannot be reasonably easily and safely achieved.

4. Monitoring of glycemia in dialysis

Glucose homeostasis is altered significantly in patients with uremia. Glycated hemoglobin (expressed as a percentage of total hemoglobin) or hemoglobin A_{1c} measurement is used as an indicator of integrated glucose control. Glycated hemoglobin is formed by the non-enzymatic reaction between glucose and the N-terminal amino group on the beta chain of hemoglobin. The good correlation between hemoglobin A_{1c} and blood glucose in non-CKD type 1 diabetic patients has been documented in the Diabetes Control and Complications Trial (DCCT) [50]. At present, this test is the most accurate method to assess chronic glycemic control based on

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clinical outcomes associated with certain hemoglobin A_{1c} levels in diabetic patients with normal kidney function [31]. The validity of glycated hemoglobin and hemoglobin A_{1c} has not been rigorously studied in patients with ESRD. These tests may be unreliable in dialysis patients because of assay interference due to the elevated blood urea nitrogen. Glycated hemoglobin tests, such as column- and ion-exchange chromatography and agar gel electrophoresis, are affected by uremia. This is due in part to analytical interference from carbamylated hemoglobin formed in the presence of elevated concentrations of urea, leading to false elevations in the hemoglobin A_{1c} level. Use of agarose affinity chromatography or the thiobarbituric acid method for analyzing hemoglobin A_{1c} can be used reliably in patients with ESRD. Other factors such as shorter life span of red blood cells, iron deficiency anemia, and recent transfusion may also cause underestimation of glucose control in diabetic hemodialysis patients (Table 1). In addition, patients treated with erythropoietin could lead to underestimation of glycemic control by using hemoglobin A_{1c} level, because of the greater proportion of young erythrocytes in the circulation of patients [51]. Therefore, hemoglobin A_{1c} levels tend to underestimate glycemic control in diabetic patients undergoing long-term maintenance hemodialysis [52, 53].

Falsely increased hemoglobin A_{1c}	**Falsely decreased hemoglobin A_{1c}**
Carbamylated hemoglobin for charge-dependent chromatography assays	Erythropoiesis supplement
Increased glycosylation rate	Shortened life span of red blood cells
Uremia	Blood transfusions
Metabolic acidosis	Hemoglobinopathy

Table 1. Glycated hemoglobin levels in dialysis patients

Despite anemia and shortened RBC lifespan in ESRD patients, hemoglobin A_{1c} in the range of 6% to 7% estimates glycemic control similarly to patients without severe renal impairment. Hemoglobin A_{1c} above 7.5% may overestimate hyperglycemia in patients with ESRD [43]. It is important to be aware of the specific assay used and the other factors affecting the accuracy of hemoglobin A_{1c} measurements in ESRD on hemodialysis and peritoneal dialysis.

Another potential method to monitor glycemic control in patients with uremia is glycated albumin. Some studies suggest that glycated albumin more accurately reflects glycemic control in diabetic hemodialysis patients than hemoglobin A_{1c} [54, 55]. However, falsely increased glycated albumin values have been measured in the presence of lipemia, hemolysis, and high bilirubin and uric acid concentrations. In addition, use of glycated albumin is hampered by conditions that alter protein metabolism including ESRD, their lack of availability in routine practice and the lack of established reference levels [56].

Despite the limitations in using hemoglobin A_{1c} in the dialysis population, this test is considered a reasonable measure of chronic glycemic control in this group. Patient self-monitoring of blood glucose is also available for patients to assess the effectiveness of the management

plan on glycemic control. It provides real-time assessments of glycemic control and results of self-monitoring of blood glucose can be useful in preventing hypoglycemia and adjusting medications (particularly prandial insulin doses), and physical activity. There are some limitations of this method, because it is subject to errors from poor technique, problems with the meters and strips, and lower sensitivity in measuring low blood glucose levels. However, hemoglobin A_{1c} does not provide a measure of glycemic variability or hypoglycemia. Thus, for patients prone to glycemic variability (especially type 1 patients, or type 2 patients with severe insulin deficiency), glycemic control is best judged by the combination of results of self-monitoring of blood glucose testing and the hemoglobin A_{1c} assay [49]. Hemoglobin A_{1c} may also serve as a check for the accuracy of the patient's meter and the adequacy of the self-monitoring schedule of blood glucose testing.

5. Insulin therapy in dialysis

Insulin regulates glucose homeostasis at many sites, reducing hepatic glucose output by decreasing gluconeogenesis and glycogenolysis, and increasing the rate of glucose uptake, primarily into muscle and adipose tissue. Insulin affects cells through binding to its receptor on the surface of insulin-responsive cells. The stimulated insulin receptor phosphorylates itself, and several substrates including membranes of the insulin receptor substrate family and initiate downstream signaling events [27].

In healthy non-diabetic people, the pancreatic β-cells secrete half of the daily insulin requirement (approximately 0.5 units/kilogram/day) at a steady basal rate independent of glucose levels and the other half is secreted in response to prandial glucose stimulation [57]. Insulin is secreted into the portal system, it passes through the liver where approximately 75% is metabolized with the remaining 25% metabolized by the kidneys. About 60% of the insulin in the arterial bed is filtered by the glomerulus and 40% is actively secreted into the nephric tubules [58]. Most of the insulin in the tubules is metabolized into amino acids, and only 1% of insulin is secreted intact.

Interestingly, endogenous insulin is substantially degraded by the liver but exogenous insulin is eliminated mainly by the kidney. For diabetic patients receiving exogenous insulin, renal metabolism plays a more significant role since there is no first-pass metabolism in the liver. Insulin is freely filtered at the glomerulus and extensively reabsorbed in the proximal tubule after enzyme degradation into smaller peptides. As renal function starts to decline, insulin clearance does not change appreciably, due to compensatory peritubular insulin uptake [59]. However, once the glomerular filtration rate drops below 20 mL/min, insulin clearance decreases and the half-life of insulin increases, an effect compounded by a decrease in the hepatic metabolism of insulin that occurs in uremia [25]. Glucose and insulin homeostasis are altered in CKD patients even in the early stages of CKD, leading to insulin resistance by various pathways. Studies even in the 1980s showed that, although insulin secretion in CKD is normal, a decreased tissue sensitivity to insulin is responsible for the abnormal glucose uptake [60]. In advanced CKD, particularly in stages 4 and 5, significant metabolic derangements in insulin

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metabolism occur. Several factors have been implicated in the pathogenesis of insulin resistance including anemia, dyslipidemia, uremia, malnutrition, excess of parathyroid hormone, vitamin D deficiency, metabolic acidosis, and increase in plasma free fatty acids and proinflammatory cytokines. Thus, despite the increase in insulin resistance caused by renal failure, the net effect is a reduced requirement for exogenous insulin in ESRD patients [61]. Despite similar duration of disease and clinical characteristics, patients with type 2 diabetes with ESRD often show marked heterogeneity in terms of insulin requirement and dosages [62]. However, predictors for exogenous insulin requirement in patients with type 2 diabetes undergoing continuous ambulatory peritoneal dialysis (CAPD) have not been defined. Possible factors include β-cell function, endogenous metabolism and elimination of insulin, insulin resistance, body size, carbohydrate intake, and extra glucose absorbed from dialysate fluid [27].

Recent evidence showed that insulin is a anti-inflammatory hormone that suppresses several proinflammatory transcription factors such as nuclear factor κB (NF-κB), early growth response protein 1 and activating protein 1, which all mediate inflammation. An impairment of the action of insulin because of insulin resistance would therefore result in the activation of these proinflammatory transcription factors and in an increase of the expression of the corresponding genes. Derangements in other biologic effects of insulin could be associated with certain pathologic states in CKD such as hypertension and insulin resistance [63, 64].

Previous studies have shown that uremia was associated with an insulin-resistant state, mainly because of decreased insulin-stimulated uptake of glucose by muscle [65]. However, in clinical practice, with progressive renal failure, the insulin requirements of patients with diabetes for glycemic control often tend to decrease [66]. The determinants of insulin requirements in patients with diabetes with ESRD remain uncertain. This can be influenced by factors such as insulin resistance, production and metabolism of endogenous insulin, oral intake, extra carbohydrate absorbed from dialysis solution, and reduction of body weight in uremic patients [27, 67]. Possible factors for this reduction in insulin requirement include reduced renal clearance of both endogenous and exogenous insulin and progressive loss of appetite and body weight in uremic patients. However, several studies have shown similar fasting insulin levels between patients with renal failure and those with normal renal function [27, 68].

In PD patients, the development of insulin resistance after a initial improvement is generally attributed to a high glucose load absorbed from dialysis fluid, contributing to a wide spectrum of metabolic abnormalities including hypertriglyceridemia, poor glycemic control, new-onset diabetes, hypertension and central obesity. An amplifying loop in the process of glucose absorption appears to be a consequence of the modifications in the peritoneum associated with a loss of ultrafiltration capacity [69]. Disturbances of carbohydrate metabolism seem to be even more intense in non-diabetic PD patients than in hemodialysis patients. After PD initiation, a large number of patients developed new-onset hyperglycemia because of their exposure to hypertonic glucose solutions [27, 70, 71]. In fact, glucose absorption through the peritoneum results in significantly higher serum glucose levels than are produced by an equivalent dose of oral dextrose. Wong et al. show considerable variations in the need for insulin treatment and dosages in patients with type 2 diabetes undergoing CAPD despite similar disease duration, dialysis regimens, renal function, and glycemic control [67]. Duration of diabetes,

hemoglobin A_{1c} level, and body weight were independent determinants of insulin requirement of patients with type 2 diabetes with ESRD patients undergoing CAPD. Dialysis regimen with estimated amount of glucose absorbed and Kt/V did not predict insulin requirement in these patients. Insulin resistance, insulin requirement, and fasting C-peptide levels, a crude measurement of basal pancreatic β-cell function in patients with diabetes with normal renal function, were not affected by dialysis dosage, reflected by a similar value of Kt/V [67]. Insulin-treated patients had lower C peptide concentrations than non-insulin-treated patients, and insulin dosage required was correlated with duration of diabetes mellitus, implying the significance of β-cell function in determination of insulin requirement in patients with type 2 diabetes with ESRD.

Insulin injection therapy remains the mainstay treatment to achieve good glycemic control in diabetic patients receiving hemodialysis therapy [72]. In hemodialysis patients, the insulin sensitivity normally improves on both an acute and chronic basis [66], mainly by clearing circulating urea, and also insulin clearance. The concentration of glucose and insulin is frequently affected by the dialysis procedure itself. Changes in glucose will vary with the concentration of glucose (dextrose) in the dialysis fluid, to which the patient's blood is indirectly exposed. Because glucose transfers to the dialysate according to its concentration gradient, dialysate lacking glucose is associated with significant decreases in plasma glucose levels in poorly and well-controlled diabetic patients as well as in some non-diabetic patients, and is no longer used. Plasma insulin levels also are decreased during the hemodialysis treatment, due to clearance by dialysis which varies among membranes and with the fall in glucose. Additional metabolic effects of dialysis include improvement in sensitivity to insulin and decrease in some cases of counter-regulatory hormones (e.g., growth hormone). In poorly controlled patients, hemodialysis-induced clearance of plasma immunoreactive insulin levels may result in hyperglycemia in the post-dialysis period [63].

Various insulin preparations are available in the market. In ESRD patients, insulin doses will need to be reduced, especially after dialysis has been initiated [63]. Sobngwi et al. show that the daily insulin needs on the day after hemodialysis should be decreased approximately 15% compared with the daily insulin needs before hemodialysis, with a significant reduction of basal hourly insulin requirement by 25%, unchanged boluses, and unchanged body weight-indexed total insulin dose in a group of type 2 diabetic patients on maintenance hemodialysis [73]. However, no evidence for the benefit of neutral protamine hagedorn (NPH) insulin or other long-acting insulin in patients with ESRD is available. On the other hand, insulin lispro which has a short onset of action and a short duration of action shows the benefit not only facilitate the correction of hyperglycemia but may also decrease the risk of late hypoglycemic episodes, which is of increased relevance in hemodialysis patients [64] because its pharmacokinetics is less affected in renal failure [74]. Long-acting insulin such as insulin glargine or NPH insulin can be widely used as basal requirements, along with a rapid-acting insulin analogue such as lispro or insulin aspart before meals two or three times daily [57]. When the glomerular filtration rate drops between 10 and 50 mL/min, the total insulin dose should be reduced by 25%. Once the filtration rate is below 10 mL/min, as in ESRD patients, the insulin dose should be decreased by 50% from the previous amount [75].

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Unexpected hypoglycemia often occurs in dialysis patients during basal-bolus insulin therapy despite careful adjustment of their insulin dose which may due to 3 main factors: (1) prolongation of the elimination half-life of insulin associated with decreased renal degradation and excretion [68]; (2) impairment of gluconeogenesis by the kidneys and (3) weak gastric peristalsis in diabetic patients on dialysis, with prolongation of stomach food retention, resulting in delays in glucose absorption [76]. It is important to note that the signs and symptoms of hyperglycemia are modified in patients with ESRD [63]. Signs and symptoms of hyperglycemia may involve thirst, fluid overload, and hyperkalemia rather than polyuria. Lacking polyuria, patients experience volume expansion, not contraction; excessive thirst will result in large weight gains, which correlate with poor glycemic control between dialysis treatments. Severe hyperglycemia may result in hyperkalemia and complicate management further. Other findings may be pulmonary edema, hypertension, anorexia, altered mental status, nausea, vomiting, and gastroparesis, although symptoms are frequently nonspecific or lacking.

6. Oral antihyperglycemic drugs in dialysis

Therapeutic options for patients with diabetes with CKD and ESRD are limited because a reduced glomerular filtration rate results in the accumulation of certain drugs and/or their metabolism [77]. Most of oral antihyperglycemic drugs include the insulin secretagogues such as sulfonylureas and meglitinides, biguanides, thiazolidinediones, and alpha-glucosidase inhibitors are contraindicated in ESRD patients. However, some agents have been used in patients with CKD and were found to be effective and safe even in those on dialysis. Therefore, some medications may be useful therapeutic options for the management of diabetes in CKD.

As shown in Table 2, insulin secretagogues can be classified as sulfonylureas and meglitinides while alpha-glucosidase inhibitors are modifiers of glucose absorption and thiazolidinediones are insulin sensitizers. Incretin-related therapies include dipeptidylpeptidase-4 (DPP-4) inhibitors and incretin mimetics. DPP-4 inhibitors are oral antidiabetic agents, whereas incretin mimetics are used by subcutaneous injection.

Since many drugs bind to serum protein, primarily albumin and plasma concentration of albumin in patients with renal impairment is commonly decreased, the concentrations of unbound drugs are increased.

Sulfonylureas

Insulin secretagogues increase endogenous insulin levels. These agents work by binding to sulfonylurea receptors or nearby sites, resulting in closure of ATP-sensitive potassium channels of the pancreatic β-cell, depolarization of the cell membranes, calcium influx, and subsequently insulin release [72]. They have a wide volume of distribution and are highly protein-bound. However, only the unbound drug exerts a clinical effect. Because of high protein binding property, dialysis cannot effectively clear elevated levels of sulfonylurea drugs. As these agents increase endogenous insulin levels, they are associated with an increased risk of hypoglycemia. This risk is mitigated when shorter-acting agents are used. Furthermore, many ESRD patients take drugs such as sulfonamides, vitamin K antagonists,

beta-blocker, salicylates and fibric acid derivatives which may displace sulfonylureas from albumin, thus increasing the risk of severe hypoglycemia.

Category	Action	Group	Medication	Medication	Medication	Dosing recommendation CKD stage 3, 4 or kidney transplant	Dialysis dose recommendation
Insulin	**Sensitizers**	**Biguanides**	Metformin			Contraindicated with kidney dysfunction defined as sCr[3]1.5 mg/dL in men or[3]1.4 mg/dL in women	Avoid
Insulin	**Sensitizers**	**TZDs (PPAR)**	Pioglitazone			No dose adjustment needed	No dose adjustment needed
Insulin	**Sensitizers**	**TZDs (PPAR)**	Rivoglitazone			No dose adjustment needed	No dose adjustment needed
Insulin	**Sensitizers**	**TZDs (PPAR)**	Rosiglitazone			No dose adjustment needed	No dose adjustment needed
Insulin	**Sensitizers**	**Dual PPAR agonist**	Aleglitazar			Use with caution	Use with caution
Insulin	**Sensitizers**	**Dual PPAR agonist**	Muraglitazar			Use with caution	Use with caution
Insulin	**Sensitizers**	**Dual PPAR agonist**	Tesaglitazar			Use with caution	Use with caution
Insulin	**Secretagogues**	**K+ ATP**	Sulfonylureas	1st generation	Acetohexamide	Avoid	Avoid
Insulin	**Secretagogues**	**K+ ATP**	Sulfonylureas	1st generation	Carbutamide	Avoid	Avoid
Insulin	**Secretagogues**	**K+ ATP**	Sulfonylureas	1st generation	Chlorpropamide	Reduce dose by 50% when GFR<70 and 50[3]mL/min/1.73m^2 and avoid when GFR<50 mL/min/1.73 m^2	Avoid
Insulin	**Secretagogues**	**K+ ATP**	Sulfonylureas	1st generation	Metahexamide	Avoid	Avoid
Insulin	**Secretagogues**	**K+ ATP**	Sulfonylureas	1st generation	Tolbutamide	Avoid	Avoid
Insulin	**Secretagogues**	**K+ ATP**	Sulfonylureas	1st generation	Tolazamide	Avoid	Avoid
Insulin	**Secretagogues**	**K+ ATP**	Sulfonylureas	2nd generation	Glipizide	Preferred, no dose adjustment needed	Preferred, no dose adjustment needed
Insulin	**Secretagogues**	**K+ ATP**	Sulfonylureas	2nd generation	Gliclazide	Preferred, no dose adjustment needed	Preferred, no dose adjustment needed
Insulin	**Secretagogues**	**K+ ATP**	Sulfonylureas	2nd generation	Glyburide	Avoid	Avoid
Insulin	**Secretagogues**	**K+ ATP**	Sulfonylureas	2nd generation	Glimepiride	Initiate at low dose, 1 mg daily	Avoid
Insulin	**Secretagogues**	**K+ ATP**	Meglitinides	Nateglinide		Initiate at low dose, 60 mg before each meal	Avoid
Insulin	**Secretagogues**	**K+ ATP**	Meglitinides	Repaglinide		No dose adjustment needed, initiate at 0.5 mg dose when GFR<40 mL/min/1.73 m^2	No dose adjustment needed
Insulin	**Secretagogues**	**K+ ATP**	Meglitinides	Mitiglinide		No dose adjustment needed	No dose adjustment needed
Insulin	**Secretagogues**	**GLP-1 analogs (Incretin Mimetics)**	Exenatide			Not recommended in patients with GFR<30 mL/min/1.73 m^2 and caution should be applied when GFR>30 and< 50 mL/min/1.73 m^2, No dose adjustment needed when GFR>50 and <80 mL/min/1.73 m^2	Avoid
Insulin	**Secretagogues**	**GLP-1 analogs (Incretin Mimetics)**	Liraglutide			No dose adjustment needed	No dose adjustment needed
Insulin	**Secretagogues**	**DPP-4 inhibitors**	Alogliptin			Reduce dose by 50% (12.5 mg/day) when GFR<50 and 30 [3] mL/min/1.73 m^2 and by 75% (6.25 mg/day) when GFR<30 mL/min/1.73 m^2	Reduce dose by 75% (6.25 mg/day)
Insulin	**Secretagogues**	**DPP-4 inhibitors**	Linagliptin			No dose adjustment needed	No dose adjustment needed
Insulin	**Secretagogues**	**DPP-4 inhibitors**	Sexagliptin			Moderate to severe kidney impairment should receive<2.5 mg/d	Moderate to severe kidney impairment should receive<2.5 mg/d
Insulin	**Secretagogues**	**DPP-4 inhibitors**	Sitagliptin			Reduce dose by 50% (50 mg/day) when GFR<50 and 30[3]mL/min/1.73 m^2 and by 75% (25 mg/day) when GFR<30 mL/min/1.73 m^2	Reduce dose by 75% (25 mg/d)
Insulin	**Secretagogues**	**DPP-4 inhibitors**	Vildagliptin			Initiate at low dose	Initiate at low dose

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Category	Action	Group	Medication	Medication	Medication	Dosing recommendation CKD stage 3, 4 or kidney transplant	Dialysis dose recommendation
Insulin	**Analogs/other insulins**	**Rapid-acting**	Regular			Preferred, normally no dose adjustment needed	Preferred, normally no dose adjustment needed but depends on dialysis factors as well
Insulin	**Analogs/other insulins**	**Rapid-acting**	Lispro			Preferred, normally no dose adjustment needed	Preferred, normally no dose adjustment needed but depends on dialysis factors as well
Insulin	**Analogs/other insulins**	**Rapid-acting**	Aspart			Preferred, normally no dose adjustment needed	Preferred, normally no dose adjustment needed but depends on dialysis factors as well
Insulin	**Analogs/other insulins**	**Long-acting**	NPH			Dose adjustment needed depends on individual factors	Reduce dose by 25% when GFR 10-50 mL/min and by 50% when GFR<10 mL/min
Insulin	**Analogs/other insulins**	**Long-acting**	Glargine			Dose adjustment needed depends on individual factors	Reduce dose by 25% when GFR 10-50 mL/min and by 50% when GFR<10 mL/min
Insulin	**Analogs/other insulins**	**Long-acting**	Determir			Dose adjustment needed depends on individual factors	Reduce dose by 25% when GFR 10-50 mL/min and by 50% when GFR<10 mL/min
Insulin	**Analogs/other insulins**	**Premixed**	70/30 human mix			Dose adjustment needed depends on individual factors	Dose adjustment needed depends on individual factors
Insulin	**Analogs/other insulins**	**Premixed**	70/30 aspart mix			Dose adjustment needed depends on individual factors	Dose adjustment needed depends on individual factors
Insulin	**Analogs/other insulins**	**Premixed**	75/25 lispro mix			Dose adjustment needed depends on individual factors	Dose adjustment needed depends on individual factors
Others	**Alpha-glucosidase inhibitor**		Acarbose			Not recommended in patients with sCr>2 mg/dL	Avoid
Others	**Alpha-glucosidase inhibitor**		Miglitol			Not recommended in patients with sCr>2 mg/dL	Avoid
Others	**Alpha-glucosidase inhibitor**		Vogibose			Not recommended in patients with sCr>2 mg/dL	Avoid
Others	**Amylin analog**		Pramlintide			No dose adjustment needed for GFR 20-50 mL/min/1.73 m^2	No data available
Others	**SGLT2 inhibitor**		Canagliflozin			No data available	No data available

Table 2. Oral anti-diabetic drugs and insulin analogs

* Modify from Masanori Abe, Kazuyoshi Okada and Masayoshi Soma "Antidiabetic agents in patients with chronic kidney disease and end-stage renal disease on dialysis: metabolism and clinical practice" Current Drug Metabolsim Volume 12, January 2011, with permission.

The first-generation sulfonylureas-chlorpropamide, acetohexamide, tolbutamide, and tolazamide are almost exclusively excreted by the kidney and are therefore contraindicated in ESRD patients [78]. Second-generation agents include glimepiride and glyburide which are metabolized in the liver. However, their active metabolites are excreted in the urine and so these medications should be avoided in ESRD patients as well [72] but low-dose initiation can be used in patients with CKD [79]. Glipizide and gliclazide are the preferred agents and no dose adjustment has been necessary in a dialysis population [11].

Most sulfonylureas are not suitable for ESRD patients due to the risk of prolonged hypoglycemic; furthermore, metformin is contraindicated [80]. From all medications in this group, the only sulfonylurea recommended in ESRD patients are glipizide and gliclazide which are also metabolized in the liver but has inactive or weakly active metabolites excreted in the urine [57]. Glipizide is eliminated primarily by hepatic biotransformation; < 10% of a dose is excreted as unchanged drug in urine or feces while approximately 90% is excreted as biotransformation products in urine (80%) and feces (10%). The major metabolites of glipizide are products of aromatic hydroxylation that have no hypoglycemic activity. A minor metabolite which accounts for < 2% of a dose, an acetylamino-ethyl benzene derivative, is reported to have 1/10 to 1/3 of the hypoglycemic activity compared to the parent compound. The suggested dose of glipizide is 2.5 to 10 mg/day. In ESRD patients, sustained-release forms should be avoids due to the concerns of hypoglycemia [81].

Meglitinides

Repaglinide, nateglinide and mitiglinide are insulin secretagogues that stimulate pancreatic β-cells. They are currently in clinical use because of their rapid onset of action resulting in improvement in hyperglycemia. Like sulfonylureas, nateglinide is hepatically metabolized, with renal excretion of active metabolites. On the other hand, repaglinide is almost completely converted to inactive metabolites in the liver, and less than 10% is excreted by the kidneys [82, 83]. Nateglinide still pose a risk of hypoglycemia especially in ESRD patients. Because of that, this drug is not recommended to use in patients on hemodialysis [82, 83]. However, mitiglinide shows selective action on the ATP-sensitive potassium channel of pancreatic β-cells and the order of affinity is mitiglinide > repaglinide > nateglinide [84]. This result suggests that mitiglinide induces insulin secretion by specifically acting on pancreatic β-cells and has few unwanted effects on the cardiovascular system. Because mitiglinide is rarely accompanied by hypoglycemia, it may be an attractive therapeutic option for patients undergoing dialysis [85]. However, the optimal daily dose of mitiglinide is suggested to be lower in the diabetic hemodialysis patients than that in the diabetic patients with normal kidney function. Mitiglinide has the potential to reduce the number of type 2 diabetics on hemodialysis who ultimately require insulin injection therapy. The daily dose of mitiglinide (23 mg) was adequate, as evidenced by the fact that it was able to induce significant reductions in glycemic parameters such as fasting plasma glucose, hemoglobin A_{1c}, glycated albumin, and homeostasis model assessment for insulin resistance (HOMA-IR) levels [86]. This suggests that appropriate blood glucose levels can be maintained even at a low dose of mitiglinide, not only during the postprandial period but also before meals, due to the prolonged half-life of mitiglinide in patients on

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dialysis compared with the half-life in those with normal renal function. Abe et al. reported that mitiglinide significantly improved glycemic control, triglyceride levels and interdialytic weight gain even when administered for only a short duration [87]. Thus, mitiglinide not only improved hemoglobin A_{1c} and glycated albumin, the overall index of glycemic control in type 2 diabetes, but also effectively improved fasting plasma glucose in dialysis patients [72, 85].

Biguanides

Metformin, the drug of choice for many patients with type 2 diabetics, is a biguanide that reduces hepatic gluconeogenesis and glucose output. Metformin does not cause increase insulin levels, but rather decreases hepatic glucose output by suppressing fasting gluconeogenesis. It is absorbed via the small intestine and the absolute bioavailability is approximately 50-60%. Intravenous single-dose studies in normal subjects demonstrate that metformin is excreted unchanged in the urine and does not undergo hepatic metabolism or biliary excretion [88]. Renal clearance of metformin is approximately 3.5-fold greater than creatinine clearance, which indicates that tubular secretion via human organic cation transporter 2 is the major route of metformin elimination [89]. Single-dose and steady-state pharmacokinetics of metformin were compared between patients with normal renal function (CrCl > 90 mL/min), mild impaired renal function (CrCl 61-90 mL/min) as well as moderate (CrCl 31-60 mL/min) and severe impaired renal function (CrCl 10-30 mL/min). The results show that in patients with moderate to severe impaired renal function, C_{max} and AUC are increased 173% and 390%, respectively, compared to the patients with normal renal function [89]. In patients with decreased renal function, based on the measurement of CrCl, the plasma half-life of metformin is prolonged and renal clearance is decreased in proportion to the decrease in CrCl [89]. Therefore, metformin should be avoided in patients with moderate to severe CKD including those on dialysis since the risk of metformin accumulation and lactic acidosis increases in line with the degree of impairment of renal function [90].

Thiazolidinediones

Rosiglitazone and pioglitazone are highly potent, selective agonists that work by binding to and activating a nuclear transcription factor, specifically, peroxisome proliferator-activated receptor gamma (PPAR-gamma) which improves insulin resistance in type 2 diabetic patients [91, 92] as well as increase glucose uptake in muscles and adipose tissue, and decrease hepatic glucose production [92, 93]. Both rosiglitazone and pioglitazone have an adequate oral bioavailability and are extensively metabolized by the liver. Rosiglitazone is mainly metabolized by CYP2C8 into inactive metabolites and < 1% of the parent drug appears in the urine in unchanged form [80, 94]. The half-life of rosiglitazone is similar in patients with ESRD and in healthy individuals, and can therefore be administered to ESRD patients without dose adjustment or risk of causing hypoglycemia [95-97]. Pioglitazone is metabolized by CYP3A4 and CYP2C8/9 [98]. Metabolites of pioglitazone are more active than those of rosiglitazone and are excreted predominantly in bile. The pioglitazone metabolites do not accumulate in CKD. The pharmacokinetics profile of pioglitazone was found to be similar in healthy subjects and patients with moderately or severely impaired renal function who did not require dialysis [98]. Moreover, in patients who did require dialysis, pioglitazone was found to have a T_{max} of 1.8 h

and a half-life of 5.4 h [98]. Therefore, a post-dialysis supplementary dose is not required, and pioglitazone can be administered irrespective of the time of dialysis. Due to the high molecular weight (392 Da), high protein-binding capacity (> 98%) and predominant hepatic metabolism of pioglitazone, its pharmacokinetics is similar in patients with normal renal function and CKD, and in those undergoing dialysis therapy. The main adverse reaction of these agents is edema, especially when they are used in combination with insulin. Because of that, a joint statement of the American Diabetes Association and the American Heart Association recommends avoiding thiazolidinediones in patients in New York Heart Association class III or IV heart failure [99]. Moreover, caution is required in patients in compensated heart failure (New York Heart Association class I or II) or in those at risk of heart failure such as patients with history of myocardial infarction or angina, hypertension, left ventricular hypertrophy, significant aortic or mitral value disease, age greater than 70 years, or diabetes for more than 10 years [99].

Thiazolidinediones have been reported to (1) reduce insulin requirements, (2) ameliorate albuminuria (3) have various roles in lipid metabolism, fibrinolysis, platelet aggregation and coagulation, (4) protect against impairment of endothelial function and (5) have an anti-inflammatory effect [100-103]. When used for the clinical management of type 2 diabetes and ESRD, thiazolidinediones are primarily metabolized in the liver and will not accumulate in patients with CKD. They might also improve uremia-associated insulin resistance and confer benefits at the metabolic, inflammatory, vascular, and hemodynamic levels [100]. The efficacy of this drug in patients with normal renal function is similar to the efficacy in those with mild to moderate renal impairment [104]. Administration of pioglitazone is also associated with mean decreases in triglyceride levels and mean increases in high-density lipoprotein (HDL)-cholesterol without consistent changes in the mean levels of total cholesterol or low-density lipoprotein (LDL)-cholesterol in non-uremic patients [105].

Thiazolidinediones are known to reduce HOMA-IR and levels of high-sensitivity C-reactive protein (hs-CRP) and tumor necrosis factor-alpha (TNF-α), and increase adiponectin levels in patients not undergoing dialysis [72]. In patients undergoing PD, thiazolidinediones have been reported to reduce hs-CRP levels, but levels of interleukin-6 (IL-6) and TNF-α were not reduced [91, 102]. In a short-term study of dialysis patients, thiazolidinediones are reported to reduce the levels of hs-CRP but not adiponectin [106]. It has been reported that pioglitazone treatment reduced the levels of hs-CRP, IL-6 and TNF-α and increased the high-molecular weight adiponectin level even in hemodialysis patients [107]. Moreover, the dosage of erythropoiesis-stimulating agents was significantly reduced during pioglitazone treatment with improvement in insulin resistance and a decrease in the levels of inflammatory cytokines [107].

It can be concluded that even though ESRD and dialysis do not affect the metabolism of thiazolidinediones, the medications in this group are not recommended in ESRD patients due to the associated risk of fluid accumulation and precipitation of heart failure.

Alpha-glucosidase inhibitors

Enzyme alpha-glucosidase is located in the gut and hydrolyzed oligosaccharides, trisaccharides and disaccharides into glucose in the brush border of the small intestine. The antihyper-

glycemic action of alpha-glucosidase inhibitors results from the reversible inhibition of membrane-bound intestinal alpha-glucoside hydrolase enzymes. Alpha-glucosidase inhibitors decrease the rate of breakdown of complex carbohydrates so that less glucose is absorbed and postprandial hyperglycemia is lowered but they do not enhance insulin secretion. The main side effects are gastrointestinal including flatulence and diarrhea.

Acarbose and miglitol slow carbohydrate absorption from the intestine. The levels of these drugs and their active metabolites are higher in patients with renal failure [80], and since data are scarce on the use of these drugs in ESRD, they are contraindicated in ESRD patients [11].

Acarbose is metabolized by intestinal bacteria and digestive enzymes exclusively within the gastrointestinal tract. Within 96 h of ingestion, 51% of an oral dose was excreted in the faces and unabsorbed drug-related radioactivity. Because acarbose acts locally within the gastrointestinal tract, low systemic bioavailability of the parent compound is therapeutically desirable. A fraction of these metabolites (about 34% of the dose) was absorbed and subsequently excreted in urine. The major metabolites have been identified as 4-methylpyrogallol derivatives (such as sulfate, methyl, and glucuronide conjugates). Moreover, one metabolite (formed by cleavage of a glucose molecule from acarbose) also has alpha-glucosidase inhibitory activity. This metabolite, together with the parent compound, recovered from the urine, accounts for < 2% of the total administered dose. Although < 2% of an oral dose of acarbose was absorbed as active drug, patients with severe renal impairment (CrCl < 25 mL/min) attained increases about 5-fold higher for peak plasma concentration of acarbose and 6-fold higher for AUC values than subjects with normal renal function [108]. Because long-term clinical trials in diabetic patients with significant renal dysfunction have not been conducted, treatment of these patients with acarbose is not recommended [108].

Miglitol is not metabolized in humans or other animal species [109]. No metabolites have been detected in plasma, urine, or feces indicating a lack of either systemic or presystemic metabolism. Miglitol is eliminated by renal excretion as unchanged drug [109]. Patients with CrCl < 25 mL/min taking the miglitol 25 mg 3 times daily exhibited a greater than 2-fold increase in miglitol plasma levels when compared to subjects with CrCl > 60 mL/min [109]. Dose adjustment to correct for the increased plasma concentrations is not feasible because miglitol acts locally. However, treatment of patients with CrCl < 25 mL/min with miglitol is not recommended because the safety of miglitol in these patients has not yet been elucidated [109].

Glucagon-like peptide-1 analogues

The intestinal hormone glucagon-like peptide-1 (GLP-1) stimulates glucose-dependent insulin release from pancreatic β-cells in a glucose-dependent manner and inhibits inappropriate postprandial glucagon release. It also shows gastric emptying and reduces food intake. However, its meal-induced secretion is generally decreased in patients with type 2 diabetes, and this may contribute to the amplification of postprandial hyperglycemia [72]. GLP-1 is rapidly inactivated by the enzyme dipeptidylpeptidase-4 (DPP-4) [110].

Therefore, an effective way to potentiate postprandial GLP-1 response is the use of selective DPP-4 inhibitors [111, 112].

Table 2 shows some of the medications in this group.

Sitagliptin is a highly selective, oral, once-daily administration DPP-4 inhibitor approved for the treatment of patients with type 2 diabetes [113]. DPP-4 inhibitors slow the degradation and the inactivation of the incretins, GLP-1 and glucose-dependent insulinotropic polypeptide [110]. These two incretins regulate glucose homeostasis by stimulating insulin release, while GLP-1 also suppresses glucagon release [72]. Sitagliptin can be used as initial pharmacologic therapy for type 2 diabetes, as a second agent in those who do not respond to a single agent such as a sulfonylurea [114], metformin [115-117], or a thiazolidinedione [118] and as an additional agent when dual therapy with metformin and a sulfonylurea does not provide adequate glycemic control [114]. CYP3A4 is the major CYP isozyme responsible for the limited oxidative metabolism of sitagliptin, with some minor contribution from CYP2C8. Sitagliptin is primarily renally eliminated with approximately 80% of the oral dose excreted unchanged in the urine [119, 120]. Excretion is thought to be via active secretion and glomerular filtration [119, 121]. Following single oral doses of sitagliptin, plasma level increases with decreasing renal function, as determined by 24 h CrCl. Relative to subjects with normal or mildly impaired renal function, patients with moderate renal insufficiency (CrCl 30-50 mL/min), severe renal insufficiency (CrCl < 30 mL/min, not on dialysis) or ESRD on dialysis have approximately 2.3-fold, 3.8-fold, or 4.5-fold higher plasma sitagliptin exposures, respectively, and the C_{max} increased by 1.4-fold to 1.8-fold [122]. T_{max} is significantly increased in patients with ESRD, and the terminal half-life increased with decreasing renal function [72]. Compared with values in subjects with normal renal function, the terminal half-life values of sitagliptin in those with mild, moderate, and severe renal impairment, and ESRD were raised to 16.1, 19.1, 22.5 and 28.4 h, respectively, compared to 13.1 h in normal renal function patients [122]. The fraction of dose removed by dialysis was low with 13.5% and 3.5% for dialysis initiated at 4 and 48 h post dose, respectively. Plasma protein binding of 38% was not altered in uremic plasma from patients with renal impairment. Based on these data, in order to achieve plasma sitagliptin concentrations comparable to those in patients with normal renal function, sitagliptin dose adjustments are recommended for patients with type 2 diabetes and moderate to severe renal insufficiency, as well as for those with ESRD requiring dialysis [123]. The usual dose of sitagliptin is 100 mg orally once daily, with reduction to 50 mg for patients with a glomerular filtration rate of 30-50 mL/min, and 25 mg for patients with a glomerular filtration rate less than 30 mL/min [122]. Sitagliptin may be used at does of 25 mg daily in ESRD patients, irrespective of dialysis timing. However, some side effects have been found after administration of sitagliptin such as anaphylaxis, angioedema and Steven-Johnson syndrome. Moreover, the risk of hypoglycemia increases when sitagliptin is used with sulfonylureas.

Vildagliptin is not a CYP enzyme substrate and does not inhibit or induce CYP enzymes, it is unlikely to interact with co-medications that are substrates, inhibitors, or inducers of these enzymes [124, 125]. The efficacy of vildagliptin in humans against the DPP-4 enzyme also

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shows a low *in vivo* IC_{50} (4.5 nM), which suggests a higher potency than that reported for sitaliptin (IC_{50} 26 nM) [119, 126]. Elimination of vildagliptin mainly involves renal excretion of unchanged parent drug and cyano group hydrolysis with little CYP involvement, suggesting a low potential for drug-drug interaction when co-administered with CYP inhibitors/inducers.

In patients with mild, moderate and severe renal impairment and ESRD patients on hemodialysis, systemic exposure to vildagliptin was increased (C_{max} 8-66%; AUC 32-134%) compared to subjects with normal renal function [72]. However, changes in exposure to vildagliptin did not correlate with the severity of renal function. In contrast, exposure of the main metabolite increased with increasing severity of renal function (AUC 1.6- to 6.7-fold), but this effect has no clinically relevant consequences because the metabolite is pharmacologically inactive. The elimination half-life of vildagliptin is not affected by renal function and it is well-tolerated in this population [127]. According to the label, no dosage adjustment of vildagliptin is required in patients with mild renal impairment. In clinical practice, special precautions are advised for the use of this drug in patients with moderate to severe renal impairment, including those on dialysis [72].

Alogliptin was rapidly absorbed and slowly eliminated primarily via urinary excretion in healthy subjects. In patients with type 2 diabetes, alogliptin is also primarily excreted renally with a renal clearance rate of 165-254 mL/min which is slightly higher than the normal glomerular filtration rate, suggesting the occurrence of some active renal secretion. The results of a single-dose (50 mg) pharmacokinetics study in patients with renal impairment showed an increase in alogliptin exposure compared with healthy volunteers; approximately 1.7-, 2.1-, 3.2- and 3.8-fold increase in patients with mild, moderate, and severe renal impairment, and in patients with ESRD, respectively [127, 128]. According to this data, to achieve plasma alogliptin concentrations comparable to those in patients with normal renal function, alogliptin dose adjustments are recommended for patients with type 2 diabetes and moderate to severe renal insufficiency, including those with ESRD requiring dialysis [72].

Saxagliptin is another DPP-4 inhibitor and its metabolite is pharmacologically active which makes saxagliptin difference from other medications in this group. The metabolism of saxagliptin is primarily mediated by CYP3A4/5 and its major metabolite is also a selective, reversible, competitive DPP-4 inhibitor which is 50% less potent than saxagliptin [129]. Saxagliptin is cleared by both metabolism and renal excretion. However, the degree of renal impairment does not affect the C_{max} of saxagliptin or its major metabolite [127]. In subjects with mild renal impairment, AUC from time 0 to infinity (AUC_{∞}) values of saxagliptin and its major metabolite are 1.2- and 1.7-fold higher than mean AUC_{∞} in controls, respectively, while they are 1.4- and 2.9-fold higher in subjects with moderate renal impairment. Corresponding value are 2.1- and 4.5-fold higher in those with severe impairment [127]. A 4-h dialysis section removes approximately 23% of saxagliptin dose, AUC_{∞} values for saxagliptin and its major metabolite are correlated with the degree of renal impairment, whereas C_{max} values are not well correlated. Renal function should be assessed before initiating saxagliptin therapy and patients with moderate to severe kidney impairment should receive less than 2.5 mg of saxagliptin/day and this drug can still be taken after dialysis in patients with ESRD.

Linagliptin is extensively protein bound (> 80% at the therapeutic dose) which is unlike other DPP-4 inhibitors. Because DPP-4 is expressed in various tissues but soluble DPP-4 is also present in plasma, binding to soluble DPP-4 may influence the pharmacokinetics of linagliptin. High-affinity but readily saturable binding of linagliptin to its target DPP-4 primarily accounted for the concentration-dependent plasma-protein binding at therapeutic plasma concentrations of linagliptin [130]. Fecal elimination is the dominant excretion pathway of linagliptin with 84.7 and 58.2% of the dose whereas renal excretion accounted for 5.4 and 30.8% of the dose administered orally or intravenously, respectively [131]. Renal excretion of unchanged linagliptin is < 1% after administration of 5 mg [132]. As absolute bioavailability is determined to be around 30%, renal excretion is a minor elimination pathway of linagliptin at therapeutic dose levels (compared to other DPP-4 inhibitors) and accordingly, a dose adjustment in patients with renal impairment is not anticipated for linagliptin [72].

Incretin mimetics

GLP-1 belongs to the incretin class of hormones which exert an influence over multiple physiologic functions, including a rapid blood glucose-lowering effect in response to enteral nutrient absorption [72]. Native GLP-1 is rapidly metabolized by DPP-4 which is found in many tissues and cell types, as well as in the circulation [133]. Clearance of native GLP-1 and its metabolites is largely mediated by the kidneys [133]. Incretins, such as GLP-1, enhance glucose-dependent insulin secretion and exhibit other antihyperglycemic actions following their release into the circulation from the gut. Exenatide and liraglutide are GLP-1 receptor agonists that enhance glucose-dependent insulin secretion by pancreatic β-cells, suppress inappropriately elevated glucagon secretion and slow gastric emptying [72].

Exenatide is one of the drugs in this group. The amino acid sequence of exenatide is partially homologous to that of human GLP-1. Exenatide binds and activates the human GLP-1 receptor which leads to an increase in both glucose-dependent synthesis of insulin and secretion of insulin from pancreatic β-cells. Exenatide is a naturally occurring GLP-1 analogue that is resistant to degradation by DPP-4 and has a longer half-life. The kidney provides the primary route for elimination and degradation of exenatide [134]. Given subcutaneously, exenatide undergoes minimal systemic metabolism. In subjects with mild to moderate renal impairment (CrCl 30-80 mL/min), exenatide exposure is similar to that of subjects with normal renal function and no dose adjustment is required. However, in subjects with ESRD receiving dialysis, mean exenatide exposure increased by 3.4-fold compared to that of subjects with normal renal function. Exenatide is contraindicated in patients undergoing hemodialysis, ESRD or in patients who have glomerular filtration rate less than 30 mL/min and it should be used with caution in patients undergone renal transplantation [135]. In patients with ESRD receiving dialysis, single dose of 5 μg exenatide are not well tolerated due to gastrointestinal side effects. Due to the side effects of exenatide such as nausea and vomiting with transient hypovolemia, treatment may worsen renal function. Caution is required when initiating or escalating doses of exenatide from 5 μg to 10 μg in patients with moderate renal impairment (CrCl 30-50 mL/min) [72].

Liraglutide is a once-daily human GLP-1 analog and has a high degree of sequence identity to human GLP-1 [136, 137]. The half-life of liraglutide is approximately 13 h after subcutaneous injection [138] and its metabolism is similar to that of large peptides which is fully degraded in the body [137]. There is no evidence that kidney is a major organ for elimination. Its pharmacokinetics parameters are essentially independent of renal function [139]. Renal dysfunction is not found to increase exposure of liraglutide and patients with type 2 diabetes and renal impairment can be treated with standard regimens of liraglutide [72].

Amylin analogs

Currently, pramlintide is the only drug in this group which is administered by subcutaneous injection and it is a naturally occurring neuroendocrine hormone co-secreted with insulin by pancreatic β-cells [140]. Amylin regulates gastric emptying [141], suppresses inappropriate postprandial glucagon secretion [142] and reduces food intake [143]. Through the mechanism similar to those of amylin, pramlintide reduces postprandial glucose, improving overall glycemic control [144, 145] and increases satiety resulting in reduced food intake and weight loss [146-148]. The half-life of pramlintide in healthy subjects, which is metabolized primarily by the kidney, is approximately 48 min. Its primary metabolite has a similar half-life and is biologically active. Patients with moderate or severe renal impairment (CrCl > 20 to < 50 mL/min) do not show increased pramlintide exposure or reduced pramlintide clearance when compared with subjects with normal renal function. However, no data is available for dialysis patients and further clinical studies are warranted in this population.

Sodium glucose co-transporter 2 (SGLT2) inhibitors

The plasma glucose level below which nearly all filtered glucose is reabsorbed by the kidneys, and above which glucose is excreted in urine, is designated as the renal threshold for glucose (RT_G) [149]. In healthy individuals, virtually all filtered glucose is reabsorbed up to a plasma glucose level of approximately 10 mmol/L (180 mg/dL), thus defining RT_G [150, 151]. At plasma glucose levels higher than RT_G, the renal glucose reabsorptive capacity is saturated and the amount of glucose in urine increases proportionately to plasma glucose concentration [152]. By inhibiting the proximal renal tubule glucose transporter responsible for the majority of glucose reabsorption, sodium glucose co-transporter 2 (SGLT2) inhibitors are predicted to lower RT_G, thereby increasing urinary glucose excretion [149]. In patients with diabetes, reduction of RT_G is expected to increase urinary glucose excretion and lower plasma glucose concentrations. Unlike other antidiabetic agents which often cause weight gain, the glucose-lowering effect with SGLT2 inhibitors is accompanied by urinary loss of calories, potentially resulting in weight loss. Moreover, SGLT2 inhibitors do not target the major pathophysiological defects in type 2 diabetes mellitus-namely insulin resistance and impaired insulin secretion-they represent a potentially promising new option in the treatment of diabetes [153]. One of the drug in this category is canagliflozin. In preclinical studies, a single oral administration of 3 mg/kg of canagliflozin decreased plasma glucose levels independent of food intake in mice on a high-fat, hyperglycemic diet [153]. In normo-glycemic mice, canagliflozin

administration led to a minimal change in plasma glucose levels. Sha et al. show that canagliflozin was well tolerated in healthy men across the range of single does studied up to 800 mg. By inhibiting SGLT2, canagliflozin treatment dose dependently decreased RT_G, leading to a dose-dependent increase in urinary glucose excretion [149]. However, no data on its safety and efficacy is available for CKD or dialysis patients and further clinical studies are warranted in this population.

7. Combination therapy

Saxagliptin plus metformin

In order to obtain the better control of plasma glucose level and decrease the side effect of some medications in renal patients, combination therapy has been used. Scheen reviewed the use of metformin plus saxagliptin in renal impairment patients [154]. Since saxagliptin's license was recently extended to include diabetic patients with moderate or severe renal impairment while metformin is still widely prescribed in patients with some degree of renal impairment in real life even though it is contraindicated, the pro and contra of using this combination in type 2 diabetic patients with renal impairment need to be reviewed. Some recent data suggested that both metformin and saxagliptin may be used safely in type 2 diabetic patients with mild-to-moderate renal impairment, provided that dose reduction is made appropriately according to individual CrCl [154]. Because of the absence of pharmacokinetics interactions between the two drugs, this should be also the case with the saxagliptin-metformin combination. In this population, DPP-4 inhibitors offer advantages compared with sulfonylureas, especially because of the absence of hypoglycemia [155, 156]. A retrospective subgroup analysis of data from five randomized, double-blind, placebo-controlled, multicenter, 24-week, Phase III trials showed that saxagliptin 5 mg once-daily monotherapy and as add-on therapy are associated with clinically relevant and significant efficacy for reducing hemoglobin A_{1c} in older patients (≥ 65 years; CrCl: 80±20 mL/min) versus younger patients (< 65 years; CrCl: 119±40 mL/min) [157]. Furthermore, saxagliptin was well-tolerated in older patients with a low incidence of hypoglycemia and no weight gain. Normally, patients with type 2 diabetes and renal impairment are exposed to a higher risk of cardiovascular disease. Therefore, reducing cardiovascular risk in this population should be considered as a main objective and drugs that have proven their efficacy and safety in this regard should be preferred. Treatment with metformin in type 2 diabetic patients is associated with a lower cardiovascular morbidity and mortality, compared with alternative glucose-lowering drugs [158]. It has also been suggested that metformin might exert direct protective effects on the heart [159]. Since both metformin and saxagliptin are excreted via the kidney, dose adjustment is required in case of moderate-to-severe renal impairment (ca. half dose of saxagliptin). Due to major discrepancies exist between guidelines (metformin excluded in case of renal impairment because of the risk of

lactic acidosis) and real life, physicians should weigh the benefit/risk ratio carefully before deciding to prescribe or withdraw this combination in renal patients.

DDP-4 inhibitor plus thiazolidinedione

Thiazolidinediones are currently considered as the most efficacious class of oral anti-diabetics [160]. However, they carry the burden of weight gain and hemodilution which may lead to cardiovascular complications. It has been considered that the use of a low dose thiazolidinedione in combination with DPP-4 inhibitor may reduce the risk of dose dependent side effects of thiazolidinediones such as weight gain and hemodilution while, simultaneously, this combination may be more effective owing to different mechanisms of action of thiazolidinediones and DPP-4 inhibitors. Roy et al. demonstrated that in aged *db*/*db* mice, a combination therapy of low dose rosiglitazone and vildagliptin is safer and equally efficacious when compared to the therapeutic dose of rosiglitazone [160]. The combination therapy (1 mg/kg/day of rosiglitazone plus 5 mg/kg/day of vildagliptin) showed similar efficacy as that of 10 mg/kg/day rosiglitazone in lowering random blood glucose. GLP-1 and insulin levels were found to be elevated significantly in both vildagliptin and combination treated groups following oral glucose load. Vildagliptin alone had no effect on random glucose and glucose excursion during oral glucose tolerance test in severely diabetic *db*/*db* mice. The combination treatment showed no significant increase in body weight as compared to the robust weight gain by therapeutic dose of rosiglitazone. Rosiglitazone at 10 mg/kg/day showed significant reduction in hematocrit, red blood cell count, hemoglobin pointing towards hemodilution associated with increased mRNA expression of Na^+, K^+-ATPase-α and epithelial sodium channel gamma in kidney. The combination therapy escaped these adverse effects. The results suggest that combination of DPP-4 inhibitor with low dose thiazolidinedione can interact synergistically to represent a therapeutic advantage for the clinical treatment of type 2 diabetes without the adverse effects of haemodilution and weight gain associated with thiazolidinediones.

DDP-4 plus metformin

The retrospective analysis by Banerji et al. found that the combination of vildagliptin and metformin in type 2 diabetic patients with mild renal impairment is safe and tolerable, similar to that in patients with normal renal function [161]. Furthermore these results were similar to those in patients receiving a combination of thiazolidinedione and metformin. Higher incidence of headache and rash was noted in both vildagliptin groups, whereas those with mild renal impairment receiving thiazolidinedione experienced a higher incidence of peripheral edema.

Mitiglinide plus voglibose

Unlike typical sulfonylurea agents, mitiglinide, a benzylsuccinic acid derivative, is a rapid- and short-acting insulinotropic sulfonylurea receptor ligand with rapid hypoglycemic action. It alleviates postprandial hyperglycemia and, as a result, improves overall glycemic control [162]. The blood concentration of mitiglinide rapidly increases after oral administration and the drug quickly disappears subsequently; therefore, it is unlikely to exert hypoglycemic

effects early in the morning and between meals. Abe et al. demonstrated that add-on therapy of mitiglinide with voglibose may be a therapeutic option for achieving good glycemic control in type 2 diabetic hemodialysis patients with otherwise poor glycemic control [86]. The daily dose of mitiglinide is suggested to be lower in the diabetic hemodialysis patients than that in the diabetic patients with normal kidney function. At low dose (23 mg), mitiglinide was adequate to induce significant reductions in glycemic parameters such as fasting plasma glucose, hemoglobin A_{1c}, glycated albumin levels and HOMA-IR. Mitiglinide also significantly improved glycemic control, triglyceride level and interdialytic weight gain even when it was administered only for a short duration [86].

8. Effects of high-flux dialyzer membranes on plasma insulin

Nowadays, several types of high-flux dialyzer membranes are on the market. The normally used ones are made from polysulfone, polyethersulfone, cellulose triacetate, polymethylmethacrylate or polyester-polymer alloy. The mechanism of plasma insulin clearance by hemodialysis is mainly by adsorption rather than diffusion or convection since no insulin is not normally detected in either the dialysate or the ultrafiltrate fluid during hemodialysis [163]. Furthermore, the amount of insulin adsorbed differed depending on the dialyzer membrane used. The insulin levels during a dialysis session depend not only on insulin removal by dialysis but also on the secretion of insulin from the pancreatic β-cells; this in turn is determined by the changes in plasma glucose induced by dialysis and the ability of the β-cells to respond to these glucose changes [163]. Therefore, it was suggested that an increase in endogenous insulin secretion may occur in response to hemodialysis treatment, in particular with the polysulfone membrane. On the other hand, plasma glucose levels at the post-dialysis stage were mainly determined by the glucose concentration in the dialysate; this is because the molecular weight of glucose is very small, and glucose rapidly transmigrates across the membrane during hemodialysis treatment. Therefore, plasma glucose levels at the post-dialysis stage should be similar in the case of polysulfone, cellulose triacetate and polyester polymer alloy membranes, regardless of the type of high-flux membrane. However, in the insulin-dependent diabetes mellitus (IDDM) subjects, who lack endogenous insulin secretion, the insulin reduction rate was significantly higher when the polysulfone membrane was used compared with the cellulose triacetate and polyester-polymer alloy membranes. This is because these patients have no residual β-cell function, which is responsible for insulin secretion; therefore, if plasma insulin was removed by hemodialysis, these cells could not have maintained the patients' insulin levels. Hence, plasma insulin removal is highly significant in the case of diabetic hemodialysis patients with low C-peptide levels, particularly those with type 1 or 2 diabetes with a deteriorated β-cell function [164]. Higher doses of injected insulin or antidiabetic agents might be added in order to achieve good glycemic control in such patients, because the surplus insulin is removed by hemodialysis, particularly when the polysulfone dialyzer is used [163]. Therefore, patient monitoring of blood glucose on the day that hemodialysis is

performed could be useful for self-assessment of glycemic state, and if hyperglycemia was recognized, and additional dose of injected insulin after hemodialysis should be considered.

Due to the development in dialyzer technology, it was found that the biocompatible dialyzer membrane used in hemodialysis patients not only causes less hemodialysis-induced inflammation but also achieves better clearance of uremic toxins and medium- to large-sized molecules [165]. Moreover, high-flux dialyzers have been shown to be superior in terms of attenuating hyperlipidemia and alleviating oxidative stress [166, 167]. There is a significant reduction in patients' plasma insulin at different time point with each type of membranes, because various biological reactions can occur in the course of contact between artificial materials and blood components in the extracorporeal circulation [163]. The clearance of plasma immunoreactive insulin (IRI), a biologically active molecule, is significantly higher in patients used polysulfone membrane than by other membranes such as polyethersulfone, cellulose triacetate, polymethylmethacrylate or polyester-polymer alloy [168]. Moreover, no clinical difference has been found in the reduction rate of IRI between hemodialysis treatments when using either polysulfone, polyethersulfone, cellulose triacetate or polymethylmethacrylate except for polyester-polymer alloy [168]. From these results, it suggests that hemodialysis patients with residual β-cell function, the course of treatment for diabetic control would be unaffected by the differences resulting from the type of membrane used. However, in diabetic hemodialysis patients, particularly in type 1 and type 2 with deteriorated β-cell function, these differences might be very significant. Higher doses of injected insulin might be required to achieve good glycemic control in hyperinsulinemic patients because the surplus insulin is removed by hemodialysis, specifically by polysulfone, polyethersulfone, cellulose triacetate or polymethylmethacrylate, excluding polyester-polymer alloy membrane dialyzer. Polysulfone membrane dialyzer may worsen glycemic control and switching to the polyester-polymer alloy membrane dialyzer which shows a lower IRI clearance rate might improve the glycemic control in hemodialysis patients.

9. Conclusion

Although diabetes is the most common cause of ESRD and diabetic control is considered as one of the most important factor to prolong patients' life and improve their quality of life, data are scarce on how diabetes should be best treated in patients with CKD or ESRD. Since the glycemic control and monitoring in CKD and ESRD patients is complex, patient education is also one of the key factors for successful treatment. Moreover, patients with diabetic nephropathy are especially susceptible to hypoglycemia and diabetic drug therapy requires special caution. Adjustment of the type of drugs used or dosage regimen should be individualized based on self-monitored blood glucose patterns.

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