Bone Mineral Density and Osteoporosis in Hyponatremic Versus Normonatremic Patients: A Retrospective 12-Month Analysis

Hiponatremik ve Normonatremik Hastalarda Kemik Mineral Yoğunluğu ve Osteoporoz: 12 Aylık Retrospektif Analiz

ABSTRACT

OBJECTIVE: To evaluate the change in osteoporosis rate and bone mineral density (BMD) in a cohort hyponatremic versus normonatremic patients under 12-month osteoporosis treatment.

MATERIAL and METHODS: A total of 280 patients with osteoporosis who were receiving anti-osteoporosis treatment were included in the study. Patients were divided into two groups based on baseline serum sodium levels including hyponatremic (n=45) and normonatremic (n=235) groups. Baseline and follow up data on T scores and rate of osteoporosis were compared in hyponatremic vs. normonatremic groups.

RESULTS: Baseline T scores of the femur neck were significantly lower in hyponatremic than in normonatremic (p=0.008) patients, while at the end of 1-year follow up, the two groups had similarly improved T scores of femur neck (p=0.43). Hyponatremic than normonatremic patients had significantly higher rate of osteoporosis (p=0.03) at baseline, whereas two groups had similar osteoporosis rates at the end of 1-year follow up (p=0.25).

CONCLUSION: In conclusion, our data suggest a reduced BMD at femur neck and higher rate of osteoporosis in case of mild chronic hyponatremia, whereas similar efficacy of 12-month osteoporosis treatment in improving BMD scores and reducing osteoporosis rate in hyponatremic and normonatremic patients regardless of the natremic status

KEY WORDS: Bone mineral density, Osteoporosis, Hyponatremia, Normonatremia

ÖZ

AMAÇ: Osteoporoz tedavisi alan hiponatremik ve normonatremik hastaların 12 aylık kohort izleminde osteoporoz oranı ve kemik mineral yoğunluğu (KMY) değişiminin değerlendirilmesi amaçlandı.

GEREÇ ve YÖNTEMLER: Osteoporoz tedavisi alan 280 hasta 12 aylık retrospektif çalışmaya dahil edildi. Bazal sodyum değerlerine göre hastalar hiponatremik (n=45) ve normonatremik (n=235) olarak iki gruba ayrıldı. Hastalara ait demografik bilgiler, bazal laboratuvar verileri, kemik mineral parametreleri ve osteoporoz oranları hasta kayıt formlarından elde edildi. Bazal ve 12 ay sonunda T skorları ve osteoporoz oranları belirlenerek hiponatremik ve normonatremik gruplar arasında karşılaştırıldı.

BULGULAR: Bazal femur boynu T skorları hiponatremik grupta (p=0.008) normonatremik gruba göre daha düşük olduğu görülürken, 1 yıllık izlem sonrası gruplar arasında anlamlı farklılık izlenmedi (p=0.43). Benzer şekilde hiponatremik grupta osteoporoz oranı normonatremik gruptan (p=0.03) daha fazla olmasına rağmen 1 yıllık izlem sonrası bu oran her iki grupta benzerdi (p=0.25).

SONUÇ: Çalışmamızda femur boynu düşük KMY değerleri ve artmış osteoporoz oranı hiponatremik grupta daha fazla olmasına karşın, 12 aylık osteoporoz tedavisi sonrasında her iki grupta osteoporoz oranları ve KMY değerleri natremik durumuna bakmadan düzeldiği görülmüştür.

ANAHTAR SÖZCÜKLER: Kemik mineral yoğunluğu, Osteoporoz, Hiponatremi, Normonatremi

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INTRODUCTION

Hyponatremia, usually defined as a serum sodium <135 mmol/L, is the commonest electrolyte disorder encountered in clinical practice with incidence ranging from 15% to 22% and classically divided into mild (130-134 mmol/l), moderate (125-129 mmol/l) and severe (<125 mmol/l) (1-3). Mild chronic hyponatremia is also a common yet neglected electrolyte imbalance (2-4) with a reported prevalence of 2% to 4% in the general population, 7% to 11% in the ambulatory elderly and 42% in hospitalized subjects (5,6).

In contrast to severe symptomatic hyponatremia which has been recognized as symptomatic and life threatening condition (2,7), mild-to-moderate chronic hyponatremia (120-135) mEq/L) is usually considered devoid of obvious symptoms and serious consequences (2,4,7). However, albeit a comparatively little awareness, there is growing evidence that even a mild degree of chronic hyponatremia is associated with multiple clinically significant outcomes in the elderly population (2,8) in regards to immobility and falls (9), bone demineralization and osteoporosis (10), hip fractures (11), cognitive impairment (1) as well as hospital readmission and need for long-term care (12).

Recent data suggest that mild chronic hyponatremia amplifies the fracture risk among elderly not only causing an unsteady gait that leads to falls but also by contributing to bone loss and thereby both to worsening osteoporosis and increased bone fragility directly (4,8-11,13).

Chronic hyponatremia has been associated with increased fracture rate (4,14-16) as well as osteoporosis at the femoral neck and total hip (13) in humans and with metabolic bone loss in rats (10).

Given the ongoing debate over the association of hyponatremia with osteoporosis in regards to inconsistent data on bone mineral density (BMD) related changes in hyponatremic patients (8), this retrospective study was designed to evaluate the change in osteoporosis rate and BMD in a cohort hyponatremic versus normonatremic patients under 12-month osteoporosis treatment.

MATERIALS and METHODS

Study Population

A total of 280 consecutive patients (median age: 63(IQR:55-71) years, 91.0% were females) who had two measures of bone mineral density taken 1 year apart and had available laboratory data were included in this 12-month retrospective study. All patients received similar treatments including alendronate 70 mg/week, 1000 mg calcium and 880 IU vitamin D3 during the study period. Patients were divided into two groups based on baseline serum sodium levels including hyponatremic (serum sodium levels of < 135 mEq/L, n=45) and normonatremic (serum sodium levels of 135-145 mEq/L, n=235) groups. Patients with history of malignancy, chronic renal failure and who take medications that can cause hyponatremia such as diuretics, antidepressants and anticonvulsants were excluded from the study. Patients who received osteoporosis treatment previously were excluded from the study. This study was approved by the institutional ethics committee.

Assessments

Data on patient demographics (age, gender), blood biochemistry (serum levels for sodium (mEq/L), 25(OH) vit D (mmol/L), parathyroid hormone (PTH, pg/mL), bone parameters (BMD and T scores (femoral neck, spinal L1-L4)) and the rate of osteoporosis were collected from medical records. Baseline and follow up data on T scores and rate of osteoporosis were compared in hyponatremic vs. normonatremic groups

Bone Mineral Densitometry Measurement

Femoral and spinal L1-L4 vertebral BMD were measured via dual energy X-ray absorptiometry (DEXA; Lunar Corporation, Model DP3, Madison, WI, USA). BMD was standardized using T-scores according to age and gender. Normal values were evaluated based on the Lunar Corporation software package, while age and gender based T-scores below -2.5 SD were considered as osteoporosis

Blood Biochemistry

Blood samples were taken at routine screening and stored at -80˚C until the final analysis.

Plasma sodium levels were measured using a Roche/Hitachi fully automated chemistry analyzer (Roche Diagnostics, Indianapolis, IN) (normal range 135-145 mmol/L).

The level of vitamin D was analyzed in serum by using a high performance liquid chromatography method (HPLC) with commercial kits (Immuchrom GmbH, Heppenheim, Germany). An UV detector was used during the analysis. Vitamin D analysis results were 2.6% at 56.5 nmol/l concentration and 1.5% at 104.8 nmol/l concentration. Inter-assay values were 4.0% at 54.1 nmol concentration and 3.6% at 105.4 nmol concentration.

The PTH level was analysed via autoanalyzer (Beckman Coulter Unicel DXI 800, Brea, California, USA) by chemiluminescense immunoassay method (Beckman Coulter Unicel DXI 800, Brea, California, USA). In human EDTA plasma samples, coefficients of variation were 2.6% within the study at 12.1 (1.3) pg/ml (pmol/L) concentration, 5.8% between the study, 1.6% within the study at 144 (15.3) pg/ml (pmol/L) concentration, 3.2% between the study, 2.2% within the study at 1439 (152.5) pg/ml (pmol/L) and 2.8% between the study.

Statistical Analysis

Statistical analysis was made using computer software (SPSS version 16.0, SPSS Inc. Chicago, IL, USA). The distribution of continuous variables for normality was tested with a one-sample Kolmogorov-Smirnov test. Differences between patients

with and without hyponatremia for normally and non-normally distributed variables were evaluated by unpaired t-test and Mann-Whitney U-test, respectively. The Wilcoxon signed ranks test was used to compare the change in T scores and sodium between baseline and 1 year. Data were expressed as "mean (standard deviation; SD)", median (interquartile ranges) and percent (%) where appropriate. $p<0.05$ was considered statistically significant.

RESULTS

Patient Demographics and Baseline Clinical Characteristics

Data for patient demographics and baseline values for bone parameters and laboratory findings in the overall study population are summarized in Table I.

Median T-score was -2.4 ((-2.9)- (-1.8)), osteoporosis was evident in 54.0% (127 patients) of patients and hyponatremia in 16.0% at baseline. Hyponatremic and normonatremic groups were similar in terms of median (IQR) age (64 (51-72) vs. 63 (55-70) years, p=0.97) and gender (40 (89.0%) vs. 215 (91.0%) females and 5(11.0% vs. 20 (9.0%) males, respectively, p=0.57).

Change in Blood Biochemistry Findings During the Study Period

Hyponatremic and normonatremic groups were similar in terms of baseline 25(OH) vitD (mmol/L) and PTH (pg/mL) values (Table II).

Table I: Patient demographics and baseline clinical characteristics (n=280)

Demographics	
Age (year), median (IQR)	63 (55-71)
Gender, n (%)	
Female	255 (91.0)
Male	25 (9.0)
Bone parameters	
T-score, median (IQR)	-2.4 ((-2.9)-(-1.8))
Osteoporosis, n (%)	
at baseline	127(54.0)
Blood biochemistry	
Sodium (mEq/L), median (IQR)	140 (138-142)
Hyponatremia (<135 mmol/L), n (%)	45 (16.0)
Normonatremia (135-145 mmol/L), n (%)	235 (84.0)
25(OH) vitD (mmol/L), median (IQR)	20 (12-32)
PTH (pg/mL), median (IQR)	45 (34-64)

Change in Baseline T Scores During the Study Period

Baseline T scores of the femur neck were significantly lower in patients with hyponatremia than in patients with normonatremia (median -2.6 ((-3.2) - (-2.2)) vs. -2.3 ((-2.8) - (-1.7)), p=0.008), while at the end of 1-year follow up, the two groups had similar T scores of femur neck (p=0.43) with improved BMD from baseline to the end of follow up in both groups (Table II).

Considering lumbar spine T scores, hyponatremic and normonatremic groups were similar in terms of baseline and follow up values. There was a significant decrease in lumbar spine T scores, indicating deterioration in BMD from baseline to the end of follow up similarly in both groups (Table II).

Change in Osteoporosis Rates During Study Period

Hyponatremic than normonatremic patients had significantly higher rate of osteoporosis (60.0% vs. 42.0%, p=0.03) at baseline, whereas two groups had similar osteoporosis rates at the end of 1-year follow up after receiving same osteoporosis treatment (26.7% vs. 19.1%, respectively, p=0.25) (Table II).

DISCUSSION

Our findings related to 12-month retrospective evaluation of osteoporosis rate and BMD in a cohort hyponatremic versus normonatremic patients under osteoporosis treatment revealed presence of osteoporosis in 45.0% and hyponatremia in 16.0% of patients at baseline. Hyponatremic than normonatremic patients had significantly lower T scores of the femur neck and higher rate of osteoporosis at baseline, whereas both T scores of femur neck and osteoporosis rate improved significantly in both groups during follow up leading no difference between hyponatremic and normonatremic patients in terms of osteoporosis rate and BMD at the end of follow up.

Our findings related to significantly lower femur neck T scores and higher osteoporosis rate in hyponatremic than in normonatremic patients at baseline seems in agreement with data from analysis of NHANES III participants aged ≥50 years by Verbalis et al. (10) which showed that patients who had hyponatremia were more likely to have osteoporosis at the femoral neck and total hip than those who had normal sodium levels along with decrease in total hip BMD by 0.037 g/cm2 for every 1 mmol/L decrease in serum sodium. Also, in a past study by Kinsella et al. (4) hyponatremic individuals were reported to have lower BMD and an increased prevalence of osteoporosis. In an experimental study by Verbalis et al. (10) rats with induced hyponatremia for 3 months were reported to have a 30% reduction in BMD as measured by dual X-ray absorptiometry when compared with control rats. In a past study by Sugimura (17), hyponatremia was shown to be associated with significantly increased risk osteoporosis using cross-sectional human data and with markedly reduced bone mass via increased bone resorption using a rat model of syndrome of inappropriate antidiuretic hormone secretion (SIADH).

Table II: Baseline and follow up data on study parameters in study groups.

	Hyponatremic group (n=45)	Normonatremic group (n=235)	p value
Blood biochemistry (baseline)			
Sodium (mEq/L), median (IQR)	133 (132-134)	141 (139-143)	**<0.001**
25(OH) vitD (mmol/L), median (IQR)	15 (10-38)	21 (12-32)	0.67
PTH (pg/mL), median (IQR)	36 (33-52)	46 (36-69)	0.23
Femur neck T score, median (IQR)			
Baseline	-2.6 ((-3.2) - (-2.2))	-2.3 ((-2.8) - (-1.7))	**0.008**
After 1-year follow up	-1.8 ((-2.5) - (-1.2))	-1.7 ((-2.25) - (-1.2))	0.43
Δ T score	-1.0 ((-1.5) - (0.1))	-0.6 ((-1.3) - (0.1))	0.12
p value	**<0.001**	**<0.001**	
Lumbar spine T score, median (IQR)			
Baseline	-0.90 ((-1.13) - (-0.70))	-0.85 ((-0.95) - (-0.71))	0.36
After 1-year follow up	-2.4 ((-2.8) - (-1.8))	-2.4 ((-3.0) - (-1.7))	0.59
Δ T score	1.4 ((0.3) - (1.9))	1.5 ((0.6) - (2.1))	0.06
p value	**<0.001**	**<0.001**	
Osteoporosis, n (%)			
Baseline	32 (71.0)	122 (52)	**0.03**
After 1-year follow up	12 (26.7)	45 (19.1)	0.25

Unlike our findings at the femur neck, our findings revealed no significant difference between hyponatremic and normonatremic patients at baseline lumbar spine T scores which showed a significant reduction from baseline to the end of follow up in both groups, regardless of the serum sodium levels.

Indeed, data from Danish National Patient Registry revealed significantly lower bone mineral content (BMC) and BMD and T-scores not only at total hip but also at lumbar spine in patients with hyponatremia indicating increased osteoporosis risk at both total hip (unadjusted OR = 2.17, 95 % CI = (1.40-3.34), p < 0.05) and lumbar spine (unadjusted OR = 1.83, 95 % CI = (1.20-2.80), p <0 .05) regions (18). Authors therefore concluded that hyponatremia could be used a screening tool and marker of secondary osteoporosis (18). In this regard, our findings seem to indicate the association of the hyponatremia with an increased risk of concurrent osteoporosis and reduced BMD at the femur neck rather than the lumbar spine.

The skeleton's natural adaptive reaction to normal external and internal factors and forces, i.e. mechanical strain especially related to weight bearing, has been considered to play a key role in physiological discordance leading rise in bone density especially in the hip and femur regions (19). Trabecular bones (typical of lumbar area) are known to have a more rapid rate of deprivation in early post-menopausal state in comparison to cortical bone (typical of proximal femur) (20). Therefore, the main potential explanation for the discrepancy of T-score changes observed in femur neck and lumbar spine in our study seems to be possibility of rate of bone loss to differ substantially between the anatomic regions in the same individual (20). The second potential explanation may be the presence of a more remarkable BMD reduction in the lumbar spine than in the hips, since most of the aetiologies of the secondary osteoporosis such as glucocorticoid excess hyperthyroidism malabsorption liver disease rheumatoid arthritis first affect spinal column (21) that would lead to a higher prevalence of lumbar osteoporosis.

Notably, while our hyponatremic patients were disadvantageous in terms of lower bone mass and higher rate of osteoporosis compared with normonatremic patients at baseline, 1-year osteoporosis treatment with alendronate showed similar efficacy in both groups leading similarly improved bone mass and decline in osteoporosis rate at the end of follow up. This seems consistent with data on previous studies indicating significant changes in BMD via alendronate treatment at the 6th and 12th month of therapy (22,23), as well as efficacy of alendronate treatment on prevention of hip fractures in females with or without vertebral fractures starting from the 18th month of therapy and being maintained for 36 months (24).

In fact, although BMD is a strong predictor of fracture, most fractures occur in individuals without osteoporosis by BMD criteria (8). Hence, the likelihood of hyponatremia to lead to fractures through other effects on bone such as decreased bone quality, which is not captured by BMD, has also been emphasized (8). In a longitudinal analysis of data from the Osteoporotic Fractures in Men Study (MrOS), it was reported that after adjusting for age, BMI, study center, and other covariates, hyponatremia was associated with up to a doubling in the risk of hip and morphometric spine fractures, independent of BMD (25).

Accordingly, aside from reduction in BMD, chronic hyponatremia has also been associated with increased fracture rates in elderly (4,8,11,14-16) and with metabolic bone loss through an uncoupling of bone resorption and formation in rats indicating the effect of hyponatremia on bone quality (10). Cellular and molecular data have confirmed increased osteoclastic bone resorption in response to low extracellular sodium levels (26) which represents attempts of the body to preserve sodium homeostasis at the expense of bone structural integrity leading hyponatremia-induced bone resorption and osteoporosis (13).

Our findings indicate that albeit 1-year treatment improved BMD and osteoporosis rates similarly in hyponatremic and normonatremic patients, based on significantly lower femur neck T scores and higher rates for osteoporosis in the hyponatremic group at baseline, we cannot exclude the possibility of ongoing fracture risk in this group via BMD independent effects of hyponatremia on bone and thus the likelihood of long-term benefit obtained from correction of hyponatremia.

Notably, data from the prospective population-based Rotterdam Study revealed that hyponatremia (n=399, 133.4 ± 2.0 mmol/L) was not associated with lower BMD, whereas associated with increased risk of vertebral fractures at baseline but not at follow-up, independent of recent falls indicating a possible effect on bone quality (14).

Actual clinical significance of mild chronic hyponatremia has been suggested to lie in its likelihood to act additively or synergistically with other potential causes of bone loss and fragility fractures commonly identified in the aging population contributing to morbidity and mortality in this population (4,10,14). Notably, given the exclusion of patients who take medications that can potentially cause hyponatremia such as diuretics, antidepressants and anticonvulsants (8), the actual prevalence of hyponatremia may be underestimated in the current study. Therefore, while recent advances in the development of new therapeutic options increase the likelihood of improved management of hyponatremia and thereby significant health and economic benefits, related evidence remains scant with ongoing debate on appropriate diagnosis and cost-effective selection of therapeutic options in the clinical practice (2).

There are limitations of the study that have to be mentioned. Firstly, due to the design of the study, it is hard to establish the temporality between cause and effect as well as generalizing our findings to overall osteoporotic patient population. Secondly, given the predictive role of body weight and body mass index on BMD and the likely impact of co-morbidities on predisposition to hyponatremia, lack of data on body mass index and co-morbidities in our cohort seems another limitation which otherwise would extend the knowledge achieved in the current study.

In conclusion, our data suggest a reduced BMD at femur neck and higher rate of osteoporosis in case of mild chronic hyponatremia, whereas similar efficacy of 12-month osteoporosis treatment in improving BMD scores and reducing osteoporosis rate in hyponatremic and normonatremic patients regardless of the natremic status. Given that mild chronic hyponatremia is a significant independent risk factor for bone fracture and the likelihood of chronic hyponatremia to affect bone loss also via mechanism other than BMD (4,8,14), our findings emphasize the importance of conduction of further prospective studies on the potential benefits as well as cost-effectiveness of correction of mild chronic hyponatremia in terms of change in BMD and/or reduction in fracture risk in the elderly population in the clinical practice.

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