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Novel approaches to hypoglycemia and burnt-out diabetes in chronic kidney disease

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Purpose of review
Diabetes mellitus is a leading cause of chronic kidney disease (CKD) that confers faster kidney disease progression, higher mortality, and various metabolic derangements including hypoglycemia.

Recent findings
Even in the absence of diabetes mellitus, growing research demonstrates that CKD patients are at heightened risk for hypoglycemia via multiple pathways. In CKD patients transitioning to end-stage renal disease (ESRD), spontaneous resolution of hyperglycemia and frequent hypoglycemia resulting in reduction and/or cessation of glucose-lowering medications are frequently observed in a phenomenon described as 'burnt-out diabetes'. In non-CKD patients, it is well established that hypoglycemia is causally associated with mortality, with pathways including arrhythmias, sudden cardiac death, stroke, and seizures. Increasing evidence shows that, in CKD and ESRD patients with and without diabetes mellitus, hypoglycemia is associated with cardiovascular complications and mortality risk.

Summary
Given the high prevalence of hypoglycemia in CKD patients and the morbidity and mortality associated with this metabolic complication, a multimodal strategy is needed to prevent dysglycemia, including individualization of glycemic targets, selection of glucose-lowering medications less likely to induce hypoglycemia, medical nutrition therapy administered by trained dietitians, and accurate and precise hypoglycemia detection methods, such as self-monitored blood glucose or continuous glucose monitoring including during dialysis treatment.

Keywords
burnt-out diabetes, chronic kidney disease, end-stage renal disease, hypoglycemia

INTRODUCTION: BURDEN OF DIABETES AND CHRONIC KIDNEY DISEASE

According to the Center for Disease Control and Prevention (CDC) National Diabetes Statistics Report, over 34 million adults suffer from diabetes (i.e. 13% of adults in the United States, among whom over 7 million are undiagnosed (i.e. 21% of United States adults with diabetes) [1]. Epidemiologic data also show that there is a higher prevalence of diabetes among patients of older age and of minority background (i.e. age-adjusted prevalence 15, 13, 12, 9, and 8% in United States adults of American Indian/Alaskan Native, Hispanic, African-American, Asian, and Caucasian backgrounds, respectively) [1].

As one of the most prevalent diabetic complications, chronic kidney disease (CKD) develops in 30 and 40% of patients with type 1 and type 2 diabetes mellitus, respectively, and also disproportionately affects the elderly and minorities [2]. Once kidney disease develops, CKD patients with diabetes experience more rapid rates of kidney disease progression compared with those without diabetes [3]. Consequently, diabetes is the predominant cause of CKD in the United States, accounting for ~46 and 38% of incident and prevalent cases of end-stage

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KEY POINTS

- CKD patients, including those receiving dialysis, are at heightened risk of hypoglycemia because of decreased renal gluconeogenesis, impaired metabolism/clearance of insulin and other glucose-lowering medications, co-existing comorbidities, accumulation of uremic toxins, intradialytic glucose shifts into erythrocytes during dialysis, limited access to food during in-center hemodialysis, and secular changes in the use of lower dialysate glucose concentrations over time.
- In advanced CKD patients transitioning to ESRD, spontaneous resolution of hyperglycemia, normalization of HbA1c, and frequent hypoglycemia leading to reduction of glucose-lowering medications are frequently observed in a phenomenon that has been coined as 'burnt-out diabetes'.
- A multimodal approach is needed to mitigate hypoglycemia-risk in CKD patients, including individualization of glycemic targets, selection of glucose-lowering medications less likely to induce hypoglycemia, medical nutrition therapy, and improved hypoglycemia detection and glycemic monitoring methods.

renal disease (ESRD), respectively [4]. Although rates of myocardial infarction, stroke, and limb amputation trended downward, the number of cases of kidney failure attributed to diabetes progressively rose in the previous two decades [5–7]. The worldwide prevalence of death because of CKD in diabetes increased 106% between 1990 and 2013 [8]. The most common causes of death are heart failure and atherosclerotic cardiovascular disease [9,10]. As a result, only about 10% of the original population with diabetic kidney disease (DKD) is likely to survive to reach kidney failure [2]. Furthermore, ESRD patients with underlying diabetes have an exceedingly high mortality (i.e. annual mortality 171 deaths per 1000 person-years follow-up), worse than those with ESRD because of hypertension and glomerular disease (i.e. annual mortality 145 and 62 deaths per 1000 person-years follow-up, respectively) [4]. Hence, there is compelling need to identify modifiable determinants of the poor survival rates of CKD patients with diabetes.

Among CKD patients with and without diabetes, there has been increasing recognition that hypoglycemia is a highly prevalent complication associated with morbidity and mortality in these populations [11▪,12▪]. In this Review, we will discuss the epidemiology of hypoglycemia in CKD, emergence of the 'burnt-out diabetes phenomenon' in advanced CKD patients transitioning to ESRD, unique determinants of dysglycemia in kidney disease, existing data on the short-term and long-term implications of hypoglycemia in CKD patients, and management of hypoglycemia and glycemic derangements in this population.

GLYCEMIC DERANGEMENTS IN CHRONIC KIDNEY DISEASE

Even in the absence of diabetes, CKD patients are susceptible to hypoglycemia and hyperglycemia via multiple pathways (Fig. 1).

Hypoglycemia in chronic kidney disease

CKD patients, including those receiving dialysis, have a heightened risk of hypoglycemia because of decreased renal gluconeogenesis, impaired metabolism and clearance of insulin and other glucose-lowering medications, impaired counter-regulatory hormone responses that raise blood glucose (e.g. glucagon, cortisol, growth hormone), and co-existing comorbidities, such as protein-energy wasting (PEW) and diabetic gastroparesis [11▪,12▪,13–16]. In ESRD patients receiving hemodialysis, it has also been suggested that they are at-risk for hypoglycemia because of accumulation of uremic toxins with glucose-lowering effects [17], intradialytic glucose shifts into erythrocytes during the hemodialysis treatment session [18], limited access to food during in-center hemodialysis [19], and secular changes in the use of lower dialysate glucose concentrations over time (i.e. dialysate glucose concentrations of 100 versus 200 mg/dl in contemporary versus prior practice) [16,18].

Growing data have revealed that hypoglycemia is commonly observed in CKD patients with and without diabetes. For example, in a study of 243 222 US Veterans, hypoglycemia, defined as a blood glucose of less than 70 mg/dl, was a frequent occurrence in both CKD patients with and without underlying diabetes (i.e. 11 and 4 events per 100 patient-months of follow-up, respectively) [20]. In a national cohort of 58 304 incident hemodialysis patients with and without diabetes from a large dialysis organization (LDO), 17 and 7% of patients, respectively, were found to have hypoglycemia as ascertained by monthly predialysis glucose levels [21].

Burnt-out diabetes phenomenon

In CKD patients transitioning to ESRD, spontaneous resolution of hyperglycemia, normalization of glycated hemoglobin (HbA1c) levels, and frequent hypoglycemia events resulting in reduction and/or cessation of glucose-lowering medications are frequently observed in a phenomenon that has been

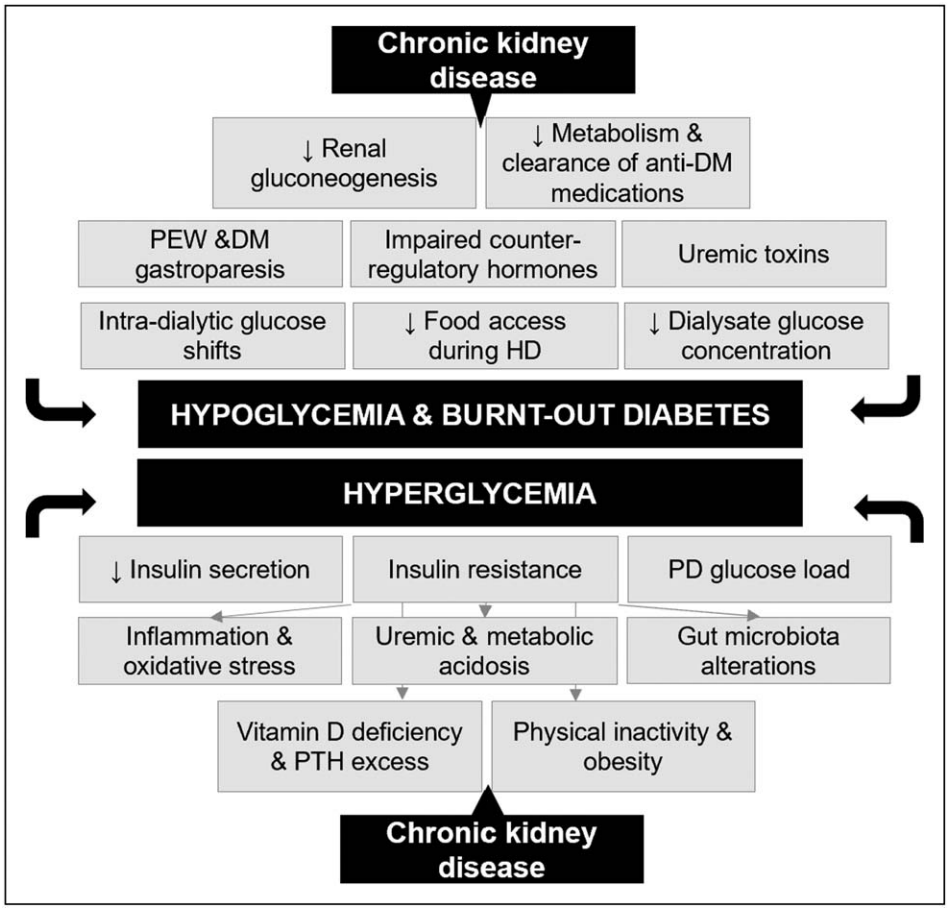

FIGURE 1. Risk factors for hypoglycemia and hyperglycemia in chronic kidney disease patients. DM, diabetes; HD, hemodialysis; PD, peritoneal dialysis; PEW, protein-energy wasting; PTH, parathyroid hormone.

coined as 'burnt-out diabetes [12▪,14–16]'. Among 63 607 incident hemodialysis patients with diabetes from an LDO, approximately one-third had low HbA1c levels below 6% at the time of transitioning to ESRD [16,22,23]. In another study of 19 977 Veterans with diabetes and advanced CKD, patients' HbA1c levels steadily declined as they progressed from CKD to ESRD (i.e. Δ in mean HbA1c −0.8% over a 1-year period) [24].

Hyperglycemia in chronic kidney disease

Conversely, CKD patients are also susceptible to hyperglycemia, which may be a direct consequence of 1) insulin resistance and 2) impaired insulin secretion [11▪,12▪,16]. With respect to insulin resistance (i.e. defined as reduced sensitivity of target organs, such as skeletal muscle, liver, and adipose tissue, to insulin), this metabolic derangement initially develops in the early stages of CKD and becomes pervasive in those who develop ESRD [25]. The causes of insulin resistance in CKD are likely because of multiple factors, including inflammation, oxidative stress, uremic toxin accumulation, metabolic acidosis, vitamin D deficiency and parathyroid hormone (PTH) excess, anemia, adipokine derangements, gut microbiota alterations, physical inactivity, and obesity [11▪,25]. In a cross-sectional analysis of 59 patients with moderate-to-severe CKD [estimated glomerular filtration rates (eGFRs) <60 ml/min/1.72 m^2] and 30 healthy controls (with eGFRs ≥ 60 ml/min/1.72 m^2), using a hyperinsulinemic euglycemic clamp as the gold-standard method for assessing skeletal muscle insulin sensitivity, participants with CKD had greater insulin resistance compared with those without CKD [26]. In CKD patients, blunted insulin secretion further exacerbates hyperglycemia, and has also been attributed to metabolic acidosis, excess PTH, and vitamin D deficiency [27–30]. Notably, it has been observed that insulin sensitivity and secretion improve following receipt of dialysis [16,31]. Finally, exposure to 3) high glucose loads via peritoneal dialysis may also contribute to hyperglycemia in dialysis patents [16,32,33]. Given the growing emphasis on home dialysis as the preferred

dialysis modality in ESRD patients, it bears mention that glucose-based solutions are the predominant form of dialysate used in peritoneal dialysis patients [32]. For example, 2.0-l (l) bags of 1.5, 2.5, or 4.25% dextrose monohydrate solution contains 30, 50, and 85 g of glucose, respectively [32]. Although the precise amount of glucose absorbed may vary across individuals (i.e. limited data suggest that ~50 to 80% of glucose is absorbed from peritoneal dialysis dialysate) [34], on average, it is estimated that CAPD patients have a glucose uptake of ~100 to 300 g/day [35].

HYPOGLYCEMIA AND OUTCOMES IN THE CHRONIC KIDNEY DISEASE POPULATION

Clinical implications of hypoglycemia

In the non-CKD population, it is well established that hypoglycemia increases risk of mortality, with potential pathways including cardiac arrhythmias, sudden cardiac death, stroke, and seizures [36–40]. Among these sequelae, cardiac arrhythmias are thought to be a principal cause of hypoglycemia-related death [37], which may in part be because of hypoglycemia-associated autonomic failure (i.e. functional sympathoadrenal failure) and reduced baroreceptor sensitivity [37,41]. In hypoglycemia-associated autonomic failure, a preceding hypoglycemia event may lead to decreased baroreceptor sensitivity, augmenting the risk of a ventricular arrhythmia, and increasing the risk of another hypoglycemic event with a sympathoadrenal discharge that leads to ventricular arrhythmia. Indeed, in an experimental model of rats with marked hypoglycemia, combined alpha-adrenergic and beta-adrenergic blockade reduced mortality, thereby supporting the role of sympathoadrenal discharge in hypoglycemia-related arrhythmias. In the non-CKD population, clinical studies have also corroborated the high fatalities associated with hypoglycemia [42,43]. In a study of 33 675 hospitalized patients (among whom 70% did not have diabetes and none were insulin-users), those who experienced a hypoglycemia event (blood glucose <70 mg/dl) or severe hypoglycemia event (blood glucose <40 mg/dl) had a 2.3-fold and 3.9-fold higher adjusted death risk, respectively, independent of comorbidity burden, compared with those without hypoglycemia [44].

Hypoglycemia and mortality risk in chronic kidney disease

ESRD patients receiving dialysis have an exceedingly high cardiovascular mortality (i.e. 40% of deaths), with sudden cardiac death as the leading cause of fatalities [4]. Given their heightened susceptibility to low glucose levels, high underlying cardiovascular risk, and established causal associations between hypoglycemia and cardiovascular disease in the non-CKD population, there has been growing interest in hypoglycemia as a potential modifiable risk factor for mortality in this population.

Greater attention to hypoglycemia has been galvanized by an increasing body of evidence demonstrating the morbidity and mortality of low glycemic status in CKD (Table 1) [20–23,40,45–50]. For example, in study of 30 156 United States Veterans with diabetes and CKD transitioning to ESRD, 6% of patients experienced a hypoglycemia-related hospitalization (i.e. severe hypoglycemia event necessitating medical attention) in the 1–2-year period preceding dialysis initiation [50]. Patients who experienced one or more pre-ESRD hypoglycemia-related hospitalizations had a 25% higher death risk compared with those without events. Moreover, an increasing frequency of pre-ESRD hypoglycemia was associated with incrementally higher post-ESRD mortality, such that those with at least three hypoglycemia-related hospitalizations had a 2.1-fold higher death risk. Similarly, in a study of 243 222 United States Veterans examining both inpatient and outpatient records, there was a graded association between severity of hypoglycemia and short-term death risk (i.e. 1-day mortality) in CKD patients (i.e. blood glucose levels <50, 50–59, and 60–69 mg/dl associated with a 6.1-fold, 4.1-fold, and 1.9-fold higher death risk, respectively, using inpatient records, and a 6.8-fold, 3.3-fold, and 4-fold higher death risk using outpatient records) [20]. It has also been suggested that glucose levels in the low-normal range are associated with higher death risk in CKD patients. In a study of 8711 advanced CKD patients with diabetes from the national VA database, those who had relative hypoglycemia, defined as an averaged random blood glucose of less than 100 mg/dl, had a 1.7-fold higher death risk independent of sociodemographics, comorbidities, nutritional status, and other clinical characteristics in comparison to those with glucose levels of 100 to less than 120 mg/dl [49].

MANAGEMENT OF HYPOGLYCEMIA AND GLYCEMIC DERANGEMENTS IN CHRONIC KIDNEY DISEASE

Given the high prevalence of low glucose levels in kidney disease and mortality associated with this glycemic derangement, a multimodal approach is needed to mitigate hypoglycemia risk in this population (Fig. 2).

Table 1. Selected studies of low glycemic levels and clinical outcomes in the chronic kidney disease population

Author (year)	Study population (country)	Hypoglycemia definition	Outcome	Results
Moen *et al.* (2009) [20]	243 222 pts with and without DM + with and without CKD (US)	Varying levels of blood glucose less than 70 mg/dl (<50, 50–59, 60–69 mg/dl)	One-day mortality	All levels of hypoglycemia associated with ↑ 1-day mortality, with effect estimates most pronounced for non-CKD patients
Kong *et al.* (2014) [48]	8767 type 2 DM patients with and without CKD (China)	Severe hypoglycemia: one or more hypoglycemia-related hospitalizations	Mortality	Severe hypoglycemia + CKD associated with 3.9-fold ↑ risk of death
Yu *et al.* (2014) [40]	46 135 patients with CKD with and without DM (Taiwan)	Diagnostic codes for hypoglycemia	Stroke Coronary heart disease (CHD) Congestive heart failure (CHF) Death	Hypoglycemia associated with: 1.6-fold ↑ risk of stroke 1.3-fold ↑ risk of CHD 1.5-fold ↑ risk of CHF 2.5-fold ↑ risk of death Recurrent episodes of hypoglycemia were associated with 33-fold ↑ risk of death
Cho *et al.* (2016) [45]	1685 HD patients (Korea)	Blood glucose level of less than 2.8 mmol/l	Early mortality Total mortality	Lower glucose levels significantly associated with early mortality
Chu *et al.* (2017) [46]	20 845 incident dialysis patients with DM (Taiwan)	ER/hospitalization diagnostic codes for hypoglycemia prior to ESRD	Post-ESRD mortality Post-ESRD myocardial infarction (MI) Post-ESRD severe hypoglycemia	One or more hypoglycemia events associated with ↑ risk of death and subsequent severe hypoglycemia
Rhee *et al.* (2018) [50]	30 156 US Veterans with diabetes and CKD transitioning to ESRD (US)	Pre-ESRD hypoglycemia-related hospitalization defined by diagnostic codes	Post-ESRD all-cause mortality	↑'ing frequency of pre-ESRD hypoglycemia-related hospitalizations associated with incrementally higher 1-year post-ESRD mortality risk
Rhee *et al.* (2019) [49]	8711 US Veterans with CKD who did not transition to dialysis	Relative hypoglycemia: Blood glucose less than 100 mg/dl	Mortality	Relative hypoglycemia associated with ↑ mortality
Hsiao *et al.* (2019) [47]	46 779 incident dialysis patients (Taiwan)	ER/hospitalization diagnostic codes for hypoglycemia prior to ESRD	1-year post-ESRD hypoglycemia or post-ESRD mortality	↑'ing frequency of severe hypoglycemia-related hospitalizations associated with incrementally higher 1-year post-ESRD mortality risk
Rhee *et al.* (2018) [22,23]	63 607 incident HD pts with DM (US)	Relative hypoglycemia: blood glucose less than100 mg/dl	Mortality	Relative hypoglycemia associated with ↑ mortality
Kang *et al.* (2020) [21]	58 304 incident HD pts with and without DM (US)	Blood glucose less than 70 mg/dl	All-cause mortality	Hypoglycemia associated with ↑ mortality in patients with and without DM

DM, diabetes mellitus; pts, patients.

Individualized glycemic targets

A cornerstone in the management of diabetes is the use of individualized glycemic targets that take into consideration patients' underlying characteristics. Indeed, using a personalized approach in lieu of a 'one-size-fits-all' strategy is essential in the prevention of hypoglycemia. For example, the National Kidney Foundation-Kidney Disease Outcomes Quality Initiative (NKF-KDOQI) and Kidney Disease Improving Global Outcomes (KDIGO) clinical practice guidelines advise a HbA1c target of ~7% and 6.5 to less than 8%, respectively, in CKD patients with diabetes to prevent or reduce progression of microvascular complications [51,52]. However, it should be highlighted that the NKF-KDOQI and KDIGO guidelines recommend using a personalized approach with less stringent glycemic targets (i.e. HbA1c level >7%) in those with high comorbidity burden, limited life

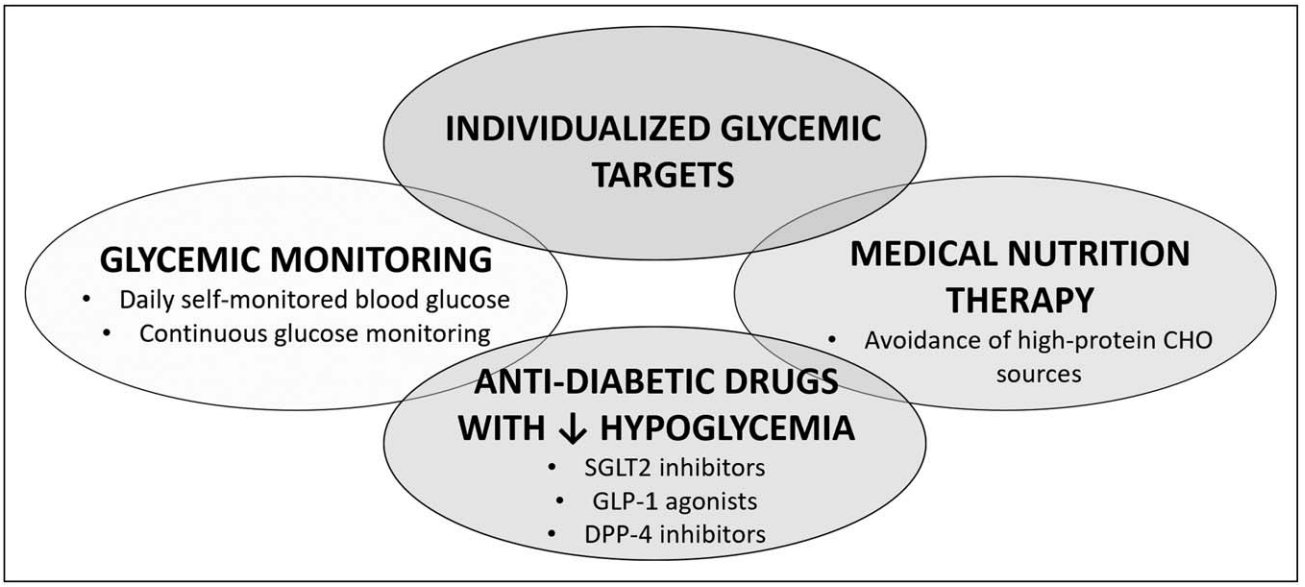

FIGURE 2. Multimodal management strategy for preventing hypoglycemia and optimizing glycemic status in chronic kidney disease. DPP-4 inhibitor, dipeptidyl peptidase-4 inhibitor; GLP-1 agonist, glucagon-like peptide 1 agonist; SGLT2 inhibitor, sodium-glucose cotransporter-2 inhibitor.

expectancy, and at-risk for hypoglycemia (i.e. defined as patients with stages 4–5 CKD, and those receiving insulin and/or sulfonylureas). Furthermore, in an expert consensus panel convened by the American Diabetes Association, NKF, and American Society of Nephrology, it was underscored that, 'while HbA1c levels between 7–8% appear to be associated with the highest survival rates in retrospective analyses of DKD patients, the imprecision of HbA1c measurements makes specific targets for people with DKD difficult to define [53,54]'.

Avoidance of intensive glycemic targets even in patients with mild-to-moderate CKD and diabetes is also supported by data from the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial. In a secondary analysis of 10 136 patients from the original ACCORD cohort with kidney function data (i.e. 3636 patients with stages 1–3 CKD and 6506 without CKD), rates of hypoglycemia were two-fold higher in CKD versus non-CKD patients [55]. Compared with standard glycemic control (i.e. HbA1c target of 7–7.9%), the annualized rates of hypoglycemia requiring medical assistance with intensive therapy (i.e., HbA1c target of <6.0%) were three-fold higher in those with CKD. Moreover, intensive glycemic targets were also associated with a 31% higher risk of all-cause death and 41% higher risk of cardiovascular death in those with CKD.

Pharmacotherapies

Risk of hypoglycemia is also attenuated by selecting glucose-lowering medications that are less likely to induce hypoglycemia, and frequently monitoring and titrating glucose-lowering medications as patients' kidney function declines, including dose reduction and/or discontinuation as patients progress to advanced CKD and ESRD.

Large population-based studies have shown that insulin and sulfonylurea use are associated with heightened risk of hypoglycemia in CKD patients with diabetes. In an analysis of 20 156 US Veterans with diabetes and advanced CKD transitioning to ESRD, while there was a graded association between the number of prescribed oral antidiabetic drugs (OADs) and risk of hypoglycemia, insulin-use alone had a similar magnitude of hypoglycemia risk as compared with the prescription of two OADs [50]. When examining the 12 most commonly prescribed glucose-lowering medication patterns by drug class, regimens that included insulin or sulfonylureas were associated with higher risk of hypoglycemia.

In contrast, newer glucose-lowering medications, such as incretin therapies [i.e. glucagon-like peptide 1 (GLP-1) receptor agonists, dipeptidyl peptidase-4 (DPP-4) inhibitors] have demonstrated low rates of hypoglycemia in clinical trials of the general population, as well as in those with CKD [56,57▪,58–60]. Notably, the suppression of glucagon and stimulation of insulin secretion by GLP-1 declines as patients approach normoglycemia [61]. Hence, the glycemia-dependent regulation of pancreatic hormone secretion by GLP-1 agonists mitigates risk of hypoglycemia. Evidence has also shown that DPP-4 inhibitors, which hinder the degradation of GLP-1 and glucose-dependent insulinotropic polypeptide

(GIP), protect against hypoglycemia by increasing levels of glucagon and GIP [62]. Recently, a dual GIP-GLP-1 agonist, terzepatide, was reported to enhance control of hyperglycemia compared with standard GLP-1 agonist therapy while still protecting against hypoglycemia in patients with type 2 diabetes [63▪,64▪▪].

In addition, sodium-glucose cotransporter-2 (SGLT2) inhibitors are unlikely to cause hypoglycemia based on their mechanisms of action (i.e. modulation of glucose levels through the inhibition of proximal tubular reabsorption of glucose in the kidney and increased glycosuria) when used alone [65▪▪,66]. Furthermore, as the glucose-lowering effects of SGLT2 inhibitors attenuate as kidney function declines, these medications have a low risk of causing hypoglycemia. Indeed, recent clinical trials of SGLT2 inhibitors in patients with type 2 diabetes and CKD did not show higher risk of hypoglycemia as compared with placebo [67,68]. However, further real-world comparative effectiveness studies are needed to determine the risk of hypoglycemia conferred by these newer versus older agents specifically in the CKD population.

Lifestyle modification: dietary intake

The NKF-KDOQI and KDIGO guidelines emphasize the integral role of medical nutritional therapy (MNT) in CKD patients with and without diabetes [52,69▪]. Among advanced CKD and ESRD patients who may suffer from PEW, adequate access to nutritional management from accredited/trained providers is particularly important in preventing hypoglycemia.

Across clinical practice guidelines, there is alignment in the recommendations for individualized and balanced diets that are high in vegetables, fruits, and whole grains, but are low in refined carbohydrates (CHOs) and sugar-sweetened beverages [52,69▪,70]. However, with respect to specific macronutrients, there are varying recommendations with respect to the precise amount of dietary protein intake (DPI) across guidelines, likely because of the paucity of randomized controlled trials (RCTs) and high-quality evidence guiding dietary therapy in CKD and diabetes. The most recent updated 2020 NKF-KDOQI Clinical Practice Guidelines for Nutrition in CKD recommend a DPI of 0.6–0.8 g/kg/day and 0.55–0.6 g/kg/day in CKD patients with and without diabetes, respectively [69▪]. As glomerular hyperfiltration and renal enlargement early on in the course of diabetes leads to CKD, which is intensified by dietary protein and amino acid intake [71], restriction of DPI may attenuate CKD progression in diabetic nephropathy (Fig. 3). Notably, although the

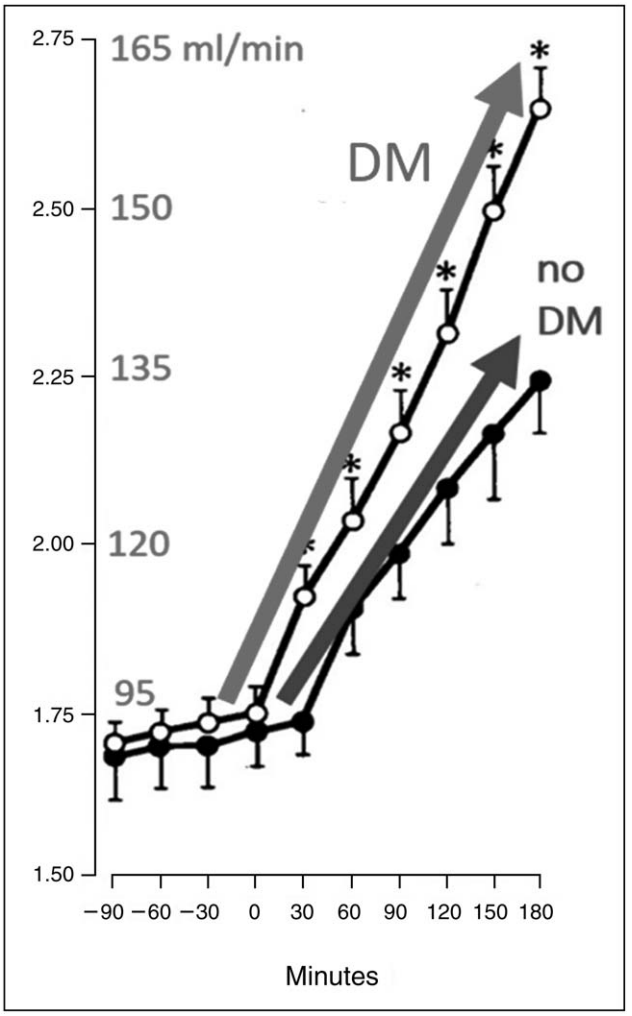

FIGURE 3. Clinical data of dietary amino acid and protein intake stimulating glomerular hyperfiltration in patients with diabetes and CKD. In a study of 12 patients with diabetes and 9 patients without diabetes who underwent glomerular filtration rate (GFR) and renal plasma flow (RPF) measurement after an overnight fast and intravenous amino acid infusion, while during the fasting phase the GFR and RPF remained normal, during the amino acid infusion there was a greater increase in GFR and RPF in patients with diabetes versus those without diabetes. Adapted from Tuttle *et al.* [71]. These findings apply to patients with both type 1 and type 2 diabetes.

ADA and KDIGO guidelines currently advise against a DPI below 0.8 g/kg/day based on insufficient evidence for DPI restriction in diabetes and CKD [52,70], it bears mention that the ADA recommends avoidance of high-protein CHO sources in patients with type 2 diabetes to prevent hypoglycemia (i.e. protein increases insulin response without rise in glucose). Further study is needed to determine the impact of macronutrients/nutrients and prescribed diets on hypoglycemia risk in CKD patients.

Improved detection and monitoring

Frequent, accurate, and precise glycemic monitoring that allows for more rapid treatment adjustments may further ameliorate the risk of hypoglycemia in CKD. Although glycated hemoglobin (HbA1c), fructosamine, and glycated albumin are utilized for assessing long-term and intermediate glycemic status, respectively, these glycemic metrics have limitations in their accuracy in advanced CKD, particularly in the setting of anemia, use of erythropoietin-stimulating agents, and altered serum protein states [11▪,12▪,16]. Whereas self-monitored blood glucose (SMBG) or point-of-care (POC) glucose levels are typically used to guide treatment decisions in advanced CKD, the accuracy of these methods may also be affected by sample stability and other factors (e.g. anemia, acute illness, medications, etc.) [11▪]. Although more frequent SMBG testing (i.e. >10 times/day) has been shown to result in better glycemic control, such that the ADA advises at least 6–10 daily SMBG measurements in patients with diabetes receiving intensive insulin regimens [72], frequent capillary fingerstick measurements may be inconvenient, burdensome, and painful for patients. Furthermore, the above-mentioned glycemic metrics do not adequately capture daily glucose dynamics, including asymptomatic, nocturnal, nor intra-dialytic hypoglycemia and hyperglycemia events [11▪,73▪].

In contrast, continuous glucose monitoring (CGM) has emerged as a convenient, automated, and less invasive method for providing comprehensive glycemic data as compared with the above-mentioned conventional metrics [11▪,73▪]. In non-CKD patients, clinical trials have shown that CGM is superior to SMBG in hypoglycemia detection and improved clinical outcomes. Several studies support the agreement of blood versus CGM-based interstitial glucose levels in advanced CKD patients [74–76], and anecdotal reports suggest that CGM may be a more practical, patient-centered tool in ESRD patients with diabetes [73▪]. Although clinical practice guidelines support the use of daily glycemic monitoring with CGM in CKD patients with diabetes [52], particularly in the context of use of glucose-lowering pharmacotherapies with hypoglycemia risk, such as insulin and insulin secretagogues (sulfonylureas, glinides), this convenient tool remains under-utilized in the kidney disease population. Hence, further studies are needed to improve the accessibility of CGM in patients with diabetes and CKD.

CONCLUSION

There have been substantial advances in our understanding of the burden, contributing factors, and clinical implications of hypoglycemia in CKD patients with and without diabetes. However, there remains uncertainty in regards to the clinical phenotype of CKD patients at heightened risk of hypoglycemia rendering closer glycemic monitoring, ideal glycemic targets among at-risk CKD patients with diabetes that confer improved outcomes, the comparative safety and effectiveness of newer versus older glucose-lowering pharmacotherapies with respect to hypoglycemia risk and glycemic control, and whether our understanding of the natural course of the burnt-out diabetes phenomenon can be leveraged to treat hyperglycemia in CKD and other chronic disease populations by extension. Given the high morbidity and mortality of dysglycemia in the CKD population, there is compelling need for further research on how to optimally manage the glycemic status of patients with kidney disease.

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Conflicts of interest

There are no conflicts of interest.

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- ▪ of special interest
- ▪▪ of outstanding interest

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This article provides a comprehensive review on the pathogenesis of dysglycemia in CKD, as well as the strengths and limitations of various glycemic monitoring methods.

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