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Original Article

The Relationship between Homocysteine and Osteoporosis in Patients Undergoing Peritoneal Dialysis Therapy

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Abstract

Introduction. The incidence of osteoporosis (OP), an important problem among patients undergoing dialysis, is higher. Recently, in normal population hyperhomocysteinemia (HHcy) has been accepted as an independent risk factor for OP. Patients undergoing dialysis have high serum levels of homocysteine (Hcy). We aimed to evaluate the relationship between HHcy and OP among patients undergoing Continuous Ambulatory Peritoneal Dialysis (CAPD).

Methods. Sixty-two patients undergoing CAPD for at least 1 year were enrolled in the study. Age, body mass index, Hcy, parathyroid hormone, C-reactive protein (CRP), biochemical, and hematological parameters of patients were recorded. Bone mineral content (BMC) and bone mineral density (BMD) were measured using dual X-ray energy absorptiometry (DXA) in the region of femur neck (FN) and spine (S). The patients were divided into 2 groups according to gender, group1: males, group 2: females, and these groups were compared.

Results. Thirty-four patients were female, and 28 were male. There was a statistically significant difference between groups in FN-BMC, BMD, and S-BMC ($p<0,001$, $p=0,003$, $p<0,001$, respectively). According to FN T-score 8 women and 6 men, according to S T-score 3 women and 1 man were osteoporotic ($p=0,731$ and $p=0,453$ respectively). In contrary to expectations, there was a positive correlation between Hcy and FN-BMD ($r=0,273$, $p=0,032$), and there was no correlation between Hcy and S-BMD ($r=0,169$, $p=0,189$)

Conclusions. Although Hcy levels were higher in CAPD patients, we did not find a negative correlation between Hcy and BMD. Even though this is a study with a limited number of patients, we suggest that HHcy may not contribute to OP among CAPD patients.

Keywords: homocysteine, peritoneal dialysis, osteoporosis

Introduction

Osteoporosis (OP), basically defined as a decrease in bone mass, is an important problem among patients undergoing dialysis. Bone diseases in end-stage renal disease (ESRD) are associated with an important increase in fracture rate; the proportion of patients with fracture among patients undergoing dialysis is between 5 % and 10 % [1,2].

Large epidemiological studies in normal population have identified many risk factors for increased loss of bone mineral content including advanced age, female gender, premature loss of gonadal function, thin body habitus, decreased physical activity, low calcium intake, smoking, alcohol abuse and excess glucocorticoid [3]. Poor nutritional status, drugs such as immunosuppressants and heparin, inadequacy of dialysis, and chronic acidosis are the factors contributing to OP in dialysis population [4].

Among patients undergoing dialysis, bone mineral density (BMD) may be adversely affected by a number of additional factors, such as elevated levels of Hcy, vitamin-D deficiency, excessive usage of phosphate binders, metabolic alterations due to renal failure, and modality of renal replacement therapy, but these situations have not been studied extensively. Recently, it has been shown that increased levels of Hcy in the general population is strongly associated with osteoporotic fractures independent of BMD, serum creatinine (Cr) levels, and other potential risk factors. This association is as strong as that between Hcy and cardiovascular disease, increasing risk by up to a factor of 2 [5,6]. Renal function is an important determinative factor for serum levels of Hcy. In many studies, the prevalence of HHcy among patients with ESRD is found up to 85-90% [7-9]. In this study we aimed to evaluate the relationship between HHcy and OP among patients undergoing Continuous Ambulatory Peritoneal Dialysis (CAPD).

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Patients and methods

Sixty-two ESRD patients on maintenance CAPD therapy for at least one year were enrolled into the study. Demographic features (age, gender, mean time of dialysis, Kt/V) were recorded from dialysis unit data. Body Mass Index (BMI) of all patients was calculated by using [weight, (kg)] / [(height) ^{2}, (m^2)] formula.

BMD was measured by HOLOGIC DEXA system osteo-densimeter (Hologic QDR-1000, Bedford, Mass) in lumbar spine (LS) and femoral neck (FN), and it was conformed to the World Health Organization criteria. More specifically T scores within 1 SD (+1 or -1) of the young adult mean accepted as normal, 1 to 2.5 SD below the young adult mean (-1 to -2,5 SD) as osteopenia, 2,5 SD or more below the young adult mean (> -2,5 SD) as osteoporosis [10].

Blood samples to assess biochemical, hematological parameters, serum levels of Hcy, intact parathyroid hormone (iPTH), vitamin-B12, folate acid and C-Reactive Protein (CRP) were collected after a night fasting period and before the first dwell in the morning. Biochemical parameters such as calcium (Ca), phosphorus (P), albumin, alkaline phosphatase (ALP) were measured using routine biochemical procedures on Aeroset/C8000 autoanalyzer (Abbott Diagnostics, USA); iPTH was detected with two-site chemiluminescent enzyme-labeled immunometric method on DPC - IMMULITE 2000 (USA). Complete blood counts were measured on Cell-dyn 3700 (Abbott Diagnostics, USA). The patients were divided into two groups, group 1: males, group 2: females.

Statistical analysis were done by Student's t-test and Pearson's correlation using SPSS-11 PC program, data were shown as mean +/- SD, and $P < 0.05$ was considered as statistically significant.

Results

Thirty-four (54,8 %) of the 62 patients were female, and 28 (45,2 %) were male with mean age 39,7 ± 12,8 and 39,7 ± 13,6 respectively (p=0,995). The mean durations of CAPD were 45,5 ± 34,3 and 44,9 ± 30,8 months in group 1 and 2, respectively (p=0,946). Demographic features, biochemical and hematological parameters, and Kt/V values of patients according to gender are shown in Table 1. Between groups there was no statistically significant difference in mean BMI. Females had 23,2 ± 4,9 kg/m^2, and males 23,2 ± 3,6 kg/m^2 (p=0,985).

The mean HCy levels were 19,6±13,7 µmol/L in males and 17,5±9,08 µmol/L in females, and there was no statistically significant difference between groups (p= 0,476). BMD and BMC measurements of male patients were higher than in female in both bone regions, FN and LS. When the groups were compared in FN, BMD was 0,95 ± 0,13 gr/cm^2 among males and 0,84 ± 0,13 gr/cm^2 among females (p=0,003), and BMC was 47,1 ± 10,6 gr in males, and 34,8 ± 6,3 gr in females (p<0.001). In LS measurements the results were similar to measurements in FN; BMD was 0.92 ± 0.13 gr/cm^2 in males and 0.85 ± 0.15 gr/cm^2 in females (p<0,001), and BMC was 57,1 ± 12,7 gr in males and 44,9 ± 10,4 gr in females (p= 0,058).

According to T-score measurements in FN 23,5% (n=8) of female patients, and 21,4 % (n=6) of males were osteoporotic, in LS T-score 8,8 % (n=3) of females, and 3,6 % (n=1) of males were osteoporotic (p=0,731 and p=0,453 respectively). T-score of patients according to groups are presented in Figures 1 and 2.

Table 1. Demographic, biochemical hematological parameters and DXA results of groups

Parameters	Group 1 (n=28)	Group 2 (n=34)	p
Age (years)	39,7±13,6	39,7±12,8	0,995
CAPD duration (months)	45,5±34,3	44,9±30,8	0,946
BMI (kg/m^2)	23,2±3,6	23,2±4,9	0,985
Hcy (µmol/L)	19,6±13,7	17,5±9,08	0,476
Vitamin-B12 (pg/ml)	364,5±32,3	382,2±42,5	0,667
Folate acid (ng/ml)	9,6±1,5	9,4±1,3	0,788
Ca (mg/dl)	8,8±0,9	11.7±1.7	0,317
P (mg/dl)	5,4±1,8	5,6±1,7	0,679
iPTH (pg/ml)	498,7±442,3	450,4±407,0	0,675
Kt/V	1,5±0,2	2,0±0,3	<0,001
Hemoglobin (g/dl)	12,4±5,6	10,7± 3,6	0,280
CRP (mg/dl)	6,9±5,8	6,7±2,5	0,152
Femur BMC (gr)	47,1±10,6	34.8±6.3	<0,001
Spine BMC (gr)	57,1±12,7	44.9±10.4	<0,001
Femur BMD (gr/cm^2)	0,95±0,13	0.84±0.13	0,003
Spine BMD (gr/cm^2)	0,92±0,13	0.85±0.15	0,058

CAPD: Continuous ambulatory peritoneal dialysis, BMI: Body mass index, Hcy: Homocysteine, Ca: calcium, P: phosphorus, iPTH: intact parathyroid hormone, CRP: C-reactive protein, BMC: bone mineral content, BMD: bone mineral density

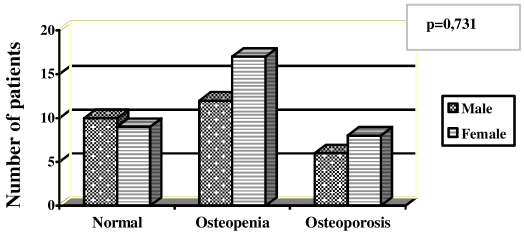

Fig. 1. Comparison of femur neck BMD

We found a positive correlation between serum levels of Hcy and BMD in FN (r=0,273, p=0,032), and there was no correlation between Hcy and BMD in LS (r=0,169, p=0,189). There was no difference between serum levels of Hcy in osteoporotic and non-osteoporotic patients; the mean levels were 19,9±12,5 µmol/L in osteoporotic and 18,9±11,9 in non-osteoporotic patients (p=0,266).

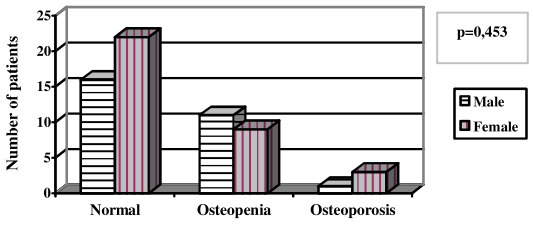

Fig. 2. Comparison of lumbar spine BMD

Discussion

Bone disorders related with end-stage renal disease (ESRD) are complex and multifactorial clinical circumstances with a wide spectrum, containing various aspects of renal osteodystrophy such as secondary hyperparathyroidism, osteomalacia or adynamic bone disease, and OP is another and prevalent bone disease in dialysis patients [11,12]. Bone strength is likely to be more severely affected during the course of chronic renal failure (CRF) than it might be expected from normal aging process because of the possible additional effects of renal failure. OP has a negative influence on quality of life among patients undergoing dialysis and it also contributes to elevated morbidity and mortality with increased fracture risk [13-16].

Large-scale epidemiological studies in general population have recognized many risk factors for OP including: advancing age, female gender, white race, decreased calcium intake, gastric acid suppression therapy [17], premature loss of gonadal functions, decreased estrogen secretion, thin body habitus, decreased physical activity, smoking, alcohol abuse, excess glucocorticoid exposure, and possibly some genetic factors [17-19]. In ESRD population, secondary hyperparathyroidism, adynamic bone disease and osteomalacia [20] and chronic acidosis, sedentary life style and medications (including previous corticosteroids, other immunosuppressives, heparin) may all be responsible for reduction in BMD and therefore may contribute to an increased OP prevalence and fracture risk.

The prevalence of low bone mass in dialysis patients is still debatable. Although Stein *et al.* [21] used Z-score (standard deviations from the mean of a healthy age and sex matched reference population) they found 8% prevalence of osteopenia at the lumbar spine, 13% at the femoral neck, and 20% at the distal radius. In another study performed in hemodialysis patients, Arici *et al.* [22] found that bone mass at the hip was lower than that in controls, but spinal BMD was not different. In another study performed among PD patients using BMD T score, Negri *et al.* [23] found that osteopenia and OP were present in 58.4 % of patients at the lumbar spine and in 78.4 % at the femoral neck. In this study, according to T-score measurements, we found rate OP of 23,5 % (n=8) among females and 21,4% (n=6) among males in FN, and 8,8 % (n=3) among females and 3,6% (n=1) among males in LS. There was no statistically significant difference between groups (p=0,731 and p=0,453 respectively). Among all patients OP rate was 21,9% in FN and 6,2% in LS. As in a previous study, T-score measurements were better in LS than in FN, and we speculate that this difference may be due to alterations in bone metabolism such as secondary hyperparathyroidism in dialysis population.

It is well known that impaired renal function cause many metabolic disorders in the body. Serum levels of Hcy, an independent risk factor for cardiovascular disease [5,6], is related to renal functions. In the previous study we showed that serum levels of Hcy was elevated among ESRF patients, treated with either hemodialysis or CAPD [24]. In many studies, the prevalence of HHcy among patients with ESRD is found up to 85-90% [7-9], and Hcy levels were higher than normal range in our patients as expected.

In recent years, many studies suggest that increased bone resorptive action by osteoclasts may contribute to OP in individuals with mild to moderate HHcy [25], and now HHcy is accepted as an independent risk factor for developing of OP among population with normal kidney functions. The link between Hcy and OP was provided in patients with hereditary homocystinuria, a rare genetic disorder characterized by severe HHcy and early onset of atherosclerosis and OP [26]. Interestingly, mild to moderate HHcy is quite prevalent in elderly individuals [27,28] and has been shown to be associated with lower bone mass [29,30] and higher fracture risk [31,32]. Although ESRD patients have high levels of Hcy, and HHcy is accepted as a risk factor for OP in normal population, we could not find any study evaluating the relationship between Hcy levels and OP among patients undergoing dialysis treatment. This is the first study evaluating the relationship between Hcy levels and OP in CAPD patients. In this study we did not find a correlation between BMD and HHcy in CAPD population, although the OP and HHcy rates were similar with the results in the literature. Pearson's correlation analysis showed a positive correlation between serum levels of Hcy and BMD in FN (r=0,273, p=0,032), and no correlation between Hcy and BMD in LS (r=0,169, r=0,189). These results suggest that there is no relation between HHcy and BMD in CAPD population in contrary to normal population. We think that finding no correlation between HHcy and BMD in LS may be due to lower percentage of OP in this region.

Conclusion

In conclusion, although Hcy levels were higher in CAPD patients, we did not find a negative correlation between Hcy and BMD. This study was with a limited number of patients suggesting that among CAPD patients, being a different group from the normal population because of the impaired kidney functions, HHcy may not contribute to OP. Large scale studies with large number of osteoporotic patients are needed to get a certain conclusion for this issue in this different population.

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Conflict of interest statement. None declared.

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