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The effect of chronic mild hyponatremia on bone mineral loss evaluated by retrospective national Danish patient data☆

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ABSTRACT

Purpose: To evaluate the effect of chronic mild hyponatremia ([Na+] = 130–137 mmol/L) on bone mineral content (BMC) and bone mineral density (BMD) loss through multiple, serial dual-energy X-ray absorptiometry (DXA) scans.
Methods: Utilizing biochemical and DXA scan data from two Danish regions between 2004 and 2011, supplemented with national Danish patient diagnosis and prescription reimbursement databases, a retrospective cohort study was performed. All subjects with more than one DXA scan were included, then stratified into "normonatremia" ($[Na^+]$ = [137.00–147.00] mmol/L) and "mild hyponatremia" ($[Na^+]$ = [130.00–137.00[mmol/L) based on mean and confidence interval (CI) values calculated from all plasma sodium measurements between each subject's first and last DXA scan. Baseline, follow-up and delta values for hip and lumbar spine BMC and BMD were estimated between groups, then adjusted for comorbidity and medication use.
Results: Hip and lumbar spine groups had 884 and 1069 patients with "normonatremia" versus 58 and 58 patients with "mild hyponatremia", respectively. Mild hyponatremia was associated with lower BMC and BMD in nearly all regions of the hip, and with worse losses in the trochanteric, femoral neck and total hip regions. Mild hyponatremia had limited effect on the lumbar spine.
Conclusions: Chronic mild hyponatremia seems to greatly affect bone in the hip, while the effect is limited in the lumbar spine. We suggest further retrospective study of patients with moderate (P–Na = 120–130 mmol/L) to severe hyponatremia (P–Na < 120 mmol/L) and prospective studies to further examine the association.

1. Introduction

Emerging literature suggests that chronic hyponatremia, commonly defined at a persistently low plasma sodium level below 136 or 137 mmol/L [1], is a novel risk factor for fracture and osteoporosis in the elderly. Previously, our group has shown that hyponatremia is associated with decreased hip bone mineral density (BMD) when evaluated retrospectively by dual-energy X-ray absorptiometry (DXA) scans [2]. A similarly increased risk of osteoporosis at the hip was observed by Verbalis et al. [3] using American NHANES data. In a rat model, Barsony et al. [4] showed evidence that hyponatremia has deleterious effects on BMD in both the spine, hip, femur and tibia. A truly causal effect remains to be demonstrated in humans, as a number of putative mechanisms exists that can interact on both bone and sodium homeostasis. Possible effects of hyponatremia on bone are increased osteoclast activation [5], possibly to mobilize sodium, and distorted mesenchymal stem cell maturation favoring adipocytes over osteoblasts in bone [6]. The purpose of this study was to examine the effect of chronic hyponatremia on BMD using retrospective data from Danish regional DXA and biochemistry databases and national patient databases.

2. Materials and methods

2.1. The Danish National Patient Registry and related databases

The national authorities in Denmark have collected information related to health and epidemiology for decades. This study used data from a case–control study of 1.6 million Danes of all ages and gender with fractures and 1.6 million age and gender matched controls without fractures. These data span January 1st, 1996 to December 31st, 2011 regarding hospital admittances, prescription reimbursements,

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epidemiologic information, socioeconomic variables and migration. The total Danish population was 5.57 million as of Q4 2011 [7].

The Danish national prescription database consists of information about purchasing date, package size, Anatomical Therapeutic Chemical (ATC) classification system codes and WHO-defined daily dose (DDD). These data are automatically recorded and transmitted by all pharmacies to the Danish Register of Medicinal Product Statistics when a prescription is collected. Therefore, non-collected prescriptions do not figure in this data.

The Danish National Hospital Discharge Register database consists of information about registration date, in- or outpatient setting, ICD10-diagnoses, admittance and discharge dates. These data are collected automatically when a patient enters an in- or outpatient relation with the hospital system. The primary sector of general practitioners does not figure in these data.

The Danish Civil Registration System (www.cpr.dk) has collected national epidemiology data since 1968 regarding birthdates, gender information and dates of death for the Danish population. The validity of fracture diagnosis is estimated at 82.7% [8].

Along with these national database, our group has collected all biochemical and DXA scan data for patients in the Central and Northern Regions of Denmark from 2004 to 2011. This amounts to approximately 39,000 patients with densitometries of the lumbar spine and hip regions. The DXA scans were performed at two centers, both using Hologic™ machines (Hologic 1000, Hologic 2000, Hologic Discovery). All machines underwent a quality control program with daily QC scans using a phantom and a cross calibration program was in place [10]. A daily quality control program was in place with a coefficient of variation (CV) estimated to 1.25% without drift over time.

No experiments and procedures were done that conflict with the Helsinki Declaration of 1975 (revised in 2000).

2.2. Study design

Two regional databases of biochemical, hip and lumbar spine DXA scan data were compiled from the North and Center Regions of Denmark, with data having been recorded between January 1st, 2004 and December 31st, 2011. All subjects aged 25 or older, both men and women, with more than one lumbar spine or hip region scan were included. The first and last DXA scan was selected for each patient with computations done separately on hip and lumbar spine datasets. Of all complete records of scan measurements, height or weight included, patients shorter than 120 cm, weighing less than 30 kg or presenting with a time difference of less than 24 months between the first and last scans were excluded. Patients with any prior diagnoses of diabetes mellitus types 1 and 2, any hemoglobin A1C (HBA1C) measurement above 48 mmol/mol, diabetic retinopathy, diabetic neuropathy, diabetic foot ulcers or any prior use of all forms of insulin and oral antidiabetic medication were excluded. Patients with measured sodium values during fewer than 40% of the quarters of the scan periods were excluded.

Following inclusion and exclusion, the time difference in months between the two scans was calculated. The absolute and relative (in percent change) differences in bone mineral content (BMC) and BMD were calculated for the trochanteric, intertrochanteric, femoral neck, Ward's triangle and total hip regions of the hip, and the first through fourth lumbar vertebrae (L1, L2, L3, L4) and total lumbar spine regions of the lumbar spine region. The absolute difference in weight, height and BMI was calculated for patients in the two sets of scans. All relative differences in percent were annualized exponentially using the time difference in months converted to years.

Using The Danish National Hospital Discharge Register, pre-existing diagnoses of heart disease, diabetes, fractures, malignancy, renal failure, alcoholism and neuropathy from 1996 to the date of the first scan was established with Boolean markers. Charlson Comorbidity Index Scores and grouping hereof was calculated for each patient. Medication use in WHO DDD was calculated for the periods from January 1st, 1996, to the date of the first scan, and from the date of the first scan to the date of the second scan for several pharmaceuticals related to both osteoporosis and hyponatremia.

Biochemical data collected for all involved DXA scanned patients from the North and Central Regions of Denmark was added. All biochemical data, whether collected in arterial blood, venous blood or capillary blood, were pooled. Mean sodium values including upper and lower bounds of 95% confidence interval (CI) were calculated for the observation periods and for each quarter. Using the CIs calculated for each sodium mean for each patient, patients were categorized as having either “normonatremia”, defined as a sodium level of [137.00; 147.00] mmol/L or “mild hyponatremia” as a sodium level of [130.00; 137.00] mmol/L. Changes in BMC, BMD were presented both unadjusted and adjusted for age, gender, length of observation period, BMI at baseline, lumbar spine (ICD10 code S32.X) and hip region fractures (ICD10 code S72.X) during the observation period and exposure to systemic glucocorticoid (ATC code H02AB), bisphosphonate (ATC code M05BA) and drugs used in alcohol abuse (ATC code N07BB) during the observation period.

2.3. Statistics

Mean and standard deviation (SD) was calculated for all continuous variables of epidemiological data, comorbidity scores, DXA scan data and differences in same. Standard error (SE) for mean sodium values during the observation periods and for each quarter was calculated and used to establish upper and lower bounds of 95% CIs of relevant means. Chi-square (χ^2) analysis was done for categorical variables for significance in difference. Independent samples T-tests were computed for all recorded variables of DXA scans, medication use and biochemical data between groups of “normonatremia” and “mild hyponatremia”. Multivariate T-tests of mean comparisons adjusting for comorbidity and epidemiology were computed using independent samples T-tests. Statistical significance was defined as a p-value $<.05$. Statistical insignificance was defined as a p-value $\geq.05$.

Statistical analyses were performed using SPSS (Version 22.0.0.1. 64-bit, International Business Machines, New Orchard Road, Armonk, New York 10504 914-499-1900).

3. Results

3A total of 945 patients with hip DXA scans and 1130 patients with lumbar spine DXA scans met the eligibility criteria for this study (Table 1). Mean length of exposure was between 12.97 to 14.33 quarters for the various groups, with sodium measurements available in 73% to 80% of these quarters (Table 1). In the hip scan group, 884 patients were normonatremic (93.8%) and 58 were mildly hyponatremic (6.2%). In the lumbar spine group, 1069 patients were normonatremic (94.9%) while 58 were mildly hyponatremic (5.1%). The mean number of sodium measurements was 9.77 versus 23.6 for normonatremia versus hyponatremia in the hip scan group, 10.74 versus 24.06 for spine group, respectively (Table 1).

In both scan groups, patients with mild hyponatremia were significantly older and weighted less at baseline, but were comparable in terms of gender prevalence, height, BMI, length of observation period (Table 1, Section 1) and Charlson Comorbidity Index scores (Table 1, Section 3). Mean observed sodium values are shown in Table 1. (Table 1, Section 2). Mild hyponatremia was also associated with increased use of antithrombotic agents, opioids, sedatives, beta-receptor antagonists, angiotensin-II-receptor antagonists, selective serotonin reuptake inhibitors (SSRI) and glucocorticoids (Table 1, Section 4). In the group of lumbar spine patients, mild hyponatremia was further associated with increased use of thiazide diuretics, oral and intravenous bisphosphonates (Table 1, Section 4).

DXA scan data at baseline and follow-up is presented in Table 2. For the hip region DXA scans, all parameters of BMC and BMD, with the