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The Relationship Between the FRAX Tool and Bone Turnover Markers in Postmenopausal Osteoporosis

Postmenopozal Osteoporozda FRAX ile Belirlenen Kırık Riski ve Kemik Döngüsü Belirteçleri Arasındaki İlişki

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Summary

Aim: In this study, we aimed to show the correlation between the ten-year fracture risk, calculated with FRAX and bone turnover markers (BTM) in a group of postmenopausal women with osteoporosis.

Material and Methods: Twenty-four postmenopausal women diagnosed as osteoporosis were included. Patients were assessed for duration of menopause, secondary diseases, medication, habits of nutrition, previous fracture, and family history of fracture. Weight and height measurements were obtained. Bone mineral density (BMD) was measured by dual-energy X-ray absorptiometry (DXA), with a Hologic-QDR 4500 plus device. The ten-year risk for major as well as hip fractures were calculated with the FRAX tool. Serum calcium, phosphorus, magnesium, 25-OH Vitamin D, parathormone (PTH), alkaline phosphatase (ALP), and biochemical markers of bone formation (Osteocalcin, Bone-ALP) and resorption (N-terminal collagen type 1 and C terminal collagen type 1) were determined.

Results: The mean age of patients was 64.3±8.6 (46-80 years). The mean ten-year major fracture and hip fracture risks were 19.5±6.2% and 16.0±5.1%, respectively. There was a strong correlation between the duration of menopause and hip fracture risk (r: 0.878, p=0.022). There was also a strong relationship between hip fracture risk and NTX (r: 0.759, p=0.042).

Conclusion: Resorption markers of bone turnover are relevant components in determining fracture risk. Rate of bone remodeling is a parameter which is not included in the FRAX tool. Since FRAX is an established tool for assessing the ten-year fracture risk, we assessed and found a correlation between hip fracture risk and NTX. Further studies, in larger groups of patients need to make clear the impact of BTM in this tool. (Turkish Journal of Osteoporosis 2013;19: 38-41)

Key words: Bone turnover markers, fracture risk, FRAX, postmenopausal osteoporosis

Özet

Amaç: Bu çalışmada postmenopozal osteoporozlu kadınlarda FRAX ile hesaplanan 10 yıllık kırık riski ve kemik döngüsü belirteçleri (KDB) arasındaki ilişkiyi araştırdık.

Gereç ve Yöntem: Osteoporoz tanısı konulan 24 postmenopozal kadın çalışmaya dahil edildi. Hastalar menopoz süresi, sekonder hastalıklar, ilaç kullanımı, beslenme durumları, önceki kırık ve ailede geçirilmiş kırık öyküsü yönünden sorgulandı. Boy ve kilo ölçümleri yapıldı. Kemik yoğunluğu ölçümü (KMY) dual enerji X-ray absorbsiyometri yöntemiyle Hologic QDR 4500 cihazı kullanılarak ölçüldü. On yıllık major osteoporotik ve kalça kırık riski FRAX aracıyla hesaplandı. Serum kalsiyum, fosfor, magnezyum, 25-OH vitamin D, parathormon, alkali fosfataz ve kemik yapım (osteokalsin ve kemik-alkali fosfataz) ve yıkım belirteçleri (N-terminal telopeptid kollajen tip 1-NTX ve C-terminal telopeptid kollajen tip 1-CTX) ölçüldü.

Bulgular: Hastaların ortalama yaşı 64,3±8,6 (46-80 yaş) idi. Ortalama 10 yıllık major osteoporotik ve kalça kırık riski % 19,5±6,2 ve % 16,0±5,1 olarak hesaplandı. Menopoz süresi ve kalça kırık riski arasında kuvvetli ilişki saptandı (r: 0,878, p=0,022). Kalça kırık riski ve NTX arasında da kuvvetli bir ilişki saptandı (r: 0,759, p=0,042).

Sonuç: Kemik döngüsünün yıkım belirteçleri kırık riskini belirlemede kullanılmaktadır. Kemik döngüsünün hızı FRAX aracında bulunmayan bir bileşendir. FRAX 10 yıllık kırık riskini değerlendirmek için kullanılan bir araç olarak kullanıldığından biz de kalça kırık riski ve NTX arasındaki ilişkiyi araştırdık ve kuvvetli ilişki saptadık. FRAX aracında kemik döngüsü belirteçlerinin etkisini araştıran daha fazla sayıda hasta içeren çalışmalara ihtiyaç vardır. (Türk Osteoporoz Dergisi 2013;19: 38-41)

Anahtar kelimeler: Kemik döngüsü belirteçleri, Kırık riski, FRAX, postmenopozal osteoporoz

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Introduction

FRAX® is a computer-based algorithm developed by the WHO in 2008. Development of country-specific FRAX tools to estimate fracture probability according to specific countries, provide guidance on fracture probability at which treatment can be recommended (1). The FRACTURK study has shown that it is possible to apply FRAX-based assessment guidelines, tailored to the epidemiology of Turkey (2). In addition to clinical risk factors, determined by FRAX, and bone mineral density (BMD) values, it is well known that increased bone turnover also contributes to fracture risk (3,4) . However, bone turnover markers (BTM) are currently not included in the FRAX for several reasons. BTM are used for assessment of bone turnover (resorption and formation) rate. Bone metabolism cannot be assessed by bone mass.

Potential Advantages of BTM are

• Integrated, dynamic assessment of skeletal metabolism is possible

• Assessment of resorption and formation independently

• Rapid and large changes with medical therapy or without treatment within a few months, before they can be detected by DXA

• Less expensive than DXA (5).

Potential Disadvantages of BTM are

• Cannot distinguish cortical vs. trabecular bone metabolism

• High day-to-day variability (biologic changes);Time of collection and fasting status may change results

• Laboratory variability, poor quality: standardization and harmonization failure

• Inconsistency of normative data; there are even fewer data available in older persons or men.

No standardization between assay devices.

• BTM cannot diagnose osteoporosis (5,6).

There are different BTM, shown in Table-1, among them CTX and NTX are frequently preferred. CTX is an abbreviation for urinary or serum collagen type 1 cross-linked C-telopeptide (CTX). CTX, the carboxy terminal of cross-linked peptide bone type I collagen are sensitive markers of bone resorption in osteolytic diseases such as osteoporosis. NTX is an abbreviation for urinary collagen type 1 cross-linked N-telopeptide. NTX, the amino terminal cross-linked peptide of bone type I collagen, is released during bone resorption (5,7).

In this study, we aimed to show if there is any correlation between the ten-year fracture risk calculated with FRAX and BTM in a group of postmenopausal women with osteoporosis.

Table 1. Biochemical Markers of Bone Turnover

Bone resorption
_ C-telopeptide (CTX)
_ N-telopeptide (NTX)
_ Pyridinoline (PYD)
_ Deoxypyridinoline (DPD)
Bone formation
_ Bone-specific alkaline phosphatase (BSAP)
_ Osteocalcin (OC)
_ Type I collagen C-terminal propeptide (PICP)
_ Type I collagen N-terminal propeptide (PINP)

Materials and Methods

Twenty-four postmenopausal women diagnosed with osteoporosis in the Osteoporosis Outpatient Clinic of the Physical Medicine and Rehabilitation Department of our University Hospital were included in the study. A comprehensive osteoporosis assessment of all patients for duration of menopause, secondary diseases, drug use, nutritional habits, previous fracture, and family history of fracture was performed. Weight and height measurements were obtained for BMI. Bone mineral density (BMD) was measured by dual-energy X-ray absorptiometry (DXA), which was a Hologic-QDR 4500 plus device, in the Nuclear Medicine Department of our University Hospital. The ten- year risk for major fractures, as well as hip fractures were calculated with the FRAX tool according to the Turkish version of FRAX, which was accepted by the WHO. Laboratory evaluation of patients for serum calcium, phosphorus, magnesium, 25-OH Vitamin D, parathormone (PTH), alkaline phosphatase (ALP) levels was performed. Biochemical markers of bone formation by Osteocalcin and Bone-ALP and resorption by N-terminal collagen type 1 (NTX) and C-terminal collagen type 1(CTX) for bone turnover were assessed. Laboratory evaluation of all patients was performed in the Central Laboratory of our University Hospital.

Statistical analyses were performed using the Statistical Package for Social Sciences (SPSS), version 16.0 for Windows. The arithmetic mean and standard deviation of the data were determined. A normalized distribution of the data was produced using the single-sample Kolmogorov–Smirnov test. Potential correlations between age; BMI; duration of menopause; and serum calcium, phosphorus, magnesium, 25-OH Vitamin D, parathormone (PTH), alkaline phosphatase (ALP), NTX and CTX levels were evaluated with Pearson's correlation test.

Table 2. Demographic Characteristics, Laboratory Findings and Fracture risk assessment according to FRAX tool

Age	64.3±8.6
Menopause age	45.4±6.4
Height (cm)	156.7±5.6
BMI (kg/m^2)	26.6±4.6
25 (OH) D3	22.1±20.1
C-telopeptide (CTX)	300.1±80.1
N-telopeptide (NTX)	10.8±4.6
Major fracture risk	19.5±6.2
Hip fracture risk	16±5.1

Correlation coefficients (R) from 1 to 0.5 or -1 to -0.5 were considered to indicate a strong correlation, those from 0.5 to 0.25 or -0.5 to -0.25 were considered to indicate a moderate correlation, and those from 0.25 to 0.1 or -0.25 to -0.1 were considered to indicate a weak correlation. Statistical significance was set at P<0.05.

Results

The mean age of the female postmenopausal patients was 64.3±8.6 (46-80 years). Mean BMI was found to be 26.6±4.6. Mean age at menopause was 45.4 ± 6.4 years. The mean ten-year major fracture and hip fracture risks were 19.5±6.2% and 16.0±5.1%, respectively. 25-OH Vitamin D level was found to be 22.1± 20.1ng/mL. CTX level was 300.1±80.1pg/ml. NTX level was 10.8±4.6 pg/ml. Demographic characteristics, laboratory findings and ten-year major and hip fracture risk assessment according to FRAX tool were demonstrated in Table-2.

In the present study, there was found a strong correlation between the duration of menopause and hip fracture risk (r:0.878, p=0.022). There also was a strong relationship between hip fracture risk and NTX (r:0.759, p=0.042). Correlation between N-telopeptide and hip fracture risk according to FRAX tool were shown in Figure 1 (r:0.759, p=0.042).

Discussion

Several markers have been developed over the past 20 years that are used to reflect the overall rate of bone formation and/or bone resorption. Most are immunoassays using antibodies that recognise specifically a component of bone matrix (type I collagen or non-collagenous proteins) that is released during osteoblastic bone formation or osteoclastic bone resorption. Other assays recognise an enzymatic activity associated with the osteoblast (bone alkaline phosphatase) or the osteoclast (tartrate resistant acid phosphatase). The most informative ones for the monitoring of osteoporosis are procollagen I N-terminal extension peptide (P1NP) for assessing bone formation and

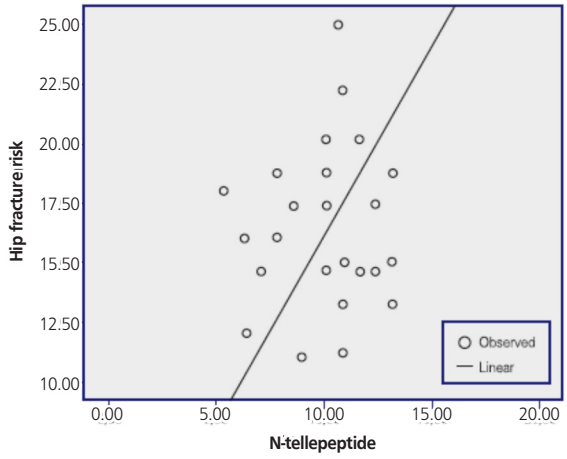

Figure 1. Correlation between N-telopeptide and hip fracture risk according to FRAX tool

C-telopeptide breakdown products (especially serum CTX and NTX) to assess bone resorption (5,8-10). Treatment-induced changes in bone markers are more rapid than changes in BMD and are generally measured 3–6 months after starting treatment. A significant association has been reported between the short-term decrease in markers of bone turnover with the use of different antiresorptive agents and gains in BMD. More importantly, significant associations have been reported between the short-term decrease in markers of bone turnover and the reduction in risk of vertebral and nonvertebral fractures with the use of antiresorptive agents (9,11).

The correlation between old age and increased fracture risk is well documented in many epidemiologic studies (2,12). Menopause is followed by a period of rapid bone resorption, which continues in later years in senile ages. The correlation between years after menopause, denoting elderly females and hip fracture risk was clearly present in this study. 25-OH Vitamin D level was found to be 22.1±-20.1ng/mL. This level was below the accepted optimal level of 30ng/mL, but over the threshold responsible for elevated PTH level causing bone resorption and bone loss leading to increased fracture risk. Low serum

25-OH Vitamin D levels predict increased risk of hip fracture, and the risk increases with decreasing quartiles of serum 25-OH Vitamin D. A consensus is emerging that an ideal level is between 32 and400 ngl/mL, and the minimum desirable level is approximately 30 ng/mL (13).

The mean ten-year major fracture and hip fracture risks were 19.5±6.2% and 16.0±5.1%, respectively. The 10-year probability of hip fracture and a major osteoporotic fracture calculated using the Turkish FRAX model (version 3.6): mean 10-year probability of a major osteoporotic fracture was 8% and of a hip fracture was 3% for women (1-2). Osteoporotic fracture risk was higher in this study, because it included patients followed in an osteoporosis outpatient clinic setting, while the epidemiologic study involved subjects in a wide population setting.

There also was a strong relationship between hip fracture risk and NTX (r:0.759, p=0.042). Serum NTX and CTX are currently considered to be the best indices for the assessment of bone resorption (5). Therefore, use of CTX and NTX is advisable for risk assessment in osteoporotic patients. Bone turnover markers predict a higher risk for fractures 9 years later in elderly (75 years) untreated women (14).

Limitation of this study is the relatively low number of patients and the lack of a control group. More research is required before evidence-based recommendations can be given (9,15).

Conclusion

Resorption markers of bone turnover are relevant components in determining fracture risk. Since FRAX is an established tool in order to evaluate the ten-year fracture risk, further studies in larger groups need to make clear the impact of BTMs in this tool.

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