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The effect of risedronate treatment on bone turnover markers in patients with hip fracture

Kalça kırıklarında risedronat tedavisinin kemik yıkım ürünlerine etkisi

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Amaç: Osteoporotik kalça kırığı geçiren hastalarda risedronat tedavisinin kemik rezorpsiyonu üzerindeki etkileri, idrarda N-telopeptid düzeylerine bakılarak araştırıldı.

Çalışma planı: Minör travma sonrası femur intertrokanterik veya boyun kırığı nedeniyle cerrahi tedavi gören 46 kadın hasta (ort. yaş 75) başvuru sırasına göre numaralandırıldı. Tek sayılı hastaların oluşturduğu tedavi grubuna (26 hasta; ort. yaş 77±5) ameliyat sonrası beşinci günden itibaren oral risedronat 5 mg/gün verilmeye başlandı. Çift sayılı hastalara (20 hasta; ort. yaş 73±6) ise kontrol grubu olarak herhangi bir ilaç tedavisi uygulanmadı. Paget hastalığı ve osteoporoz nedeniyle tedavi görmekte olan veya böbrek yetmezliği bulunan olgular çalışma dışı bırakıldı. Hastaların tümünden yatışlarının ertesi sabahı ve hastaneye yatışlarının üçüncü ayında idrar örnekleri alındı. Çalışma sonunda Osteomark NTx ELISA laboratuvar kiti ile ikinci gün ve 90. gün idrarlarında, kemik yıkım ürünlerinden biri olan N-telopeptid düzeylerine bakıldı.

Sonuçlar: Risedronat tedavisi gören grupta idrar N-telopeptid düzeyi tedavi öncesine göre ortalama %49.7 düşüş gösterirken ($p<0.0001$), kontrol grubunda %5.8 artış gösterdi. Risedronat tedavisi gören hastaların idrarındaki kemik yıkım göstergelerindeki azalma, kontrol grubuna göre anlamlı idi ($p<0.0001$).

Çıkarımlar: Minör travma sonrası kalça kırığı geçiren hastalarda tekrar kırık riskinin azaltılması için risedronat tedavisinin kemik yıkımının azaltılmasında etkili olduğu görüldü.

Anahtar sözcükler: Kemik yoğunluğu/ilaç etkisi; etidronik asit/terapötik kullanım; kalça kırığı/etyoloji; osteoporoz, postmenopoz/komplikasyon.

Objectives: The effect of risedronate treatment on bone resorption was investigated quantitatively by measuring N-telopeptide levels in urine of patients with hip fracture.

Methods: Forty-six women (mean age 75 years) who underwent surgical treatment for intertrochanteric or femoral neck fractures due to minor trauma were di vided into two groups according to the order of presentation. One group (26 patients; mean age 77±5 years) received oral risedronate 5 mg/day after the fifth postoperative day, while the other group (20 patients; mean age 73±6 years) received no drug treatment. Patients who had been on treatment for Paget's disease or osteoporosis or those with renal failure were excluded. Urine samples were collected from all the patients on the second day of hospitalization and at the end of three months to measure N-telopeptide levels, one of the bone turnover markers, with the use of the Osteomark NTx ELISA laboratory kit.

Results: The mean urine N-telopeptide level decreased by 49.7% at the end of three months of treatment with risedronate ($p<0.0001$), whereas there was a 5.8% increase in the N-telopeptide level of the control group. The two groups differed significantly with respect to the levels of bone resorption at the end of three months ($p<0.0001$).

Conclusion: Risedronate treatment was found effective in decreasing bone resorption and thus in reducing the risk for refractures in patients with hip fractures due to minor trauma.

Key words: Bone density/drug effects; etidronic acid/therapeutic use; hip fractures/etiology; osteoporosis, postmenopausal/complications.

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Osteoporosis is defined as a disease which is characterized by reduced bone mineral density (BMD), micro-architectural detoriation of bone tissue followed by the increase of bone fragility and susceptibilty to fractures.[1] Diagnosis of osteoporosis may be made by a SD (standart deviation) score under -2.5 of young population's mean score. Dual energy X-ray absorptiometry (DEXA) is the golden standart for measuring BMD, but it is not showing acute changes at the begining phase or the effectiveness of a pharmacological treatment. Further tests may be required to follow the response to treatment.[2]

Hip fractures due to osteoporosis is commonly seen in elder patients and medical treatment is recommended in addition to surgery.[3,4] Some drugs like calcium,[5] calcitonin,[6] raloxifen,[7] teriparatid[8] and bisphosphanate group[9-12] are pharmacological agents used for osteoporosis treatment. Bone loss in osteoporosis can be shown by the bone turnover markers in the urine.[13] There are various methods that can measure turnover markers in urine. Urine N-telopeptide level is a highly sensitive marker of bone turnover.[14]

In our study, efficacy of oral risedronat treatment is researched by measuring N-telopeptide levels in urine, to our patients admitted to our clinic with hip fractures with minor trauma.

Patients and method

Between February 2004 and September 2004, 66 women submitted to our hospital between age 60-90 with intertrochanteric or neck femoral fractures with minor traumas were included in this study . They all signed informed consent forms. During registration process, 3 patients with renal failure, 3 patients that were already taking osteoporosis treatment and 1 patient with pagets disease were excluded from the study.

All patients were recorded with their admission order. Patients were divided into two groups. Upon their hospitilization order, odd numbered patients were formed the treatment group and oral risedronat 5mg/day was started at 5th post operative day. Even numbered patients formed the control group and received no drug treatment. In the 3 month control, 3 of the patients deceased, 6 patients lost in the follow up and 4 patients diagnosed with renal failure They also excluded from the study. Finally the study group consisted 46 patients (mean age 75) . There were 26 (mean age 77±5) patients in the treatment group and 20 patients (mean age 73±6) in the control group.

Urine samples were taken from all patients on the second day of hospitilization and placed in sterile urinary containers. Patient's initals and recorded numbers were written on the container and they were frozen and stored at -20º until analyzed. Blood urea and creatinin levels of patients were evaluated to asess renal function. Evaluation for urine creatinine clearances, 24 hour urine were collected.Also at 3rd month follow up, patients first morning urine samples were taken again in another sterile urinary container and stored under same conditions. Urinary creatinine clearences were measured same day.

Osteomark (Ostex International Inc., Seattle, WA, ABD) NTx ELISA laboratory kits were used to analyze urine NTx levels. Urine samples kept at room temparature for 12 hours before they were studied. After ELISA tests, values we calculated due to a standart measurement curve from spectrophotometrically detected optic densities. Values are corrected upon urine creatinine values and nM BCE/mM were converted to creatinin's unit.

Treatment and control group patients's urine samples were studied to research the difference between Urine N-telopeptide levels. GraphPad Prisma V.3 statistics package program (GraphPad Software, San Diego, CA, ABD) was used to evaluate the results. In data analyses,descriptive statistical methods (mean, standart deviation) were used. Also Mann-Whitney U test was used to compare two groups and Wilcoxon test was used in two group variance analyses. $P<0.05$ was taken as cut off point of significancy.

Results

There were no significant diffeences between demographic datas of patient groups. ($p>0.05$).

Mean begining urine NTx level for oral risedronate treatment group was 67.8±24.3 nM BCE/mM (distribution 43.7-118) creatinin.After three months of treatment mean urine NTx values were 34.1± 9.4 nM BCE/mm (distribution 19.6-52.7). In this group mean urine N-telopeptide level decreased by %49.7 at the end of three months peri-

od of treatment. This decrease was statistically significant. (p<0.0001).

Mean beginning urine NTx level for control group was 61.7±34.1 nM BCE/mM (distribution 43.4-158). This group's mean urine NTx level at the end of three months was 65.3±37.9 nM BCE/mM (distribution 44.3-172). The mean urine NTx level of control group increased by 5.8%. There was a 8.9% increase in mean urine NTx level in control group, but in three patients (15%) levels decreased by %2.6.

The decrease in born turnover product markers in urines of patients receiving risedronate treatment was found to be statistically significant (p<0.0001).

Discussion

Distal radius, vertebrae, vertebrate and hip fractures are the most common fractures seen in osteoporosis. Commonly no functional problems were expected after treament of distal radius fractures; but height loss with chronic lumber pain are among the problems patients encounter after vertebrae fractures. Only half of the patients with hip fractures can walk without assistance postoperatively and mortality rate in the first year after the fracture is about 20%.[15] In our study, three patients (3/59,%5.1) deceased during the follow up

Oral calcium treatment should be considered in every patient and vitamin D should be added to treatment of patients who have limited exposure to sunlight or can not take adequate amounts of vitamin D with diet or those with malabsorption syndromes. With nasal calcitonin application, %36 decrease in vertebrate fractures were reported.[6]

Studies on RaloxifenE like selective estrogen receptor modulators, 40% decrease in the spinal fracture risk after treatment is reported, but a decrease on the hip or other fracture risk can not be shown.[7] Recently many studies investigating bisphophantes efficacy have been conducted. In FIT study (Fracture Intervention Trial Research) %50 decrease in vertebral and hip fracture risk after treatment with alendronat is reported, [9] in another study vertebral fracture risk decreased by %49 and nonvertebral fracture risk decreased by %39.[10] Today bisphospahnates are accepted as the most effective drugs in the pharmacological treatment of osteoporosis.[16] In our study, risedronat is administered 5mg/day to 26 patients in study group.

Bone turnover markers take role in bone cyclus and a decrease in these markers have an important clinical value in the asssesment of mineral density.[17] Bone turnover markers have an important role in demonstration of response to drug treatment with parathyroid hormone which is attenuated in another study.[18]

Carbonterminal telopeptides,deoxypyridolin and pyridolin are bone turnover markers shown to increase in urines of patients with a fracture history and low bone mineral density.[19] After fractures, in early phase bone turnover marker increases but in the late phase osteoblastic markers increases.[20] In our study aminoterminal telopeptide, a bone turnover marker, increased in the control group which received no risedronate treatment but a significant decrease was seen in treatment group which received risedronate treatment. This outcome shows that risedronate treatment decreases bone turnover markers in a three months of time and it has favorable effects on bone cyclus.

Measuring bone turnover product levels only show bone resorption rate but it does not diagnose osteoporosis. Bone density measurement is still the golden standart for diagnosing osteoporosis. Bone turnover product measurements are sensitive enough to show the changes in bone density at the third month after administration of antiresorptive treatment. There are different ELISA laboratory kits to measure carbonterminal and aminoterminal telopeptides and free deoxypyrdynolin (fDDP) quantities to determine amount of bone turnover (type I collagen turnover products in urine and blood). In our study, we concluded that detection of collagen turnover products in urine is important to visualize short term effects of osteoporosis treatment on patients and evaluate response to treatment.

References

1. Consensus development conference: prophylaxis and treatment of osteoporosis. Am J Med 1991;90:107-10.
2. U.S. Preventive Services Task Force. Screening for osteoporosis in postmenopausal women: recommendations and rationale. Ann Intern Med 2002;137:526-8.
3. Hodgson SF, Watts NB, Bilezikian JP, Clarke BL, Gray TK, Harris DW, et al. American Association of Clinical Endocrinologists medical guidelines for clinical practice for the prevention and treatment of postmenopausal osteoporo-

sis: 2001 edition, with selected updates for 2003. Endocr Pract 2003;9:544-64.
4. North American Menopause Society. Management of postmenopausal osteoporosis: position statement of the North American Menopause Society. Menopause 2002;9:84-101.
5 Reid IR, Ames RW, Evans MC, Gamble GD, Sharpe SJ. Long-term effects of calcium supplementation on bone loss and fractures in postmenopausal women: a randomized controlled trial. Am J Med 1995;98:331-5.
6. Chesnut CH 3rd, Silverman S, Andriano K, Genant H, Gimona A, Harris S, et al. A randomized trial of nasal spray salmon calcitonin in postmenopausal women with established osteoporosis: the prevent recurrence of osteoporotic fractures study. PROOF Study Group. Am J Med 2000;109: 267-76.
7. Ettinger B, Black DM, Mitlak BH, Knickerbocker RK, Nickelsen T, Genant HK, et al. Reduction of vertebral fracture risk in postmenopausal women with osteoporosis treated with raloxifene: results from a 3-year randomized clinical trial. Multiple Outcomes of Raloxifene Evaluation (MORE) Investigators. JAMA 1999;282:637-45.
8. Neer RM, Arnaud CD, Zanchetta JR, Prince R, Gaich GA, Reginster JY, et al. Effect of parathyroid hormone (1-34) on fractures and bone mineral density in postmenopausal women with osteoporosis. N Engl J Med 2001;344:1434-41.
9. Black DM, Cummings SR, Karpf DB, Cauley JA, Thompson DE, Nevitt MC, et al. Randomised trial of effect of alendronate on risk of fracture in women with existing vertebral fractures. Fracture Intervention Trial Research Group. Lancet 1996; 348:1535-41.
10. Harris ST, Watts NB, Genant HK, McKeever CD, Hangartner T, Keller M, et al. Effects of risedronate treatment on vertebral and nonvertebral fractures in women with postmenopausal osteoporosis: a randomized controlled trial. Vertebral Efficacy With Risedronate Therapy (VERT) Study Group. JAMA 1999;282:1344-52.
11. McClung MR, Geusens P, Miller PD, Zippel H, Bensen WG, Roux C, et al. Effect of risedronate on the risk of hip fracture in elderly women. Hip Intervention Program Study Group. N Engl J Med 2001;344:333-40.
12. Chesnut CH. Treating osteoporosis with bisphosphonates and addressing adherence: a review of oral ibandronate. Drugs 2006;66:1351-9.
13. Majkic-Singh N, Ilic M, Ignjatovic S, Aleksandra-Postic-Grujin. Assessment of four biochemical markers of bone metabolism in postmenopausal osteoporosis. Clin Lab 2002; 48:407-13.
14. de la Piedra C, Traba ML, Dominguez Cabrera C, Sosa Henriquez M. New biochemical markers of bone resorption in the study of postmenopausal osteoporosis. Clin Chim Acta 1997;265:225-34.
15. Cooper C, Atkinson EJ, Jacobsen SJ, O'Fallon WM, Melton LJ 3rd. Population-based study of survival after osteoporotic fractures. Am J Epidemiol 1993;137:1001-5.
16. Bauer DC, Garnero P, Hochberg MC, Santora A, Delmas P, Ewing SK, et al. Pretreatment levels of bone turnover and the antifracture efficacy of alendronate: the fracture intervention trial. J Bone Miner Res 2006;21:292-9.
17. Miller PD. Bone density and markers of bone turnover in predicting fracture risk and how changes in these measures predict fracture risk reduction. Curr Osteoporos Rep 2005; 3:103-10.
18. Bauer DC, Garnero P, Bilezikian JP, Greenspan SL, Ensrud KE, Rosen CJ, et al. Short-term changes in bone turnover markers and bone mineral density response to parathyroid hormone in postmenopausal women with osteoporosis. J Clin Endocrinol Metab 2006;91:1370-5.
19. Hoesel LM, Wehr U, Rambeck WA, Schnettler R, Heiss C. Biochemical bone markers are useful to monitor fracture repair. Clin Orthop Relat Res 2005;440:226-32.
20. Veitch SW, Findlay SC, Hamer AJ, Blumsohn A, Eastell R, Ingle BM. Changes in bone mass and bone turnover following tibial shaft fracture. Osteoporos Int 2006;17:364-72.