

Drug-Induced Glucose Alterations Part 2: Drug-Induced Hyperglycemia

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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 1. Signs and Symptoms of Hyperglycemia

Signs	Symptoms		
Increased heart rate	Catecholamine-Mediated (Adrenergic)	Acetylcholine-Mediated (Cholinergic)	Neurohyperglycemic
Elevated systolic blood pressure	Anxiety Tremor Dry mouth Dehydration	Hunger Dry, itchy skin Frequent urination	Ischemic injury Cognitive impairment Behavioral changes Irritability Drowsiness Blurred vision Confusion Feeling faint Seizure Coma

Table 2. Select Drug Categories and Drugs Associated With Hyperglycemia

Antibiotics
Quinolone
Gatifloxacin (also associated with hypoglycemia)
Levofloxacin
Atypical antipsychotics
Most Risky
Clozapine
Olanzapine
Intermediate
Paliperidone
Quetiapine
Risperidone
Least Risky
Aripiprazole
Ziprasidone
Unknown
Iloperidone
β-blockers*
Atenolol
Metoprolol
Propranolol
Corticosteroids
Calcineurin inhibitors
Cyclosporine
Sirolimus
Tacrolimus
Protease Inhibitors
Atazanavir
Darunavir
Fosamprenavir
Indinavir
Nelfinavir
Ritonavir
Saquinavir
Tipranavir
Thiazide and thiazide-like diuretics
Chlorthiazide
Chlorthalidone
Diazoxide
Hydrochlorothiazide
Indapamide
Methyclothiazide
Metolazone

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

nausea and vomiting, dry skin, and flushing of the skin.

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 American Diabetes Association (ADA) provides hospital admission guidelines when people exhibit hyperglycemia.² Specifically, hospitalization is recommended when DKA or HHS are present and when the following are noted: hyperglycemia associated with volume depletion, metabolic deterioration associated with persistent refractory hyperglycemia, and recurring fasting hyperglycemia > 300 mg/dl refractory to outpatient therapy.²

Common drug categories and drugs associated with contributing to hyperglycemia are discussed below.

Antibiotics (Fluoroquinolones)

Fluoroquinolones are the only class of antibiotics consistently associated with the development of hyperglycemia. The most commonly implicated fluoroquinolone is gatifloxacin, whereas levofloxacin is weakly implicated.³ Interestingly, gatifloxacin is also associated with the development of hypoglycemia.

The proposed hypoglycemic mechanism involves binding of the antibiotic to the pancreatic β-cell similar to the action of sulfonylureas.⁴ The mechanism for fluoroquinolone-associated hyperglycemia has not been precisely elucidated, but hyperglycemia has been reported to occur with gatifloxacin within 5 days of initiation of therapy.^{3,5} In one study³ 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,⁸ 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.⁸ Hydrochlorothiazide has been implicated in contributing to new-onset diabetes in as few as 9–18 weeks of therapy initiation.⁸

Second-Generation Antipsychotics (SGAs)

Newer SGAs, also known as “atypical antipsychotics,” may increase the risk of hyperglycemia or type 2 diabetes.¹⁶ 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-HT_{2C}, 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.²¹ 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 \geq 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 because 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.^{28,29} 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.²⁸ 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 CNI 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

- Kitabchi AE, Umpierrez GE, Murphy MB, Kreisberg RA: Hyperglycemic crises in adult patients with diabetes: a consensus statement from the American Diabetes Association. *Diabetes Care* 29:2739–2748, 2006
- American Diabetes Association: Hospital admission guidelines for diabetes. *Diabetes Care* 27 (Suppl. 1):S103, 2004
- Park-Wyllie LY, Juurlink DN, Kopp A, Shah BR, Stukel TA, Stumpo C, Dresser L, Low DE, Mamdani MM: Outpatient gatifloxacin therapy and dysglycemia in older adults. *N Engl J Med* 354:1352–1361, 2006
- Saraya A, Yokokura M, Gonoi T, Seino S: Effects of fluoroquinolones on insulin secretion and beta-cell ATP-sensitive K⁺ channels. *Eur J Pharmacol* 497:111–117, 2004
- LaPlante KL, Mersfelder TL, Ward KE, Quilliam BJ: Prevalence of and risk factors for dysglycemia in patients receiving gatifloxacin and levofloxacin in an outpatient setting. *Pharmacotherapy* 28:82–89, 2008
- Frothingham R: Glucose homeostasis abnormalities associated with use of gatifloxacin. *Clin Infect Dis* 41:1269–1276, 2005
- Luna B, Feinglos MN: Drug-induced hyperglycemia. *JAMA* 286:1945–1948, 2001
- Cooper-DeHoff RM, Wen S, Beitelshes AL, Zineh I, Gums JG, Turner ST, Gong Y, Hall K, Parekh V, Chapman AB, Boerwinkle E, Johnson JA: Impact of abdominal obesity on incidence of adverse metabolic effects associated with antihypertensive medications. *Hypertension* 55:61–68, 2010
- Wicklmayr M, Rett K, Deitze G: Effects of beta blocking agents on insulin secretion and glucose disposal. *Horm Metab Res* 22 (Suppl. 22):29–33, 1990
- Torp-Pedersen C, Metra M, Charlesworth A, Spark P, Lukas MA, Poole-Wilson PA, Swedberg K, Cleland JGF, Di Lenarda A, Remme WJ, Scherhag A: Effects of metoprolol and carvedilol on pre-existing and new onset of diabetes in patients with chronic heart failure: data from the Carvedilol Or Metoprolol European Trial (COMET). *Heart* 93:968–973, 2007
- Rosei EA, Rizzoni D: Metabolic profile of nebivolol, a beta-adrenoreceptor antagonist with unique characteristics. *Drugs* 67:1097–1107, 2007
- De Boer RA, Doehner W, van der Horst ICC, Anker SD, Babalis D, Roughton M, Coats AJ, Flather MD, van Veldhuisen DJ: Influence of diabetes mellitus and hyperglycemia on prognosis in patients \geq 70 years old with heart failure and effects of nebivolol (data from the study of effects of nebivolol intervention on outcomes and rehospitalization and rehospitalization in seniors with heart failure [SENIORS]). *Am J Cardiol* 106:78–86, 2010
- Gress TW, Nieto FJ, Shahar E, Wofford MR, Brancati FL: Hypertension and antihypertensive therapy as risk factors for type 2 diabetes mellitus. *N Engl J Med* 342:905–912, 2000
- Carter BL, Einhorn PT, Brands M: Thiazide-induced dysglycemia: call for research from a working group from the National Heart, Lung, and Blood Institute. *Hypertension* 52:30–36, 2008
- Tham DM, Martin McNully B, Wang YX: Angiotensin II is associated with activation of NF- κ B-mediated genes and downregulation of PPARs. *Physiol Genomics* 11:21–30, 2002
- Levbovitz HE: Metabolic consequences of atypical antipsychotic drugs. *Psychiatr Q* 74:277–290, 2003
- Lean MEJ, Pajonk F-G: Patients on atypical antipsychotic drugs. *Diabetes Care* 26:1597–1605, 2003
- Mahmoud R, Gianfrancesco F, Grogg A, Nasrallah HA: Differential effects of antipsychotics on type 2 diabetes: findings from a large health plan database. In Proceedings of the 39th Annual Meeting of the American College of Neuropsychopharmacology. San Juan, Puerto Rico, Dec. 10-14, 2001. p. 199
- Scheen AJ, De Hert MA: Abnormal glucose metabolism in patients treated with antipsychotics. *Diabetes Metab* 33:169–175, 2007
- Savoy YE, Ashton MA, Miller MW, Nedza FM, Spracklin DK, Hawthorn MH, Rollemma H, Matos FF, Hajos-Korcsok E: Differential effects of various typical and atypical antipsychotics on plasma glucose and insulin levels in the mouse: evidence for the involvement of sympathetic regulation. *Schizophr Bull* 36:410–418, 2010
- Clore JN, Thurby-Hay L: Glucocorticoid-induced hyperglycemia. *Endocr Pract* 15:469–474, 2009
- Kallock E, Neher JO, Safranek S: Clinical inquiries: do intra-articular steroid injections affect glycemic control in patients with diabetes? *J Fam Pract* 59:709–710, 2010
- Patel R, Patel M, Tsai R, Lin V, Bookout AL, Zhang Y, Magomedova L, Li T, Chan JF, Budd C, Mangelsdorf DJ, Cummins CL: LXR β is required for glucocorticoid-induced hyperglycemia and hepatosteatosis in mice. *J Clin Invest* 121:431–441, 2011
- Friedman JE, Sun Y, Ishizuka T, Farrell CJ, McCormack SE, Herron LM, Hakimi P, Lechner P, Yun JS: Phosphoenolpyruvate carboxykinase (GTP) gene transcription and hyperglycemia are regulated by glucocorticoids in genetically obese db/db transgenic mice. *J Biol Chem* 272:31475–31481, 1997
- Clore JN, Thurby-Hay L: Glucocorticoid-induced hyperglycemia. *Endocr Pract* 6:469–474, 2009
- Van Raalte DH, Ouwens DM, Diamant M: Novel insights into glucocorticoid-mediated diabetogenic effects: towards expansion of therapeutic options? *Eur J Clin Invest* 39:81–93, 2009
- Van Raalte DH, Nofrate V, Bunck MC, Van Lersel T, Nasander UK, Heine RJ, Mari A, Dokter WHA, Diamant M: Acute and 2-week exposure to prednisolone impair different aspects of beta-cell function in healthy men. *Eur J Endocrinol* 162:729–735, 2010
- Mora PF: Post-transplantation diabetes mellitus. *Am J Med Sci* 329:86–94, 2005
- Johnston O, Rose CL, Webster AC, Gill JS: Sirolimus is associated with new-onset diabetes in kidney transplant recipients. *J Am Soc Nephrol* 19:1411–1418, 2008
- Dumler F, Kilates C: Metabolic and nutritional complications of renal transplantation. *J Ren Nutr* 17:97–102, 2007
- Bernal-Mizrachi E, Cras-Méneur C, Ye BR, Johnson JD, Permutt MA: Transgenic overexpression of active calcineurin in beta-cells results in decreased beta-cell mass and hyperglycemia. *PLoS One* 5:e11969, 2010 (DOI: 10.1371/journal.pone.0011969)
- Panel on Antiretroviral Guidelines for Adults and Adolescents: Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents [article online]. Available from <http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf>. Accessed 22 April 2011

³³Mulligan K, Grunfield C, Tai VW, Algren H, Pang M, Chernoff DN, Lo JC, Schambelan M: Hyperlipidemia and insulin resistance are induced by protease inhibitors independent of changes in body composition in patients with HIV infection. *J Acquir Immune Defic Syndr Hum Retrovirol* 23:35–43, 2000

³⁴Vyas AK, Koster JC, Tzekov A, Hruz PW: Effects of the HIV protease inhibitor ritonavir on GLUT4 knock-out mice. *J Biol Chem* 285:36395–36400, 2010

³⁵American Diabetes Association, American Psychiatric Association, American Association of Clinical Endocrinologists,

North American Association for the Study of Obesity: Consensus development conference on antipsychotic drugs and obesity and diabetes. *Diabetes Care* 27:596–601, 2004

³⁶Goldberg PA: Comprehensive management of post-transplant diabetes mellitus: from intensive care to home care. *Endocrinol Metab Clin North Am* 36:907–922, 2007

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