The applicability of biochemical markers of bone metabolism for predicting the risk of bone fractures and for the assessment of bone tissue resorption in the course of osteoporosis

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Summary

The role of increased metabolism of bone tissue as a risk factor for bone fractures in the course of osteoporosis has been investigated. The importance of the assay of biochemical markers of bone remodelling for determining the degree of bone tissue resorption has been evaluated.

Key words: Biochemical markers of bone remodelling; Osteoporosis; Femoral fracture.

Introduction

The disruption of bone microarchitecture which takes the form of gradual loss of trabeculae in the cancellous bone layer and of porosity in the cortical layer results in deterioration of the mechanical qualities of bone tissue. Another factor which increases bone fragility is the decrease in its density [7].

Bone fractures in the course of osteoporosis are most common among the inhabitants of highly developed countries.

Another important factor determining the risk of osteoporosis is diet, characterised by high consumption of proteins, fats, carbohydrates, salt and low consumption of calcium and fruit. Consumption of alcohol, coffee and smoking also influence the risk of osteoporosis. In more than 25% of women and 10% of men older than 60 years of age, high levels of stress and low sun exposure result in osteoporosis, with all its negative consequences. Physiologically, about 25% of trabecular bone and 5% of compact bone undergoes remodelling [7].

Femoral fracture is the most serious complication of osteoporosis. It is assumed that 5-20% of patients die during the first year following the fracture and more than 50% of the survivors become severely handicapped.

The incidence of femoral fractures in Poland, in the years 1979-1995, ranges between 106.5 and 1,138.1 per 100,000 for women and 60.1 and 85.4 per 100,000 for men. The most frequent cause of fractures involves an accidental fall. The mortality rate for this disease is increasing with age and for people over 80 years of age it reaches 20%. The diagnosis of osteoporosis is preceded by many years of asymptomatic bone degradation. Therefore, more and more resources are being allocated to prophylaxis and early diagnosis of osteoporosis.

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The level of biochemical markers of bone metabolism is a derivative of the intensity of remodelling processes within the whole skeleton at a given time point. The markers are divided into markers of mineralisation and markers of resorption of bone tissue.

Biochemical markers of bone metabolism are substances (or products of their degradation) released into the circulation as a result of the metabolic activity of osteoblasts (bone forming cells) and osteoclasts (bone resorbing cells).

Bone mineralisation marker levels are measured in the serum and include total activity of alkalin phosphatase and activity of its bone isoenzyme, the levels of osteocalcin and type I collagen propeptides [3, 4]. Bone resorption markers are measured in the urine and in the serum and their diagnostic importance is enhanced by the fact that, until now, no reliable methods have been devised for determining the resorption rate in biopsied bone tissue [2, 7]. The most commonly used methods are those of measuring the total urine calcium excretion (as related to creatinine clearance) and the level of total and dialysable hydroxyproline and hydroxylysine. The new currently applied methods include the serum tartrate resistant acid phosphatase (TRAP) assay, carboxyterminal telopeptide (ICTP) assay and pyridinyl and deoxypyridinyI bonds, of type I collagen in the urine assay.

The goal of the study

The study aimed at comparing markers of bone tissue metabolism in women hospitalised due to femoral fractures and a control group of women of corresponding age.

The markers included serum concentrations of osteocalcin (OC) and carboxyterminal telopeptide with cross bonds of type I collagen (ICTP).

Material and Methods

Twenty-three women hospitalised because of femoral fracture were examined. The age averaged at 80.3 years. The control group comprised 15 healthy women, with an average age of 81.7 years.

The biochemical markers of bone metabolism were assayed in the serum of women not later than two days following the fracture. Both groups of women underwent a thorough physical examination and had their history taken to rule out any secondary causes of osteoporosis.

Osteocalcin assay: Osteocalcin was assayed by means of the immunoradiometric assay method with an "ELSA-OSTEO" kit manufactured by "CIS bio international" and the specific monoclonal antibody labelled with radioactive iodide (^{125}I). The results are presented in ng/ml.

ICTP carboxyterminal telopeptide assay: ICTP was assayed by means of immunoradiometric assay with the kit manufactured by Oriona Diagnostica containing (^{125}I) labelled monoclonal antibody. The results are presented in μg/ml.

Statistical methods: For normal distribution of the analysed parameters a norm was not confirmed and the statistical appraisal of differences was employed with the nonparametric Mann-Whitney test. The calculations were conducted in the Department of Medical Statistics in Poznań, using Statistica v. 5.0 software.

Results

In the group of patients hospitalised due to femoral fractures a significantly higher concentration of bone resorption marker (ICTP) was shown, as compared to the control group ($p<0.05$), indicating increased activity of osteoclasts. Average values of ICTP serum concentration for the test and the control group were, respectively, 14.05 μg/l and 6.84 μg/l.

The results are shown in Figure 1.

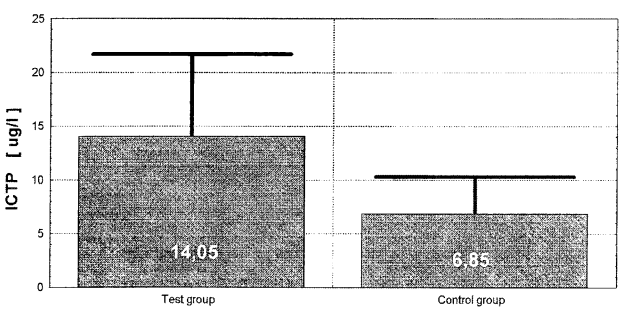

Figure 1. — Comparison between average ICTP telopeptide levels of women hospitalised due to femoral fracture and the control group (n=23 and n=15).

In the test group, a significantly lower concentration of bone mineralisation marker (OC) was shown, indicating a decreased metabolism of osteoblasts, as compared to the control group ($p<0.05$). Average values of OC serum concentration for the test and the control group were, respectively, 27.35 ng/ml and 46.06 ng/ml.

The results are shown in Figure 2.

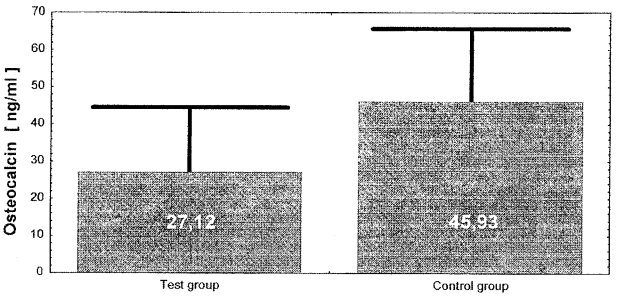

Figure 2. — Comparison between average osteocalcin levels of women hospitalised due to femoral fracture and the control group (n=23 and n=15).

Discussion

There are three indications for determination of biochemical markers of bone metabolism in osteoporosis.

1. Predicting bone mass loss

After menopause, both bone mineralisation and bone resorption are increased, and the increase in the metabolic rate lasts for several years and is observed also in elderly women [5]. A direct relation can be noted between accelerated metabolism of bone tissue and increased loss of bone mass [2]. Garnero suggests that the concentration of bone metabolism rate markers may have a prognostic value with respect to the degree of bone mass loss, thus facilitating the prognosis in the population of postmenopausal women [2, 3].

2. Predicting bone mass changes following treatment

The markers of metabolic rate of bone tissue seem to be a useful element in monitoring the results of treatment aimed at prevention of bone resorption in patients with osteoporosis [5, 6]. Because of the degree of change in bone mass, at least one year is necessary to detect a significant drug action. Marcus believes that assessment of the efficacy of treatment is possible after six months of treatment on the basis of the markers of metabolic rate of bone tissue [5].

3. Predicting fractures

In women with accelerated bone tissue metabolism the rate of bone mass loss is higher which increases the risk of bone fractures.

Garnero, Kleerekoper and Melton reported the results of prospective studies which indicate that the rate of metabolism of bone tissue is also of prognostic value with respect to osteoporotic fractures, independent of the initial bone mass [2, 4, 6]. This holds true particularly for the population with a decreased bone mineralisation. It has also been confirmed in our research. Most data which are prognostic for bone mass loss or for bone fractures come from the individual determination of the markers. From the clinical point of view, it seems advantageous to combine the assays of one marker of mineralisation and one marker of resorption of bone tissue. Marcus suggests

that the accuracy of prognosis may be increased by measuring markers in two or three time intervals [5].

The main disadvantage of markers of bone tissue metabolism assays is that they do not provide information on the activity of single cells and that they do not reflect the process of mineralisation. Moreover, both their serum and urine concentrations may be affected by renal clearance [1]. Error of the currently used methods of bone metabolism rate assays ranges between 5 and 10%.

Assuming a rise of serum and urine markers by 30 - 150%, the assays for detection of ongoing changes and determination of the subpopulations are characterised by a fast, normal or slow metabolic rate of bone tissue. Selecting these groups should become one of the basic elements in osteoporosis prophylaxis.

Conclusions

The results obtained in our study confirm that accelerated metabolism of bone tissue, particularly with respect to increased activity of osteoclasts, coexisting with decreased activity of osteoblasts, increases the risk of fractures in osteoporosis.

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