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Results of Application of Traditional Methods for Predicting Impairments of Bone Regeneration in Closed Fractures of Tubular Bones

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Abstract: While traditional tests are sensitive to nonspecific wound infections in the early stages after surgery, in the long term they transform into the process of allergization. This can be confirmed by the dynamics of the specificity of LIB, the severity of which increases with the onset of long-term periods of treatment for a fracture of long bones, which indicates the need for a more in-depth study of the immunological aspects of both the cellular and humoral links, which will most likely allow optimizing the method for predicting impaired regeneration of long bone fractures. tubular bones.

Keywords: Закрытый перелом, трубчатая кость, прогнозирование, регенерация

Relevance. It is believed that a violation of bone regeneration in closed fractures of tubular bones, leading to the formation of a false joint, occurs in about 2% of all fractures, but with certain injuries this violation can reach 20% with certain injuries (1,3,5,7,18,20)_.

The main problems associated with impaired bone regeneration in closed fractures of tubular bones are associated with prolonged pain syndrome, loss of limb function and mental stress conditions. The financial consequences can often be significant for patients due to the loss of potential earnings and estimated medical costs of up to £79,000 per case. Most often, a violation of bone regeneration, leading to the formation of a false joint, occurs with fractures of the bones of the forearm, humerus, tibia, collarbone and femur (2,4,6,8,26).

There is information regarding the controlled role of cytokines in the process of bone regeneration. Specific morphogenetic proteins and cytokines of tumor necrosis factor (in particular β) determine the process of bone regeneration (9,11,13,15,17,22,24).

In all cytokines, bone morphogenetic proteins, which are the largest subfamily of the TGF-β superfamily, are the most commonly used growth factors because they are already present in bone tissue and are reported to be necessary for fetal tissue development and fracture repair.TGF-β itself is also known as an important growth factor in the regulation of osteoblastic and osteoclastic activity, which is an important process of bone homeostasis and remodeling (10,12,14,16,18,28).

The IGF-β, TGF-β and bone morphogenetic proteins families are subfamilies of the TGF-β superfamily. It is known that members of the TGF-β superfamily are produced by osteoblasts and other bone cells, and they are abundant in the bone matrix. They are also known to stimulate the proliferation and differentiation of osteoblasts in vitro, bone formation with external administration in vivo, as well as cell migration, survival differentiation, proliferation of osteoprogenes, early differentiation, adherence to the osteoblastic line through the TGF-β family (19,21,23,25,27).

Thus, the importance of immunological aspects of predicting bone regeneration disorders in closed fractures of tubular bones, at the present level, is becoming relevant, both on fundamental issues and applied ones that affect the outcome of treatment in general.

The purpose of the study: to study the results of the application of traditional methods for predicting bone regeneration in patients with closed fractures of tubular bones.

1. Material and Methods

The studies were conducted in patients treated at the Samarkand regional branch of the Republican Scientific and Practical Center of Traumatology and Orthopedics of the Ministry of Health of the Republic of Uzbekistan in the period 2017-2019. The study group included 114 patients with closed fractures of long tubular bones, in whom traditional methods based on visual control of the process of bone marrow formation according to radiographs and ultrasound, as well as indicators of leukocyte blood reaction were used to predict bone regeneration disorders. The criteria for inclusion of patients in the study were: age of patients from 18 to 70 years; closed fracture of the femur or tibia; absence of concomitant diseases from the musculoskeletal system; absence of concomitant diseases in the acute stage; absence of local complications of bone fractures (damage to blood vessels and nerves); absence of general complications of bone fractures (traumatic shock, fatty embolism and thromboembolism); the use of surgical methods of treatment. The criteria for excluding patients from the study were: the age of patients younger than 18 years or older than 70 years; open and complex fractures of the femur or tibia; the presence of concomitant diseases of the musculoskeletal system; the presence of concomitant diseases in the acute stage; complicated fractures; the use of conservative treatment methods.

2. The results and their discussion

In patients after extramedullary osteosynthesis in the early postoperative period (1-3 days), ultrasound examination of the fracture zone revealed the presence of interruption of periosteal echoes 2-4 mm in size in the direction of the fracture line. Edema of all layers was observed in the soft tissues around the fracture zone, but to a greater extent in subcutaneous fat. Compared with healthy areas of soft tissues, soft tissues in the fracture zone had an intermittent character, which were combined with high and low signals of echogenic path formation. There were no signs of blood accumulation in the fracture zone and in the area of the postoperative wound. The extramedullary structure for osteosynthesis is visualized in full contour, with smooth edges. The presence of small vessels with their different types is traced.

In a subgroup of patients with intramedullary osteosynthesis, an interruption of a high sound signal in the periosteal zone was detected. In most cases, it was variable in the form of steps. The area of the fracture line is traced by a linear image with jagged contours. The furrow of the fracture line, between the clearly traceable bone ends, has a regular shape with a thickness of 2.1 ± 0.4 cm. Fragments of fractures of increased echogenicity located around the fracture line averaged up to 28.1±1.2 mm in volume. Their shape was not even, which is usually considered characteristic of bone fragments. The contours of soft tissues, especially in the area around the bone fracture zone, do not have clear boundaries. The structure of the soft tissues is not uniform, edematous. Areas of formed hematomas were visualized between the muscles and in the bone fracture zone. Their boundaries were clearly traced, however, in some cases it was possible to notice the spread of accumulated blood at a short distance into the intermuscular space. Ultrasound assessment of the blood supply in the fracture zone showed no signs of angiogenesis.

During 7-10 days after surgery, ultrasound examination of the fracture zone showed no fundamental differences compared to the previous period, except for a local increase in the number of microvessels by 1.8 times in patients with extramedullary osteosynthesis and 2.6 times in patients with intramedullary osteosynthesis. The blood flow through these vessels in patients with extramedullary osteosynthesis, compared with the previous period, indicated the achievement of relative maturity. This sign was considered as a positive dynamics of changes, which differed from the visual data in patients with extramedullary osteosynthesis. We considered this feature as the formation of primary bone fusion. Externally, the local pattern of the skin was characterized by obvious hyperemia, which was associated with vascular germination and restoration of microcirculation in the fracture zone.

3 months after the operation, the bone groove was not visualized both in the fracture zone and in the area of bone fragments. The bone density acquired the same character. Vascular localization decreased. In a number of patients, signs of callus formation could be detected. This pattern was characterized by a decrease in echogenic signals, the periosteal part of the callus had a linear shape. It could completely cover the fracture zone and spread both above and below the structure.

Starting from 6 months after surgery and in the subsequent period up to 1 year, the changes were identical in both patients with extramedullary and intramedullary osteosynthesis. The bone callus in the fracture zone

acquired a continuous character of echogenicity throughout. In patients with intramedullary osteosynthesis, density increased in the area of callus formation against the background of a decrease in the number of germinating vessels.
In the long term, the callus overlapped the defect area throughout. This type of echogenic changes was typical for patients with a normal course of the regenerative process.
Thus, visual control of bone regeneration in patients with fractures of tubular bones revealed the division of the process into 2 phases. The first phase of the regenerative process was characterized by the prevalence of vascular changes, which were more manifested both by their formation and active growth. At the same time, the growth activity depended on the type of osteosynthesis. Extramedullary osteosynthesis, due to the extended preservation of the bone marrow, was manifested by a greater activity of angiogenesis. The second phase of regenerative processes was characterized by a decrease in the process of angiogenesis with the predominance of the process of bone marrow formation. In this phase, there was an increase in bone density.
However, in patients with delayed bone regeneration, the process of vascular formation followed by their germination in the fracture zone in the early stages after surgery was delayed 2-3 times longer. Such processes were characterized by a low number of vessels in the bone growth zone and the preservation of soft tissue edema with loss of differentiation of structural components. We will describe these changes in more detail below.

Naturally, not everyone had a stable postoperative period during the treatment process. Among the patients of the control group, we identified patients in subgroups whose postoperative period proceeded with certain complications that affected the timing of the stages we identified in the form of: acute circulatory disorders, periosteal reaction and vascularization in the fracture zone, formation of bone-cartilaginous corns and formation of bone corns.

We identified 3 subgroups out of 114 patients. The first subgroup included 52 (45.6%) patients whose postoperative period proceeded without any local complications.
The second subgroup included 48 (42.1%) patients who had a complication in the form of postoperative wound suppuration, contact and/or spoke osteomyelitis during the treatment, but bone regeneration occurred without additional (reconstructive) surgical intervention.
The third subgroup included 14 (12.3%) patients who developed a purulent-inflammatory complication of the bone and in the process of regeneration, patients developed unsatisfactory results (false joint, improperly fused fracture, non-fused fracture), who required repeated reconstructive surgery.
The average duration of the course of the regeneration stages of a tubular bone fracture is shown in Table 1.
Table 1.

The timing of the stages of bone regeneration among patients of various subgroups

NAME OF STAGES (day)	SUBGROUPS OF PATIENTS		
	I	II	III
Acute circulatory disorders	5,4±2,1	10,7±3,1	17,8±3,9
Periosteal reaction and vascularization in the fracture zone	25,8±3,5	42,3±12,9	73,6±18,3
Formation of bone-cartilaginous callus	67,9±12,5	105,9±25,4	154,2±22,8
Formation of a bone callus	121±29,3	172,3±21,9	215,4±21,1

In the first subgroup of patients, the longest period was noted by us at the stage of bone marrow formation with a relatively pronounced confidence interval.
In the second and third subgroups of patients, the highest variability of the confidence interval was noted at the stage of bone-cartilaginous callus formation, respectively.
The shortest confidence interval in the last stage of tubular bone regeneration was noted by us among patients in whom the treatment process was completed without an overgrown bone fracture. In all other stages of bone regeneration, patients of the first subgroup accounted for.
Thus, the analysis of visual control of bone regeneration after a fracture allows you to structure the stages of this process. The method is effective for controlling the dynamics of the process. However, the possibilities of this method for forecasting are limited, since the basis of the ongoing regeneration processes is determined by the timing. In other words, having statistical information about the timing of the changes that are taking place, we can only state the fact that has happened, but in no way predict.

The analysis of the nature of changes in the leukocyte blood reaction in patients in the control group was carried out according to protocols of generally accepted standards. The number of not only leukocytes, but also their main fractions (neutrophils, monocytes, lymphocytes) was estimated.
In the first subgroup of patients with a normal outcome of the course of reparative processes after a closed fracture of tubular bones, we noted the peak of high values of leukocytes in the blood on day 10 (5.68; 9.74) and 3 months after surgery – table 2. The intermediate period between these two terms had a relatively low confidence interval of values.
Analysis of changes in the nature of leukocyte fractions in patients of the first subgroup revealed high values of neutrophil cells for a 3-6-month period, respectively). At the same time, the minimum value of confidence intervals was revealed in patients upon admission, and the maximum value was found for 3 months of treatment.
Table 2.

The nature of changes in the dynamics of the leukocyte blood reaction in patients of the first subgroup

DYNAMICS	LEUKOCYTE BLOOD CELLS ($x10^9/_l$)			
	Neutrophils	Lymphocytes	Monocytes	White blood cells
Upon admission	4,21±0,52	1,96±0,11	0,52±0,09	7,15±1,98
, 3 days	4,27±0,49	1,63±0,08	0,43±0,05	6,51±1,46
10 days	4,49±0,33	2,15±0,19	0,67±0,08	7,71±2,03
1 month	4,57±0,28	2,22±0,27	0,48±0,03	7,47±1,84
3 months	4,75±0,14	2,17±0,23	0,50±0,04	7,63±1,77
6 months	4,64±0,16	2,10±0,19	0,39±0,03	7,32±1,48
12 months	4,19±0,21	2,08±0,15	0,37±0,04	6,81±1,28

*$p<0.05$ – significantly relative to the time when the patient was admitted to the clinic
High values of lymphocytes occurred during the period of 1 month of treatment, and the minimum values occurred on the 3rd day after surgery. As for monocytes, the maximum peak increase occurred on the 10th day after surgery (0.59; 0.75), and the minimum one year after surgery (0.33; 0.41).
The percentage of leukocyte fractions was characterized by relative neutrophilesis (65.6%) on the 3rd day after surgery, lymphocytosis – 1 month after surgery (29.7%) and monocytosis (8.7%) – on the 10th day after osteosynthesis.
Thus, the dynamics of changes in the leukocyte blood reaction in patients of the first subgroup was characterized by relative stability of changes, which is confirmed by the lack of comparative reliable values.
The confidence interval of leukocytes in patients of the second subgroup was characterized by relatively high values on day 10 [6.71; 9.45] and 1 month (7.09; 9.11) after osteosynthesis (Table 3). At the same time, in the period 3 months after the operation, we detected a decrease in leukocytes in the blood with a minimum confidence interval (4.74; 5.78), which again showed an increase in subsequent periods.
Table 3.

The nature of changes in the dynamics of the leukocyte blood reaction in patients of the second subgroup

DYNAMICS	LEUKOCYTE BLOOD CELLS ($x10^9/_l$)			
	Neutrophils	Lymphocytes	Monocytes	White blood cells
Upon admission	4,10±1,19	2,31±0,08	0,62±0,08	7,49±2,11
, 3 days	4,00±0,93	2,34±0,14	0,68±0,07	7,20±1,83
10 days	4,67±0,87	2,47±0,18	0,54±0,03	8,08±1,37
1 month	5,09±1,31	2,15±0,13	0,66±0,05	8,10±1,01
3 months	2,90±0,11*	1,84±0,08*	0,31±0,04*	5,26±0,52
6 months	3,47±0,39	2,42±0,16	0,38±0,09	6,47±0,58
12 months	4,57±0,19	2,20±0,25	0,58±0,05	7,54±1,04

*$p<0.05$ – significantly relative to the time when the patient was admitted to the clinic
The minimum value of the studied leukocyte populations in the second group of patients showed a low value of lymphocytes and monocytes also within 3 months after osteosynthesis. However, the percentage balance of the leukocyte response was different.
Relative neutrophilosis was noted by us within 1 month and 1 year after surgery. Lymphocytosis manifested earlier, within 3-6 months after osteosynthesis, whereas monocytosis even earlier – on the 3rd day after surgery.

Thus, in patients of the second subgroup, the relative increase (compared with the first subgroup) of the leukocyte reaction was not characterized by a certain regular reaction, which confirms the low prognostic significance of using this method of analysis.
In patients of the third subgroup, the laboratory characteristics of changes in the level of leukocytes in the blood showed high values throughout the postoperative period (Table 4).

Table 4.The nature of changes in the dynamics of the leukocyte blood reaction in patients of the third subgroup

DYNAMICS	LEUKOCYTE BLOOD CELLS ($x10^9/_l$)			
	Neutrophils	Lymphocytes	Monocytes	White blood cells
Upon admission	4,68±0,95	2,53±0,41	0,62±0,09	7,83±1,18
, 3 days	9,19±1,12*	1,62±0,39*	0,38±0,08*	11,19±1,58*
10 days	7,19±0,83*	2,03±0,44*	0,34±0,04*	9,56±1,04*
1 month	6,47±0,87	2,12±0,49	0,79±0,05	9,38±0,94*
3 months	5,99±0,69	2,74±0,14	0,61±0,01	9,34±0,81*
6 months	5,76±0,71	2,92±0,85	0,58±0,02	9,26±1,09*
12 months	5,42±1,35	3,02±0,82	0,78±0,06	9,22±1,35*

*$p<0.05$ – significantly relative to the time when the patient was admitted to the clinic
We noted the maximum leukocytosis in patients on the 3rd day after surgery, which reached the level of 11.19±1.58 x 109/l ($p<0.05$). The confidence interval of leukocytes at this time was CI=(9.61; 12.77).
In subsequent follow-up periods, the level of leukocytes decreased relatively, however, in relation to the reference values, these data can be considered leukocytosis. Judging by the dynamics of changes in leukocyte populations, it is possible to note the identical nature of the change in the ratio of neutrophils. The peak of its increase was noted by us in patients on the 3rd day after surgery. For example, in patients admitted to the clinic with a tubular bone fracture, the confidence interval of neutrophils varied at low levels (3.73; 5.63). On the 3rd day after surgery, the confidence interval significantly increases (8.07; 10.31), reaching a percentage of 82.1%. This was a peak change, which decreased in subsequent periods, which was apparently due to the use of a wide range of antibacterial therapy. Nevertheless, even 1 year after osteosynthesis in patients of this subgroup, the confidence range of neutrophils ranged from 4.07-6.77 x109/l.
In comparison with the period of the first study of the level of lymphocytes and monocytes in patients admitted to the clinic with closed fractures of long tubular bones, on the 3rd day after surgery, relative lymphopenia (2.2 times) and monocytopenia (1.5 times) were noted.
The confidence interval for lymphocytes and monocytes decreased on day 3 (1.23; 2.01) and (0.3; 0.46), respectively) and on day 10 (1.59; 2.47) and (0.3; 0.38), respectively). In subsequent periods of treatment, the confidence interval for these leukocyte populations gradually increased, reaching a maximum value only 1 year after the operation of osteosynthesis of long tubular bones (2.1; 3.94) and (0.72; 0.84), respectively).
Thus, in patients of the third subgroup, in comparison with patients of the previous subgroups, we revealed a pattern of changes in the leukocyte reaction by type of inflammatory character in a more pronounced variant. At the same time, the registered leukocytosis was characterized by a shift of the leukocyte formula to the left in the early stages after surgery. This was due to the development of purulent-inflammatory complications from the wound. Meanwhile, we also noted a similar pattern of changes in the early stages after surgery among patients of the second subgroup, who also experienced the development of a postoperative complication of a purulent-inflammatory nature. However, as we know, bone regenerative processes were not disrupted in patients of the second subgroup. Most likely, in relation to the mechanism of formation of this pathological process and the corresponding leukocyte reaction of the blood, it is necessary to look for late treatment of patients. Moreover, it seems that we can get a similar answer when evaluating changes in leukocyte indices.
Thus, the dynamics of the average LII value in patients in the postoperative period was equal to 1.56±0.27 units. The maximum values occurred on day 3 (1.65±0.31 units) and 1 month later (1.64±0.32 units) after osteosynthesis. In the future, the growth of LII was suspended, reaching its minimum value 1 year after surgery (1.46± 0.28 units).
Throughout the study, the predominant equity participation in the organization of the LII level belonged to patients of the second and third subgroups (Figure 4). When patients were admitted to the clinic, the percentage of the total LII level in the first subgroup of patients was 20.2%, in the second – 38.8%, and in the third subgroup – 41.0%.
On the 3rd day after surgery, with a relative increase to 26.5% in the share of LII in the first subgroup of patients, there was a decrease in the second subgroup to 36.6% and to 36.8% in the third subgroup of patients. On the 10th day after osteosynthesis, the balance of the LII ratio changes again as in the time when patients are

admitted to the clinic. At the same time, in the first subgroup of patients, the value of LII decreased to 21.1%, and in the second and third subgroups it increased to 38.5% and 40.4%, respectively. It was from this period that the trend no longer changed and against the background of a decrease in the proportion of LII in the first subgroup of patients, it only increased among patients of the second and third subgroups.
In the first subgroup of patients, the average LII level for the entire examination period was 0.94±0.17 units. In the second and third subgroups, the average level of LII for the entire period of examination of patients exceeded the values of the first group by 1.9 times (1.78± 0.23 units) and 2.1 times (1.98±0.41 units), respectively (Table 5).

Table 5.The comparative nature of changes in the level of leukocyte intoxication index (units) in patients of various subgroups with fractures of long tubular bones in dynamics after osteosynthesis

DYNAMICS	SUBGROUPS OF PATIENTS		
	I	II	III
Upon admission	0,92±0,18	1,77±0,34*	1,87±0,26*
, 3 days	1,31±0,48	1,81±0,29	1,82±0,16
10 days	1,02±0,21	1,86±0,13*	1,95±0,39*
1 month	0,89±0,13	1,97±0,15*	2,05±0,67*
3 months	0,85±0,09	1,58±0,22*	2,32±0,59*
6 months	0,81±0,07	1,68±0,19*	1,95±0,31*
12 months	0,75±0,04	1,76±0,31*	1,88±0,49*

*p<0.05 – significantly relative to the indicators of patients of the first subgroup
The maximum values of LII in the dynamics of the conducted studies in patients of the first subgroup occurred on the 3rd day after osteosynthesis surgery (CI: 0.83; 1.79), followed by a progressive decrease in the level of this indicator to a minimum value for a period of 1 year after surgery (CI: 0.71; 0.79).
In the second subgroup of patients, early on the day after surgery, there was the growth of the LII reached its peak for a period of 1 month (CI: 1.82; 2.21). This increase was 2.2 times greater than in patients of the first subgroup at this time.
In subsequent periods, the level of LII gradually decreased (CI: 1.36; 2.07), however, it remained 2.3 times higher in patients of the first subgroup even a year after surgery. In other words, the presence of a postoperative purulent-inflammatory complication contributed to the preservation of high values of LII. We found confirmation of this judgment among patients of the third subgroup, who also had postoperative purulent-inflammatory complications.
The minimum values of LII among patients of the third subgroup were noted by us among patients on the 3rd day after surgery (CI: 1.66; 1.98). Starting from 10 days after osteosynthesis, the LII level increased, reaching its maximum value for a period of 3 months (CI: 1.73; 2.91). The excess values were 2.7 times higher than in patients of the first subgroup.
Thus, a comparative assessment of laboratory parameters during the regeneration of a fracture of long tubular bones did not show the presence of great reliability between subgroups, especially in leukograms. However, when analyzing the reliability of LII, reliable values were revealed in relation to patients of the first subgroup, which confirms the similarity of changes among patients of the second and third subgroups. Apparently, this can be recognized as a pattern, since such an assessment reflects the nonspecific reaction of leukocytes and the formation of cell populations. It is precisely this reaction that has become possible to evaluate by calculating the LII.
The similarity of the change in LII among patients of the second and third subgroups indicates the identity of the occurring body responses, which coincided with the development of lymphopenia.
The tendency to high monocyte values in the early stages after a closed fracture of long tubular bones and in the early postoperative period, apparently, was associated with the scale of traumatic injury. This assumption can be made based on the importance of monocytes in the regulation of macrophage reaction and, accordingly, osteogenesis.
The high value of LII that we identified remains interesting, which directly indicated the presence of a purulent-inflammatory process in the postoperative period. It is also interesting that this indicator has been growing for a long period after injury and surgery, which was noted among patients of both the second and third subgroups.
The noted changes in the leukocyte reaction of blood in closed fracture of long tubular bones, apparently, were also associated with the peculiarities of healing of long tubular bones. This fact should be taken into account when conducting prognostic monitoring in the treatment of patients with closed fractures of long tubular bones.

The leukocyte allergization index, in contrast to the leukocyte intoxication index, was characterized by a more pronounced manifestation in patients of the first subgroup (Table 6).
The average value of LIA in patients of the control group, which was 0.83±0.17 units, indicated a fluctuation of values within the reference values. The maximum level of LIA in patients of the control group was on the 10th day after osteosynthesis (1.01±0.12 units), and the minimum level was for the period of 3 months of the postoperative period (0.80±0.13 units). All this indicates that the overall dynamics of LIA in patients of the control group was not unambiguous.

Table 6.Comparative nature of changes in the level of leukocyte allergization index (units) in patients of various subgroups with fractures of long tubular bones in dynamics after osteosynthesis

DYNAMICS	SUBGROUPS OF PATIENTS		
	I	II	III
Upon admission	1,01±0,32	0,72±0,14*	1,05±0,33
, 3 days	1,00±0,28	0,79±0,19*	0,72±0,11*
10 days	1,48±0,17	0,78±0,11*	0,76±0,08*
1 month	1,09±0,27	0,87±0,13	0,64±0,06*
3 months	1,05±0,22	0,77±0,14*	0,58±0,04*
6 months	1,01±0,31	0,98±0,17	0,94±0,15
12 months	0,95±0,11	0,78±0,11	0,74±0,09

*p<0.05 – significantly relative to the indicators of patients of the first subgroup.
In patients of the second subgroup, the confidence interval of LIA in these periods fluctuated within the reference values (0.58; 0.86) and (0.60; 0.98), respectively), and in patients of the third subgroup, we noted an excess of the norm only when patients were admitted to the clinic (0.72; 1.38) and (0.61; 0.83), respectively).
Above the reference average values of LIA were noted by us in patients of the first subgroup on day 10 and 1 month after osteosynthesis. In other cases, such episodes were noted only within the confidence interval in all patients of the control group.
Thus, the leukocyte allergization index was not manifested in patients with purulent-inflammatory complications of osteosynthesis, both during the chronic process and impaired bone regeneration. The fact of high values of this indicator in patients with closed fractures of long tubular bones even before surgical treatment remains interesting.
The nuclear index of leukocyte shift in patients of the control group was characterized by fluctuations in dynamics within the reference values (0.03-0.05 units) and averaged 0.04±0.01. However, the randomization of patients by subgroups revealed a differentiated nature of the reflection of UIS in patients in the dynamics of the postoperative period of tubular bone regeneration (Table 7).

Table 7.The comparative nature of changes in the level of the nuclear shear index (units) in patients of various subgroups with fractures of long tubular bones in dynamics after osteosynthesis

DYNAMICS	SUBGROUPS OF PATIENTS		
	I	II	III
Upon admission	0,03±0,01	0,03±0,01	0,04±0,01
, 3 days	0,02±0,01	0,03±0,01	0,09±0,01*
10 days	0,02±0,01	0,04±0,01*	0,08±0,01*
1 month	0,03±0,01	0,04±0,01	0,07±0,01*
3 months	0,03±0,01	0,03±0,01	0,06±0,01*
6 months	0,03±0,01	0,03±0,01	0,05±0,01*
12 months	0,03±0,01	0,03±0,01	0,04±0,01

*p<0.05 – significantly relative to the indicators of patients of the first subgroup
The average values of the division by subgroup showed the same values of NPS among patients of the first and second subgroups (0.03±0.01) and the maximum level of reference values in the third subgroup of patients (0.06±0.01).
Data from patients of the third subgroup played an important role in the shared participation in the organization of the NPS value. Most of these transformations could be noted in patients of the third subgroup on day 3-10 of bone tissue regeneration (64.3% and 57.1%, respectively).

During 1-3 months, in patients of the third subgroup, the share of the organization of the value of the NPS was equal to half (50%). Against this background, in the subsequent periods of bone tissue regeneration, a stable identical value can be observed in both the first and second subgroups of patients during 3-12 months of bone tissue regeneration. All possible changes in the change in the level of UIS in the second subgroup of patients could be noted only in the early stages after osteosynthesis.
Thus, the analysis of the leukocyte reaction of blood in patients with closed fractures of long tubular bones and in dynamics after osteosynthesis allows us to draw certain conclusions regarding their informational possibilities in predicting violations of bone consolidation. First of all, it should be noted that immune disorders in the body are most pronounced in the early stages after osteosynthesis, especially in patients with purulent-inflammatory complications in the form of suppuration of a postoperative wound and/or the development of osteomyelitis, which is apparently associated with activation of leukopoiesis. Such a conclusion can also be made based on the ongoing changes in the nuclear shift index, which was associated with shifts in the immunological reactivity of the body in patients with impaired bone regeneration after fracture and osteosynthesis.
Also, the LII indicators and the studied leukocyte populations can directly indicate signs of endogenous intoxication in the early stages of the development of purulent-inflammatory complications from wounds and long tubular bones.

In predicting the course of reparative processes of fracture of long tubular bones, the functional activity of the leukocyte reaction, in particular phagocytes, was also evaluated as a laboratory criterion.
The average level of phagocytic activity in patients throughout the dynamic study was 87.45±4.13%. The minimum average level of phagocytic activity occurred at the time of admission of patients to the clinic (86.46±3.49%) and 12 months after osteosynthesis (85.85±3.55%). This indicated, perhaps, the completion of phagocytosis processes in connection with the formation of a bone callus. The peak values of the average phagocytic activity in patients of the control group occurred during the period 3-90 days after osteosynthesis surgery. Such phagocyte activity was manifested already on the 3rd day after surgery in the form of an increase in its level to 90.40± 4.35%.

Thus, the phagocytic index in patients was characterized by wave-like changes, demonstrating activation in the early period of callus formation with a decrease in the indicators already in the process of completing the consolidation of bone fragments. A separate analysis of patients based on the results of bone regeneration revealed an ambiguous picture (Table 3.8). In particular, during the entire examination period, the average phagocytic index level was high among patients of the second and first subgroups (87.85±4.02% and 87.95±5.12%, respectively), and the lowest in patients of the third subgroup (86.89±3.11%).

Table 8.The comparative nature of changes in the phagocytic index level (%) in patients of various subgroups with fractures of long tubular bones in dynamics after osteosynthesis.

DYNAMICS	SUBGROUPS OF PATIENTS		
	I	II	III
Upon admission	85,93±4,17	87,17±3,18	86,28±3,11
, 3 days	86,39±5,28	88,18±4,83	96,63±2,93*
10 days	87,29±6,13	88,49±3,77	86,59±3,18
1 month	88,13±4,82	89,19±4,91	85,53±4,19*
3 months	89,48±3,92	88,29±3,99	85,39±3,84*
6 months	88,19±7,29	87,12±4,28	84,69±2,19*
12 months	87,62±5,25	86,48±3,19	83,12±2,33*

*p<0.05 – significantly relative to the indicators of patients of the first subgroup
In the first subgroup of patients, the maximum fluctuations in the values of the confidence interval occurred within 6 months of the postoperative period (CI: 80.9%; 95.48%).
A decrease in the phagocytic index was noted among patients with fractures of long tubular bones on the day of admission to the clinic (CI: 81.76%; 90.10%) and on the 3rd day after osteosynthesis (CI: 81.11%; 91.67%). Subsequently, during the normal process of bone regeneration without any purulent-inflammatory complications, a gradual increase in the phagocytic index occurred. The decline in the phagocytic index in patients of the first subgroup began after 6 months of the course of the process of bone marrow formation (CI: 80.90%; 95.48%) and in the long-term period after 12 months of treatment (CI: 82.83%; 93.07%).
Thus, in patients of the first subgroup, 2 characteristic periods of phagocytic index changes can be noted, in the form of a gradual increase in the early stages of bone marrow formation (up to 3 months after surgery), followed

by stabilization of the curve at the end of regenerative processes. And even a year after the operation, in the case of bone regeneration without the development of any complications, the phagocytic index remains above the initial values, which, apparently, was associated with the transformation of the hematopoietic process in the bone marrow.
The dynamics of changes in the phagocytic index in patients of the second subgroup, where normal bone consolidation occurred against the background of the development of purulent-inflammatory complications, also had a two-phase course. However, the phagocytic index in patients of the second subgroup was leveled in relation to the dynamics of patients of the first subgroup.
The first phase of changes in the phagocytic index in patients of the second subgroup occurred during the periods of patients' admission to the clinic (CI: 83.99%; 90.35%) and up to the first month of the postoperative period (CI: 84.28%; 94.10%). In the subsequent periods of the course of the regenerative process of bone tissue (3-12 months), there is a gradual decline (CI: 83.29%; 92.28%) of the phagocytic index, reaching its minimum within 1 year of the course of regenerative processes (CI: 83.29%; 89.67%). The leveling of phagocytic activity between patients of the first and second subgroups occurred during the period of 1-3 months of the course of the regenerative process (CI: 84.28%; 94.10%) and (CI: 84.30%; 92.28%), respectively). In subsequent periods, they were also characterized by a relatively low value of the phagocytic index in patients of the second subgroup compared with the first.
In patients with a complicated course of bone tissue regeneration, which ended with unsatisfactory results, changes in the phagocytic index occurred in three phases and completely differed from the dynamics of patients of the first and second subgroups.
The average phagocytic index level for the entire examination period in patients of the third subgroup was lower compared with patients of the first and second subgroups. At the same time, the first phase of the dynamics of changes in the phagocytic index occurred for up to 3 days after surgery, which manifested itself in a sharp increase in the value, exceeding the values of patients of the first and second subgroups (an increase in the confidence interval from 83.17% to 99.56%, respectively). Such a pronounced activation reaction of the phagocytic index was, apparently, due to the peculiarity of the condition of patients of the third subgroup.
The second phase was also fleeting and lasted for 3-10 days of the postoperative period. It was characterized by a progressive decrease in the phagocytic index on day 10 of the course of the bone tissue reparative process (CI: 83.41%; 89.77%). This decrease in the phagocytic index fell lower than in patients of the first and second subgroups.

Subsequently, remaining at such a low level, phagocytic activity continues to gradually decrease, reaching its minimum value even a year after osteosynthesis (CI: 80.79%; 85.45%).
We did not find any special difference between the subgroups in the share participation in the formation of the phagocytic index value of the entire control group. It should only be noted: the presence of a peak proportion of phagocytic activity among patients of the third subgroup on the 3rd day after osteosynthesis (35.6%); an increase in the proportion due to patients of the second subgroup in the early stages after surgery on 10-30 days (33.7% and 33.9%, respectively); a stable high proportion value during subsequent periods of treatment, up to a distant period.

Thus, regarding the dynamics of changes in the phagocytic index, it can be noted that there is a differentiated manifestation in the randomized separation of patients depending on the course and outcome of the disease. At the same time, in patients with impaired bone regeneration, the phagocytic index changes repeatedly, reflecting the processes of development of a chronic inflammatory process against the background of a low immunological reaction of neutrophils.

Table 9.The comparative nature of changes in the number of phagocytes (x109/l) in patients of various subgroups with fractures of long tubular bones in dynamics after osteosynthesis.

DYNAMICS	SUBGROUPS OF PATIENTS		
	I	II	III
Upon admission	3,56±0,21	3,86±0,18	3,42±0,22
, 3 days	3,61±0,26	3,95±0,22	4,56±0,22
10 days	3,68±0,24	3,97±0,27	3,51±0,25
1 month	3,42±0,18	3,99±0,31	3,50±0,21
3 months	3,44±0,23	3,92±0,30	3,54±0,20
6 months	3,42±0,24	3,91±0,29	3,56±0,31
12 months	3,43±0,25	3,92±0,26	3,57±0,28

*p<0.05 – significantly relative to the indicators of patients of the first subgroup
The interpretation of the features of the change in the nature of phagocytic activity will be valid in the content with a change in the number of phagocytes themselves (Table 9).
The average number of phagocytes in the control group of patients was equal to 3.7±0.24 x109/l. We noted peak maximum values on the 3rd day after osteosynthesis (4.04±0.23 x109/l), and minimum values on the day of patients' admission to the clinic (3.61±0.20 x109/l) and in the period 3-6 months after bone regeneration (3.63±0.24 x109/l and 3.63±0.28 x109/l, respectively).

In the division into subgroups, we found the maximum number of phagocytes in patients of the second subgroup (3.93±0.26 x109/l), and the minimum in patients of the first subgroup (3.51±0.23 x109/l).
The overall dynamics of changes in the number of phagocytes in each subgroup of patients was relatively stable, with the exception of cases in the third subgroup of patients. It was in them that the peak growth in the number of phagocytes was recorded on the 3rd day after osteosynthesis (CI: 4.34 x109/l; 4.78 x109/l). However, in subsequent periods, it decreased, acquiring identical dynamics, both in the first and in the second subgroups of patients.

Regarding the percentage of the share of the number of phagocytes in the context of subgroups, priority can be noted in the second subgroup of patients (on average 35.4%), with the exception of 3 days after osteosynthesis, where the leading role was occupied by patients of the third subgroup (37.6%).

Thus, drawing parallels between changes in phagocytic activity and the number of phagocytes, a certain correspondence can be noted. With a stable number of macrophages, the activity index changed in patients with different outcomes of bone regeneration. This indicates the activation of functional activity over hematopoietic, which, apparently, was associated with the transfer of cell formation towards osteoclasts and osteoblasts.
Such changes contribute not only to the formation of a callus, but also, albeit indirectly, indicate the course of regenerative processes. To confirm this judgment, we also studied the metabolic activity of phagocytes in patients of the control group according to the NBT test (Table 10).

Table 10.The comparative nature of changes in the metabolic activity of phagocytes (NBT test) in patients of various subgroups with fractures of long tubular bones in dynamics after osteosynthesis.

DYNAMICS	SUBGROUPS OF PATIENTS		
	I	II	III
Upon admission	1,00±0,20	1,41±0,19*	0,75±0,21*
, 3 days	1,83±0,27	1,84±0,36	1,64±0,24*
10 days	1,52±0,26	1,56±0,20*	1,65±0,13*
1 month	1,73±0,14	1,92±0,11	1,51±0,22*
3 months	2,81±0,56	1,44±0,31*	1,50±0,14*
6 months	2,82±0,55	1,43±0,29*	1,40±0,16*
12 months	2,81±0,54	1,45±0,33*	1,30±0,18*

*p<0.05 – significantly relative to the indicators of patients of the first subgroup.
With the exception of the case when patients went to the clinic, in all other cases, the metabolic activity of phagocytes was within normal limits.
Immediately after injury, even before the use of surgical methods of treatment, the level of metabolic activity of phagocytes in patients of the control group was equal to 1.05 ± 0.2 units.
The maximum metabolic activity of phagocytes was noted by us in patients of the control group. The 3-month duration of treatment was 1.92±0.34 units.
In the following days, its activity gradually decreased, but remained above the average value (that is, more than 1.68 ± 0.27 units).

In the context of subgroups, the average maximum level of metabolic activity of phagocytes was recorded by us in patients of the first subgroup of 2.07±0.36 units, and the minimum level in patients of the third subgroup with an unsatisfactory result of regeneration of a fracture of long tubular bones was 1.39±0.18 units.
In all three subgroups of patients, the metabolic activity of phagocytes increased sharply on the 3rd day after osteosynthesis surgery in relation to the preoperative period. At the same time, the increase in patients of the

first and second subgroups was almost identical (1.83±0.27 units and 1.84±0.36 units, respectively), with the exception of patients of the third subgroup, whose activity growth was the least (up to 1.64±0.24 units).
This nature of the change in the metabolic activity of phagocytes in patients of the third subgroup contributed to maintaining the stability of changes in flesh until the end of the study.

For up to 1 month, the dynamics of the phagocyte metabolic activity curve changed identically. However, in the future, in patients of the first subgroup, the metabolic activity of phagocytes increased significantly (CI: 2.27; 3.37), which apparently contributed to bone regeneration without purulent-inflammatory complications, culminating in normal regeneration of long tubular bone fractures. At the same time, in the case of a purulent-inflammatory complication, the metabolic activity of phagocytes progressively decreases.
A comparative change in the metabolic activity of phagocytes showed that the main increase in the metabolic activity of macrophages occurred in patients with purulent-inflammatory complications – 72.1%. Such changes intersected, creating an identical picture of changes in the metabolic activity of phagocytes.
However, in the long-term periods of treatment, starting from the 3-month treatment period, the entire priority in the proportion of the level of metabolic activity of phagocytes was determined by patients of the first subgroup (48.9%, 49.9% and 50.5%, respectively, at 3, 6 and 12 months of the study).
In 62 (54.4%) patients of the study group, the postoperative period proceeded with various types of local complications. In most cases, these complications were combined and could occur in each patient in several of their varieties.

In total, according to the medical history, 128 postoperative local complications were registered – on average, 2 complications per patient. This frequency of local postoperative complications was due to the frequency of postoperative complications of hematomas and seromas, which was noted in all 62 patients.
Of the 128 names of postoperative local complications, suppuration of the postoperative wound was registered in 48.4% of cases. Of these, in 25% of cases, we found the presence of contact postoperative osteomyelitis. 20 (15.6%) patients developed osteomyelitis spokes. All these complications were detected by us in the first month of the treatment.

In the long-term period, postoperative complications were characterized by the development of a false joint (7.8%), an improperly fused fracture and an ungrown fracture with a frequency of 1.6% each name.
Thus, out of 62 postoperative complications, only 48 patients had postoperative local complications that developed early and were eliminated with satisfactory bone regeneration results. In the remaining 14 (11%) patients, in the long-term period, the results of treatment were unsatisfactory, which subsequently required the use of repeated reconstructive orthopedic operations.
Among the traditional methods of predicting bone regeneration disorders in fractures of tubular bones, we used the LII, LIA and NBT test.

The maximum sensitivity and specificity in predicting bone regeneration disorders were noted with the use of LIA (74.5% and 53.9%, respectively).
When patients were admitted to the clinic, LIA (67.9%) turned out to be among the tests sensitive to impaired bone regeneration, whereas LII (38.1%) turned out to be more specific.
On 3-10 days after osteosynthesis, we noted the maximum sensitivity in predicting impaired bone regeneration in relation to LII (69.9% and 72.1%, respectively), and specificity – to LIA (51.1% and 50.8%, respectively).
The sensitivity of LII in the early stages after osteosynthesis was naturally due to the development of a purulent-inflammatory process, as a harbinger of impaired bone regeneration in the future. However, the high values of specificity of LIA tests in predicting impaired bone regeneration were probably associated with impaired hematopoietic processes and involvement of immune complexes formed in response to a nonspecific infection in the mechanisms of bone marrow formation.

Such a conclusion is valid for reasoning in connection with changes in the long-term course of the bone regeneration process. The LIA test becomes more sensitive, which exceeds not only the LII and NBT test at a given time, but also its own early period of bone tissue regenerative processes.
Thus, with the sensitivity of traditional tests to non-specific wound infection in the early stages after surgery, in the long term, their transformation into the process of allergization occurs. This conclusion can be confirmed by the dynamics of the specificity of LIA, the severity of which increases with the onset of long-term periods of treatment of a fracture of tubular bones. All this indicates the need for a more in-depth study of the

immunological aspects of both the cellular and humoral link, which will most likely optimize the method of predicting a violation of the regeneration of a fracture of long tubular bones.

3. Conclusions

1. The analysis of visual control of bone regeneration after a fracture allows you to structure the stages of this process. The method is effective for controlling the dynamics of the process. However, the possibilities of this method for forecasting are limited, since the basis of the ongoing regeneration processes is determined by the timing.
2. Analysis of the leukocyte reaction of blood in patients with closed fractures of long tubular bones and in dynamics after osteosynthesis allows us to draw certain conclusions regarding their informational possibilities in predicting violations of bone consolidation. First of all, it should be noted that immune disorders in the body are most pronounced in the early stages after osteosynthesis, especially in patients with purulent-inflammatory complications in the form of suppuration of a postoperative wound and/or the development of osteomyelitis, which is apparently associated with activation of leukopoiesis.
3. Out of 128 names of postoperative local complications, suppuration of the postoperative wound was registered in 48.4% of cases. Of these, in 25% of cases, we found the presence of contact postoperative osteomyelitis. 20 (15.6%) patients developed osteomyelitis spokes. All these complications were detected by us in the first month of the treatment
4. On 3-10 days after osteosynthesis, we noted the maximum sensitivity in predicting impaired bone regeneration in relation to LII (69.9% and 72.1%, respectively), and specificity to LIA (51.1% and 50.8%, respectively). The sensitivity of LII in the early stages after osteosynthesis was naturally due to the development of a purulent-inflammatory process, as a harbinger of impaired bone regeneration in the future. However, the high values of specificity of LIA tests in predicting impaired bone regeneration were probably associated with impaired hematopoietic processes and involvement of immune complexes formed in response to a nonspecific infection in the mechanisms of bone marrow formation.
5. With the sensitivity of traditional tests to non-specific wound infection in the early stages after surgery, their transformation into the process of allergization occurs in the long term. This conclusion can be confirmed by the dynamics of the specificity of LIA, the severity of which increases with the onset of long-term periods of treatment of a fracture of tubular bones. All this indicates the need for a more in-depth study of the immunological aspects of both the cellular and humoral link, which will most likely optimize the method of predicting a violation of the regeneration of a fracture of long tubular bones.

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