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Metabolic bone tissue disorders in patients with long bone fractures complicated by chronic osteomyelitis

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Introduction The article deals with a topic of how disorders of bone tissue metabolism affect the treatment outcomes after fractures of long bones complicated by chronic osteomyelitis. **Purpose** To study the feasibility of therapy aimed at correcting metabolic disorders in the bone tissue in patients with long bone fractures complicated by chronic osteomyelitis. **Materials and methods** Assessment of bone metabolic disorders in fractures of long bones complicated by chronic osteomyelitis, and of the effectiveness of treatment involving a combined therapy including surgical, antibacterial and anti-inflammatory treatment, and also a drug correction of the metabolic disorders detected. A retrospective study was conducted with stratified randomization of comparison groups. **Results** Changes in bone remodeling that are specific to this group of patients with increased resorption intensity were identified. In addition, high frequency of secondary hyperparathyroidism and metabolic disorders of the D hormone was observed in the patients with this pathology. The effectiveness of a combination of drugs for the correction of bone tissue metabolism disorders (calcium supplements, ossein-hydroxyapatite complex, active metabolite of vitamin D and bisphosphonate) was evaluated by comparing the terms of consolidation. **Conclusion** Evidence was obtained of a significant reduction in the duration of treatment in the external fixation device by using the combined therapy aimed at correcting bone tissue metabolism.

Keywords: chronic osteomyelitis, osteoporosis, delayed consolidation, anti-resorption therapy, transosseous osteosynthesis

INTRODUCTION

Currently, the rates of post-traumatic osteomyelitis range from 5 to 10 % depending on the fracture location and type [1]. Among the main problems in the treatment of patients with chronic osteomyelitis are:

- long-term consolidation (an average of 4–6 months longer when compared with fractures not complicated by post-traumatic chronic osteomyelitis) [2–4].
- recurrence of the infection process after surgery in 15 to 30 % of patients [5].
- high incidence of patients' disability (50–90 %) [6].

Impaired bone remodeling may be one of the causes of delayed consolidation or nonunion in these patients due to exposure to pro-inflammatory cytokines, even with adequate surgical intervention [7]. At least, it is known that Staphylococcus aureus, in addition to its long-studied invasiveness, has a pronounced negative effect on the balance of bone formation and resorption, as well as on separate links of these mechanisms, namely, osteoblasts (osteogenic link) and osteoclasts (bone destruction link) [7–9]. Moreover, microbial pathogens are able to change and distort the immune response, affecting the balance of interleukins [10]. Deviations in the immune processes, in turn, exacerbate metabolic disorders of bone tissue. Obviously, not only complete surgical debridement, stabilization of the damaged segment, adequate antibacterial and anti-inflammatory therapy but also additional treatment aimed at correcting the disturbed bone tissue metabolism are necessary to optimize the treatment process under the conditions of this inflammatory process.

Level of evidence: II

Purpose To substantiate the expediency of therapy aimed at correcting metabolic bone disorders in patients with long bone fractures complicated by chronic osteomyelitis

MATERIAL AND METHODS

This study was retrospective with stratified randomization of comparison groups. The work includes the results of treatment of 112 patients with fractures of long bones complicated by chronic osteomyelitis (the average duration of the inflammatory process wa37 months). Two groups of patients were compared: the index and the control ones.

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In the index group, the complex treatment included the operative stage, antibacterial, anti-inflammatory therapy and drug correction of metabolic bone disorders.

In the control group, the operative stage, antibacterial and anti-inflammatory treatments were performed.

Stratified randomization was a random inclusion into the indicated groups of patients who were treated at the department of injuries and purulent complications of the locomotor system of the N.N. Priorov institute in the period from July 2017 to August 2018. Due to a small number of patients with disorders of consolidation of the humerus in the main group (6 patients), the initial sample was randomized only to form the corresponding control group with the same total number.

The index group included 56 patients, aged from 27 to 77 years (mean age, 47 ± 13 years), among them 25 women (45 %) and 31 men (55 %).

The control group included 56 patients aged from 29 to 75 years (mean age, 53 ± 12 years). Twenty-six were women (46 %) and 30 men (54 %). Within each group, the distribution of patients according to the damaged segment was: humerus – 6 patients, femur – 25, tibia – 25 people (see Table 1).

The prevailing diagnosis in both groups was a pseudarthrosis complicated by chronic osteomyelitis. Distribution by nosology is shown in Table 2.

Before admission, patients has previous surgeries at other medical institutions: plating in 25 patients (45 %), intramedullary nailing in 15 (27 %), and external fixation was used in 16 cases (28 %) of the main group; in the control group: plating in 30 patients (54 %), intramedullary nailing in 12 (21 %), and external fixation in 14 (25 %).

Upon admission, patients of both groups underwent surgical treatment, including the following stages:

1) removal of metal or dismantling the external fixation device;

2) radical fistulosequestrnecrectomy/sequestrnecrectomy, resection of the nonunion zone with recanalization of the bone marrow canal;

3) biomechanically based re-osteosynthesis taking into account the levers of bone fragments and mechanical (strength and rigidity) properties of external fixation devices [11, 12].

Table 1

Injured segments in the groups studied

	Index group	%	Control group	%
Humerus	6	10.2	6	10.72
Femur	25	44.64	25	44.64
Tibia	25	44.64	25	44.64
Total	**56**	**100.0**	**56**	**100.0**

Table 2

Distribution of patients by nosological criteria after inclusion in the study and their orthopedic status

Diagnosis	Index group				Control group			
	N			%*	N			%*
	WC	ADS	I		WC	ADS	I	
Psedarthrosis complicated by osteomyelitis	33			58.93	32			57.14
	7	20	6#		9	17	6#	
Open infected fracture, complicated by osteomyelitis	5			8.93	4			7.14
	2	3	–		2	2	–	
Nonunion complicated by osteomyelitis	5			8.93	10			17.85
	1	4	–		3	7	–	
Delayed fracture consolidation complicated by osteomyelitis	6			10.71	5			8.92
	2	4	–		2	3	–	
Maluniting fracture complicated by chronic osteomyelitis	4			7.14	3			5.35
	1	3	–		2	1	–	
Consolidating fracture complicated by chronic osteomyelitis	2			3.57	2			3.57
	–	2	–		1	1	–	
Neglected fracture complicated by chronic osteomyelitis	1			1.79	–			–
	–	1	–					
Total	**56**			**100.00**	**56**			**100.00**

Notes: WC – patient moves in a wheelchair; ADS – patient moves with the help of additional support; I – patient moves independently; * – percentage of the total number (excluding orthopedic status) of patients in each subgroup; # – patients with fractures of the humerus

Before surgery, bone tissue metabolism was assessed in patients of both groups. Calcium homeostasis indicators were investigated (blood: total calcium (**Ca**), ionized calcium (**Ca^{++}**), phosphorus (**P**), calcium regulating hormone (parathyroid hormone), 25(OH)D_3 – transport D-hormone, and also bone formation markers (alkaline phosphatase (**AP**), osteocalcin (**OC**) and resorption markers (C-terminal telopeptide of collagen type 1 (**β-Cross Laps**)).

Calcium and phosphorus in daily urine and a resorption marker DPID deoxypyridinium (DPD) (as the ratio of urine deoxypyridinoline to creatinine) were determined. Therapy aimed at correcting the disturbed metabolism and at controlling the effect of therapy on the dynamics of disorders was chosen according to the data obtained in the index group.

Statistical analysis was performed on IBM SPSS Statistics 22 software. For all statistical calculations, the threshold significance level was p = 0.05.

The assessment of the dynamics of bone metabolism markers in the index group was carried out using the Wilcoxon W-test; findings before the operation were compared with those after three months.

To compare the treatment time in the external fixation device, the Mann-Whitney U-test was used, and the duration of transosseous osteosynthesis in two groups (index and control) was compared separately for the same segments (humerus, femur, tibia). The main parameter studied was the term of fixation of the affected segment in the device.

RESULTS

Among the indicators which reflect bone metabolism, the level of vitamin 25 (OH) D3 is of special attention as it averaged 17.79 ng/ml. It was almost 2 times less than the lower normal level (N = 30–100 ng/ml), which, in turn, indicated D-deficiency (11 patients – 20 %) or D-deficit (38 patients – 68 %). DPID level (11.637 nmol/mmol on average) was two times higher than normal values (N = 2.3–5.4) in men and 1.5 times in women (N = 3–7.4). It indicated an increase in the intensity of bone resorption.

The average level of blood calcium was close to the lower normal limit and was 2.29 mmol/l (N = 2.10–2.55), ionized calcium (Ca^{++}) was 1.12 mmol/l (N = 1.03–1.23). The average calcium level in daily urine was 3.1 mmol/day (N = 2.5–7.0); parathyroid hormone level of 12.47 pm/l (N = 1.7–6.4) was higher than normal level and reflected the reaction of the body to deficiency or deficit of D-hormone. The diagnosis of secondary hyperparathyroidism was identified in one third of the patients. Calcium homeostasis and remodeling markers abnormalities are shown in Table 3.

In the postoperative period, the index group was prescribed therapy aimed at correcting identified disorders of bone tissue metabolism, including calcium preparations (calcium carbonate, ossein-hydroxyapatite complex) and an active metabolite of vitamin D (alfacalcidol) to correct D-deficiency and secondary hyperparathyroidism. The dose of these drugs was chosen individually depending on the initial level of blood calcium (RF Patent for invention No. 2176519, dated December 10, 2001) [13].

Table 3

Laboratory test results for markers of impaired metabolic processes in bone tissue (index group, calculation using IBM SPSS Statistics 22 software)

	Parameter					
	Minimum	Maximum	Mean value (M)	Standard deviation (σ)	Normal values	Unit
DPD /creatinine	5	38.38	11.6367	6.44523	2.3–5.4	nmol/mmol creatinine
P in daily urine	10.5	42.45	24.0079	9.55659	12.9–42.0	mmol/day
Ca in daily urine	1	6.34	3.6632	1.53267	2.5–7.0	mmol/day
25(OH)D_3	6.6	40	17.79	10.2238	30–10	ng/ml
parathyroid hormone	1.77	60	12.4647	15.5422	1.7–6.4	pmol/l
Osteocalcin	2	46	22.5509	11.0964	< 46	ng/ml
β-cross-laps	0.086	1.14	0.63271	0.26686	< 0.704	ng/ml
Alkaline phosphatase	60.29	373	123.451	65.6687	53–128	u/l
P in blood	0.72	1.56	1.1861	0.19647	0.78–1.42	mmol/l
(Ca^{++})	0.96	2.2	1.2207	0.19725	1.03–1.23	mmol/l
(Ca) in blood	2.1	2.71	2.425	0.13485	2.10–2.55	mmol/l

In addition, anti-resorptive therapy was prescribed in all cases and aimed at reducing the intensity of bone resorption. As an anti-resorption drug, bisphosphonate (BP) – ibandronic acid in a dose of 3 mg/3 ml was used once every three months.

After three months, an assessment of calcium homeostasis and resorption rates was performed in 18 of 56 patients in the index group. In all cases, a decrease in the level of DPD was observed within 30 % of the initial value, which indicated the presence of an anti-resorption effect.

Prior to the administration of the therapy aimed at correcting disorders of bone tissue metabolism, no differences between groups were determined by laboratory parameters ($p >> 0.05$). When comparing the laboratory data in the index group after 3 months, statistically significant differences were found ($p < 0.05$) in the following parameters:

- osteocalcin ($p = 0.043$);
- parathyroid hormone ($p = 0.043$);
- DPID / creatinine ratio ($p = 0.041$).

Full statistic findings are given in table 4.

Pharmacotherapy in the patients of the index group continued until the formation of a full-fledged callus.

According to the results of the comparison of the duration of treatment in external fixation devices in patients of two groups for the same segments (statistics are given in Table 5 and **Fig. 1**) statistically significant differences were found (in all cases $p < 0.05$): in the index group the consolidation period was significantly shorter.

Table 4

Summary statistics on laboratory findings in the index and control groups

Indicator	Mean value, M ± σ	Range	Unit	p value by comparison*	Threshold value p
Ca – 0 months	2.425 ± 0.135	2.1 – 2.71	mmol/l	0.172	0.05
Ca – 3 months	2.46 ± 0.62	2.38 – 2.63			
Ca^{2+} – 0 months	1.221 ± 0.198	0.96 – 2.2	mmol/l	0.807	
Ca^{2+} – 3 months	1.189 ± 0.051	1.11 – 1.33			
P – 0 months	1.186 ± 0.196	0.72 – 1.56	mmol/l	0.18	
P – 3 months	1.232 ± 0.147	1.03 – 1.39			
AP – 0 months	123.45 ± 65.67	60.29 – 373	u/l	0.893	
AP – 3 months	113.67 ± 24.32	90.00 148			
b-cross-laps – 0 мес.	0.633 ± 0.267	0.086 – 1.14	ng/ml	0.18	
b-cross-laps – 3 months	0.65 ± 0.298	0.18 – 0.99			
Osteocalcin – 0 months	22.55 ± 11.096	2.00 – 46.00	ng/ml	**0.043**	
Osteocalcin – 3 months	24.917 ± 11.465	11.5 – 39.0			
ПТГ – 0 months	12.465 ± 15.542	1.77 – 60.00	pmol/l	**0.043**	
ПТГ – 3 months	2.562 ± 1.032	1.01 – 4.15			
25-OH-D3 – 0 months	17.79 ± 10.224	6.6 – 40.0	ng/ml	0.715	
25-OH-D3 – 3 months	18.96 ± 10.78	5.0 – 33.0			
Ca daily urine – 0 months	3.663 ± 1.533	1.00 – 6.34	mmol/day	0.18	
Ca daily urine – 3 months	2.483 ± 0.819	1.40 – 3.60			
P daily urine – 0 months	24.008 ± 9.557	10.50 – 42.45	mmol/day	0.18	
P daily urine – 3 months	9.878 ± 5.3	3.46 – 17.10			
DPD / creatinine – 0 months	11.637 ± 6.445	5.00 – 38.38	nmol/mmol creatinine	**0.041**	
DPD / creatinine – 3 months	8.596 ± 3.254	3.50 – 17.50			

Notes: 1 – Wilcoxon W-test; 0 month – before surgical treatment; 3 months – 3 months after surgical treatment. Bold font shows statistically significant p values

Table 5

Summary statistics on the timing of consolidation in the index and control groups

Segment	Group	Consolidation term, days M ± σ	Range, days	p value by comparison*	Threshold value p
Humerus	Index	199.834 ± 31.626	147 – 243	0.041	0.05
Humerus	Control	254.167 ± 45.124	196 – 321		
Femur	index	266.84 ± 52.647	190 – 399	0.009	
Femur	Control	338.00 ± 107.173	197 – 559		
Tibia	Index	235.04 ± 49.308	154 – 351	0.041	
Tibia	Control	270.08 ± 61.110	189 – 427		

* – U-Mann-Whitney test

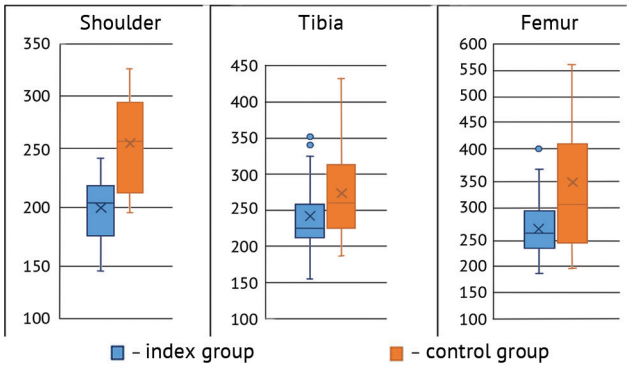

Fig. 1 Interpretation of the obtained results from Table 4 in the boxplot diagram format

Thus, the use of a combination of calcium preparations of alfacalcidol and ibandronic acid in the postoperative period in patients with long bone fractures complicated by chronic osteomyelitis normalizes impaired bone remodeling and shortens the period of consolidation as compared to the control group.

DISCUSSION

Metabolic shifts in chronic osteomyelitis in the patients studied are characterized by a pronounced change in laboratory counts. The key ones are the following:

– alkaline phosphatase (AP) – the enzyme activity correlates with the level of bone tissue formation (a low level reflects a weak activity of osteoblasts, a high level reflects a disorder in bone mineralization, including when the remodeling goes to a high level when resorption is increased);

– β-Cross Laps – a degradation product of type 1 collagen, which comprises more than 90 % of the organic bone matrix;

– osteocalcin – one of the most informative markers of bone formation. It is the main non-collagen bone protein involved in the binding of calcium and hydroxyapatite. It is synthesized by osteoblasts (a high level may indicate increased bone resorption);

– DPID (morning urine) is the main cross-linking material of collagen in bones which reflects the intensity of bone resorption.

The patients showed an increase in the level of alkaline phosphatase (123.45 ± 65.67 with N = 53–128), β-Cross Laps (0.63271 ± 0.267 with N < 0.704), as well as the DPID / creatinine ratio (11.6367 ± 6.445 with N = 2.3–5.4 in men and 3–7.4 in women). These changes indicate an increase in the intensity of bone remodeling, similar to changes in high-speed type of osteoporosis. In our opinion, it can be explained, among other things, by the compensatory reaction of bone tissue, which occurs in response to its destruction by causative agents of chronic osteomyelitis. According to a number of studies [7], Staphylococcus aureus (found in microbiological studies in 35.51–59.1 % of cases) [14–16] induces osteoblast death due to the production of toxins, such as phenol soluble modulins (PSMα, PSMβ) and δ-toxin. Also, inflammatory cytokines (interleukin (IL–1β), tumor necrosis factor (TNF-α), and others) resulting from a prolonged inflammatory process trigger a cascade of biochemical reactions leading to the activation of necrosis or apoptosis in osteoblasts.

On the other hand, it is known about the stimulating effect of Staphylococcus aureus on osteoclastogenesis via enhanced production of membrane-bound RANK-L, sRANK-L (soluble) and small forms of RANK-L. These ligands activate a specific RANK receptor, which is located on osteoclasts and dendritic cells. RANK-L is a major stimulating factor in the formation of mature osteoclasts. At the same time, under the conditions of chronic infection, the production of osteoprotegerins, osteoclast inhibiting (osteoclast-binding) factor which is a key element in inhibiting the differentiation and activation of osteoclasts, decreases. These factors together lead to enhanced osteoclastogenesis, and, consequently, to an increase in bone resorption that runs without adequate replacement [7]. The processes of bone mineralization are disturbed during the cascade of these biochemical reactions [8–9]. Forced hypodynamics and prolonged absence of axial loads on the affected limb lead to an additional decrease in bone mineral density. Severe osteopenia of the affected segment was observed in all patients of the index and control groups.

Low level of vitamin 25 (OH) D3 (17.79 ± 10.223 versus N = 30–100), noted in the observed patients, may be associated with climatic factors, namely, patients live in the climate zone of central Russia [17], as well as with the absence of the official program for the enrichment of products with vitamin D in Russia, except for baby food [18].

The identified metabolic disorders, according to the reports [19–20], are preferably corrected with a complex of preparations (ossein-hydroxyapatite complex and active metabolites of vitamin D). At present, it has also been established that drugs from the group of bisphosphonates should be included in the treatment plan for high rates of bone tissue resorption and no response to the combination of the preparation, which makes it possible to increase the bone mineral density and treatment efficiency as a whole by reducing the resorption rate [21– 22]. Among these drugs, ibandronic acid was chosen, the mechanism of action of which is to inhibit farnisyl diphosphate synthase (FDPS) along the mevalonate pathway, which inhibits the formation of intracellular signaling molecules of osteoclasts and disrupts their vital activity until apoptosis. The advantages of ibandronic acid over alendronic are in the long-term persistence of the drug in the bone tissue, which allows an increase in the interval between injections up to 3 months [23]. Its efficacy in combination with alfacalcidol for increased resorption intensity was previously shown in high-speed systemic osteoporosis [22].

Based on our data, we can conclude that the complex therapy which was applied by us normalized the consolidation process statistically reliably (for the humerus and tibial bones $p = 0.009$, for the femur $p = 0.041$) and reduced the duration of treatment with the external fixation device in patients with long bone fractures complicated by chronic osteomyelitis.

According to the preliminary results, the therapy aimed at correcting metabolic disorders of bone tissue enables, already after three months, to achieve improvements in some laboratory parameters in comparison with the baseline values, and namely, of osteocalcin and parathyroid hormone levels ($p = 0.043$) and DPID/creatinine ratio ($p = 0.041$), which has a positive effect on the mechanisms of bone tissue remodeling. In our opinion, long-term (more than 3 months) observation of the key indicators of bone metabolism is necessary.

CONCLUSIONS

1. Changes in bone metabolism, complicating the course of chronic osteomyelitis, are characterized by an increase in remodeling intensity in most patients, which, on the one hand, is evidence of a compensatory reaction to the processes occurring in the inflammatory focus, but on the other, disturbs the fracture consolidation process.

2. Administration of the therapy aimed at correcting the metabolism of bone tissue in the postoperative period, in addition to adequate surgical intervention, assists in normalizing the terms of consolidation.

3. A comprehensive treatment should be performed in order to obtain an optimal result; and, namely, a surgical component, antibacterial and anti-inflammatory therapy should be combined with correction by medical preparations of disturbed calcium homeostasis, D-deficiency or D-deficit and resorption intensity disorders.

4. It is necessary to further study the influence of metabolic bone disorders on the results of treatment with the method of transosseous osteosynthesis in patients with chronic osteomyelitis, including the search for new frame assemblies that ensure stable fixation of damaged segments and functionality of the limb.

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