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HOSPITAL MANAGEMENT OF DIABETES (A WALLIA AND JJ SELEY, SECTION EDITORS)

Inpatient Glycemic Management in the Setting of Renal Insufficiency/Failure/Dialysis

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Abstract

Purpose of this Review Chronic diabetic nephropathy and renal dysfunction from other causes are common in hospitalized patients with diabetes. Available diabetes management guidelines aim to reduce hyperglycemia and hypoglycemia, both independent risk factors for hospital outcomes. Renal dysfunction, which increases the risk of hypoglycemia, adds a layer of complexity in diabetes management. Therefore, modified glucose goals and treatment regimens may be required.

Recent Findings Recent prospective and retrospective studies provide direction on safe insulin therapy for diabetes inpatients with renal compromise. Studies of newer diabetes pharmacotherapy provide data on oral agent use in the inpatient setting.

Summary Diabetes therapy should be modified with changing renal function. Glucose management in patients on peritoneal or hemodialysis is challenging. Reducing weight-based doses of insulin and use of newer insulins can reduce hypoglycemia risk. Safety and efficacy of DPP-4 inhibitors has been evaluated in the hospital and nursing home setting. Metformin, SGLT-2 inhibitors, and GLP1 receptor agonists can be used in several stages of renal dysfunction prior to and at discharge.

Keywords Inpatient diabetes · Insulin management · End-stage renal disease · Hemodialysis · Peritoneal Dialysis · Antidiabetic agents

Introduction

Renal disease is a frequent microvascular complication of diabetes, with diabetic nephropathy being the most common cause of chronic kidney disease and end-stage renal disease (ESRD), requiring dialysis in up to 50% [1, 2]. In an observational study of diabetes patients, up to 29% of those admitted to the hospital experienced one episode of acute kidney injury increasing the cumulative risk of progression to end-stage renal disease [3]. This necessitates close glucose follow-up as decreasing glomerular filtration rate (GFR) is a known risk factor for hypoglycemia. In addition, several diabetes medications, including insulin, need dose-adjustment as renal function declines.

Hyperglycemia and hypoglycemia are now well-established independent risk factors for inpatient outcomes, and guidelines for inpatient management from various societies are available [4, 5]. Currently, specific glucose management regimens in renal dysfunction are not well-evaluated, as there is a paucity of robust prospective studies in this setting. Renal dysfunction adds a layer of complexity to diabetes management as it increases the risk of hypoglycemia. In a recent Veterans Affair study, when serum creatinine increased by 50% from baseline, the risk of hypoglycemia after discharge increased by 27% [6•].Therefore, the management is challenging and modified glucose goals and regimens are needed.

Several recent reports show encouraging data of reduced rates of renal dysfunction in type 1 diabetes patients [7], likely attributed to RAAS blockade with angiotensin-converting enzyme inhibitors (ACE-Is) or angiotensin II receptor antagonists (ARBs). Unfortunately, the incidence of nephropathy in T2DM continues to rise and makes diabetes the most common

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cause of ESRD. There has been an explosion in diabetes pharmacotherapy over the last few years. Newer diabetes drugs are safe in renal dysfunction, and some may need dose-modification for appropriate stages of renal failure. Several of these drugs, including SGLT-2 inhibitors and GLP-1RAs, have been shown to reduce progression of renal dysfunction in diabetes [8•, 9•], though require appropriate dose modification per FDA recommendations (Table 1). The DPP-4 inhibitors have been evaluated in the treatment of diabetes in the hospital and nursing home setting, and in the transition from hospital to home. Insulin remains the gold standard for diabetes therapy in hospitalized patients. Recent studies, both prospective and retrospective, have evaluated safe insulin doses and timing of insulin therapy in the hospitalized patient with diabetes and renal compromise.

This review aims to focus on the importance of considering renal function in managing inpatient diabetes and also provides an update on insulin dosing, with guidance on insulin therapy in peritoneal and hemodialysis. We additionally review the use of newer agents in diabetes management in the inpatient setting.

Pathophysiology The pathophysiology of renal dysfunction and glucose metabolism is complex and involves several different mechanisms. Endogenous insulin enters the blood stream via the portal vein and has a half-life of 3 to 7 min with the liver being the main site of clearance. The kidney has a secondary role in the metabolism of endogenous insulin; however, it is the main site for exogenous insulin metabolism which bypasses the liver and directly enters the systemic circulation (40–60%). Therefore, renal function directly affects the metabolism of injected insulin for treatment of diabetes mellitus. Insulin clearance is further reduced in renal failure, especially when the glomerular filtration rate is less than 15–20 ml/min. Hepatic clearance may also be affected due to the presence of early insulin resistance in renal failure and uremic toxins in ESRD.

Insulin resistance commonly occurs in patients with ESRD. The mechanism is not well-known, but given that adipose tissue accounts for less than 2% of the glucose load, skeletal muscle is most likely the primary site of resistance [10]. In the uremic patient, impaired degradation of insulin in liver and muscle contributes to insulin's prolonged half-life—there is some evidence that this toxin is pseudouridine [11]. Accumulation of dialyzable uremic toxins with progressive loss of renal function may cause further inhibition of the insulin degradation system, particularly by the liver which removes approximately 50% of the insulin secreted into the portal circulation [10].Changes in calcium metabolism that occur with uremia may also contribute to decreased insulin secretion [12]. Hyperparathyroidism and/or vitamin D deficiency is often seen in patients with ESRD and may cause abnormal insulin secretion in these patients [13, 14]. Together, these factors may lead to a compensatory rise in insulin secretion as observed in one recent study, which found higher insulin resistance with resultant increased insulin production in patients with ESRD and no diabetes on a transplant waiting list, compared to a normally matched cohort without ESRD [15]. When patients are not eating, the liver produces glucose via glycogenolysis and gluconeogenesis (75 and 25%). However, uremia can cause nausea and loss of appetite, thus reducing glycogen stores. Approximately 20% of gluconeogenesis occurs in the kidney, which is further reduced in ESRD. These factors combined make patients prone to fasting hypoglycemia.

Challenges in Management

Blood Glucose Goals

In view of hypoglycemia risk, blood glucose (BG) goals need to be modified in patients with ESRD and renal insufficiency. A 2018 retrospective review of 150 hospitalized patients with T2DM receiving hemodialysis found over half experienced glucose values less than 70 mg/dL, and 11% experienced hypoglycemia with BG less than 40 mg/dL [16•].The 2018 American Diabetes Association standards of care recognize less stringent HbA1c goals of less than 8.0% (estimated average glucose 183 mg/dL or 10.1 mmol/L) may be warranted for patients at risk for hypoglycemia [17]. It is also well-known that uncontrolled diabetes in patients with renal dysfunction increases mortality. A large Canadian study of over 23,000 patients with estimated GFR less than 60 mL/min identified a U-shaped mortality curve with HbA1c levels less than 6.5% or greater than 8.0% [18], suggesting a BG goal between these values may be ideal. There was no significant increase in mortality between HbA1c 7.5 to 8.4%, particularly in younger patients, further supporting modified glycemic targets [19]. It is appropriate to conclude a HbA1c range between 7.0 and 8.0% may be most beneficial in patients with T2DM and ESRD, with a suggested BG goal of approximately 154–183 mg/dL and up to 200 mg/dL for intravenous insulin in hospitalized diabetes patients [20].

Monitoring Glycemic Control

There are several diagnostic tests that can be used to determine a patient's glycemic control. These tests include HbA1c, fructosamine, and glycated albumin. Each has its own limitations in renal dysfunction.

The relationship between HbA1c and renal failure is complex. Factors that affect glycation rate include temperature, pH, hemoglobin concentration, glucose concentrate, and the length of exposure to glucose [21]. Uremia can also interfere with accurate measurement of HbA1c by the formation of

Table 1 Dose adjustments for antidiabetic agents in renal dysfunction

Class	Drug name	Dosing adjustments by GFR (mL/min)			
		> 60	45–60	30–45	< 30
Biguanides	Metformin	No change. Monitor annually	No change. Monitor every 3–6 months	Can continue but do not initiate. Consider 50% dose reduction, monitor every 3 months	Contraindicated
Sulfonylureas	Glipizide	Safe in renal impairment, initial dose of 2.5 mg to reduce risk of hypoglycemia			
	Glyburide	No change	Long-acting sulfonylureas contraindicated due to risk of hypoglycemia		
	Glimeperide	No change			
Glinides	Repaglinide	No change		0.5 mg with one or two meals daily	Not studied with eGFR < 20 mL/min
	Nateglinide	No change			60 mg three times daily with meals. Can be used in HD as active metabolite is cleared
Thiazolidinediones	Pioglitazone	No dose-adjustment with renal dysfunction, but cautious use due to bone loss			
SGLT-2 inhibitors	Canagliflozin	No change	Maximum dose 100 mg daily		Contraindicated
	Dapagliflozin	No change	Initiation not recommended		Contraindicated
	Empagliflozin	No change	No change		Contraindicated
GLP-1 receptor agonists	Exenatide	No change	Use with caution. Initiation not recommended		Contraindicated
	Liraglutide	No dose changes necessary. Use with caution in renal impairment due to nausea and emesis			
	Albiglutide				
	Dulaglutide				
DPP-4 inhibitors	Sitagliptin	No change		50 mg daily	25 mg daily
	Saxagliptin	No change		2.5 mg daily	2.5 mg daily
	Linagliptin	No change			
	Alogliptin	No change	12.5 mg daily	12.5 mg daily	6.25 mg daily

DPP-4 dipeptidyl peptidase 4; *GFR* glomerular filtration rate; *GLP-1* glucagon-like peptide 1; *HD* hemodialysis; *SGLT-2* sodium-glucose cotransporter 2

carbamylated hemoglobin [22]. Metabolic acidosis additionally increases the rate of formation of HbA1c. Other factors that influence HbA1c levels in patients on dialysis include blood transfusions, anemia, a shortened erythrocyte life span, and routine use of erythropoietin [21].

Similarly, point-of-care (POC) glucose testing in the hospital is standard and can be influenced by multiple factors, particularly in patients with renal dysfunction. Anemia or polycythemia may result in falsely low or falsely elevated glucose recordings, respectively. Hypotension results in hypoperfusion and blood stagnation, with correlating low glucose recordings. Low pH (< 6.95) in the critically ill patient can lead to falsely low POC testing; similarly, elevated pH levels can give a falsely high reading [23]. With regard to renal dysfunction, it is well-studied that patients receiving peritoneal dialysis with icodextrin can have falsely elevated glucose recordings with meters utilizing glucose dehydrogenase pyrroloquinoline quinone (GDH-PQQ) reactions [24, 25] resulting in severe hypoglycemia due to inappropriate insulin dosing. The majority of GDH-PQQ meters have mostly been phased out of the hospital setting, but this correlation with elevated glucose recordings is important for all health care providers to be aware of. The gold standard for glucose measurement is by lab analysis; however, this often does not result in real-time measurements. Acceptable levels of glucose meter variation compared to laboratory analysis vary by organization, with ± 20 mg/dL (1.1 mmol/L) per the FDA and ± 15% per the American Diabetes Association [23].

Fructosamine is a general measure of glycated serum protein. It correlates with measurements of mean blood glucose and HbA1c and, therefore, has been suggested as an alternative measurement of glycemic control [26]. Fructosamine is not influenced by anemia or variant hemoglobin complexes, and its measurement represents glycemic control over a 2- to 3-week period as compared with 3 months for HbA1c [27]. However, fructosamine levels are influenced by serum protein concentrations and by low molecular weight compounds in the plasma (bilirubin, albumin, uric acid) [28, 29] and may be falsely low in low-protein states including nephrotic syndrome or liver disease. Conversely, it may increase in states of higher protein turnover, such as dialysis [30].

Glycated albumin is unaffected by hemoglobinopathies and can be a more accurate measurement of glycemic control in renal dysfunction than fructosamine [31, 32]. Increased glycated albumin in diabetic patients with ESRD is also associated with diabetic complications including increased

cardiovascular mortality and decreased survival [33, 34].However, there are still limitations for the use of glycated albumin for glycemic control. Data on therapeutic targets is minimal, and variability exists in high albumin turnover states, such as patients with proteinuria or on peritoneal dialysis.

Management

Insulin Therapy in Renal Disease

A limited number of studies evaluate insulin management in patients with varying degrees of renal impairment, and they are primarily confined to outpatient encounters and dialysis centers, but more studies are emerging. Practical applications can be transitioned to inpatient management. Fluctuating glucose control surrounding variable inpatient dialysis schedules and dietary restrictions significantly influence treatment regimens. Additionally, dialysate formulations in hemodialysis (HD) and peritoneal dialysis (PD) can impact glucose control. Insulin is used exclusively in hospitalized patients with diabetes mellitus requiring dialysis. It is important to monitor the patient's blood glucose level sequentially with the patient's kidney function and adjust the insulin dose to prevent hypoglycemia. In general, it has been recommended that when the GFR declines to between 10 and 50 mL/min, the insulin dose should be decreased by 25%. When the GFR decreases to less than 10 mL/min, the insulin dose should be reduced by 50% [35]. Here, we review recommendations for insulin management in accordance with renal dysfunction.

CKD Stages I and II (eGFR > 60 mL/min)

Insulin dose-adjustments are generally not required for patients with creatinine clearance (CrCl) above 60 mL/min. In the hospitalized setting, special considerations must be taken into account for dietary restrictions or NPO status, requiring up to a 25–30% reduction in basal insulin [36, 37]. Additionally, the use of total parenteral nutrition (TPN) or glucocorticoids may prompt the need for higher doses and basal bolus insulin therapies.

CKD Stages IIIa, IIIb, and IV (eGFR 15–59 mL/min)

Reductions in total daily insulin requirements by 50% (from 0.5 units/kg to 0.25 units/kg) in 107 hospitalized diabetes mellitus patients with eGFR < 45 mL/min receiving glargine and glulisine at three institutions have been shown to reduce the frequency of hypoglycemic events without compromising control of hyperglycemia [38]. We recommend for insulin-naïve patients with eGFR < 60 mL/min a starting total daily insulin dose of 0.2–0.3 units/kg/day in accordance with the Endocrine Society standards of care [4]. Patients with eGFR < 50 mL/min may consider a total daily insulin reduction of 25–50% [35]. Fifty percent of the total daily dose can be used for basal insulin and 50% for prandial insulin, further divided by a factor of three to account for three meals per day. A correctional insulin component should be added with mealtime insulin to account for hyperglycemic variability. Prandial insulin should be held if the patient is NPO. Factors that influence further insulin reduction include dietary restrictions, poor appetite, and pending procedures. Certain prandial insulins, namely insulin aspart, may not require any dose reduction. A study of 346 patients with T1DM found no association between aspart doses and eGFR, though a 33% reduction in lispro was necessary for patients with eGFR < 60 mL/min compared to those with eGFR > 90 mL/min [39]. Patients with stable renal function who demonstrate adequate glucose control with rare hypoglycemic events at home may not require changes to insulin therapy upon admission depending on clinical context.

CKD Stage 5/ESRD (eGFR <15 mL/min)

Insulin requirements are further decreased once the patient starts dialysis as peripheral insulin resistance improves after initiating dialysis [35]. Patients receiving peritoneal dialysis can receive insulin directly in the dialysate. This is more reliable and physiologic delivery than subcutaneous delivery of insulin and results in fewer hypo- and hyperglycemic episodes [40].

Hemodialysis

Sobngwi et al. demonstrated using a euglycemic clamp that outpatients required a 25% reduction in basal insulin up to 24 h after hemodialysis (HD) with no change in bolus requirements [41]. A previous, smaller study observed insulin analogues reach peak concentration faster than human insulin with a shorter duration of action and more rapid metabolism when given at the onset of hemodialysis [42]. This offers an explanation for prandial insulin dosing to remain relatively less affected than basal insulin with renal impairment. Few studies have gone further to suggest equal efficacy of basal-only versus prandial-only insulin regimens [43]; however, due to variability of inpatient dietary status and timing of dialysis, we recommend utilizing a combination of basal-bolus regimen.

Basal insulin regimens studied in ESRD include NPH, detemir, glargine, and degludec. Patients switching from twice daily NPH insulin or pre-mixed insulin to once daily glargine at equivalent or reduced doses were demonstrated to have an improvement in HbA1c and 96% less hypoglycemic episodes, with increased patient satisfaction [44]. The previously stated reduction in basal insulin requirements up to 24 h after dialysis additionally

suggests different insulin regimens may be needed on dialysis versus non-dialysis days. Some institutions have demonstrated improved glycemic control with basal insulin only on dialysis days (three times weekly), administered by the dialysis team [45]. This has not been reported in the inpatient setting and is likely difficult to achieve due to variable dialysis schedules. We recommend a 50% reduction in glargine for patients admitted to the hospital requiring acute dialysis. Patients admitted for non-renal causes receiving maintenance hemodialysis may not require dose changes.

Degludec is another basal insulin with an ultra-long duration of action exceeding that of glargine. Pharmacokinetic studies have demonstrated its half-life to exceed 25 h and achieve a steady state within 3 days and cause less nocturnal hypoglycemia. Degludec is dosed daily with its glucose-lowering properties shown to last over a 42-h period [46]. In one study, 30 subjects with varying degrees of renal impairment, including ESRD on hemodialysis, received a single dose at 0.4 units/kg and demonstrated no statistical difference in total exposure to degludec between 0 and 120 h [46].

Jacobsen et al. demonstrated in a small study administering 1.2 nmol/kg of insulin detemir in patients with varying degrees of renal dysfunction showed no statistical difference in the area under the curve (AUC) over 24 h [47]. Therefore, degludec and detemir can be used in dialysis patients at an appropriate dose to maintain adequate BG levels in patients with CKD.

Regarding prandial insulin, a small study observed insulin analogues reach peak concentration faster than human insulin with a shorter duration of action and more rapid metabolism, resulting in fewer hypoglycemic episodes in patients receiving HD [42]. Holmes et al. demonstrated a subset of T2DM patients with eGFR < 30 mL/min receiving aspart had no significant difference in pharmacokinetic parameters than those with eGFR > 50 mL/min [48]. This was further corroborated by the previously mentioned study of 346 patients with T1DM [39]. We recommend utilizing insulin analogues rather than regular insulin with meals. Dose reductions of insulin lispro and glulisine may be required as opposed to insulin aspart.

Asymptomatic hypoglycemia is a feared complication in patients on HD [49].Utilization of glucose-containing dialysate versus glucose-free dialysate is thought to avoid this complication [50], with lower concentrations of glucose in dialysate (100 mg/dL vs. 200 mg/dL) helping to avoid the opposite spectrum of significant hyperglycemia after HD [51]. In a recent retrospective review, hospitalized patients with ESRD receiving weight-based insulin doses greater than 0.23 units/kg/day had a much higher risk of hypoglycemia. Hypoglycemia was more common in the morning before dialysis than after dialysis, and the total daily dose (TDD) of insulin rather than timing of the dose was the more important predictor of hypoglycemia [16•]. Patients with T1DM are more at risk than those with T2DM; thus, careful attention and lower insulin doses may need to be utilized for these patients.

Peritoneal Dialysis

Peritoneal dialysis can have significant effects on BG variability depending on the type of dialysis and dialysate used. Types of peritoneal dialysis include continuous ambulatory peritoneal dialysis (CAPD) and continuous cycling peritoneal dialysis (CCPD) or automated peritoneal dialysis (APD). The former requires manual exchanges of dialysate versus the latter which utilizes a machine to automate dialysis exchanges. Dialysate options include higher and lower dextrose concentrations (4.5 and 2.5%, respectively) and icodextran. Dialysate concentrations are typically labeled by color, where patients may often know the color but not the concentration of their specific dialysate (Table 2). Extrapolating data from ambulatory centers, intraperitoneal delivery of regular insulin is superior to subcutaneous insulin administration [52]. This may be explained by direct access of insulin to portal circulation. However, higher insulin doses are required due to mechanical adsorption, dilution within the dialysate, and loss of insulin in the peritoneal cavity [53]. Doses are typically double that of subcutaneous insulin. Addition of a subcutaneous insulin correction scale is recommended with intraperitoneal insulin. Glucose monitoring should occur before and after each PD cycle. Peritonitis can be a complication of intraperitoneal insulin—reported rates are not higher with intermittent PD but may be slightly higher in continuous PD [53]. Other complications of focal hepatic necrosis and subcapsular steatosis have been reported.

Dosing of subcutaneous insulin with PD is again dependent on the dextrose concentration in the dialysate and timing of PD cycles. NPH insulin given at the start of nocturnal PD, or regular insulin administered at the start and 6-h post-initiation, may be sufficient to stabilize glycemic trends. A starting dose of 10% TDD can be given for 2.5% dextrose concentrations, or 20% TDD for 4.5% dextrose concentrations. Special attention should be given to glucose monitoring after PD as patients can be insulin-sensitive and prone to hypoglycemia during this time. Patients utilizing icodextran will have falsely elevated glucose values on glucometers using glucose dehydrogenase pyrroloquinoline-based reactions, though the majority of these have been phased out of the hospital setting [24, 25].

Table 2 Peritoneal dialysis concentrations

1.5% Dextrose	Yellow
2.5% Dextrose	Green
4.25% Dextrose	Red

Non-Insulin Antidiabetic Agents

In the hospitalized setting, we recommend discontinuation of all non-insulin antidiabetic agents (ADAs) in accordance with the American Diabetes Association standards of care until more data is available [17]. Optimization of glycemic control in an acute setting can be difficult to achieve with non-insulin ADAs and is often limited by side effects. However, certain clinical scenarios exist where continuation of non-insulin ADAs may be reasonable and beneficial.

Incretin-based therapies, specifically DPP-4 inhibitors, are being studied in the inpatient setting with potential benefits of improving glycemic control, avoiding hypoglycemia, and simplifying therapy by reducing number of prandial insulin injections. An initial pilot study in 2013 by Umpierrez et al. found in hospitalized patients with moderate glucose control (defined as total daily insulin use < 0.4 units/kg/day, fasting glucose < 180 mg/dL, and HgbA1c < 7.5%) no differences in patients using sitagliptin alone versus in combination with glargine or basal-bolus insulin alone [54]. This was later corroborated in a multi-center, prospective randomized trial in hospitalized patients utilizing less than 0.6 units/kg/day total daily insulin. The DPP-IV inhibitor sitagliptin in combination with glargine demonstrated non-inferiority compared to basal-bolus insulin regimens [55•]. DPP-IV inhibitors need to be dose-adjusted for eGFR (sitagliptin, alogliptin, saxagliptin), and some can be used without dose modification (linagliptin) in patients with renal impairment. The use of saxagliptin has been evaluated in the inpatient setting for patients with eGFR > 50 mL/min and found to be non-inferior to basal-bolus insulin in T2DM patients treated with diet control or up to two oral agents without insulin prior to admission [56•]. A trial of linagliptin in 280 hospitalized post-surgical patients compared to basal bolus insulin and showed equal efficacy in treatment of mild-to-moderate hyperglycemia, and notably significantly less hypoglycemia (12% vs. 2%) [57•]. Recently, data on the use of linagliptin in long-term care facility/nursing home patients was published. It compared the use of linagliptin at 5 mg daily versus basal bolus insulin at 0.1 units/kg/day plus correction scale in nursing home residents with T2DM and eGFR > 45 ml/min. BG control was not significantly different between groups, but there were significantly fewer BG levels less than 70 mg/dL in the linagliptin group [58•].

Intravenous GLP-1RAs have been evaluated in the inpatient setting and show adequate improvement in BG levels when compared to IV insulin. They do have a high incidence of nausea and are very expensive [59, 60]. Subcutaneous GLP1-RA use in the hospital is currently under investigation. Injectable GLP-1 agonists, however, are used with caution in renal impairment due to increased risk of nausea and vomiting, with exenatide contraindicated in ESRD. In the ambulatory setting, liraglutide was efficacious in patients with moderate renal impairment (eGFR 30–59 mL/min) without further decline in renal function [61•]. Further studies are needed in the inpatient setting to observe potential benefits in patients with renal dysfunction.

Long-acting sulfonylureas such as glimepiride and glyburide can cause prolonged hypoglycemia in patients with renal insufficiency, and hospital admission may be an opportunity to alter therapy. Glyburide should not be administered to patients with a creatinine clearance less than 30 mL/min due to accumulation of metabolites that have some hypoglycemic activity. Out of the sulfonylureas, glipizide is the best option in patients with T2DM and ESRD.

Metformin can be restarted in preparation for discharge home. Newer FDA guidelines replace serum creatinine with eGFR as a measure of renal function to allow more patients with mild-to-moderate renal impairment gain its benefits. FDA guidelines state that metformin is contraindicated in patients with eGFR < 30 mL/min, and continued use in patients with eGFR between 30 and 45 mL/min should be monitored. However, a recent 2018 study demonstrated the safety of metformin at specific doses in moderate-to-severe renal impairment. Three complementary studies were performed identifying safe dosing limits in CKD stages 3 and 4 in addition to investigating pharmacodynamics and observing chronic metformin use in this population. They recommend doses of 1.5 g (500 mg/morning and 1000 mg/evening) in CKD stage 3a and 1.0 g (500 mg/morning and 500 mg/evening) in CKD stage 3b, with measurement of GFR every 6 months. Elevations in lactate > 5 mmol/L or two consecutive measurements > 2.5 mmol/L were indications to hold further metformin [62•]. Metformin was studied further in CKD stage 4, with promising results though more data is needed. For inpatient procedures, metformin is recommended to be stopped for 48 h after an iodinated contrast imaging procedure in patients with an eGFR < 60 mL/min/1.73 m^2 or a history of liver disease, alcoholism, heart failure, or in those receiving intra-arterial contrast. GFR should be re-evaluated before treatment is restarted [63].

Conclusion

Managing hospitalized patients with diabetes and chronic renal disease poses challenges with glucose management especially in terms of balancing hyperglycemia with the increased risk of hypoglycemia. Therefore, glucose goals need to be modified to higher ranges. Recent studies suggest weight-based dosing of 0.2–0.3 units/kg with the lower end of this range recommended for patient with ESRD. Emerging data on DPP-4 inhibitors is promising and suggests they are safe and efficacious for BG management in the inpatient setting when used with or without basal insulin and have low risks of hypoglycemia.

Compliance with Ethical Standards

Conflict of Interest Ravi Iyengar, Jennifer Franzese, and Roma Gianchandani declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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