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Hyponatremia and bone disease

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Abstract Hip fractures represent a serious health risk in the elderly, causing substantial morbidity and mortality. There is now a considerable volume of literature suggesting that chronic hyponatremia increases the adjusted odds ratio (OR) for both falls and fractures in the elderly. Hyponatremia appears to contribute to falls and fractures by two mechanisms. First, it produces mild cognitive impairment, resulting in unsteady gait and falls; this is probably due to the loss of glutamate (a neurotransmitter involved in gait function) as an osmolyte during brain adaptation to chronic hyponatremia. Second, hyponatremia directly contributes to osteoporosis and increased bone fragility by inducing increased bone resorption to mobilize sodium stores in bone. Low extracellular sodium directly stimulates osteoclastogenesis and bone resorptive activity through decreased cellular uptake of ascorbic acid and the induction of oxidative stress; these effects occur in a sodium level-dependent manner. Hyponatremic patients have elevated circulating arginine-vasopressin (AVP) levels, and AVP acting on two receptors expressed in osteoblasts and osteoclasts, Avpr1α and Avpr2, can increase bone resorption and decrease osteoblastogenesis. Should we be screening for low serum sodium in patients with osteoporosis or assessing bone mineral density (BMD) in patients with hyponatremia? The answers to these questions have not been established. Definitive answers will require randomized controlled studies that allocate elderly individuals with mild hyponatremia to receive either active treatment or no treatment for hyponatremia, to determine whether correction of hyponatremia prevents gait disturbances and changes in BMD, thereby reducing the risk of fractures. Until such studies are conducted, physicians caring for elderly patients must be aware of the association between hyponatremia and bone disorders. As serum sodium is a readily available, simple, and affordable biochemical measurement, clinicians should look for hyponatremia in elderly patients, especially in those receiving medications that can cause hyponatremia. Furthermore, elderly patients with an unsteady gait and/or confusion should be evaluated for the presence of mild hyponatremia, and if present, treatment should be initiated. Finally, elderly patients presenting with an orthopedic injury should have serum sodium checked and hyponatremia corrected, if present.

Keywords Hyponatremia · Osteoporosis · Fractures · Gait disturbances · Falls · Arginine vasopressin

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1 Introduction

Severe acute hyponatremia induces a symptomatic condition known as hyponatremic encephalopathy that can result in brain injury [1] This condition is primarily produced by cerebral edema [2], which can lead to intracranial hypertension and severe complications such as transtentorial herniation of the brainstem. Individuals with a high risk of developing this complication include young females, children, postoperative patients, and those with hypoxia or central nervous system disease [2, 3]. Although the brain seems to be the main target for acute hyponatremia, other organs can be affected as well

(Fig. 1). Recent evidence indicates that pulmonary abnormalities, such as respiratory failure, can be a consequence of hyponatremic encephalopathy [4]. Ayus-Arieff syndrome is a distinct consequence of severe acute hyponatremia. This is a form of noncardiogenic pulmonary edema secondary to elevated intracranial pressure due to cerebral edema, which can be found in healthy marathon runners [5, 6]. By contrast, mild to moderate chronic hyponatremia (serum sodium 120 to 135 mmol/L) is generally considered to be asymptomatic, as a result of volume regulatory processes in the body [1]; it is commonly believed to be without consequences.

Fractures represent a serious health problem, especially in the elderly. They are associated with significant morbidity and mortality [7]. The primary identifiable risk factors for fractures are advanced age, female sex, osteoporosis, low vitamin D levels, reduced calcium intake, physical inactivity, dizziness and balance disorders, and a history of fractures [7]. In 1999, our group reported that an orthopedic injury was a frequent presenting manifestation of chronic hyponatremic encephalopathy in elderly women [8]. There is now emerging literature suggesting that mild to moderate chronic hyponatremia may be a risk factor for falls, osteoporosis, and fractures.

2 Prevalence and etiology of hyponatremia

Hyponatremia, typically defined as a serum sodium <135 mmol/L, is a clinical feature in 15 % to 20 % of emergency admissions to the hospital [9]. In a population-based, cross-sectional study of 14,697 adults (≥18 years old) who participated in the nationally representative National Health and Nutrition Examination Survey (NHANES) for 1999–2000, the prevalence of hyponatremia in the United States population was 1.72 % (weighted analysis). The prevalence of hyponatremia was significantly higher in women (2.09 %) than men and increased with age [10].

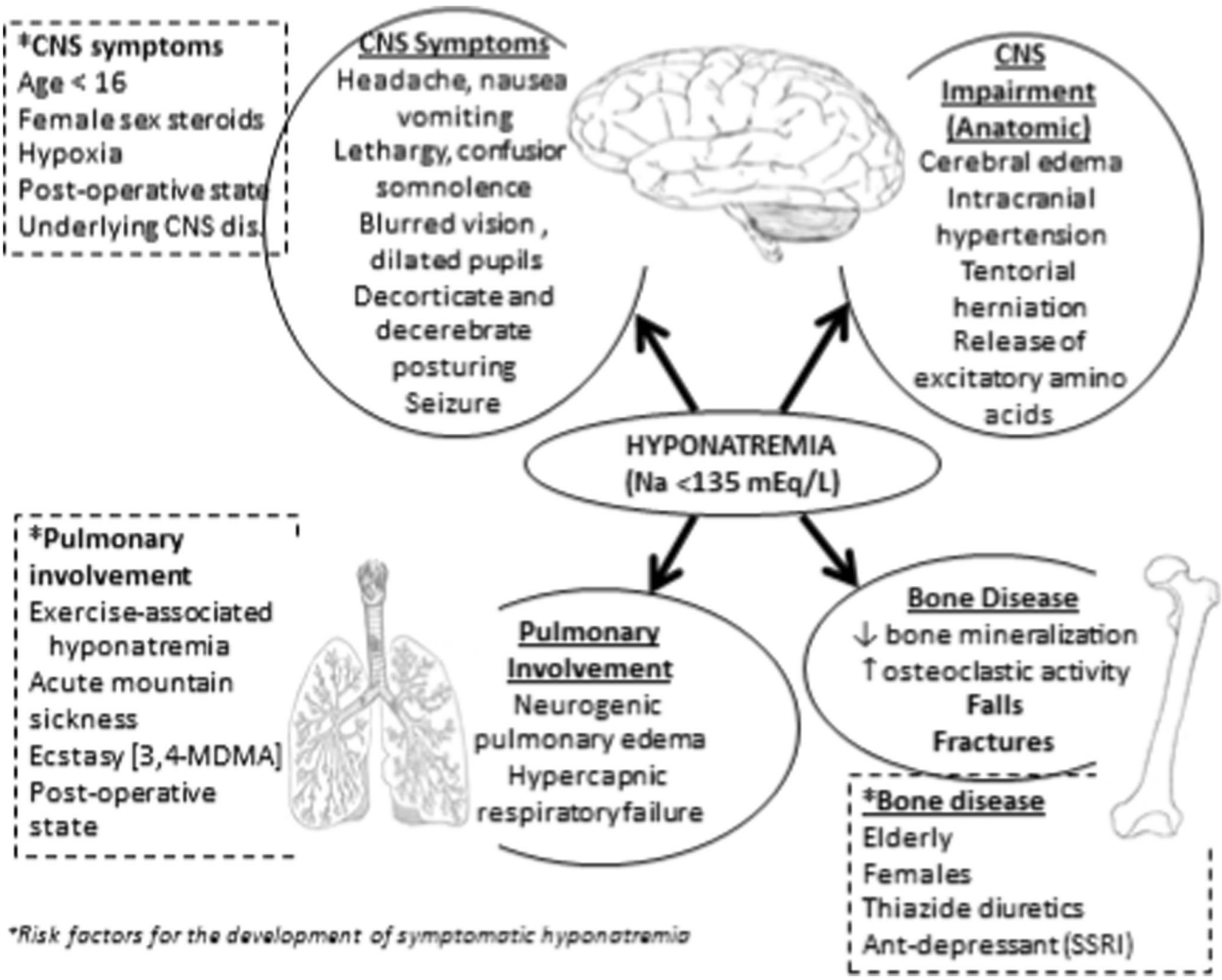

Fig. 1 Overview of the pathophysiology of manifestations of hyponatremia in multiple organs CNS, central nervous system; MDMA, 3,4-methylenedioxymethamphetamine; Na, serum sodium concentration; SSRI, selective serotonin reuptake inhibitor

Hyponatremia is a common disorder in the elderly, affecting approximately 10 % of individuals living at home and 20 % living in a nursing home [11]. It has been estimated that as many as 50 % of nursing home residents will suffer one or more episodes of hyponatremia in a 12-month period [12]. Numerous medical conditions and medications can produce hyponatremia in older individuals [11]. In studies evaluating the relationship between hyponatremia and orthopedic injury in the elderly, the primary causes of hyponatremia were syndrome of inappropriate antidiuretic hormone (ADH) secretion (SIADH), antidepressants, antiepileptic medications, and thiazide diuretics.

Among antidepressants, selective serotonin reuptake inhibitors (SSRIs) are probably the most frequent cause of ADH release and SIADH [13–15]. The precise prevalence and incidence of antidepressant-induced hyponatremia in the elderly is difficult to determine because of the presence of confounding factors, including various medical conditions and other prescription medications. Although hyponatremia has been reported with all SSRIs, as well as the selective serotonin and norepinephrine reuptake inhibitor venlafaxine, most of the evidence consists of either individual case reports or small, retrospective studies limited by confounding variables. The risk of developing hyponatremia while receiving an SSRI increases with age, female sex, previous history of hyponatremia, and concomitant use of other medications that produce hyponatremia [11]. The sodium concentration of most patients with SSRI-associated hyponatremia returns to normal within days to weeks after SSRI withdrawal. A few reported cases of rechallenge with SSRIs indicate that hyponatremia may at times be a transient effect, with tolerance developing over time [11].

The importance of thiazide-induced hyponatremia (TIH) is reemerging because thiazide diuretic prescription use seems to be increasing after the introduction of guidelines recommending thiazides as first-line treatment for essential hypertension [16]. Risk factors predisposing to TIH are old age, female sex, reduced body mass, and concurrent use of other medications that impair water excretion [1]. During thiazide treatment, the elderly may exhibit greater reduction of free water excretion after a water load, compared with younger subjects. However, thiazide diuretics decrease urinary calcium excretion and have been shown to reduce age-related bone loss and decrease the risk of hip fractures [17].

3 Epidemiological association between hyponatremia and fractures

Several studies have demonstrated that the incidence of hyponatremia is significantly higher in elderly patients presenting with a fracture than in those without a fracture (Table 1). Gankam Kengne and colleagues [18] evaluated the incidence of hyponatremia (serum sodium <135 mmol/L) in 513 elderly patients presenting to the emergency department with a bone fracture and compared them to a sex- and age-matched control group of ambulatory patients. Patients with a bone fracture had a significantly higher incidence of hyponatremia than controls (13 % vs. 3.9 %), with an adjusted OR of 4.16 for bone fractures associated with hyponatremia. Sandhu et al. [19] conducted a similar study comparing the incidence of hyponatremia in 364 elderly patients presenting to an emergency department with and without a fracture. The incidence of hyponatremia was significantly higher in the fracture group (9.1 % vs. 4.1 %), with a mean serum sodium in the fracture group of 131 ± 2 mmol/L. Tolouian et al. [20] identified 249 patients aged 65 years or older who were admitted during a 3-year period to the hospital with the diagnosis of hip fracture secondary to a fall and compared their serum sodium levels on admission with that of 44 control ambulatory patients admitted for elective hip or knee replacement surgery during the same time frame. Hyponatremia was present in 16.9 % of individuals with a fracture versus 4.6 % of controls (P = 0.03). Using a lower cutoff value for hyponatremia (<130 mmol/L), which eliminated patients with mild hyponatremia, McPherson and Dunsmuir found an incidence of preoperative hyponatremia in only 2.8 % patients with hip fractures [21].

Two recent studies have likewise demonstrated that hyponatremia is associated with bone fractures. Kinsella et al. [22] analyzed data of 1408 consecutive women who underwent bone densitometry. Fractures were found in 18 % of these women and hyponatremia in 4.2 %. Patients with a fracture had a significantly higher incidence of hyponatremia than those with no fracture (8.7 % vs. 3.2 %), with hyponatremic patients having a 2.25-fold increased likelihood (adjusted OR) of a fracture. Hoorn et al. [23] similarly evaluated 5208 elderly patients, of whom 7.7 % were hyponatremic. Hyponatremic patients exhibited increased adjusted ORs for both vertebral and non-vertebral fractures: 1.34 and 1.61, respectively.

3.1 Hip fractures and hyponatremia

Hip fractures are among the most serious types of fracture in the elderly and are associated with a high mortality (14 % to 36 %) during the first year post-fracture [24]. Furthermore, death from any cause in the first 3 months after a hip fracture is 5.75-fold higher in women and 8-fold higher in men, compared with age-matched controls [25]. Post-fracture morbidity is also a major problem, with many patients experiencing a marked decline in functional capabilities and the need for long-term care.

In a recent cross-sectional and longitudinal analysis using data from the Osteoporotic Fractures in Men Study (MrOS), involving 5122 community-dwelling men ≥65 years old

Table 1 Studies examining the epidemiological association between hyponatremia and fractures

Authors	Study design	Serum sodium in hypona group (mmol/L)[a]	Number	Outcome
Ayus and Arieff, 1999[8]	Prospective study; postmenopausal women with chronic symptomatic HypoNa (Na <130 mmol/L)	111 ± 12	53	19 % presented with orthopedic injury
McPherson and Dunsmuir, 2002[21]	Retrospective study; incidence of moderate HypoNa (Na <130 mmol/L) in patients with hip fractures	N/A	107	2.8 % incidence of HypoNa at presentation
Gankam Kengne et al., 2008[18]	Case-control study; prevalence of HypoNa in elderly patients (>65 years) presenting with and without bone fracture	131 ± 3	1026	13 % incidence of HypoNa in fracture patients vs. 3.9 % in controls
Sandhu et al., 2009[19]	Case-control study comparing incidence of mild HypoNa (Na <135 mmol/L) in elderly patients (>65 years) with and without large bone fractures	131 ± 2	728	9.1 % incidence of HypoNa in patients with fractures vs. 4.1 % in controls
Tolouian et al., 2011[20]	Case-control study; patients admitted for hip fracture secondary to fall compared to patients admitted for elective hip or knee replacement	131 ± 2	249	Prevalence of HypoNa 16.9 % in cases vs. 4.65 % in controls ($P = 0.03$); OR with HypoNa, 4.80; P = 0.04)
Kinsella et al., 2010[22]	Cross-sectional cohort study; incidence of HypoNa (Na <135 mmol/L) in women with and without a fracture who underwent previous bone densitometry	132.2 ± 1.8	1408	8.7 % incidence of HypoNa in women with fracture vs. 3.2 % in those without
Hoorn et al., 2011[23]	Cross-sectional cohort study; incidence of falls and fractures in an elderly population with and without HypoNa (Na <136 mmol/L)	133.4 ± 2	5208	OR of vertebral/ nonvertebral fractures with HypoNa,1.39/ 1.78
Jamal et al., 2015[26]	Cross-sectional and longitudinal cohort study; community-dwelling men ≥65 years followed for 9 years	132.3 ± 1.8	5122	HR, 3.04 for hip fracture (95 % CI, 1.37–6.75)
Ayus et al., 2016[27]	Retrospective cohort study; adults >60 years with prolonged chronic hyponatremia (Na <135 mmol/L for more than 90 days)	132 ± 5	31,527	Adjusted HR, 4.52 for hip fracture (95 % CI, 2.14–9.6)

CI, confidence interval; HR, hazard ratio; HypoNa, hyponatremia; N, number; Na, serum sodium; N/A, not available; OR, odds ratio

[a] mean ± standard deviation

followed for up to 9 years, Jamal et al. [26] found that hyponatremic men had an increased risk of hip fracture (hazard ratio [HR], 3.04; 95 % confidence interval [CI], 1.37 to 6.75). Although this was a restricted study, with low number of exposed subjects (64 males) and low number of events (9 hip fractures), the investigators found a strong association between hyponatremia and the risk of hip fracture in men. We recently found that patients with prolonged chronic hyponatremia (plasma sodium <135 mmol/L for more than 90 days) had a significantly elevated rate of hip fracture (adjusted HR, 4.52; 95 % CI, 2.14 to 9.6), which was even higher in individuals with moderate hyponatremia (serum sodium <130 mmol/L) (adjusted HR, 7.61; 95 % CI, 2.8 to 20.5) [27]. In our study, 71.5 % of patients with chronic hyponatremia were female. The adjusted HR for hip fracture was higher for chronic prolonged hyponatremia than for any of the known risk factors for fractures in the World Health Organization's Fracture Risk Assessment Tool (FRAX), except for the presence of a previous fracture (Fig. 1).

The above observations thereby indicate that the literature clearly suggests a strong epidemiologic association between chronic hyponatremia and hip and other bone fractures in the elderly.

4 Epidemiological association between hyponatremia and osteoporosis

Osteoporosis is defined as low bone mineral density (BMD) and microarchitectural deterioration of bone that leads to enhanced bone fragility and an increased risk of fractures [28]. In clinical practice, osteoporosis is diagnosed as BMD ≤2.5 standard deviations (SD) below the mean peak bone mass, as measured by dual-energy x-ray absorptiometry (DXA). It should be emphasized, however, that the sensitivity of DXA is limited and may thereby underestimate the true incidence of osteoporosis. The causes of osteoporosis are generally divided into potentially modifiable factors (e.g., diet, physical activity, drugs, underlying disease, hypogonadism) and non-modifiable causes (e.g., age, sex, genetic predisposition).

Several, although not all, epidemiological studies have demonstrated an association between hyponatremia and low BMD or osteoporosis (Table 2). A cross-sectional, population-based study involving data from the NHANES III was the first to suggest an association between hyponatremia and decreased BMD [29]. Adults >50 years old with hyponatremia (serum sodium <135 mmol/L) were compared with non-matched controls with normonatremia. The degree of hyponatremia was relatively mild, with a mean serum sodium of 133.0 mmol/L in the hyponatremia group. Logistic regression analysis (adjusted for various factors) showed that the presence of hyponatremia increased the odds of osteoporosis (T-score ≤ 2.5 SD) by approximately 2.9-fold, both at the total hip and femoral neck. Total hip BMD decreased 0.037 g/cm^2 for every 1 mmol/L decrease in serum sodium.

Two other studies published around the same time as the NHANES III-based study showed conflicting results. In the cross-sectional population study by Kinsella et al. [22] described above, reduced BMD was observed in individuals with hyponatremia, although there was a large difference in age between those with and without hyponatremia, which may have contributed to the findings. This study also showed that hyponatremia was associated with fractures independent of a low BMD. By contrast, in the prospective study by Hoorn et al. [23], the authors found an association between hyponatremia and fractures, but not between hyponatremia and decreased BMD.

More recent studies have demonstrated associations between hyponatremia and osteoporosis, although not necessarily in all body areas. In a retrospective cohort study from Denmark of patients followed with multiple, serial DXA scans, Kruse et al. [30] reported that chronic mild hyponatremia (serum sodium 130 to 137 mmol/L) was associated with reduced bone mineral content and BMD in nearly all regions of the hip but had limited effect on the lumbar spine. In a large (24,784 individuals, mostly female) single center cross-sectional study, Afshinnia et al. [31] analyzed the relationship between osteoporosis (T-score BMD ≤2.5 SD) and hyponatremia (serum sodium <135 mmol/L). The rate of total hip osteoporosis was higher in the 703 individuals with hyponatremia than in those with a serum sodium of 140 to 145 mmol/L (17.6 % versus 6.6 %, $P < 0.001$). After multivariable adjustments, hyponatremia was associated with 2.46-fold higher odds of total hip osteoporosis (95 % CI, 1.36 to 4.46) in individuals <55 years old, 1.96-fold (1.13 to 3.41) in those 55 to 67 years old, and 1.55-fold (1.13 to 2.12) in those >67 years old (age-sodium interaction $P = 0.002$). Thus, age appeared as a modifier of the independent association between hyponatremia and osteoporosis, with the highest risk in the youngest age group. In their historical cohort study of 5610 patients, Holm et al. [32] reported that hyponatremia was associated with significantly lower T-scores at the total hip and borderline significantly lower T-score at the femoral neck, but there was no association between hyponatremia and lumbar spine T-scores (in their adjusted multivariate analysis). Furthermore, hyponatremia was associated with an increased HR of sustaining a major osteoporotic fracture 6 months before to 12 months after the serum sodium measurement. There was also a direct relationship between increasing serum sodium concentrations and increasing T-scores, as well as decreasing major osteoporotic fracture HRs (Fig. 2).

Patients with anorexia nervosa have a greater risk of osteoporosis and hyponatremia, and various studies have attempted to determine whether hyponatremia is independently associated with decreased BMD in these individuals. In a cross-sectional study in 404 young women with anorexia

Table 2 Studies examining the epidemiological association between hyponatremia and osteoporosis

Authors	Study design	Serum Na in hypona group (mmol/L)[a]	Number of subjects	Outcome
Verbalis et al., 2010 [29]	Cross-sectional study; NHANES III data in persons >50 years old, excluding factors that could be related to comorbidities affecting BMD	133 ± 0.2	5598 with NNa	OP risk at total hip and femoral neck ncreased 2.9 fold in presence of HypoNa
Hoorn et al., 2011[23]	Cross-sectional study; elderly population with and without HypoNa (Na <136 mmol/L)	133.4 ± 2	5208	No association between hyponatremia and decreased BMD
Kinsella et al., 2010 [22]	Cross-sectional study; incidence of HypoNa (Na <135 mmol/L) in women with and without a fracture who previously underwent bone densitometry measurements	132.2 ± 1.8	1408	Higher rate of OP in HypoNa vs NNa (8.7 vs 3.2 %); fractures independent of low BMD
Usala et al., 2015 [47]	Case-control study; MedStar Health (health system) database; matched for age, sex, race and patient record length with controls without osteoporosis	N/A	30,517 with OP vs. 30,517 without OP	Association with OP chronic HypoNa OR 3.97; recent HypoNa OR 3.06; chronic + recent HypoNa OR 12.09
Kruse et al., 2015[30]	Retrospective cohort study; National Danish patient registry data evaluating effect of chronic HypoNa (Na = 130-137 mmol/L) on BMC and BMD	131.5 ± 2.5	1575	Mild HypoNa associated with lower BMC and BMD in all hip areas; limited effect on lumbar spine
Afshinnia et al., 2015 [31]	Cross-sectional study; hospital database of consecutive patients with BMD and laboratory	N/A	24,784,703 with HypoNa	Total hip OP in 17.6 % with HypoNa and 6.6 % in normal Na
Holm et al., 2016 [32]	Historical cohort study with fracture follow-up; patients with available serum sodium and bone density measurement results	132. 7 ± 2.6	5610	HypoNa associated with lower T-scores at total hip, and borderline significant lower T-scores at femoral neck
Lawson et al., 2012 [33]	Cross-sectional study; females with AN comparing BMD in those with and without HypoNa (<135 mmol/L)	N/A	404	Lower BMD and lower T and Z scores at every site in those with HypoNa
Levy-Shraga Y et al., 2016 [34]	Historical cohort study in adolescent females with AN	N/A	174	Decreased BMD in HypoNa

BMC, bone mineral content; BMD**,** bone mineral density; HypoNa, hyponatremia; NNa, nortmonatremia; NHANES, National Health and Nutrition Examination Survey; OP, osteoporosis; OR, odds ratio; N/A, not available; AN Anorexia nervosa

[a] mean ± standard deviation

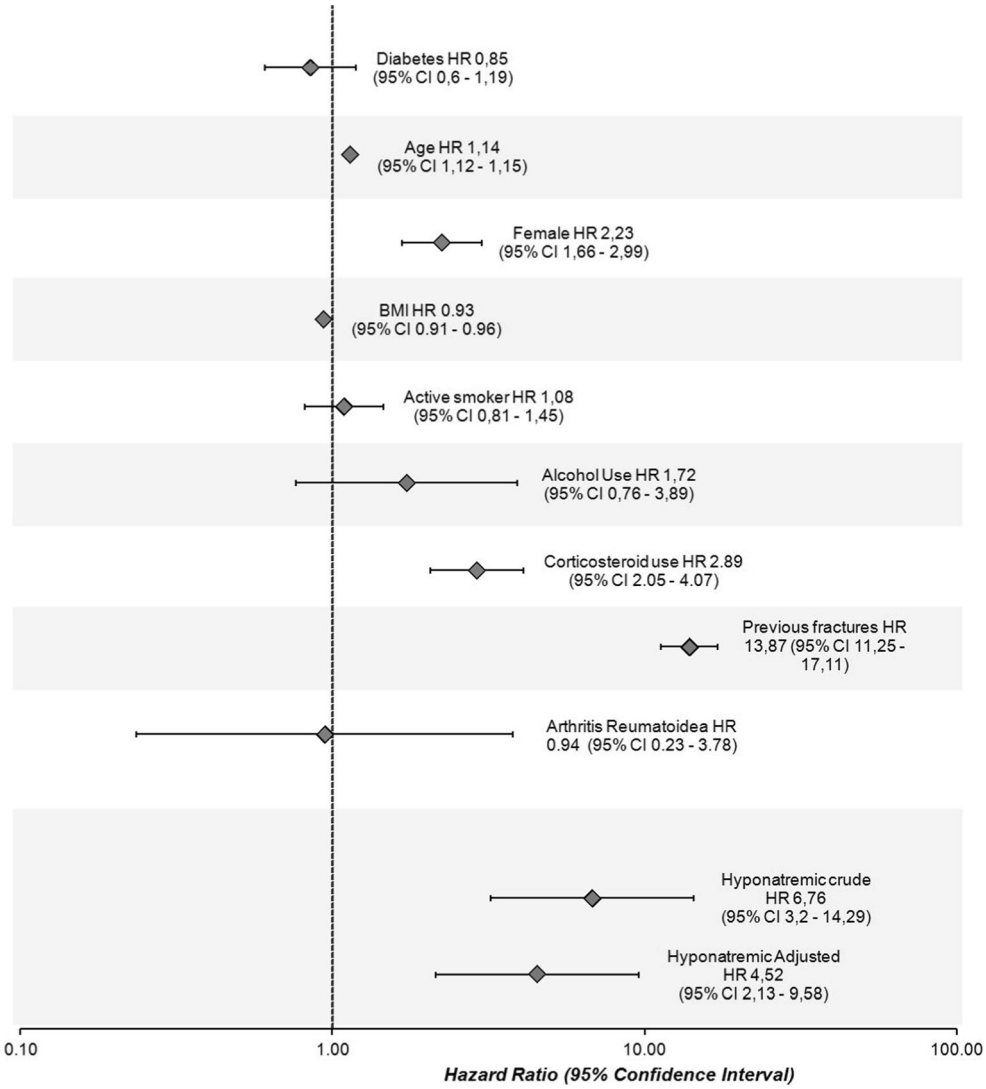

Fig. 2 Hazard ratios for prolonged hyponatremia and other potential risk factors for hip fracture in elderly adults BMI, body mass index; CI, confidence interval; HR, hazard ratio This figure is adapted from reference [27]

nervosa, those with hyponatremia had significantly lower BMD in all skeletal regions after controlling for age, body mass index (BMI), psychiatric drug use, and duration of disease [33]. In another study involving 174 adolescent females with anorexia nervosa, a history of at least one episode of hyponatremia was identified as an independent predictor of the BMD z-score [34].

5 Possible mechanisms involved in the relationship between hyponatremia and fractures

Hyponatremia could contribute to the production of fractures through two possible mechanisms: 1) impaired cognitive function with gait disturbances, inducing instability and falls, or 2) osteoporosis resulting from decreased bone mass or bone quality (Fig. 3).

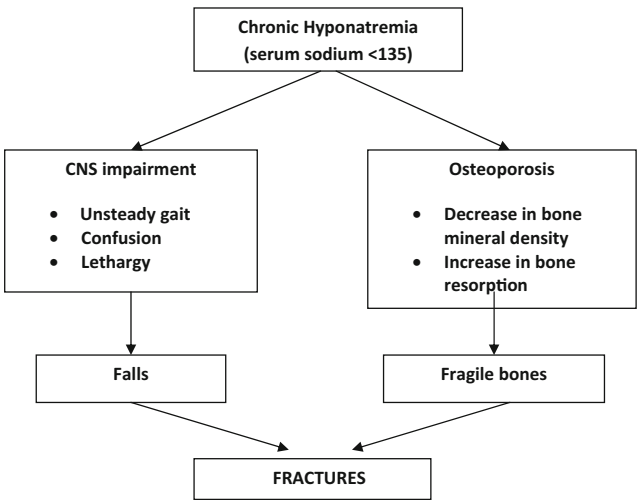

Fig. 3 Mechanisms involved in the relationship between hyponatremia and fractures CNS, central nervous system

5.1 Hyponatremia, gait disturbances, and falls

Hip fractures in the elderly are generally associated with simple falls. These falls are frequently produced by gait disturbances that are common in older individuals. A population-based study found a 35 % prevalence of gait disorders among persons older than 70 [35]. Gait is mainly controlled by the premotor and motor areas of the frontal cortex; these areas project fibers to the basal ganglia and onward to the locomotor centers of the brainstem and cerebellum, which, in turn, control the spinal generators. Several types of gait disturbances are particularly common among elderly patients: 1) sensory (e.g., polyneuropathy); 2) hypokinetic (e.g., Parkinson's disease); 3) ataxic (e.g., degenerative cerebellar atrophy); and 4) anxiety-related (e.g., fear of falling).

Recent data have revealed that mild chronic hyponatremia is associated with unsteady gait and falls. Renneboog et al. [36] evaluated the incidence of falls among 122 patients admitted through the emergency department (mean age 72 years) with asymptomatic chronic hyponatremia (mean serum sodium 126 mmol/L) compared to 244 normonatremic, matched controls. The incidence of falls was 21.3 % in the hyponatremic group and 5.3 % in the controls, with a 67 (95 % CI, 7.5 to 607) adjusted OR of falls in patients with hyponatremia. To evaluate the etiology of the falls, the authors performed attention and gait testing in 16 adults with chronic asymptomatic hyponatremia (mean sodium 128 mmol/L). These patients exhibited marked attention and gait impairments, which were more severe than those observed in volunteers who acutely consumed a moderate amount of alcohol (mean blood alcohol 0.6 g/L). The attention and gait abnormalities completely resolved following correction of the hyponatremia.

The brain adapts to chronic hyponatremia with the loss of osmolytes, such as glutamate [37, 38], which is a neurotransmitter involved in gait function [39, 40]. Thus, loss of glutamate may play a role in gait abnormalities that lead to falls in patients with chronic hyponatremia. In a rat model of chronic hyponatremia, sustained reduction in serum sodium induced gait disturbances, facilitated extinction of a conceptual fear memory, and caused cognitive impairment in an object recognition test. *In vivo* microdialysis of the hippocampus of these animals showed an elevated extracellular glutamate concentration [41]. Other studies, in both humans and animals, have also demonstrated cognitive impairment with chronic asymptomatic hyponatremia [42, 43]. Therefore, mild hyponatremia by itself can result in unsteady gait, cognitive impairment, and falls by inducing subtle neurologic changes.

5.2 Hyponatremia and osteoporosis

Verbalis et al. [29] were able to produce similar results to those seen in humans in an animal model of hyponatremia. They found that rats rendered hyponatremic for 3 months had a 30 % reduction in BMD (as measured by DXA), compared with controls. Bone histomorphology was highly abnormal, with a reduction in both trabecular and cortical bone contents and an increase in the number of osteoclasts per bone area. The rats also had decreased serum concentrations of osteocalcin. Further studies by this group demonstrated similar findings in cell cultures, with low extracellular sodium directly stimulating osteoclastogenesis and bone resorptive activity [44]. Through cellular and molecular approaches, these researchers showed that chronic reduction of serum sodium produced a dose-dependent decrease in intracellular calcium without depleting endoplasmic reticulum calcium stores. Moreover, reduced serum sodium decreased cellular uptake of ascorbic acid in a dose-dependent manner, and reducing ascorbic acid concentrations in the culture medium mimicked the osteoclastogenic effects of low serum sodium. Increased accumulation of intracellular free oxygen radicals and proportional changes in protein expression and phosphorylation were identified as the downstream effects of reduced ascorbic acid uptake, providing evidence that hyponatremia induced oxidative stress **(**Fig. 4**).** These results, therefore, reveal a novel sodium-signaling mechanism in osteoclasts that may serve to mobilize sodium from bone stores during prolonged hyponatremia [44]. These findings are supported by the results of older studies [45, 46] demonstrating that one third of total body sodium is located within bones. As 40 % of bone sodium is easily exchangeable with serum sodium, this supports the

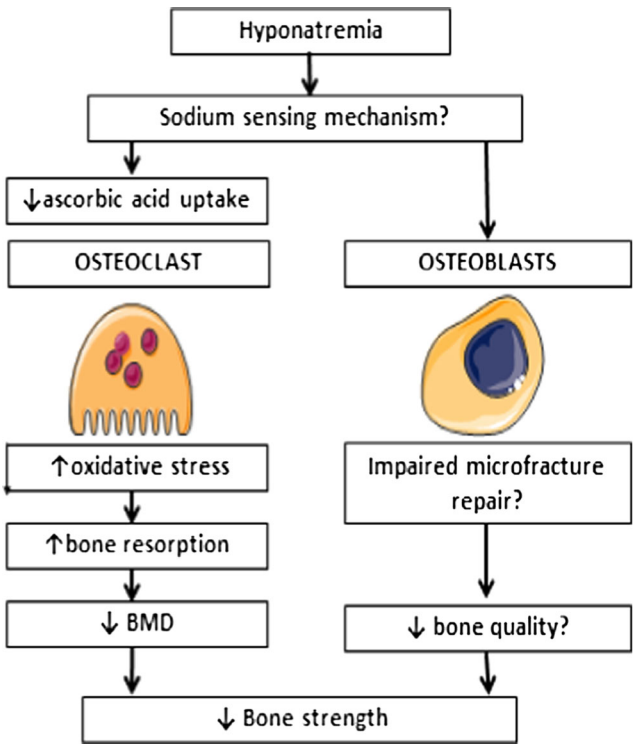

Fig. 4 Effects of hyponatremia on bone cells

notion that chronic sodium depletion could lead to sodium loss from bone with consequent bone demineralization.

The importance of studies suggesting an increased risk of bone fragility fractures with hyponatremia through mechanisms of induced bone loss, as well as an increased risk of falls, has not been established in large patient populations with different types of hyponatremia. In a matched case-control study, Usala et al. [47] evaluated the effects of hyponatremia on osteoporosis and fragility fractures in a population of more than 2.9 million. Individuals with osteoporosis (n = 30,517) and fragility fractures (n = 46,256) from a large United States health system database were matched on age, sex, race, and patient record length with similar numbers of controls without osteoporosis or fractures. Multivariate conditional logistic regression analysis demonstrated that hyponatremia was associated with both conditions. This occurred with chronic hyponatremia (osteoporosis: OR, 3.97 [95 % CI, 3.59–4.39]; fractures: OR, 4.61 [95 % CI, 4.15–5.11]), recent hyponatremia (osteoporosis: OR, 3.06, [95 % CI, 2.81–3.33]; fractures: OR, 3.05 [95 % CI, 2.83–3.29]), and combined chronic and recent hyponatremia (osteoporosis: OR, 12.09 [95 % CI, 9.34–15.66]; fractures: OR, 11.21 [95 % CI, 8.81–14.26]). The likelihood of osteoporosis or fragility fracture increased incrementally with categorical decreases in serum sodium concentration. These results support the hypothesis that hyponatremia is a risk factor for osteoporosis and fractures.

6 Role of hyponatremia: direct effect on bone versus a surrogate marker

In the various studies that found a relationship between hyponatremia and osteoporosis or fractures [22, 23, 25, 27], there were several differences in baseline characteristics between hyponatremic and normonatremic patients. Hyponatremic individuals were generally older, had a lower BMI, were more likely to have diabetes or cardiac insufficiency, or used diuretics more frequently than their normonatremic counterparts. Although the studies adjusted for these parameters or used propensity score-matching (as in our study) [27], there remains the possibility of residual confounding factors (e.g., comorbidities or drugs) that may explain the relationships between hyponatremia, osteoporosis, and fractures. This is the same situation as the observed relationship between hyponatremia and increased mortality: whether hyponatremia is a cause of mortality or merely a surrogate marker is the subject of considerable debate.

The animal study by Verbalis and colleagues [29] clearly suggests a direct relationship between hyponatremia and increased bone turnover and altered bone architecture. As bone is rich in sodium, increased bone resorption could represent an attempt by the body to preserve sodium homeostasis at the expense of structural integrity. However, the degree of hyponatremia in this animal study was much more severe than that observed in human population studies. Furthermore, other changes in severely hyponatremic animals, such as reduced testosterone and elevated follicle stimulating hormone levels, may have contributed to the decreased BMD. Hypovitaminosis D was excluded as a confounder, as supplementation with vitamin D did not prevent osteoporotic changes.

Another important question that arises is whether bone cells are sensing changes in extracellular sodium concentration itself or the low osmolality associated with hyponatremia. Basony and colleagues [44] have clearly shown that low sodium but not low osmolality activates osteoclasts *in vitro*, which argues against osmolality playing an important role. However, it has not been firmly established whether these findings apply to the *in vivo* setting.

7 Bone effects of vasopressin

Although hyponatremia is known to be associated with osteoporosis and a high risk of fractures, the mechanism through which bone loss ensues remains unclear. As hyponatremic patients have elevated circulating arginine-vasopressin (AVP) levels, Tamma et al. [48] examined whether AVP could affect the skeleton directly, as a component of a hypothetical pituitary-bone axis. These investigators found that two AVP receptors, called Avpr1α and Avpr2, are expressed in osteoblasts and osteoclasts. AVP injected into wild-type mice enhanced the production of osteoclasts and reduced the production of osteoblasts, whereas genetic deletion of *Avpr1α*, as well as exposure of osteoblast precursors to Avpr1α or Avpr2 antagonists (SR49059 or ADAM, respectively), increased osteoblastogenesis. By contrast, osteoclast formation and bone resorption were both reduced in $Avpr1\alpha^{-/-}$ cell cultures, which lacked the ability to produce Avpr1α. Furthermore, profound increases in bone mass were observed in $Avpr1\alpha^{-/-}$ mice and in wild-type mice injected with SR49059. Together, these data not only establish a prominent role for AVP signaling in bone mass regulation but also suggest the need for further studies on the skeletal actions of Avpr inhibitors, which are sometimes used to treat hyponatremia.

Oxytocin is structurally similar to AVP, and the two hormones can interact with each other's receptors. They have opposing actions on the skeleton, with both hormones exerting their effects through high-affinity G protein-coupled receptors. Recently, Sun et al. [49] demonstrated that Avpr1α and the oxytocin receptor (Oxtr) have opposite effects on bone mass: $Oxtr^{-/-}$ mice have osteopenia, whereas $Avpr1\alpha^{-/-}$ mice have a high bone mass (consistent with the results of Tamma et al. [48]). Furthermore, $Oxtr^{-/-}$:$Avpr1\alpha^{-/-}$ double-mutant mice, which lack the genes for both Oxtr and Avpr1α have an only slightly increased bone mass. These and other findings

led the authors to conclude that AVP interacts with both receptors in regulating bone mass, but the predominant effect of high AVP levels that may be found in patients with chronic hyponatremia likely involves interaction with Avpr1α, leading to osteoporosis. Of note, an Avpr2-specific inhibitor, tolvaptan, did not affect bone formation or bone mass, suggesting that Avpr2, which primarily functions in the kidney, does not have a significant role in bone remodeling.

Despite the above observations, AVP levels are highly variable in hyponatremia and often do not exceed those observed in normonatremic patients. However, measuring AVP in clinical practice has methodological drawbacks, which have contributed to difficulties in trying to relate plasma AVP concentrations to serum sodium or BMD. Recent studies have demonstrated that copeptin, the C-terminal glycoprotein of the AVP prohormone, is a stable surrogate for endogenous AVP secretion, which is easier to measure [50, 51] and may, thus, allow more accurate determination of the relationship between AVP and BMD in future studies.

Multiple previous studies have indicated that hyponatremia-induced osteoporosis is independent of AVP levels both *in vivo* and *in vitro*. In the model of SIADH used by Verbalis et al. [29], chronic hyponatremia was induced by a continuous infusion of the Avpr2-agonist desmopressin (DDAVP) in combination with a liquid diet to produce water loading and subsequent water retention. Of interest, one of the controls in the study was a group of rats infused with the same dose of DDAVP but fed an isocaloric solid diet. In the absence of water loading, this group did not become hyponatremic, their BMD was not significantly reduced compared with that of the hyponatremic group, and the number of osteoclasts in excised bones was also not increased [29]. However, the drawback of this SIADH model is that it used DDAVP, and although DDAVP has potent agonist activity at the Avpr2 receptor, it has only minor effects on the Avpr1α receptor. As mentioned above, Avpr2 primarily functions in the kidney and does not have a significant role in bone remodeling.

8 Is it necessary to screen for hyponatremia in osteoporotic patients or for osteoporosis in hyponatremic patients?

What does the aforementioned discussion mean for the practicing clinician? Should serum sodium be viewed as a novel risk factor for gait disturbances and bone disease, especially in the elderly, that must be screened for and corrected, similar to vitamin D?

One viewpoint suggests that measuring serum sodium can only be recommended if treatment of hyponatremia corrects gait disturbances and bone abnormalities. There is some evidence suggesting that gait abnormalities and attention deficits observed with hyponatremia can be corrected by normalizing serum sodium [31]. Tolvaptan was effective in reversing mild to moderate chronic asymptomatic hyponatremia, and this correlated with improvements in the results of a variety of neurocognition tests, particularly rapid motor movements, which tended to reverse following return to a low serum sodium concentration after treatment withdrawal [52]. Yet data showing that correction of serum sodium can improve osteoporosis or decrease the risk of bone fractures are scarce. Recently, Sejling et al. [53] described a man with severe osteoporosis associated with SIADH due to a sinus esthesioneuroblastoma. After the tumor was removed, ADH and sodium levels normalized, and a DXA scan 7 months later showed significant improvement of BMD in the lumbar vertebrae.

As serum sodium determination is such a reliable and affordable measurement that can be easily obtained in even low complexity settings, one could take a more pragmatic approach. In an osteoporosis clinic, serum sodium could be included as part of general risk factor screening, similar to the approach used for vitamin D. For many patients in whom hyponatremia is detected, treatment is simple: thiazide diuretic or SSRI antidepressant medications, which are frequent causes of hyponatremia, can be discontinued or switched to another drug. In the emergency department setting, when a patient is admitted with a fracture, determination of the serum sodium would be important, as the hospital length of stay could be prolonged [54]. Finally, in the ambulatory care setting, when patients are found to have chronic hyponatremia (most commonly elderly individuals, often with SIADH), determination of BMD should be considered.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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