KRONİK İNFLAMATUVAR HASTALIKLARDA SEROPOZİTİVİTENİN KEMİK MİNERAL YOĞUNLUĞUNA ETKİSİ

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ÖZET

Kronik inflamatuvar hastalıklarda görülen lokalize ve jeneralize kemik kaybı, kırık riskinde artış ile morbidite ve mortaliteye sebep olabilir. Bu çalışmada amacımız seropozitif ve seronegatif kronik inflamatuvar hastalıklarda kemik mineral yoğunluğu (KMY) değişikliklerini incelemek ve klinik karakteristik özelliklerin kemik mineral yoğunluğu üzerine etkilerini araştırmaktır. 75 seropozitif, 15 seronegatif Romatoid Artrit (RA) ve 27 Ankilozan Spondilitli(AS) hasta ile 25 sağlıklı gönüllü denek çalışmaya alındı. Seronegatif RA hastaları ve AS'li hastalar seronegatif grup olarak kabul edildi. DEXA ile femur boynu ve lomber vertebralarda KMY ölçüldü. Seropozitif hastalar ve kontrol grubu arasında T skorları açısından anlamlı fark mevcuttu. Seronegatif grup kendi içinde değerlendirildiğinde seronegatif RA hastaları ve spondiloartropati hastaları arasında da spinal ve femoral T skorları farklı değildi.

Seropozitif ve seronegatif gruplar karşılaştırıldığında ise seropozitif grubun değerleri daha düşük olmakla birlikte farkın iki bölgede de (femur ve L2-4) anlamlı olmadığı görüldü. Sonuçta, kronik inflamatuvar hastalıklarda osteoporoz riskinin arttığı ancak bu riskin hastalığın seronegatif veya seropozitif olmasından bağımsız olduğuna karar verildi.

Anahtar kelimeler: *kemik mineral yoğunluğu, osteoporoz, seropozitif, seronegatif*

ABSTRACT

EFFECT OF SEROPOSITIVITY ON BONE MINERAL DENSITY IN CHRONIC INFLAMMATORY DISEASES

Localised and generalised bone loss in chronic inflammatory diseases result in an increased risk of fractures with associated morbidity and mortality. Our aim was to observe bone mineral density (BMD) changes in seropositive and seronegative chronic inflammatory diseases and to evaluate the effect of clinical characteristics on BMD. 75 seropositive, 15 seronegative RA and 27 AS patients with 25 healthy volunteers were included in the study. Seronegative RA patients and all AS patients were accepted as the seronegative group. BMD measurements were carried out at lumbar spine and femur neck by DEXA. We found significant difference between T scores of seropositive patients and control groups. The difference was not statistically significant between seronegative and seropositive groups though BMD values were lower for the seropositive group at either site. For the seronegative group, we found no statistically significant difference between spondyloarthropathy and seronegative RA patient groups in terms of spinal and femoral T scores.

We suggest that the increased risk of OP in chronic inflammatory diseases is present but not dependent on the seropositive and seronegative characteristic of the disease.

Key Words: *Bone mineral density, osteoporosis, seropositive, seronegative*

INTRODUCTION

In seropositive and seronegative chronic inflammatory diseases, localised and generalised bone loss due to various factors (high inflammatory activity, immobility and glucocorticoid therapy) is commonly present (1-2). Bone loss result in an increased risk of fractures and associated morbidity, mortality and healthcare costs.

Rheumatoid arthritis (RA) and Ankylosing spondylitis (AS) are the prototypes of seropositive and seronegative chronic inflammatory diseases respectively. These diseases differ principally by inflammatory damage of peripheral and axial skeleton but patients also share similar features like inflammatory cytokine production, antiinflammatory drug usage, disability, hypogonadism etc (3).

Approximately 15 % of RA patients experience the seronegative form of the disease. In most studies these patients have been reported to have more frequent involvement of large lower and upper extremity joints resembling seroneg-

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ative spondylarthropathies with a benign course in contrast to the severe involvement of the hands and feet in seropositive disease (4,5).

Aim of this study was to observe bone mineral density (BMD) changes in seropositive and seronegative chronic inflammatory diseases and to evaluate the effect of clinical characteristics on BMD.

PATIENTS AND METHODS

Seventy five rheumatoid factor (RF) positive (61 male-14 female), 15 RF negative (13 female-2 male) rheumatoid arthritis patients fulfilling 1987 ARA criteria (6) and 27 ankylosing spondylitis patients (23 male, 4 female) according to modified New York criteria (7) were included in the study. All patients were recruited from our outpatient clinic records. Both AS and RA patients had been treated with several nonsteroidal antiinflammatory drugs and disease modifying drugs during the disease course. None of the patients were seriously disabled or immobile and also none were receiving drugs which could effect bone mass or metabolism (glucocorticoids, calcium, vit D, bisphosphonates and hormone replacement therapy etc.). 25 healthy volunteers with no known rheumatological disorder or musculoskelatal complaints were accepted as the control group. Control subjects did not have any history of neurologic, endocrinologic diseases and medication that might affect bone metabolism. The demographic and clinical characteristics of the patients as well as their informed consent were obtained by self report and clinical examination.

Patients having a RF titer >5mg with latex agglutination were considered to be RF positive (+). None of the AS patients had (+) RF titers. Seronegative RA patients and all AS patients were accepted as the seronegative patient group. Bone mineral density measurements were carried out at axial (lumbar spine, L-2-4) and appendicular (femur neck) regions by DEXA (Lunar). T scores more than 1 S.D below the mean value were accepted as low BMD (T scores <-1 S.D are accepted as osteopenia and <-2.5 S.D are accepted as osteoporotic) according to WHO recommendation.

The statistical analysis were carried out using the SPSS program for Windows version 8.0. We used nonparametric tests to compare patient and control groups. Correlation between variables were quantified by the Spearman correlation coefficient . p values less than or equal to 0.05 were considered statistically significant.

RESULTS

Ninety Rheumatoid arthritis, 27 Ankylosing spondylitis and 25 control subjects participated in the study. Some of the data about patient and control groups are listed in Table I. There was no statistically significant difference between seropositive, seronegative and control groups, RF(+) RA, RF (-) RA groups for gender, age and disease duration.

Low T scores were noticed at femur and/or L2-4 vertebrae in 49 seropositive RA patients (65.6 %) and in 6 seronegative RA patients (40 %). For the AS group, OP and osteopenia were present in 15 of patients (55.5%). 11 of healthy controls revealed low T scores at femur neck and/or L2-4 vertebrae (44 %).

Tablo I. Mean (mean ±S.D) values for age, disease duration and important laboratory data of patient and control groups

group	n	Age	Disease duration	ESR	ALP	Calcium
Seropositive	75	50.9±11.8	8.6±7.3	42.5±26.7	105.9±39.6	8.8±0.4
Seronegative	42	49.5±9.9	8.1±6.4	29.2±17.2	107.1±35.5	9.0±0.4
Control	25	54.12±11.2		6.5±2.6	102.4±4.4	8.9±1.6

We found statistically significant difference between T scores of seropositive patients and control groups in L-2-4 vertebrae and femur neck regions in our analyses ($p<0.05$ and $p<0.05$). The difference was not statistically significant at axial and appendicular BMD between seronegative and seropositive groups though the BMD values were lower for the seropositive group at both sides ($p=0.260$ and $p=0.311$). There was statistically significant difference at femur neck measurements between seronegative patients and controls ($p=0.043$). But when we seperated the seronegative group as spondyloarthropathy and seronegative RA patients, we found no statistically significant difference between these groups in terms of spinal and femoral T scores ($p=0.176$ and $p=0.081$ respectively) (Figure 1).

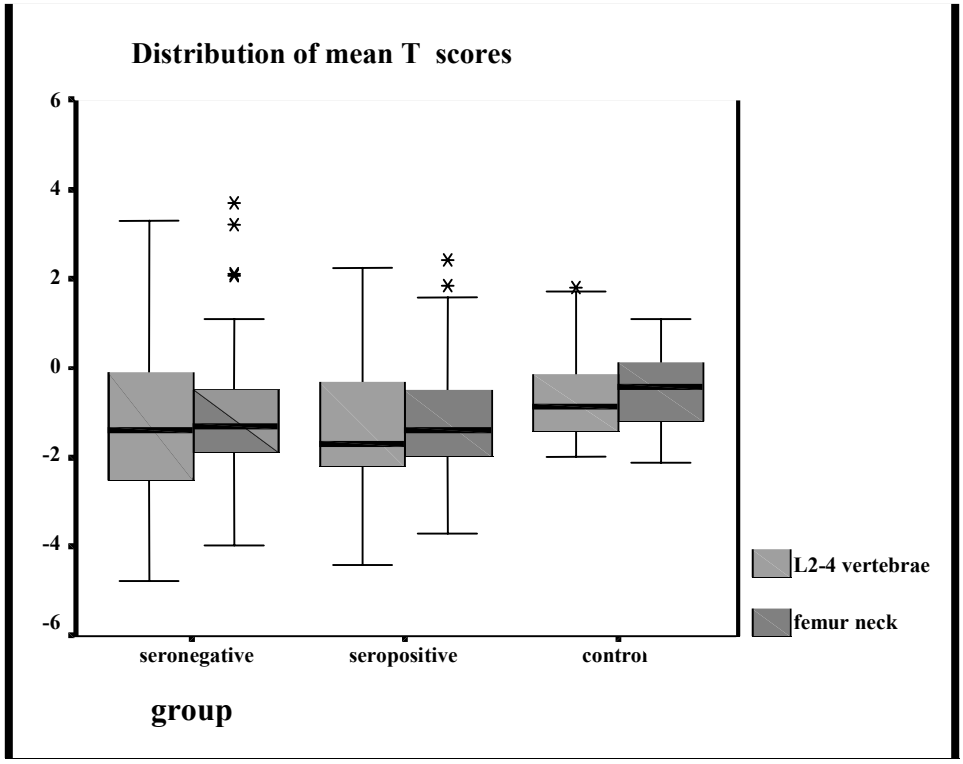
When RA patients were grouped according to gender, femur neck T scores of male patients were found to be lower than female patients. Comparison of male RA- male AS patients revelaed no statistically significant difference in any of the measured sites.

There was no correlation between individual measures of disease activity and ESR, CRP in any patient group. For both RA groups, T scores in femur neck and L2-4 vertebrae were correlated with patients' ages and the length of disease duration. No such correlation could be found for AS group.

DISCUSSION

Osteoporosis (OP) is recognised as a common complication of chronic inflammatory diseases, especially RA, with two characteristic patterns, juxtaarticular and generalised bone loss (2,8). OP result in an increased risk of fracture and associated morbidity, mortality and healthcare costs (9). The etiology is multifactorial involving disease spesific and general factors but the relative importance of the various risks remain uncertain (8).

Figure 1. Distribution of mean T scores of three groups at two regions: L2-4 vertebrae and femur neck



Our primary aim was to evaluate the effect of seropositivity in chronic inflammatory diseases on BMD. Seronegative and seropositive chronic inflammatory diseases differ in some clinical characteristics like patterns of arthritis, gender preference, HLA subtypes, extraarticular manifestations etc. On the other hand, they share basic mechanisms of inflammatory responses and chronic nature of the disease leading to disability. Systemic OP seen in axial and appendicular skeleton in chronic rheumatologic disorders reflect these common features; systemic inflammation as well as the sedentary lifestyle of patients with disability (3).

Rheumatoid factor (+) RA patients were assessed as seropositive chronic inflammatory disease group and seronegative RA patients and AS patients were accepted as the seronegative group. Seronegative RA patients may mimic spondyloarthropathies with more frequent involvement of large lower and upper extremity joints and a milder course.

In our study when compared to healthy individuals, low T scores were significant at femur and spine for the seropositive group. Seronegative patient group consisting of seronegative RA and AS patients revealed statistically significant low values compared to the control group only at the femur neck. When we analysed the difference between patient groups, we found lower but not statistically significant different values at the seropositive group. Haugeberg et al.revealed that older age, low body weight and RF positivity were identified as statistically significant independent predictors of BMD reduction in femoral neck. In their study BMD was generally lower in RF(+) patients comprising 204 women, compared with RF(-) patients (10). In another study Haugeberg also reported that the RF status were found to be indirectly associated with reduced bone mass (11). On the other hand Dreher et al. claimed that inceased risk of OP in RA is not dependent on the seropositive and negative disease entity but on to the severity, functional capacity and duration of the disease (12). Our results are in concordance with this study, reflecting minor differences between seropositive and seronegative patient groups.

Recently Haugeberg et al. reported a significant decrease of bone mass in the proximal femur in 94 patients with RA, but no difference in lumbar bone mass between RA and controls (11). Also, Hansen's results showed that BMD of the spine was not significantly reduced in patients with RA, compared to the healthy population (2). But none of the studies emphasized the RF status of the patients. Relatively higher spinal BMD for RA patients has been reported in Shibuya's report too (13). Shibuya claimed that arthritis was shown to be synchronise with BMD in peripheral bone and OP in RA is characterised by marked bone loss in the peripheral bone compared with the lumbar vertebrae.

We found statistically significant lower spinal T scores for the seropositive RA group but not for the seronegative group. For the seronegative group L2-4 vertebrae T scores are relatively higher than femur T scores and this difference can be explained by spinal syndesmophytes and new bone formation which can be documented by spinal radiographs. Spinal measurements in these patients must be interpreted with care and it is recommended to evaluate these patients by proximal femur measurements (10). Osteoporosis in these patients can be more apparent at earlier stages of the disease. Sambrook et al serially evaluated BMD and found a significant higher ratio of decrease in the distal end of the radius of patients (14). He stated that unlike postmenapausal OP, OP associated with RA is characterised with relatively preserved bone mass in lumbar vertebrae and marked bone loss in the peripheral bone.

In contrast to above studies and to our results, Keller (1) suggested that male and female RA above 60 years of age did not differ significantly from the reference values for an age and sex matched healthy population both at the spine and hip regions. Our patients have younger mean age values than Keller's subjects and age is a major factor in osteoporosis.

When we grouped RA patients according to gender, the femur neck T scores of male patients were found to be lower than female patients (p=0.043). Keller stated that in RA male patients below 60 year of age there was trend towards lower BMD values compared with the reference population (1). Increased frequency of reduced BMD in male RA patients indicates that disease related mechanism of bone loss are important, although no disease related factors were found to be associated with a reduction in BMD in cross sectional study. As there are conflicting reports, further studies are needed to evaluate the role of BMD measurements in predicting the risk of fracture especially in male RA patients for whom no fracture data exist.

The effect of disease activity and inflammatory status of rheumatologic patients is controversial. High levels of inflammatory activity heve been suggested as an important factor for increased generalized bone loss. However Cortet et al. failed to display a correlation between biological data (ESR, CRP, morning stiffness) and changes in BMD (4). Our patients also displayed significant difference in ESR between groups which did not effect BMD measurements. Thus this lack of association can be explained by the cross-sectional design of the study. The disease course is characterized by remissions and exacerbations and disease activity measures change on a short term basis, whereas bone density is affected from cummulative effect of various factors over years (11).

To determine the difference between seronegative patient groups, we also compared AS and seronegative RA patients, but there was no statistically significant difference between these groups in terms of spinal and femoral BMD values. This comparison may not be satisfactory due to the small number of patients in either group.

In the light of recent studies and our results we suggest that the increased risk of OP in chronic inflammatory diseases is apparent but not dependent on the seropositive and seronegative characteristic of the disease. Age, diasease duration, disability, medication as well as the systemic inflammation are possible risk factors and more studies in large series are needed to identify the effect of clinical characteristics on the risk of OP.

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