# **Q50.** Are there any blood tests my doctor might check when I am taking chlorthalidone?

**Learning Objective:** Chlorthalidone has been associated with decreased serum levels of potassium, magnesium, sodium, chloride, and increased levels of calcium. Therefore, it is recommended to test electrolyte levels before and during treatment with chlorthalidone.

**Evidence Summary:**

Electrolyte abnormalities are common in patients receiving chlorthalidone.[1](#_ENREF_1) Chlorthalidone can cause hypokalemia, hyponatremia, hypochloremia, hypomagnesemia, and hypercalcemia.[1](#_ENREF_1) Therefore, it is recommended that serum electrolytes be checked before initiating therapy and periodically during therapy.[1](#_ENREF_1),[2](#_ENREF_2)

Bengtsson et al. studied the effects of chlorthalidone in 40 untreated hypertensive women (systolic ≥160 mmHg, diastolic >95 mmHg).[3](#_ENREF_3) After one month of placebo, followed by three months of chlorthalidone 50 mg daily, mean serum potassium decreased from 4.1 to 3.4 mmol/L (p<0.001).[3](#_ENREF_3) Participants were receiving 75 mg potassium chloride supplements twice daily.[3](#_ENREF_3) After the trial, 11 women continued taking chlorthalidone at doses of 50 mg three times a week while the potassium regimen remained unchanged.[3](#_ENREF_3) Serum potassium before treatment was 3.9 mmol/L , 3.4 mmol/L after 3 months of daily treatment, and 3.7 mmol/L with thrice weekly treatment (p<0.05).[3](#_ENREF_3)

A sub-analysis of the Systolic Hypertension in the Elderly Program (SHEP) examined the effects of chlorthalidone-associated hypokalemia.[4](#_ENREF_4) After one year of treatment, average baseline serum potassium (4.52 mmol/L) decreased in all groups who were receiving varying doses of chlorthalidone.[4](#_ENREF_4) The lowest dose, 6.25 mg, resulted in a serum potassium level of 4.29 mmol/L, while 12.5 and 25 mg resulted in potassium levels of 4.1 and 3.97 mmol/L, respectively (p<0.001).[4](#_ENREF_4)

The Treatment of Mild Hypertension Study compared the efficacy of a nutritional-hygienic intervention alone to a nutritional-hygienic intervention combined with pharmacological treatment.[5](#_ENREF_5) Along with the nutritional-hygienic intervention, participants were randomized to receive one of the following treatments: placebo, chlorthalidone (15 mg), acebutolol (400 mg), doxazosin (2 mg), amlodipine (5 mg), or enalapril (5 mg).[5](#_ENREF_5) By the 12 month follow-up, changes in serum potassium occurred in the chlorthalidone group only.[5](#_ENREF_5) Serum potassium decreased by an average of 0.4 mmol/L (p<0.001).[5](#_ENREF_5) At the 4 year follow-up, average serum potassium decreased by 0.38 mmol/L in the chlorthalidone group (p=0.04).[6](#_ENREF_6) Average serum potassium decreased by ≤ 0.07 mmol/L in the other treatment groups.[6](#_ENREF_6)

Decreases in serum potassium appear to be dose dependent. Morledge et al. conducted a placebo-controlled study to evaluate the dose response of chlorthalidone.[7](#_ENREF_7) Participants (n=176), 60 years of age and older with isolated systolic hypertension (sitting systolic BP ≥160 mmHg and diastolic BP ≤90 mmHg), were randomized to receive chlorthalidone 12.5, 25 or 50 mg or placebo for 12 weeks.[7](#_ENREF_7) After one week of treatment, mean serum potassium decreased in the chlorthalidone 12.5, 25, and 50 mg groups by 0.3, 0.5, and 0.7 mEq/L, respectively (p<0.05).[7](#_ENREF_7) With the exception of a 0.1 mEq/L serum potassium increase in the 50 mg group at the 12th week, serum potassium was unchanged after one week of treatment.[7](#_ENREF_7) In the placebo group, mean serum potassium increased by 0.1 mEq/L and remained constant for the remainder of the study.[7](#_ENREF_7) No further serum potassium changes were noted.[7](#_ENREF_7)

In a meta-analysis of thiazide diuretic efficacy, 25mg of chlorthalidone lowered serum potassium significantly more than the 12.5 and 15 mg doses (p<0.0001).[8](#_ENREF_8) However, higher doses of chlorthalidone did not result in significantly different changes in serum potassium.[8](#_ENREF_8) Average serum potassium in subjects from 5 chlorthalidone studies (n=1203), decreased by 0.4 mmol/L (95% CI [0.45-0.34]).[8](#_ENREF_8)

A double-blind clinical trial compared electrolyte changes caused by chlorthalidone alone to ramipril/chlorthalidone combination therapy.[9](#_ENREF_9) Participants were men and women 32 to 63 years of age with untreated primary hypertension (diastolic blood pressure between 95 and 115 mmHg).[9](#_ENREF_9) Following a 4-week placebo period, participants were randomized to receive chlorthalidone 25 mg (n=15) or the combination therapy of ramipril 5 mg and chlorthalidone 25 mg (n=17).[9](#_ENREF_9) Serum sodium, potassium, calcium, and magnesium were not affected during the 12-weeks of active treatment.[9](#_ENREF_9) Both the monotherapy and combination therapy groups had an increased sodium excretion (p=0.009 and p=0.003, respectively).[9](#_ENREF_9) Average urinary calcium decreased by 1.98 mmol in the combination group (p=0.01) and 1.74 mmol in the monotherapy group (p=0.001).[9](#_ENREF_9) The combination therapy group had a 0.51 mmol (p=0.16) decrease in magnesium excretion while the monotherapy group had a 0.86 mmol increase in magnesium excretion (p=0.04). [9](#_ENREF_9)

The effects of chlorthalidone on magnesium are further illustrated by a one-year comparison study of mono and combination antihypertensive therapy.[10](#_ENREF_10) Participants (n=90) with mild to moderate essential hypertension were randomized to receive beta-blocker (BB) or beta-blocker plus chlorthalidone therapy.[10](#_ENREF_10) Magnesium depletion was assessed using the magnesium load test.[10](#_ENREF_10) Participants were given magnesium sulfate (300 mmol) in 5% glucose (500 ml) intravenously over an eight-hour period. [10](#_ENREF_10) A 24-hour urine collection began with the start of the IV.[10](#_ENREF_10) Magnesium depletion was present when retention of the infused magnesium was more than 50% and absent when retention was less than 20%.[10](#_ENREF_10) Magnesium depletion was considered possible when retention values were between 20 and 50%.[10](#_ENREF_10) At the baseline, six month, and 12-month measurements, magnesium depletion in the BB group was less than 10%.[10](#_ENREF_10) At baseline, magnesium depletion was 10.8% in the combination therapy.[10](#_ENREF_10) At the six-month and 12-month follow-up, magnesium depletion was 38.7 and 43.3%, respectively.[10](#_ENREF_10) These data suggest that the addition of chlorthalidone was associated with lower magnesium.

In a retrospective cohort of 29,873 patients aged 66 years or older, Dhalla et al. examined the effectiveness and safety of chlorthalidone and hydrochlorothiazide.[11](#_ENREF_11) Hypokalemia (serum potassium <3.5 mmol/L) and hyponatremia (serum sodium <135 mmol/L) occurred in 109 of the 10,384 patients taking chlorthalidone.[11](#_ENREF_11) The annualized event rate for hypokalemia and hyponatremia was 0.69%.[11](#_ENREF_11) Compared to hydrochlorothiazide, patients treated with chlorthalidone were 3 and 1.7 times more likely to be hospitalized for hypokalemia and hyponatremia, respectively.[11](#_ENREF_11)

Risk of hyponatremia with chlorthalidone and hydrochlorothiazide was examined in a population based case control study (n=738,016).[12](#_ENREF_12) Hyponatremia was more likely to occur with chlorthalidone than with hydrochlorothiazide.[12](#_ENREF_12) The risk of developing hyponatremia compared to no drug use was calculated for patients taking chlorthalidone. Compared to no medication use, patients taking chlorthalidone 12.5 and 25 mg daily were 5.46 (95% CI [3.01–9.92]) and 5.62 (95% CI [3.92–8.06]) times more likely to develop hyponatremia, respectively (p<0.001).[12](#_ENREF_12)

The incidence of chlorthalidone induced hypercalcemia was studied in 39 untreated hypertensive subjects.[13](#_ENREF_13) Mean serum calcium level prior to chlorthalidone treatment was 9.7 mg/dl.[13](#_ENREF_13) Participants were given 50 mg of chlorthalidone daily for 4 weeks.[13](#_ENREF_13) After the 4 weeks, mean serum calcium level was 10.0 mg/dl, with 30 participants (77%) having a rise in serum calcium levels.[13](#_ENREF_13) Six participants had hypercalcemia, defined as serum calcium levels between 10.6 and 11.3 mg/dl.[13](#_ENREF_13) Seven participants had a 0.1–0.2 mg/dl decrease in serum calcium levels and 2 participants had no change in calcium levels.[13](#_ENREF_13)

References

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**Patient-Facing Text:**

Your doctor may do blood tests to check your electrolyte levels when you start taking chlorthalidone and while you are taking it. Electrolytes are minerals in the blood. They help control important functions in the body.

Changes in electrolyte levels are common with chlorthalidone. It is an expected effect of the medicine. Chlorthalidone can cause low levels of the following electrolytes:

* Potassium
* Sodium
* Magnesium
* Chloride

Chlorthalidone can also cause an increase in calcium in the blood.

Small changes in electrolyte levels are okay, but big changes can be dangerous. Because of this, your doctor may do blood work to make sure your electrolyte levels are in a safe range.

# **Teaser:** Blood tests to check your

**Assessment Question:**

Are there any blood tests my doctor might check when I am taking chlorthalidone?

1. Blood tests to check electrolyte levels

Correct!

1. No, there are no blood tests

Incorrect. Your doctor may do blood tests to check your electrolyte levels when you are taking chlorthalidone.

1. Blood tests to check thyroid levels

Incorrect. Blood tests are done to check your electrolyte levels.

1. I don’t know

Your doctor may do blood tests to check your electrolytes because chlorthalidone can cause changes in electrolyte levels.

**Audiovisual:** Not yet developed.