DIABETIC NEPHROPATHY
Review • DOI: 10.2478/dine-2022-0006 • DINE • 1(2) • 2021 • 67–76

Insulin therapy in diabetic kidney disease

Received 12 September 2020
Accepted 20 February 2022

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Abstract

Diabetic kidney disease (DKD) is the main cause of end-stage renal disease (ESRD). The use of insulin represents a challenge in patients with DKD due to the patient and medication issues. Insulin regimens, insulin dosing, and titration need to be individualized based on the patient's age, renal function, and comorbidities to improve glycemic control and reduce the risk of hypoglycemia. Insulin is the primary treatment in all patients with type 1 diabetes mellitus (T1DM) and DKD. For patients with type 2 diabetes mellitus (T2DM) and early stage of DKD, basal insulin combined with oral antidiabetic drugs (OADs) is recommended. In patients with middle and advanced DKD, it is necessary to adjust the dose of insulin according to stages of DKD, and the use of insulin analogs is recommended. In particular, elderly patients with DKD can simplify their insulin regimen to reduce the risk of hypoglycemia. In pregnant women with DKD, insulin requirements also vary based on parity and the stage of pregnancy.

Keywords

diabetic kidney disease • hypoglycemia • insulin

1. Introduction

Diabetic kidney disease (DKD) is a chronic kidney disease (CKD) caused by diabetes, and it is one of the most frequent complications of diabetes. According to the US Renal Data System, the prevalence of CKD in 2017 was 29.1% among patients with diabetes who are aged ≥65 years [1]. DKD can progress to end-stage renal disease (ESRD), which may require renal replacement therapy. Moreover, approximately 30%–50% of ESRD cases involve a diabetic origin [2]. DKD is associated with diverse alterations in glucose and insulin metabolism [3]. Thus, glycemic management in patients with DKD poses a challenging task due to declining kidney function. Insulin is an important component of glucose-lowering therapy. At present, various types of insulin have been widely used in the treatment of DKD. The time of the initial use of insulin, the adjustment of the insulin dose, and the selection of the type of insulin represent clinical issues that need to be resolved urgently [4]. In this review, we mainly discuss the use of insulin in various stages of DKD patients and among special populations.

2. The Value of Insulin in DKD

The progression of CKD and DKD results in changes in glucose metabolism (increased insulin resistance [IR], reduced insulin secretion and insulin clearance rate). Glucose metabolism alterations in patients with CKD or DKD may be expressed as normoglycemia in combination with hyperinsulinemia, hypoglycemia, fasting hyperglycemia, or glucose intolerance depending on many variables [3]. IR is a common feature of patients with CKD or DKD. Multiple factors underlie the insulin-resistant state in CKD and DKD, including metabolic acidosis, uremia with accumulation of uremic toxins, the heightened inflammatory state, vitamin D deficiency, altered intestinal flora, and decreased adiponectin [5]. Besides, both secondary hyperparathyroidism and vitamin D deficiency associated with CKD reduce the insulin-secreting capacity of pancreatic beta cells [3]. In patients with both diabetes mellitus (DM) and advanced CKD, insulin clearance is markedly decreased. And there is increased resistance to the effects of insulin in the peripheral tissues (due to CKD) that contributes to decreased insulin clearance, leading to higher plasma insulin concentrations [6]. So there is an increased risk of hypoglycemic events in patients with advanced DKD that necessitates lowering the total daily insulin requirements.

Insulin is the primary treatment in all patients with type 1 diabetes mellitus (T1DM) and CKD. Insulin therapy in patients with DKD is characterized by two features: (1) patients suffer from a considerably increased risk of severe hypoglycemic episodes [7, 8] and (2) patients exhibit poorer metabolic control than diabetic patients with normal renal function [9]. For patients with type 2 diabetes mellitus (T2DM) and CKD, the American Diabetes Association (ADA) recommends metformin as the first-line treatment if it is not contraindicated. Other agents, including insulin, should be added to metformin [10].

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Decreased estimated glomerular filtration rate (eGFR) levels lead to altering the pharmacokinetics of glucose-lowering agents [11], increasing the risk of sulfonylurea-related hypoglycemia, biguanide-related lactic acidosis, thiazolidinedione-related water and sodium retention, and weight gain [12]. Many medications are not advised, however, dose adjustments are required in more advanced CKD. Insulin has the advantage of being effective when other agents are not, and it should be considered as part of any combination regimen when hyperglycemia is severe, especially if catabolic features (weight loss, hypertriglyceridemia, and ketosis) are present [10].

At present, various types of insulin have been widely used in the treatment of DKD. The types of insulin used clinically are classified into rapid-acting insulin analogs (insulin lispro, insulin aspart, and insulin glulisine), short-acting insulin (regular insulin), intermediate-acting insulin (neutral protamine Hagedorn insulin, NPH insulin), long-acting insulin analogs (insulin glargine and insulin detemir), and premixed insulin. Insulin analogs can simulate the physiological insulin spectrum more closely [13–15]. Besides insulin analogs exhibit better glycemic control and a lower risk of hypoglycemia compared with human insulin [15].

To achieve glycemic control, physicians have used continuous subcutaneous insulin infusion (CSII) and multiple daily injections (MDI) of insulin. In recent years, the use of CSII in T1DM and T2DM has become increasingly popular, as CSII is associated with better glycated hemoglobin (HbA1c) reduction with significantly less insulin and overall hypoglycemic events than MDI, especially in patients with poor glycemic control [16–18]. What's more, studies have shown that using CSII could reduce urinary albumin/creatinine ratio [19, 20]. Recent studies have examined the efficacy of CSII use in older patients with diabetes. Individuals on CSII exhibit better glycemic outcomes and lower rates of microalbuminuria [21, 22]. But the results were mixed for pregnant women with diabetes. Some data showed a higher rate of large-for-gestational-age neonates in the CSII group compared with the MDI group [23], but there are also data suggesting similar glycemic control and no differences in pregnancy outcome [24]. For patients, there is no consensus on which form of insulin administration is best, but attention should be paid to individualized dose titration.

3. Glycemic Targets in DKD

Based on the currently available evidence, ADA recommends an HbA1c target of <7% for most patients with diabetes. Less stringent HbA1c goals may be appropriate for patients with advanced microvascular or macrovascular complications and extensive comorbid conditions [25]. Some studies have found that <6% or >9% HbA1c increases the risk of death [26, 27]. The European Renal Best Practice also provides recommendations for HbA1c targets. For patients with CKD 3b-5, HbA1c should be controlled at ≤8.5% if they exhibit any of the following risk factors: (1) risk for hypoglycemia; (2) poor patient motivation and attitude; (3) decreased general life expectancy; (4) cardiovascular disease; and (5) presence of microvascular complications. For patients without the above risk factors, if the diabetes duration is >10 years, HbA1c should be controlled at ≤8.0%; if ≤10 years, then HbA1c should be controlled at ≤7.5% [28]. DKD is a chronic disease that may progress over time. Glycemic targets should be reevaluated over time to balance the risks and benefits.

4. Insulin Therapy in DKD G1-2

At present, data about insulin regimens, insulin dosing, and titration in patients with various stages of CKD are limited [4]. It is generally advocated that the type, dosage, and frequency of administration of insulin and oral antidiabetic agents (OADs) should be individually tailored according to the patient's renal function, life expectancy, and comorbid conditions [25]. For patients with T2DM and CKD1-2, most OADs do not need to be reduced. Charpentier *et al* [29] and the American College of Physicians recommended no change in insulin dose if GFR >50 mL/min/1.73m^2 [30]. A large number of clinical studies have demonstrated that the treatment of basal insulin combined with OADs has benefited numerous patients with DKD, and ADA has also recommended this program [10, 31, 32]. If patients with T2DM and CKD1-2 present with blood glucose levels ≥300 mg/dL (16.7 mmol/L) or HbA1c >10% (86 mmol/mol) or symptoms of hyperglycemia (i.e., polyuria or polydipsia) or evidence of catabolism, insulin therapy should be initiated based on OADs treatment. Janka *et al* [32] demonstrated that initiating insulin treatment by adding basal insulin once daily to OADs was safer and more effective than beginning twice-daily injections of premixed insulin and discontinuing OADs in type 2 diabetic patients inadequately controlled with OADs. Stepwise addition of prandial insulin is recommended in patients inadequately controlled on basal insulin plus OADs. The results of the Full STEP Study showed that stepwise prandial insulin intensification provided glycemic control non-inferior to a full basal-bolus regimen after 32 weeks with significantly lower hypoglycemia risk and improved patient satisfaction [33].

Typically, T1DM patients will require initiation with MDI of insulin at the time of diagnosis. Short-acting insulin or rapid-acting insulin analogs are typically administered 0–15 min before meals together with one or more daily separate injections of intermediate- or long-acting insulin. Two or three premixed insulin injections per day may be used [34]. Patients with T1DM and CKD1-2 can continue to use the original treatment regimen.

5. Insulin Therapy in DKD G3-5

With the development of DKD, although IR increases and renal glucose synthesis decreases, the metabolic rate of insulin decreases, resulting in prolonged insulin action, and increased risk of hypoglycemia in these patients [35, 36]. Careful assessment of the patient's daily glycemic pattern is

Review • DOI: 10.2478/dine-2022-0006 • DINE • 1(2) • 2021 • 67–76

essential, and switching from insulin to OADs that are not contraindicated in DKD would be appropriate in patients with less advanced renal disease (up to stage G3b). Targeting IR with pioglitazone is effective whose active metabolites are mainly excreted by the liver. Repaglinide can also be used because it is predominantly metabolized by the liver. Besides, it is necessary to reduce the dose of insulin to prevent hypoglycemia. For example, when GFR <60 mL/min/1.73m^2, the dose of insulin glargine and insulin detemir would be reduced by 29.7% and 27.3%, respectively [37]. The use of insulin aspart in CKD patients at different stages does not require a dose adjustment, but insulin lispro and human insulin need to be reduced when eGFR <60 mL/min/1.73m^2 [37]. According to the recommendations of the Duke University Medical Center Glycemic Safety Committee, the total daily dose typically needs to be quickly adjusted by 30%, 50%, and 60% in stages 3, 4, and 5 of CKD, respectively [38]. The American Association of Physicians suggests that when GFR is 10–50 mL/min, insulin is reduced to 75% of the total daily dose; however, when GFR is <10 mL/min, insulin is reduced to 50% [39]. Guidelines from different associations for the usage of insulin are provided in **Table 1**.

The British Association of Clinical Diabetologists and the British Association of Nephrology believe that premixed insulin may be helpful for diabetic patients with CKD3–5 who receive insulin once a day but have poor blood glucose control [40]. The International Diabetes Federation guidelines for postprandial blood glucose management suggest that premixed insulin analogs can better control postprandial blood glucose than premixed human insulin [41]. It is suggested that the adjustment of insulin type in patients with renal insufficiencies, such as the use of insulin analogs, may bring clinical benefits to patients, especially patients with CKD3-5.

Duke University Medical Center Glycemic Safety Committee	
GFR (mL/min/1.73m^2)	% reduction of TDD
≥60	No reduction
30–59	30
15–29	50
<15	60
India expert committee	
GFR (mL/min/1.73m^2)	% reduction of TDD
>60	No reduction
15–60	25
<15	50
American Association of Physicians	
GFR (mL/min/1.73m^2)	% reduction of TDD
>50	No reduction
10–50	25
<10	50

GFR, estimated glomerular filtration rate; TDD, total daily dose.

Table 1. Recommendation on insulin dose titration

Various uratoxins can act on insulin receptors, inhibit the production of the second messenger of insulin in cells, affect insulin secretion, or lead to IR [42–44]. Dialysis reduces toxins, improves peripheral IR, and decreases the need for exogenous insulin [45, 46]. For patients who have already taken the established insulin treatment regimen and started dialysis, the insulin dose should decrease to reduce the risk of hypoglycemia by closely monitoring blood glucose and readjusting the insulin dose according to the glucose value [29]. A study demonstrated that a 25% reduction in basal insulin after hemodialysis can avoid hypoglycemia [47]. However, continuous absorption of glucose from the dialysate may impair blood glucose control for dialysis patients, and the requirements for insulin increase by 2- to 3-fold [48, 49]. Intraperitoneal insulin usually leads to better blood glucose control and lower insulin demand than subcutaneous injection [50–52]. However, intraperitoneal insulin may have adverse effects on plasma lipids [51, 53]. In addition, in DKD hemodialysis patients, saxagliptin can significantly improve postprandial blood glucose and HbA1c compared with insulin [54]. Therefore, the insulin regimen of diabetic ESRD patients should be adjusted in a timely fashion after receiving dialysis treatment, and these patients should switch to noninsulin hypoglycemic drugs as appropriate.

Some diabetic dialysis patients may prefer insulin analogs [55–57]. One set of data showed that diabetic ESRD patients who maintained hemodialysis had higher levels of regular insulin and insulin analogs but a lower metabolic response to regular insulin [58, 59]. In addition, compared with regular insulin, insulin lispro has a faster effect, higher peak concentration, and shorter action time in T2DM hemodialysis patients [55, 58, 60]. In patients with type 2 diabetes undergoing hemodialysis, the glycemic variability of insulin detemir is reduced compared with that of insulin glargine [61]. In a study of peritoneal dialysis (PD), diabetic patients undergoing PD treated with insulin detemir and insulin aspart exhibited reduced HbA1c levels without significant increases in hypoglycemic events [62].

6. Hypoglycemia

The increased risk of severe hypoglycemia in patients with DKD is mainly due to the decline in renal function, the accumulation of insulin in blood circulation, and insufficient compensatory gluconeogenesis [4, 63–65]. A retrospective cohort analysis of approximately 244,000 patients with and without diabetes showed that patients with CKD exhibited an increased frequency of hypoglycemia events compared with those without CKD [66]. Severe hypoglycemia with DKD leads to the risk of premature death [67–69]. Long-term hypoglycemia can lead to brain damage, seizures, arrhythmia, coma, or death [70–74]. In addition, previous hypoglycemia can lead to a reduced response to subsequent attacks, resulting in recurrent hypoglycemic circulation [75].

Proper adjustment of the dose of hypoglycemic agents such as reduction of insulin dose, avoidance of missed meals, and self-monitoring of blood glucose (SMBG) may lower the risk

of hypoglycemia. In diabetic patients with CKD, the dosage of insulin should be adjusted according to the level of renal function to prevent hypoglycemia. In a retrospective study, Biesenbach *et al* [76]. found that patients with T2DM received insulin treatment, and the demand for insulin decreased gradually from CKD 1–5 (from 0.68 IU/(kg/day) to 0.33 IU/(kg/day)).

The risk of hypoglycemia is related to the pharmacokinetic characteristics of insulin [77, 78]. These disadvantages may be overcome by designing optimally absorbed analogs. Long-acting insulin analogs, including U300, insulin degludec, exhibit a flatter pharmacological curve with no obvious peak value, and less within-subject variation is noted compared with NPH [14, 79]. Furthermore, irrespective of kidney function, compared with glargine U300, insulin degludec has a reduction in HbA1c from baseline and a lower total daily insulin dose [80]. Rapid-acting insulin analogs have a quicker onset and peak and shorter duration of action, and are not prone to hypoglycemia before the next meal compared with regular human insulin [58, 60, 81, 82]. Insulin lispro, aspart, and glulisine do not exhibit obvious pharmacokinetic changes even in patients with severe renal insufficiency [57, 58, 83]. In insulin-treated T2DM, compared with biphasic insulin aspart 30 twice daily, insulin degludec/insulin aspart 70/30 twice-daily can improve long-term glycemic control with a lower dose and less nocturnal hypoglycemia [84, 85]. Switching from basal insulin to Insulin Degludec/Insulin Aspart (Ryzodeg) does not increase the burden on patient, and is more effective in reducing blood glucose after dinner and before bedtime without increasing the incidence of hypoglycemia [86]. Regardless of T1DM or T2DM, oral insulin agent ORMD-0801 can reduce HbA1c without increasing the risk of hypoglycemia [87, 88], but its effect in DKD needs to be further explored.

Besides avoiding hypoglycemia, considerations for DKD management include a desire to mitigate the high risks of CKD and CVD progression. Intensive diabetes education and care management can be effective in providing significant improvements in patient outcomes, glycemic control, and better quality of life [89]. Patient SMBG may help with self-management and medication adjustment, particularly in individuals taking insulin. Glucose monitoring allows patients to evaluate their response to therapy and assess whether glycemic targets are being safely achieved [25]. For patients with T2DKD, some glucose-lowering medications having effects on the kidney that are direct, not mediated through glycemia could be prioritized, such as SGLT2 inhibitors and GLP-1 RAs [90].

7. Insulin Treatment in Special Populations

7.1. Insulin in elderly patients with DKD

Age is an important risk factor for renal damage and severe hypoglycemia [91–93]. Progressive renal insufficiency, strict glycemic control, unexpected weight loss, and failure to adjust drug doses make elderly patients with DKD at higher risk of hypoglycemia [94–99]. The continued use of insulin in elderly people with a high risk of hypoglycemia and limited future benefits suggests that insulin treatment options need to be adjusted to reduce the risk of hypoglycemia. When patients find that the complexity of insulin therapy is beyond their self-management ability, reducing the insulin dose may not be sufficient, so it is necessary to simplify the insulin treatment plan based on the individual situation of the patient [34, 100, 101].

Basic insulin injection therapy once daily may be a reasonable choice for many elderly patients if the glycemic target can be met [34, 101–103]. In a prospective study, patients with T2DM over the age of 70 simplified their treatment by switching to basal insulin plus noninsulin preparations once daily [31]. The simplified insulin regimens reduced the risk of hypoglycemia without affecting blood glucose control, and patients also noted improvements in diabetes-related pain [31, 101, 104, 105]. The use of a mixed insulin regimen one, two, or three times a day may increase the risk of hypoglycemia and limit diet and lifestyle flexibility [106, 107]. Janka *et al* [106] found that injecting insulin glargine once a morning was a simple and effective method for elderly type 2 diabetic patients with poor oral drug control, and this regimen can more effectively control glucose and reduce the risk of hypoglycemia compared with the use of 70/30 twice a day alone.

If elderly patients receive basal insulin at bedtime, then the injection time should be postponed until morning [101, 108]. Postprandial blood glucose contributes more to overall hyperglycemia than fasting blood glucose in elderly patients [109]. Thus, administering basal insulin in the morning is more tolerable, and higher doses of insulin can be used to titrate to fasting blood glucose levels and reduce the risk of early-morning hypoglycemia [108]. Saudek *et al* [110] suggested not using too much NPH insulin before dinner given that its activity tended to peak in the middle of the night, leading to hypoglycemia at night and uncontrolled blood glucose in the morning.

Patients with large postprandial blood glucose fluctuations may require rapid-acting insulin analogs [101, 108]. The insulin dose should be tailored according to the amount of carbohydrates taken at meals. The World Journal of Diabetes recommends that if meal consumption is reduced by 50%, the insulin should be reduced by 50%; if the meal consumed is small or if there is no meal due to medical intervention, insulin will not be given or reduced to 25% [111]. However, rapid-acting insulin needs to take into account the patient's cognitive ability and support system [101, 112].

7.2. Insulin in pregnant patients with DKD

Proper control of maternal blood glucose levels during pregnancy can improve maternal and fetal outcomes in DKD pregnant patients [113–117]. Although the use of insulin

can cause maternal hypoglycemia [118–120] and increase maternal weight [121–123], it has been shown that insulin when used at therapeutic concentrations does not directly affect the fetus through the placenta [124–126], and maternal insulin treatment can reduce poor perinatal prognosis [113, 115]. Oral hypoglycemic drugs, such as metformin and glibenclamide, will have some benefits on weight control and insulin sensitivity [127, 128], but they can cause giant fetuses and skeletal malformations by entering the fetus through the placenta as well as maternal complications due to the massive transfer between the placenta or ineffective blood glucose control [129–132]. Therefore, insulin may be the first choice of hypoglycemic drugs for patients with DKD during pregnancy.

During pregnancy, most diabetic patients use a multidose insulin regimen, which includes rapid-acting insulin up to three times a day and medium-/long-acting insulin [133]. Ideally, pregnant women should receive basic or bolus insulin treatment. The basal insulin dose should be <50% of the total daily dose, and prandial insulin matched with mealtime and size should be >50% [134]. Premixed insulin is also a suitable choice. Premixed insulin analogs and premixed human insulin exhibit no significant differences in glycemic control or fetal outcome [135, 136].

During pregnancy, insulin requirements also vary with parity and the stage of pregnancy. Insulin demands increase with parity [137]. In the first 3 months, women with diabetes treated with insulin may reduce insulin requirements [129, 134, 138, 139]. During this period, glucose control is more unstable with a trend of reduced fasting blood glucose and increased postprandial drift and nocturnal hypoglycemia [113, 140]. Thus, it is common to reduce the dose by approximately 10% compared with that before pregnancy [113]. Given that IR increases exponentially in the second and early third trimesters of pregnancy, this situation is quickly reversed by approximately 16 weeks [129, 134, 138]. At the end of the third trimester of pregnancy, the requirement for insulin tends to stabilize or decrease slightly with placental aging [141].

The incidence of hypoglycemia, especially nocturnal hypoglycemia, increases in diabetic women in the first trimester of pregnancy [142, 143]. An Endocrine Society Clinical Practice Guideline recommends that diabetic women who receive insulin therapy and want to conceive should be treated with insulin lispro or insulin aspart instead of regular insulin, and those who successfully used long-acting insulin analogs before pregnancy can continue to use this treatment during pregnancy [144]. Studies have shown that the use of insulin detemir can improve fasting blood glucose levels and reduce the incidence of hypoglycemia without increasing the incidence of adverse pregnancy and drug reactions in pregnant women with diabetes [145–149]. A randomized controlled study reported no nocturnal hypoglycemia in the detemir group, and hypoglycemia occurred before lunch; however in the NPH group, hypoglycemia was irregular, and nocturnal hypoglycemia threatened the safety of the fetus [147].

A large randomized controlled trial showed that when using a basal-bolus therapy with NPH insulin in pregnant women with type 1 diabetes, insulin aspart could better control postprandial blood glucose and prevent severe hypoglycemia compared with human regular insulin [150]. Compared with regular insulin, insulin lispro reduces the rates of neonatal jaundice [151], the peak of postprandial blood glucose fluctuation [152], maternal hypoglycemia, and the total demand for insulin during pregnancy [153]. Given the rapid development of proliferative diabetic retinopathy, Kitzmiller *et al*. suggest that insulin lispro should be used cautiously in pregnant women who may have severe preexisting retinal ischemia [154]. However, a prospective, open study observed no difference in the progression of retinopathy [155].

8. Conclusion

Insulin therapy is an adequate option for improving glycemic control in DKD. However, a variety of factors, such as renal insufficiency and concomitant therapy (drugs, dialysis, and immunosuppressive therapy), may make insulin therapy challenging. Decreased renal function will alter the clearance and metabolism of insulin, and too strict glycemic control will increase the risk of hypoglycemia, especially in the elderly and patients with severely impaired renal function. Factors, such as different stages of DKD and pregnancy also make insulin treatment more difficult. Therefore, closely monitoring blood-glucose levels, carefully formulating individual blood-glucose control targets and individual insulin doses, educating different patients, and improving the vigilance of hypoglycemia are all essential elements of DKD management.

Source of Funding

This work was supported by the National Natural Science Foundation of China (81730018) and the National Key R&D Program of China (2018YFC1314002).

Conflict of interest

Lin Sun is an Editorial Board Member of the journal. The article was subject to the journal's standard procedures, with peer review handled independently of this editor and his research groups.

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