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Review Article

Hidden Plague of Thiazide Induced Hyponatremia among Elderly Patients

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ABSTRACT

Thiazide Induced Hyponatremia (TIH) is one of the main causes of fatal hyponatremia among elderly. The global and Indian prevalence ranges from 4-14% and 30%, respectively. This paper reviewed the clinical implications of thiazide usage and its side effect especially hyponatremia from the global and Indian perspective. A literature review was performed using databases such as PubMed and Google Scholar between January and May, 2023. This review deals with prevalence, mechanism of TIH development, risk factor, signs and symptoms, mortality, treatment modalities of hyponatremia, pharmacist roles and prevention. Advancing age, female gender, alcohol consumption, low body mass index, several medications such as antidepressants, antiepileptics, corticosteroid withdrawal, hydrochlorothiazide, indapamide, etc., are also the risk factor for TIH. The signs and symptoms include headache, lethargy, mental confusion, etc., The mortality rate in India varies from 7-51%. The management is influenced by the presence or absence of neurologic symptoms. Treatment involves stopping thiazides, maintaining a regular diet (especially K+ supplements), limiting water intake, furosemide administration and administering isotonic saline or hypertonic saline in case of severe hyponatremia. Clinical pharmacists have an important role in identifying and managing TIH. Early diagnosis, better management and prevention strategies improve the quality of life among elderly.

Keywords: Thiazide induced hyponatremia, Prevalence, Risk factors, Mortality, Management.

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INTRODUCTION

Thiazide diuretics have been routinely used to treat hypertension since its introduction in 1957. On rare occasions, they are also used along with diuretics to treat heart failure. However, there are risks associated with its use and thiazides can cause potentially fatal hyponatremia, kidney injury, hypokalemia, syncope, etc.,[1,2] A Serum Sodium (SNa+) level <135 mEq/L is considered as hyponatremia and water retention is the most frequent cause. Hyponatremia of any severity is linked to increased Length of Stay (LOS) and mortality.[3] The frequency of hyponatremia varies depending on the clinical situation.[4,5] The global prevalence of hyponatremia among elderly patients varies between 2% and 33%.[2] The prevalence of hyponatremia among Asians was found to be 18%.[6] The prevalence within India varies between 5 and 29%.[7] The risk factors of hyponatremia include medications such as antidepressants, antiepileptics, Hydrochlorothiazide (HCTZ), etc., which may result in a Syndrome of Improper Antidiuretic Hormone secretion (SIADH), Congestive Heart Failure (CHF), cirrhosis and Chronic Kidney Disease (CKD).[7,8] Advancing age, female gender, alcohol consumption and having a low Body Mass Index (BMI) are also the risk factor for hyponatremia. The signs and symptoms include headache, lethargy, mental confusion etc.,[1,9] Thiazide diuretics are typically not prescribed by doctors as a first-line anti-hypertensives drugs, nor are they generally suggested by clinicians. This attributes to concerns about electrolyte disturbances such as hyponatremia, hypokalemia etc.,[10] The global prevalence of Thiazide-Induced Hyponatremia (TIH) varies between 4 and 14%.[1] Indian prevalence of TIH is between 18% and 29%.[7] The mortality rate in India varies between 6.7% and 51%.[11,12] Management of hyponatremia includes the administration of 3% Normal Saline (NS).[13] Callahan *et al.* (2009) from the USA reported that the median cost for treatment of hyponatremia ranges between $13,066 and $14,266.[14] This review deals with prevalence, risk factor, signs and symptoms, mortality, treatment modalities of hyponatremia.

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MECHANISM OF THIAZIDE INDUCED HYPONATREMIA

Mechanism

The pathophysiological mechanisms leading to TIH remain unclear despite extensive research. The three main factors associated with TIH are decreased free-water clearance, increased water consumption and renal Na+ and/or K+ losses.[13] When the amount of free water consumed exceeds, the kidney's eliminating capacity, TIH develops.

Pathogenic mechanisms

Reduced Sodium Chloride (NaCl) reabsorption from the renal tubules results in decreased free water excretion. Thiazides' propensity to cause hyponatremia is reinforced by the distal renal tubules' diminished capacity to absorb NaCl, which dilutes the urine (lowering the osmolality).[13]

Decreased intrarenal generation of prostaglandins. Thiazides can amplify prostaglandin deficiency-related deficit resulting in increased water reabsorption and decreased NaCl reabsorption at the distal tubule, reducing the urine osmolality.[15]

Increased water consumption

Thiazide-induced hypokalemia facilitates cellular exchange between K+ and Na+ (inward cellular movement of Na+ exchange with K+) and may significantly contribute to the development of hyponatremia.[16]

Direct upregulation of the expression of renal tubular aquaporin-2 receptors, resulting in increased permeability of water in the collecting duct.[17]

Aging and Lean Body Mass (LBM) impair renal diluting capacity.[12]

Decrease in glomerular filtration rate

Thiazide diuretics worsen hyponatremia in the presence of SIADH.[12] Antidiuretic Hormone (ADH) is secreted more frequently through non-osmotic baroreceptors when thiazide causes extracellular volume depletion. Increased ADH causes water retention in renal tubules and triggers water intake in response to thirst.[13,18]

Effective solutes (K^+ and Na^+) are lost as a result of thiazide-induced electrolyte excretion and this, along with the excess water due to ADH-mediated water retention results in hypertonic losses.[19]

Prevalence

The global prevalence of TIH varies from 4% to 73% and even up to 30%.[1] The prevalence[1,6,13,20-24] of TIH from different countries is represented in the following Table 1 and Figure 1.

Risk Factors

Hyponatremia is typically noticed during the initial weeks of treatment or can be noticed years later. The risk factors of TIH include LBM, female gender and age.[1] As SNa+ levels are influenced by the ratio of total solute to body water, variability in SNa+ concentrations are more pronounced in individuals with lower TBW. Age-related declines in water homeostasis maintenance can occur. Additionally, renal function decline with age, which may affect the ability to eliminate medications and water.[25] Chow *et al.* (2003) from China reported that every ten-year increment in age was linked to a 2-fold increase in the risk of TIH (Hazard Ratio (HR) 2.14, 95% CI 1.59-2.88). The study also reported that for every 5 kg increment in mass, there was a 27% decrease in risk of TIH (Odds Ratio (OR) 0.77, 95% CI 0.68-0.87) and one Standard Deviation (SD) increase in K+ level (0.84 mmol/L) was associated with a 63% decreased risk of TIH (OR 0.37, 95%CI 0.27-0.50;$p<0.0001$), which shows that TIH is inversely correlated with SK+ concentrations. These were the independent risk factors for TIH.[26] Clark *et al.* (1994) from Boston reported that younger individuals are less prone to develop TIH than elderly adults.[15]

Patients using multiple therapies, such as tricyclic antidepressants, Non-Steroidal Anti-Inflammatory Drugs (NSAIDs), or Selective Serotonin Reuptake Inhibitors (SSRIs) are more likely to experience TIH.[12] Rastogi *et al.* (2012) from the USA reported the use of thiazide diuretics with either Angiotensin-Converting Enzyme Inhibitors (ACEIs) or an Angiotensin (AT)-II Receptor Blockers (ARBs) is also associated with TIH. ACEIs use was independently associated with a higher risk of TIH. Multivariate analysis revealed that age (OR 1.75, 95% CI, 1.58-1.93), ACEIs use (OR 1.53; 95% CI, 1.16-2.00) and hypokalemia (OR 40.94; 95% CI, 26.46-66.33) were highly associated with hospitalizations associated TIH.[27] Kim *et al.* (2013) from Korea reported two patients who were receiving thiazide and ARBs developed acute hyponatremia.[28] Adults and elderly's treated with chlorthalidone appear to experience hyponatremia more frequently than those treated with HCTZ.[29] Blijderveen *et al.* (2014) from Netherlands showed that hyponatremia was more common with chlorthalidone (12.5-25 mg/d) compared to HCTZ (12.5-25 mg/d). Administration of indapamide may potentially be related to the occurrence of hyponatremia.[30] Yong *et al.* (2011) from Australia reported that indapamide resulted in an admission of eleven patients with severe TIH. Elderly people experienced severe TIH (SNa+ <125 mmol/L) even at lower dose (indapamide sustained release tablets 1.5 mg daily).[31]

Thiazides along with SIADH, gastrointestinal loss, cirrhosis and CKD) are also associated with TIH.[32]

Genetic predisposition of TIH

There are specific patient categories that can experience a significant drop in Na+ levels after taking thiazides.[33] Chin-Chou

et al. (2015) from Taiwan reported that severe TIH was more likely to develop in patients with hypertension who were elderly, female, had a low BMI and had the Potassium Inwardly Rectifying Channel Subfamily J Member 1 (KCNJ1) rs2509585 C/T or T/T polymorphism. Nonetheless, the author contends that additional research is required to corroborate these results in different populations.[34]

The inappropriate water retention, diminished Na+ reabsorption, or both, by definition, be the outcomes of the molecular pathways underpinning predisposition to TIH.[35] Thiazide diuretics imitate the implications effects of loss of function in NaCl cotransporter (NCC mutation) and this functional decline in NCC mutations can lead to lack of water and Na+ which is also seen in Mendelian syndrome of Gitelman.[36]

Clinical Presentation

Drug-induced hyponatremia requiring hospital admission is most frequently caused by TIH.[37]

Classification of hyponatremia

Mild: SNa+130-134 mEq/L,

Moderate: 125-130 mEq/L,

Severe: < 125 mEq/L.[38]

The clinical manifestations associated with mild, moderate and severe TIH are shown in Table 2.[20,39]

Blood Urea Nitrogen (BUN) and Serum Creatinine concentration (SCr), are usually low-normal and hypouricemia (increased Uric Acid (UA) excretion) might be present in TIH patients.[40]

Barber *et al.* (2015) from the UK reported different frequencies of clinical symptoms in TIH patients as shown in Table 3.[41]

Comorbidities

The most frequent comorbidities of TIH include Diabetes Mellitus (DM), CKD, Cardiovascular Disease (CVD), etc., (41). Ware *et al.* (2017) from the UK also reported that 6%, 17% and 19% of patients had a comorbidity and were treated for hypothyroidism, DM and CKD (eGFR 30-60 mL/min), respectively.[42]

Complications

Central Pontine Myelinosis (CPM) (a component of Osmotic Demyelination Syndrome (ODS) and cerebral edema) are the two primary neurologic side effects of severe hyponatremia. CPM is due to the quick correction of hyponatremia. Fortunately, most TIH patients recover without neurologic after-effects with the right care.[43,44] When there is severe acute hyponatremia, cerebral edema develops. Patients with severe TIH have shown clinical symptoms such as obtundation, convulsions and coma. Rapid

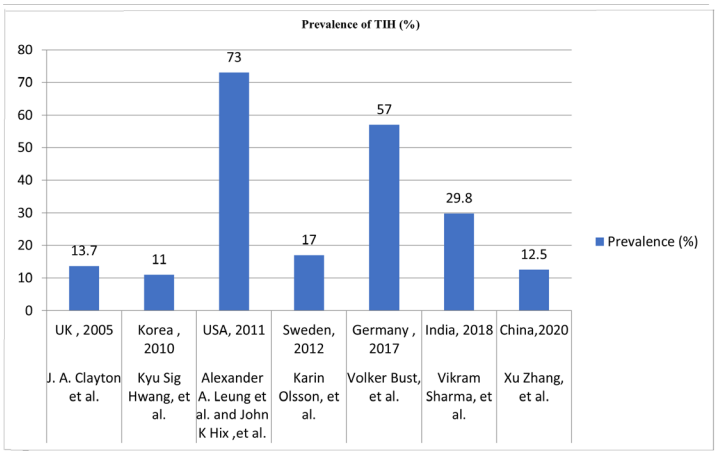

Figure 1: Prevalence of TIH in different countries.

Table 1: Prevalence of TIH in different countries.

Name of author	Place	Year of Publication	Prevalence
Clayton *et al.*[20]	UK	2005	14%
Hwang, *et al.*[13]	Korea	2010	11%
Leung *et al.*[21] and Hix, *et al.*[22]	USA	2011	30-73%
Olsson, *et al.*[23]	Sweden	2012	17%
Burst, *et al.*[1]	Germany	2017	57%
Zhang, *et al.*[26]	China	2020	12.5%

UK=United Kingdom USA=United States of America TIH=Thiazide Induced Hyponatremia

Table 2: Clinical manifestations.

Severity	Clinical Manifestations
Mild (Typically asymptomatic)	Nausea Gait Attention deficits with increased risk of falls Fractures
Moderate (Asymptomatic or Symptomatic)	Fatigue Nausea Vomiting Confusion Dizziness Stomach pain Ataxia
Severe	Cerebral edema Coma Seizures Brain damage Brain stem herniation Respiratory arrest Death

Table 3: Different study reports of frequency of symptoms in TIH patients.

Symptoms	95% CI	Percentage (%) of case report data
Falls	0.17 to 0.88	4
Dizziness	0.15 to 0.51	8
Fatigue	0.21 to 0.72	38
Seizures	0.08 to 0.34	21
Weakness	0.32 to 0.58	27
Unconsciousness	0.15 to 0.48	27
Confusion	0.32 to 0.56	33
Nausea	0.24 to 0.50	21
Vomiting	0.25 to 0.46	19

correction can result in intracellular fluid extrusion, hyperosmolar demyelination and cellular dehydration, in the pons and other locations, which can induce neurologic dysfunction such as quadriplegia, pseudobulbar palsy, convulsions, coma and death.[43]

Onset of TIH

The time between the first thiazide intake and the onset of hyponatremia varies considerably. Although it usually occurs two weeks after treatment, hyponatremia can occur at any time throughout treatment if complicating variables including taking multiple drugs that alter free water clearance, aging-related declines in renal function, or modifications to water or Na+ intake

Table 4: Parameters for diagnosis of TIH.

Parameters useful in diagnosis of TIH
Kaliuria and coexisting hypokalemia (FE of K+ >13%). FE of K+ can be used to distinguish between hyponatremia brought on by thiazides and other causes.
Thiazide-related hyponatremia typically has a low FE of UA (<12%).
When the diuretic impact has worn off in patients with extracellular volume depletion-induced hyponatremia, urine sodium is <20 mEq/L. Values above >20 mEq/L, however, are not diagnostic.
Patients with TIH can be divided into two subgroups based on their serum UA levels: those with levels <4 mg/dL typically have a biochemical profile consistent with a SIADH-like state, while those with levels >4 mg/dL typically have extracellular volume depletion.

FE- Fecal excretion, K+- Potassium, UA- Uric acid, SIADH- Syndrome of inappropriate antidiuretic hormone secretion.

are present.[13] Friedman *et al.* (1989) from Israel showed that intake of a single thiazide diuretic tablet within 6 hr in individuals with previously afflicted TIH had a minor rise in urine osmolality and a decline in SNa+ of 5.5 mEq/L associated with a slight weight gain. However, in controls, the mean weight decreased and their SNa+ level was found to be only slightly decreased.[45]

Sharabi *et al.* (2002) from Israel reported that 10% of older hypertensive women who received HCTZ (12.5 mg/day) developed TIH, indicating that the effects are dose-dependent.[12] Yong TY *et al.* (2011) from Australia reported that even a small dose (1.5 mg daily) of indapamide might cause severe hyponatremia in elderly.[31] Gantait *et al.* (2017) from West Bengal reported that the combined antihypertensive doses of HCTZ (12.5 mg) and chlorothiazide (6.25 mg) with an ARB or CCB were given to all patients. Sixty percentage of patients (the majority were older than 65 years old) had hyponatremia when it was first identified and 40% had it after more than six months of treatment.[46] Although the authors did not evaluate water consumption, they hypothesized that thiazides would promote polydipsia, that, when paired with the renal effects, causes an increase in TBW and the onset of hyponatremia.[33]

Mortality

Thiazides have the potential to cause severe hyponatremia with long-term brain impairment.[19] Yamazo *et al.* (2018) from Japan reported that patient in the thiazide group died due to all causes (49%) and Cardiovascular (CV) cause (30%), thiazide use was independently linked to all-cause (HR 2.52, 95% CI, 1.81-3.50) and CV mortality (HR 3.08, 95% CI, 1.99-4.76. TIH results in permanent neurological damage or death. For instance, metolazone causes increased urine Na+ loss and reduces the kidney's ability to dilute the urine and remove excess water. Thiazides may therefore rapidly cause severe hyponatremia

with long-term neurologic impairment or death in susceptible subgroups of out-patients.[19] More research is required in this area due to a paucity of information on mortality from TIH. Randomized Control Trials (RCTs) have shown solid and clear evidence that thiazides are effective in lowering CV morbidity and death. Leung *et al.* (2011) from Boston showed there was no association between TIH and mortality. Several RCTs supports the effectiveness of thiazides in lowering mortality.[21] In addition, the "Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial" found no differences in mortality between thiazides, ACE inhibitors, or CCBs, irrespective of the patient's age, sex, ethnicity, or underlying comorbidities.[21,47]

Diagnosis

Whenever a patient on thiazide comes with hyponatremia, TIH should be taken into consideration. The various reasons for lower SNa+ concentration must be distinguished from TIH. A thorough medical history analysis and physical examination should be performed. TIH is accurately diagnosed when normonatremia occur following thiazide discontinuation. After discontinuation of thiazide, it may take up to two weeks for the diluting capacity of the kidney to fully recover and the SNa+ levels to return to normal. When examining the subset of patients who may have TIH and a SIADH-like profile, this delay should be taken into consideration.[12]

When evaluating a patient with suspected TIH, Urine and Electrolyte (U&E) test must be performed and other possible causes of hyponatremia should be ruled out. Barber *et al.* (2015) from UK reported that the average-mean trough U&E were; Na+=117 mM (95% CI 114 to 120), with reduced osmolality of 242 mOsm/kg (95% CI 238 to 246 mOsm/kg) and K+=3.3 mM (95% CI 3.0 to 3.5)(41). James *et al.* (2017) from UK showed that among hospitalized TIH patients, had SNa+ levels of 122±0.6 mM, reduced osmolality of 255±4 mOsm/kg and K+3.7±0.06 mM.[42] Additionally, fractional excretion of Na+, urea, K+, UA and SCr should be estimated in a spot urine sample. With euvolemia and a SIADH-like presentation, the patients typically exhibit a rapid development of severe hyponatremia.[48] The parameters useful in diagnosis are shown in Table 4.[12]

Treatment strategies followed in TIH

More than the Na+ level itself, the acute management of TIH is influenced by the presence or absence of neurologic symptoms. Treatment involves stopping thiazides, maintaining a regular diet (often added with K+ supplements), limiting water intake, furosemide administration and administering isotonic saline or hypertonic saline in case of severe hyponatremia.[13] The Treatment algorithm of TIH is shown in Table 5.[43]

Acute management of Symptomatic TIH

To limit the risk of cerebral edema, rapid but partial SNa+ correction is the initial objective. followed by gradual correction of Na+ to lower the chance of CPM.[43]

NS or hypertonic saline are the two main therapeutic choices for symptomatic patients.[49] After infusing saline for 2 hr, if the SNa+ level has not increased, hypertonic saline should be given. It is advised to initiate hypertonic saline in patients who have severe symptoms like seizures or coma to ensure a quick commencement of response.[43,49]

Administration of furosemide along with hypertonic saline can increase the SNa+ levels in individuals with euvolemic or hypervolemic hyponatremia while preventing volume overload.[50] Furosemide should not be given to patients who have hypovolemic hyponatremia or whose volume status is unknown.[51]

Table 5: Treatment Algorithm of TIH.

Thiazide-induced hyponatremia (TIH) that is neither symptomatic or only mildly symptomatic
Acute Management
1. Withdraw the harmful thiazide diuretic from use.
2. Limit fluid consumption to less than 1-1.5 L/day, if necessary, to create a negative water balance.
3. If hypovolemic, depending on how severe the hyponatremia is, infuse NS or increase oral salt intake.
Chronic Management
1. Prevent routinely consuming too much fluid.
2. If a diuretic is required, switch out the thiazide for a loop diuretic or with some other antihypertensives like CCBs, ARBs, or ACEIs.
3. Continually check SNa+levels.
Hyponatremia with symptoms (normally 120 mEq/L)
1. Remove problematic thiazide diuretic from use.
2. If hypovolemic with just minor symptoms, administer NS infusion.
3. Infuse hypertonic saline if euvolemic, hypervolemic, or if symptoms are severe.
a) Inject 1-2 cc/kg/h of hypertonic saline (3% NaCl; 5 mEq NaCl per 10 cc).
b) Can co-administer intravenous furosemide if volume overload is a problem or if hyponatremia needs to be corrected quickly.
4. Treatment objective
a) Increase SNa by 1-2 mEq/L/h for the first 3-4 hr, or until symptoms improve or SNa has increased by 6-8 mEq/L.
b) The next objective is to raise SNa by nmt 12 mEq/L/d.
5. Check Na every 2-3 hr.

NS-Normal saline, CCBs- Calcium channel blockers, ARBs- Angiotensin receptor blockers, ACEIs- Angiotensin converting enzyme inhibitors, SNa+- Serum sodium, NaCl- Sodium chloride.

Table 6: To aid medical professionals (viz. Clinical Pharmacists) in identifying and recognizing hyponatremia.

To determine which drugs/risk factors may cause hyponatremia
Pharmacists are responsible for identifying medication-induced hyponatremia.
Pharmacists should monitor SNa+ and more complex medications to reduce the risk of hyponatremia.
To improve medication regimen.
Pharmacists should be aware of the available treatment options for hyponatremia and know the appropriate dosage, administration and duration.
Pharmacovigilance should be applied.
Patient medication adherence should be considered.
Pharmacists is responsible for monitoring patients' responses to any recommended medication regimen.

SNa+-Serum Sodium.

Although it has been shown that tolvaptan, (a V2-selective arginine vasopressin-receptor antagonist), increase SNa+ in hyponatremic patients however, its effectiveness in the treatment of TIH has not been studied.[52] Evidence suggests that tolvaptan may induce fatal ODS. CPM, a complication of TIH and a part of ODS, precludes clinicians from often providing the medication at the same time.[43,44,53]

Asymptomatic TIH management

The following ways are used to correct TIH.

Correction of Hyponatremia

The reduction in SNa+ concentration is typically milder with asymptomatic patients compared to symptomatic hyponatremic patients. At first, the problematic diuretic should be discontinued; SNa+ between 12 and 15 mEq/L/d should be maintained. It is not recommended to administer hypertonic saline unless volume depletion correction is indicated.[50]

Fluid Restriction

Patients who consume too much fluid (e.g., >2.5 L/day) should be instructed to cut back to about 1.5 L/day.[43]

Salt intake

Decreased salt intake, which is frequently used to manage hypertension, can increase the chance of developing hyponatremia.[54] Although increasing the intake may be beneficial, however, advising a hypertensive patient on a thiazide diuretic to do so seems counterproductive. An alternative to thiazide diuretics might be preferred in this situation replacement of thiazide diuretics: with loop diuretics or other antihypertensive agents.[43]

Table 7: Preventive strategies for TIH.

In older patients with a history of diuretic-induced hyponatremia, thiazides should not be administered
Administration of thiazides should be done with caution in patients taking medications that alter water homeostasis, such as SSRIs and NSAIDs.
During the initial days after starting thiazides, SCr and electrolyte values should be measured to check for an unusually abrupt drop in SNa+ levels.
Patients taking diuretics and other medications have an influence on renal function and electrolyte balance should undergo routine laboratory testing (SNa+, SK+, renal function test).
In cases of an acute sickness accompanied by decreased water intake, renal or extra-renal water losses, nausea, or other conditions increasing ADH secretion, diuretics and other medications that impact renal function and electrolyte balance should be abruptly stopped.

SSRI's-Selective serotonin reuptake inhibitors, NSAIDs-Nonsteroidal anti-inflammatory drugs, SCr-Serum Creatinine, SNa+-Serum Sodium SK+-Serum Potassium, ADH=Antidiuretic hormone.

Pharmacist role in the management of TIH

In addition to assisting doctors in identifying hyponatremia, the pharmacist's responsibilities also include managing hyponatremia caused by medications, optimizing drug regimens for treating hyponatremia and carrying out additional research to improve the treatment of hyponatremia. The functions of clinical pharmacists in the management of TIH are listed[55] in Table 6.

Prevention

The first step in preventing TIH is becoming aware that it can occur especially in people over 70 years. People who consume a lot of fluids and who's typical SNa+ concentration falls within the normal range are probably at higher risk. The preventive strategies are shown in the Table 7.[56-58]

CONCLUSION

Internal medicine practitioners frequently encounter TIH, that frequently affects older, weak patients and cause significant morbidity. In this population, careful attention should be paid to the SNa+ level, as well as advice against the dangers of consuming too much fluid.

Older age, female sex and LBM are the major risk factors for the development of TIH. Even though TIH usually manifests right away after starting thiazide, this is not always the case and manifestation might occur months or even years later. Even though sudden onset cases are more likely to result in seizures and/or comas, many cases are symptomless or exhibit little symptoms.

Treatment with either saline or hypertonic saline is urgently necessary for patients with severe and symptomatic hyponatremia. Care must be taken to prevent an unduly quick restoration of SNa+ concentration, though. Withdrawing the thiazide and limiting fluid consumption are typically effective treatments for patients with mild-moderate TIH.

Prompt identification and ideal care of hyponatremia in hospitalized patients may improve the management of underlying comorbidities and quality of life. This will also allow for less intensive care, a reduction in LOS and its associated costs. In order to manage hyponatremia as effectively as possible, pharmacists also play a crucial part.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

TIH: Thiazide-induced hyponatremia; **SNa+:** Serum sodium; **LOS:** Length of stay; **HCTZ:** Hydrochlorothiazide; **SIADH:** Syndrome of improper antidiuretic hormone secretion; **CHF:** Congestive heart failure; **CKD:** Chronic kidney disease; **NS:** Normal saline; **NaCl:** Sodium chloride; **LBM:** Lean body mass; **HR:** Hazard ratio; **OR:** Odds ratio; **SD:** Standard deviation; **ARB:** Angiotensin receptor blockers; **ACEI:** Angiotensin converting enzyme inhibitors; **NSAIDS:** Non steroidal anti-inflammatory drugs; **SSRI:** Selective serotonin reuptake inhibitors; **AT:** Angiotensin; **ADH:** Antidiuretic hormone; **BUN:** Blood urea nitrogen; **SCr:** Serum creatinine; **UA:** Uric acid; **DM:** Diabetes mellitus; **CVD:** Cardiovascular disease; **CPM:** Cerebral pontine myelinosis; **ODS:** Osmotic demyelination syndrome; **CV:** Cardiovascular; **RCT:** Randomised controlled trial; **CCB:** Calcium channel blockers; **U&E:** Urine and electrolyte; **SK+:** Serum potassium.

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