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Thiazide–associated hyponatremia in the elderly: what the clinician needs to know

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Abstract

Thiazide-induced hyponatremia is one of the main causes of decreased sodium levels in elderly individuals. This review presents the current evidence regarding the thiazide-associated hyponatremia. Thiazide-associated hyponatremia is observed mainly in patients with certain risk factors such as those receiving large doses of thiazides, having much comorbidity, such as heart failure, liver disease or malignancy, and taking several medications, such as non-steroidal anti-inflammatory drugs, selective serotonin re-uptake inhibitors or tricyclic antidepressants. Sodium concentration should be monitored in patients with risk factors for developing thiazide-associated hyponatremia and clinicians should measure promptly serum sodium levels in patients with neurologic signs indicating reduced sodium levels. The clinical and biochemical profile of patients with thiazide-associated hyponatremia may be that of extracellular volume depletion or the syndrome of inappropriate antidiuretic hormone secretion (SIADH). The investigation of possible thiazide-associated hyponatremia includes the exclusion of other causes of decreased sodium levels and the identification of the characteristics of hyponatremia due to thiazides (extracellular volume depletion-related or SIADH-like). Treatment should be carefully monitored to avoid serious neurologic complications due to overcorrection. Clinicians should discourage prescribing thiazides in patients with a history of diuretic-associated hyponatremia and should prefer low doses of thiazides in patients with risk factors for developing thiazide-associated hyponatremia.

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1 Introduction

Hyponatremia (serum sodium < 136 mEq/L) is the most common electrolyte imbalance observed in clinical practice. This common electrolyte disorder is even more frequent in older patients and, indeed, increased age (> 60 years) represents a risk factor for the development of hyponatremia.[1–3] Moreover, the most common symptoms associated with acute hyponatremia (developed in less than 48 h), such as nausea, vomiting, headache, and/or seizures, as well as conditions associated with chronic hyponatremia due to any cause (even mild), such as fatigue, cognition impairment, gait deficits, falls and fractures and even increased mortality, are more frequent and severe in elderly patients.[4–6]

Among the various causes of drug-induced hyponatremia, thiazide-induced hyponatremia comprises a main cause, while loop diuretics only occasionally induce hyponatremia.[3,7–17] The incidence of thiazide–induced hyponatremia has not been clearly determined, since in many cases other potential risk factors for low serum sodium levels are concurrently present. Hence, the reported incidence of thiazide-induced hyponatremia in various studies depended on several variables such as the definition of hyponatremia, the studied population (for example more frequent in the elderly), the healthcare setting, and differences in diuretic choice and dosage. In this context, a study reported that approximately 14% of 951 thiazide-treated outpatients had hyponatremia (serum sodium concentration < 135 mmol/L), whereas age > 70 years was associated with a fourfold increase in hyponatremia risk.[18] On the other hand, the Systolic Hypertension in the Elderly Program (SHEP) study reported hyponatremia (serum sodium concentration < 130 mmol/L) in 4.1% of patients taking chlorthalidone compared with 1.3% in the control group.[19] Generally, thiazide-associated hyponatremia (serum sodium concentration < 136 mmol/L) is a relatively frequent condition in elderly individuals. The aim of this review is to practically present the current evidence regarding the thiazide-induced hyponatremia in elderly patients.

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2 Risk factors for thiazide-induced hyponatremia

The risk factors for the development of thiazide–associated hyponatremia are shown in Table 1.[11,20,21] Even though hyponatremia is usually observed within the first few weeks of treatment, it can also be observed after years of treatment especially when concomitant contributory factors shown in Table 1 supervene.[20,22,23]

Low-normal or unmeasured baseline sodium levels and increased comorbidity burden (≥ 5 comorbidities), such as heart failure, depression, dementia, respiratory diseases, chronic kidney disease, nausea, vomiting and/or malignancy, have been reported as strong predictors of hyponatremia in older adults.[24] Additionally, female gender or type 2 diabetes mellitus are significant risk factors for reduced sodium levels in patients receiving hydrochlorothiazide or indapamide.[22]

Thiazide-associated hyponatremia is more commonly encountered in elderly individuals with low body mass or low-sodium diet.[7–10,20,25] Furthermore, patients with habitual increased water intake (such as those with underlying psychiatric disorders, beer drinkers, etc) are particularly prone to the development of hyponatremia.[20] Concomitant administration of drugs affecting water homeostasis, such as selective serotonin reuptake inhibitors (SSRIs), serotonin–norepinephrine re-uptake inhibitors (SNRIs), non-steroidal anti-inflammatory drugs (NSAIDs) or benzodiazepines, is frequent in elderly patients with thiazide-associated hyponatremia.

The presence of hypokalemia is frequent in patients with thiazide-induced hyponatremia. However, hypokalemia is not only a risk factor for the development of hyponatremia but also for difficulty in the correction of hyponatremia.[26,27]

Table 1. Risk factors for thiazide-associated hyponatremia in the elderly.

Low-normal or unmeasured baseline sodium levels
Many comorbidities (> 5)
Low body mass
Low-sodium diet-tube feeding
Habitual increased water intake
Concominant administration of drugs affecting water homeostasis, such as SSRIs, NSAIDs or even benzodiazepines
Underlying psychiatric diseases associated with polydipsia
Female gender
Type 2 diabetes mellitus
Hypokalemia
Increased dose of thiazides
Co-administration of amiloride/spironolactone

SSRIs: selective serotonin re-uptake inhibitors; NSAIDs: non-steroidal anti-inflammatory drugs.

A study reported that only 10% of elderly hypertensive women with diuretic-associated hyponatremia received a low dose of hydrochlorothiazide (12.5 mg/day), suggesting that the effects of thiazides are dose-dependent.[28] Interestingly, hyponatremia seems to be more common in patients treated with chlorthalidone compared with hydrochlorothiazide both in young and elderly individuals.[29,30] A retrospective population-based cohort study of 29,873 individuals aged ≥ 66 years showed that chlorthalidone was associated with an increased hospitalizations due to hyponatremia by approximately 1.7 times compared with hydrochlorothiazide.[30] Indapamide administration may also be related with the development of hyponatremia.[31] Even the low dose of indapamide (sustained release 1.5 mg daily) can induce severe hyponatremia (serum sodium < 125 mmol/L) in elderly individuals.[32] However, indapamide, although not consistently, has been associated with less hyponatremia compared with hydrochlorothiazide in elderly hypertensive patients.[22,33] It should be mentioned that the risk of hyponatremia increases with the concomitant administration of thiazides with amiloride or spironolactone.[34]

3 Biochemical characteristics of thiazide-associated hyponatremia

Patients with thiazide-associated hyponatremia are broadly divided into two subgroups according to their biochemical profile; a subgroup with laboratory results consistent with extracellular volume depletion (increased serum urea/creatinine ratio, increased uric acid levels, urine Na^+ < 20 mmol/L after discontinuation of the thiazide) and a subgroup with a biochemical profile suggesting the syndrome of inappropriate antidiuretic hormone secretion (SIADH) (low to normal serum creatinine and urea, decreased uric acid levels, increased urine Na^+).[35] However, in many cases the distinction of these subgroups is difficult since they may have features from both entities.[25,36]

4 Pathogenetic mechanisms of thiazide–associated hyponatremia

A number of interrelated mechanisms are implicated in the pathogenesis of thiazide–induced hyponatremia in the elderly (Table 2).

(1) The propensity of thiazides to promote hyponatremia is explained by the inhibition of urinary dilution due to reduced reabsorption of NaCl in the distal renal tubules.[25] In contrast, loop diuretics do not impair urinary dilution and are not associated with reduction of sodium levels.[37] Indeed, loop diuretics generally cause hypotonic renal losses

Table 2. Pathogenetic mechanisms of thiazide-induced hyponatremia in the elderly.

Decreased free water excretion (diminished urine diluting ability) due to the reduced NaCl reabsorption in the renal tubules
Excess renal losses of electrolytes ($K^+ + Na^+$) as compared to water excretion (hypertonic losses)
Aging and associated smaller muscle mass impair renal diluting capacity
Decreased intrarenal generation of prostaglandins
Decreased glomerular filtration rate
Increased water intake
Extracellular volume depletion leading to ADH-mediated water retention (non-osmotic baroceptor mediated) and to activation of thirst-stimulation of water intake
Coexistent diuretic–induced hypokalemia leading to transcellular cation exchange (K^+ leaves the cells, while Na^+ moves into cells)
Inappropriate secretion of ADH (thiazides can exacerbate hyponatremia in patients with underlying SIADH or can increase the secretion of ADH)
Direct upregulation of aquaporin-2 receptors expression in the renal tubules resulting in increased water permeability in the collecting duct

ADH: antidiuretic hormone; SIADH: syndrome of inappropriate antidiuretic hormone secretion.

and are used to treat euvolemic and hypervolemic hyponatremia. Furthermore, hypernatremia rather than hyponatremia may develop if renal water losses induced by loop diuretics are not sufficiently replaced.[3]

(2) Elderly patients usually have decreased muscle mass, which is associated with impairment of the renal diluting capacity.[38] In fact, decreased body mass is an independent risk factor for the development of thiazide–associated hyponatremia.[20,24,28] In this context, it has been proposed that the higher incidence of thiazide-associated hyponatremia in women may be mediated by body size.[21] It should be noted that serum sodium concentration is associated with exchangeable total (sodium + potassium)/total body water ratio. Hence, fluctuations in serum sodium concentration occur more frequently in subjects with less total body water. Additionally, low body mass in elderly subjects may be related to an underlying illness, which can also be associated with the development of hyponatremia. Decreased protein intake (habitually or due to superimposed illness) also affects water excretion and may play a role in the development of hyponatremia.[39]

(3) A decreased intrarenal generation of prostaglandins may also be involved in the impaired ability of elderly individuals to excrete water. In fact, a defect in water excretion due to prostaglandin deficiency would be amplified by thiazides, since the reabsorption of NaCl without water at the thiazide-sensitive site in the distal tubule normally lowers the urine osmolality.[38]

(4) The high prevalence of decreased glomerular filtration rate (GFR) in elderly individuals may also play a role in the thiazide-induced impaired water excretion. In this context, a study showed that patients who developed thiazide-associated hyponatremia had lower baseline GFR compared with patients who remained normonatremic during therapy.[39]

(5) Thiazide–induced extracellular volume depletion results in increased non-osmotic baroreceptor-mediated secretion of antidiuretic hormone (ADH). The increased ADH induces water retention in renal tubules and activates thirst–stimulation water intake.[25,39]

(6) The thiazide-induced electrolyte excretion leads to loss of effective solutes ($K^+ + Na^+$), which in association with the excess of water due to ADH-mediated water retention results in hypertonic losses.[9]

(7) Increased water intake is a prominent factor related with hyponatremia, especially in patients with an acute idiosyncratic reduction in serum sodium concentration.[8,40,41] The role of drugs causing xerostomia, such as anticholinergics, SSRIs, tricyclic antidepressants, phenothiazines, is important in many elderly patients.[42]

(8) The thiazide-induced hypokalemia may play a significant role in the development of hyponatremia, since it promotes a transcellular exchange between K^+ (exits from cells) and Na^+ (moves into cells).[26,27]

(9) Thiazides are associated in some cases with the development of euvolemic hyponatremia due to inappropriate secretion of ADH. Usually in these cases hyponatremia occurs acutely after thiazide initiation.[35,43] It should also be mentioned that enhanced ADH release may also be induced by nausea or other neurological symptoms.

(10) It has been reported that the idiopathic SIADH (a relatively rare phenomenon) is more common among the elderly.[44] The increased incidence of idiopathic SIADH in older subjects may be due to a higher sensitivity to osmotic stimuli.[45]

(11) It is important to note that thiazides can also exacerbate hyponatremia in patients with underlying SIADH due to drugs (SSRIs, SNRIs, NSAIDs, benzodiazepines, tricyclic antidepressants) or other causes.[20] Moreover, various drug categories that elderly patients frequently take (e.g., NSAIDs, SSRIs, SNRIs, benzodiazepins, angiotensin converting enzyme inhibitors, sartans) impair water excretion. A multidrug regimen including some of these drugs is a risk factor for the development of thiazide-induced hyponatremia.

(12) Elderly individuals frequently follow a low salt diet, especially if they have hypertension or heart failure, and suffer from diseases (e.g., diabetes mellitus, infections, heart

failure) that stimulate water intake or ADH release.

(13) A direct effect of thiazides on aquaporin-2 receptor expression in the renal tubules has also been proposed as a mediating mechanism promoting hyponatremia. In some cases, these receptors are acutely up-regulated by thiazides resulting in increased water permeability in the collecting duct and, hence, water retention and decreased sodium concentration.[46–48] Indeed, it has been shown *in vitro* that thiazides increase water permeability and water reabsorption in the inner medullary collecting duct in an ADH-independent manner.[46–48]

5 Diagnosis of thiazide-induced hyponatremia

Thiazide-induced hyponatremia should be considered when the hyponatremic patient takes a thiazide. However, it is necessary to distinguish the thiazide-induced hyponatremia from the other causes of reduced serum sodium concentration. A thorough medical history helps to identify the presence of underlying diseases, polydipsia or concurrent administration of drugs that may be related with reduced serum sodium levels.[20,36,49] Moreover, a detailed physical examination should focus on signs of extracellular volume depletion.

Laboratory investigation should be initiated with the measurement of serum osmolarity (Posm) (Figure 1). It is crucial to differentiate non-hypotonic hyponatremia from the "true" hypotonic (Posm < 280 mOsm/kg) hyponatremia.[50] When the latter has been confirmed, serum urea, creatinine, potassium, uric acid as well as thyroid stimulating hormone and cortisol levels (for the exclusion of endocrine diseases-associated hyponatremia) should be determined.[51–54] Additionally, urine urea, sodium, potassium, creatinine and uric acid should be measured in a spot urine sample and the fractional excretion of sodium, urea, potassium and uric acid levels should be appropriately calculated.

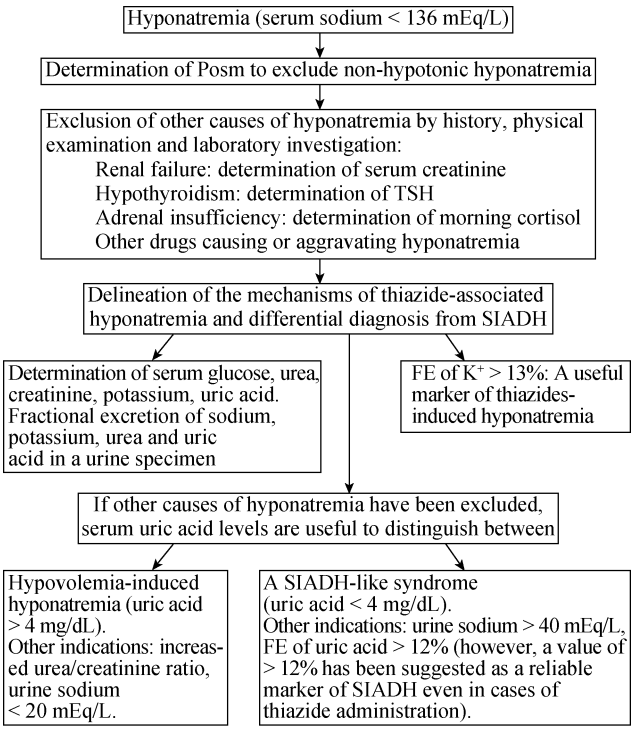

Figure 1. Laboratory investigation of possible thiazide-associated hyponatremia. FE: fractional excretion; Posm: serum osmolarity; SIADH: syndrome of inappropriate antidiuretic hormone secretion; TSH: thyroid stimulating hormone.

The evaluation of laboratory tests for the diagnosis of thiazide-induced hyponatremia is presented in Table 3. It is important to note that although low uric acid levels combined with increased urate fractional excretion [fractional excretion (FE) of urate > 12%] favor the diagnosis of SIADH even in patients on diuretics,[55] these abnormalities may also point to a subgroup of patients with thiazide–induced hyponatremia. This subgroup of patients is presented with a SIADH-like picture with euvolemia, but usually with a quick onset of severe hyponatremia.[35] It should be noted that increased potassium excretion (FE of K^+ >13%) is a useful marker for the diagnosis of thiazide-induced hyponatremia.[56]

Table 3. Diagnosis of thiazide-induced hyponatremia.

Coexistent hypokalemia with kaliuria (FE of K^+ >13%). FE of K can help to differentiate hyponatremia due to thiazides from other causes
A low FE of uric acid (< 12%) is usually observed in thiazides-associated hyponatremia
Urine sodium is < 20 mEq/L in patients with extracellular volume depletion-induced hyponatremia when the diuretic effect has warned off. However, values > 20 mEq/L are not diagnostic
Serum uric acid levels can differentiate between two subgroups of patients with thiazide-associated hyponatremia: patients with serum uric acid levels < 4 mg/dL usually exhibit a biochemical profile coexistent with a SIADH-like state, whereas patients with uric acid levels > 4 mg/dL usually have extracellular volume depletion

FE: fractional excretion; SIADH: syndrome of inappropriate antidiuretic hormone secretion.

The restoration of normonatremia after thiazide withdrawal aids to the accurate diagnosis of thiazide-induced hyponatremia. However, up to two weeks may be needed after stopping the thiazide for full recovery of the diluting capacity and serum sodium normalization. This delay should be taken into account when investigating the subgroup of patients with possible thiazide-associated hyponatremia and a SIADH-like profile. In these patients, a thorough diagnostic work up for the presence of other causes for underlying SIADH should be done only if mild hyponatre-

mia persists 2–3 weeks after the discontinuation of the thiazide.

6 Treatment of thiazide-induced hyponatremia

Hyponatremia, especially when attributed to diuretics, should be carefully managed.[57] The first step is the discontinuation of the possible offending agent. The drug withdrawal results in restoration of urinary diluting ability leading to increased water diuresis. This effect increases the risk of rapid or even dangerous correction of hyponatremia. The measurement of urine electrolytes and calculation of urine/plasma electrolyte ratio [(urine Na^+ + urine K^+)/serum Na^+] are helpful. An urine/serum electrolyte ratio < 0.5 is indicative of increased water excretion, which is associated with potentially dangerous overtreatment of hyponatremia. In any case, frequent (every few hours) determination of serum electrolytes and careful evaluation of diuresis are mandatory for the safe and effective correction of hyponatremia.[53,54,58,59]

Acute hyponatremia (developed in less than 48 h) may produce neurological symptoms, from simple such as nausea, vomiting, or headache to serious such as seizures, coma or death, which are associated with the degree of brain edema. In cases of acute symptomatic hyponatremia, administration of 100 mL of 3% NaCl (2 mL/kg body weight) should be immediately given. If it is needed, up to two additional infusions at 10-min intervals may be given.[60] Target of treatment is an increase of serum sodium by 4–6 mEq/L within the first 6 h for symptoms to subside. However, the increase in serum sodium should not exceed the 8 mEq/L during the first 24 h, the 12–14 mEq/L during the first 48 h, and the 14–16 mEq/L during the first 72 h. More rapid correction of hyponatremia increases the risk of developing the osmotic demyelination syndrome (ODS), a disorder involving central demyelinating lesions, particularly in the pons, and major neurologic disability or even fatal outcome.[61–63] Brain magnetic resonance imaging is sensitive to diagnose the demyelination in the brainstem pons.[64,65] Elderly patients with hypokalemia, malnutrition, underlying liver disease and hypoxia are at particularly increased risk for the development of ODS.[53,54,58,66] Moreover, it has been shown that elderly women are more susceptible to develop neurological complications as a result of rapid correction of hyponatremia.[62,67,68]

In cases of chronic oligosymptomatic hyponatremia, therapy is based mainly on patients' extracellular volume status. In euvolemic states, discontinuation of thiazide and water restriction (up to 1 L/day) are usually enough to correct serum sodium levels. In hypovolemic hyponatremia, normal saline (0.9% sodium chloride solution) should be administered.[60] The rate of infusion of normal saline should be individualized and special attention should be given in elderly patients with underlying heart failure.[69]

Importantly, the potassium depletion that is frequently observed in thiazide-related hyponatremia should also be corrected. However, clinicians should be very careful in this setting. First, potassium anions should be taken into account in the calculation of the tonicity of the infused solutions. Thus, when intravenous potassium administration is required, potassium chloride should be added in hypotonic fluids. The administration of potassium chloride in normal saline should be avoided because it can result in rapid correction of hyponatremia and circulatory overload.[69] Second, the correction of hypovolemia and hypokalemia may be followed by an increased water diuresis, which increases substantially the risk of overcorrection of hyponatremia and its devastating consequences.[53,54,58,59] In these cases, careful and frequent monitoring (every few hours) of serum sodium concentration and diuresis is mandatory. The correction rate in serum sodium, which should be < 8 meq/L in the first 24 h of therapy in patients with chronic hyponatremia, should be even lower (i.e., < 4–6 mmol/L per 24 h) in the presence of hypokalemia.[70] It should be noted that vasopressin receptor inhibitors (Vaptans) do not have any role in hypovolemic hyponatremia due to thiazide administration.[71]

7 Prevention of thiazide–induced hyponatremia

Since thiazide-induced hyponatremia, even mild, is associated with a considerable increase in patients' morbidity, special attention should be given to the prevention of this abnormality in elderly patients (Table 4).[34,57–59,72] A low dose of diuretic (equivalent to 12.5 mg hydrochlorothiazide) should be preferred if additional risk factors coexist. A calcium channel blocker or beta-blockers are useful choices for patients who need an alternative antihypertensive treatment. Finally, in patients with a history of thiazide-associated hyponatremia who need to take diuretics, furosemide may be used without risk of recurrent hyponatremia.[73]

8 Conclusions

Thiazide-induced hyponatremia is frequent in elderly individuals. Clinicians should be aware for neurologic signs indicating decreased sodium levels and should monitor sodium concentration in patients with risk factors for thiazide-associated hyponatremia. The investigation of possible thiazide-associated hyponatremia includes the exclusion

Table 4. Measures for the prevention of thiazide-induced hyponatremia.

Thiazides should not be prescribed in elderly individuals with a history of diuretic-induced hyponatremia
Careful assessment of water intake especially in patients with underlying psychiatric disease and xerostomia
Careful administration of thiazides in patients taking drugs affecting water homeostasis, such as SSRIs and NSAIDs
A loop diuretic, which does not impair renal diluting ability, is desirable in patients with heart failure
Careful assessment of symptoms suggestive of decreased sodium levels (neurological symptoms, instability, frequent falls, decreased attention) shortly after thiazides prescription and regularly during therapy is mandatory
Measurement of serum creatinine and electrolyte values within the first days of thiazide initiation to identify an idiosyncratic acute decrease in serum sodium levels
Periodic laboratory investigation of patients on diuretics as well as on other drugs affecting renal function and electrolyte balance
Rapid discontinuation of diuretics as well as of other drugs affecting renal function and electrolyte balance in cases of an acute illness associated with decreased water intake, renal or extra-renal water losses, nausea or other conditions leading to increased ADH secretion

ADH: antidiuretic hormone; NSAIDs: non-steroidal anti-inflammatory drugs; SSRIs: selective serotonine re-uptake inhibitors.

of other causes of reduced sodium levels and the identification of the characteristics of hyponatremia due to thiazides (extracellular volume depletion-related or SIADH-like). Serum sodium levels should be carefully monitored to avoid overcorrection, which is associated with serious neurologic complications. Clinicians should avoid prescribing thiazides in patients with a history of diuretic-associated hyponatremia.

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