A variety of pharmacological agents affect glucose homeostasis resulting in either hypo- or hyperglycemia. Hormones such as insulin, glucagon, catecholamines, growth hormone, and cortisol, among others, contribute to normoglycemia. Drug-induced serum glucose alterations manifested as hyperglycemia or hypoglycemia can have perpetual effects on the body, particularly in patients with diabetes. This article is the second of a two-part series reviewing drug-induced serum glucose alterations. The first article in the series appeared in the previous issue of this journal (Diabetes Spectrum 24:171-177, 2011). In this article, we review select therapies commonly contributing to the development of hyperglycemia.

Hyperglycemia is clinically defined as a serum glucose level > 180 mg/dl that persists for more than 2 hours. Unlike hypoglycemia, acute hyperglycemia is often benign and may persist without any clinically significant signs or symptoms; however the development of diabetic ketoacidosis (DKA) or hyperosmolar hyperglycemic state (HHS) are hyperglycemic emergencies.

Often signs and symptoms of hyperglycemia manifest when serum glucose levels are in the range of 270–360 mg/dl for an extended period and include the classical symptoms of polyphagia, polydipsia, and polyuria (Table 1). Untreated hyperglycemia, when accompanied with excretion of ketones in urine (DKA), is a medical emergency more common in people with type 1 diabetes. It results in the following symptoms: fatigue, weakness, fruity odor of the breath, confusion, lack of concentration, shortness of breath,

<table>
<thead>
<tr>
<th>Signs</th>
<th>Symptoms</th>
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<tbody>
<tr>
<td>Increased heart rate</td>
<td>Catecholamine-Mediated</td>
</tr>
<tr>
<td>Elevated systolic blood</td>
<td>Mediated (Adrenergic)</td>
</tr>
<tr>
<td>pressure</td>
<td>Acetylcholine-Mediated</td>
</tr>
<tr>
<td></td>
<td>Mediated (Cholinergic)</td>
</tr>
<tr>
<td>Anxiety</td>
<td>Hunger</td>
</tr>
<tr>
<td>Tremor</td>
<td>Dry, itchy skin</td>
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<tr>
<td>Dry mouth</td>
<td>Frequent urination</td>
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<tr>
<td>Dehydration</td>
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<td></td>
<td>Ischemic injury</td>
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<td>Cognitive impairment</td>
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<td>Behavioral changes</td>
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<td>Irritability</td>
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<td>Drowsiness</td>
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<td>Blurred vision</td>
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<td></td>
<td>Confusion</td>
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<td></td>
<td>Feeling faint</td>
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<td></td>
<td>Seizure</td>
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<td>Coma</td>
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Table 1. Signs and Symptoms of Hyperglycemia
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Table 2. Select Drug Categories and Drugs Associated With Hyperglycemia

<table>
<thead>
<tr>
<th>Antibiotics (Fluoroquinolones)</th>
<th>Gatifloxacin (also associated with hypoglycemia)</th>
<th>Levofloxacin</th>
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</thead>
<tbody>
<tr>
<td>Calcineurin inhibitors</td>
<td>Cyclosporine</td>
<td>Sirolimus</td>
</tr>
<tr>
<td>Protease Inhibitors</td>
<td>Atazanavir</td>
<td>Tacrolimus</td>
</tr>
<tr>
<td>Thiazide and thiazide-like diuretics</td>
<td>Chlorthalidone</td>
<td>Diazoxide</td>
</tr>
<tr>
<td></td>
<td>Hydrochlorothiazide</td>
<td>Indapamide</td>
</tr>
<tr>
<td></td>
<td>Methylclothalidiazide</td>
<td>Metolazone</td>
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</tbody>
</table>

*Note: Carvedilol and nebivolol are not associated with the development of hyperglycemia.

People with type 2 diabetes are more likely to develop HHS, formerly known as hyperosmolar hyperglycemic nonketotic coma. Characteristics of HHS are 1) plasma glucose ≥ 600 mg/dl, 2) serum osmolality ≥ 320 mOsm/kg, 3) dehydration up to an average of 9 L, 4) serum pH > 7.30, 5) small ketones and absent to low ketonemia, and 6) altered consciousness.1

The exact mechanism of how thiazide diuretics cause the development of hyperglycemia is unknown. However, it is postulated to involve worsening of insulin resistance, inhibition of glucose uptake, and decreased insulin release, among other pathways. In addition, thiazide diuretics are postulated to down-regulate peroxisome proliferator-activated receptor gamma, thereby decreasing insulin release in addition to activating the renin-angiotensin-aldosterone system, thus resulting in elevated levels of aldosterone and resulting hyperglycemia.14,15

Another proposed mechanism of thiazide-induced hyperglycemia involves thiazide-induced hypokalemia. However, hypokalemia is an inconsistent finding in people who

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Hyperglycemia has not been precisely elucidated, but hyperglycemia has been reported to occur with gatifloxacin within 5 days of initiation of therapy.1,5 In one study involving residents ≥ 66 years of age in Ontario, Canada, when compared with macrolide antibiotics (e.g., azithromycin and clarithromycin), gatifloxacin was associated with a substantially increased risk of hyperglycemia (adjusted odds ratio 16.7 [95% CI 10.4–26.8]). Specific guidelines addressing the treatment of gatifloxacin induced hyperglycemia are not available. However, avoiding the use of gatifloxacin in patients with diabetes has been proposed.6

β-blockers

In people with diabetes, β-blockers such as propranolol, metoprolol, and atenolol can result in consistently elevated fasting blood glucose levels.7 In a recent study, atenolol was also shown to contribute to new-onset diabetes and to worsen hyperglycemia in people with abdominal obesity. In this study, adverse metabolic effects, including the development of hyperglycemia manifesting as impaired fasting glucose, were apparent within 9 weeks of therapy initiation.

β-blockers are thought to contribute to the development of hyperglycemia by impairing the release of insulin from the pancreatic β-cell.9 Interestingly, carvedilol and nebivolol are not associated with the development of hyperglycemia or new-onset diabetes.10–12

Thiazide and Thiazide-Like Diuretics

Thiazide antihypertensive drugs (e.g., hydrochlorothiazide) and thiazide-like drugs (e.g., metolazone) are often prescribed to control blood pressure in people with diabetes. Thiazide diuretics are known to promote hyperglycemia and in some cases contribute to the new onset of diabetes.8,13

The exact mechanism of how thiazide diuretics cause the development of hyperglycemia is unknown. However, it is postulated to involve worsening of insulin resistance, inhibition of glucose uptake, and decreased insulin release, among other pathways. In addition, thiazide diuretics are postulated to down-regulate peroxisome proliferator-activated receptor gamma, thereby decreasing insulin release in addition to activating the renin-angiotensin-aldosterone system, thus resulting in elevated levels of aldosterone and resulting hyperglycemia.14,15

Another proposed mechanism of thiazide-induced hyperglycemia involves thiazide-induced hypokalemia. However, hypokalemia is an inconsistent finding in people who
develop hyperglycemia or diabetes when taking a thiazide diuretic. Hydrochlorothiazide has been implicated in contributing to new-onset diabetes in as few as 9–18 weeks of therapy initiation.

Second-Generation Antipsychotics (SGAs)
Newer SGAs, also known as “atypical antipsychotics,” may increase the risk of hyperglycemia or type 2 diabetes. In particular, olanzapine and clozapine are most likely to increase the risk of diabetes when used in people with schizophrenia.17 The estimated odds ratio of developing type 2 diabetes in the first year of treatment with clozapine are 7.44 (95% CI 1.603–34.751) compared to psychotic patients not receiving antipsychotics.18 For olanzapine, the odds ratio is 3.10 (95% CI 1.620–5.934). The estimated odds of a person receiving risperidone developing type 2 diabetes is 0.88 (95% CI 0.372–2.070) compared to those not receiving antipsychotics in their first year.18

The exact mechanism of how atypical antipsychotics promote the development of hyperglycemia and diabetes is unknown. The development of diabetes and resultant hyperglycemia, however, is likely a complex interplay of the atypical antipsychotic’s likelihood of promoting weight gain (e.g., olanzapine and clozapine) through the involvement of multiple mechanisms. These mechanisms involve, but are not limited to, antagonism at 5-HT receptors (serotonin receptors) mainly involving 5-HT2C, which is involved in regulation of food intake; antagonism at central histamine H1 receptors; development of insulin resistance through effects on cellular glucose transporters; compromised insulin secretion; and alterations in leptin levels.17,19 Sympathetic activation by SGAs in a mouse study appeared to promote hyperglycemia.20

Corticosteroids
Use of corticosteroids is very common in clinical practice for treating and controlling inflammation and inflammatory conditions (e.g., rheumatoid arthritis, temporal arteritis), and inducing immunosuppression and for their chemotherapeutic effects. It is well known and recognized that glucocorticoid use in people with or without diabetes results in hyperglycemia.21 The odds ratio for new-onset type 2 diabetes in people treated with glucocorticoids ranges from ~1.5 to 2.5, and larger total corticosteroid dose and longer duration of use are associated with increased risk of new-onset diabetes.22 Even intrarticular injection of prednisone in people with diabetes may result in hyperglycemia.22

Corticosteroids blunt the action of insulin and promote hepatic gluconeogenesis, possibly by activation of liver x receptor-β involving phosphoenolpyruvate carboxykinase gene transcription.23,24 From a clinical standpoint, corticosteroids primarily increase postprandial blood glucose levels, whereas fasting levels are unaffected or only mildly elevated.25 Clore and Thurby-Hay25 propose a weight-based dosing guideline using NPH insulin for treating glucocorticoid-induced hyperglycemia associated with tapering dosages of prednisone. This guideline suggests using 0.4 units/kg of NPH for prednisone doses ≥ 40 mg/day, with the NPH insulin dose being decreased by 0.1 unit/kg for each 10 mg/day decrease in prednisone dose.

Clinicians must keep in mind that glucocorticoids impair insulin sensitivity and β-cell function and contribute to gluconeogenesis, patients may be placed at increased risk of DKA or HHS while on glucocorticoid therapy.26,27

Calcineurin Inhibitors (CNIs)
Calcineurin is a protein phosphatase that activates T cells of the immune system.28 The CNIs cyclosporine, sirolimus, and tacrolimus are often used to avoid allograft rejection in transplantation therapy.

The sustained use of these agents results in post-transplantation diabetes.29,30 Risk factors for the development of hyperglycemia and a diagnosis of post-transplantation diabetes include age, nonwhite ethnicity, glucocorticoid therapy for rejection, and the use of cyclosporine or tacrolimus.24 The incidence of post-transplantation diabetes is estimated to be 24% at 36 months post-transplant.30

The postulated mechanism of hyperglycemia results from inhibition of pancreatic islet β-cell expansion promoted by calcineurin.31

Protease Inhibitors
Protease inhibitors are essential components of antiretroviral therapy for the treatment of people with HIV and AIDS. Protease inhibitor–associated hyperglycemia may occur in treated people with or without diabetes and occurs in 3–17% early in therapy or after extensive and prolonged use.32

Protease inhibitor drugs are thought to create a homeostatic stress response that decreases insulin sensitivity, thereby promoting insulin resistance–associated hyperglycemia.33 Ritonavir has been shown to directly inhibit glucose transporter type 4 activity in vivo, accounting for its ability to cause hyperglycemia.34

Clinical Management
Drug-induced or drug-associated hyperglycemia, irrespective of previous diabetes diagnosis, should be suspected in patients newly started or maintained on any of the drug categories or drugs reviewed in this article. Vigilant monitoring of blood glucose should be instituted at the discretion of the prescriber because patient response to therapy will vary.

In general, at the time of or shortly after initiating corticosteroids, blood glucose levels may be altered, whereas patients on hydrochlorothiazide may not experience altered levels for weeks or longer (or not at all) if doses are kept low (12.5–25 mg).7

In regard to SGAs, a consensus statement developed by the ADA in conjunction with other medical professional organizations recommends monitoring fasting blood glucose for 12 weeks after initiation of therapy and annually thereafter in those without diabetes.35 However, cases involving hyperglycemic crises have been reported within weeks of starting SGAs.35 Furthermore, the panel recommends that consideration be given to switching a patient with blood glucose abnormalities to an SGA that is not associated with
contributing to the development of diabetes (e.g., aripiprazole or ziprasidone). For patients with diabetes who are on SGAs, specific treatment guidelines are not available. However, the authors recognize that more diligent or frequent monitoring and medication adjustment is medically prudent.

Transplantation patients with new-onset or concurrent diabetes often remain on the most effective post-transplant drug regimens with management of blood glucose following current recommendations. However, modification of the immunosuppressive regimen could be considered and consists of reduction or split-dosing of corticosteroids, reduction or alteration of CNIs therapy, and consideration of instituting steroid-sparing immunosuppressive therapies. 36

Summary
The antibiotic gatifloxacin, β-blockers, thiazide diuretics, some SGAs, corticosteroids, the CNIs cyclosporine and tacrolimus, and protease inhibitors may elevate blood glucose levels in those with or without diabetes. Clinicians need to be aware of the potential for drugs to contribute to the development of elevated blood glucose in their patients regardless of a diagnosis of diabetes.

References
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Pharmacy and Therapeutics


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