

# Drug-Induced Glucose Alterations Part 1: Drug-Induced Hypoglycemia

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Many pharmacological agents commonly used in clinical practice affect glucose homeostasis, interfering with the body's balance between insulin, glucagon, catecholamines, growth hormone, and cortisol. Drug-induced serum glucose alterations manifested as hyperglycemia or hypoglycemia and ranging from mild to moderate to severe symptoms either appearing acutely or chronically, have perpetual effects on the body, particularly in patients with diabetes. This article and a second one that will appear in the next issue of this journal review drug-induced serum glucose alterations in a two-part series. In this article, we review pertinent clinical information on the incidence of drug-induced hypoglycemia and discuss the underlying pathophysiological mechanisms involved.

Hypoglycemia is clinically defined as a serum glucose concentration low enough to cause the signs and symptoms differentiated in Table 1.<sup>1-4</sup> Depending on the severity, hypoglycemic symptoms include irritability, impaired concentration, neurological deficits, seizures, coma, and even neuronal death.<sup>5</sup> However, clinical manifestations vary from individual to individual, and some report hypoglycemic symptoms even when serum glucose levels do not reflect hypoglycemia or vice versa.

Although definitions of hypoglycemia differ in the literature, many trials will differentiate between hypoglycemia (asymptomatic and symptomatic low serum glucose levels) and severe hypoglycemia. This article will cover and report both when applicable.

The American Diabetes Association (ADA) Workgroup

on Hypoglycemia has defined and classified hypoglycemia based on the severity of symptoms in patients diagnosed with diabetes as outlined in Table 2.<sup>2</sup> In general, severe hypoglycemia develops when a reduction in blood glucose is enough to require assistance from another person to actively administer carbohydrate, glucagon, or other corrective actions.<sup>2</sup> Severe hypoglycemia is a serious clinical syndrome that continues to be the most common endocrine emergency faced by health care providers and remains the limiting factor in effective diabetes management for many patients.<sup>6</sup>

Hypoglycemia has been associated with a higher number of hospital admissions, longer hospital stays, and significant morbidity and mortality in patients with diabetes or hyperglycemia.<sup>6,7</sup> In a systemic review of 448 publications describing drug-induced hypoglycemia,<sup>8</sup> 90% of reported cases were classified as severe hypoglycemia in which symptoms were present and required assistance by someone other than the patient.

Although hypoglycemia can be iatrogenic, in which normal body defenses are impaired, treatment with insulin or insulin secretagogues (e.g., sulfonylureas [SUs] and meglitinides), as monotherapy or in combination, account for a majority of hypoglycemic events.<sup>3</sup> In addition to glucose-lowering agents, many commonly used non-antidiabetic drugs have been reported to cause or contribute to drug-induced hypoglycemia, even in individuals without diabetes. Furthermore, as people age and their number of comorbidities and medications increase over time, they expose themselves to an

Table 1. Signs and Symptoms of Hypoglycemia<sup>3,4</sup>

Signs	Symptoms		
Diaphoresis Pallor Increased heart rate Elevated systolic blood pressure	Neurogenic (Autonomic)		Neuroglycopenic
	Catecholamine-mediated (adrenergic)	Acetylcholine-mediated (cholinergic)	Cognitive impairment Behavioral changes Irritability Drowsiness Blurred vision Difficulty with speech Confusion Feeling faint Seizure Coma
	Tremor Palpitations Anxiety/arousal	Sweating Hunger Tingling Trembling	

Table 2. ADA Workgroup on Hypoglycemia Definition and Classification of Hypoglycemia in People With Diabetes<sup>1,2</sup>

Type of Hypoglycemia	Presentation of Symptoms
Severe hypoglycemia	An event requiring assistance of another person to actively administer resuscitative actions
Documented symptomatic hypoglycemia	An event during which typical symptoms of hypoglycemia are accompanied by a measured plasma glucose concentration $\leq 70$ mg/dl
Asymptomatic hypoglycemia	An event not accompanied by typical symptoms of hypoglycemia but with a measured plasma glucose concentration $\leq 70$ mg/dl
Probable symptomatic hypoglycemia	An event during which symptoms typical of hypoglycemia are not accompanied by a plasma glucose determination (but that was presumably caused by a plasma glucose concentration of $\leq 70$ mg/dl)
Relative hypoglycemia	An event during which the person with diabetes reports any of the typical symptoms of hypoglycemia and interprets those as indicative of hypoglycemia, with a measured plasma glucose concentration $> 70$ mg/dl but approaching the hypoglycemic level

exponential risk for possible drug interactions or cumulative adverse effects that may result in asymptomatic or symptomatic hypoglycemia. Thus, thoroughly reviewing a patient's medication history is essential, and drug-associated causes should always be included in the differential diagnosis of hypoglycemia until ruled out by other causes (e.g., non-endocrine disease, trauma, or infections).

Serum glucose reductions secondary to pharmacological agents are caused by multiple actions that include pharmacokinetic or pharmacodynamic drug interactions or additive hypoglycemic effects from polypharmacy. Recognition of underlying pathophysiological mechanisms responsible for drug-induced hypoglycemia from pharmacological treatments other than those used

in the management of diabetes will allow for more practical and safe health care practices.

Medications commonly used for diabetes treatment are not discussed in detail in this review because hypoglycemia has been well established with the use of insulin, SUs, and meglitinides as monotherapy or in combination with other agents such as metformin, thiazolidinediones (TZDs), exenatide, or dipeptidyl peptidase-4 (DPP-4) inhibitors. However, metformin, TZDs, and  $\alpha$ -glucosidase inhibitors such as acarbose and miglitol, when administered as monotherapy at usual doses, should have little to no risk of hypoglycemia based on their mechanisms of action. As a point of reference, Table 3<sup>9,10</sup> provides the absolute risk of hypoglycemia for common glucose-lowering agents

used in the management of diabetes. Although numerous drugs can lower serum glucose concentrations, this article will review non-antidiabetic drugs or drug classes associated with hypoglycemia used in patients with diabetes (Table 4).

#### ACE Inhibitors

In 1985, the first case of ACE inhibitor-induced hypoglycemia was reported with the administration of captopril.<sup>11</sup> Since then, several reports and small studies have published the incidence of hypoglycemia associated with ACE inhibitor use, but the data remain controversial.

In a small case-control study from the Netherlands,<sup>12</sup> 94 patients were identified and admitted to the hospital with hypoglycemia, and 654 control subjects were selected from the same cohort. As many as

**Table 3. Absolute Risk of Mild-to-Moderate Hypoglycemia With Commonly Used Glucose-Lowering Agents<sup>9,10</sup>**

Drug Class	Drug	Monotherapy	Combination Therapy	
Biguanides	MET	†	See combinations with MET below.	See combinations with MET below.
Second-generation sulfonylureas (SUs)	Glimepiride	0.9–1.7%	+ pioglitazone + rosiglitazone	13.4–15.7% 3.6–5.5%
	Glipizide	3%	+ MET	7.6–12.6%
	Glyburide	21.3%	+ MET	11.4–37.7%
Meglitinides	Nateglinide	1.3–3%	*	*
	Repaglinide	16–31%	+ MET	33%
Glucagon-like peptide-1 (GLP-1)	Exenatide	4.5–35.7%	+ MET + SU + MET + SU + TZD	4.5–5.3% 14.4–35.7% 19.2–27.8% 11%
	Liraglutide	9.7%	+ MET + glimepiride + MET + glimepiride	3.6% 7.9% 27.4%
Thiazolidinediones (TZDs)	Pioglitazone	†	+ MET + SU + insulin	4.4% 26.7–28.8% 53.4–56.4%
	Rosiglitazone	†	+ MET + glimepiride	3.6–5.5% 3.6–5.5%
α-Glucosidase inhibitors	Acarbose	†	+ SU or insulin	2%
	Miglitol	†	*	*
DPP-4 inhibitors	Sitagliptin	0.6–12.2%	+ MET + glimepiride +/- MET	1.6% 12.2%
	Saxagliptin	2.7–14.6%	+ MET + glyburide + TZD	3.4–7.8% 13.3–14.6% 2.7–4.1%
Amylinomimetic	Pramlintide	16.8%	*	*

MET, metformin; SU, sulfonylurea; TZD, thiazolidinedione.

\*Risk not reported.

†Absolute risk data are not available because these agents cause little to no risk of hypoglycemia when used in monotherapy and within normal dosing ranges. Although hypoglycemia risk is low in monotherapy, when given in combination with oral hypoglycemic agents or insulin, additive effects increase the risk of hypoglycemia, as shown above.

13.8% of all hospital admissions for hypoglycemia were significantly attributable to the use of ACE inhibitors (odds ratio 2.8 [95% CI 1.4–5.7]), but this was among patients with diabetes concomitantly treated with insulin or oral antidiabetic agents for at least 1 year.

Another small study<sup>13</sup> determined that ACE inhibitor use in people with diabetes was associated with a

three- to fourfold increased risk of hypoglycemia. Although the exact mechanism for its glucose-lowering effects is unknown, the hypothesis involves an indirect increase in insulin sensitivity by increasing circulating kinine, which in turn leads to vasodilatation in the muscles and ultimately increased glucose uptake in muscle tissue. Bradykinin may also have a contributory role in downreg-

ulating hepatic glucose production. Suppression of peripheral sympathomimetic overactivity may also be involved in blood glucose-lowering effects of ACE inhibitors.<sup>14</sup>

#### Alcohol/Ethanol

Hypoglycemia associated with alcohol ingestion is a well-established problem in patients with diabetes. Patients who are treated with anti-

Table 4. Non-Diabetes Drugs Associated With Hypoglycemia<sup>1,3,9,17,20</sup>

Drug Class	Drug	Mechanism of Glucose-Lowering Effects	Common Indications	Clinical Significance
ACE inhibitors	<ul style="list-style-type: none"> <li>• Benazepril</li> <li>• Enalapril</li> <li>• Lisinopril</li> <li>• Perindopril</li> <li>• Ramipril</li> <li>• Captopril</li> <li>• Fosinopril</li> <li>• Moexipril</li> <li>• Quinapril</li> <li>• Trandolapril</li> </ul>	Indirectly increases insulin sensitivity by increasing circulating kinins, which leads to vasodilatation in the muscles and increased glucose uptake in muscle tissue	Hypertension, congestive heart failure (CHF), diabetic nephropathy, post-myocardial infarction (MI)	+
β-Blockers	<p>Noncardioselective:</p> <ul style="list-style-type: none"> <li>• Levobunolol</li> <li>• Metipranolol</li> <li>• Nadolol</li> <li>• Propranolol</li> <li>• Sotalol</li> <li>• Timolol</li> </ul> <p>Cardioselective:</p> <ul style="list-style-type: none"> <li>• Acebutolol</li> <li>• Atenolol</li> <li>• Betaxolol</li> <li>• Bisoprolol</li> <li>• Esmolol</li> <li>• Nebivolol</li> <li>• Metoprolol</li> </ul>	Inhibits glycogenolysis; attenuates signs and symptoms	Post-MI, chronic angina pectoris/coronary artery disease, hypertension, acute coronary syndromes, CHF, perioperative prevention of cardiac events, acute myocardial infarction	+
Chloramphenicol		May inhibit the metabolism of SUs	Bacterial meningitis, cystic fibrosis, salmonella infection, typhoid fever, acne	+
Chloroquine		Unknown	Malaria, hemophagocytic syndrome, porphyria cutanea tarda, sarcoidosis, ulcerative colitis	+
Clofibrate		Enhances the effect of SUs	Acne, diabetes insipidus, glaucoma, hyperlipidemia, migraine, multiple sclerosis, prophylaxis for MI, neonatal jaundice	+
Disopyramide		Unknown; appears to result from endogenous insulin secretion	Ventricular arrhythmia	++
Ethanol		Impairs gluconeogenesis; increases insulin secretion		+++

*continued on p. 175*

diabetic agents such as insulin and SUs (e.g., glyburide) are at higher risk for developing hypoglycemia, particularly those who have been previously fasting or who have a history of chronic abuse.<sup>15</sup>

The proposed mechanism of alcohol-induced hypoglycemia in a fasting and intoxicated patient is primarily the inhibition of gluconeogenesis along with depleted glycogen stores as a response from starva-

tion.<sup>16</sup> Alcohol may also indirectly increase endogenous insulin secretion, contributing to hypoglycemic effects observed in individuals.<sup>17</sup> Furthermore, symptoms of hypoglycemia can bear such a resemblance

**Table 4: Non-Diabetes Drugs Associated With Hypoglycemia<sup>1,3,9,17,20</sup>, continued from p. 174**

Quinolones (Fluoroquinolone)	<ul style="list-style-type: none"> <li>• Ciprofloxacin</li> <li>• Gatifloxacin</li> <li>• Levofloxacin</li> <li>• Moxifloxacin</li> <li>• Norfloxacin</li> <li>• Ofloxacin</li> </ul>	Unknown; enhanced insulin secretion appears to result from blockade of ATP-sensitive potassium channels in pancreatic $\beta$ -cells	Bacterial conjunctivitis, bronchitis, community-acquired pneumonia, gonorrhea, uncomplicated skin infections, pyelonephritis, acute sinusitis, urinary tract infections	+
Pentamidine		Cytolytic release of insulin	Pneumocystis pneumonia, cutaneous leishmaniasis, trypanosomiasis, visceral leishmaniasis	+++
Salicylates	<ul style="list-style-type: none"> <li>• Aminosalicilyc acid</li> <li>• Aspirin</li> <li>• Choline magnesium trisalicylate</li> <li>• Magnesium salicylate</li> <li>• Salsalate</li> </ul>	Increases insulin secretion and sensitivity; may alter pharmacokinetic disposition of SUs	Pain, fever, inflammation, cerebrovascular accident, MI	+

+ Low probability of occurrence and/or low level of drug-induced hypoglycemia expected in patients.

++ Moderate-to-high probability of occurrence but degree of drug-induced hypoglycemia may or may not be clinically significant.

+++ High probability of occurrence; drug-induced hypoglycemia is clinically significant.

to symptoms of mild alcohol intoxication that patients may be negligent of the differences. Patients should be appropriately cautioned about close monitoring of blood glucose levels to ensure the actual cause.<sup>15,17</sup>

### $\beta$ -blockers

$\beta$ -blockers can cause or exacerbate hypoglycemia in some individuals, either by worsening an already present hypoglycemic episode or by delaying recovery time.<sup>17</sup>

The mechanism responsible for  $\beta$ -blocker-induced hypoglycemia involves inhibition of hepatic glucose production, which is promoted by sympathetic nervous stimulation. In addition, adrenergic counterregulation is diminished, resulting in a reduction in glycogenolysis.<sup>17,18</sup>

Non-cardioselective  $\beta$ -blockers such as propranolol are more likely to cause hypoglycemia than cardioselective ones such as atenolol and metoprolol. Nevertheless, patients on the latter should still be cautioned about the potential for drug-induced hypoglycemia.<sup>19</sup>

Furthermore,  $\beta$ -blockers have the potential for masking symptoms of

hypoglycemia. The catecholamine-mediated neurogenic hypoglycemic symptoms masked by this class of medications include tremor and palpitations. Hunger, tremor, irritability, and confusion may be concealed as well. Sweating, however, remains unmasked and may be the only recognizable sign of hypoglycemia in individuals treated with  $\beta$ -blockers.<sup>17,20</sup>

### Pentamidine

Pentamidine is used in the treatment of opportunistic infections associated with immunosuppression such as Pneumocystis pneumonia, although it is no longer considered a first-line therapy because of its glucose-altering adverse effects.<sup>9</sup> Hypoglycemia is the most common metabolic abnormality observed within 5–14 days of initiating therapy and occurs in about 6–40% of patients.<sup>17,20</sup>

Pentamidine-induced hypoglycemia is caused by an increase in insulin secretion via a cytolytic response in the pancreas. Intravenous glucose or oral diazoxide at initiation of therapy is often given in anticipation of this cytolytic release of

insulin.<sup>21</sup> Over time, patients become increasingly deficient in insulin as the pancreatic destruction progresses, eventually resulting in hyperglycemic episodes. Within a matter of weeks to months, this consequential adverse effect can lead to the development of new-onset diabetes.<sup>9,17,20</sup>

### Quinolone (Fluoroquinolone) Antibiotics

Quinolones, commonly known as fluoroquinolones, are widely used as broad-spectrum antibiotics against community- and health care-associated infections. Incidences of quinolone-induced hypoglycemia in the literature vary within the class, but gatifloxacin has been associated with having a greater effect on increasing insulin levels and reducing blood glucose compared to other quinolones.<sup>1</sup> In fact, the prescribing information for gatifloxacin specifically states that diabetes is a contraindication for use.<sup>22</sup> The prescribing information for other quinolones (e.g., ciprofloxacin, levofloxacin, and moxifloxacin) include information about altering serum glucose levels but only suggest cau-

tion regarding their use in patients with diabetes.

The mechanism is unknown, but it has been theorized that quinolones indirectly cause hypoglycemia through blockade of adenosine 5'-triphosphate (ATP)-sensitive potassium channels in the pancreatic  $\beta$ -cells that regulate calcium influx. This enhances insulin release in a dose-dependent manner.<sup>23</sup>

Furthermore, because quinolones are excreted primarily by the renal route, patients with renal insufficiency may be at higher risk for developing hypoglycemia if accumulation occurs, particularly in the elderly.<sup>1,24</sup> Although incidences of quinolone-induced hypoglycemia have mostly been reported in older adults with diabetes concomitantly taking insulin or SUs, the adverse effect has been reported to develop in individuals without a history of diabetes.<sup>1</sup>

### Salicylates

In the early 1900s, salicylates were considered a treatment for diabetes because of their potential to decrease glycosuria in older patients. However, the therapy was relatively short-lived.<sup>25</sup> Limited by their associated adverse effects (i.e., gastrointestinal [GI] bleeding) as a blood glucose-lowering agent, salicylates are now used primarily as analgesic, anti-inflammatory, antipyretic, and antiplatelet agents.<sup>9</sup>

In addition to an increased risk for GI bleeds, salicylates have also been recognized to induce hypoglycemia, especially in concomitant use with SUs. Salicylate-induced hypoglycemia is thought to be caused by several mechanisms: increasing insulin secretion in those with type 2 diabetes, increasing insulin sensitivity, displacing SUs from protein-binding sites, and inhibiting renal excretion.<sup>17,20,26</sup>

More than a century later, preliminary small studies are re-investigating the use of salicylates, particularly with salsalate, a nonacetylated prodrug of salicylate in the treatment of type 2 diabetes. In a recent, small study<sup>26</sup> involving 108 type 2 diabetic patients randomized to receive placebo or salsalate in doses of 3.0, 3.5, or 4.0 g/day for 14

weeks, A1C was lowered by  $\geq 0.5\%$  from baseline ( $P = 0.009$ ). Patients were concomitantly treated with diet and exercise alone, an insulin secretagogue, or a DPP-4 inhibitor, either as monotherapy or in combination. Other studies have shown high-dose aspirin therapy (e.g., 4–7 g/day) to indirectly enhance insulin sensitivity in liver and muscle through reduced rates of lipolysis and lowered levels of plasma fatty acid.<sup>27</sup>

Although salicylates have been reported to lower blood glucose concentrations, results are conflicting and warrant further safety investigations. Nonetheless, the potential for salicylate-induced hypoglycemia should be considered in patients, particularly those administered high doses or taking concurrent insulin or oral insulin secretagogues.

### Summary

Numerous pharmacological agents that are commonly used in patients with or without diabetes have the potential to alter serum glucose levels. Although drug-induced hypoglycemia is often mild, it is a serious concern when life-threatening symptoms lead to increased hospitalizations, excessive costs, and significant mortality rates. A comprehensive understanding and awareness of the drug mechanisms responsible for lowering serum glucose concentrations may allow for better prediction of drug interactions and adverse effects and ultimately the implementation of more individualized, rational, and safe therapies for patients.

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