Diabetes Ther
https://doi.org/10.1007/s13300-024-01628-0

REVIEW

Medication-Induced Hyperglycemia and Diabetes Mellitus: A Review of Current Literature and Practical Management Strategies

Akshay B. Jain · Valerie Lai

Received: May 20, 2024 / Accepted: July 15, 2024

ABSTRACT

With the increasing global incidence of diabetes mellitus, physicians may encounter more patients with acute and chronic complications of medication-induced hyperglycemia and diabetes. Moreover, medication-induced diabetes may be an important contributing factor to the high rates of diabetes, and recognizing its impact and risk is a critical step in curtailing its effect on the global population. It has long been recognized that multiple classes of medications are associated with hyperglycemia through various mechanisms, and the ability to foresee this and implement adequate management strategies are important. Moreover, different antihyperglycemic medications are better suited to combat the hyperglycemia encountered with different classes of medications, so it is critical that physicians can recognize which agents should be used, and which medications to avoid in certain types of medication-induced hyperglycemia. In this review, we will discuss the evidence behind the main classes of medications that cause hyperglycemia, their mechanism of action, specific agents that are associated with worsened glycemic control, and, most importantly, management strategies that are tailored to each specific class.

Keywords: Medication; Hyperglycemia; Diabetes mellitus; Drug induced hyperglycemia; Steroid hyperglycemia; Drug-induced diabetes

A. B. Jain (✉)
Division of Endocrinology, Department of Medicine, University of British Columbia, Vancouver, BC, Canada
e-mail: oxyjain@gmail.com

V. Lai
Division of Endocrinology and Metabolism, Department of Medicine, University of Calgary, Calgary, AB, Canada

Published online: 31 July 2024

Key Summary Points

The exact incidence of medication-induced hyperglycemia and diabetes is unknown, but there is evidence that glucocorticoids, antipsychotic medications, cardiovascular medications (statins, beta blockers, diuretics), certain anti-infectives, antineoplastic medications, immunosuppressive agents, and hormonal treatment are associated with changes in glucose metabolism and increased incidence of hyperglycemia and/or diabetes.

The main mechanisms of medication-induced hyperglycemia include insulin resistance, weight gain, and direct effect on beta cell action, but certain medications alter glucose metabolism in other specific ways which can change management, and are important to recognize.

Assessment of underlying patient risk factors, dose and duration of a medication that can cause hyperglycemia or diabetes, and pre-existing comorbidities (e.g., cardiovascular disease, renal disease) are key factors to evaluate risk of medication-induced hyperglycemia and diabetes, and a frank discussion with the patient regarding these risks is warranted.

Patient education, discussion of glucose monitoring, involvement of allied health care, and ensuring that all members of the health care team (including physician prescribing hyperglycemia-inducing medication and physician responsible for managing diabetes, if different) are aware of hyperglycemia risks are critical factors to ensure proper management.

Management of medication-induced hyperglycemia generally includes lifestyle measures and if required, pharmacologic treatment (with metformin generally first line). Depending on factors discussed in this review, addition of other antidiabetes medications may also be required.

INTRODUCTION

The global prevalence of diabetes is estimated at 10.5% in 2021 in those aged 20–79 years old, and is projected to rise to 12.2% in 2045, affecting approximately 783.2 million people by then [1].

Drugs used in the management of various conditions can sometimes lead to impairment of glucose homeostasis, leading to abnormally elevated blood glucose or worsening of previously existent diabetes mellitus (Fig. 1). These commonly include medications such as glucocorticoids, antipsychotics, thiazides, statins, antineoplastic agents, and beta blockers. As such, patients requiring these medications are at high risk of developing medication-induced diabetes.

The importance of monitoring for and recognizing medication-induced hyperglycemia is significant. Certain medications (e.g., antineoplastic treatment, immunosuppression in inflammatory conditions) require long-term use and have benefits that potentially outweigh the risks of hyperglycemia. Moreover, adequate management of hyperglycemia could allow for continuation of these agents. However, if left unrecognized and/or untreated, both acute and chronic (including micro- and macrovascular) complications of hyperglycemia can arise [2].

The exact incidence and prevalence of drug-induced hyperglycemia and diabetes are unknown as a result of limited studies, the sometimes transient nature of hyperglycemia with resolution upon discontinuation of the implicated medication, the lack of distinguishing features between naturally occurring versus medication-induced diabetes, and the lack of monitoring and testing [3]. In addition, many individuals may have undiagnosed diabetes that comes to light when there is further worsening of hyperglycemia due to use of such medications. Finally, the occurrence of hyperglycemia and/or diabetes following the initiation of an implicated medication can range from days to years [2], with the dose and duration of treatment also affecting the probability of hyperglycemia. As a general overview, LaPreze and Robinson have reported the incidence of drug-induced

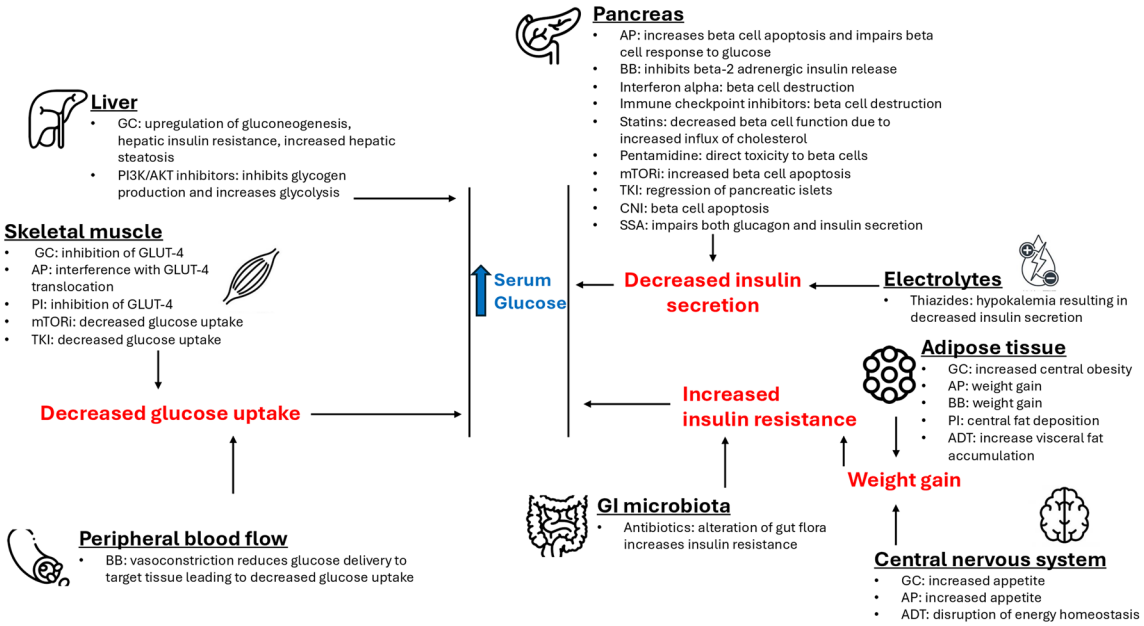

Fig. 1 The main mechanisms of medication-induced hyperglycemic based on medication class. *GC* glucocorticoids, *AP* antipsychotics, *BB* beta blockers, *PI* protease inhibitor, *mTORi* mammalian target of rapamycin inhibitors, *TKI* tyrosine kinase inhibitor, *PI3K* phosphoinositide 3-kinase, *AKT* protein kinase B, *CNI* calcineurin inhibitors, *SSA* somatostatin analogue, *ADT* androgen deprivation therapy, *IFN-A* interferon alpha

diabetes or hyperglycemia to be 40–65% with glucocorticoid use, 10–30% with antipsychotic use, 3–17% with antiretroviral use, 0.8–1.9% with immune checkpoint inhibitors use, 63% with alpelisib use, 15–30% in transplant immunosuppression use, 10% with thiazide diuretic use, 7–48% in statin use, 6.8–19.8% in niacin use, and 22% with beta blocker use [4]. We recognize that lack of robust, prospective, and randomized trials proving causality can often lead to wide variability of incidence with certain medications (e.g., statin therapies). Important considerations when evaluating medication-induced hyperglycemia are shown in Table 1. We would like to elaborate on some of these considerations with the following medications implicated in leading to hyperglycemia, both well-known as well as newer therapies.

This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

GLUCOCORTICOIDS

Current Evidence

Perhaps the most well-known class of medication that leads to hyperglycemia and diabetes is glucocorticoids. A meta-analysis ($N = 34{,}907$) by Liu et al. reports that glucocorticoid-induced hyperglycemia and diabetes occur at a rate of 32.3% ($p = 0.003$) and 18.6% ($p = 0.002$), respectively, in patients without pre-existing diabetes [5]. On a global level, glucocorticoid use is linked to 2% of new-onset diabetes mellitus [6]. Another study found that in a hospitalized population receiving high dose glucocorticoids, 56% of patients without diabetes developed hyperglycemia (defined as blood glucose ≥ 11.1 mmol/L or 200 mg/dL) [7]. Furthermore, the incidence of glucocorticoid-induced diabetes mellitus is likely underreported as a result of the use of fasting blood glucose instead of postprandial/random blood glucose as glucocorticoids typically cause elevated postprandial blood glucose values [8].

Table 1 Different aspects of medication-induced hyperglycemia

Risk factors/patient characteristics	Drugs implicated	Management considerations
Pre-existing diabetes	Glucocorticoids	Mechanism of action of impaired glucose homeostasis
Impaired fasting glucose	Antipsychotics	Dose of implicated drug leading to hyperglycemia
Impaired glucose tolerance family history of diabetes	Beta blockers	Duration of treatment with implicated drug leading to hyperglycemia
Personal history of GDM (gestational diabetes mellitus)	Thiazide diuretics	Potential for altered nutritional intake on therapy
BMI > 27	Statins	Renal and hepatic function
Abdominal obesity	Antibiotioics (gatifloxacin)	Absolute or relative contraindications for use of antihyperglycemic therapy
Age	Antivirals (protease inhibitors, nucleoside reverse transcriptase inhibitors)	Individualized glycemic targets
	Antineoplastic medications	Side effects associated with antihyperglycemic therapy
	Immunosuppression	Frequency of self-monitoring of blood glucose
	Somatostatin analogues	
	Androgen deprivation therapy	
	Interferon alpha	
	Thyroid hormone	
	Diazoxide	
	Phenytoin	
	Teprotumumab	

Mechanism of Action

Glucocorticoid-induced hyperglycemia is mediated via binding of glucocorticoid receptors within hepatic, adipose, skeletal, and pancreatic tissue [8]. Within the liver, glucocorticoids upregulate the enzymes involved in gluconeogenesis [8]. Gluconeogenic precursors such as amino acids from protein catabolism [9] and fatty acids from lipolysis [10] get delivered to the liver to further accelerate gluconeogenesis. Hepatic insulin resistance is another critical mechanism. Normally, insulin suppresses gluconeogenesis, but in the presence of glucocorticoids, gluconeogenesis is allowed to continue despite presence of insulin [11]. At the skeletal muscle level, glucocorticoids inhibit glucose transporter type 4 (GLUT4) recruitment, thereby decreasing glucose uptake into skeletal muscle [12]. Glucocorticoid effects on increased central obesity, increased hepatic steatosis due to increased lipolysis, and increased

appetite stimulation all contribute to the development of steroid-induced hyperglycemia and/or diabetes [8].

Different Agents

All routes of glucocorticoid use are associated with increased risk of hyperglycemia at high doses, but oral routes of administration confer a high risk of hyperglycemia [8]. Commonly used oral glucocorticoids include prednisone, prednisolone, and dexamethasone. Although worsening of hyperglycemia can occur even at physiologic replacement doses of glucocorticoids, the risk increases as the dose of glucocorticoids increases. It is thought that the risk particularly increases at a glucocorticoid dose equivalent to prednisone 7.5 mg/day [13]. A systematic review reported an even higher risk of hyperglycemia with intravenous steroids compared to oral steroids, with an odds ratio of 2.39 (95% CI 1.16–4.91) [14]. Inhaled glucocorticoids (e.g., fluticasone > 1000 µg/day) have been reported to increase the incidence of diabetes mellitus by 34% [15]. Another study demonstrated that intra-articular steroid injections may cause hyperglycemia and generally occurs within 24–72 h [16]. Andersen et al. reported a positive link between topical steroids and the incidence of type 2 diabetes mellitus (T2DM) that was dose related with an adjusted hazard ratio of 1.27 (95% CI 1.26–1.29) [17].

Management

Successful management of steroid-induced hyperglycemia begins with appropriate monitoring of blood glucose. Capillary glucose measurements can be used but have limitations including pain, frequent monitoring in some patients, and potential to miss glycemic excursions. The advent of continuous glucose monitors may be a useful alternative. Glucose monitoring should not be limited to fasting blood glucose and should ideally be measured postprandially given that glucocorticoids tend to cause postprandial hyperglycemia [18]. Specifically, the postprandial glucose after lunch has been suggested as offering the highest diagnostic sensitivity, especially with the use of intermediate-acting glucocorticoids such as prednisone [18]. Shorter courses and smaller doses of glucocorticoids in patients with minimal risk factors who are not critically ill may be managed with non-insulin agents such as metformin or sulfonylureas [19]. Dipeptidyl peptidase 4 (DPP4) inhibitors have been shown in a small study to reduce the mean amplitude of glycemic excursions in a population who developed glucocorticoid-induced diabetes [20]. Similarly, there is a paucity of high-quality studies showing adequate effect with sodium glucose co-transporter 2 (SGLT2) inhibitors in this setting. One study showed that the use of dapagliflozin did not result in better glycemic control compared to placebo in patients with prednisone-induced hyperglycemia during acute exacerbation of chronic obstructive pulmonary disease (AECOPD) [21]. Diabetes Canada also has a list of sick day medications that should be held when an individual is acutely ill, which includes SGLT2 inhibitors [22]. Furthermore, the Joint British Diabetes Societies for inpatient care have published consensus guidelines for management of hyperglycemia and steroid therapy, and state that there is no evidence for SGLT2 inhibitors in steroid-induced hyperglycemia [23]. Considering the evidence, we feel that the use of SGLT2 inhibitors may not be appropriate in most settings where glucocorticoids are used for a short duration for the management of acute sickness. Typically, if the duration of glucocorticoid use is longer, or the patient has a history of poorly controlled diabetes, or is critically ill, then insulin therapy is perhaps the best option to manage elevated blood glucose levels, as it offers significant efficacy and considerable flexibility. Glucocorticoids generally increase postprandial compared to fasting blood glucose, so selection of the type of insulin to match the pharmacokinetics of glucocorticoids is important. The use of insulin NPH or insulin detemir matches the glucose profile of prednisone, whereas longer-acting insulins such as insulin glargine can match the longer-acting duration of dexamethasone [19]. Initiation of prandial insulin using regular insulin or shorter-acting insulin analogues should be considered

if one has predominantly postprandial hyperglycemia despite optimization with the above [19]. Although pre-mixed insulin can also be an option, the lack of flexibility in addressing postprandial hyperglycemia with these insulins can be a challenge, in our opinion. Lifestyle management is also the cornerstone of managing steroid-induced hyperglycemia, and involving allied health including consultation with a dietician and diabetes nurse educator for patient education is of significant value. Development of new medications that can disconnect the hyperglycemic effects from the anti-inflammatory effects is challenging but currently being investigated [8].

ANTIPSYCHOTIC MEDICATIONS

Current Evidence

The prevalence of diabetes in patients taking antipsychotics is estimated to be 20%, which is 2–3 times greater than the general population [24]. A study of almost 346,000 patients in Denmark by Kessing et al. reported that patients taking first- or second-generation antipsychotics had an incident rate of diabetes of 53% and 32%, respectively, and long-term follow-up showed increased risk with number of antipsychotic prescriptions received in addition to the number of antipsychotics used [25]. When compared to non-users of antipsychotics, first- and second-generation antipsychotics had a hazard ratio of 1.53 (95% CI 1.49–1.56) and 1.32 (95% CI 1.22–1.24) for new-onset diabetes. In pediatric populations, the risk of diabetes mellitus increased by threefold in children and adolescents treated with antipsychotic drugs [26]. Moreover, weight gain is estimated to occur in as many as 20–50% of patients using antipsychotics [27], especially with olanzapine and clozapine, which may further worsen hyperglycemia [28].

Mechanism of Action

Three main mechanisms are responsible for antipsychotic-induced diabetes: insulin resistance, weight gain, and beta cell dysfunction and apoptosis [29]. Insulin resistance can occur independently of weight gain by interfering with GLUT4 translocation to the membrane in skeletal cells [30]. The underlying mechanism for weight gain is thought to be caused by increased appetite and food consumption via acting at the serotonergic 5-HT_{2C} receptor, the histaminergic H_1 receptor, muscarinic M3 receptors, and dopaminergic D2 receptors [31–34]. Direct effects on pancreatic beta cells due to increased apoptosis [35] in addition to impaired beta cell response to changes in blood glucose [34] also contribute to antipsychotic-induced hyperglycemia, and this occurs most commonly with clozapine and olanzapine [36].

Different Agents

Hyperglycemia is most common with typical antipsychotics such as haloperidol and chlorpromazine; however, agents such as clozapine and olanzapine, which belong to the atypical antipsychotic class, can result in significantly worsened obesity, weight gain, insulin resistance, and diabetes [29, 37]. In addition, a systematic review by Taylor et al. showed that all atypical antipsychotics except ziprasidone have been associated with weight gain [38]. Aripiprazole and lurasidone also show less effect on glycemic disturbances [39].

Management

Prevention of antipsychotic-induced diabetes mellitus should first be considered, if possible, given the above evidence that certain agents may confer much less risk. As such, in patients with many risk factors, consideration can be given to using ziprasidone, aripiprazole, or lurasidone first. Non-pharmacologic management with healthy diet and regular exercise is also always recommended [40]. With use of the higher-risk antipsychotics such as olanzapine or clozapine, close monitoring of glycemic status should be initiated, and any evidence of hyperglycemia and/or weight gain should be promptly addressed as they may lead to non-compliance

[29]. Specifically, fasting serum glucose has been recommended to be measured annually in patients starting on antipsychotic medication [28]. In those with increased risk factors, fasting serum glucose can be obtained at the 3- and 6-month mark of antipsychotic use for closer monitoring [28]. Metformin, in addition to standard diabetes management, is also the mainstay of managing antipsychotic-induced hyperglycemia [41]. Liraglutide was also shown to improve glucose tolerance in patients taking clozapine or olanzapine, and 63.8% of patients with prediabetes eventually had restoration of normal glucose tolerance [42], with added benefits of weight loss and reduced waist circumference. A case series of patients with antipsychotic-associated weight gain showed successful weight loss with the use of once weekly low dose semaglutide; however, statistically significant reduction in fasting glucose and A1c were not seen [43]. More research in the form of randomized control trials is warranted regarding the potential use of potent incretin therapies including dulaglutide, semaglutide, and tirzepatide in this population.

BETA BLOCKERS

Current Evidence

In a prospective study of 12,550 patients without diabetes, Gress et al. studied the incidence of new-onset diabetes and found a 28% higher risk after adjusting for other risk factors [44]. Two other studies showed that the addition of atenolol or propranolol to a thiazide diuretic increased incident diabetes by 40% [45, 46]. Treatment with metoprolol and atenolol has also been shown to result in elevated fasting glucose levels [47]. Another meta-analysis showed that beta blocker use led to a 22% increased risk for new-onset diabetes mellitus [48].

Mechanism of Action

Hyperglycemia induced by beta blockers is thought to be due to weight gain, inhibition of beta-2 adrenergic-mediated insulin release, and decreased insulin sensitivity [49]. A systematic analysis of eight prospective randomized controlled trials revealed that body weight was increased in patients using beta blockers compared to controls, with a median difference of 1.2 kg [50] which can further worsen insulin resistance. Other mechanisms that contribute include decreased first-phase insulin secretion, which is known to be a key factor in development of T2DM [47, 51]. There is also evidence regarding the implications of changes in peripheral blood flow with beta blocker use. In healthy individuals, insulin increases blood flow and improves delivery of substrate to skeletal muscle and enhances glucose uptake [52]. Beta blocker use increases total peripheral resistance which impedes substrate delivery, and further contributes to the unwanted metabolic effects of beta blocker use [52].

Different Agents

Certain beta blockers contribute to worsened hyperglycemia due to their intrinsic vasoconstrictive properties. Non-selective beta blockers that act on beta-2 receptors prevent vasodilation and reduce delivery of glucose to target tissue, leading to decreased glucose uptake. Vasodilatory beta blockers that have additional alpha-1 blocking activity such as carvedilol are shown to possibly improve insulin sensitivity due to the increased glucose delivery to target tissues as opposed to other agents such as metoprolol that have less vasodilatory effect [52]. Atenolol seems to have a worsened risk of incident diabetes [48].

Management

Lifestyle changes and education should be implemented in all patients, especially considering the weight gain seen with beta blocker use. Limiting high doses of beta blockers or combining treatment with other agents such as calcium channel blockers may also be helpful [49]. Choosing third-generation beta blockers such as carvedilol may also be implemented [53]. Other antihypertensives such as angiotensin-converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARBs) may also be added on

as combination treatment instead of increasing the dose of beta blockers, as they have not shown to have any effect on glycemic regulation [54]. Another large meta-analysis showed that the lowest risk for incident diabetes was with ACE inhibitors and ARBs, followed by calcium channel blockers [55].

THIAZIDE DIURETICS

Current Evidence

The ALLHAT trial found that the incidence of diabetes was significantly increased (48%) in the chlorthalidone group compared to lisinopril use [56]. A meta-analysis reported that thiazide diuretics increased fasting plasma glucose compared to non-thiazide agents or placebo, although the mean difference was relatively small at 4.8 mg/dL or 0.27 mmol/L [57]. Shafi et al. reports that the risk of chlorthalidone was twice as high compared to placebo, with a number needed to harm of 29 (95% CI 17–60) over 1 year, but there was no further risk afterwards [58].

Mechanism of Action

Diuretic use commonly causes hypokalemia, which then results in a reduction of insulin secretion [58]. Other mechanisms that have been suggested are related to increases in free fatty acid levels which decrease insulin secretion in response to glucose, significant reduction in insulin sensitivity, and enhanced hepatic gluconeogenesis in addition to catecholamine secretion [59].

Management

A study by Cooper-DeHoff has demonstrated that new-onset diabetes caused by hydrochlorothiazide may occur at 9–18 weeks of initiation [60]. On the basis of this finding, we suggest screening for diabetes between 3 and 6 months after initiation of diuretics, depending on clinical suspicion. Since hypokalemia is postulated to be the main trigger for decreased insulin secretion, maintaining normal potassium levels (including potential use of potassium supplementation, if needed) is recommended. Diuretic-induced hyperglycemia is also dose dependent, so using the lowest effective dose or combining with other first-line antihypertensives such as calcium channel blockers, ACE inhibitors, or ARBs should also be considered [2]. As always, lifestyle measures should also be implemented.

STATINS

Current Evidence

The incidence of diabetes mellitus was estimated to be between 9% and 12% with statin use in a recent meta-analysis [61]. Another meta-analysis showed a significant increase (25%) in the incidence of new diabetes mellitus with rosuvastatin 20 mg daily compared to placebo [62]. The JUPITER trial reported similar findings, with incident diabetes occurring more frequently in the rosuvastatin arm (hazard ratio 1.25 [95% CI 1.05–1.49, $p = 0.01$]) [63]. The number needed to harm per year ranged from 125 to 250 in a meta-analysis [64], and in another study comparing risk of incident diabetes to cardiovascular events [65], the number needed to treat per year to prevent one myocardial infarction is 39, so the benefit of statin use on cardiovascular outcomes greatly outweighs risk [64].

Mechanism of Action

The main cause of statin-induced hyperglycemia is due to decreased insulin secretion and action [3]. Beta cell function may be disrupted via increased influx of cholesterol due to inhibition of HMG-CoA intracellularly, which leads to mitochondrial oxidative stress and beta cell apoptosis [66]. Insulin resistance via inflammation has also been postulated as another mechanism [66]. Under the conditions of obesity and dysregulated metabolic states, statins may activate inflammation leading to insulin resistance [67]. Another observational study revealed that statin use allowed patients to be more liberal in caloric and fat intake leading to increased weight gain and worsening insulin resistance [68].

Management

A recently published study showed that serum glucose changes within an individual are quite small, and the benefit of measuring A1c or serum glucose levels routinely after initiation of a statin is likely negligible [69]. However, routine screening for diabetes in those that were previously not diagnosed should be continued according to local guidelines. The incidence of new-onset diabetes mellitus is noted to be higher with rosuvastatin compared to atorvastatin (9.5% vs. 7.7%; OR 1.25, 95% CI 1.02–1.53; $p=0.03$) [70]. Less potent statins such as pravastatin are considerably less diabetogenic [71], so consideration of switching statins could be an option. Another study compared the effects of atorvastatin, pitavastatin, and pravastatin on blood glucose and A1c in patients with pre-existing diabetes and found that pitavastatin and pravastatin had minimal effects on both parameters [72]. However, it is highly recommended to assess the benefits of cardiovascular risk reduction versus any potential risk of worsening blood sugars before switching to lower potency statins. Monitoring of lipid panels to assess LDL levels is important in this regard. Reducing the dose of the statin may also be helpful, in addition to standard diabetes medications [3]. It is also worth mentioning niacin use, which has also been linked to a moderate increased risk of diabetes development regardless of the use of statin; however, niacin use is now greatly reduced given lack of cardiovascular benefit when added to statin use, in addition to its increased side effects [73].

ANTI-INFECTIVES

Antibiotics

Current Evidence

A large retrospective study reported that antibiotic use for greater than 90 days had a higher risk of diabetes with an adjusted hazard ratio of 1.16 (95% CI 1.07–1.26), and those who used five or more classes were at higher risk (adjusted hazard ratio 1.14, 95% CI 1.06–1.23) [74]. Specifically, the fluoroquinolone gatifloxacin was shown to have an adjusted odds ratio of 16.7 (95% CI 10.4–26.8) for hyperglycemia [75]. Levofloxacin has also been implicated in hyperglycemia [76]. Another study by Mikkelsen et al. showed that although no specific group of antibiotics was associated with diabetes risk, there was a slightly higher odds ratio with narrow-spectrum antibiotics [77]. However, the authors also concluded that their findings may simply reflect an increased demand for antibiotics due to the increased risk of infection in patients with diabetes. Data from Ye et al. showed no association between antibiotic use and risk of diabetes, suggesting some potentially confounding factors in prior studies [78].

Mechanism of Action

Antibiotic use alters normal gut flora. Animal studies have shown that altered gut microbiota increases insulin resistance; furthermore, patients with T2DM or prediabetes have altered gut flora with resultant changes in the balance of short chain fatty acids [74]. As with other medications, causality is often not definitive as the occurrence of infections, for which antibiotics are used, can itself lead to increased predisposition to development of diabetes by multiple mechanisms including increased inflammation, hepatic gluconeogenesis, and insulin resistance.

Management

There are limited guidelines on treating antibiotic-induced hyperglycemia [76]. There is some dose association with the risk of hyperglycemia [77]; as such, using the lowest dose for the shortest duration can mitigate the risk, and avoiding gatifloxacin is reasonable.

Antivirals

Current Evidence

Protease inhibitors (PI) such as atazanavir or ritonavir are usually part of a combination of drugs that is used to treat human immunodeficiency virus (HIV), and while there has been significant

improvement in morbidity and mortality, side effects such as increased glucose and lipid levels have been observed. Hyperglycemia is seen in 3–17% of patients treated with protease inhibitors [76]. Tsiodras et al. showed that protease inhibitors had a fivefold increase in the incidence of hyperglycemia [79]. In addition, NRTIs (nucleoside reverse transcriptase inhibitors) can also affect glucose metabolism by causing mitochondrial dysfunction [80].

Mechanism of Action

Koster et al. suggest that PIs cause hyperglycemia by inhibiting GLUT4 transporters leading to insulin resistance, and they can also directly impair insulin secretion in animal models [81]. Carr et al. also report that PIs impair chylomicron uptake in the liver as well as triglyceride clearance resulting in central fat deposition and insulin resistance [82].

Management

Screening with baseline fasting serum glucose followed by monitoring every 3 months for the first year has been suggested to prevent acute and chronic complications of hyperglycemia [83]. Metformin should be considered first line for pharmacologic management, and there is some evidence with pioglitazone use as well, but this must be balanced with the risk of fluid retention and fracture risk [84]. Given the significant reduction in morbidity and mortality of HIV treatment, standard treatment of diabetes instead of altering doses of PI therapy is typical.

ANTINEOPLASTIC MEDICATIONS

Mammalian Target of Rapamycin (mTOR) Inhibitors

Current Evidence

mTOR inhibitors such as everolimus or sirolimus are used to treat a variety of malignancies, including renal, breast, or neuroendocrine tumors, by inhibiting tumor proliferation and angiogenesis. A meta-analysis conducted by Lew and Chamberlain showed a 5.3% incidence rate of severe hyperglycemia (>13.0 mmol/L) [85]. Clinical trials also show rates of hyperglycemia and new onset of diabetes ranging from 13% to 50% [86]. In the RADIANT-3 trial, the frequency of hyperglycemia was 13% vs. 4% in placebo [87]. In another trial, hyperglycemia occurred in 14% of patients on temsirolimus [88].

Mechanism

The mTOR pathway regulates glucose metabolism by working downstream of insulin binding, which ultimately leads to decreased glycogen synthesis and glucose uptake in skeletal muscle [89]. Decreased insulin secretion is also observed in in vitro studies due to increased beta cell apoptosis [90].

Management

Metformin has been postulated to help prevent and to treat everolimus-associated hyperglycemia as it may affect mTORC1 signalling [91]. Busaidy et al. also propose modification of mTOR inhibitor dose if standard treatment of hyperglycemia is not sufficient [92]. Fasting serum glucose should be measured every 2 weeks for 1 month after initiation of mTOR inhibitor therapy, followed by monthly fasting blood glucose, and A1c levels every 3 months [93]. As always, lifestyle changes and patient education are crucial, along with standard antidiabetic agent use.

Tyrosine Kinase Inhibitors (TKIs)

Current Evidence

TKIs are used to treat a variety of malignancies such as chronic myeloid leukemia and lung cancers. It is estimated that hyperglycemia occurs in 20–36% of patients on nilotinib and imatinib [94]. Specifically, insulin-like growth factor 1 (IGF-1) receptor TKIs have been reported to cause high-grade-severity hyperglycemia in

13–46% of patients, and epidermal growth factor receptor (EGFR) TKIs have been reported to cause hyperglycemia in between 5% and 25% of patients [95].

Mechanism

Janssen et al. found that nilotinib therapy decreases peripheral insulin sensitivity with resultant hyperinsulinemia as compensation, leading to hyperglycemia [96]. There is also suggestion that TKIs may cause regression of pancreatic islets, decreased glucose uptake, and changes in IGF-1 signalling [97].

Management

Preventing symptoms of hyperglycemia and acute complications such as infection, diabetic ketoacidosis (DKA), and osmotic diuresis while balancing quality of life would be the goals of therapy in this cancer specific population, especially if disease is advanced [98]. Liberalizing glucose targets (e.g., A1c < 8%) can be considered as well. Given that there is an increase in insulin resistance, reasonable first-line options would be insulin-sensitizing agents such as metformin. DPP4 inhibitors are also a good option given low risk of hypoglycemia. Newer agents such as SGLT2 inhibitors may have concerns for euglycemia DKA, and sulfonylureas may not be ideal given unpredictable oral intake in patients who may be in advanced stages of cancer. Glucagon-like peptide 1 receptor agonists (GLP-1 RAs) may lead to weight loss and appetite suppression, which may not be desired. Thus, insulin therapy may be the best option if hyperglycemia is uncontrolled owing to flexibility of dosing [98].

Phosphoinositide 3-Kinase (PI3K) and Protein Kinase B (AKT) Inhibitors

Current Evidence

These agents are mainly used to treat breast cancer or hematologic malignancies. PI3K inhibitors may cause hyperglycemia but fortunately it is quite infrequent, with < 8% affected in patients on pilaralisib and pictilisib [99, 100]. AKT inhibitors also have low rates of hyperglycemia, occurring in < 3% for afuresertib [101]. However, Liu et al. reported that hyperglycemia is amongst the most common side effects of PI3K and AKIT inhibitors, occurring up to 80% in trials [102].

Mechanism

PI3K and AKT are downstream mediators of insulin binding and lead to production of glycogen and a decrease in glycolysis [95]. As such, when these pathways are disrupted, the intracellular response to insulin is disturbed, and hyperglycemia can occur.

Management

Metformin is recommended as first-line treatment, followed by use of an SGLT2 inhibitor, which has been found to have greatest reduction in serum glucose, but carries the risk of euglycemic DKA [102]. Hyperglycemia may also be mitigated by dose interruption or modification of PI3K and AKT inhibitors as well, in addition to using insulin or sulfonylureas [102].

Immune Checkpoint Inhibitor (ICI) Therapy

Current Evidence

Mulla et al. suggested that use of ICI therapy is associated with hyperglycemia in 8.6% of patients without pre-existing diabetes [103]. Furthermore, combination checkpoint therapy has higher rates in a meta-analysis [104]. Another study reported a significant increase in hyperglycemia (27%) after treatment with checkpoint inhibitors [105].

Mechanism

ICI therapy has a higher association with type 1 diabetes mellitus (T1DM) physiology due to immune-mediated damage to pancreatic beta cells; however, the incidence is reported at 1–2% [103, 106]. Glucocorticoid therapy to help treat other immune-mediated side effects of checkpoint inhibitors may further confound

the picture. The mechanism is similar to T1DM, and in the patients that did develop new-onset diabetes requiring insulin, 83% had low or undetectable C-peptide, and autoantibodies were elevated in 71% [106]. Different classes of ICI also seem to cause varying degrees of hyperglycemia. New-onset diabetes occurred most frequently with pembrolizumab (2.2%) compared to nivolumab (1%), both of which are anti-programmed cell death 1 (PD-1) antibodies, but 0% with ipilimumab, which is an anti-cytotoxic T lymphocyte-associated antigen 4 (CTL4-A) antibody [106].

Management

Routine screening with C-peptide, A1c, and ketones to prevent rapid metabolic decompensation is suggested with endocrinology involvement as needed [107]. Given the mechanism of action, insulin management is usually required; glucocorticoid treatment is not recommended to treat ICI-induced diabetes because of exacerbation of hyperglycemia [107].

IMMUNOSUPPRESSIVE AGENTS

Calcineurin Inhibitors (CNIs)

Current Evidence

These medications are used for inflammatory disorders or immunosuppression after organ transplantation, and new-onset diabetes is reported to occur in 15–30% of this patient population [108]. A meta-analysis by Heisel et al. found that the incidence of diabetes in patients receiving calcineurin inhibitors (tacrolimus, cyclosporine) is 13.4% [109].

Mechanism

Calcineurin promotes islet beta cell expansion, and so CNIs lead to pancreatic beta cell apoptosis and decreased insulin secretion [110]. Cyclosporine and tacrolimus have been implicated to cause higher rates of hyperglycemia compared to sirolimus [111].

Management

Implementation of early monitoring and ensuring to adjust for renal function when considering antidiabetes medication is important. Insulin is usually the mainstay of management, and it is important to ensure that oral antihyperglycemic agents do not interfere with absorption of immunosuppressants (e.g., GLP-1 RAs may reduce gastrointestinal transit and decrease absorption) [112]. Current evidence based on Munoz Pena et al.'s comprehensive review reveals that non-insulin antihyperglycemic medications (e.g., metformin, DPP4 inhibitors, SGLT2 inhibitors, GLP-1 RAs) can also be used that further add cardiovascular and renal benefits without any significant disruptions in renal or allograft function and immunosuppressive agent doses [112].

HORMONES

Somatostatin Analogues (SSAs)

Current Evidence

SSAs are used to treat acromegaly, Cushing's disease, and neuroendocrine tumors. Hyperglycemia has been documented as a common side effect of SSA use, with 41.4% of patients developing elevated blood glucose levels in one study [113], and incident diabetes of 19% in another study [114]. Specifically, pasireotide tripled the incidence of hyperglycemia and diabetes in 30% of patients compared to octreotide and lanreotide [115]. However, other studies contradict this finding; Ni et al. used the Surveillance, Epidemiology and End Results (SEER) database and found a non-statistically significant hazard ratio (1.19, 95% CI 0.95–1.49) of developing diabetes with SSA use [116]. Interestingly, SSAs have also been used to treat some forms of hyperinsulinemic hypoglycemia [117]. There is further conflicting evidence regarding development of diabetes with SSA use [118, 119], but in general, there is enough evidence to warrant monitoring of blood sugars.

Mechanism

The mechanism of SSA-induced hyperglycemia is complex. SSA therapy is meant to reduce IGF-1 and growth hormone levels, which should lead to improved insulin sensitivity. However, SSAs also act on alpha and beta cells in the pancreas, which impairs both glucagon and insulin secretion leading to abnormal regulation of glucose [120]. Some studies have found that SSAs have beneficial effects on carbohydrate metabolism as well [121].

Management

The discontinuation of SSAs leads to reversal of diabetes [121]. However, in those requiring long-term use of SSAs, Samson et al. reported metformin is a good first-line medication followed by use of GLP-1 RAs [118]. Active surveillance and standard diabetes treatment including lifestyle and other antidiabetes medications also apply [3]; however, it should be noted that acromegaly and Cushing's syndrome also have diabetogenic effects.

Androgen Deprivation Therapy (ADT)

Current Evidence

ADT is used for treatment of prostate cancer, and it has been linked to a 28% risk of diabetes, with 20% of patients having an A1c increase by 1% [122]. In the meta-analysis by Wang et al. of almost 66,000 patients, ADT use was associated with a 39% higher rate of diabetes than non-ADT users; there was also a strong association with longer duration of use (>6 months) [123].

Mechanism

Lower testosterone levels increase insulin resistance via several mechanisms. Androgens prevent visceral fat accumulation which is known to increase insulin resistance. Serum adiponectin is elevated in hypogonadal men; thus, the suppression of adiponectin by testosterone may lead to decreased adipocytes, improved adipose function and sensitivity [124]. Rodent studies also show that there is a relationship between low testosterone and hepatic steatosis which decreases fatty acid oxidation leading to increase de novo lipid synthesis [125]. Aside from peripheral actions, testosterone may act centrally to control energy homeostasis and total energy expenditure [126].

Management

There is limited literature on the treatment of hyperglycemia secondary to ADT use. As such, general measures such as education, lifestyle changes, and standard diabetes medications should apply [3].

OTHER MEDICATIONS

Interferon Alpha

This medication is indicated in treatment of hepatitis C and has been associated with beta cell destruction and subsequent risk of developing T1DM by 0.09–0.45% [127]. At times, DKA has been observed and requires ongoing insulin management [127]. Insulin resistance has also been reported in interferon alpha use [128]. General management measures apply, with surveillance, and standard antidiabetes medications.

Thyroid Hormone Supplementation

There is evidence that a hyperthyroid state may worsen pre-existing diabetes mellitus, and that insulin resistance can be improved by restoring a euthyroid state [129]. It is postulated that a hyperthyroid state increases glucose absorption, food intake, hepatic gluconeogenesis, and serum insulin levels, and there is also a complex interplay of thyroid hormone and its interaction with leptin, ghrelin, and adiponectin that may cause disturbances in non-euthyroid states [130]. Furthermore, the half-life of insulin is decreased in a hyperthyroid state as a result of increased degradation [130]. As such, overtreatment of hypothyroidism with thyroid hormone replacement may worsen pre-existing diabetes. Metformin

is reported to have beneficial effects on both T2DM and thyroid disease, whereas the use of sulfonylureas and thiazolidinediones increase the risk of hyperthyroidism and decreases FT4, respectively [131].

Diazoxide

This medication is used to treat hypoglycemia in hyperinsulinemic causes and acts by decreasing insulin secretion and increasing epinephrine secretion, and possibly also by directly increasing gluconeogenesis and inhibiting peripheral glucose uptake [132]. Cases of DKA and hyperosmolar hyperglycemic state (HHS) have also been reported [2]. There are no guidelines on management; as such, discontinuation of diazoxide if hyperglycemia occurs is reasonable.

Phenytoin

Used as an anti-seizure medication, phenytoin has been documented to induce hyperglycemia via inhibiting insulin release and possibly also due to insulin resistance [133]. Management includes lowering phenytoin dose [133]. A case report of DKA in a patient with pre-existing diabetes also reveals that discontinuation of phenytoin resolved the hyperglycemia [134].

TEPROTUMUMAB

Current Evidence

Teprotumumab is a new medication used to treat Graves' orbitopathy and targets the IGF-1 receptor. In 2021, Kahaly et al. reported an 8% incidence rate of hyperglycemia in those using teprotumumab compared to placebo, and the majority of patients (63%) had pre-existing diabetes [135]. A case of HHS has also been reported after the initial infusion of teprotumumab [136]. A more recent observational study reported in 2023 by Amarikwa et al. found an overall A1c increase of 0.5% at 3 months, and 52% of their patients had hyperglycemia; the risk was higher in patients with pre-existing diabetes [137].

Mechanism

Teprotumumab is a monoclonal antibody that inhibits the IGF-1R, which has partial homology to the insulin receptor [136]. Thus, hyperglycemia is driven by inhibition of the insulin receptor by teprotumumab [136].

Management

There are currently no published guidelines for teprotumumab-induced hyperglycemia. However, Amarikwa et al. recommend that prior to initiation with teprotumumab, the patient should be educated regarding the risks of hyperglycemia, and it is suggested that the patient is screened for diabetes or prediabetes with an A1c and fasting glucose level [137]. In those diagnosed with diabetes, optimization of A1c should be targeted to be $<7\%$ prior to treatment. Since most hyperglycemia occurs within 12 weeks of treatment, a repeat A1c should be done during this timeframe. Referral and co-management with endocrinology and ophthalmology is recommended as well [137].

UPCOMING ANTINEOPLASTIC MEDICATIONS

Alpelisib

Alpelisib is a PI3K inhibitor used to treat metastatic breast cancer. The mechanism of action is the same as per the discussion of PI3K inhibitors above. Shen et al. found that 29% of patients developed grade 3–4 hyperglycemia [138]. Another study reported grade 3 hyperglycemia occurring in 32.7% of patients with median onset of 15 days [139]. The grades of hyperglycemia are classified according to the Common Terminology Criteria for Adverse events (CTCAE): grade 1 is defined as abnormal glucose above baseline with no medical intervention; grade 2 is defined as change in the daily management from baseline for a patient with diabetes, or the initiation of oral antihyperglycemic agents, or new workup for diabetes mellitus; grade 3 is

defined as the initiation of insulin therapy or where hospitalization is indicated; grade 4 is defined as life-threatening consequences requiring urgent intervention; and grade 5 is defined as death. Optimizing glycemic control prior to initiation of alpelisib, if possible, should be considered [138]. Initiation of metformin in patients who developed hyperglycemia was most common, and 20% required referral to endocrinology [138]. The importance of early recognition and treatment of side effects with dose modifications of alpelisib helped reduce toxicities and can lead to reductions in treatment discontinuations which ultimately can improve progression-free survival [139].

R1507

R1507 is a monoclonal antibody against IGF-1 receptor and was studied for the treatment of Ewing's sarcoma. Use of this medication had a low incidence of subclinical hyperglycemia [140], and in another study by Pappo et al., hyperglycemia occurred in < 5% of patients [141]. Routine monitoring is suggested.

GSK2141795 (Uprosertib)

Uprosertib is an AKT inhibitor used in advanced solid tumors. Hyperglycemia occurred in 15% of patients [142]. A more recent publication found that combining uprosertib with other agents to treat endometrial cancer or melanoma was poorly tolerated by patients and did not reach effective doses due to side effects [143]. Hyperglycemia was reported in up to 21% of patients [95]. However, a more recent study showed that combination of uprosertib and another agent was poorly tolerated with minimal clinical activity, but hyperglycemia was not listed as a common side effect [144].

MK-2206

MK-2206 is used for advanced solid tumors. Yap et al. reported that hyperglycemia was mild and transient, but that elevated blood glucose was still seen in 57% of patients [145]. Ramanathan et al. reported a 30% incidence of hyperglycemia as an adverse event; however, antitumor response was not significant and there was no further testing of this medication for ongoing treatment [146].

BEZ235

BEZ235 is a combination PI3K and mTOR inhibitor for treatment of advanced solid tumors, and 24% of patients were reported to experience any grade hyperglycemia [147]. Currently, this agent is not tolerable for patients because of multiple reported adverse effects and the phase I study in 2016 was terminated as a result of lack of clinical efficacy as well [148].

GDC-0980 (Apitolisib)

Apitolisib is a dual PI3K-mTOR inhibitor and was used in patients with endometrial cancer. Makker et al. reported grade 3 and 4 hyperglycemia in 46% of patients, and 61% of patients with pre-existing diabetes had to discontinue use because of hyperglycemia, with 31% of patients with DM requiring dose reductions [149]. Dolly et al. reported similar findings, with grade 3 hyperglycemia occurring in 18% of patients [150].

PF-04691502

PF-04691502 is also a dual PI3K inhibitor with a reported 27% incidence of hyperglycemia in treatment of patients with solid tumors [151]; however, no objective antitumor responses were observed. Britten et al. found that in patients treated with this agent, there were increases in fasting serum glucose, insulin, and C-peptide levels.

PF-05212384/PKI-587 (Gedatolisib)

Gedatolisib is a dual PI3K/mTOR inhibitor and is used in patients with advanced cancer. Shapiro et al. reported hyperglycemia occurring in 26% of patients treated with this agent [152]. Currently, different combinations of this drug are being investigated for breast cancer, colorectal

cancer, and acute myeloid leukemia in ongoing clinical trials.

General Management Principles of Medication-Induced Hyperglycemia

Overall, the potential of a drug to cause hyperglycemia and diabetes needs to be known and balanced with the patient's underlying risk factors. More importantly, the benefits and risks of continuing the current medication, the duration and dose of the medication, and a discussion with the patient regarding future microvascular and macrovascular complications should be had, especially if the patient has pre-existing comorbidities such as cardiovascular or renal disease. The current landscape of evidence leaves some questions unanswered, including the precise role of the dose and exposure time of each medication, and these would be excellent future directions of research.

Instituting measures to assess glycemic status prior to initiation of a diabetogenic medication and ongoing monitoring during treatment is critical, as most medications are duration and dose dependent. The advent of technology with continuous glucose monitors can also be implemented for convenience and real-time monitoring to target specific periods of hyperglycemia (e.g., fasting vs. postprandial). The involvement of allied health including dieticians, diabetes nurse educators, and referrals or consultations with endocrinology can also be of use. Education of patients regarding acute symptoms of hyperglycemia, including polyuria, polydipsia, or weight loss, is also essential.

In general, treatment of medication-induced hyperglycemia and diabetes is similar to standard treatment with lifestyle measures including balanced diet and exercise applying to almost all cases. Acute episodes of hyperglycemia, particularly those causing DKA or HHS, should be treated with IV insulin. The medications listed above that cause pancreatic beta cell destruction, such as immune checkpoint inhibitors or interferon alpha, may require upfront treatment with insulin. The wide array of non-insulin antidiabetic medications should also be selectively used on the basis of each patient's specific situation. Metformin has generally been first-line treatment in all the above causes of medication-induced hyperglycemia given its safety and efficacy. GLP-1 RAs and glucose-dependent insulinotropic polypeptide (GIP) receptor/GLP-1RAs were initially designed for management of diabetes; however, it is now well known that these agents can also lead to significant weight loss, with side effects including nausea and abdominal pain. While the weight loss may be desired in patients who have overweight/obesity, these should be avoided in patients where weight loss is unwanted, such as patients with advanced cancer or in those that are frail or malnourished. In addition, the nausea and vomiting may also affect absorption of crucial medications (e.g., immunosuppression for organ transplant, oral antineoplastic agents) and should be reconsidered. SGLT2 inhibitors are another class of medications that may be used for glycemic control, but there is a risk of euglycemic DKA especially in sick individuals [153]. Sulfonylureas in general should be avoided in those who have unpredictable oral intake because of the risk of hypoglycemia; DPP4 inhibitors have minimal risk of hypoglycemia but are not as potent [98].

CONCLUSION

Medication-induced hyperglycemia requires recognition, screening, monitoring, and proper management to prevent acute and chronic complications. Specifically, the growing prevalence and incidence of diabetes globally, the increasing number of antineoplastic agents and their prolonged use, and the large number of patients with pre-existing cardiovascular disease that may be exacerbated by hyperglycemia and diabetes with the aforementioned antihypertensive medications warrant special attention and ongoing vigilance for medication-induced hyperglycemia by all health care professionals.

Author Contribution. Akshay B. Jain was involved in conceptualizing, literature review, writing, editing, and creation of the tables and figure. Valerie Lai was involved in literature

review, writing, editing, and creation of the tables and figure.

Funding. No funding or sponsorship was received for this study or publication of this article.

Data Availability. Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

Declarations

Conflict of Interest. Akshay B. Jain reports receipt of speaking honoraria or consulting fees from Abbott, AstraZeneca, Amgen, Antibody, Bausch Healthcare, Bayer, Boehringer Ingelheim, Care to Know, CCRN, Connected in Motion, CPD Network, Dexcom, Diabetes Canada, Eli Lilly, Embecta, EOCI,Gilead Sciences, GSK, HLS Therapeutics, Insulet, Janssen, Liv, Master Clinician Alliance, MDBriefcase, Merck, Medtronic, Moderna, Novartis, Novo Nordisk, Partners in Progressive Medical Education, Pfizer, Roche, Six Degrees, Timed Right, Unik, WebMD, Ypsomed. Valerie Lai has nothing to disclose.

Ethical Approval. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

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