Personalizing Diabetes Management in Liver Transplant Recipients: The New Era for Optimizing Risk Management

Brooks Richardson,[1] Mohammad Qasim Khan (iD) ,[2] Sara A Brown,[3] Kymberly D Watt (iD) ,[2*] and Manhal Izzy (iD) [3*]

Post-transplant diabetes mellitus (PTDM) is a significant contributor to morbidity and mortality in liver transplant recipients (LTRs). With concurrent comorbidities and use of various immunosuppression medications, identifying a safe and personalized regimen for management of PTDM is needed. There are many comorbidities associated with the post-transplant course including chronic kidney disease, cardiovascular disease, allograft steatosis, obesity, and *de novo* malignancy. Emerging data suggest that available diabetes medications may carry beneficial or, in some cases, harmful effects in the setting of these co-existing conditions. Sodium-glucose co-transporter 2 inhibitors and glucagon-like peptide 1 receptor agonists have shown the most promising beneficial results. Although there is a deficiency of LTR-specific data, they appear to be generally safe. Effects of other medications are varied. Metformin may reduce the risk of malignancy. Pioglitazone may be harmful in patients combatting obesity or heart failure. Insulin may exacerbate obesity and increase the risk of developing malignancy. This review thoroughly discusses the roles of these extra-glycemic effects and safety considerations in LTRs. Through weighing the risks and benefits, we conclude that alternatives to insulin should be strongly considered, when feasible, for personalized long-term management based on risk factors and co-morbidities. (*Hepatology Communications* 2022;6:1250-1261).

Liver transplant recipients (LTRs) are at an increased risk for developing significant comorbidities including diabetes mellitus, obesity, cardiovascular disease (CVD), renal impairment, and *de novo* malignancy.[1] Although diabetes mellitus carries a significant burden in the general population, it poses unique challenges within LTRs. The incidence of post-transplant diabetes mellitus (PTDM) at 1 year ranges from 10.8% to 33%, with an annual incidence of 3.3%-30.8%.[2] Many risk factors predispose patients to PTDM[2] (Table 1). PTDM is associated with CVD, hepatic steatosis, chronic kidney disease (CKD), obesity, malignancy, graft rejection, infection, hepatic artery thrombosis, and, above all, decreased patient survival.[3-7]

Although insulin is universally used for the treatment of PTDM in the short term, diabetes medication selection for long-term glycemic control should not only adhere to the basis of safety and efficacy but also seek to maximize the potential for secondary benefits given the multitude of post-transplant complications. The aims of this review are to identify the potential extra-glycemic benefits and harms of the commonly used diabetes medications in LTRs.

TABLE 1. POST-TRANSPLANT DIABETES MELLITUS RISK FACTORS AND ASSOCIATIONS

Risk Factors for DM		Outcomes Associated With DM	
Modifiable	Nonmodifiable	Liver-related	Non-liver-related
Obesity		Graft rejection	Increased mortality
Calcineurin inhibitors	Donor history of DM	Hepatic artery thrombosis	Chronic Kidney Disease
Corticosteroids	Recipient history of cirrhosis	NAFLD	Obesity
Hypomagnesemia	Advanced donor or recipient age		Infection
HCV infection	African-American race		Cardiovascular events
CMV infection	Family history of DM		

Abbreviations: CMV, cytomegalovirus; DM, diabetes mellitus; HCV, hepatitis C virus; NAFLD, Non-alcoholic fatty liver disease.

Non-insulin Therapies

While insulin is routinely used in the immediate post–liver transplant (LT) course, the optimal timing of transitioning to alternative therapies is unclear. Some experts suggest that the transition to non-insulin therapies is safe in the weeks following transplant when steroid-based treatments are reduced and total daily insulin requirements fall to modest values (below 20 units/day).[8] Each drug class carries a unique mechanism with varied adverse effects and use recommendations in renal or hepatic impairment (Table 2).

BIGUANIDES

Metformin is the first-line oral medication for most patients with type 2 diabetes (T2DM). Administration results in decreased hepatic gluconeogenesis, increased insulin sensitivity, and decreased intestinal glucose absorption.[9] Common adverse effects (AEs) include gastrointestinal intolerance, B12 deficiency, and headache.[10] Use is traditionally not recommended in patients with advanced renal or hepatic impairment due to the risk of lactic acidosis.[11] However, more recent data suggest that use may be safe in patients with stage III CKD.[12] There are no documented interactions between metformin and calcineurin inhibitors (CNIs), anti-metabolites, or mammalian target of rapamycin inhibitors (mTORi).[13] CNIs, however, are associated with renal impairment, which may limit concurrent use. Although rare, case reports of drug-induced cholestatic hepatic injury have been documented.[9]

SULFONYLUREAS

Sulfonylureas (SUs) increase the release of endogenous insulin through action on pancreatic beta-islet cells.[9] Common AEs include weight gain and hypoglycemia.[10] Dosage adjustment is recommended in the setting of kidney impairment due to decreased clearance and increased risk of hypoglycemia.[11] There are no recommendations for dose reductions in the setting of hepatic impairment; however, prior investigations regarding this are minimal. Use of SUs may be limited in combination with CNIs due to the associated renal impairment. In addition, one retrospective study found steady-state serum concentrations of cyclosporine to be elevated with co-administration of glyburide, suggesting the need for monitoring.[14] There are no documented interactions to limit safety in combination

ARTICLE INFORMATION:

From the [1]Department of Internal Medicine, Vanderbilt University Medical Center, Nashville, TN, USA; [2]Division of Gastroenterology and Hepatology, Mayo Clinic, Rochester, MN, USA; [3]Division of Gastroenterology, Hepatology and Nutrition, Vanderbilt University Medical Center, Nashville, TN, USA.

ADDRESS CORRESPONDENCE AND REPRINT REQUESTS TO:

Manhal Izzy, M.D.
Division of Gastroenterology, Hepatology and Nutrition
1660 The Vanderbilt Clinic

Nashville, TN 37232, USA
E-mail: Manhal.izzy@vumc.org
Tel.: +1-615-322-0128

TABLE 2. CONSIDERATIONS IN THE USE OF DIABETES MEDICATIONS

	DILI Likelihood Score*	Interactions With Immunosuppression	AEs
Biguanide *Metformin (Glucophage, Fortamet, Glumetza)*	B	—	Gastrointestinal intolerance, headache, B12 deficiency
Sulfonylureas *Glipizide (Glucotrol)* *Glimepiride (Amaryl)* *Glyburide (Diabeta, Micronase, Glynase)*	B-D	Glyburide may increase concentration of CsA	Weight gain, hypoglycemia
Sodium-glucose cotransporter-2 inhibitors *Canagliflozin (Invokana)* *Empagliflozin (Jardiance)* *Dapagliflozin (Farxiga)* *Ertugliflozin (Stegaltro)*	D-E	CsA may increase concentration of canagliflozin	Dehydration, genitourinary infections, euglycemic DKA
Glucagon-Like Peptide-1 Receptor Agonists *Exenatide (Byetta, Bydureon)* *Liraglutide (Victoza)* *Dulaglutide (Trulicity)* *Semaglutide (Ozempic)* *Lixistenatide (Lyxumia)*	E	May delay absorption of tacrolimus and MMF	Gastrointestinal intolerance, headache, delayed gastric emptying
Dipeptidyl Peptidase-4 Inhibitors *Alogliptin (Nesina)* *Saxagliptin (Onglyza)* *Linagliptin (Tradjenta)* *Sitagliptin (Januvia)*	D-E	CsA may increase sitagliptin concentration Vildagliptin may decrease tacrolimus concentration	Headache, upper respiratory infections
Thiazolidinediones *Pioglitazone (Actose)* *Rosiglitazone (Avandia)*	C	Rosiglitazone may increase risk of MMF toxicity	Weight gain, fluid retention, anemia, bone loss
Metiglinide analogue *Repaglinide (Prandin)* *Nateglinide (Starlix)*	D-E	CsA may increase concentration of repaglinide	Gastrointestinal intolerance, headache, dizziness, hypoglycemia
Alpha-glucosidase inhibitor *Acarbose (Precose)* *Miglitol (Glyset)*	B, E	—	Gastrointestinal intolerance

Abbreviations: AE, adverse effects; CsA, cyclosporine-A; DILI, drug-induced liver injury; DKA, diabetic ketoacidosis; MMF, mycophenolate mofetil.
*LiverTox national database DILI likelihood scores: A, well recognized cause of clinically apparent liver injury; B, likely rare cause; C, probable rare cause; D, possible rare cause; and E, unlikely/unproven cause.

with anti-metabolites or mTORi.[13] Reports of drug-induced cholestatic hepatic injury have been described, primarily limited to the first-generation agents.[9]

GLUCAGON-LIKE PEPTIDE-1 RECEPTOR AGONISTS

Glucagon-like peptide-1 receptor agonists (GLP1-RAs) promote the release of endogenous insulin through activation of the GLP-1 receptor on pancreatic beta-islet cells.[15] Additional effects include delayed gastric emptying and suppression of glucagon release.[15] Common AEs include gastrointestinal intolerance and headache.[10] Possible associations include thyroid malignancy and pancreatitis.[16,17] With the exceptions of exenatide and lixisenatide, there are no dose adjustment recommendations in kidney impairment. Hepatic impairment may reduce serum concentrations of certain agents[18]; however, there are no recommendations for dosage adjustments. There are no drug–drug interactions among GLP1-RAs and CNIs, anti-metabolites, or mTORi.[13] The side effect of delayed gastric emptying, however, may result in delayed absorption of CNIs and mycophenolate[19]; thus, careful monitoring may be required. There are no data to suggest GLP1-RAs as an etiology of drug-induced liver injury.[9]

DIPEPTIDYL PEPTIDASE-4 INHIBITORS

Dipeptidyl peptidase-4 inhibitors (DPP-4i) suppress the degradation of GLP1, thereby increasing insulin secretion and suppressing the release of glucagon.[9] The most common AE is headache.[10] Similar to GLP1-RAs, there are concerns regarding a possible association with acute pancreatitis.[16] Excluding linagliptin, the DPP-4i are excreted by the kidneys and generally require dosage adjustment in renal impairment.[11] There are no dosage adjustment recommendations in hepatic impairment; however, recommended use is typically limited to patients with mild to moderate impairment.[20] Cyclosporine was shown to increase the serum concentration of sitagliptin in a small pharmacokinetic study.[21] Furthermore, two studies assessed co-administration of vildagliptin with tacrolimus. One reported a decrease in tacrolimus levels while the other did not.[22,23] The available data do not raise safety concerns for concurrent use of DPP-4i with CNIs, anti-metabolites, or mTORi. Although

rare, there are case reports of drug-induced cholestatic and mixed hepatic injury.[9]

SODIUM-GLUCOSE COTRANSPORTER-2 INHIBITORS

Sodium-glucose cotransporter-2 inhibitors (SGLT2i) decrease renal glucose reabsorption.[9] AEs include genital mycotic infections, urinary tract infections, polyuria, dehydration,[10] and euglycemic diabetic ketoacidosis.[24] Use is not recommended with stage IV CKD due to decreased efficacy.[11] Patients with hepatic impairment may have increased serum drug concentrations[18]; however, there are no dose-adjustment recommendations. One study demonstrated clinically insignificant elevation of canagliflozin concentration with concurrent cyclosporine use.[25] There are otherwise no interactions between SGLT2i and tacrolimus, anti-metabolites or mTORi.[13] Drug-induced liver injury is exceedingly rare.[9]

THIAZOLIDINEDIONES

Thiazolidinediones (TZDs) increase insulin sensitivity through activation of peroxisome proliferator–activated receptor gamma (PPAR-γ).[9] AEs include weight gain, fluid retention, anemia, and possibly increased risk for heart failure and bone fractures.[10] There are no recommendations for dosage adjustment in renal impairment. Patients with hepatic impairment may have decreased drug clearance and multiple guidelines recommend avoiding use in this setting.[20] One case report involving a kidney-transplant recipient suggested an interaction between rosiglitazone and mycophenolate as the etiology of drug toxicity.[26] There are otherwise no interactions with CNIs, azathioprine, or mTORi.[13] The currently available agents are an uncommon etiology of hepatic injury.[9]

METIGLINIDE ANALOGUES

Metiglinide analogues augment glucose-stimulated insulin secretion from pancreatic beta cells.[9] AEs include gastrointestinal intolerance, headache, dizziness, and hypoglycemia.[10] They are partially excreted in the urine, and thus require cautious titration with renal impairment.[11] Although use in hepatic impairment has not been investigated, significant metabolism occurs within the liver and accumulation may conceptually occur. Cyclosporine may increase the
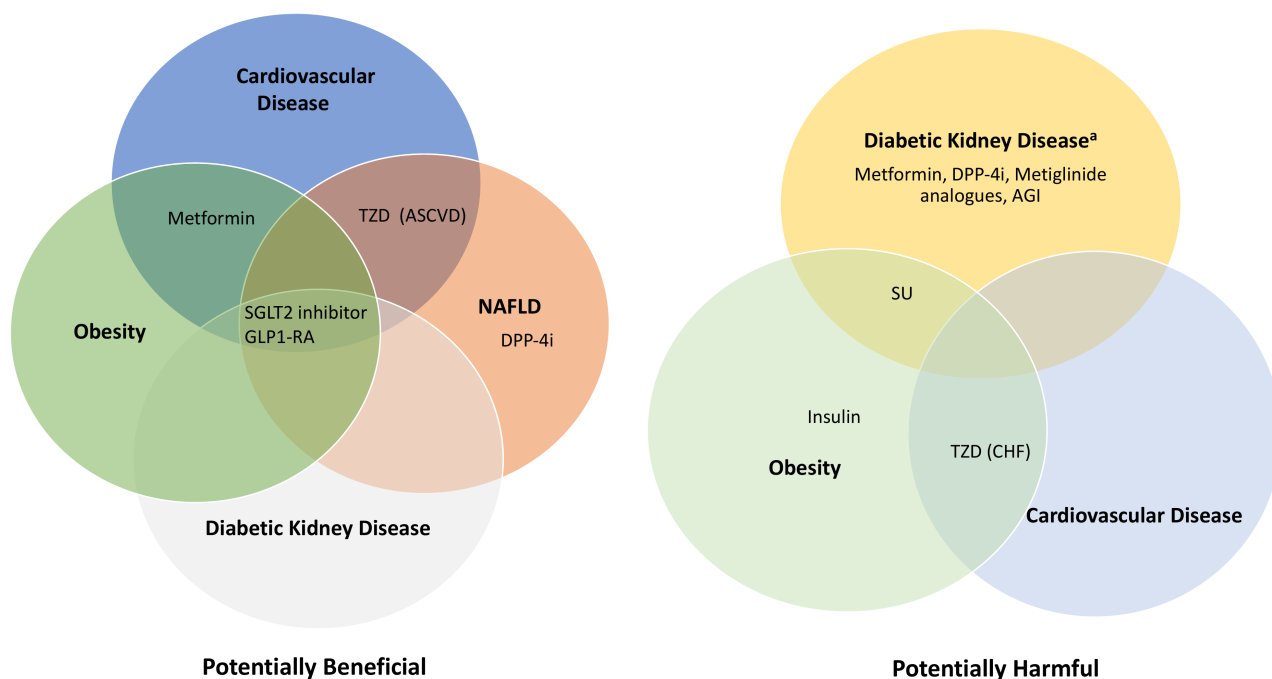
FIG. 1. Venn diagram—the good and the bad of diabetes therapies: settings where certain medications may provide benefit or harm. [a]Listed medications are not directly nephrotoxic but use may result in AEs in the setting of reduced glomerular filtration rate. Malignancy was excluded from the Venn diagram due to mixed/inconclusive data. Abbreviations: AGI, alpha-glucosidase inhibitor; ASCVD, atherosclerotic cardiovascular disease; CHF, congestive heart failure; DPP-4i dipeptidyl peptidase 4 inhibitor; GLP1-RA, glucagon-like peptide 1 receptor agonist; NAFLD, non-alcoholic fatty liver disease; SGLT2, sodium-glucose co-transporter 2; SU, sulfonylurea; TZD, thiazolidinedione.

concentration of repaglinide, with mild episodes of hypoglycemia documented but no identified need for dose adjustment.[19] There are no documented interactions between metiglinide analogues and anti-metabolites or mTORi.[13] Case reports have implicated metiglinide analogues as the etiology of mixed and cholestatic hepatitis.[9]

ALPHA-GLUCOSIDASE INHIBITORS

These medications inhibit the intestinal brush border enzyme alpha-glucosidase, which results in decreased absorption of carbohydrates.[9] They are uncommonly prescribed due to gastrointestinal intolerance including flatulence, abdominal bloating, and diarrhea.[10] They have minimal systemic absorption; however, cautious use is recommended in patients with stage IV CKD.[11] There are no dosage adjustments required in hepatic impairment. No significant interactions with CNIs, mTORi, or anti-metabolites have been documented.[13] Acarbose has been implicated in acute hepatocellular injury.[9]

Insulin

Insulin is commonly prescribed in the immediate post-transplant period, as it can be titrated to achieve glycemic control and does not interact with immunosuppressive agents.[13] Furthermore, intensive insulin therapy may decrease the rate of graft rejection.[27] Nevertheless, there are challenges that come with administration. Insulin degradation and clearance primarily occurs in the liver; however, there is a lack of specific dosage-adjustment guidelines in the setting of hepatic dysfunction.[20] Additionally, there are multiple adverse associations with long-term use that are extensively reviewed below.

Extra-glycemic Reflections in LTRs

The currently available therapies have emerging data to support use for extra-glycemic indications. Personalizing pharmacotherapeutic options in LTRs should be considered to maximize secondary benefits

and minimize potential harm (Fig. 1). Figure 1 provides a graphic representation demonstrating when certain diabetes therapies may provide overlapping effects in the setting of common comorbid conditions observed in LTRs. These effects need to be considered in conjunction with weighing the impact of various immunosuppressants on these comorbidities.

WEIGHT MANAGEMENT

At 3 years following LT, up to 40.8% of patients are obese.[5] The impact of post-transplant weight gain yields an increased risk of PTDM and metabolic syndrome with associated complications: CVD, renal disease, and allograft steatohepatitis.[28] Thus, diabetes medications that promote weight loss should be considered early in the post-LT course. These include biguanides, SGLT2i, and GLP1-RAs.[29] Conversely, SUs, TZDs, and insulin often cause weight gain. DPP-4i are weight-neutral.[29]

Trials evaluating the effects of metformin on weight loss revealed 2.1% weight loss over the first 2 years of therapy.[30] A randomized control trial (RCT) following kidney transplant showed a trend toward less weight gain in the metformin group.[31] Metformin promotes weight loss through modulation of hypothalamic appetite–regulatory centers, peripheral fat metabolism, and alteration of the gut microbiome.[32] Tissue-specific effects of metformin on adenosine-monophosphate kinase play an important role in appetite suppression, decreased lipogenesis, increased lipid oxidation, and decreased ectopic lipid depots.[32]

SGLT2i promote weight loss through renal excretion of glucose with modest caloric elimination. An RCT evaluating empagliflozin in kidney-transplant recipients with PTDM revealed a median 2.5-kg weight loss at 24 weeks.[33]

GLP1-RAs promote weight loss by slowing gastric emptying and increasing satiety. A meta-analysis, conducted in patients with T2DM, suggested significantly greater weight loss with these agents relative to controls.[34] Furthermore, a recent RCT demonstrated a mean 14.9% weight reduction in non-diabetic patients treated with subcutaneous semaglutide compared to 2.4% in those treated with placebo over 68 weeks.[35] One retrospective study evaluating solid organ transplant recipients, including LTRs, demonstrated a mean 4.86-kg weight loss over 12 months in patients receiving GLP1-RAs.[36]

Insulin and SUs cause weight gain through decreased glycosuria and increased hypoglycemia with subsequent overtreatment.[37] Insulin additionally promotes lipid synthesis and deposition and stimulates central appetite centers.[37] In patients with T2DM, the average weight gain after 10 years of insulin therapy is about 7 kg.[37] SUs can result in weight gain of 1.6-2.6 kg within the first year of treatment.[37]

TZDs cause weight gain through adipogenesis, mediated by stimulation of PPAR-γ on adipocytes, as well as improved glucose control, decreased glycosuria, and flux in fluid balance.[37] Within 1 year of therapy, patients may gain between 2.6 and 3.2 kg.[37] However, stable weights have been noted after 26 weeks of therapy in liver and kidney-transplant recipients.[2]

Although the focus of this section surrounds the weight-loss benefits of diabetes medications, it is noteworthy that there are emerging data highlighting the potential benefits of post-LT bariatric surgery including improved glycemic control and weight loss. A recent meta-analysis examining four studies demonstrated a 27% absolute reduction in body mass index (BMI) at 33.8 months following bariatric surgery in LTRs.[38] Furthermore, 41% of these patients experienced resolution of T2DM.[38] Given the remarkable findings, surgical weight-loss options may be considered in diabetic patients with BMI > 35 who fail lifestyle changes and medical therapies.

STEATOSIS

At 10 years following LT, up to 48% of patients develop *de novo* allograft steatosis[39] with increased risk for non-alcoholic steatohepatitis (NASH).[4] PTDM has been identified as a predictor of developing allograft steatosis.[4]

RCTs of GLP1-RAs have demonstrated histological resolution and decreased disease progression in non-transplant patients with NASH taking liraglutide or semaglutide versus placebo.[40,41] Exenatide has shown the ability to reduce serum transaminase values in patients with non-alcoholic fatty liver disease (NAFLD) and improve sonographic disease severity relative to patients treated with insulin alone.[42] This class may also associate with decline in liver stiffness measured by elastography.[43] Proposed mechanisms for these benefits include weight loss, alterations in lipid metabolism, attenuated release of pro-inflammatory cytokines, and improved hepatic insulin sensitivity.[44] The data for DPP-4i are less convincing, with the available data showing mixed results.[45]

SGLT2i have also provided promising results. One study found attenuation of both hepatic steatosis and fibrosis measured radiologically and decreases in serum ALT in patients treated with dapagliflozin.[46] Another investigation found significant decreases in the fat fraction, measured by magnetic resonance imaging, in patients with T2DM receiving dapagliflozin.[47] Histological assessments in humans are limited, although improvements in scores of steatosis, inflammation, and fibrosis have been noted.[48] Proposed mechanisms for this benefit include improved glucose control, weight loss, and reductions in oxidative stress and inflammation.[49]

Pioglitazone is the only diabetes medication with guideline endorsement for patients with biopsy-proven NASH. Safety and efficacy have been supported in a long-term RCT with results of improved NAFLD activity scores and, in some cases, resolution of NASH.[50] Unfortunately, the concern about AE profile, including weight gain and associated risk for bladder cancer, is often a limiting factor in use. The mechanistic benefit likely involves some combination of free fatty acid reduction, attenuated gluconeogenesis, improved insulin sensitivity, and reduced inflammation.[51]

The role of these medications in the prevention of NAFLD/NASH is not established. Additionally, these beneficial effects have not yet been demonstrated in LTRs, although could conceivably be applicable to allograft steatohepatitis.

CARDIOVASCULAR DISEASE

LTRs have a 30.8% risk of cardiovascular disease within 8 years following transplant.[5] PTDM is an independent predictor of these events.[5] Thus, diabetes medication selection in LTRs should target downstream cardiovascular morbidity and mortality benefit.

Large RCTs in the non-transplant population have reported significant reductions in cardiovascular events with the use of SGLT2i, particularly empagliflozin and canagliflozin.[52] The cardiovascular benefits include significant reductions in the risk of cardiovascular death and hospitalizations for congestive heart failure (CHF).[52] These benefits arise from modulation of sodium-hydrogen exchangers in the heart, kidneys and inflammatory cells, and direct effects on myocardial electrolyte channels, leading to rhythm stability, natriuresis, and augmented myocardial

function.[52] Notably, SGLT2i are also associated with a 4-10-mmHg reduction in systolic blood pressures,[53] a favorable increase in high-density lipoprotein cholesterol and a decrease in triglycerides.[54] These medications may also cause mild elevations in low-density lipoprotein cholesterol, likely due to reduced circulatory clearance and enhanced lipolysis of triglyceride-rich lipoproteins.[53]

GLP1-RAs also promote improved cardiovascular outcomes. Liraglutide, subcutaneous semaglutide, albiglutide, and dulaglutide have shown significant reductions in cardiovascular death, myocardial infarction, and stroke.[55] These findings arise secondary to weight loss, lower blood pressures, lower triglyceride levels, as well as anti-inflammatory and anti-atherothrombotic effects.

As a result, the American Association of Clinical Endocrinology and American College of Endocrinology recommend that an SGLT2i or GLP1-RA be considered as first-line therapy for patients with established or high risk of atherosclerotic cardiovascular disease (ASCVD) or CKD.[56] Given the prevalence of post-LT CVD, these recommendations should be extended to LTRs.

TZDs are associated with increased CHF hospitalizations.[57] Pioglitazone, however, showed significant reductions in the composite endpoint of all-cause mortality, nonfatal myocardial infarction, or nonfatal stroke in a large clinical trial.[57] Nevertheless, a significant reduction in the primary composite endpoint was not observed.[57]

CHRONIC KIDNEY DISEASE

Up to 25% of LTRs develop stage IV-V CKD within 5 years following LT.[58] T2DM is a known risk factor for developing CKD in this population.[6]

Although SGLT2i are contraindicated in end-stage renal disease (ESRD), they have demonstrated benefit with respect to progression of renal disease. An RCT with primary renal endpoints showed a reduction in ESRD, creatinine doubling, and renal deaths in patients receiving canagliflozin versus placebo.[59] A meta-analysis involving three additional large RCTs confirmed a reduction in adverse renal composite outcomes.[60] Multiple mechanisms are proposed, including reduced inflammation and attenuation of hyperfiltration through decreased intraglomerular pressures.[15] This likely occurs secondary to

a tubuloglomerular feedback mechanism triggered by increased distal nephron sodium delivery.[15]

A meta-analysis found that administration of GLP1-RAs significantly reduced adverse renal composite outcomes including new-onset macroalbuminuria, decline in glomerular filtration rate, progression to ESRD, and renal deaths.[61] Similar to SGLT2i, GLP1-RAs cause natriuresis, which may result in decreased intraglomerular pressures.[15] GLP1-RAs may also have anti-inflammatory effects within the kidneys.[15]

While these findings are encouraging, they have not been confirmed in LTRs. Notably, LTRs are at risk for CNI-induced nephrotoxicity, which may be superimposed on the effects of diabetes. CNIs can cause arteriolar vasoconstriction and direct tubular toxicity, which may ultimately result in glomerular sclerosis, arteriolar hyalinosis, and interstitial fibrosis.[62] Given the mechanistic effects of SGLT2i and GLP1-RAs, future investigation looking into outcomes in this population is certainly warranted.

MALIGNANCY

Malignancy, whether recurrent or *de novo*, is a major late cause of morbidity and mortality occurring in up to 20% of LTRs.[63] There are notable data that diabetes and hyperinsulinemia increase the risk of malignancy in the general population.[64] The proposed mechanism is that insulin acts as a growth factor allowing for selective growth of malignant cells.[64] Data on exogenous insulin have been mixed, with only some noting increased risk of malignancy.[64] One study noted that there was no increased risk for overall cancer in patients with type 1 diabetes but there was increased risk among these patients for gastric, liver, pancreas, endometrial and renal cancer, and decreased risk for prostate and breast cancer[65] More data, particularly in T2DM where hyperinsulinemia is more notable, are needed.

Non-insulin-based regimens may reduce or eliminate any insulin-related risk association but prospective data are needed to determine whether any true benefit or risk for malignancy is associated with their use. Metformin has properties that may correlate with decreased risk of some malignancies in patients with diabetes.[66] The mechanism involves metformin acting on the adenosine-monophosphate-kinase pathway, functioning as a tumor suppressor kinase as well

as inhibiting mTOR activity. Unfortunately, most of the data are retrospective or observational, making the true effect unclear. TZDs are activators of PPAR-γ, which is suspected to induce differentiation and cause growth arrest or apoptosis of cancer cells.[67] A meta-analysis suggested a reduced risk of hepatocellular carcinoma in patients taking TZDs,[68] but other studies have suggested a link with bladder, prostate, and pancreatic cancer (thought to be attributable to detection bias).[7,69] Similarly, SGLT2i have been associated with bladder cancer but a meta-analysis did not support this association.[70] Given the risk of medullary thyroid cancer in mice models only, the Food and Drug Administration has recommended against use of GLP1-RAs in patients with personal or family history of medullary thyroid cancer or multiple endocrine neoplasia type 2. A recent meta-analysis found no increased risk of malignancy with GLP1-RAs in humans.[17] Prospective studies in this domain are needed to assess malignancy outcomes. Until then, given the relationship between obesity and diabetes with increased risk of malignancy,[71] the agents most able to manage these metabolic derangements may have the most impact on malignancy risk management.

Practical Considerations

Managing diabetes in the setting of multiple comorbidities can be challenging, but overlapping benefits provide opportunities to have a greater impact on long-term outcomes. An algorithm is proposed for individualized decision making (Fig. 2), and corresponding knowledge gaps are proposed for future studies (Table 3). The algorithm serves as a guide to clinicians to aid in medication selection in the setting of comorbid conditions and should be balanced by factors including insurance coverage, affordability, patient preference, and compliance considerations. Within Fig. 2 there are pathways in which providers may consider multiple first-line therapies. Societies including the American Association of Clinical Endocrinology and American College of Endocrinology have provided recommendations to use GLP1-RAs and SGLT2i as first line in patients with high risk for/established ASCVD and/or CKD due to the abundance of promising data.[56] Furthermore,
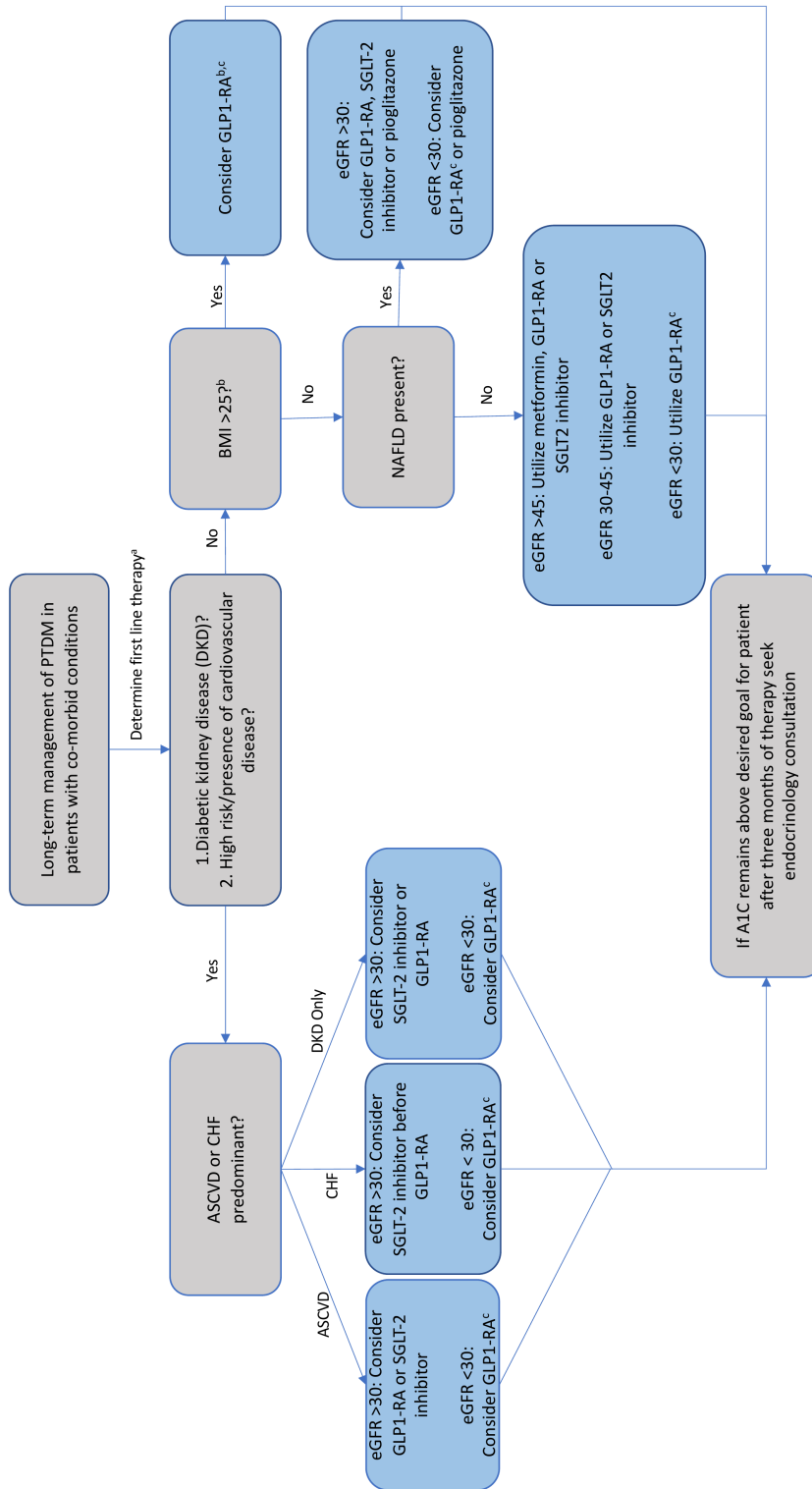
FIG. 2. Proposed personalized management algorithm for diabetes medications in the treatment of patients with PTDM and comorbid conditions. [a]First-line therapy for T2DM is metformin per American Diabetes Association guidelines. The American College of Endocrinology & American Association of Clinical Endocrinologists recommend consideration of SGLT2 inhibitor or GLP1-RA as first line for those with DKD, ASCVD, or CHF. If selecting SGTL2 inhibitor or GLP1-RA, ensure use of agent with existing data to support use. [b]BMI > 25 proposed for goal of achieving a healthy weight; in patients with weight–related comorbidity, semaglutide and liraglutide are Food and Drug Administration–approved for weight loss in those with BMI > 27. [c]Lixisenatide and exenatide manufacturers call for dosage adjustment/discontinuation in severe renal impairment (use of these two agents have not been associated with improved cardiovascular outcomes). Abbreviations: ASCVD, atherosclerotic cardiovascular disease; A1C, hemoglobin A1C; BMI, body mass index; CHF, congestive heart failure; DKD, diabetic kidney disease; eGFR, estimated glomerular filtration rate; GLP1-RA, glucagon–like peptide 1 receptor agonist; NAFLD, non–alcoholic fatty liver disease; PTDM, Post–transplant diabetes mellitus; SGLT–2, sodium–glucose co–transporter 2.

TABLE 3. KNOWLEDGE GAPS THAT MAY IMPACT CLINICAL CARE AND OUTCOMES

Clinical significance, if any, of unstudied interactions between immunosuppression agents and diabetes medications.

Infection risk upon co-administration of immunosuppressants with SGLT-2 inhibitors.

Extent of renal and cardiovascular benefits of SGLT-2 inhibitors and GLP1-RAs in the LT population.

Role of GLP1-RAs and SGLT-2 inhibitors in treatment and prevention of allograft steatosis and steatohepatitis.

True associations, if any, between discussed diabetes medications and de-novo malignancy.

these medications are considered acceptable monotherapy options for patients with a low entry glycated hemoglobin.[56] To emphasize this option, the proposed management algorithm in Fig. 2 suggests consideration of these agents in patients with obesity and steatosis to provide overlapping benefits based on the data previously discussed. The American Diabetes Association continues to recommend metformin as first-line therapy for T2DM.[12] With this, however, recommendations are provided by each of these societies for the management of patients at high risk for/established ASCVD, established CKD, or heart failure, to include an SGLT2i or GLP1-RA with established CVD benefit regardless of glycated hemoglobin or concurrent metformin use.[12,56]

As more data in LTRs become available, a multidisciplinary approach to care involving transplant providers, primary care physicians, medical weight loss specialists, and endocrinologists will be of utmost importance. Figure 2 provides an approach to prescribing clinicians seeking guidance for medication selection. Depending on the practice settings and policies, transplant providers are often not the primary prescriber for non-insulin-based diabetes therapies that tend to be more frequently prescribed by primary care providers and endocrinologists. However, interdisciplinary discussion remains critical to optimize long-term care and outcomes in these patients. In many cases it may simply require sanction of use from the transplant team to allow the providers confidence in prescribing these agents.

Conclusion

The long-term management of PTDM should be personalized based on risk factors and comorbidities. Insulin is universally used in the immediate postoperative period, but transition to alternative agents in the long-term setting, when feasible, is strongly encouraged. With the available data, interactions between diabetes medications and immunosuppression medications appear to be clinically insignificant. While metformin remains the choice first-line agent for most patients, alternatives including SGLT2i and GLP1-RAs should be considered as first line in those with CVD or CKD. SGLT2i and GLP1-RAs generally have the most convincing data to support use in the setting of obesity, CVD, and/or CKD. SGLT2i are preferential to GLP1-RAs in the setting of CHF-predominant CVD. In the absence of CHF, however, GLP1-RAs have more abundant data to support use in patients with obesity and steatohepatitis. More studies are needed to determine the extent of these benefits in LTRs.

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Author names in bold designate shared co-first authorship.