

Are thiazides contraindicated in patients with type 2 diabetes?

Thiazides, or benzothiadiazine-derivatives, and thiazide-type diuretics are drugs that historically have been considered among the first-line agents for general prevention of cardiovascular (CV) events and CV risk reduction in most patients with hypertension.^{1,2} Drugs in this class include chlorthalidone, hydrochlorothiazide, indapamide, metolazone, and bendroflumethiazide (note: bendroflumethiazide is only available in combination with nadolol, a beta-blocker).¹⁻³

Thiazides and thiazide-type drugs inhibit sodium chloride (NaCl) transport in the distal convoluted tubule of the nephron, leading to increased NaCl excretion.² They have also been shown to affect excretion of other electrolytes, including calcium (increasing reabsorption) and magnesium (increasing excretion), when administered chronically. Most of the serious adverse effects associated with thiazides involve abnormalities in fluid and electrolyte balance; these include hypokalemia, hyponatremia, hypomagnesemia, hypercalcemia, and hyperuricemia. Thiazides have also been associated with reduced glucose tolerance and latent diabetes mellitus (DM), possibly due to a decrease in insulin secretion (associated with hypokalemia) and changes in glucose metabolism.

The potential for fluctuations in blood glucose with use of thiazides and related agents has been recognized by several sources, including the manufacturers.⁴⁻⁹ However, none of these sources state that thiazides or thiazide-type drugs are contraindicated in patients with DM. Instead, the manufacturers state that patients with DM may require dose adjustments of antidiabetic agents (e.g., insulin) if using thiazides or thiazide-type drugs.⁵⁻⁹ Several organizations recommend thiazides for management of hypertension in patients with DM, as first-line drugs or add-on therapy for patients with uncontrolled hypertension.¹⁰⁻¹⁷ A summary of recommendations from these organizations is available in Table 1.

Table 1. Recommendations on use of thiazides and thiazide-type diuretics in patients with hypertension and diabetes from selected organizations.¹⁰⁻¹⁷

Organization (publication date)	Thiazide-related recommendations
T2DM guidelines	
AACE (2016)	<ul style="list-style-type: none"> • ACEIs, ARBs, beta-blockers, CCBs, and thiazide diuretics are recommended as first-line agents for patients with T2DM and HTN. • ACEIs and ARBs are preferred for patients with T2DM because they can slow the progression of nephropathy and retinopathy. • Choice of medication should be based on factors such as presence of albuminuria, CVD, heart failure, or post-MI status, race/ethnicity, pill burden, and drug cost.
ADA (2016)	<ul style="list-style-type: none"> • Drug therapy for patients with DM and HTN should include an ACEI or ARB. • Multiple drug therapy, including a thiazide diuretic and ACEI or ARB, at maximal doses, is generally required to control BP in patients with DM and HTN.
NICE (2015)	<ul style="list-style-type: none"> • A generic ACEI should be used first-line, except in pregnant women and patients of African or Caribbean origin. In pregnant women, CCBs are first-line; in patients of African or Caribbean origin, ACEIs should be used in combination with a diuretic or CCB. • If HTN is uncontrolled with first-line therapy, addition of a CCB or thiazide/thiazide-type diuretic is recommended.
HTN guidelines	
ASH/ISH (2014)	<ul style="list-style-type: none"> • ACEIs or ARBs are recommended first-line in patients with DM. CCBs or thiazides should be added if needed to achieve goal BP. • In black patients with DM, it is acceptable to start with a CCB or thiazide. If BP remains uncontrolled, an ARB or ACEI should be added.
ESH/ESC (2013)	<ul style="list-style-type: none"> • ACEIs or ARBs are preferred for patients with DM, due to their effect on urinary protein excretion. • Because BP control may be difficult in patients with DM, most may require combination therapy. Thiazides and thiazide-like diuretics are useful and often used together with ACEIs or ARBs.

Organization (publication date)	Thiazide-related recommendations
ISHIB (2010)	<ul style="list-style-type: none"> • Thiazide-type diuretics are considered very useful for treatment of HTN, either as monotherapy or in conjunction with other agents. Blacks and elderly patients usually respond well to diuretic monotherapy. • Specific drugs preferred for treatment of HTN in patients with DM or prediabetes include ACEIs or ARBs. Beta-blockers and CCBs are deemed likely to benefit these patients. No recommendations were found regarding thiazide use in these patients.
JNC 8 (2014)	<ul style="list-style-type: none"> • First-line drugs for treatment of HTN in non-black patients, including those with DM, are ACEIs, ARBs, CCBs, or thiazide-type diuretics. • In blacks with HTN, including those with DM, a CCB or thiazide-type diuretic should be used first.

AACE=American Association of Clinical Endocrinologists; ACEIs=angiotensin-converting enzyme inhibitors; ADA=American Diabetes Association; ARBs=angiotensin II receptor blockers; ASH=American Society of Hypertension; BP=blood pressure; CCBs=calcium channel blockers; CVD=cardiovascular disease; DM=diabetes mellitus; ESC=European Society of Cardiology; ESH=European Society of Hypertension; HTN=hypertension; ISH=International Society of Hypertension; ISHIB=International Society on Hypertension in Blacks; JNC 8=eighth Joint National Committee; MI=myocardial infarction; NICE=National Institute for Health and Care Excellence; T2DM=type 2 diabetes mellitus

Though several organizations recommend thiazides and thiazide-type diuretics for management of hypertension in patients with diabetes, some experts have stated that use of these drugs in patients may increase their risk of morbidity and mortality.⁴ However, Barzilay et al note that these conclusions were extrapolated based on findings from case-control studies and trials that were not specifically designed to evaluate the glycemic effects of antihypertensive medications. From a search of the literature, a meta-analysis was identified in which investigators sought to quantify the effects of diuretics, as well as beta-blockers, on glycemic control in patients with DM.¹⁸ Hirst et al included randomized controlled trials and evaluated glycemic control based on measurements of glycosylated hemoglobin (HbA1c) or fasting blood glucose, and/or hypoglycemic episodes. The investigators found 12 randomized controlled trials involving diuretics; 8 of these utilized thiazide (hydrochlorothiazide; n=3) or thiazide-type (indapamide [n=1], bendroflumethiazide [n=3], cyclopenthiazide [n=1]) diuretics. (Of note, cyclopenthiazide is not available in the United States, and, as mentioned previously, bendroflumethiazide is only available in combination with nadolol). The duration of these studies ranged from 3 to 12 weeks (4 to 48 weeks for non-thiazide diuretics). Fasting blood glucose measurements were reported in 8 trials; those involving thiazides indicated a larger effect size on fasting blood glucose (mean increase of 1.69 mmol/L [30.5 mg/dL], 95% confidence interval [CI] 0.69 to 2.69 mmol/L [12.4 to 48.5 mg/dL]) compared to non-thiazide diuretics (mean increase of 0.18 mmol/L [3.24 mg/dL], 95% CI -0.62 to 0.98 mmol/L [-11.2 to 17.7 mg/dL]).^{18,19} Trials of thiazide-type diuretics also showed a slightly greater increase in HbA1c compared to trials of non-thiazide diuretics, but these findings (for both types of diuretics) were not statistically significant (results not specified).¹⁸ None of these trials reported on glucose-related adverse events. Additionally, Hirst et al reported significant heterogeneity (p=0.021) and potential publication bias for the trials reporting fasting blood glucose (p=0.045).

Hirst et al concluded that there was an overall increase in fasting blood glucose and HbA1c observed with diuretic use in patients with diabetes, and a higher increase in glycemic measurements associated with thiazide-type diuretics vs. non-thiazide diuretics.¹⁸ However, these comparisons were made indirectly, across studies that separately evaluated the 2 types of drugs. Importantly, these trials were mostly of short duration and heterogeneous. Not all of the available thiazide-type diuretics were assessed (e.g., chlorthalidone, metolazone). None of the studies evaluated clinical outcomes related to glycemic control (i.e., hypoglycemic episodes, microvascular or macrovascular outcomes). Thus, while diuretics may affect glycemic control, these findings alone are insufficient to discount use of diuretics in patients with diabetes. Instead, the overall benefit of these drugs should be considered, as well as potential adverse effects, ideally in terms of clinical outcomes.

Based on the available literature, clinicians may be advised to consider thiazides and thiazide-type diuretics for management of hypertension in patients with DM, and to monitor blood glucose more closely in these patients.⁴⁻¹⁸ In patients with DM who develop uncontrolled blood glucose while on a thiazide or thiazide-type diuretic, adjustment of antidiabetic therapy is recommended.

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