What's New in 2022: The Diabetes Pharmacotherapy Guideline Update

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Abstract

Every January the American Diabetes Association (ADA) publishes its *Standards of Medical Care in Diabetes*. Healthcare professionals with an interest in diabetes anxiously await this annual publication to learn of the updates and changes in the management and care for people with diabetes. This year, the updates and changes are minimal for most sections of the Standards. However, several changes are significant, specifically the updates to the pharmacologic approaches to glycemic treatment section. No longer is metformin the sole option for first line therapy.

Introduction

In 2021, insulin celebrated its'100th anniversary (1). Yet a century after the discovery of insulin, the United States (U.S.) is experiencing an escalation in the number of diabetes cases. The Centers for Disease Control and Prevention (CDC) reported that 37.3 million Americans (11.3% of the U.S. population) have diabetes and 96 million American adults (38% of the U.S. adult population) have prediabetes (2). Coupled with this is the obesity epidemic, where overweight is defined as a BMI of 25 - 30 kg/m^2, obesity as a BMI of greater than or equal to 30 kg/m^2 and severe obesity as a BMI greater or equal to 40 kg/m^2. In the U.S., obesity in adults was reported at 42.4% in 2017–2018 and is anticipated to rise over the next few years. The relationship between diabetes and obesity is well known and is commonly referred to as "diabesity." Although not all people living with obesity will develop diabetes, 80% of people with diabetes also live with overweight/obesity. Additionally, obesity is associated with coronary heart disease and end-stage renal disease, which are common complications related to diabetes (3). Therefore, when treating people with diabetes, looking at more than just glycemic measures is imperative to the overall health and management of this disease. Weight management, cardiovascular (CV) and renal disease must be addressed and treated, along with glucose lowering (3,4). It is complicated, but the goal of meeting glycemic targets is to minimize related complications such as retinopathy, nephropathy, and neuropathy. Despite the advancement of drugs and technology to treat diabetes, many people still struggle to reach the ADA recommended goals: an A1C <7%, a blood pressure <140 mmHg/90 mmHg, or their lipid and weight goals (1,5).

Standards of Medical Care in Diabetes - 2022 Updates

Annually, at minimum, the ADA *Standards of Medical Care in Diabetes* are updated to reflect the ongoing developments and best practices in the management, care and education for people with diabetes. Since 2018, the Standards are updated in real-time as new information and drug indications are updated. In 2022, several noteworthy changes are highlighted in the Standards, including the revision to recommend screening for prediabetes and diabetes starting at 35 years of age, to better individualize monitoring in people with prediabetes, the need for recommending an intensive lifestyle behavior change program for individuals with overweight/obesity, and the need to fully incorporate time in range into the glycemic assessment, to list a few (6).

One of the most notable updates to the Standards is within the pharmacologic approaches to glycemic treatment section; metformin is no longer the sole option for first line therapy. The guidelines address first line therapy based on: 1) comorbidities, 2) patient-centered treatment factors, and 3) management needs (4). Although the guidelines indicate this generally includes metformin and lifestyle modification, other medications, specifically glucagon-like peptide-1 receptor agonists (GLP-1 RAs) and sodium-glucose cotransporter 2 inhibitors (SGLT2i) that have pertinent outcome data, can be used as first line treatment

(with or without metformin) for people with type 2 diabetes (T2D) that have or are at high risk for atherosclerotic cardiovascular disease (ASCVD), heart failure, and/or chronic kidney disease (CKD) (4).

ASCVD is defined as a history of acute coronary syndrome, myocardial infarction (MI), stable or unstable angina, coronary heart disease with or without revascularization, other arterial revascularization, stroke, or peripheral artery disease atherosclerotic in origin. People at high risk for ASCVD include those with end organ damage, left ventricular hypertrophy, retinopathy, and/or multiple CV risk factors (such as hypertension (HTN), smoking, dyslipidemia, obesity) (4). CKD or diabetic kidney disease (DKD) is defined as people with reduced estimated glomerular filtration rate (eGFR), presence of albuminuria, or both (4). Additionally, GLP-1 RAs and SGLT2 inhibitors are also recommended for use in people when striving for weight loss and minimizing hypoglycemia risk, regardless of ASCVD risk.

A key concept is that pharmacotherapy should be started at the time of diagnosis. Additionally, it is important to remember that lifestyle modification (healthy eating, physical activity, stress reduction, sleep management, tobacco cessation, etc.) is the cornerstone to managing diabetes and that medication is always adjunct to lifestyle. Often, people believe that medication will replace lifestyle behaviors, a myth which must be dispelled (4,5).

Pharmacotherapy for T2D

T2D is a result of eight organ defects (the pancreatic beta cell, pancreatic alpha cell, liver, muscle, gastrointestinal (GI) tract, adipose tissue, brain and kidney) which result in hyperglycemia (7). Although there are 12 classes of drugs to treat T2D, no single drug addresses all eight defects (8). This is the reason monotherapy only provides glucose lowering for a short duration of time and combination therapy is warranted for optimal management. Metformin, which primarily targets the liver, has previously been recognized as the first line choice for most people with diabetes (4). Due to the multi-organ defects, metformin's ability to control glucose is often not sustainable (9). As a matter of fact, early combination therapy has been recommended for some people at the start of drug therapy to extend the time before drug treatment failure (4).

GLP-1 RAs

The GLP-1 RAs target five of the eight organ defects: the pancreatic beta cell, pancreatic alpha cell, liver, gastrointestinal tract (GI) and brain (8). This class of drugs is highly efficacious, with an A1C lowering of approximately 1.0 to 1.8%, depending on the specific drug. Short-acting GLP-1 RAs target postprandial glucose with moderate to high efficacy, whereas long-acting GLP-1 RAs target fasting and post prandial glucose levels and have greater efficacy (10). In addition, many of the agents in this class, specifically the injectable analogs (liraglutide, dulaglutide and semaglutide) have demonstrated favorable effects beyond glucose lowering. Specifically, the GLP-1 RAs analogs, which are greater than 90% similar to the endogenous GLP-1 which is secreted in the GI, demonstrate an ASCVD benefit. The GLP-1 RA mimetics, (exenatide, lixisenatide) which are closer to 50% homogenous to our endogenous GLP-1 hormone, show neutrality in ASCVD (9). For this reason, the GLP-1 RAs with outcome data are favored in people that have established CV or are at high risk, as previously defined (4). Table 1 provides a comparison beyond glucose lowering of the various GLP-1 RAs, as well as SGLT2 inhibitors.

GLP-1 RAs also utilize both direct and indirect mechanisms to aid the kidneys that go beyond their glucose lowering effects (11). Unlike the SGLT2 inhibitors, some of the GLP-1 RAs (liraglutide, semaglutide and dulaglutide) can be utilized in advanced kidney disease to prevent further damage, whereas others (lixisenatide and exenatide) are renally cleared and cannot be used at GFR <30 ml/min/1.73m^2.

When counseling patients taking GLP-1 RAs, it is important to review the device injection preparation and technique to ensure proper medication delivery. For the oral GLP-1 RA, semaglutide, patients need to know to take the drug on an empty stomach with a small sip of water (maximum of 4 ounces). People should avoid taking any other medications, foods or beverages for 30 minutes (10). For all GLP-1 RAs, including the oral formulation, educate patients on eating smaller, more frequent meals and paying attention to when they feel full, as this can minimize potential nausea and vomiting that may occur with these agents.

SGLT2 Inhibitors

The SGLT2 inhibitors target one organ defect, the kidney, and produce moderate A1C lowering of approximately 0.8 to 1.0% (10). This drug induces glucose elimination through the kidneys resulting in lower blood glucose, as well as

Table 1. GLP-1 RA and SGLT2 Inhibitor Comparison (4)

Drug		Efficacy	ASCVD	HF	Renal effects (DKD)
GLP-1 RA analogs (injectable)	Dulaglutide (once weekly) Liraglutide (once daily) Semaglutide (once weekly)	High	Benefit	Neutral	Benefit via albuminuria outcomes
GLP-1 RA analog (oral)	Semaglutide (once daily)	High		Neutral	
GLP-1 RA mimetic (injectable)	Exenatide (twice daily) Exenatide (once weekly) Lixisenatide (once daily)	High	Neutral	Neutral	
SGLT2 inhibitor	Canagliflozin Dapagliflozin Empagliflozin Ertugliflozin	Intermediate	Benefit Neutral Benefit Neutral	Benefit	Benefit Benefit Benefit

GLP-1 RA = glucagon like peptide -1 receptor agonist; SGLT2 = sodium glucose cotransporter 2; ASCVD = atherosclerotic cardiovascular disease; HF = heart failure; DKD = diabetic kidney disease

contributes to blood pressure reduction, weight loss, decreased arterial stiffness, decreased vascular resistance, decreased oxidative stress, and increased natriuresis (4,10).

Although there are four drugs currently approved in the SGLT2 inhibitor class, there are subtle differences in their benefits beyond glucose lowering. Out of the four medications, three have clinical evidence and Food and Drug Administration (FDA) indication supporting their CV protective effects. Canagliflozin and empagliflozin are indicated to reduce the risk of CV death in people with T2D and established CVD. In addition, canagliflozin, dapagliflozin, and empagliflozin have various indications for risk reduction in hospitalization in adults with hypertensive heart failure (HHF) (5). Canagliflozin can reduce risk of HHF in T2D with either established CVD or multiple CV risk factors, dapagliflozin is approved for use in people with or without diabetes to reduce HHF with reduced ejection fraction (HFrEF), and empagliflozin has an indication for risk reduction in HHF regardless of left ventricular ejection fraction (5).

Another benefit for some of the medications in the SGLT2 inhibitor class is their favorable effects on CKD. Canagliflozin is labeled to reduce risk of end stage kidney disease, doubling of serum creatinine, and nephropathy with albuminuria, whereas dapagliflozin is approved to reduce risk of sustained eGFR decline (12). SGLT2 inhibitors reduce intra-glomerular pressure which chronically slows progression of kidney damage with albuminuria, stabilizes the long-term GFR, and decreases the incidence of dialysis (12,13). These benefits are not immediate as the GFR often decreases slightly over the initial 1-3 months, but positive outcomes emerge with persistent use beyond six months (13). The renal and cardioprotective effects of SGLT2 inhibitors medications seem to be retained all the way down to approximately a GFR of 20/ml/min/1.73m^2, but current FDA labeling considers them contraindicated once GFR reaches <30 or 45 ml/min/1.73m^2, due to the declining glucose lowering effectiveness as renal function worsens (less ability to pump out glucose) (13). Specifically, dapagliflozin should not be used for glucose improvement in people with eGFR < 45 ml/min/1.73m^2 and canagliflozin and empagliflozin should not be used in people with eGFR < 30 ml/min/1.73m^2 (12).

When counseling patients taking SGLT2 inhibitors it is important to emphasize the need for hydration (increased water intake and moderation of caffeinated/alcoholic beverages), potential for low blood pressure, and proper genitourinary hygiene to minimize the side effects of dehydration and urinary tract infections (10).

Pharmacotherapy Considerations

A key concept for healthcare professionals to understand is that most people with diabetes also have CVD, with the CVD commonly preceding diabetes. Therefore, when discussing a pharmacotherapy treatment plan, consideration beyond lowering glucose must be taken into account. Healthcare professionals should also assess the weight effects of diabetes drugs. Prescribing a drug that

causes weight gain for a person with diabetes that needs to lose weight is counterintuitive. Next, the hypoglycemia risk of the drug needs to be considered, as hypoglycemia itself is a CVD risk factor. Severe hypoglycemia, defined as an event characterized by altered mental and/or physical status requiring assistance for treatment, is recognized to be one of the strongest predictors of macrovascular events, adverse clinical outcomes, and mortality in people with T2D (14). Low blood glucose (< 70 mg/dl) results in an increase in the cardiac workload and potential weakening of the heart, electrophysiological changes, stimulation of a prothrombotic state, and release of inflammatory markers which leads to ischemia (hardening of the arteries) (14,15). Lastly, diabetes is a well-known risk factor for developing heart failure. Dysglycemia is associated with abnormal cardiac structure and function, associated with a 2-5-fold increase risk of heart failure (16). Based on these assessments, the healthcare professional can work with the patient to select the optimal medication therapy. The ADA guidelines support the use of GLP-1 RAs and SGLT2 inhibitors for people with diabetes and a goal of weight loss and/or minimizing the risk of hypoglycemia.

Another consideration is that the effects of monotherapy are rarely sustainable, therefore selecting a combination of medications that work synergistically, target different organ defects, and have benefits beyond lowering glucose is warranted (8). Emerging data suggest use of GLP-1 RAs in combination with SGLT2 inhibitors (with or without metformin) can provide better blood glucose lowering, weight loss, low hypoglycemic risk, as well as CVD and kidney benefit (4).

Management of Type 1 Diabetes (T1D)

Another important addition to the 2022 Standards of Medical Care is the inclusion of recommendations from the EASD/ADA consensus report on the management of T1D (17). The initial report was released in September 2021 and solely focuses on considerations and therapy for people with T1D. The report addresses: new treatments and technology, diagnosis, goals of management, schedule of care, diabetes self-management education and support, glucose monitoring, insulin therapy, hypoglycemia, behavior considerations, psychosocial care, diabetic ketoacidosis, pancreas and islet transplantation, adjunctive therapies, special populations, and inpatient management (17).

Table 2. Adjunct Therapies for Type 1 Diabetes* Comparison (15)

	Metformin	Pramlintide	GLP-1 RA	SGLT2 and SGLT1/2 inhibitors
A1C reduction	0.1%	0.3 to 0.4%	0.2 to 0.4%	0.2 to 0.4%
FG	Minimal effect	No effect	Minimal effect	Modest decrease (~15mg/dl)
PPG	Minimal effect	Significant decrease	Modest decrease	Modest decrease
Time in range	No data	No data	No data (at this time)	Increased (~12%)
Insulin dose	Unchanged	Mealtime reductions	Mostly mealtime reductions	Basal & mealtime reductions (~10%)
Body weight	Modest (~1 kg)	Modest (~1 kg)	Significant decrease (~5kg)	Moderate decrease (~2-3kg)
Hypoglycemia	Low risk	Increase in level 3 risk if prandial insulin dosage not decreased	Potential increase if bolus insulin dosage not decreased	Low risk
Systolic blood pressure	No change	No change	4mmHg decrease	3-4mmHg decrease
Specific benefit (population)	Women with PCOS	No specific group	Overweight, Obese, high insulin dose, CVD & renal risk	CVD and renal risk

FG = fasting glucose; PPG = postprandial glucose; PCOS = polycystic ovary syndrome; CVD = cardiovascular disease

Level 3 hypoglycemia = a severe event characterized by altered mental and/or physical status requiring the assistance of another person for recovery

* The FDA has not approved these drugs in the treatment of T1D so this is an off-label use

In terms of adjunctive therapies, the report recognizes that insulin therapy is essential for people with T1D, however, meeting glucose goals with insulin alone can be difficult. Weight gain and hypoglycemia are undesirable side effects of insulin therapy. Additionally, it is estimated that more than 40% of people with T1D are living with overweight/obesity and have metabolic syndrome (17). Adding more insulin will not fix the insulin resistance which is frequently present with overweight and obesity. Furthermore, insulin resistance promotes pancreatic alpha cell dysfunction and increases ASCVD risk. Therefore, the addition of medications traditionally used for T2D are now being suggested for people with T1D as adjunct to their existing insulin regimen. The medications that have been identified, although not approved by the FDA at this time, include: 1) metformin, 2) pramlintide, 3) GLP-1 RAs, and 4) SGLT2 inhibitors (17). Although these drugs do not produce a significant A1C reduction, their effects on weight loss have been modest to significant. Weight loss improves insulin resistance, thereby reducing the amount of the total daily insulin dose, which can lead to a lower risk of hypoglycemia. Table 2 provides a comparison of these adjunct agents in people with T1D.

Summary

Diabetes treatment has come a long way since the discovery of insulin 100 years ago. Pharmacotherapy needs to look beyond the single goal of lowering blood glucose and must consider the cardiovascular, metabolic and renal systems for optimal treatment outcomes, as well as weight management goals and minimizing the risk of hypoglycemia. Diabetes treatment regimens should be designed to set people up to succeed, as opposed to a treat-to-fail approach.

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