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FEATURES OF CELLULAR HUMORAL IMMUNITY DURING BONE TISSUE REGENERATION IN PATIENTS WITH CLOSED FRACTURES OF TUBULAR BONES

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Abstract:

Clinical and immunological comparison of the course of regenerative processes of bone tissue, carried out on the basis of a comparison of ultrasound data from the fracture zone and the obtained information from monitoring changes in immunological blood parameters, made it possible to identify a number of features of the body's immunological reaction. This, to a certain extent, reflects the features of the course of bone tissue regeneration, which can be interpreted as possible effective prognostic markers. To conduct such an assessment, it may be most effective to apply principles and analyzes based on the rules of evidence-based medicine.

Keywords: Regeneration, Bone Tissue, Immunity

RELEVANCE: It is believed that impaired bone regeneration in closed fractures of long bones, leading to the formation of a pseudarthrosis, occurs in approximately 2% of all fractures, but in certain injuries this impairment can reach 20%.

The main problems associated with impaired bone regeneration in closed fractures of long bones are associated with prolonged pain, loss of limb function and mental stress conditions. Over the past decades, scientists have paid attention to studying the close connection between the immune system and bone tissue. This close attention has led to the emergence of a new term – osteoimmunology. To date, it has been convincingly proven that most components of the immune system, including numerous molecules, cytokines, chemokines , hormones, receptors and transcription factors, etc., have a close connection with the regenerative processes of bone tissue. Moreover, studies were carried out under both physiological and pathological conditions.

Today it is already known that the main immune cells interact with bone tissue as the main components of the system, and sometimes as auxiliary ones. In particular, it has become known that T cells, as well as their auxiliary components, are actively involved in the regeneration of bone tissue and their auxiliary cells. First of all, this directly concerns the formation of the process of osteoclastogenesis.

There is information regarding the controlled role of cytokines in the process of bone tissue regeneration. Specific morphogenetic proteins and tumor necrosis factor cytokines determine the process of bone regeneration.

Inhibition of T cell activation suppresses induced T cell expression, resulting in inhibition of osteoclastogenesis. It has been proven that T cells can influence osteoclastogenesis both indirectly and directly by actively secreting IL-17, which leads to the secretion of TNF-α and IL-1, which in turn support osteoclastogenesis.

Activated T cells induce osteoclastogenesis by directly influencing osteoclast progenitor cells . In contrast, resting T cells inhibit osteoclastogenesis through a mechanism that involves the mediation of complete suppressive mechanisms by B cells (15,20,24). In addition, T cells can also differentiate into CD4 and CD8 T cells, which go on to influence osteoclastogenesis . CD4 T cells have no effect on osteoclast formation, while depletion of CD8 T cells results in a 40% increase in osteoclast formation.This suggests that differentiated T cells play a role primarily in promoting osteoclastogenesis .

Thus, the significance of the immunological aspects of predicting impaired bone regeneration in closed fractures of long bones, at the modern level, becomes relevant both in fundamental and applied issues that affect the outcome of treatment in general.

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PURPOSE OF THE STUDY: to study the indicators of cellular humoral immunity during bone tissue regeneration in patients with closed fractures of long bones.

MATERIAL AND METHODS. The results of a comprehensive examination and treatment of 226 patients with closed fractures of long bones are analyzed. All patients were treated and examined at the Samarkand branch of the Republican Specialized Scientific and Practical Medical Center for Traumatology and Orthopedics from 2017 to 2022 inclusive.

We divided the clinical material into two groups: control and main. The main group of patients consisted of 112 patients in whom, in order to predict bone tissue regeneration, clinical and immunological monitoring was used using the IPBR program (Method for predicting bone tissue regeneration) developed by us. In the control group, against the background of the use of traditional methods for assessing bone tissue regeneration, a study of the main parameters of cellular and humoral immunity was carried out. Patients of young and mature age (61.5%) were predominantly male (77.4%).

In the control group of patients in 71.1%, and in the main group in 74.1% of cases, patients were treated for a closed fracture of the tibia. The remaining patients had closed fractures of the femur (28.9% and 25.9%, respectively). In the control and main groups, the main causes of fractures of long bones were household and street injuries (44.7% and 49.1%, respectively). When making the diagnosis, the classification of ME by Muller et al was used . (1996).

All patients with fractures of long tubular bones were operated on. In 79 (35%) patients, intramedullary osteosynthesis was used, in 93 (41.2%) patients, extramedullary osteosynthesis was used, and in 54 (23.9%) patients, transosseous osteosynthesis was used using the Ilizarov apparatus . Each group of patients was divided into three subgroups depending on the course and outcome of treatment. The first subgroup consisted of patients in whom the postoperative period proceeded without complications with normal bone tissue regeneration (39.8% of patients). The second group consisted of patients in whom the postoperative period proceeded with the development of a local purulent-inflammatory complication, and the outcome of treatment was completed in a satisfactory condition (50.4%). The third subgroup consisted of patients whose bone regeneration was impaired due to the development of postoperative local purulent-inflammatory complications.

The research methods were comprehensive and were carried out in accordance with the regulations approved by the Ministry of Health of the Republic of Uzbekistan for the standards of medical care for traumatological and orthopedic patients.

RESULTS AND DISCUSSION: Analyzing the monitoring data for changes in cellular immunity parameters during bone tissue regeneration, it can be noted that in patients of the first subgroup, the uncomplicated course of bone tissue regeneration was accompanied by a stable curve. At the same time, in patients of the second subgroup, the regenerative processes of bone tissue after a fracture occurred with double leveling in relation to the dynamics of patients in the first subgroup.

Leveling occurred during the development of a local purulent-inflammatory process, including osteomyelitis, in the range of the number of CD 3 $^{+}$ T-lymphocytes in the blood from 51.31% to 60.32%. This variation in the change in the number of CD 3 $^{+}$ T-lymphocytes in the blood in patients of the second subgroup apparently made it possible to achieve normal consolidation of a bone fracture even after suffering from a chronic local purulent-inflammatory disease. However, in patients of the third subgroup, the lack of recurrent leveling, unfortunately, did not lead to normal bone tissue regeneration.

Regarding the monitoring of changes in the number of CD 19 $^{-}$ B-lymphocytes in the blood of patients of the second subgroup, the development of a local chronic purulent-inflammatory process led to a leveling of dynamics, the transition period of which occurred in the long-term period of regeneration of long tubular bones. We deliberately state this fact of leveling the dynamics of the curve, since in patients of the third subgroup such a graphic mane did not manifest itself. A progressive decrease in the number of CD 19 $^{-}$ B-lymphocytes in the blood of patients of the third subgroup was characteristic of impaired regeneration after osteosynthesis of long tubular bones.

The dynamics of changes in the concentration of Ig - A in the blood in patients with impaired bone tissue regeneration was characterized by a decrease in this indicator, which was not able to return to the original level.

However, judging by the dynamics of changes in the concentration of Ig - M in the blood of patients of the first subgroup, it can be stated that the high value of its production led to increased bone tissue regeneration, creating conditions for satisfactory results in the treatment of fractures of long tubular bones.

In patients of the third subgroup, a pronounced progressive decrease in Ig - M in the blood was accompanied by the development of not only a local chronic purulent-inflammatory complication, but also a violation of bone tissue regeneration.

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Ig - M concentration in patients of the third subgroup was exactly 2 times less than in patients of the first subgroup (p <0.05), which may indicate the key nature of this indicator in predicting the outcome of regeneration of long tubular bones.

Judging by the concentration curves, one can notice a double leveling of Ig - G in the blood of patients of the third subgroup. The first leveling , occurring in the early period of bone tissue regeneration, was characterized by a low concentration of Ig - G , which, apparently, was associated with the development of local chronic purulent-inflammatory complications after bone osteosynthesis. Subsequently, as the postoperative period progresses, the concentration of this immunoglobulin increases, which exceeds both the initial values and the values of the first and second subgroups, which, apparently, was associated with the development of chronic inflammatory processes with impaired regeneration of long tubular bones.

The studied cytokine profile in patients with closed fractures of long tubular bones made it possible to identify certain patterns of dynamics when dividing them into subgroups.

The concentration of the level of IL -1α, IL -1β and TNF -α in the blood at the maximum value made it possible to achieve bone tissue regeneration without the development of local purulent-inflammatory complications, while the lack of release of this cytokine led to the development of chronic osteomyelitis and slower callus formation.

We noted identical dynamics of the IL -8 concentration curve in patients of all subgroups. In patients of the first subgroup, the level of increase was maximum (p <0.05). Its increase was 9.67 times compared to the original value.

A very ambiguous picture of changes in concentration curves was observed among patients with closed fractures of long tubular bones when studying the anti-inflammatory cytokine IL -10 in the blood. An increase in the concentration of this cytokine in the blood of patients with the development of local chronic purulent-inflammatory complications (second and third subgroups) reflects an anti-inflammatory response. Moreover, in patients of the second subgroup it was higher than in the third, which probably served as the basis for normal bone tissue regeneration despite the development of a local chronic purulent-inflammatory complication. In contrast to the dynamics of pro-inflammatory cytokines, it can be noted that in relation to patients of the third subgroup, the value of these indicators has a reliable prognostic value.

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.

In patients of the second subgroup, the relative increase (compared to the first subgroup) of the leukocyte reaction was not characterized by a specific natural reaction, which confirms the low prognostic significance of the use of this analysis method.

In comparison with the period of the first study of the level of lymphocytes and monocytes in patients upon admission 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 .

In patients with impaired bone tissue regeneration, compared with patients with a normal treatment outcome, we identified a more pronounced pattern of changes in the leukocyte reaction of an inflammatory nature. 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 nature of changes in the early stages after surgery among patients of the second subgroup, who also developed a postoperative complication of a chronic purulent-inflammatory nature. However, as we know, in patients of the second subgroup, bone regenerative processes were not impaired. 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 periods of treatment for patients. Moreover, it seems to us that we can get a similar answer by assessing changes in leukocyte indices.

Throughout the study, the predominant share in organizing the level of leukocyte index of intoxication belonged to patients of the second and third subgroups .

Upon admission of patients to the clinic, the percentage of the total level of leukocyte index of intoxication 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 of up to 26.5% in the proportion of the leukocyte intoxication index 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 ratio of the leukocyte index of intoxication changes again, as at the time when patients were admitted to the clinic. At the same time, in the first subgroup of patients, the value of the leukocyte intoxication index decreased to 21.1%, and in the second and third

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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 the leukocyte index of intoxication in the first subgroup of patients, among patients in the second and third subgroups it only increased.

A comparative assessment of laboratory parameters during the regeneration of fractures of long tubular bones did not show high reliability between subgroups, especially in leukograms . However, when analyzing the reliability of the leukocyte index of intoxication, reliable values were identified in relation to patients of the first subgroup, which confirms the similarity of changes among patients of the second and third subgroups. This is precisely what can apparently be recognized as a pattern, since such an assessment reflects a nonspecific reaction of leukocytes and the formation of cell populations. It became possible to evaluate such a reaction by calculating the leukocyte index of intoxication.

The similarity of changes in the leukocyte index of intoxication among patients of the second and third subgroups indicates the identity of the body's ongoing responses, which coincided with the development of lymphopenia .

The trend towards high monocyte counts in the early stages after a closed fracture of long bones and in the early postoperative period was apparently associated with the extent of the traumatic injury. This assumption can be made based on the importance of monocytes in regulating the response of macrophages and, accordingly, osteogenesis .

What remains interesting is the high value of the leukocyte index of intoxication that we identified, which directly indicated the presence of a purulent-inflammatory process in the postoperative period. Also interesting is the fact that this indicator increased over a long period after injury and surgery, which was noted among patients in both the second and third subgroups. The noted changes in the leukocyte reaction of the blood during a closed fracture of long tubular bones were apparently also associated with the peculiarities of healing of long tubular bones. This fact must be taken into account when conducting prognostic monitoring in the treatment of patients with closed fractures of long bones.

The average share of the distribution of the leukocyte allergization index among patients with fractures of long tubular bones showed that in 40.54% of cases the level of this indicator, the maximum level of this indicator occurred in patients of the first subgroup. At the same time, among patients of the second subgroup it was 25.0%, and among patients of the third subgroup – 31.3% .

allergization index in patients of the first subgroup occurred on the 10th day after osteosynthesis surgery (49%), which accounted for almost half of all values in patients with fractures of long tubular bones.

The minimum fractional level of the leukocyte allergization index in patients of the first subgroup was recorded by us for a period of 6 months during the bone regenerative process. However, this level of the indicator still exceeded the proportional value than among patients of the second (33.4%) and third (32.1%) subgroups.

Thus, the leukocyte allergization index did not appear in patients with purulent-inflammatory complications of osteosynthesis, either during the chronic process or during bone regeneration disorders. An interesting fact remains the high values of this indicator in patients with closed fractures of long tubular bones even before surgical treatment.

The data from patients of the third subgroup played a large role in the organization of the value of the nuclear index of leukocyte shift .

Most of these transformations could be noted in patients of the third subgroup on days 3-10 of bone tissue regeneration (64.3% and 57.1%, respectively).

Over the course of 1-3 months, in patients of the third subgroup, the share of organization of the value of the nuclear shift index of leukocytes was exactly half (50%). Against this background, in subsequent periods of bone tissue regeneration, one can notice a stable, identical value in both the first and second subgroups of patients over 3-12 months of bone tissue regeneration. All possible changes in the level of nuclear shift index of leukocytes in the second subgroup of patients could be noted only in the early stages after osteosynthesis.

Thus, an analysis of the leukocyte blood reaction in patients with closed fractures of long tubular bones and in dynamics after osteosynthesis allows us to draw certain conclusions regarding their informational potential in predicting impaired bone tissue 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 . This conclusion can also be made based on the changes occurring in the nuclear shift index, which was associated with changes in the immunological reactivity of the body in patients with impaired bone regeneration after a fracture and osteosynthesis.

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Also, indicators of the leukocyte index of intoxication and the studied populations of leukocytes can directly indicate signs of endogenous intoxication in the early stages of the development of purulent-inflammatory complications from the wound and long tubular bones.
The average level of phagocytic activity in patients with closed fractures of long bones throughout the dynamic study was 87.45±4.13%. The minimum average level of phagocytic activity occurred when patients were admitted to the clinic (86.46±3.49%) and 12 months after osteosynthesis (85.85±3.55%). This possibly indicated the completion of phagocytosis processes in connection with the formation of callus.
Peak values of average phagocytic activity in patients with closed fractures of long tubular bones occurred in the period 3-90 days after osteosynthesis surgery. This activity of phagocytes manifested itself 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 with closed fractures of long tubular bones was characterized by wave-like changes, demonstrating activation in the early period of callus formation with a decrease in indicators in the process of completing the consolidation of bone fragments.
In patients of the first subgroup, 2 characteristic periods of change in the phagocytic index can be noted, in the form of a gradual increase in the early stages of callus formation (up to 3 months after surgery), followed by stabilization of the curve at the end of the 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 higher than 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 consolidation of bone tissue occurred against the background of the development of a purulent-inflammatory complication, also had a two-phase course. However, the phagocytic index in patients of the second subgroup leveled out in relation to the dynamics of patients in the first subgroup.
We did not find any particular difference between the subgroups in the share of participation in the formation of the phagocytic index value of all patients with fractures of long tubular bones.
It should only be noted: the presence of a peak fractional value of phagocytic activity among patients of the third subgroup on the 3rd day after osteosynthesis (35.6%); an increase in the proportional value due to patients of the second subgroup in the early stages after surgery on days 10-30 (33.7% and 33.9%, respectively); stable high proportional value throughout the subsequent periods of treatment, right up to the long-term period.
Thus, regarding the dynamics of changes in the phagocytic index, it can be noted that there is a differentiated manifestation in the random division of patients depending on the course and outcome of the disease.
At the same time, in patients with impaired bone tissue regeneration, the phagocytic index changes more than once, reflecting only the development of a chronic inflammatory process against the background of a low immunological reaction of neutrophils.
Regarding the percentage of the share of the number of phagocytes in the context of subgroups, one can note the priority 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 tissue regeneration. This indicates an increase in functional activity over hematopoietic activity, which was apparently associated with a shift in cell formation towards osteoclasts and osteoblasts.
Such changes not only contribute to the formation of callus, but also, although indirectly, indicate the course of regenerative processes.
The relative 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 overlapped, creating an identical picture of changes in the metabolic activity of phagocytes.
However, in the long term of treatment, starting from the 3-month treatment period, the entire priority in the lobar formation 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 month of study).
Thus, changes in the results of monitoring indicators of cellular humoral immunity and ultrasound diagnostic data of the fracture zone during bone tissue regeneration are of a phase nature in the form of: acute circulatory disturbances and increased leukocyte blood reaction, increased phagocytic activity and active production of lymphocyte subpopulations ; periosteal reaction with increased vascularization in the fracture zone, the formation of an immunological response with the participation of subpopulations of leukocytes, with active expression of T-lymphocytes and B-lymphocytes,

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increased metabolic activity of macrophages and other populations of leukocytes; formation of osteochondral callus and fully formed cellular and humoral immune response of the body (expression of T-lymphocytes and B-lymphocytes against the background of the active release of pro-inflammatory cytokines; formation of bone callus against the background of the completion of the production of immunoglobulins and anti-inflammatory cytokines.

The clinical and immunological comparison of the course of regenerative processes of bone tissue, carried out on the basis of a comparison of ultrasound data from the fracture zone and the obtained information from monitoring changes in immunological blood parameters, allowed us to identify a number of features of the body's immunological reaction. This, to a certain extent, reflects the features of the course of bone tissue regeneration, which can be interpreted as possible effective prognostic markers. To carry out such an assessment, it may be most effective to apply principles and analyzes based on the rules of evidence-based medicine

CONCLUSIONS:

1. 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 tissue regeneration, which indicates an increase in functional activity over hematopoietic activity, which was apparently associated with the transfer of cell formation towards osteoclasts and osteoblasts.
2. Clinical and immunological comparison of the course of regenerative processes of bone tissue, carried out on the basis of a comparison of ultrasound data from the fracture zone and the obtained information from monitoring changes in immunological blood parameters, made it possible to identify a number of features of the body's immunological reaction. This, to a certain extent, reflects the features of the course of bone tissue regeneration, which can be interpreted as possible effective prognostic markers. To carry out such an assessment, it may be most effective to apply principles and analyzes based on the rules of evidence-based medicine

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