Original Article

Evaluation of Bone Mineral Densitometry Measurements in Patients with BCR/ABL-Negative Chronic Myeloproliferative Neoplasm

BCR / ABL-Negatif Kronik Miyeloproliferatif Neoplazlı Hastalarda Kemik Mineral Dansitometrisi Ölçümlerinin Değerlendirilmesi

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ABSTRACT

Introduction: This study aims to determine the changes in and the factors related to the bone mineral density in patients with bcr/abl-negative chronic myeloproliferative neoplasm (cmpd).

Methods: The data of 38 males (52.1%) and 35 females (47.9%) patients diagnosed with cmpd were analyzed retrospectively. The age, gender, diagnosis (polycythemia vera (pv), essential thrombocythemia (et)), jak2v617f mutation positivity, the presence of the cmpd complications and the bone mineral densitometry (bmd) measurements of femur neck and lumbar spine carried out during the diagnosis were recorded for each patient. The patients were divided into four groups: under 65 and over 65 years old for men, premenopausal and postmenopausal status for women. They were also grouped according to the t score of the femur neck and lumbar spine with normal and decreased bone density.

Results: Female patients were found to have more bone loss in the lumbar spine (p=0.031). In female patients, the reduction in the lumbar spine bmd was greater in the postmenopausal group (p=0.012). The decrease in bone density in the femur neck was found to be greater in the group above 65 years of age (p=0.01). There was no relationship between bmd and et, pv, jak2v617f mutation positivity, and cmpd complications such as thrombosis and hemorrhage.

Discussion and conclusion: according to the results obtained in our study, the presence of cmpd increases bone loss in lomber area in female patients. Therefore, the bmd measurement and calcium-d supportive treatment planning in the premenopausal group are thought to be beneficial in female patients.

Keywords: bone mineral densitometry, BCR/ABL-negative chronic myeloproliferative neoplasm, polycythemia vera, essential thrombocythemia

ÖZET

Giriş ve amaç: Bu çalışmada, BCR / ABL-negatif kronik miyeloproliferatif neoplazmı (KMPH) olan hastaların, kemik mineral dansitometri ölçümlerindeki değişiklikleri ve prognostik faktörlerle ilişkisini incelemeyi amaçladık.

Yöntem ve gereçler: KMPH tanısı alan 38 erkek (%52.1) ve 35 kadın (%47.9) olgunun verileri retrospektif olarak incelendi. Tanı sırasında gerçekleştirilen femur boynu ve lomber omurganın yaş, cinsiyet, tanı (polisitemia vera (PV), esansiyel trombositoz (ET)), JAK2V617F mutasyon pozitifliği, KMPH komplikasyonlarının varlığı ve kemik mineral dansitometrisi (KMD) ölçümleri her hasta için kaydedildi. Hastalar; erkekler için 65 yaş altı ve 65 yaş üstü, kadınlar için menopoz öncesi ve menopoz sonrası durum olarak dört gruba ayrıldı. Ayrıca T skoru; femur boynu ve lomber omurgaya göre normal ve azalmış kemik yoğunluğu olarak gruplandırıldı.

Bulgular: Kadın hastalarda lomber omurgada daha fazla kemik kaybı olduğu bulundu (p = 0.031). Kadın hastalarda, lomber omurga KMD'sindeki azalma postmenopozal grupta daha fazlaydı (p = 0.012). Femur boynundaki kemik yoğunluğunda azalma 65 yaş üstü grupta daha fazla bulundu (p = 0.01). KMD ile ET ya da PV tanısı, JAK2V617F mutasyon pozitifliği, tromboz ve kanama gibi KMPH komplikasyonları arasında ilişki yoktu.

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Tartışma ve sonuç: Çalışmamızda elde edilen sonuçlara göre, KMPH varlığı kadın hastalarda lomber bölgede kemik kaybını arttırmaktadır. Bu nedenle, menopoz öncesi grupta KMD ölçümü ve kalsiyum destekleyici tedavi planlamasının kadın KMPH hastalarda faydalı olduğu düşünülmektedir.

Anahtar Kelimeler: kemik mineral dansitometri, BCR / ABL-negatif kronik miyeloproliferatif neoplazm, polisitemia vera, esansiyel trombositoz

Introduction:

BCR/ABL-Negative Chronic Myeloproliferative Neoplasm (CMPD) is a clonal hematopoietic stem cell disease. Polycythemia vera, essential thrombocythemia, primary myelofibrosis take part in this group. There are studies showing that inflammatory processes play an important role in the pathogenesis of the CMPD. Inflammatory cytokines such as lipocalin, TNF-alpha, and IL-6 have been shown to increase in the PV and ET cases [1,2,3].

Osteoporosis is characterized by an increase in the risk of fracture as a result of the decreased bone mass and microarchitectural bone deterioration [4]. It has been reported in the literature that one out of every three females and one out of six males are at risk for osteoporotic fractures throughout their lifetime [5].The relationship between BMD and the incidence of fracture has been demonstrated by several large-scale studies. The BMD measurement using the DXA method is the gold standard for the diagnosis of osteoporosis[6-11]. Studies have shown that major inflammatory cytokines such as c-reactive protein (CRP), interleukin -6 (IL-6), and monocytechemotactic protein-1 (MCP-1) are increased in patients with osteoporosis and osteopenia, but no consensus has been reached on this issue [12,13,14].There is a small number of studies suggesting that osteoporosis may develop as a complication in CMPD cases [15]. In a study, CMPD cases were shown to have an increased risk of fracture relative to the general population, but the relevant pathophysiology was not fully explained.

Our study aims to investigate the BMD changes in CMPD cases comprising of ET and PV and the factors that may be cause in these changes.

Methods

Patients and samples: The study includes patients diagnosed with PV and ET among those who applied to our hematology clinic. There were a few myelofibrosis cases, so they were excluded from the study. The data were analyzed retrospectively. Male patients were divided into those under 65 and over 65 years old, female patients were divided into those under premenopausal period and post-menopausal period. Patients with additional systemic diseases (celiac disease, chronic obstructive pulmonary disease, asthma bronchiale, hyperparathyroidism, hyperthyroidism, inflammatory bowel disease, kidney stone disease, rheumatoid arthritis, solid neoplasia, steroid use history, alcohol use) were not included in the study. Presence of JAK2V617F mutation, the presence of the story of the hemorrhage and thrombosis from the CMPD complications, the status of receiving the ASA-hydroxyurea treatment, 25-OH-D levels, and calcium levels were recorded. The vitamin D level <20 ng/ml was accepted as a deficiency. Patients with a calcium value of <8.5 mg/dl were considered to have hypocalcemia. The BMD measurements were performed on the femur neck and lumbar spine using the DXA method. Those with BMD T score above -1 were considered normal, those with BMD T score -1 and below were considered to have decreased bone mineral density. The relationship between the lumbar spine and femur neck bone density and gender, age, JAK2V617F positivity, diagnosis (ET, PV), hypocalcemia and D vitamin levels, ASA and hydroxyurea use, and the thrombosis and hemorrhage complications were investigated.

Statistical analysis: The statistical analysis was performed by the chi-square test using the SPSS 16.0 program (SPSS inc. Chicago, IL, USA). Values below $P < 0.05$ were accepted to be statistically significant.

Table 1: Demographic features of patients

	JAK2V617F positive (n=47)	JAK2V617F negative (n=26)	Total (n=73)	p
Age[1]	62.49±14.72	54.58±11.21	59.67±14.02	0.013
Gender[2] (male)	25 (53.2)	13 (50.0)	38 (52.1)	0.987
Subtype of diagnosis (ET)	15 (31.9)	16 (61.5)	31 (42.5)	0.027
Treatment with HU+ASA	37 (78.7)	14 (53.8)	51 (69.9)	0.051
Thrombosis	9 (19.1)	1 (3.8)	10 (13.7)	0.086
Hemorrhage	3 (6.4)	3 (11.5)	6 (8.2)	0.659
Hemoglobine[3](g/dL)	16.4 (11.8 - 21.3)	15.2 (11.5 – 20.3)	16.0 (11.5 - 21.3)	0.330
White Blood Cell(x10[3])	12.870 (0.18– 30.500)	8.515 (2.930– 18.760)	11.120 (0.18–30.500)	<0.001
Platelets (x10[3])	612 (179 - 2021)	682.5 (155 - 2130)	629 (155 - 2130)	0.876

[1] mean±ss, [2] n(%), [3] median (min-max)

Table 2: The bone mineral densitometry results according to JAK2V617F mutation positivity

	JAK2V617F positive N:47 (65.3%)	JAK2V617F negative N:25 (34.7%)	p
Femur Neck T score			
Normal	23 (48.9%)	11 (44%)	0.805
Abnormal	24 (51.1%)	14 (56%)	
Lomber Spine T score			
Normal	30 (63.8%)	17 (68%)	0.799
Abnormal	17 (36.2%)	8 (32%)	

Results:

The study included a total of 73 CMPD patients consisting of 38 males (52.1%) and 35 females (47.9%). The median age of the patients was 60 years (min=29, max=83). Of the patients, 42(57.5%) were diagnosed with PV and 31(42.5%) with ET. The demographic data of the patients were shown in Table 1. The JAK2V617F positivities of the patients were 76.2% in the PV group and 51.6% in the ET group. The results of bone mineral densitometry according to JAK2V617F mutation positivity are shown in Table 2. Of the patients, 51 (69.9%) were using hydroxyurea and ASA, and 22 (31.1%) were using only ASA. From the CMPD complications, thrombosis was seen in 10 patients (13.7%) and hemorrhage was seen in 6 patients (8.2%). Of the female patients, 9 premenopausal (26.4%) and 26 were postmenopausal (73.6%). The number of patients with vitamin D level below 20 was 51(69.9%) and the number of patients with hypocalcemia was 8 (10.9%). In the lumbar spine, 47.1% of females and 23.1% of males had a decrease in bone density. BMD results according to menopausal status in women and under or over 65 years age of men, are shown in table 3. The decrease in the lumbar spinal bone density of the females was statistically significant (p=0.04). Of the female patients, 9(26.4%) premenopausal and 26(73.6%) were postmenopausal. In postmenopausal female patients, the reduction in lumbar spine BMD was significantly greater than in male and premenopausal female patients (p=0.012). There was no statistically significant correlation between the decrease in lumbar spine bone density and age, JAK2V617F positivity, diagnosis (ET, PV), hypocalcemia and 25-OH-D level, ASA and hydroxyurea use, thrombosis and hemorrhage comp-lications. The decrease in the femur neck bone density of the patients over 65 years was

Table 3: Distribution of bone mineral densities according to localization of the body

Women Premenopausal			Postmenopausal	Men ≤ 65 years old	≥ 65 years old
The bone mineral density of the femur neck	Normal	5 (14,3%)	9 (25,7%)	15 (42,9%)	6(17,1%)
	Abnormal	4(10,5%)	17 (44,7%)	9 (23,7%)	8 (21,1%)
The bone mineral density of the lumbar spine	Normal	6 (12,5%)	11 (22,9%)	19 (39,6%)	12 (25%)
	Abnormal	3 (12%)	15*(60%)	5 (20%)	2 (8%)

*(p=0,012)

70%, while this frequency was below 39.5% in patients under the age of 65. The decrease in BMD in the femur neck of older CMPD patients was significantly higher (p=0.01). The relationship between the decrease in the femur neck BMD and gender, JAK2V617F positivity, diagnosis (ET, PV), hypocalcemia and vitamin D levels, ASA and hydroxyurea use, and the thrombosis and hemorrhage complications was not statistically significant.

Discussion:

In our study, the BMD measurements showed and increased bone loss in the femur neck and lumbar spine in ET and PV patients with increasing age and this bone loss was even more in the lumbar spine in female patients. In the normal population, while the decrease in femur neck BMD was more frequent in female patients in the postmenopausal period, it was remarkable that BMD decrease was observed more frequently in the lumbar spine in patients included in this study. It is known that osteoporosis is a common health problem in both genders in advanced age. Many studies have shown that premenopausal and postmenopausal bone loss in women occurs in the femur neck, and bone loss in the lumbar vertebra occurs in the postmenopausal first decade [16-23]. There are studies showing that bone loss in males increases with age and there is a lifelong loss of bone, especially in the femur neck regionally [24-30]. In a study including PV and ET patients, it has been shown that there is a tendency for trabecular bone loss in a bone biopsy performed to investigate the bone loss detected by the DXA method [31,32]. In another study, PV and ET patients were shown to have increased femoral fracture risk within the next 5 years of diagnosis [33].

The fact that there is no difference between 25 OH D and calcium levels of the patients with normal or decreased BMD suggests that reduced BMD may be due to the disease-related factors. Our study has some limitations. Firstly, a relatively small group was evaluated, and, consequently, the different results that the studies with the larger groups could reveal cannot be ignored. In addition, patients who have already undergone osteoporosis treatment were excluded from the study, which may have led to a bias in this study.

In the literature, it has been shown that the T-score measurements of postmenopausal patients with PV fell from -1.7 to -4.3 in 8-year follow-up. After excluding other causes that could lead to bone loss increase, it has been suggested that this situation may be related to the presence of CMPD [34]. A normal bone remodeling is based on the maintenance of the balance between osteoclasts and osteoblasts [35]. Any imbalance of the bone turnover leads to changes in the skeletal structure and clinical findings that can result in fractures. A study comparing 339597 healthy individuals without the osteoporosis and fracture history with 7595 CMPD patients showed increased fracture risk in ET, PV, and CML patients [33]. A recent study comparing the risk of osteoporotic fracture of a healthy control group with that of 45 patients with ET and PV suggests that fatigue and inactivity caused by disease-related constitutional symptoms may

be effective in increasing fracture risk in patients with ET and PV [15].

In general, it is known that systemic inflammatory diseases are associated with osteoporosis and that the fracture risk increases as a consequence of the decrease in bone density. CMPD patients have also been shown to be under the influence of chronic inflammation [36]. Symptoms including reduced muscle mass, weight loss, decreased activity and fatigue can also lead to BMD deterioration in CMPD patients [37, 38]. The effect of EPO dependent and EPO independent erythropoiesis on bone remodeling was investigated in a rat model. While there were reductions in the osteoblast count and bone formation in both JAK mutation model and erythropoietin-enhanced model, the osteoclast count and activity were found to be normal, and, consequently, the bone loss was associated with the myeloproliferative process [39]. However, there was no significant relationship between the JAK2 mutation positivity and the BMD measurements in this study.

Osteoporosis is associated with low body mass index and increased fracture risk, and progresses without being noticed until a fracture occurs [40]. Many cross-sectional studies have shown that osteoporosis awareness is inadequate both in the groups at risk and in the general population [41, 42, 43, 44]. The osteopenic group with a T score of between -1 and - 2.5 in BMD measurements has also been reported to have a high fracture rate [45]. It has been suggested that the potential risk of fall and impaired bone quality may be influential in these factors [46, 47]. In the patient population in this study, it is considered that factors associated with the myeloproliferative process are also risk factors for osteoporosis and fracture in addition to advanced age.

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Conclusion

Our current result showed that unlike the expected femur neck osteoporosis in the general population, the fact that there is a decrease in the BMD in the lumbar spine in the study group consisting of PV and ET cases. As well as a decrease in the BMD also in patients under the age of 65 shows that this group of patients should be evaluated for osteopenia and osteoporosis, so that the vitamin D support therapy should be planned earlier

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