The Evaluation of Renal Osteodystrophy in Patients on Hemodialysis by Biochemical and Radiological Methods

Hemodiyaliz Hastalarında Renal Osteodistrofinin Radyolojik ve Biyokimyasal Yöntemlerle Değerlendirilmesi

Sibel Mandıroğlu, Ece Ünlü*, Deniz Aylı**

Ankara Physical Therapy and Rehabilitation Education And Research Hospital, Department of Physical Medicine And Rehabilitation, Ankara, Turkey
*Dışkapı Yıldırım Beyazıt Education and Research Hospital, Department of Physical Medicine and Rehabilitation, Ankara, Turkey
**Dışkapı Yıldırım Beyazıt Education and Research Hospital, Department of Nephrology, Ankara, Turkey

Summary

Aim: We planned this study in order to evaluate the radiological and biochemical parameters that may be useful in the early diagnosis of renal osteodystrophy in the patients with chronic renal failure, prospectively.

Meterial and Methods: In this study, 50 cases on hemodialysis due to chronic renal failure were included and 50 cases without renal and bone pathology were included as control group. Serum levels of calcium, phosphate, alkalen phosphatase, βm, osteocalcin (BGP) and intact parathormon (iPTH) were measured. Right hand graphies of both case and control groups were taken by magnifying techniques. Bone mineral densities (BMD) of lumbar vertebra and femur neck were calculated by DEXA method.

Results: The average disease duration and the average of duration of hemodialysis of cases were 8.38±5.61years and 6.9±4.01years, respectively. There were significant differences between case and control groups in all biochemical parameters, except calcium levels (p<0.05). There were a negative correlation between iPTH and BMD (r=-0.4, p<0.05), and pozitif correlations between iPTH and BGP (r=0.6, p<0.05), and between PTH and β-m (r=0.5, p<0.05). A low level negative but statistically significant correlation between dialysis duration and femur neck bone mineral density was determined (r=0.2, p<0.05). There were positive correlations between dialysis duration and PTH levels (r:0.3, p<0.05), and between dialysis duration and β_2 m (r=0.4, p<0.05). In the hand graphies, osteopenia, subperiostal resorption, radial artery calcification and endoosteal resorption were seen. Ostepenia was determined in 80% of our cases, however, subperiostal resorption was found in 58% of patients. The cases that had iPTH levels over than 200 pg/ml and cases that have osteopenia have sensitivity of 93% and spesifity of 92% for RO diagnosis. Sensitivity and spesifity for high iPTH-BGP levels were 90.3% and 87%, respectively. Sensitivity and spesifity in the evaluation of high iPTH-subperiostal resorption were 83.9% and 84.2%, respectively.

Conclusion: Measure of iPTH, BMD, BGP and evaluation of hand graphies may be used in early diagnosis and follow-up of RO. (Turkish Journal of Osteoporosis 2013;19: 7-11)

Key words: Bone mineral density, hemodialysis, renal osteodystrophy

Özet

Amaç: Bu çalışmada kronik böbrek yetmezliği olan olgularda renal osteodistrofinin erken tanısında faydalı olabilecek radyolojik ve biyokimyasal parametreleri prospektif olarak araştırmayı planladık.

Gereç ve Yöntem: Kronik böbrek yetmezliği nedeni ile hemodiyalize giren 50 olgu ve dahil edildi. Böbrek problemi ve kemik hastalığı olmayan 50 olgu kontrol grubu olarak çalışmaya dahil edildi. Serum kalsiyum, fosfor, alkalen fosfataz,β–microglobulin (βm), osteokalsin (BGP), intact parathormon (iPTH) seviyeleri ölçüldü.Her iki grupta sağ el grafileri magnifiye teknikle çekildi. Lomber vertebra ve femur boyun kemik mineral yoğunluğu (KMY) DEXA yöntemi ile ölçüldü.

Bulgular: Olgularımızın ortalama hastalık süresi 8,38±5,61 yıl, diyalize girme süresi 6,9±4,01 yıldı. Kalsiyum dışındaki bütün biyokimyasal parametrelerde olgu ve kontrol grubumuz arasında önemli derecede fark mevcuttu (p<0,05).İPTH ve KMY arasında negatif korelasyon mevcuttu (r=-0,4, p<0,05). İPTH ve BGP, İPTH ve β_2 m arasında pozitif korelasyon mevcuttu (r=0,6, p<0,05), (r=0,5, p<0,05). Diyaliz süresi ve femur boyun KMY arasında istatistiksel olarak anlamlı, düşük düzeyde negatif korelasyon mevcuttu (r=0,2,p<0,05). Diyaliz süresi ve İPTH, diyaliz süresi ve βm arasında pozitif korelasyon mevcuttu (r=0,3, p<0,05),(r:0,4, p<0,05).El grafilerinde osteopeni ve subperiostal resorbsiyon, radyal arter kalsfikasyonu ve endosteal resorbsiyon görüldü. Olgularımızın %80'de osteopeni, %58'de subperiostal resorbsiyon saptandı. İPTH seviyesi 200 pg/ml üzerinde

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olan olgular ve osteopenisi olan olgularda RO tanısı için sensitivite %93, spesifite %92'dü. Yüksek İPTH-BGP için sensitivite ve spesifite sırası ile %90,3 ve %87 'di. Yüksek İPTH-subperiostal resorbsiyon için ise sensitivite %83,9, spesifite %84,2 'di.
Sonuç: İPTH, BMD, BGP ölçümleri ve el grafilerinin değerlendirilmesi RO'nin erken tanısı ve izleminde kullanılabilir. (Türk Osteoporoz Dergisi 2013;19: 7-11)
Anahtar kelimeler: Kemik mineral yoğunluğu, hemodiyaliz, renal osteodistrofi

Introduction

The number of patients with chronic renal failure (CRF) is increasing with the development of new diagnostic methods. Although the average life span of the patients with CRF has increased with treatment modalities such as hemodialysis and peritoneal dialysis, many complications began to be seen more frequently. Renal osteodystrophy (RO) is one of these complications and it causes mineral and bone metabolism impairment, and morbidity and mortality in most of patients (1-3). Osteitis fibrosa sistica, osteomalacia, skeletal abnormalities related to β_2 mikroglobulin (β_2 m), osteosclerosis and osteoporosis are histopatologically observed in RO (4). Hypocalcemia, phosphate retention, changes in vitamin D metabolism, decrease of PTH degradation, changes in calcium regulation are led to secondary hyperparathyroidism pathophysiologically. Increase of PTH levels results in rise of osteoclastic activity and bone resorption. Such an osteoclastic activity occurs in Haversian channels of cortical bone and subperiostal and endosteal surfaces. Cortical bone resorption occurs with PTH stimulated increased osteosit activity. Possible causes of osteoporosis in CRF include changes in vitamin D levels, immobilisation and chronic protein deficiency. Hyperphosphatemia can be observed in the phases which the catabolism increases due to the protein metabolism and catabolism. RO which becomes clinically evident with cases like bone aches, myopathy, muscle cramps, calciphylaxis and skeleton deformities affects the life quality of the cases with CRF and causes serious mortality and morbidity (5). Bone biopsy is advised for definitive diagnosis but its usage is limited due to its invasive process (6). That's why evaluation of the current laboratory and scanning procedures and not skipping the RO diagnosis are of the importance (7). For this reason in this prospectively planned study, we aimed to investigate the noninvasive methods that can be useful in early diagnosis of RO.

Material and Method

Fifty patients on chronic hemodialysis were included in this study which was planned prospectively in order to examine RO with noninvasive methods in the patients on hemodialysis. Fifty voluntary subjects without any primary renal problem and bone disease were also included in this study as a control group. The physical examinations of members of both patient and control groups were performed. The serum calcium, phosphorus, alkalen phosphatase, β_2 mikroglobulin (β_2 m) and intact parathormon (iPTH) levels of both groups were measured. Osteocalcin (BGP) levels were determined by Enzyme-linked immunosorbent assay (ELISA) method.
Right hand graphies of both case and control groups were taken by magnifying techniques. Thereafter, bone mineral

dansities were measured from lumbar vertebra and femur neck by Dual energy X-ray absorptiometry (DEXA) method.
T-test, chi-square test and Pearson correlation analysis were used for statistical analysis of study parameters of patient and control groups. Statistically $p<0.05$ value was considered as significant.

Results

The average age of our cases; 30 of whom were male, whereas 20 of whom were female; was 46.4±11.5 (19-69) years. The average disease duration of our cases was 8.38±5.61 (1-23) years and the duration of hemodialysis was 6.9±4.01 (1-16) years. Thirty-one members of the control group were male and 19 of them were female, and their average age was 45.8±11.5 (25-66) years. "There was no significant difference between case and control groups in age and sex distribution ($p>0.05$). The distribution of cases according to etiologies were shown at Graphic 1.
The average and standart deviation values of alkalen phosphatase (ALP), calcium, phosphorus, β_2-microglobulin, osteocalcin (BGP) and parathormon of cases and controls were given at Table 1. There was significant difference between case and control groups in all biochemical parameters, except calcium levels ($p<0.05$).
The bone mineral densities of femoral neck and lumbar vertebra were measured in both groups; and Z-value and T-value were calculated. Both of lumbar vertebra (BMDL) values and femoral neck (BMDF) values have shown significant difference between two groups ($p<0.05$) (Table 2).
The correlation of iPTH with BMD, BGP, ALP and β_2 m were examined, there was negatif correlation between iPTH and BMD ($r=-0.4$, $p<0.05$), whereas, there were positive correlations between iPTH and BGP ($r=0.6$, $p<0.05$), and between PTH and β_2 m ($r=0.5$, $p<0.05$).
When the correlations of dialysis duration with BMDF, BMDL, iPTH, BGP, ALP and β_2 m were evaluated, there was low level

Table 1. The values of biochemical parameters (x±SD) of cases and controls

	Case (n=50)	Control (n=50)	P
ALP(u/l)	137.4±68	89.2±22	p<0.05
Ca (mg/dl)	9±0.7	9.5±0.5	p>0.05
P (mg/dl)	5.6±1.8	3.4±0.6	p<0.05
β_2 m (mg/dl)	21.27±11.80	1.26±0.24	p<0.05
BGP (µg/L)	124.36±42.88	13.52±9.12	p<0.05
PTH (pg/ml)	202±131	30.5±10.4	p<0.05

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but statistically significant negative correlation between dialysis duration and BMDF (r=-0.2, p<0.05), whereas, there were positive correlation between dialysis duration and PTH (r=0.3, p<0.05) and between dialysis duration and β_2 m (r=0.05, p<0.05) (Table 3).

The right hand (dominant hand) graphies of all patients in both case and control groups were evaluated radiologically (Figure 1). The hand graphies were prepared by a special magnifying technique. Osteopenia and subperiostal resorption were found to be most frequent findings. Less frequently, radial artery calcification and endosteal resorption were determined. Osteopenia was found in 80% of cases, and subperiostal resorption were determined in 58% of cases (Table 4). Subperiostal resorption were frequently determined at radial, ulnar and radioulnar sites of phalanges (Graphic 2).

For diagnosis of RO occuring as a result of secondary hyperparathyroidism, we investigated the sensitivity and specificity values of parameters evaluated in our cases. When we take into account osteopenia cases which have iPTH values

higher than 200 pg/ml, we determined sensitivity as 93% and specifity as 92%. By such a similar evaluation, the sensitivity was 90.3% for high iPTH-BGP levels, whereas specifity was 87%. In the presence of high iPTH values and the subperiosteal resorption, the sensitivity and specifity were found 83.9 and 84.2%, respectively.
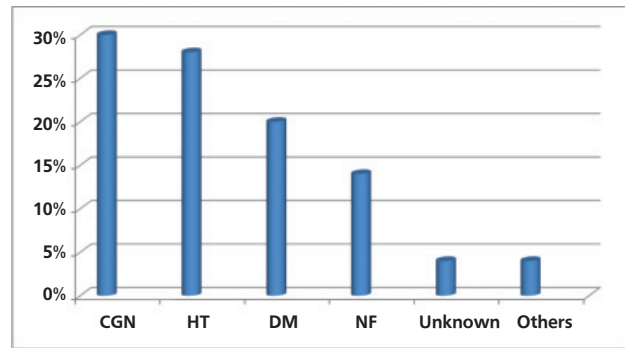

Figure 1. Right hand graphy of one of our case with evident osteopenia. Subperiostal resorption at radial side of middle phalanges of third finger and radioulnar side of middle phalanges of second finger are present. Interdigital artery calcification at radial side of third phalanges and radial artery calcification at wrist are seen.

Table 2. The comparision of DEXA BMD results of cases and controls

	Case (n=50)	Control (n=50)	P
Femur Total Z score	-1.4±0.8	0.01±0.8	p<0.05
LumbarTotal Z score	-1.2±0.9	0.01±0.08	p<0.05
Femur Total T score	-1.6±0.9	0.2±0.8	p<0.05
LumbarTotal T score	-1.4±0.9	0.4±0.1	p<0.05
BMD Lumbar	0.8±0.1	1.0±0.1	p<0.05
BMD Femur	0.7±0.1	0.8±0.1	p<0.05

Table 3. The comparion of dialysis duration with some parameters in case group

		Dialysis Duration
İPTH	r=0.3	p<0.05
β_2 m	r=0.4	p<0.05
BMD (F)	r=-0.2	p<0.05
BMD (L)	r=0.1	p>0.05
BGP	r=0.1	p>0.05
ALP	r=0.4	p<0.05

Table 4. The distribution of radiological findings

Radiological Finding	%	Number of cases
Osteopenia	%80	40
Subperiostal resorption	%58	29
Radial artery calcification	%20	10
Interdigital artery calcification	%16	8
Soft Tissue calcification	%8	4
Endosteal resorption	%4	2

Graphic 1. The distribution of cases according to etiologies.
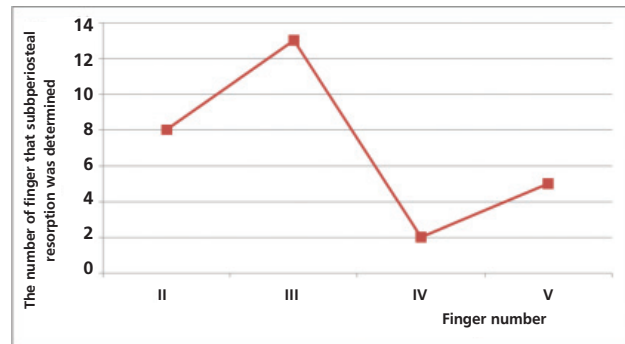
Graphic 2. The distribution of subperiostal resorption according to fingers.

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Discussion

RO; which is seen in patients with chronic renal failure; is a pathology that causes morbidity and disturbs the life quality. It was firstly defined by Liu and Chu in 1943. Osteitis fibrosa cystica, osteomalacia, adynamic bone disease (ABH) and osteoporosis are the clinical components (8,9,16,17).

In recent studies, it is mentioned that, bone loss on femur neck is higher than lumbar vertebra, because decrease in load at femur neck is more prevalent than lumbar vertebrae due to decreased physical activity (10,11). It is known that risk of hip fracture is increased in hemodialysis patient when compared with normal population (12-14). Although no fracture was determined, the DEXA values of cases were found to be significantly lower than the control group (p<0.05). Therefore, when the hemodialysis durations were compared with femur neck and lumbar vertebra, there was an inverse and weak relationship with femur neck BMD (r=-0.2). Because twelve postmenopausal subjects were present among women cases, effect of postmenopausal period on BMD values could not be ignored. This condition cause some limitations in this study. However, BMDF and BMDL T values of other 8 subjects which have regular menstrual period were respectively -1,7 and -1,5. On the other side, when all of the women subjects (n=20) were evaluated it was seen that BMDF values were smaller than BMDL values. This results support the effect of RO on BMD.

In the evaluation of secondary hyperparathyroidism, it was mentioned that the measure of iPTH values were found to be more sensitive, and it was shown that there was an inverse relationship between BMD and iPTH (10,15). Similarly, there was a inverse correlation between iPTH and BMD values in our cases (r=-0.4).

Serum level of BGP is accepted as indicator of bone formation. If the bone formation and degradation process is together in evaluated patients, it is accepted that BGP reflects the formation and degredation rates. It is also known that, decrease in clerearance of BGP in patients with CRF may cause increase in serum BGP levels (19,20). In our study, the BGP values of cases were found higher than control group, and the difference was found to be statistically significant (p<0.05).

It is pointed out that iPTH level is important in evaluation of RO (21). It has been shown that there is correlation between BGP level and iPTH level. Similarly, a significant correlation between iPTH and BGP was shown in case group (r=0.6). In our study, significant difference was determined between case and control groups in iPTH level (p<0.05).

It is known that there is no correlation between serum ALP level and clinical types of RO (22). It is mentioned that ALP level is decreased with calcitriol therapy and this shows parallelism with decrease in PTH level. The ALP level was compared between case and control groups, and the difference was found to be statistically significant (p<0.05). However, no correlation was determined between ALP and iPTH in our case group.

In hemodialysis cases, β_2 m; which accumulates within osteoarticular structures; is responsible for dialysis amiloidosis,

and it frequently causes carpal tunnel syndrome and supraspinatus tendinitis. The relationships of β_2 m levels with hemodialysis duration and iPTH levels were shown (23,24). In our study, significant difference was determined between cases and controls in β_2 m level (p<0.05). Moderate positive correlations were found between β_2 m and hemodialysis duration, and between β_2 m and iPTH in our case group (r=0.4,r=0.5).

It was mentioned that, the bone changes that are caused by secondary hPTH are most frequently seen in hand bones (25,26). When the graphies of dominant hands were evaluated in our case group, osteopenia was found in 80%, subperiosteal resorption was found in 58%, radial artery calcification was found in 20% and interdigital artery calcification was found in 16% and endosteal resorption was found in 4% of the patients. In our study, subperiosteal resorption was most frequently seen in third and second phalanges; respectively. It was prominent especially in radial side (Graphic 2).

Although bone biopsy is accepted as gold standart in classification of RO, the disadvantage of this method is being an invasive method (27,28). A recent study; in which iPTH level was evaluated with radiologically evident erosions; the sensitivity, specifity and positive estimate value of iPTH levels over than 200 pg/ml for the diagnosis of osteitis fibrosa cystica were found 83%, 88%, and 88%; respectively (29).

According to these findings, we determined the sensitivity and specifity related with the diagnosis of RO in our cases with iPTH levels over than 200 pg/ml (31 cases) and in our cases with osteopenia (40 cases) as 93% and 92%; respectively. By such a similar evaluation, the sensitivity was 90.3% for high iPTH-BGP levels, whereas spasifity was 87%. When the high İPTH and the presence of subperiosteal resorption was evaluated, the sensitivity and specifity were found 83.9 and 84.2%, respectively.

Conclusion

We are opinion that when osteopenia and subperiosteal resorption detected radiologically and high İPTH values with high BGP values in CRF cases were evaluated, RO diagnosis related with secondary hPTH may be foreseen. For that purpose, measure of iPTH, BMD, BGP and evaluation of hand graphies may be used in early diagnosis and follow-up of RO.

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