**Q34.** Will chlorthalidone raise my blood sugar?

**Learning Objective:** Chlorthalidone may raise blood sugar. However, the increase is usually of no clinical significance. Lower doses of chlorthalidone and potassium supplements may prevent increases in blood sugar.

**Evidence Summary:**

Thiazide diuretics such as chlorthalidone have been associated with increases in blood sugar as well as an increased incidence of new onset diabetes.[1-6](#_ENREF_1)

In an analysis of the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), researchers compared fasting glucose (FG) and incident diabetes mellitus (DM) among participants receiving three different antihypertensives.[1](#_ENREF_1) The analysis consisted of 31,512 adults over the age of 55, randomized to receive a daily dose of either chlorthalidone (12.5 mg-25 mg), amlodipine (5-10 mg), or lisinopril (10-40 mg).[8](#_ENREF_8) Participants taking chlorthalidone had the highest risk of developing FG levels greater than 125 mg/dL (6.9 mmol/L).[1](#_ENREF_1) After two years of treatment, mean FG increased by 8.5 mg/dL in the chlorthalidone group, compared to the 5.5 and 3.5 mg/dL increase seen in the amlodipine and lisinopril groups, respectively (p<0.001).[1](#_ENREF_1) At the four-year and six-year follow-up, chlorthalidone users continued to have to the largest increase in FG.[1](#_ENREF_1) By year four and six, those taking chlorthalidone had a FG increase of 10.8 and 12.7 mg/dl from baseline, respectively.[1](#_ENREF_1) Incident DM (FG ≥126 mg/dL) occurred at a rate of 14% in the chlorthalidone group, 11.1% in the amlodipine group, and 9.5% in the lisinopril group (p<0.001).[1](#_ENREF_1) Although the risk of developing FG levels above 125 mg/dL was greater in the chlorthalidone group, researchers were not able to conclude that the risk was associated with an increase in clinical events.[1](#_ENREF_1)

Additional analyses of the ALLHAT data investigated the clinical outcomes associated with thiazide diuretics, incident DM, and elevated blood glucose.[7](#_ENREF_7),[8](#_ENREF_8) Both analyses found that thiazide use led to similar if not fewer adverse cardiovascular outcomes.[7](#_ENREF_7),[8](#_ENREF_8) For patients with diagnosed incident DM, an intention-to-treat analysis of the ALLHAT data found similar rates of cardiovascular disease outcomes in those taking chlorthalidone compared to those taking lisinopril or amlodipine, while providing the same if not better antihypertensive effects.[8](#_ENREF_8) Based on baseline glucose levels, participants fell into one of three groups: diabetes mellitus (DM), impaired fasting glucose (IFG), or normoglycemic (NG).[8](#_ENREF_8) Diabetes mellitus was defined as a FG ≥126 mg/dL.[8](#_ENREF_8) Participants with no history of DM and FG levels between 110 and 125 mg/dL were considered to have an IFG, while participants with fasting or non-fasting glucose levels <110 mg/dL were considered normoglycemic.[8](#_ENREF_8) There was no significant difference in the relative risk (RR) of fatal CHD and nonfatal MI between treatment groups.[8](#_ENREF_8) However, within the IFG stratums, those in the amlodipine group had significantly higher rates of CHD/MI outcomes than those in the chlorthalidone group (RR 1.73 95% CI [1.10-2.72], p=0.01).[8](#_ENREF_8)

A post hoc analysis of the Systolic Hypertension in Elderly People (SHEP) trial revealed that the incidence of diabetes was greater among participants taking chlorthalidone.[9](#_ENREF_9) At the one-year follow-up, the unadjusted annual incidence rate (IR) of diabetes per 100 persons was 6.1 in the chlorthalidone group and 3.0 and in the placebo group (p<0.001).[9](#_ENREF_9) However, after the first year there was no significant difference in the unadjusted IR of diabetes between the two groups, 2.4 in the chlorthalidone group compared to 2.3 in the placebo group.[9](#_ENREF_9) Decreases in serum potassium were associated with a higher incidence of diabetes.[9](#_ENREF_9) Each 0.5 mEq/L decrease in serum potassium from baseline was associated with a 45% higher risk of incident diabetes (95% CI [24-70], p<0.001).[9](#_ENREF_9) Risk of incident diabetes was also higher in patients taking 25 mg of chlorthalidone compared to those lower doses.[9](#_ENREF_9) Participants taking 25 mg were 2.37 (95% CI [1.55-3.65]) times more likely to develop diabetes compared to those taking placebo (p<0.001).[9](#_ENREF_9) Participants taking 12.5 were 1.7 (95% CI [1.19-2.43]) times more likely to develop diabetes compared to placebo (p=0.003).[9](#_ENREF_9) Researchers concluded that thiazide-induced diabetes is likely to occur during the early stages of treatment, and may be prevented by potassium supplementation as decreased serum-potassium is theorized to play a role in diabetes development.[9](#_ENREF_9)

Increases in blood sugar related to thiazides may be dose dependent. A 12-week study by Vardan et al. compared the efficacy and metabolic effects of chlorthalidone 15 mg to chlorthalidone 25 mg and to placebo.[6](#_ENREF_6) Average blood glucose in the 15 mg chlorthalidone group (n=66) decreased by 0.05 mg/dL, compared to the 25 mg group (n=66), which had an increase of 0.61 mg/dL (p<0.05).[6](#_ENREF_6) In the placebo group (n=70), average blood glucose decreased by 0.10 mg/dL.[6](#_ENREF_6) Comparison of blood pressure response revealed similar response rates in the 15 and 25 mg treatment groups.[6](#_ENREF_6) However, blood pressure changes in the treatment groups compared to the placebo group were statistically significant (p<0.001).[6](#_ENREF_6) These findings suggest that lower doses of chlorthalidone can produce similar antihypertensive effects to that of higher dose while lowering the risk of elevated blood glucose levels.

A systematic review of 59 trials examined the metabolic effects of thiazide diuretics on potassium and glucose.[10](#_ENREF_10) The review consisted of 58,520 subjects, of which 26,625 were receiving a thiazide diuretic.[10](#_ENREF_10) The average change in mean glucose was an increase of 7.07 mg/dL.[10](#_ENREF_10) In addition, researchers found an inverse relationship between potassium and glucose, with a Pearson’s correlation of -0.54 (p<0.001).[10](#_ENREF_10) Further evidence to support the relationship between potassium and glucose was provided by a comparison of trails using potassium supplements to those not using potassium supplements.[10](#_ENREF_10) In trials using supplementation, potassium decreased by an average of 0.23 meq/L, and glucose increased by an average of 3.26 mg/dL (p<0.01).[10](#_ENREF_10) In trails not using supplementation, potassium levels decreased by an average of 0.37 meq/L and glucose increased by 6.01 mg/dL.[10](#_ENREF_10) These results propose that the use of potassium supplements with thiazide diuretics may lessen glucose intolerance and the development of diabetes.

Another systematic review and meta-analysis, reported similar dose dependent findings.[11](#_ENREF_11) Patients receiving lower doses of thiazides (hydrochlorothiazide or chlorthalidone ≤25 mg daily) had a smaller change in FG than those receiving higher doses.[12](#_ENREF_12) Mean FG among those receiving low doses of thiazides (n=5,148) increased by 2.7 mg/dL compared to higher doses (n=130) where mean FG increased by 10.8 mg/dL.[11](#_ENREF_11)

Guidelines established by the Task Force for the Management of Arterial Hypertension of the European Society of Hypertension and Cardiology list metabolic syndrome and glucose intolerance as possible contraindications with diuretics and thiazide diuretics.[13](#_ENREF_13) The guidelines preferred treatment for patients with diabetes are angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARBs).[13](#_ENREF_13) However, the guideline states that ACE inhibitors or ARBs can be used in combination with either a thiazide, calcium antagonist, or beta-blocker.[13](#_ENREF_13) It is not recommended to use ACE inhibitors and ARBs in combination with one another.[13](#_ENREF_13) The American Diabetes Association has a similar recommendation; diabetic hypertensives should be treated with either an ACE inhibitor or an ARB, adding a thiazide diuretic if needed to achieve blood pressure control.[14](#_ENREF_14) The Eight Joint National Commission (JNC-8) does not make this distinction, and instead recommends diuretics as an agent of first choice for all hypertensives, including diabetic hypertensives.[12](#_ENREF_12)

References

1. Barzilay JI, Davis BR, Cutler JA, et al. Fasting glucose levels and incident diabetes mellitus in older nondiabetic adults randomized to receive 3 different classes of antihypertensive treatment: a report from the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *Arch Intern Med.* Nov 13 2006;166(20):2191-2201.

2. Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension. Final results of the Systolic Hypertension in the Elderly Program (SHEP). SHEP Cooperative Research Group. *JAMA.* Jun 1991;265(24):3255-3264.

3. Musini VM, Nazer M, Bassett K, Wright JM. Blood pressure-lowering efficacy of monotherapy with thiazide diuretics for primary hypertension. *Cochrane Database Syst Rev.* 2014(5):CD003824.

4. Pareek A, Karnik N, Salagre S, et al. Clinical effectiveness of low-dose chlorthalidone (6.25 mg)+ atenolol combination in stage I hypertensive patients: a multicenter, randomized, controlled study. *Current medical research and opinion.* 2008;24(6):1771-1779.

5. Siegel D, Saliba P, Haffner S. Glucose and insulin levels during diuretic therapy in hypertensive men. *Hypertension.* 1994;23(6 Pt 1):688-694.

6. Vardan S, Mehrotra KG, Mookherjee S, Willsey GA, Gens JD, Green DE. Efficacy and reduced metabolic side effects of a 15-mg chlorthalidone formulation in the treatment of mild hypertension: A multicenter study. *JAMA.* 1987;258(4):484-488.

7. Barzilay JI, Davis BR, Pressel SL, et al. Long-term effects of incident diabetes mellitus on cardiovascular outcomes in people treated for hypertension: the ALLHAT Diabetes Extension Study. *Circ Cardiovasc Qual Outcomes.* Mar 1 2012;5(2):153-162.

8. Whelton PK, Barzilay J, Cushman WC, et al. Clinical outcomes in antihypertensive treatment of type 2 diabetes, impaired fasting glucose concentration, and normoglycemia: Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *Arch Intern Med.* Jun 27 2005;165(12):1401-1409.

9. Shafi T, Appel LJ, Miller ER, 3rd, Klag MJ, Parekh RS. Changes in serum potassium mediate thiazide-induced diabetes. *Hypertension.* Dec 2008;52(6):1022-1029.

10. Zillich AJ, Garg J, Basu S, Bakris GL, Carter BL. Thiazide diuretics, potassium, and the development of diabetes. *Hypertension.* 2006;48(2):219-224.

11. Zhang X, Zhao Q. Association of Thiazide-Type Diuretics With Glycemic Changes in Hypertensive Patients: A Systematic Review and Meta-Analysis of Randomized Controlled Clinical Trials. *J Clin Hypertens (Greenwich).* Apr 2016;18(4):342-351.

12. James PA, Oparil S, Carter BL, et al. 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). *JAMA.* Feb 5 2014;311(5):507-520.

13. Mancia G, Fagard R, Narkiewicz K, et al. 2013 ESH/ESC Guidelines for the management of arterial hypertension: the Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *J Hypertens.* Jul 2013;31(7):1281-1357.

14. Association AD. Hypertension management in adults with diabetes. *Diabetes care.* 2004;27(suppl 1):s65-s67.

**Patient-Facing Text:**

Chlorthalidone may raise blood sugar in some people. However, these changes are usually small and may not be a problem. Lower doses of chlorthalidone have less of an effect on blood sugar. The most commonly prescribed doses of chlorthalidone are low, so blood sugar changes may never be a problem for many people taking chlorthalidone.

If chlorthalidone does raise your blood sugar, taking a lower dose of chlorthalidone may help keep your blood sugar down. Taking potassium supplements may also help.

Even if chlorthalidone causes your blood sugar to rise, it may still be a good choice for you.

In studies, people whose blood sugar rose on chlorthalidone still had lower chances of heart disease and stroke. This was true even in people with diabetes.

*Less pressure, more health!*

Talk to your doctor if your blood sugar rises after beginning chlorthalidone. Your doctor can help you decide if another medicine is a better fit for you.

**Teaser:** Chlorthalidone may raise

**Assessment Question:**

Which of the following is true of chlorthalidone?

1. It does NOT affect your blood sugar

Incorrect. Chlorthalidone can raise blood sugar levels in some people.

1. Lower doses cause the biggest rise in blood sugar

Incorrect. Lower doses of chlorthalidone have less of an effect on blood sugar compared to higher doses.

1. It can raise your blood sugar

Correct! The increases are usually small, but you should still talk to your doctor if your blood sugar rises after beginning chlorthalidone. Together, you can decide if chlorthalidone is a good fit for you.

1. I don’t know

Chlorthalidone can raise your blood sugar, but it may still be a good fit for you. Usually the increases in blood sugar levels are small. Talk to your doctor if your blood sugar rises after beginning chlorthalidone.

**Audiovisual:** Not yet developed.