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Metabolic Disorders in Patients with Chronic Osteomyelitis: Etiology and Pathogenesis

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Abstract

In this study, we discuss the peculiarities of metabolic disorders that follow the development of chronic osteomyelitis. For the purposes of this study, we analyzed the available data as well as results of our own clinical and scientific research. Chronic osteomyelitis leads not only to the destruction of bone tissue by pathogen but also to the shift of equilibrium between osteogenesis and bone resorption in the locus of bone infections. Such shift leads to additional damage not only to the bone cells (primarily osteoblasts) but also to the bone matrix. The final complications include difficulties with bone consolidation and prolongation of therapy, even when the patient is treated using an external fixation method like Ilizarov or similar techniques. Etiopathogenetic therapy, aimed at correction of metabolic disorders, allows to shorten the bone consolidation time (and respectively, the treatment time), preventing different pathogenetic processes that exacerbate and enhance each other's effects. This study emphasizes the importance of etiopathogenetic therapy of metabolic disorders in patients with chronic osteomyelitis. Etiopathogenetic therapy should be combined with other necessary methods of the patient's treatment, such as surgical debridement of the infection locus and antibiotic therapy.

Keywords: chronic osteomyelitis, metabolic disorders, bone tissue

1. Introduction

The empirical experience of surgeons operating patients with orthopedic infection shows that the mechanical properties of the bone (including strength) differ from physiological ones. The bone in or near the infected area tends to be more fragile and soft. Proper mechanical strength of the bone tissue is one of the key factors for completing successful osteosynthesis as the mechanical strength of the bone directly influences the stability of fixators, treatment of bone tissues in the surgery process, and other technical but pivotal aspects of the treatment.

Despite some empirical data, the change of mechanical properties of the bone in orthopedic infection remained practically unresearched for a long time. The change of the mechanical properties of the bone in inflamed areas had been connected to tissue destruction or lysis caused by bacterial pathogen. In other words, this change of the mechanical properties of the bone happening in the inflamed area was

viewed similarly as the complications in soft tissues in the purulent surgery, widely known for a long period of time.

Consequently, this falsely simplified view of the problem has led to a shortage of publications. For example, the search query in the PubMed database based on Mesh terms “Osteomyelitis” and “Bone mineral density” (latest access time: December 08, 2019, 0:01 UTC +3) has provided only 30 search results, the earliest of them is signed as published in February 1991. Most publications refer to dentistry and maxillofacial surgery but not to traumatology and/or orthopedics. Another search based on Mesh terms “Osteomyelitis” and “Metabolic disorders” (latest access time: December 08, 2019, 0:03 UTC +3) has provided 596 results, but most papers refer to other topics and problems: “combinations” of chronic osteomyelitis and diabetes mellitus [1, 2], chronic osteomyelitis and bisphosphonate-induced necrosis of the jaw [3, 4]; less papers refer to the problem of treating chronic osteomyelitis in patients with genetic, systemic, neuropathic, and oncological diseases [5–8]. In several papers, the accent is put on the clinical aspects of bone infection with particular pathogens only [9–11]. Some papers can be considered of a relatively good quality but the accent is put on clinical results themselves and not on the pathogenesis of metabolic bone tissue disorders in the presence of bone infection [12, 13].

Numerous clinical guidelines and publications on osteoporosis and related disorders have much to offer about the pathophysiology of these diseases, but have a rather serious common disadvantage: they do not describe or poorly describe the interaction of pathogen and bone tissue, although the infectious and purely osteoporotic metabolic processes have similar mechanisms.

Lack of understanding of the metabolic bone tissue disorders as a result of its interaction with bacterial pathogen during orthopedic infection practically eliminated the possibility of providing adequate etiological treatment; in most cases, the treatment methods were limited to surgical treatment (necrectomy, debridement, external fixation, and related methods) and antibiotic therapy. Despite being approved and reliable, these methods themselves are not enough to treat chronic osteomyelitis. The correction of the impaired bone tissue metabolism is also needed. For this purpose, a clinician should be familiar with the aspects of biochemistry, physiology, and pathophysiology of the bone affected by orthopedic infections.

At this moment, several fundamental papers in the domain of bone tissue and pathogen interaction are available [14, 15], which can be evaluated as a positive trend. These works can be useful to systematize the knowledge cumulated by the scientific community.

Within this chapter, we made an attempt to synergize the knowledge in pathophysiology of the disorders described, as well as illustrate the importance of correction of impaired bone tissue metabolism using the results of our own work published in 2019 [16].

2. Pathogenesis of metabolic bone tissue disorders at the site of orthopedic infection

Current views on chronic osteomyelitis allow its understanding not simply as a “bone-lytic” or “infectious” process, but also as a condition associated with bone metabolism alteration. Understanding the nature of these alterations is one of the key points in treating chronic osteomyelitis. Without this understanding, the process of treatment may not succeed or may be less successful even if supported by superb surgery and antibiotic therapy (**Figure 1**).

As an attempt to describe the links between changes in bone tissue metabolism during orthopedic infection, we created a scheme displayed above. From our point of view, deep understanding of the pathogenesis is of paramount importance for a clinician.

3. Osteoblast cell death and proliferation lowering

One of the most obvious effects of bacterial pathogen on a bone tissue is the destruction of osteoblasts.

Destruction of osteoblasts includes necrotic and apoptotic pathways. Papers contributing to the study of *S. aureus*' influence on the osteoblast culture show that these two pathways work independently. Apoptosis is triggered by ligand TRAIL

Figure 2. Pathogenetic stages and processes associated particularly with osteoblast cell death and proliferation lowering. The link between bone matrix destruction processes and associated decrease in osteoblast proliferation rate (will be shown and illustrated in the corresponding part of the chapter).

linking with “death receptors” DR4 and DR5, and necrosis is triggered by *S. aureus* toxins PSM α и PSM β that destroy the osteoblast cell membrane [15, 17, 18].

Lowering of the osteoblast number leads to slowing of ossification and mineralization of the bone. The level of bone resorption can remain stable or be increased at the same time (see “Bone remodeling shift”).

As a result, the production of bone alkaline phosphatase lowers [15]. We must say that alkaline phosphatase itself is not very convenient as a marker: it is produced by different cell types in four different forms. In this case, we have an interest in bone alkaline phosphatase that is coded with ALPL gene [19]. For precise diagnostics, a laboratory should have a specially trained personnel and corresponding equipment. A clinician should note that children and adolescents have normally elevated levels of bone alkaline phosphatase in comparison to adults, and the association between age and serum level of BAP is inverse [20] (**Figure 2**).

Deficit of D hormone is a background factor that lowers ossification and is therefore marked as yellow block [21–23]. It is well known that low level of hormone D leads to increase in PTH level and lowering of bone mineral density [24]. Presence of generalized osteoporosis can additionally intensify this negative trend [25].

4. Bone remodeling (bone turnover) shift

Orthopedic infection and excessive production of pro-inflammatory cytokines [15] influence the bone remodeling balance. Such hyperproduction can be triggered by infection itself and can increase when the pathogen persists inside the osteoblasts. Furthermore, some pathogens can additionally increase the inflammatory response because of paracrine action of their factors, interfering with the cytokine balance [26]. As it will be shown later, the inflammatory response tends to turn into a hyperergic response because of excessive activation of the cell immunity, which is an important factor for chronization of the process.

One of the most well-studied bacterial pathogens that is convenient for illustration is *S. aureus*. Many authors [14, 15, 27] show that *S. aureus* influences both parts of the bone turnover-bone resorption and ossification. During infection, *S. aureus* not only destroys (damages) osteoblasts through necrosis and apoptosis, but also lowers their proliferation rate. Influence on bone resorption is based on rapid maturation and additional activation of the osteoclasts by this pathogen. This mechanism is based on excessive synthesis of prostaglandin E2 (PGE2) by osteoblasts and persisting of *S. aureus* inside the osteoblasts, as well as auto and paracrine regulatory mechanisms in which PGE2 plays its biochemical role. The synthesis of osteoprotegerin (OPG) is also impaired because of lowering of the level of corresponding mRNA; [28] as a result, more RANK-ligand (RANKL) molecules remain unbound and act as osteoclast activators. Excessive activation of the osteoclasts and lowering of the number and proliferation rate of the osteoblasts lead to obvious shift of the bone turnover to bone resorption. As a result, the loss of bone tissue and impairment of its mineralization at the site of orthopedic infection (bone infection) can lead to difficulties in bone consolidation in patients with bone defects and/or fractures (**Figure 3**).

“Red blocks” of this part include the OPG and RANK-ligand (RANKL) level changes.

“Yellow blocks” include the pre-existing low level of the osteoprotegerin. An example is a case of chronic osteomyelitis development in a patient with pre-existing low-speed bone turnover and associated osteoporosis with OPG synthesis impairment.

These markers are rarely used in routine clinical practice but can be of a certain value when an appropriate laboratory is available.

Figure 3.
Pathogenetic stages and processes associated particularly with bone turnover shift.

OPG is a soluble glycoprotein synthesized by different cell types, including osteoblasts [29]. This compound can be found in monomeric (50 kDa) or dimeric (120 kDa) form (the dimeric form contains disulfide bonds between monomers). Dimeric form has a higher affinity to RANKL than a monomeric one, and the chemical analogues of OPG should have the features of dimeric form.

RANKL (RANK-ligand) is a compound synthesized by several cell types. It can be expressed in three different molecular forms: transmembrane trimer, primary (secreted) form, and cell ectodomain [30]. RANKL serves as a ligand for RANK receptor that activates osteoclasts. RANKL is a target for osteoprotegerin; if OPG is secreted in low amounts, more RANKL remains unbound and the intensity of resorption increases.

Therefore, a “pathogenetic chain” is as follows: infection-osteoblast cell death and proliferation rate decrease-OPG synthesis decrease-RANKL inhibition decrease-osteoclastogenesis activation-bone resorption increase-shift of bone remodeling toward a resorption prevalence-decrease in bone tissue quality and quantity in the infection site. The resulting clinical effect is slowing of the consolidation of the bone tissue defects, pseudarthroses, and related conditions.

5. Matrix destruction

The matrix destruction in infection can be explained by several factors. The “starting point” in pathogenesis is the infection itself. *S. aureus* is, as shown by

several authors [14, 31, 32], capable of persisting in osteoblasts and that leads to additional stimulation of inflammatory process that stepwise turns into local hyperergic reaction. It is important to take into account that pathogens also play a role in matrix destruction—particularly *S. aureus* can adhere to matrix elements and destroy them [33].

The hyperergic reaction leads to excessive synthesis of matrix metalloproteases (MMPs). Among them, MMP-2 (gelatinase A) and MMP-9 (gelatinase B) [34] play the main role. Excessive synthesis of MMP is a key point in the process because it has two major effects:

- Osteoblast cell death and lowering of the proliferation rate; this effect weakens the regenerative potential of bone tissue.
- MMPs damage the matrix by themselves, being synthesized in excessive amounts [34, 35].

Figure 4.
Pathogenetic stages and processes associated particularly with bone matrix destruction.

The matrix destruction leads to increase in following resorption markers: B-cross-laps (C-terminal telopeptide) and desoxypyridinoline/creatinine ratio.

- B-cross-laps: This marker is a product of collagen destruction that is a basis of bone tissue matrix. B-cross-laps have two octapeptide fragments in structure, which are linked with a transverse molecular bond. Its level can be evaluated using the immunoassay method [36].
- Increase in the desoxypyridinoline/creatinine ratio: Desoxypyridinoline is a molecular basis for transverse bonds between collagen I type molecules in bone tissue matrix. Its level increases while the matrix is destroyed. It is important to note that this factor can be increased as a result of not only osteoclast activation, but also of a MMP action.

A clinician should note that the destruction of the matrix is combined with lowering of its synthesis by osteoblasts. Therefore, both processes act in a synergic way and occur at the same time, which negatively influences the treatment (**Figure 4**).

6. Background factors

The main background factors that can exacerbate bone tissue metabolism impairment at the site of bone infection are: generalized osteoporosis, D-deficit, D-insufficiency, and secondary hyperparathyreosis. These factors exacerbate also the condition of patients with bone infection, lowering the regenerative potential of bone tissue. On the scheme, these factors are marked as yellow blocks.

- The lack of D hormone leads to lowered absorption of calcium in the intestine, lowered mineralization of the bone, and consequent decrease of the osteoblast function [21–23].
- Secondary hyperparathyreosis: This condition is a result of D-deficit or D-insufficiency and is actually a compensative reaction. It has rather complex pathogenetic action mechanism [37]. It is shown that during short-term increase in PTH level, its influence on bone tissue is anabolic, while during a long-term constant increase, its effect becomes catabolic with bone loss as a result, for example, at the condition of chronic hormone D-deficit or hormone D-insufficiency [37].

Thus, because of the excessive PTH action on bone tissue, two major effects, that can be “found out” using markers, occur [38–40]:

- “Mobilization” of calcium and phosphates from the bones.
- Increase in calcium and phosphate levels in the urine because of relatively high secreted amounts.

As a result, calcium and phosphates are being literally “washed out” of the bone in amounts more than physiological. After that, they are secreted out of the organism through urine. A bright example is an increase in vertebral bodies fractures risk in patients with primary hyperparathyreosis. Even simple densitometry can help to diagnose the lowered bone density and trabecular thinning.

Removal of calcium and phosphates exceeds not only the physiological values or amounts, but also the compensative intake with the food leading to progressive lowering of bone tissue quality in general and its mineralization in particular. To cope successfully with these changes, the secondary parathyreosis should be treated and compensative therapy, including calcium, phosphates, and hormone D medication, introduced.

7. Summary of scheme review

In this part of the chapter, the etiopathogenetic mechanisms of bone tissue metabolism impairment are discussed, as well as reasons for change of laboratory-measured bone metabolism markers and their levels.

The mentioned markers have a direct link with metabolic impairments of a certain type. Such impairments can be found in different diseases, especially in patients with chronic osteomyelitis and other forms of bone infection.

The therapy of metabolic bone tissue impairments due to bone (orthopedic) infection should combine etiopathogenetic and compensating approaches. For example, bisphosphonates can be recommended for use in addition to antibiotic therapy and surgery, as well as calcium, D hormone, and other drugs because of the bisphosphonates' ability to decrease the osteoclasts' activity.

8. Our experience

Nowadays, the published data on epidemiology of metabolic diseases in healthy volunteers and orthopedic patients without bone infection (except patients with osteoporosis and related diseases) are scarce. Therefore, these data cannot serve as statistical material for comparison with data in patients with bone infection.

Accordingly, our work is limited to patients with bone infection (chronic osteomyelitis and related diseases) already diagnosed. The dynamics of the parameters was studied with addition of metabolic disorders therapy and without it.

In 2019, we published a retrospective study; the aim was to evaluate dynamics and values of markers and parameters of bone metabolism [16], which included 112 patients with infected pseudarthroses of long bones (humerus, femur, tibia) developing as an exacerbation of chronic osteomyelitis. The study had three main purposes:

- Gaining the whole “picture” of metabolic bone tissue disorders in these patients.
- Studying the dynamics of corresponding marker level and parameters.
- Comparing the duration of consolidation of pseudarthroses after surgical treatment, antibiotic treatment, and using external fixation apparatus (with and without bone metabolism correction therapy).

We formed two groups of 56 patients each using anatomical segment-stratified randomization. The main group received not only surgery and antibiotic therapy but also medication for correction of impaired bone metabolism. The control group received the same therapy except correction of bone metabolism.

The dynamics of parameters was evaluated only in the main study group. Data from the control group patients were used to evaluate the duration of bone consolidation and comparing them between groups.

To form a “picture” of a bone tissue metabolism, we evaluated the following parameters:

- Homeostasis of Ca and P-values: blood Ca, ionized Ca, blood P, PTH, transportation form of D hormone (25(OH)D3).
- Ossification markers: bone alkaline phosphatase, osteocalcin.
- Resorption markers: beta-cross-laps (C-terminal telopeptide).
- Ca and P (daily amount secreted with urine); deoxypyridinoline/creatinine ratio.

For therapy, we used calcium medicaments (Ca carbonate, ossein-hydroxyapatite complex) and active metabolite of D hormone (alfacalcidol). Dosage was set individually for each patient according to a patented way [41] on the basis of the following key parameters:

- Sex and age.
- Densitometry results.
- Values of the parameters listed above.

As an anti-resorptive drug, the ibandronate acid was administered (with the dosage of 3 mg (3 ml) one time in 3 months).

The described therapy was empirically proved to be effective not only against osteoporosis in patients that underwent arthroplasty but also in cases of osteoporosis connected with low intensity of ossification; that was the key reason why it was selected for treatment.

The numerical data of patients are described using descriptive statistics. To compare the changes in metabolic values after 3 months and before treatment, we used the Wilcoxon test. To compare the consolidation duration in main and control groups, we used Mann-Whitney U-test. The threshold p-value in all cases was set as $p < 0.05$. The software used was IBM SPSS Statistics 22. All values, including theoretically possible outliers, were considered in the statistics (**Table 1** and **Figure 5**).

Routine screening of the whole population described above exceeds the ranks of this study.

We found statistically significant changes after 3 months in osteocalcin level (decrease), PTH (decrease), and desoxypyridinoline/creatinine ratio (decrease) (respectively: $p = 0.043$, $p = 0.043$, $p = 0.041$). Changes in daily amounts of calcium and phosphate secreted with urine, as well as beta-cross-laps were not statistically significant but, in our opinion, the follow-up tie of 3 months can be insufficient. We suppose that the following mechanisms can take part in forming this “picture”:

- Lowering of the resorption because of ibandronic acid use leads to decrease in desoxypyridinoline/creatinine ratio.

Metabolic marker	Value ¹ , median ± SD	Range ¹	Units	Test p-value ²	Threshold p-value	Plot ³
Ca—0 months ⁴	2.4 ± 0.1	2.1–2.71	mmol/l	0.172	0.05	A
Ca—3 months ⁵	2.5 ± 0.6	2.38–2.63				
P—0 months	1.2 ± 0.2	0.7–1.6	mmol/l	0.180		B
P—3 months	1.2 ± 0.147	1.0–1.39				
Ca ²⁺ —0 months	1.2 ± 0.2	0.96–2.2	mmol/l	0.807		C
Ca ²⁺ —3 months	1.2 ± 0.1	1.11–1.33				
Bone alkaline phosphatase—0 months	123.5 ± 65.7	60.3–373.0	U/l	0.893		D
Bone alkaline phosphatase—3 months	113.7 ± 24.3	90.0–148.0				
B-cross-laps—0 months	0.7 ± 0.3	0.1–1.1	ng/ml	0.18		E
B-cross-laps—3 months	0.7 ± 0.3	0.2–1.0				
Osteocalcin—0 months	22.6 ± 11.1	2.0–46.0	ng/ml	0.043		F
Osteocalcin—3 months	24.9 ± 11.5	11.5–39.0				
PTH—0 months	12.5 ± 15.5	1.8–60.0	mol/l	0.043		G
PTH—3 months	2.6 ± 1.0	1.0–4.2				
P (urine, day amount)—0 months	24.0 ± 9.6	10.50–42.5	mmol/day	0.180		H
P (urine, day amount)—3 months	9.9 ± 5.3	3.5–17.1				
25-OH-D3—0 months	17.8 ± 10.2	6.6–40.0	ng/ml	0.715		I
25-OH-D3—3 months	19.0 ± 10.8	5.0–33.0				
Deoxypyridinoline/creatinine—0 months	11.6 ± 6.4	5.0–38.4	nmol/ mmol Cre	0.041		J
Deoxypyridinoline/creatinine—3 months	8.6 ± 3.3	3.5–17.5				
Ca (urine, day amount)—0 months	3.7 ± 1.5	1.00–6.34	mmol/day	0.180		K
Ca (urine, day amount)—3 months	2.5 ± 0.8	1.4–3.6				

Data represent the study group (56 patients). Control group is quantitatively equal (56 patients).
¹Rounded to first decimal place.
²Wilcoxon signed-rank test. Values are rounded to the third decimal place.
³Letters represent the particular plots at **Figure 5A-K** for the information to be easily followed.
⁴0 months—value before operative treatment.
⁵3 months—value at 3 months after the operative treatment.
Statistically significant values ($p < 0.05$) are labeled as bold.

Table 1.
Comparative data of patients before and after 3-month therapy of metabolic bone disorders.

- Decrease in osteocalcin level can be explained by lowering of the earlier increased (in a compensative way) osteoblast activity that at least partially normalized.
- Decrease of PTH level can be explained by administration of D hormone and elimination of D deficit, which also led to decrease in blood calcium. In other words, the immediate mechanism of secondary hyperparathyreosis was eliminated.

Figure 5. (A-K) “Box and whiskers” plots illustrating the data provided in **Table 1**. Blue box and whiskers (left at all figures) represent data of patients before therapy. Orange boxes and whiskers represent data of the same patients after 3 months of therapy. A: blood calcium. B: phosphate of the blood. C: ionized calcium, D: bone alkaline phosphatase levels, E: beta-cross-laps (C-terminal telopeptide), F: osteocalcin, G: PTH. H: phosphate (urine, day amount), I: 25 (OH) D3, J: deoxyypyridinoline/creatinine, K: calcium (urine, daily amount). Units: see **Table 1**.

- Decrease of Ca and phosphates in blood and their daily amounts secreted with urine is not statistically significant at 3-month follow-up ($p = 0.172$ for Ca, $p = 0.18$ for phosphates, $p = 0.18$ for both daily secreted amounts of Ca and phosphates in urine), but we can potentially explain these changes as an effect—even statistically insignificant—of PTH level decrease (partial normalization).

The rationale of metabolic bone tissue impairment correction is proved by clinical results (decrease of fracture consolidation type in the main group that received corresponding therapy). In each group (56 patients), the “anatomical distribution” of patients according to a treated segment was as follows:

- Humerus—6 patients
- Femur—25 patients
- Tibia—25 patients

The software used was SPSS Statistics 22. All values, including theoretically possible outliers, were considered in the statistics. Statistically significant changes between groups were found in all studied segments (**Table 2** and **Figure 6**).

As shown, the additional therapy of metabolic disorders of bone tissue has a statistically significant effect on shortening the duration of bone consolidation in patients treated by external fixation apparatus.

In our opinion, the next step should be a comparative analysis of bone metabolism aspects in orthopedic patients with and without bone infection and a study of the dynamics of mentioned parameters during a long follow-up period (more than 3 months).

Anatomical segment/study group	No. of patients	Consolidation duration ¹ , days, mean $\pm$ SD	Range	Test p-value ²	Threshold p-value	Plot ³
Humerus, main group	6	199.9 $\pm$ 31.6	147–243	0.041	0.05	A
Humerus, control group	6	254.2 $\pm$ 45.1	196–321			
Femur, main group	25	266.9 $\pm$ 52.7	190–399	0.009		B
Femur, control group	25	338.0 $\pm$ 107.1	197–559			
Tibia, main group	25	235.0 $\pm$ 49.3	154–351	0.041		C
Tibia, control group	25	270.0 $\pm$ 61.1	189–427			

Both groups received “standard” surgery and antibiotic therapy.

¹Rounded to first decimal place.

²Mann-Whitney U-test. Values are rounded to the third decimal place.

³Letters represent particular plots in **Figure 6A–C**.

Table 2.
Comparison of consolidation time in patients with (main group) or without (control group) bone tissue metabolism correction therapy.

Figure 6. (a-c) “Box-and-whiskers” plots illustrating the duration (in days) of bone consolidation in patients that underwent treatment of the fractures of different segments exacerbated by orthopedic infection using the external fixation apparatus. Left (a): humerus; in the middle (b): femur; right (c): tibia. Blue box and whiskers (at the left at all figures) represent data for the main study group that received surgery, antibiotic and etiologic metabolism impairment therapy; red box and whiskers (at the right at all figures) represent the control group that received surgery and antibiotic therapy, but no treatment of bone metabolism impairment.

9. Conclusion

In this chapter, we attempted to describe the basic pathophysiology of metabolic processes at the site of orthopedic infection. Knowledge of peculiarities of such processes is important for an orthopedic surgeon because the general success of treatment relies not only on surgery and antibiotic therapy but also etiologic therapy of bone metabolism impairment. This thesis is supported not only by pathophysiological rationale but also by the results of our study.

Metabolic disorders of bone tissue associated with orthopedic infection are complex and yet poorly understood. Research of this topic will improve not only the existing treatment strategy but also the philosophy of it and will greatly contribute to development of traumatology and orthopedics.

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