

Magnesium and Thiazide Diuretics

Uwe Gröber

Academy of micronutrient medicine, Essen, Germany

Abstract

Thiazide diuretics are an FDA-approved class of drugs that inhibit reabsorption of luminal sodium in the distal convoluted tubule of the nephron. They have been used for the treatment of hypertension. Hypertension guidelines have underscored the importance of thiazide diuretics for all patients, but particularly for those with salt-sensitive and resistant hypertension. Thiazide diuretics are associated with a decrease of serum magnesium levels. Whereby the drug-induced magnesium depletion is more severe in the elderly. Hypomagnesemia occurs more often in the elderly, and in those receiving continuous high-dose diuretic therapy which may increase cardiovascular morbidity and mortality. Subclinical magnesium deficiency is a principal driver of cardiovascular diseases such as arrhythmias, arterial calcifications, atherosclerosis, heart failure, hypertension, and/or thrombosis. Hypertensive patients on long-term treatment with thiazide diuretics should therefore be monitored for magnesium deficiency, particularly those with additive risk factors, such as age > 60, hydrochlorothiazide doses ≥ 25 mg/day, insulin resistance, cardiovascular diseases (e.g. hypertension, arrhythmias), inadequate dietary intake, secondary aldosteronism and kidney dysfunction

Introduction

Thiazide-type diuretics are the second most commonly prescribed class of antihypertensive medication, and thiazide-related diuretics have increased at a rate greater than that of antihypertensive medications as a whole. For more than 5 decades Thiazide Diuretics (TD), including thiazide-type (e.g. hydrochlorothiazide, chlorthalidone) and thiazide-like diuretics (e.g. indapamide, chlorthalidone) have been used for the treatment of hypertension. The latest hypertension guidelines have underscored the importance of thiazide diuretics for all patients, but particularly for those with salt-sensitive and resistant hypertension [1]. Thiazide-type diuretics decrease efficaciously systolic and diastolic blood pressure and reduce at the same time cardiovascular morbidity and mortality associated with hypertension. A meta-analysis including 19 randomized controlled trials enrolling 112,113 patients showed that thiazide diuretics have an additional cardioprotective effect. During a mean follow up of 3.91-years, a 14% reduction in the risk of cardiac events (odds ratio (OR): 0.86, $P = 0.007$) and 38% reduction in the risk of heart failure (OR: 0.62, $P < 0.001$), were found in thiazide treated patients [2]. Additionally, thiazide and loop diuretics are important tools in the therapy of volume-overload conditions, such as congestive heart failure, nephrotic syndrome, and cirrhosis, by improving the symptoms of fluid congestion, volume overload and edema.

Side effect: Electrolyte disorders

Although thiazide-type diuretics are among the best tolerated antihypertensive drugs they are often associated with related adverse side effects, such as electrolyte, acid-base and/or metabolic disorders (e.g. impaired glucose tolerance, dyslipidemia). All type of diuretics promote excretion of sodium. Depending upon the site and mode of action, some diuretics increase excretion of potassium, magnesium, chloride, calcium, or bicarbonate. In general electrolyte disorders, such as hyponatraemia, hypo-/hyperkalaemia are well considered and monitored in clinical practice therefore they are not further discussed at this point. For instance, hyperkalaemia due to potassium-increasing drug-drug interactions is a clinically important, but well described

adverse drug event. Instead, in order to provide a review of current knowledge, I will focus in previously more neglected drug-nutrient interactions between thiazide-type diuretics and magnesium (Figure 1).

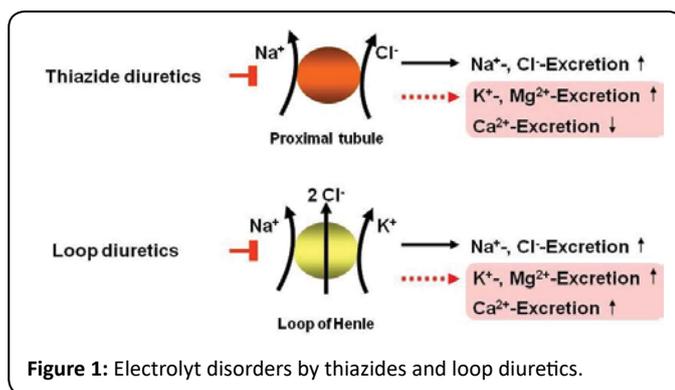
In general, thiazide diuretics are associated with a decrease of serum magnesium levels by 5% to 10%. Whereby the drug-induced magnesium depletion is more severe in the elderly. Up to 50% of treated patients have cellular magnesium depletion, regardless of normal serum concentrations. Hypomagnesemia occurs more often in the elderly, and in those receiving continuous high-dose diuretic therapy which may increase cardiovascular morbidity and mortality. About 80% of hypertensive patients treated for at least 6 months with hydrochlorothiazide have been found to have magnesium depletion based on retention of a parenterally administered magnesium load, even though their magnesium serum levels were normal [3]. In an elderly population of a Somerset village 48% of the thiazide-treated patients were hypomagnesaemic and 28% of the thiazide-treated patients were hypokalaemic. Thus, magnesium and potassium depletion are commonly associated with thiazide therapy in the elderly [4,5]. Hypomagnesemia is often associated with hypokalemia, hypocalcemia, hypophosphatemia and hyponatremia. Hypokalemia, hypocalcemia and/or hypovitaminosis D found in association with low serum magnesium blood levels can prove refractory to all treatment measures until the underlying magnesium deficiency is corrected [6]. Remarkable are the results of a cross-sectional study in hypertensive patients that determined serum and mononuclear cell magnesium concentrations. This study shows that although the patients had normal serum magnesium, thiazide diuretics can induce intracellular magnesium depletion not detectable by assessment of blood serum. Therefore the serum magnesium level reflects only a small part of total body content magnesium. In a patient with clinical magnesium deficiency cellular magnesium concentration can be low despite normal magnesium levels in blood serum.

Magnesium loss: consequences on metabolism

Furthermore it has been shown that magnesium is a kind of second messenger for insulin action. Magnesium plays a crucial role in glucose and insulin metabolism, mainly through its impact on tyrosine kinase activity of the insulin receptor, by transferring the phosphate from ATP to protein. Magnesium may also affect phosphorylase b kinase activity by releasing glucose-1-phosphate from glycogen. In addition,

*Corresponding Author: Dr. Uwe Gröber, Academy of micronutrient medicine, Essen, Germany, Email: uwegroeber@gmx.net

Received: Feb 15, 2019; Accepted: Feb 26, 2019; Published: Feb 28, 2019



magnesium may directly affect glucose transporter protein activity 4 (GLUT4), and help to regulate glucose translocation into the cell [7]. Intracellular magnesium deficiency may affect the risk of insulin resistance and alter the glucose entry into the cell. It is imaginable that the subclinical magnesium deficiency and intracellular magnesium depletion associated with thiazide treatment may interfere with the activity of the tyrosine kinase and the insulin receptor increasing the risk of insulin resistance. Patients with magnesium deficiency show a more rapid progression of glucose intolerance and have an increased risk for insulin resistance. The supplementation of magnesium may contribute to an improvement in both islet Beta-cell response and insulin action in thiazides treated patients and in type-2 diabetics. In a recent randomized, double-blind, clinical study with thiazide-treated hypertensive women (age: 40-65 years) the effects of magnesium supplementation (600mg/day) on blood pressure and vascular function were evaluated. After 6 months, the magnesium group had a significant reduction in systolic (SBP: 144 ± 17 vs. 134 ± 14 mmHg, $P=0.036$) and Diastolic Blood Pressure (DBP: 88 ± 9 vs. 81 ± 8 mmHg, $P=0.005$), and as a sign of improved endothelial function a significant increase of brachial Flow-Mediated Dilatation (FMD) ($r=0.44$, $P=0.011$). The constant oral supplementation of magnesium was associated with better blood pressure control, improved endothelial function and amelioration of subclinical atherosclerosis in these thiazide-treated hypertensive women [8-10].

Recommendation for clinical practice:

Subclinical magnesium deficiency is a principal driver of cardiovascular diseases such as arrhythmias, arterial calcifications, atherosclerosis, heart failure, hypertension, and/or thrombosis. In other words disorders of magnesium metabolism are a principal, under-recognized, driver of cardiovascular disease in medical practice everyday life. Hypertensive patients on long-term treatment with thiazide diuretics should therefore be monitored for magnesium deficiency, particularly those with additive risk factors, such as age > 60, hydrochlorothiazide doses ≥ 25 mg/day, insulin resistance, cardiovascular diseases (e.g. hypertension, arrhythmias), inadequate dietary intake, secondary aldosteronism and kidney dysfunction.

The most common and valuable test in clinical medicine for the rapid

assessment of changes in magnesium status is the serum magnesium concentration, even though serum levels have little correlation with total body magnesium levels or concentrations in specific tissues. In healthy individuals, magnesium serum concentration is closely maintained within the physiological range. The normal reference range for the magnesium in blood serum is 0.76-1.05 mmol/L. A serum magnesium <0.82 mmol/L (2.0 mg/dL) with a 24-hour urinary magnesium excretion of 40-80 mg per day is highly suggestive of magnesium deficiency. According to many magnesium researchers the appropriate lower reference limit of the serum magnesium concentration should be 0.85 mmol/L, especially for patients with diabetes. Furthermore, the ionized magnesium concentration and the magnesium loading (or tolerance) test have been shown to be more accurate. The reference range for serum ionised magnesium concentration is 0.54-0.67 mmol/L. To comprehensively evaluate magnesium status, both laboratory tests and the clinical assessment of magnesium deficit symptoms might be required [11].

References

1. Roush GC, Sica DA, (2016) Diuretics for Hypertension: A Review and Update. *Am J Hypertens* 29: 1130-1137.
2. Chen P, Chaugai S, Zhao F, Wang DW, (2015) Cardioprotective Effect of Thiazide-Like Diuretics: A Meta-Analysis. *Am J Hypertens* 28: 1453-1463.
3. Seelig CB (1990) Magnesium deficiency in two hypertensive patient groups. *South Med J* 83: 739-742.
4. Petri M, Cumber P, Grimes L, Treby D, Bryant R et al. (1986) The metabolic effects of thiazide therapy in the elderly: a population study. *Age Ageing* 15: 151-155.
5. Arampatzis S, Funk GC, Leichtle AB, Fiedler GM, Schwarz C, et al. (2013) Impact of diuretic therapy-associated electrolyte disorders present on admission to the emergency department: a cross-sectional analysis. *BMC Med* 11: 83.
6. Dyckner T, Wester PO, (1981) Effects of magnesium infusions in diuretic induced hyponatraemia. *Lancet* 1: 585-586.
7. Paolisso G, Scheen A, D'Onofrio F, Lefèbvre P (1990) Magnesium and glucose homeostasis. *Diabetologia* 33: 511-514.
8. Cunha AR, D'El-Rei J, Medeiros F, Umbelino B, Oigman W, et al. (2017) Oral magnesium supplementation improves endothelial function and attenuates subclinical atherosclerosis in thiazide-treated hypertensive women. *J Hypertens* 35: 89-97.
9. Kisters K Gröber U, (2013) Lowered magnesium in hypertension. *Hypertension* 62: e19.
10. Gröber U, Schmidt J, Kisters K (2015) Magnesium in Prevention and Therapy. *Nutrients* 7: 8199-8226.
11. Gröber U, Kisters K, Schmidt J, (2018) Important drug-micronutrient interactions: A selection for clinical practice. *Crit Rev Food Sci Nutr* 23: 1-19.