# Bone Disease as a New Complication of Hyponatremia: Moving Beyond Brain Injury

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Brain injury is the main result of acute symptomatic hyponatremia, and it is associated with significant morbidity and mortality (1,2). The symptoms of hyponatremic encephalopathy primarily result from cerebral edema, which is caused by an influx of water into the brain down a concentration gradient (2). Patients at high risk for this complication include postoperative patients, young female individuals, children, and patients with hypoxia or central nervous system disease (1–3); however, although the brain seems to be the main target for hyponatremia, it can no longer be considered the only organ affected by this condition.

Recent information indicates that the systemic effects of hyponatremia also affect other organs. Lung abnormalities, such as respiratory failure as a consequence of hyponatremic encephalopathy, have been described (4). One distinct aspect of this condition is the so-called Ayus-Arieff syndrome: A form of noncardiogenic pulmonary edema secondary to increased intracranial pressure from cerebral edema (5–7).

Can bone abnormalities be a consequence of hyponatremia? In 1999, our group noted that for a large percentage of elderly women, orthopedic injury was the presenting manifestation of hyponatremic encephalopathy (8). It has subsequently been confirmed that mild chronic hyponatremia, mean serum sodium (SNa) 128 mEq/L, in adults can result in subtle neurologic impairment that affect both gait and attention, similar to that of moderate alcohol intake (9). This seems to explain why hyponatremia has been increasingly associated with falls and bone fractures in the elderly. Approximately 20% of adults who are admitted to the hospital with chronic asymptomatic hyponatremia (mean SNa 126 mEq/L) are admitted for falls, compared with 5.3% in control subjects with normonatremia (9). Elderly ambulatory patients who are admitted for fractures have a 13% incidence of hyponatremia (SNa 131 mEq/L) compared with 5% in a control population (10).

In this issue of *CJASN*, Kinsella *et al.* (11) evaluated whether hyponatremia is associated with fracture occurrence and osteoporosis in women. A total of 1408 women with bone densitometry studies were retrospectively evaluated, 18% of whom had fracture and 4.2% of whom had hyponatremia (mean SNa 132 mEq/L). Patients with fractures had a significantly higher incidence of hyponatremia than those without: 8.7 *versus* 3.2%. Patients with hyponatremia were older and had slightly lower bone mineral density. Hyponatremia was a major risk factor for the development of fracture with an odds ratio of 2.25 even after controlling for age, bone density, chronic kidney disease stage, and other osteoporotic risk factors.

Although this information indicates an association of hyponatremia and bone disease, it does not prove causality. Thus, the question remains: Can hyponatremia *per se* produce bone abnormalities? Older studies may point to an answer to this question. Approximately one third of total body Na resides in the bone, with 40% of bone Na being exchangeable with the SNa; therefore, chronic Na depletion could theoretically lead to Na loss from the bone with consequent bone demineralization (12,13). Recent work by Verbalis *et al.* (14) in animals suggests that hyponatremia *per se* does in fact induce osteoporosis. They found that rats that were made hyponatremic for 3 months had a 30% reduction in bone mineral density as measured by dual-energy x-ray absorptiometry as compared with controls. Bone histomorphology was striking, 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 concentration of osteocalcin, which is indicative of increased bone resorption and decreased bone formation. Verbalis *et al.* (14) also evaluated whether hyponatremia contributed to the development of osteoporosis in adults by analyzing data from the Third National Health and Nutrition Examination Survey (NHANES III). They found the adjusted odds ratio for developing osteoporosis to be 2.87 times higher among adults with mild hyponatremia, with mean SNa of 133 mEq/L, compared with those without. There was also a positive linear association between SNa and femoral neck bone mineral density in patients with hyponatremia.

What does this information mean for the practicing clinician? Mild chronic hyponatremia (Na 130–134 mEq/L) can no longer be viewed a benign condition. Mild hyponatremia can contribute to orthopedic injuries in the elderly by two separate mechanisms (Figure 1): (A) Impaired cognitive function with unsteady gait and falls and (B) osteoporosis resulting from increased bone resorption to mobilize Na. Thus, to prevent bone disease in the elderly and nursing home population, SNa

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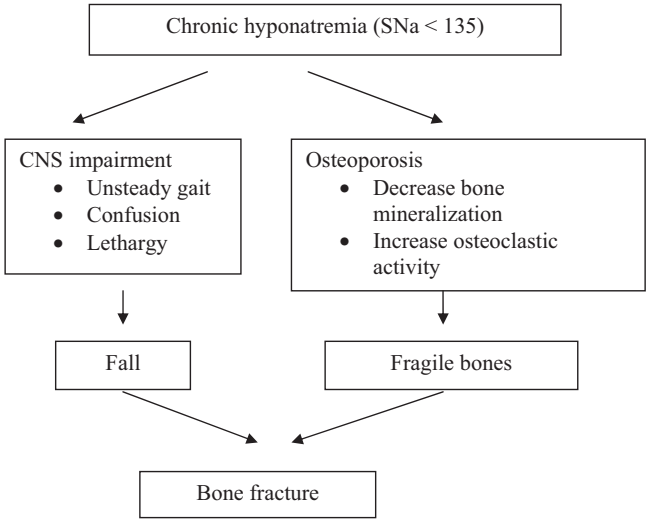


*Figure 1.* Mechanism of bone injury from chronic hyponatremia in the elderly.

should be viewed as a novel marker to be monitored, and hyponatremia should be corrected when it develops, similar to the approach of measuring vitamin D levels and correcting vitamin D deficiency. Furthermore, bone quality should be evaluated in patients with long-standing hyponatremia. The most common causes of outpatient hyponatremia in the elderly are the use of thiazide diuretics and selective serotonin reuptake inhibitors, syndrome of inappropriate antidiuretic hormone, congestive heart failure, and liver disease (9). If these patients present with hyponatremia and mild neurologic findings, such as unsteady gait or confusion, then a 100-ml intravenous bolus of 3% Na chloride (Na 513 mEq/L) should be considered to reverse neurologic symptoms acutely and get them out of harm's way, as recently proposed by our group (15). Further therapies would depend on the cause of hyponatremia. Medications should be discontinued in elderly women with either thiazide or selective serotonin reuptake inhibitor-induced hyponatremia. Reintroduction, if necessary, could be considered when the hyponatremia resolves with close monitoring. The use of V2-receptor antagonists, or Vaptans, would seem to be an attractive choice for patients with syndrome of inappropriate antidiuretic hormone, congestive heart failure, and liver disease.

In summary, these data indicate that bone abnormalities should be added to the complications of chronic hyponatremia. Hyponatremia by itself can lead to decreased bone mineral density with increasing bone fragility. When weak bones are coupled with gait abnormalities as a result of the neurologic impairment secondary to hyponatremia, these two factors work in an additive manner, resulting in a vicious cycle to produce falls, bone injury, and increased morbidity and mortality.

## Disclosures

None.

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See related article, "Hyponatremia Independent of Osteoporosis is Associated with Fracture Occurrence," on pages 275–280.