BONE TURNOVER MARKERS IN TUBERCULOUS SPONDYLITIS

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ABSTRACT

A comparative analysis of bone turnover markers in patients with tuberculous spondylitis, nonspecific spondylitis and patients with low back pain due to degenerative diseases of the spine was carried out. The results of the study showed an increased level of ß-CrossLaps due to inflammatory process. The P1NP marker in blood serum exceeds the norm in patients with tuberculous spondylitis due to bone destruction and can be used in the differential diagnosis of tuberculous and pyogenic spondylitis.

Keywords: Tuberculous spondylitis, pyogenic spondylitis, bone turnover markers.

INTRODUCTION

In the structure of tuberculosis disease, bones and joints tuberculosis is the second most frequently occuring pathology after pulmonary tuberculosis, and is the most severe of the chronic infectious diseases. Tuberculous spondylitis (TS) in the structure of osteoarticular tuberculosis takes the first place and ranges from 40 to 82.4% [10], [8].

X-ray, magnetic resonance imaging and multispiral computed tomography methods of examination play a leading role in the diagnosis of destructive bone changes in tuberculous lesions of the spine [11], [5], [4].

Osteoporosis is one of the most frequent and important symptoms of tuberculous lesions of the osteoarticular sistem. The cause of osteoporosis and its course in bone tuberculosis cannot be considered fully clarified in all the details. G.A. Zedgenidze, 1958 considers the phase of focal osteoporosis to be the first phase of tuberculous osteitis, but how this phenomenon is associated with tuberculous inflammation is not clear, at the same time, there is a violent sclerotic reaction from the bone tissue on X-ray in non tuberculous osteomielitis cases [13].

Diagnosis of osteoporosis and osteopenia of any origin is based on the determination of bone mineral density by X-ray absorptiometry. However, the assessment of the intensity of the processes of bone resorption and bone formation is based on the determination of the metabolic products of bone tissue in the patient's blood and urine. Markers determined in blood serum are more accurate, since changes in their indicators by more than 30% are considered clinically significant, in contrast to markers determined in urine, changes in indicators of which even by 50% are not considered clinically significant. The most sensitive and specific markers of changes in bone metabolism are the N-terminal telopeptide (P1NP) and collagen degradation products (β-cross-laps) [3], [1].

The cause of osteoporosis and its course in bone tuberculosis has not been fully clarified.

Purpose

To study changes in markers of bone metabolism in the blood in patients with tuberculous spondylitis.

Materials and research methods

This study is based on the analysis of the results of a comprehensive examination of 91 patients with spinal lesions carried out in the bones and joints tuberculosis department of the Republican Specialized Scientific and Practical Medical Center of Phthisiology and Pulmonology of Ministry of Health of Republic of Uzbekistan.

The patients' age ranged from 17 to 81 years. The average age was equal to 50. There were 53 men (58.2%), 38 women (41.8%).

The examination plan for each patient included a general examination, collecting data about the patient's concomitant diseases simptoms, medication intake, hereditary predisposition to certain diseases, past injuries and their consequences, especially cases of fractures with low energy trauma, functional disorders, and previous operations were clarified. Moreover orthopedic examination and neurological examination were taken. To assess the degree of the inflammatory reaction, the function of internal organs and identify concomitant diseases, all patients underwent laboratory tests to determine hemoglobin, the number of erythrocytes, the color index, the number of leukocytes and leukoformula, as well as the sedimentation rate of erythrocytes and C reactive protein. The biochemical blood test included the determination of liver function by the level of aspartate aminotransferase (AST) and alanine aminotransferase (ALT), total bilirubin, as well as renal function by the level of urea and creatinine in the blood serum. The state of hemostasis was ascertained by determining the hematocrit, prothrombin time, plasma fibrinogen, fibrinogen activity in percent. Investigated the general analysis of urine with the determination of color, transparency, reaction, protein and microscopy of urine sediment with the determination of the cellular composition, as well as the presence of salts, bacteria, fungi and cylinders. Electrocardiography was performed to detect cardiac pathology, echocardiography and MSCT with contrast were performed according to indications. Ultrasound examination of the abdominal cavity and retroperitoneal space in patients complemented the picture with concomitant diseases of internal organs. The study made it possible to assess the size, density and location of anatomical and pathological structures. According to the indications, ultrasound of the pleural cavity, large vessels, thyroid gland and soft tissues was performed. A standard dose of 5 tuberculin units, was injected intradermally and results assessed 72 hours later.

All the patients underwent X-ray, magnetic resonance imaging and multispiral computed tomography.

Bone metabolism, namely the intensity of bone resorption processes, was studied using the ß-CrossLaps marker. CrossLaps markers - formed as a result of the breakdown of type 1 collagen, which constitutes more than 90% of the organic matrix of the bone, measurement of ß-CrossLaps allows you to assess the rate of degradation in relation to old bone, and ά-CrossLaps of newly formed one. The intensity of bone formation was studied based on P1NP - total amino-terminal propeptide of type I procollagen, which is formed during the synthesis of type 1 collagen.

Sputum, fistula discharge, abscess punctates and surgical material were subjected to bacteriological examination; urine, punctates, pleural fluid and feces were examined according

to indications. The methods of bacteriological research were: smear microscopy, molecular genetic analysis of GeneXpert MTB / Rif or HAINtest, followed by automated incubation and cultivation of mycobacterial cultures in a liquid MGIT960 medium on a BACTECMGIT 960 apparatus and Levenstein Jensen media with determination of the sensitivity of mycobacterium tuberculosis to antibiotics.

After the diagnosis was established, the patients received antibiotic therapy. The duration of antibiotic therapy ranged from 3 weeks to 2 months before evaluating the effectiveness of therapy and identifying indications for surgical treatment, indications for surgery were: no positive dynamics for 4-6 weeks on MRI or CT, differential diagnostic cases, as well as patients with negative dynamics of neurological symptoms.

Anterior debridement and radical excision of the disease foci, decompression of the spinal cord according to indications and spondylodesis with an auto-bone graft, or a combination of a titanium mesh cage and an auto-bone graft was perfomed during surgical intervention.

Statistical processing of data was carried out using modern computing systems IBM / PQ of the latest generation using standard Excel programs.

Results

On the basis of a comprehensive examination, the patients are divided on:

- a group of patients with tuberculous spondylitis - 31 patients,
- a group of patients with pyogenic spondylitis -23 patients,
- a group of patients with spine degenerative diseases - 24 patients, each group was additionally subdivided into patients older and younger than 55 years.

In the group of patients with tuberculous spondylitis, the P1NP level varied from 29.38 ng / ml to 420.9 ng / ml, mean 86.53 ± 70.74 ng / ml; at its normal value <58.59 ng / ml. When studying the age difference, it was found that in patients over 55 years old of the same group, the P1NP level varied from 29.4 ng / ml to 120.9 ng / ml, on average 72.6 ± 21.9 ng / ml, in 4(12.9%) patients, the P1NP level remained within the normal range. In the age group under 55 years of age in patients with tuberculous spondylitis, the P1NP level varied from 31.9 ng / ml to 420.9 ng / ml, mean 99.6 ± 95.6 ng / ml, remaining within the normal range in 3 (9,7%) of patients. That is, with the same pathological process, in patients over 55 years old, the rate of bone tissue formation was on average 46% less than in patients under 55 years old. At the same time, the dependence of the P1NP level on the severity of inflammation according to ESR was not observed.

The average ß-CrossLaps level in the group of patients with tuberculous spondylitis exceeded the normal values by 2 times, amounting to 0.88 ± 0.4 ng / ml (from 0.27 g / ml to 1.7 ng / ml) with a norm of <0.394 ng / ml in men, <0.299 ng / ml in women and <0.556 ng / ml in postmenopausal women. At the age of up to 55 years in patients of this group, the average level of ß-CrossLaps was 0.75 ± 0.4 ng / ml (from 0.269 ng / ml to 1.69 ng / ml), and at the age over 55 it was 1 ± 0.3 ng / ml (0.6 ng / ml to 1.74 ng / ml). When analyzing the relationship with other laboratory parameters, it was found that in the age group under 55 years of age, the level of resorption was strongly influenced by the degree of inflammation severity, that is, the correlation between ESR and ß-CrossLaps was equal to r = 0.6; and in the age group over 55, no such association was noted. Thus, the rate of bone resorption in the elderly is 3 times higher than normal, regardless of the severity of the course of specific inflammation. Analysis of the

factors of the development of osteoporosis in the group showed an inverse correlation between the duration of the disease and bone density r = -0.5.

In the group of patients with pyogenic spondylitis, the level of bone formation marker P1NP averaged 36.03 ± 15.1 ng / ml (from 17.4 ng / ml to 67.6 ng / ml). In the age group over 55 years old, the rate of bone tissue formation averaged 37.4 ± 19.4 ng / ml (from 37.4 ng / ml to 67.6 ng / ml), and in patients under 55 years of age with pyogenic spondylitis, the average the P1NP level was 35.4 ± 13.3 ng / ml (from 17.1 ng / ml to 57.6 ng / ml). Thus, the rates of new bone formation were comparatively the same in patients with pyogenic spondylitis older and younger than 55 years old, which signicantly differs from the results of P1NP levels in the tuberculous spondylitis group.

The average value of the rate of bone resorption according to the level of ß-CrossLaps in the group of pyogenic spondylitis was 0.724 ± 0.4 ng / ml (from 0.137 ng / ml to 1.48 ng / ml), in patients older than 55 years the mean ß-CrossLaps in the blood serum was 0.559 ± 0.29 ng / ml (from 0.137 ng / ml to 0.908 ng / ml), and at the age of less than 55 years, the average ß-CrossLaps level in blood serum was 0.796 ± 0.37 ng / ml (from 0.15 ng / ml up to 1.5 ng / ml). At the same time, the correlation between ß-CrossLaps and ESR was r = 0.24 for the entire group, r = 0.27 in patients under 55 years old, and r = 0.45 in patients over 55 years old, respectively. This means that in patients with pyogenic spondylitis over 55 years of age, total bone resorption increases, but less than in patients under 55 years of age, on average by 30%, and the total bone resorption in pyogenic spondylitis patients is always increased.

In the group of patients with degenerative diseases of the spine, the P1NP level was 44.2 ± 13.7 ng / ml (from 10.9 ng / ml to 70.4 ng / ml), in patients older than 55 years of the same group, the P1NP level averaged 38 , 5 ± 14.5 ng / ml (from 10.9 ng / ml to 57.2 ng / ml), in patients with degenerative diseases of the spine younger than 55 years old, the average P1NP level was 47.1 ± 12.8 ng / ml (from 25.7 ng / ml to 70.4 ng / ml). Thus, the rates of bone tissue formation in the group of patients with degenerative diseases of the spine remained within the normal range. The average level of bone resorption in the group of patients with degenerative diseases of the spine was 0.530 ± 0.3 ng / ml (from 0.1 ng / ml to 1.5 ng / ml), in patients over 55 years old ß-CrossLaps = 0.614 ± 0, 4 ng / ml (from 0.28 ng / ml to 1.5 ng / ml), and in patients younger than 55 years old ß-CrossLaps = 0.488 ± 0.2 ng / ml (from 0.1 ng / ml to 1, 1 ng / ml). The rate of bone resorption turned out to be increased in general in the age group over 55, which is quite natural.

DISCUSSION

Osteoporosis is one of the most frequent and important symptoms of tuberculous lesions of the osteoarticular sistem. Diagnosis of osteopenia is essential in the prevention of pathological fractures.

The average level of the marker of bone tissue formation P1NP in the blood serum was higher than normal in the group of patients with tuberculous spondylitis. In the group of patients with pyogenic spondylitis, the level of the P1NP marker in the blood serum was within its normal range. However, in 2 (8.7%) patients from the group with pyogenic spondylitis, the level of the P1NP marker was elevated, a distinctive feature of these patients from other patients in the group was the presence of bone destruction, that is, in other patients in the group there was no bone destruction, and the P1NP values were normal. The P1NP marker in the group of patients with degenerative diseases of the spine remained within the normal range, although in 3 (12.5%)

patients the indicators of this marker were higher than normal, and 2 (8.3%) of them had a concomitant focus of bone destruction visible on tomograms. We concluded that the P1NP marker increases during bone destruction and is a sensitive marker of ongoing destruction, which indicates its value not only in the differential diagnosis of tuberculous and pyogenic spondylitis, but also for determining the activity of a specific process, as well as determining the completion of these processes. The specificity of the P1NP marker in the differential diagnosis of tuberculous and pyogenic spondylitis was 91.7%, the sensitivity was 90.3% in the age group under 55 years old and 87% in patients over 55 years old.

The high percentage of bone destruction in the vertebral bodies in tuberculous spondylitis is explained by the hematogenous spread of tuberculous infection from the lungs during dissemination [6], [115]. Low percentage of bone destruction in pyogenic spondylitis, frequent spread of nonspecific infection in the spine in adults from the intervertebral disc, which is a non-vascular formation sensitive to infection, for example, after paravertebral manipulations, in which, in addition to everything, strong prolonged glucocorticoids are used for low back pain [1], [2].

The process of bone resorption, which we studied on the basis of the ß-CrossLaps marker in the blood serum in the group of patients with tuberculous spondylitis, exceeded normal values 2 times in the group, 1.5 times in relatively young and 3 times in older patients, which corresponded to the rate the formation of new bone tissue (according to the increased P1NP marker levels) following the resorption of old bone tissue, but slowing in the older age group. At the same time, the severity of the course of tuberculous inflammation increased the rate of bone resorption in young patients. The average value of the rate of bone resorption in pyogenic spondylitis was always increased regardless of the severity of the inflammatory reaction, and in the group of patients with degenerative diseases, the rates of bone resorption were generally increased in the age group over 55 years old.

In general, it is necessary to point out that specific and nonspecific inflammation increases the level of bone resorption, which was repeatedly pointed out by various authors [7] and was confirmed in our study, with the only difference that in young people the rates of bone resorption induced by inflammation were higher.

Thus, signs of osteopenia were detected in all groups, and the main factor leading to a decrease in bone mass was the presence of inflammation. The inflammation was chronic in the group of patients with tuberculous spondylitis, in patients with aseptic spondylitis and degenaration, as well as in patients with systemic autoimmune diseases; in patients with pyogenic spondylitis, the nature of the inflammation was acute. In the older age group, the rate of bone mass decrease is the most intense, and the main factor is involution of bone tissue.

CONCLUSION

A decrease in bone mass occurs with tuberculosis infection in a population of patients younger than 55 years old, and in a population older than 55 years, bone mass also decreases, but does not exceed the rate of involution, i.e. senile osteoporosis. Osteoporosis is not only a component of the clinical picture of osteoarticular tuberculosis, but also, due to its high prevalence among people, is often a concomitant disease, especially in older age groups. The marker of bone formation P1NP in blood serum exceeds the norm in patients with tuberculous spondylitis due to bone destruction and can be used in the differential diagnosis of tuberculous and pyogenic spondylitis.

Table. Patients' serum bone turnover markers.

Patients over 55 years					Patients under 55 years				
N	**ESR**	**P1NP**	**β-Cross Laps**	**Bone destruction**	**N**	**ESR**	**P1NP**	**β-CrossLaps**	**Bone destruction**
Pyogenic spondylitis									
N1	37	19,6	0,14	No	N1	19	50,2	0,57	No
N2	20	40,7	0,41	No	N2	20	31,6	0,44	No
N3	7	17,7	0,30	No	N3	35	29,2	0,72	No
N4	39	33,5	0,91	No	N4	13	48,5	0,15	No
N5	46	67,6	0,86	Yes	N5	8	25,6	0,37	No
N6	7	58,7	0,59	Yes	N6	19	25,0	0,46	No
N7	34	24,2	0,71	No	N7	15	34,7	1,1	No
					N8	33	17,1	0,84	No
					N9	3	24,2	0,88	No
					N10	73	26,1	1,15	No
					N11	7	26,2	1,11	No
					N12	28	52,1	1,48	No
					N13	10	28,0	0,38	No
					N14	15	52.8	1,18	No
					N15	9	57,6	1,1	No
					N16	25	54,6	0,82	No
Tuberculous spondylitis									
N1	19	76,7	0,82	Yes	N1	6	420,1	1,18	Yes
N2	5	81,1	1,74	Yes	N2	4	59,9	0,27	Yes
N3	20	57,3	0,63	Yes	N3	3	104,9	0,61	Yes
N4	47	64,4	1,08	Yes	N4	67	87	1,69	Yes
N5	18	95,3	1,28	Yes	N5	39	186,8	1,36	Yes
N6	56	90,2	0,90	Yes	N6	13	78,8	0,7	Yes
N7	17	56,4	1,07	Yes	N7	19	94,7	1,17	Yes
N8	13	62,7	1,33	Yes	N8	11	85,1	0,30	Yes
N9	50	63,1	1,55	Yes	N9	15	31,9	0,54	Yes
N10	46	69,1	0,69	Yes	N10	17	59,8	0,40	Yes
N11	18	62,0	0,99	Yes	N11	33	49,3	0,58	Yes
N12	20	87,3	0,81	Yes	N12	10	64,4	0,80	Yes
N13	41	120,9	0,77	Yes	N13	7	65,9	0,68	No
N14	16	29,4	0,66	Yes	N14	33	65,5	0,51	No
N15	6	57,5	0,72	Yes	N15	28	39,2	0,60	Yes
					N16	28	65,2	0,45	Yes
Spine degenerative deseases									
N1	4	42,5	0,62	No	N1	8	38,3	0,10	No
N2	16	29,8	0,42	No	N2	17	40,2	0,45	No
N3	18	10,9	0,28	No	N3	51	70,4	0,32	No
N4	3	31,2	0,45	No	N4	3	50,2	0,35	No
N5	31	41,5	0,71	No	N5	26	36,1	0,43	No
N6	10	42,8	0,60	No	N6	40	50,6	1,1	No
N7	23	52,1	1,48	No	N7	7	36,8	0,42	No
N8	8	57,2	0,36	No	N8	5	47	0,33	No
					N9	28	64,7	0,84	Yes
					N10	16	37,8	0,73	No
					N11	10	38,7	0,57	No
					N12	10	56,1	0,44	No
					N13	5	38,4	0,30	No
					N14	6	67,2	0,58	Yes
					N15	6	25,7	0,25	No
					N16	30	54,7	0,61	No

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