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## Hyponatremia and fractures: should hyponatremia be further studied as a potential biochemical risk factor to be included in FRAX algorithms?

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### Abstract

The Fracture Risk Assessment Tool (FRAX<sup>®</sup>) was developed by the WHO Collaborating Centre for metabolic bone diseases to evaluate fracture risk of patients. It is based on patient models that integrate the risk associated with clinical variables and bone mineral density (BMD) at the femoral neck. The clinical risk factors included in FRAX were chosen to include only well-established and independent variables related to skeletal fracture risk. The FRAX tool has acquired worldwide acceptance despite having several limitations. FRAX models have not included biochemical derangements in estimation of fracture risk due to the lack of validation in large prospective studies. Recently, there has been an increasing number of studies showing a relationship between hyponatremia and the occurrence of fractures. Hyponatremia is the most frequent electrolyte abnormality measured in the clinic, and serum sodium concentration is a very reproducible, affordable, and readily obtainable measurement. Thus, we think that hyponatremia should be further studied as a biochemical risk factor for skeletal fractures prediction, particularly those at the hip which carries the greatest morbidity and mortality. To achieve this will require the collection of large patient cohorts from diverse geographical locations that include a measure of serum sodium in addition to the other FRAX variables in large numbers, in both sexes, over a wide age range and with wide geographical representation. It would also require the inclusion of data on duration and severity of hyponatremia. Information will be required both on the risk of fracture associated with the occurrence and length of exposure to hyponatremia and to the relationship with the other risk variables included in FRAX and also the independent effect on the occurrence of death which is increased by hyponatremia.

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Compliance with ethical standards

**Conflicts of interest** None.

## Keywords

Fractures; FRAX; Hyponatremia; Osteoporosis; Risk assessment

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## Introduction

The Fracture Risk Assessment Tool (FRAX<sup>®</sup>) was developed by the World Health Organization Collaborating Centre for metabolic bone diseases to evaluate fracture risk of patients [1]. It is based on models of data on patient samples that integrate the risks associated with clinical variables (history of previous fractures, family history of fracture, smoking, alcohol use, rheumatoid arthritis, corticosteroid use) and bone mineral density (BMD) measured by DXA at the femoral neck. The FRAX<sup>®</sup> tool has been developed from studies in population-based cohorts from Europe, North America, Asia, and Australia and are country specific. In its most sophisticated form, FRAX<sup>®</sup> is computer-driven, but there are also several simplified paper versions for office use, based only on the number of risk factors. The FRAX<sup>®</sup> algorithms output is a 10-year probability of hip fracture and the 10-year probability of a major osteoporotic fracture (spine, forearm, hip, or shoulder fracture). Although FRAX is a step forward in fracture prediction, its sensitivity remains low [2].

The FRAX tool has acquired worldwide acceptance by some workers and is widely used by primary care physicians because of its relative simplicity. The clinical risk factors included in FRAX were chosen carefully to limit their number and complexity, to include only well-established contributors to fracture risk and to include factors that could be amenable to intervention [3, 4]. Despite this, FRAX has several limitations that have been extensively reviewed [3–7]. One is that it does not account for the length of time of exposure to risk factor. For example, although the risk of fracture increases with length of exposure to glucocorticoid treatment, FRAX only uses a “yes/no” input to its use. The same applies to the number of previous fractures or the amount of alcohol consumption that also have a length of exposure effect.

Perhaps the most important defect with FRAX is the omission of falls as a risk variable that has been included in other risk assessment tools [8]. The reason for not including falls at the time of the initial release of the FRAX tool was that there were no reliable data on falls and that the interrelationship between fall risk and other FRAX variables had not been adequately established. Further, FRAX have not included biochemical derangements again due to the lack of validation in prospective cohorts. Therefore, investigators and clinicians are in continuous search for additional risk factors that could improve FRAX fracture prediction capability.

## Hyponatremia as a risk factor for fractures

Hyponatremia, generally defined as a serum sodium <135 mmol/L, is the most common electrolyte disorder seen in clinical practice. Hyponatremia is a clinical feature in 15 to 20% of emergency admissions to the hospital [9]. It is a common disorder in the elderly, affecting approximately 10% of individuals living at home and 20% living in a nursing home [10]. 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 [11]. The most serious complication of hyponatremia is encephalopathy, which is associated with significant morbidity and mortality [12–15]. In addition to the neurologic manifestations, it can be associated with respiratory failure and non-cardiogenic pulmonary edema [16, 17]. In 1999, Ayus et al. noted that orthopedic injury was a presenting manifestation of chronic symptomatic severe hyponatremia [18]. Since then, there has been a number of studies corroborating the relationship between hyponatremia and the risk of fractures [19–23].

In the largest published prospective study on the risk of osteoporosis and fragility fractures associated with hyponatremia, the Rotterdam study, using a single serum sodium value at time of entry and a 7.4-year follow-up, hyponatremia was associated with a 1.4-fold increase in non-vertebral fractures and a 1.8-fold increase in prevalent hip fractures [19]. In a matched case control study in a sample of more than 2.9 million, Usala et al. [24] found that patients having chronic hyponatremia had an odds ratio (OR) for fractures of 4.61 (95% CI, 4.15–5.11). In those with hyponatremia within 30 days of the outcome measure, OR was 3.05 (95% CI, 2.83–3.29), and in those with chronic and recent hyponatremia OR for fractures was 11.21 (95% CI, 8.81–14.26).

Hip fractures represent a serious health risk in the elderly, with a significant associated morbidity and mortality. We have hypothesized that hyponatremia could be a risk factor for hip fracture in the elderly [25]. Jamal et al. reported an analysis of data from the Osteoporotic Fractures in Men study (MrOS) [26]. In this cross-sectional and longitudinal analysis, 5122 community dwelling men  $\geq 65$  years were enrolled and followed for fractures for up to 9 years. They found that hyponatremic men were at increased risk for hip fracture with a hazard ratio of 3.04 (95% CI, 1.37 to 6.75). Although it was a very restricted study, because of a low number of exposed subjects and low number of events, there was a strong association between hyponatremia and risk for hip fracture in men. In our recent study [27] that included predominantly women (71.5%), patients with prolonged chronic hyponatremia (two or more determinations of hyponatremia during 90 days) were at greater risk for hip fracture than those with just one low serum sodium (adjusted HR 4.52 vs. 2.35), 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). In this analysis, we adjusted for the propensity score of having hyponatremia and for FRAX clinical risk factors. The propensity score of having hyponatremia was constructed in that study in order to reduce the effect of possible selection bias, as it was not a randomized study. The adjusted HR for hip fracture was higher for chronic prolonged hyponatremia than for any of the risk factors used in FRAX, except history of previous fracture (Fig. 1). Our study strongly suggests that the duration and severity of hyponatremia are important risk factors for hip fracture in the elderly and that it is independent of the clinical risk factors included in the FRAX algorithm.

### **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 among persons older than 70 years found a 35% prevalence of gait disorders [28]. Recent studies have revealed that mild chronic hyponatremia is associated

with unsteady gait and falls. Renneboog et al. [29] evaluated the incidence of falls among 122 patients admitted through the emergency department (mean age 72 years) with 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 an adjusted OR for falls of 67 (95% CI, 7.5 to 607) 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 [30–32], which is a neurotransmitter involved in gait function [33, 34]. 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 [34]. Other studies, in both humans and animals, have also demonstrated cognitive impairment with chronic asymptomatic hyponatremia [35, 36]. Therefore, mild chronic hyponatremia by itself can result in unsteady gait, cognitive impairment, compromised nerve-muscle conduction [37], and falls that are reversible upon correction of serum sodium.

### Hyponatremia and osteoporosis

Several, although not all, epidemiological studies have demonstrated an association between hyponatremia and low BMD or osteoporosis. A cross-sectional, population-based study involving data from the NHANES III was the first to suggest an association between hyponatremia and decreased BMD [38]. 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 mean serum sodium of 133.0 mmol/L in the hyponatremic group. Logistic regression analysis (adjusted for various factors) showed that the presence of hyponatremia increased the odds of osteoporosis (BMD T-score  $-2.5$  SD) by approximately 2.9-fold, both at the total hip and femoral neck.

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. [23], 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. In the Rotterdam study [19], there was an association between hyponatremia and fractures, but not between hyponatremia and BMD.

In other retrospective cohorts [39, 40], mild chronic hyponatremia was associated with reduced BMD at the hip but not at the lumbar spine. Kruse et al. [39] used biochemical and DXA scan data from two Danish regions between 2004 and 2011, supplemented with

national Danish patient diagnosis and prescription reimbursement databases, to evaluate the effect of chronic mild hyponatremia ( $[Na^+] = 130\text{--}137$  mmol/L) on bone mineral content (BMC) and bone mineral density (BMD) loss through multiple, serial dual-energy X-ray absorptiometry (DXA) scans. Chronic mild hyponatremia seems to greatly affect bone in the hip, while the effect is limited in the lumbar spine. Holm et al. [40] analyzed a historical cohort that consisted of 5610 patients with available serum sodium and bone density measurements. Hyponatremia was associated with significant lower T-scores at the total hip and a borderline significant lower T-score at the femoral neck in the multivariate analysis. No association was found between hyponatremia and the lumbar spine T-score. Hyponatremia was associated with an increased hazard ratio of sustaining a major osteoporotic fracture in the period from 6 months prior to 12 months after serum sodium measurement.

In a large (24,784 individuals) single-center cross-sectional study mostly in females, Afshinnia et al. [41] studied the relationship between osteoporosis and hyponatremia. Presence of osteoporosis at the total hip was higher in individuals with hyponatremia than in those with normal serum sodium (17.6 vs. 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 was a modifier of the independent association between hyponatremia and osteoporosis, with the highest risk in the youngest age group. Therefore, the current evidence strongly suggests that hyponatremia is not an epiphenomenon of aging. Further, patients with at least one hyponatremic episode were classified into quartiles of the observed duration of hyponatremia. Compared to the first category, the longest duration of observed hyponatremia was associated with the highest risk of osteoporosis. The observed OR for osteoporosis in the younger subgroup in the study by Afshinnia et al. [41] corroborates the analysis of the NHANES II population, while the OR observed in older subgroups corroborates the findings in the Rotterdam study. The lack of a significant difference in the Rotterdam Study is probably explained by the predominance of elderly patients in that cohort. Thus, in the analysis of an association between hyponatremia and osteoporosis, three important factors should be taken in consideration: the duration and severity of hyponatremia and the age of the population.

### **Possible mechanisms of hyponatremia-induced osteoporosis**

Verbalis et al. [38] reproduced the osteoporosis present in humans in a rat 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 histomorphometry was highly abnormal, with a reduction in both trabecular and cortical bone and an increase in the number of osteoclasts per bone area. The rats also had decreased serum concentrations of osteocalcin, suggesting decreased bone formation. Rats (both in normonatremic and hyponatremic) had low levels of serum vitamin D metabolites. Replacement of vitamin D only slightly decreased hyponatremia-induced reductions in bone mass. The lack of under-mineralization by histology supports the notion that vitamin D deficiency is not a major mechanism responsible for the hyponatremia-induced decline in BMD. Similar

findings were found in cell cultures, with low extracellular sodium directly stimulating osteoclastogenesis and bone resorptive activity [42]. These results, therefore, reveal a novel sodium signaling mechanism in osteoclasts that may serve to mobilize sodium from bone stores during prolonged hyponatremia. These findings are supported by the results of older studies [43, 44] 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 notion that chronic sodium depletion could lead to sodium loss from bone with consequent bone demineralization.

Interestingly, a recent study described a male patient with the syndrome of inappropriate secretion of antidiuretic hormone (SIADH)-induced hyponatremia, who had severe osteoporosis, despite having no identifiable risk factors apart from hyponatremia [45]. Plasma arginine vasopressin (AVP) was elevated by ~30-fold, raising the possibility that high circulating AVP levels may cause the profound bone loss. A magnetic resonance imaging scan, however, revealed a tumor in the sinus, and biopsies showed an esthesioneuroblastoma, immunohistochemically positive for AVP. After the tumor was removed, serum AVP and sodium levels normalized. A dual-energy X-ray absorptiometry scan performed 7 months after the patient's last surgery showed a significant spontaneous improvement in bone mineral density in the lumbar vertebrae [46], suggesting reversibility of bone loss induced by hyponatremia. Tamma et al. [47] recently reported that the two Avp receptors, Avpr1 $\alpha$  and Avpr2, coupled to Erk activation, are expressed in osteoblasts and osteoclasts. AVP injected into wild-type mice enhanced and reduced, respectively, boneresorbing osteoclasts and bone-forming osteoblasts. Conversely, the exposure of osteoblast precursors to Avpr1 $\alpha$  or Avpr2 antagonists, SR49059 or ADAM, increased osteoblastogenesis, as did the genetic deletion of Avpr1 $\alpha$ . In contrast, osteoclast formation and bone resorption were both reduced in Avpr1 $\alpha$ -/- cultures. This process increased bone formation, and reduced resorption resulted in a profound enhancement of bone mass in Avpr1 $\alpha$ -/- mice and in wild-type mice injected with SR49059. Collectively, these data not only establish a primary role for Avp signaling in bone mass regulation, but also call for further studies on the skeletal actions of Avpr inhibitors used to treat hyponatremic patients to establish if the inhibitors recover bone mass in patients.

### Hyponatremia and FRAX

If FRAX is to be made more accurate, biochemical risk factors associated with fractures need to be analyzed for inclusion. Hyponatremia is a strong candidate for several reasons: (1) it is the most frequent electrolyte abnormality found in the clinic, (2) it induces unsteady gait that is reversible upon correction of serum sodium, (3) it is independently associated with the risk of fractures, (4) it induces bone loss that can be reversible upon correction of hyponatremia, and (5) serum sodium determination is a very reliable and affordable measurement that can be easily obtained in even low complexity settings.

If hyponatremia is to be considered as a biochemical risk factor for fractures, the collection of new population cohorts that include serum sodium measurement as well as the FRAX variables in sufficient number and with wide geographical representation will be required. It will also require different degrees of exposure to the biochemical risk factor: duration

and severity of hyponatremia. Information will be required not only on the risk of fracture associated with these exposures but also to their dependence on the other risk variables included in FRAX and their independent effect on the death hazard that is increased by the presence of hyponatremia.

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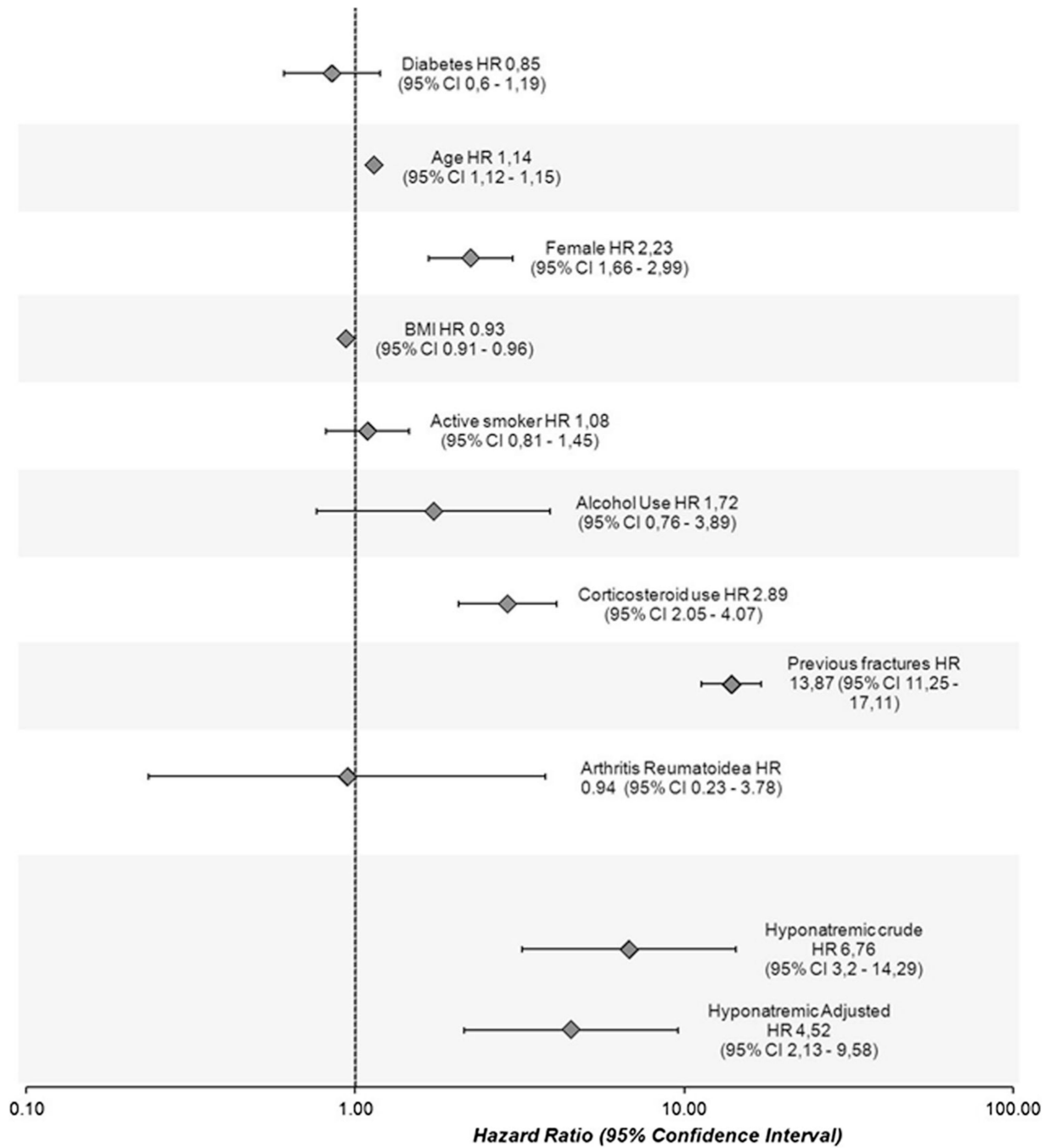
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**Fig. 1.** Hazard ratios for hip fracture for prolonged hyponatremia and other clinical risk factors included in FRAX studied in a sample of elderly adults (figure from Ayus JC et al. *Nephrol Dial Transplant* 2016; 31(10):1662–9)