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MARKERS OF BONE TURNOVER AND BONE MINERAL DENSITY IN MEN OVER 60 YEARS OF AGE

Key words: bone mineral density, markers of bone turnover, elderly, men.

ABSTRACT

The aim of the study was to determine correlations between markers of bone turnover and age in a group of men over 60 years old. The correlations between markers and values of bone mineral density (BMD) and T-score were also measured. Eighty-four community dwelling men over 60 years of age from Poznań were selected for the study. Hip bone mineral density, T-score and markers of bone turnover: osteocalcin (OC) and C-terminal type I collagen (ICTP) were calculated. ICTP was found to be correlated with age in the group of men, and with BMD of men from an older group (over 70 years old). ICTP predicts changes connected with age in bone turnover in elderly men better than osteocalcin. The use of markers of bone turnover should be treated as a medical inspection method in osteoporosis treatment. However, ICTP seems to be a more useful marker in diagnosing changes in bone turnover during rehabilitation or treatment.

INTRODUCTION

After the body reaches the peak bone mass, when the length of bones does not change any more, bone tissue remains in the state of intensive remodelling [25]. In a healthy adult until the fourth decade of life bone mass is in a dynamic balance and bone remodelling makes it possible to repair microscopic damages of the tissue [3]. This phenomenon is a consequence of the constant activity of osteoclasts, which remove bone cells as well as of osteoblasts related to the reconstruction of bone tissue. The processes of bone resorption and bone-formation are on similar levels. However, with the ageing of the body the balance between them is disturbed. Then the rate of resorption processes prevails over the synthesis of bone tissue, which at an older age may be manifested with excessively low bone mineral density (BMD) and an increased risk of fractures [14]. The rate of bone turnover is determined not only by involution processes related to the gonadal dysgenesia, but also depends on other factors, e.g. the level of the subject's physical activity, life style, diet, taken medicines as well as external factors [21, 28].

A sensitive indicator of the state of the skeleton, which allows evaluation of metabolic changes of bone tissue within months and even

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weeks is the assessment of the concentration of biochemical markers of bone turnover in blood serum and in urine [4, 10]. As far as the assessment of the skeletal system in elderly people is concerned a higher rate of bone turnover usually determines lower bone mineral density and indicates a higher risk of fracture [9, 27]. Markers of bone turnover do not indicate, however, the state of bone tissue mineralisation, hence they cannot be used as an individual diagnosis of osteopenia or osteoporosis [11]. Therefore, it is necessary to use a method which allows for a reliable assessment of BMD and estimation of individual fracture risk. Nowadays a good standard is the DXA technique (Dual Energy X-ray Absorptiometry) [16]. In spite of its many advantages DXA does not allow, however, for the assessment of metabolic changes in bone tissue metabolism occurring within a short period of time, e.g. within weeks or months [1, 2, 19]. Thus, it might be useful to apply two methods of assessment of the state of the skeleton at the same time, i.e. the DXA and the assessment of concentration of bone turnover markers [8]. A study of the specificity of relations between BMD and changes in bone turnover markers may allow an additional diagnostics of changes in bone resorption and bone formation.

The aim of the study was to assess changes in the bone turnover markers, which take place with age in elderly men as well as correlations between selected markers of bone turnover (osteocalcin and C-terminal type I collagen) and parameters descrybing the BMD obtained with the use of the DXA method.

METHODS

The material for the study consisted of a group of 84 men aged over 60 years ($\overline{x} = 69.14 \pm 5.97$) from the city of Poznań, Poland (pop. over 500,000). The participants lived in their own homes. The men were divided into two groups: Group A (60.0-70.0 years of age; n=42) and Group B (70.1-82.1 years of age; n=42).

Bone mineral density (BMD) of the thigh bone was measured using an Eclipse – DXA densitometer made by Norland Medical Systems at the Rheumatology and Osteoporosis Ward of the University of Medical Sciences in Poznań. Subject to the measurement was the area of the left hip joint within the neck of the femur – BMD_f. Also the T index was calculated for the BMD of the femoral neck ($T\text{-}score_f$): standard deviation for the mean result for the peak bone mass divided by standard deviation for the mean. T-score is one of the most important diagnostic indicators in osteoporosis diagnosing bone fracture risk [13].

The concentration of markers of bone turnover was assessed in the Department of Hygiene of the University School of Physical Education in Poznań. In order to eliminate the influence of the daily rhythm on the preanalytic changeability, the concentration of markers of bone turnover was determined in samples of venous blood serum taken from the basilica vein, with an empty stomach between 8 and 9 a.m. The concentration of the marker of bone tissue synthesis – osteocalcin (OC) was determined using the ELISA immunoenzymatic method with the test made by Metra Biosystems (USA) and the indicator of bone resorption: C-terminal type I collagen (ICTP) using a radioimmunologic method with the test made by Orion Diagnostica (Finland).

The results of all tests were subjected to statistical analysis. The analysis of significance of differences in the mean values for all parameters in the two studied groups was carried out using the U-Mann-Whitney test. For the assessment of the relation between pairs of parameters Spearman's rank correlation coefficients were calculated.

RESULTS

Positive and statistically significant correlations between age and the ICTP concentration ($R=0.26$; $p<0.05$) were found in the studied subjects (n=84). No significant correlations were noted in the case of values of concentration of the marker of bone formation – OC (Table 1).

Table 1. Spearman's correlation for concentration of C-terminal type I collagen (ICTP) and osteocalcin (OC) with subjects' age in Groups A+B (n=84)

Markers of bone turnover	R
ICTP [μg/l]	0.26 *
OC [ng/ml]	0.19 ^{NS}

^{NS} – statistically non-significant
* $p<0.05$

A comparative analysis (Table 2) between groups A and B indicated significantly higher values of ICTP concentration in group B, i.e. the group of subjects above the age of 70 ($p<0.05$). The mean value of ICTP concentration in group B was higher by 22.9% than the value obtained in group A. No corresponding differences were found as far as OC was concerned.

The markers of bone turnover do not show relations between each other in the studied groups of subjects (Table 4), which indicates a far-reaching specificity and the need to analyse the levels of ICTP and OC separately.

Table 2. Comparative analysis of concentration of markers of bone turnover: C– terminal type I collagen (ICTP) and osteocalcin (OC) between Groups A and B

	($\overline{X}$ ± SD)			
Markers of bone turnover	Group A	Group B	Z	p
ICTP [μg/l]	2.79 ± 0.78	3.43 ± 0.88	–2.42	0.016*
OC [ng/ml]	9.21 ± 3.13	10.08 ± 3.32	–0.95	0.343 NS

NS – statistically insignificant
* $p<0.05$

Table 3. Spearman's correlation between the concentration of C-terminal type I collagen (ICTP) and concentration of osteocalcin (OC) and parameters describing the skeleton, obtained in the DXA examination: T-score$_f$, BMD$_f$

	Groups A+B		Group A		Group B	
Markers of bone turnover	ICTP	OC	ICTP	OC	ICTP	OC
T-score$_f$	–0.18 NS	–0.09 NS	0.11 NS	–0.11 NS	–0.30*	–0.06 NS
BMD$_f$	–0.23*	–0.10 NS	0.07 NS	–0.10 NS	–0.34*	–0.08 NS

NS – statistically non-significant
* $p < 0.05$

Also relations between the concentration of markers of bone turnover – ICTP and OC and selected characteristics describing BMD were analysed (Table 3). Correlations were noted only in the case of the marker of bone resorption ICTP. The values of concentrations of this marker were negatively correlated with the values of bone mineral density determined within the femoral neck (BMD$_f$). These correlations were related to the entire group of subjects (A+B), and the age group B, i.e. people above the age of 70, ($R = –0.23$ and $R = –0.34$, respectively; $p<0.05$). A significant negative correlation was also noted between the concentration of ICTP and the value of T-score$_f$ in Group B ($R = –0.30$; $p<0.05$). No significant correlations were found between OC and the BMD values obtained in the DXA examination.

Table 4. Correlations between the concentration of C–terminal type I collagen (ICTP) and concentration of osteocalcin (OC)

Groups A+B	Group A	Group B
0.15 NS	0.12 NS	0.17 NS

NS – statistically non-significant

DISCUSSION

The biochemical assessment of bone tissue reconstruction is based on the assessment of concentration of markers of bone-forming and bone resorption in blood serum and in urine. Biochemical markers of bone reconstruction are proteins and enzymes which take part in the process of bone tissue synthesis or products of its degra-

dation, secreted to blood during the metabolic activity of osteoblasts and osteoclasts [4].

The consequence of osteoblast stimulation is, among other things, secretion of non-collagen proteins: osteocalcin, osteonectin and osteoprotegerin and sialoproteins, which initiate and regulate the process of bone mineralisation [23]. Osteocalcin in blood serum comes from the fraction of synthesised protein, of which 10-25% is not deposited in the bone matrix but is released to the circulatory system. For the assessment of bone resorption, markers released during degradation of collagen are mainly used [14]. ICTP contained in serum is made up of three cross-linked proteins and secreted to blood during the disintegration of mature type I collagen under the influence of action of metaloproteinases [22]. Changes of the ICTP concentration in blood serum depend on bone metabolism and are correlated with the degree of bone tissue resorption measured histomorphometrically and with other resorption markers [7].

In a study carried out on a large group of men the authors [27] proved that the rate of skeleton reconstruction slowed down significantly after the age of 25, and from the age of 40 to 55-60 years it decreased only to a small extent. In elderly people the concentration of markers of synthesis of bone tissue usually remains on the same level, and the concentration of bone resorption markers slightly increases with age. In another study [20] lowering of the level of markers of synthesis of bone tissue was noted in elderly men and women, whereas in the group of women there was also a fall in the level of markers of bone tissue resorption.

Statistically significant positive correlations between the subjects' age and ICTP concentration ($R=0.26$, $p<0.05$) noted in the authors' own study point to an increase of the concentration of this marker with age. At the same time there is also an increase in the level of degradation of bone tissue and an increase in the risk of osteoporosis and fractures. The comparison of marker concentration between groups A and B in the case of ICTP produced clear differences indicating significant intensification of bone resorption after the age of 70 (Group B). Statistical analysis did not disclose, however, any significant correlations between the level of osteocalcin (OC) and the subjects' age. The obtained results confirm other authors' observations [15, 27] which indicated that the rate of bone degradation was subject to greater changes in the body of an elderly person that the rate of bone formation. Hence, according to those researchers [18] markers of bone resorption have a higher diagnostic value in diagnosing the risk of osteoporosis that the markers of bone formation.

In the authors' own studies negative correlations were noted between bone mineral density measured within femoral neck (BMD_f) and values of ICTP concentration both in the entire group of subjects and in the group of men over 70 years of age (Group B). The other marker of bone turnover – osteocalcin (OC) – did not show any correlation with bone mineral density (measured at femoral neck and on the trochanter of the femur) or to the T-$score_f$. The reason for intensification of changes in BMD and in bone metabolism in people over 70 years of age is not only hypogonadism, or decrease in secretion of the growth hormone, but it can also be involution changes within other organs, e.g. kidneys, alimentary system or the immune system [17]. Physiological changes within the skeleton intensifying with age may be also related to a reduced level of physical activity and infrequent participation of the elderly in everyday activities. The lack of stimulation of bone tissue with movement in physically inactive seniors results in a growing tendency towards demineralisation of bones and an increase in ICTP concentration [5]. Many reports indicate that the level of physical activity decreases with age [12, 24]. After the age of 65, people lose 1% of physical efficiency and approx. 3.5% of lower limb muscle strength per year [26].

The changes (rising and falling) in the concentration of markers of bone turnover and the BMD noted in a 3-month therapeutic programme for elderly women displayed strong correlations between markers of bone turnover (OC and ICTP) and an increase in the number of bone fractures. In this study no beneficial changes in the BMD were noted. The above authors recognise the diagnostic value of the results of markers of bone turnover, which make it possible to detect changes in the skeleton before the changes are possible to observe in a densitometric picture.

In the authors' own study no correlation between the values of ICTP and OC concentration was found. Some authors [27] explain the lack of correlation between the markers of synthesis and resorption of bone tissue with co-existing diseases in the subjects, taking medicines and differences in the method of study (e.g. taking measurements at various times of day or year). It should also be

emphasised that the majority of previous studies of markers of bone turnover usually included groups of perimenopausal women and there are relatively few studies of the population of elderly men [6].

Additionally, the recommendations of the International Society for Clinical Densitometry relating to the DXA method [16] emphasise that the standards related to T-score may be applied in diagnostics of patients of both sexes: in women after menopause and in men after the age of 55. There is still no sufficient evidence to prove that in relation to the diagnostics with the use of markers of bone turnover similar action can be taken, i.e. the same criteria for men and women can be applied [28].

The above results indicate rather limited usefulness of selected markers of bone turnover (OC and ICTP) in screening tests of elderly people, and show that each of the parameters of the markers should be analysed separately on the basis of the current biochemical and medical knowledge. Only the ICTP displayed correlations with the subjects' age (and in older groups also with BMD). Its usefulness in the assessment of bone changes in elderly men seems to be higher than that of bone formation markers.

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