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Review article

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Posttraumatic hemarthrosis in view of the inflammation theory

Olga V. Berdiugina[1]✉, Valery A. Chereshnev[1], Kirill A. Berdiugin[2]

[1] Institute of Immunology and Physiology of the Ural Branch Russian Academy of Sciences, Ekaterinburg, Russian Federation
[2] Ural Institute of Traumatology and Orthopaedics named after V.D. Chaklin, Ekaterinburg, Russian Federation

Corresponding author: Olga V. Berdiugina, berolga73@rambler.ru

Abstract

Introduction Post-traumatic hemarthrosis is identified as intra-articular hemorrhage accompanied by five classic signs of inflammation: hyperemia, hyperthermia, edema, pain and changes in the joint function. **The objective of the study** was to establish whether inflammation should be underestimated in post-traumatic hemarthrosis based on the analysis of the world scientific literature of recent years. **Material and methods** Internet search platform Web of Science (Clarivate Analytics, USA): databases Web of Science Core Collection (subscription access), Publons (open access), Medline (open access) were used to review scientific articles. Papers from the Scopus Elsevier database (Netherlands) were explored. The search depth was 15 years. Topics that did not receive coverage in the literature of this period were studied until the 1960s in some cases. More than 200 sources were identified on the subject. The literature published in the current year was analyzed covering 15.0 % of the materials, brought out in the last 5 years including the current year covering 56.3 %, in the last 10 years including the current year covering 73.8 %, in the last 15 years including the current year covering 81.3 %. **Results and discussion** The severity of injury and the accompanying inflammatory factors would characterize a rapid resolution or a more severe course of post-traumatic hemarthrosis during treatment. The combination of several variants of inflammation can lead to the development of complications including osteoarthritis in cases that show mechanisms of chronic systemic inflammation of low intensity being manifested at the time of injury; ankylosis of the joint resulting from chronic systemic inflammation of low intensity involving degenerative processes. Synovitis, as a complication of post-traumatic hemarthrosis, should be differentiated with signs of low-grade inflammation, chronic course of classical inflammation and presystemic inflammation (purulent arthritis) in view of the inflammation theory. **Conclusion** The analysis of modern literature has shown the complexity and versatility of aspects of inflammation in posttraumatic hemarthrosis. The lack of emphasis on the assessment of the inflammatory response in rehabilitation of patients with post-traumatic hemarthrosis can result in complications causing preconditions for the development of osteoarthritis, ankylosis, synovitis.

Keywords: posttraumatic hemarthrosis, inflammation, synovial membrane, immunology, cartilage, osteoarthritis, synovitis, ankylosis

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INTRODUCTION

The use of mobile vehicles across different age groups of the population in urban areas has led to a significant increase in the number of injuries to large joints. About 22 % of acute injuries of large joints are associated with injuries caused by the use of gyroscooters, electric scooters, roller skates and other electric powered devices [1]. Participation in the activities with large-amplitude movements including football, volleyball, alpine skiing and others remains the leading factor of injury accounting for 72 % of all sports-related injuries [2]. About 36 % of patients with knee injuries develop hemarthrosis of the joint [3, 4].

There are several reasons determining the high risk of hemorrhage in the joint. The pathological process is often associated with the destruction of bone and joint structures, injury to the vessels of the articular capsule or bleeding from cancellous bone tissue in case of epiphyseal fracture [5, 6]. Impaired blood coagulation caused by the synthesis of autoantibodies to factor VIII [7], congenital deficiency of factor XI [8] and other hereditary and acquired changes in the rheological properties of blood can cause hemarthrosis and the risk of the factors can be reduced by artificial introduction of missing hemocomponents and selective use of clotting factor inhibitors [9, 10]. Rare causes of hemarthrosis can include collagen vascular diseases, arthritis, hemochromatosis and myeloproliferative diseases [11, 12]. Pigmented villonodular synovitis, atrioventricular fistulas, and traumatic pseudoaneurysm are exquisite causes of intra-articular hemorrhage [13, 14].

The outcomes of hemarthrosis are dependent on the methods used and also correlate with the causes of the pathological condition [15]. In particular, it is known that the nature of the medical manipulations undertaken can determine the risk of complications in the early and long-term follow-up periods. The outcome of post-traumatic hemarthrosis often result in early osteoarthritis [16] and a five-fold risk as compared to the intact joint [17]. Fibrosis may develop in some joints and

transform into ankylosis [18, 19]. The reasons behind the phenomena are not fully understood; a stimulus can be associated with organization and sclerosis of an intraarticular thrombus [20]. It has been experimentally established that a 48-hour delay in blood aspiration from an injured joint becomes sufficient to cause long-term side effects of hemofluid in the joint [21]. Active or passive (caused by the presence of pain syndrome) immobilization of the joint, used for the first time after a hemorrhage, can increase the harmful effect of blood on the articular cartilage [22]. Unregulated inflammatory reactions can occur in 27-38 % of cases after joint injury. Osteoarthritis develops in 50 % of patients within 15 years after injury. The complication can be caused not only by the blood in the joint, but rather the development of certain processes that trigger the long-term results of hemorrhage into the joint cavity with manifestations of primary and secondary alteration, causing local and systemic changes [23].

Summarizing, it can be revealed that all cases of blood detected in the joints that can be detected were not detected, some cases of the body's manifestation of its presence can be detected, and other cases include events at a short or long terms.

One can expect some general body response to the presence of blood in the joint, whatever the cause which can be implemented and completed within a short time without significant consequences for the health of the individual and can cause complications at a short or long term in other cases. If we focus on the fact that a high-strength mechanical impact associated with trauma creates conditions for the activation of a cascade of local metabolic reactions [24], it can be assumed that the phenomenon observed is the inflammation that develops in response to mechanical damage to joint tissues, including ruptured walls of the peripheral vessels.

Therefore, the study of the body's response to intra-articular hemorrhage in view of the inflammation theory becomes an important task for understanding the outcomes of treatment and the occurrence of complications at a short- and long-term follow-up periods. Post-traumatic hemarthrosis in young patients without concomitant pathology can be the optimal clinical model of the study, because it develops due to external causes of force majeure, without the involvement of internal factors including hemophilia of various origins, chronic inflammation of internal organs and activated aging programs.

The objective of the study was to establish whether inflammation should be underestimated in post-traumatic hemarthrosis based on the analysis of the world scientific literature of recent years.

MATERIAL AND METHODS

Design of the study An internet search of Web of Science (Clarivate Analytics, USA): Web of Science Core Collection (subscription access), Publons (open access), Medline (open access) was performed to review scientific articles. Papers from the Scopus Elsevier database (Netherlands) were explored. The selection of articles was based on the keywords "hemarthrosis", "inflammation", "posttraumatic", "synovial membrane", "immunology", "cartilage", "osteoarthritis", "synovitis", "ankylosis", "injuries", "knee trauma", "biomarker", "matrix metalloproteinase", "repair", "arthrocentesis", "synovium", "interleukin", "non-haemophilic", "acute phase", "synovial fluid", "ADAMTS", "blood-induced", "immune cell", "intra-articular", "joint aspiration". The search depth was 15 years. Topics that did not receive coverage in the literature of this period were studied until the 1960s. More than 200 sources were identified on the subject. The literature published in the current year was analyzed covering 15.0 % of the materials, brought out in the last 5 years including the current year covering 56.3 %, in the last 10 years including the current year covering 73.8 %, in the last 15 years including the current year covering 81.3 %.

RESULTS

Post-traumatic hemarthrosis is viewed by the medical community as an intra-articular hemorrhage. The pathological process is not considered an inflammation from this point of view because it is not always possible to identify the characteristic signs of inflammation in all compartments of the joint. Post-traumatic hemarthrosis is characterized by five classic signs of inflammation including hyperemia, hyperthermia, edema, pain, and changes in the joint function [25]. There is unequivocal attributive evidence that the process in question is inflammation and the pathological process is caused by a pronounced mechanical injury [26]. A careful study of the circumstances of the occurrence of hemarthrosis suggests that post-traumatic hemarthrosis develops due to two sequential damaging factors that cause a response of the body: the first (exogenous), which is a mechanical impulse of high intensity, and the second, additional (endogenous), hemorrhage into the joint cavity resulting from injury to the synovial vessels, mainly capillaries [27].

Severe local damage, which determines the development of post-traumatic hemarthrosis, is the starting point for the development of classical (canonical) inflammation with the need to stop the damaging factor, localize the focus of the process and restore damaged tissues [28]. The boundaries of the focus of inflammation is an important aspect to be identified inside the synovial layer or with a transition from the joint cavity and affecting the cartilage and then the bone. The classical (canonical) inflammation is known to be associated with the participation of the vascular bed to ensure a rapid influx of cells and humoral factors to the site of injury, activation, progress, and elimination of the destruction focus [29]. The functional state of the body can return to normal in a short time in the case of a fixed time interval of the changes and a small amplitude of tissue reactions. In this case, it can be assumed that inflammation is a process aimed at maintaining the metabolic integrity of tissues and organs. It is obvious that there must be such a time point, the type and volume of an intervention, which can create prerequisites for the return of inflammation to the physiological norm to avoid complications at a short and long term. This statement can be confirmed by rapid stabilization of the patient condition, absence of long-term consequences of damaging effects during rapid evacuation of blood from the joint cavity [30]. In general, we can talk about the possibility of reversibility of acute inflammation by blocking complications, including chronicity of the process. The inflammatory response in hemarthrosis in young patients without concomitant pathology is characterized by classical (canonical) inflammation along with the borderline state of extreme normal physiology and rapid elimination of the consequences of hemarthrosis leads to pronounced normalization of joint function in the majority of clinical cases. However, it is not uncommon for post-traumatic hemarthrosis to occur in patients who already have other types of inflammation; in this scenario, the outcome may depend on the type of inflammatory reaction present.

Development of the inflammation theory

More than 2 thousand years have passed since the main signs of inflammation were first described as the reaction of body tissues to phlogogens of various origins, with the processes not explained so far due to a variety of clinical manifestations, which may be dependent on the extent of injury, duration of the course, involvement of organs or organ systems, and a number of other factors. The concept of inflammation as a typical pathological process focuses on the characteristics of pro-inflammatory stress reactions of individual cells, organs and tissues and the body as a whole [31], with the identification of several general pathological processes associated with tissue stress, including classical inflammation, systemic high-intensity inflammation, chronic local and systemic inflammation of low intensity [29, 32], low-grade inflammation [33], study of local and systemic manifestations of classical (canonical) inflammation [34], and other divergences (Table 1). Different types of inflammatory reactions are associated with the prevalence of cellular and tissue stress, and with the functional transformation of the microvasculature [35, 36]. With the inflammation as a general pathological process, new facts about the endocrine, nervous, circulatory and immune systems being involved in the reaction appear. The repertoire of cells, the receptor apparatus, and synthesized cytokines are shown to be specific for different localizations and types of the process. There is an assumption that the process is regulated in such a way as to ensure the recruitment of certain types of cells both in the focus and outside. For this, extracellular mediators and regulators are used to include vesicles, eicosanoids (prostaglandins, leukotrins, etc.), growth factors, cytokines, and complement. A wide range of factors can determine which cells and mediators will be involved in the process and may explain the variety of inflammation types.

The differentiation of the inflammation types in clinical practice is one of the key points that allows assessing not only the patient's condition during treatment, but also predicting the type and timing of the onset of complications. It becomes important to consider various aspects of damage to cells and tissues of the joint in post-traumatic hemarthrosis in order to assess them comprehensively and determine the type of inflammatory reaction.

Damage caused by red blood cells and their components

Numerous blood cells resulting from an injury cause intensive attack to the physiological reactions of the tissues of a normal joint. Erythrocytes that enter the cavity during hemorrhage undergo hemolysis with the release of hemoglobin, hemin and iron. Toxic reactions of hemoglobin are realized through pro-oxidant and pro-inflammatory mechanisms, leading to the consumption of nitric oxide (NO) by endothelial cells with endothelial dysfunction. Hemoglobin destruction products reduce and deplete the NO reserve changing vasodilation [37].

Table 1

Types of inflammatory reactions from the point of view of the inflammation theory according to the literature data [29, 31, 32]

Stress types and manifestations of stress reactions		Correlation between damage and body response	Variant of impaired functioning	External signs (at the level of the organism)	Internal signs: in the focus of the process (local manifestations)	Internal signs: outside the focus of the process (systemic manifestations)
Cellular stress	Daily life activities	The impact of a force (one powerful inductor or a combination of weak ones) corresponds to the potential response of the body	Mild disturbance (physiological)	leveled out	•Response to DNA damage • Emergence of stress miniRNAs • Stress of the endoplasmic reticulum • Mitochondrial stress • Lysosomal stress (autophagy) • Oxidative stress • Formation of an intracellular network of signaling pathways • Emergence of stress receptors • Synthesis of heat shock proteins • ATP synthesis • Formation of inflammosomes	Limited by the threshold of normal values
Tissue stress	Low-grade inflammation	The impact of low intensity force corresponds to an adequate response of the body	Short-term adaptive tissue stress (low intensity process)	pain	•Local manifestations are associated with the accumulation of phagocytes •Broad involvement of scavenger receptors • Recognition of relatively low concentrations of PAMP and DAMP, aberrant metabolites •Allostasis •Absence of exudative-vascular reactions •Does not lead to inflammation	May occur with progression
	Canonical (classic) inflammation	The impact of a local force of high intensity is greater than the possible response of the body (defensive reaction with the ability to stop the destruction process)	Severe impairment (change in function)	•Pain •Hyperemia •Edema •Hyperthermia •Muscle spasm •Functional change	•Limited focus of the main process •Migration of phagocytes that infiltrate tissues •Participation of the microvascular bed, tissue edema, exudative reaction •Involvement of lymphoid tissue (chemokines, polarization of lymphocytes, immune complexes)	Sub-threshold activation (reversible tissue stress): • liver (synthesis of APP) • bone marrow (formation of monocytes-macrophages) • lymph nodes (differentiation of lymphocytes) • mediator reactions • enzymatic • hemostatic • hormonal (corticosteroids, catecholamines)
	Presystemic inflammation	A short balance between the destructive factor and the body's response; a significant influence not of the damaging factor itself, but of previous inflammation	Violations for a short time (from several hours to several days), transition to another quality level	•Pain •Hyperemia •Edema •Hyperthermia •Muscle spasm •Function change	•Generalized inducible production of cytokines and other regulatory stress molecules •Intravascular activation of complement and various types of leukocytes •Systemic degranulation of mast cells •Disseminated intravascular coagulation	•Systemic microcirculatory disorders •Damage to significant areas of tissue, •Lack of perfusion, •Presence of an infectious agent
	Chronic systemic inflammation of low intensity	The impact of an external force is comparable to the response of the body; a delayed response develops and is not sufficient to cause classical or systemic inflammation	Prolonged exposure to one or more factors of low intensity above the physiological threshold	•No hyperemia •No swelling •No severe leukocyte infiltration •Situational assessment	•Gradual accumulation of genome damage, changes in proteomics and metabolomics •Involvement of parenchyma and stroma cells in the process •Reduced involvement of professional inflammatory cells •Appearance of specific inducers of inflammation	•Process delocalization •Low activity of the process (boundary values of norm and pathology): •in the liver (synthesis of APP) •mediator reactions (cytokines) •signs of organ dysfunction develop slowly •accelerate the aging process •no connection with severe manifestations of chronic classical inflammation •may present with metabolic syndrome, more commonly with type 2 diabetes mellitus, neurodegeneration and chronic heart failure
	Acute systemic inflammation	Systemic damage comparable to local damage. The strength of the damaging factor overcomes buffer barriers that prevent systemic activation of pro-inflammatory mechanisms	Systemic metabolic disorders, transfer of program mechanisms from the focus of inflammation to the system level	• Septic shock •Acute respiratory distress syndrome, •DIC	•Release of PAMP and DAMP into the bloodstream •Intravascular hemolysis •Mast cell response •Synthesis of cytokines •Pathological activation of intravascular leukocytes, monocytes/macrophages •Accumulation of toxins •Increase in blood thrombin, complement anaphyloxins •Intravascular NETosis •Critical changes in homeostasis associated with hyperthermia, hypoxia, osmotic resistance, the ratio of energy balance molecules (AMP/ADP/ATP)	•Organ dysfunctions •Tissue destruction •Critical micro- and macrogenomic disorders •Systemic activation of endotheliocytes •Microthrombosis of postcapillary venules •Intravascular complement activation and hemostasis •Dysfunction of the immune system •Toxic accumulation of inflammatory mediators in the blood •Systemic degranulation of mast cells

Note: AMP/ADP/ATP, adenosine monophosphate/adenosine diphosphate/adenosine triphosphate; ATP, adenosine triphosphate; APP, acute phase proteins; DIC, disseminated intravascular coagulation; DNA, deoxyribonucleic acid; RNA, ribonucleic acid; DAMP, damage-associated molecular patterns; NET, neutrophil extracellular traps; PAMP, pathogen-associated molecular patterns

Binding to haptoglobin synthesized by liver cells is one of the mechanisms for reducing the toxicity of hemoglobin which is a manifestation of systemic reactions in classical (canonical) inflammation. An excess of hemoglobin, the inability to bind into complexes with haptoglobin can lead to the formation of metHb (methemoglobin) containing Hb-Fe3+ (hemoglobin-iron), with the release of hemin, the main product of oxidative reactions. This process is accompanied by the transfer of reactive porphyrin to cell membranes or soluble plasma proteins. The hemin released acts as a ligand for molecular signaling interactions, developing cytotoxic and inflammatory activity and damaging blood vessels [37]. Free hemin can selectively bind to cellular receptors, DNA (deoxyribonucleic acid) binding factors and enzymes. The significance of the binding potential lies in altering cellular metabolism and gene transcription. When hemin is integrated into the cell, this compound is neutralized by heme oxygenases 1 and 2 with the release of iron and carbon monoxide (CO), providing anti-inflammatory, antioxidant and anti-apoptotic effects [37]. Hemoglobin can effect the ability of synovial tissues to produce plasminogen activators and matrix metalloproteinases, which play an important role in the degradation of articular cartilage. Hemoglobin added to the culture of human joint synovial cells leads to a marked increase in fibrinolytic and gelatinolytic activity. Fibrinolytic activity is associated with increased activity of uPA (urokinase-type plasminogen activator), and gelatinolytic activity is related to increased content of MMP-2 (matrix metalloproteinase) and MMP-9 [38]. The participation of scavenger receptors does not allow to properly inactivate the excessive amount of free hemoglobin, iron, and hemin causing oxidative stress, damage to the vascular endothelium, impaired microcirculation, microthrombosis, formation of reactive oxygen species, and pro-inflammatory processes [37]. Long-term presence of erythrocytes in the joint cavity in the absent absorption by macrophages leads to the accumulation of iron in the form of deposits of synovial hemosiderin with activation of inflammation, proliferation, and angiogenesis [39]. Deposition of iron in the synovial membrane and subsequent inflammatory reaction experimentally persisted for 8 weeks. Immobilization may interfere with the removal of hemosiderin with prolonged "hemosiderin" inflammation. Inflammation in the cases is confirmed by the presence of $CD68^+$ (cluster of differentiation) cells in the synovial membrane with increased population of the cells after 1 month and return to the normal level at 2 months. The effect of joint hemorrhage on inflammation decreases at 4 weeks with immobilization being the main cause of inflammation [22, 37].

Iron is reported to be involved in several mechanisms leading to synovial inflammation [40]. Iron deposition (hemosiderosis) may be irreversible and serve as a permanent trigger for inflammatory activity in the synovial environment of macrophages [21]. Another mechanism of damage associated with exposure to erythrocyte components may be the activation of oxidative stress by iron and lead to cartilage destruction [41]. Reactive oxygen species, hydrogen peroxide (H_2O_2), in particular, begin to be synthesized by activated mononuclear cells and chondrocytes. In the presence of iron, H_2O_2 leads to the formation of highly toxic hydroxyl radicals, stimulating apoptosis of chondrocytes followed by irreversible changes in the cartilage tissue. Iron deposition can lead to increased expression of genes that bind the p53 (protein) [39], initiating a change in the regulation of the cell cycle.

Heme, a breakdown product of erythrocytes, can also activate pro-inflammatory mediators, causing pathological effects on cartilage and synovium [16]. Heme promotes production of reactive oxygen species by disrupting the balance of endothelial vasodilators and vasoconstrictors. This process is a factor in the formation of coagulopathy [37]. Hemopexin, a heme-binding plasma glycoprotein, a second-line defense protein (in addition to haptoglobin) inhibits the consequences of the hemolytic damaging effect of toxic blood components by involving liver cells in the inflammatory response preventing heme from entering endothelial cells [37].

Circulating erythrocytes are the main source of IL-33, a member of the IL-1 cytokine superfamily, which is released during hemolysis causing a cascade of activation of various cytokines, thus contributing to the pathogenesis of inflammation [42]. There is evidence that platelet activating factor can be released from erythrocytes, exposing phosphatidylserine to the cell surface, thus disrupting the interaction of erythrocytes with the endothelium [37]. The release of MIF (macrophage migration inhibitory factor) is another important consequence of RBC destruction. In recent years, it has become obvious that erythrocytes are the main reservoir of this factor, an enzymatically and chemotactically active cytokine, one of the most powerful inflammatory mediators of the immune system [37, 43].

In general, the potential consequences of free hemoglobin in the joint cavity that have been established so far include radical oxygen reactions, oxidative stress, local vasoconstriction, pro-inflammatory disorders of cellular metabolism, tissue damage, inflammatory infiltrates, ceramide release, endothelial cell dysfunction, vascular damage, eryptosis, dysfunction of mesenchymal stem cells, pain [37]. There are experimental data

showing that erythrocytes can disappear from the joint cavity within 48 hours without causing macrophage recruitment [21]. The available information may not reflect the existing significant discrepancies between the degree of blood exposure to cartilage *in vivo* and *in vitro*.

Biochemical changes

Intra-articular hemorrhage is the cause of a significant increase in the level of proteoglycans in the articular cartilage with the articular surface being more fibrillated with decreased chondrocytes in the superficial areas of cartilage [44]. The load-bearing properties of articular cartilage are provided by large and highly charged side chains of glycosaminoglycans. Inflammation leads to a decrease in cartilage stability: large aggregates of aggrecan are cleaved by agrecanases. The latter are members of the ADAMTS family of zinc-dependent enzymes (disintegrin and metalloproteinase with thrombospondin motifs) within metalloproteinases. ADAMTS-4 and ADAMTS-5 are the main aggrecanases responsible for the degradation of aggrecan. Aggrecan fragments, which are formed as a result of cleavage of the CS-2 domain (chondroitin sulfate, chondroitin sulfate) increase in the synovial fluid after a knee joint injury. Cleavage in IGD (aggrecan interglobular domain) occurs after cleavage of the CS-2 domain. Fragments containing G3 (globular domain) originate from impaired cartilage by means of ADAMTS-9. The G3 domain is involved in the binding of complement factors C1q and C3, activating the classical and alternative inflammatory pathways. ADAMTS-9 plays an important role in complement regulation during inflammation in the joints [45].

A change in the concentration of sulfated glycosaminoglycans (sGAG) located on the cell surface and in the extracellular matrix was seen in the fluid aspirated from the knee joint with post-traumatic hemarthrosis. There is a close relationship between changes in the synthesis of collagen proteins and inflammation, exudation, in particular. The sGAG level increased to the upper normal limit by day 1 of injury and, the concentration exceeded the level observed in healthy individuals by 5 times at 2-23 days [46]. The level of the ARGS-fragment of aggrecan (ARGS-neoepitope aggrecan), a cartilage-specific proteoglycan nuclear protein, increased in the aspirate of the knee within a few hours of injury reaching the upper limit of normal. The concentration increased by 1.5 times the next day after the injury and maintained at a consistently high level, exceeding the values of intact joints by 23 times at 2 to 23 days [46].

An experimental 4-day exposure of cartilage tissue to a significant volume of blood (in a ratio of 1:1) led to long-term inhibition of the synthesis of cartilage matrix proteoglycan and to a long-term decrease in the content of proteoglycan in the tissue, leading in the long term to degenerative changes in the cartilage [47]. Inhibition of proteoglycan synthesis caused by exposure to blood, blood clots, and concomitant bleeding factors in the articular space on cartilage tissue was reversible depending on the duration of exposure. Almost complete reversibility of the inhibitory effects was observed after a one-day contact of the cartilage with blood, 65 % inhibition of proteoglycan synthesis noted after a two-day exposure; 3-4 day exposure to blood showed no significant restoration of synthesis in the absence of blood [47]. With a 12-day exposure to blood, a complete suppression of proteoglycan synthesis was noted in the experiment [47]. The combination of erythrocytes and mononuclear cells among all components of whole blood led to the greatest dose-dependent irreversible inhibition of proteoglycan synthesis by cartilage [48].

Some authors have shown that the combination of the plasminogen-plasmin system, MMPs, and enzymes of the ADAMTS family can significantly destroy the extracellular matrix. Hemoglobin acts as an inducer of uPA, MMP-2, and MMP-9 expression by fibroblasts. Elevated levels of aggrecanases, gelatinolytic and fibrinolytic enzymes after stimulation with hemoglobin can contribute to degradation of the articular cartilage extracellular matrix [49], and MMPs are activated with blood in a direct correlation with exposure time. Removing blood later does not stop this process. The MMP activity doubled within 12 days after blood aspiration in cases where a one-day exposure was noted [47].

Despite the injury to cartilage, (not to the bone), changes in the concentration of SPARC (secreted protein acidic and rich in cysteine), a marker of the synthesis and accumulated type I bone collagen, OPN (osteopontin), a regulator of bone matrix mineralization are sometimes recorded in the synovial fluid osteopontin) that can be associated with activation of endothelial cells and macrophages in response to tissue damage and with an increase in bone matrix degradation over time after injury [46]. It is impossible to assess the way the blood acts in the joint with hemarthrosis on the first day, whether it undergoes clotting or not. If there is coagulation, then to what extent and how quickly does clotting occur? The effects of clotting blood were compared with those of non-clotting blood. No differences in the effect of blood on cartilage have been identified regardless of the coagulation/noncoagulation of the biofluid [47]. The study of biochemical reactions involving various metabolites in post-traumatic hemarthrosis is important because the articular cartilage may undergo irreversible damage with degenerative changes of the joint as a result of transformation [47, 50].

Interestingly, contralateral cartilage damage was found in induced experimental hemarthrosis, suggesting that this process is caused by systemic modulators (signs of systemic inflammation) that are activated by intraarticular bleeding. Moreover, neurogenic inflammation has been proposed as a cause of contralateral injury [51]. Local inflammatory processes induce local neurogenic stimulation, which can cause a bilateral response of the nervous system leading to bilateral cartilage degeneration. The involvement of autoimmune mechanisms cannot be ruled out, since some proteoglycans are isolated from the immune system and cause an autoimmune response upon contact with blood [52]. The use of the contralateral knee as a control in research is questioned due to the fact that damage to the opposite cartilage is observed up to 16 days after induced hemarthrosis [52]. Additionally, a short contact of cartilage with blood – up to two days – can be observed with inflammation, if the tissue injury is not very severe.

Changes in the cells of synovial fluid in hemarthrosis

An experimental study of the aspirate of the knee in post-traumatic hemarthrosis showed that, the population of M1 monocytes increases in the synovial fluid on the first day after injury with the volume being 6 times greater than the number of the cells in the norm. The second day after injury is associated with an increase in the M2 population of monocytes, which exceeds the number of similar cells in healthy individuals by 2.5 times [53]. Various populations of macrophages/monocytes are able to secrete anti-inflammatory factors and chondrogenic cytokines that inhibit inflammation, promoting cartilage repair. They can also initiate tissue fibrosis: stimulate cartilage degradation through matrix metalloproteinases prolonging inflammation and terminating chondrogenic differentiation of stem cells [24]. Monocytes/macrophages in the mononuclear cell population, together with erythrocytes present in the hematoma, are responsible for the irreversible inhibition of matrix synthesis. Small amounts of IL-1, which is produced by activated monocytes/macrophages, increase the production of hydrogen peroxide by chondrocytes. Hydrogen peroxide reacts with hemoglobin iron of impaired and phagocytized erythrocytes, which leads to the formation of hydroxyl radicals near chondrocytes causing chondrocyte apoptosis and irreversible suppression of cartilage matrix synthesis [47].

Response of synoviocytes

Macrophages of the synovial membrane absorb and remove blood components from the joint fluid after bleeding including toxic iron (Fe^{2+}) [54] and phagocytizing blood with synovial tissue cells reducing the negative effect on joint tissues [47]. However, there is evidence that synovial tissue can enhance cartilage damage by contributing to inflammatory responses through changes in the polarization of macrophages. Even low doses of hemoglobin induce the expression of ADAMTS-5 and ADAMTS-9 by synovial cells [45].

The initial stage of hemorrhage into the joint has been shown to be associated with hypertrophic changes and proliferation of synovial tissue using an experimental model of hemarthrosis with neovascularization and a perivascular acute inflammatory reaction. The terminal stage of hemarthrosis includes destruction of the articular cartilage, the articular effusion, formation of fibrous tissue and secondary osteoarthritis [49]. Synoviocytes of both subtypes (fibroblasts and macrophage-like synoviocytes) can express high levels of the NLRP3 (nucleotide-binding oligomerization domain, leucine rich repeat and pyrin domain containing) inflamosome when damage, which is a sign of the cellular pro-inflammatory stress [55].

Chondrocyte reaction

Cartilage and blood contact leads to apoptosis of chondrocytes [56]. Since the articular cartilage is not vascularized and contains no phagocytes, apoptotic bodies formed during the destruction of articular surface can be absorbed by the cells of the synovial membrane. Phagocytic reactions are characteristic of inflammation. Following injury, chondrocytes produce MMPs and agrecanases, enzymes that destroy the extracellular matrix. Activation is mediated in various ways: through NF-kB (nuclear factor kappa-light-chain-enhancer of activated B cells, nuclear factor kappa-bi) and MAP kinase (mitogen-activated protein kinase, mitogen-activated protein kinase), synthesis of active forms of oxygen organized by mitochondria. Degrading proteases gradually destroy the collagen network, promoting the loss of proteoglycans and leading to destructive changes in the matrix, which affects the function of chondrocytes. The transfer when chondrocytes reduce the production of essential extracellular matrix (ECM) proteins and increase the production of unfavorable enzymes, is thought to be due to altered mitochondrial function. Trauma also leads to increased crosswise interference between cartilage and the surrounding joint tissues including subchondral bone and synovium. The latter is the central source of acute inflammation factors, as it is rapidly infiltrated by activated immune cells in response to joint injury [55]. Cells of the bone proliferation zone and articular chondrocytes can secrete growth factors and cytokines into the hematoma [18]. The uneven surface and heterogeneity of the cartilage within the joint due to damage by blood components make the distribution of tension and fluid pressure in the tissue uneven, while gene expression can differ in different places depending on the magnitude, frequency and time of loading. There is a critical upper and lower load threshold to

trigger the expression of certain genes. Chondrocytes respond to a changing load, including hydrostatic pressure during movements by mechanical and osmotic stress, and membrane stretching. The pressure can also change during normal movement of the body, however, pathological changes are associated with more pronounced loads. The processes are mediated by the involvement of membrane ion channels of the transient receptor potential TRPV1, TRPV4, TRPC3 and TRPC1 (TRP, transient receptor potential; V, vanilloid; C, canonical) with TRPV1 serving as a hydrostatic pressure transducer in chondrocytes. However, TRPV1 inhibition does not completely suppress the effects of hydrostatic loading on S-GAG production in chondrocytes [57]. A number of ion channels mediate inflammatory responses.

Local immune response

Fibrin networks and a collagen matrix are formed in the joint space on the side of hemarthrosis during the first 24 hours of hematoma organization and serve as a framework for infiltrating cells (leukocytes, fibroblasts). Intact articular surfaces (in a small hemorrhage) prevent penetration into the hematoma of key signaling factors that regulate collagen mineralization and osteogenic differentiation of mesenchymal stem cells (MSCs). A large number of macrophages migrate to the injury site for immediate removal of debris, necrotic tissues at the injury site within the next 48-96 hours [18]. The focus of hemarthrosis is imbibed by a significant amount of neutrophilic granulocytes on the first day. There is an active immune response activated through the T-cell receptor, co-stimulation of T-lymphocytes and chemotaxis. There are signs of a pronounced inflammatory reaction [18]. Several genes are overexpressed at the stage including CD86, a co-stimulatory signal for T-cell activation, MRC1 (mannose receptor C-type 1), promoting endocytosis of glycosylated protein and collagen in macrophages, and CD163 (involved in any phagocytic reactions, in the phagocytosis of the hemoglobin/haptoglobin complex regulating the clearance of hemoglobin in the bloodstream) [58].

Changes in cytokine synthesis

Activation of the synovial membrane in post-traumatic hemarthrosis affects the cartilage through production of pro-inflammatory cytokines and proteinases that destroy the cartilage matrix [59]. Synthesized by chondrocytes and synoviocytes, IL-6, a mediator of the acute phase response, has the potential to initiate joint damage and sensitize nociceptors [60].

Iron-loaded synovial tissue synthesizes TNF-α (tumor necrosis factor), INF-γ (interferon), IL-1 and IL-6. The induction is carried out by the receptor activator RANKL. The mechanism is associated with an increase in inflammation and in myc expression by synovial fibroblasts [39]. Short-term exposure to blood leading to dose-dependent inhibition of proteoglycan synthesis, does not depend on the production of IL-1 and TNF-α [61]. Hemorrhage in the joint increases the expression by neutrophils, chondrocytes, synovial fibroblasts of MMP-8 and MMP-13 – type II collagen endopeptidases, the basis of the articular cartilage. MMP-8 interacts with cytokines that support the inflammatory process contributing to the chronicity of the pathology. MMP-13 expression, which increases 2 weeks after injury, remains high up to 1 month. Moreover, the increased expression of TNF-α 14 days after the onset of hemarthrosis seems to maintain the high expression of matrix metalloproteinases that support inflammation [22].

Inflammatory cytokines (TNF-α, IL-1 and IL-6), synthesized by M1 macrophages, destroy chondrocytes, inhibit the synthesis of collagen II and glycosaminoglycans, stimulating the production of MMP-1, MMP-3, MMP-13, MMP-9, ADAMTS and COX-2 (cyclooxygenase), which are proteolytic enzymes [62]. Changes in the concentration of IL-1β increasing to 10.9 pg/ml (the norm is 0.1-4.4 pg/ml), IL-6 increasing to 3386.4 pg/ml (the norm is 0,1-503.9 pg/ml), IL-8 increasing to 163.1 pg/ml (the norm is 2.1-421.9 pg/ml), TNF-α increasing to 8.7 pg/ml (the norm is 0.4-9.8 pg/ml) in the aspirate of the knee joint with hemarthrosis [46].

Molecular mechanisms of the reaction

POSTN (periostin or osteoblast-specific factor OSF-2, periostin), a gene specifically expressed in collagen-rich tissues, is activated on the first day after joint hemorrhage being associated with increased mechanical stress [18]. POSTN acts as a structural matrix component that regulates collagen cross-linking and plays an important role in tissue responses to stress [63]. POSTN is considered to be a key extracellular matrix protein required for reparative processes. The other important role is to promote the formation of the periosteal callus. Signaling in this case is carried out from undifferentiated mesenchymal cells and immature preosteoblasts of periosteal tissues [64].

Vascular reaction

Blood and platelets have a direct effect on the permeability of synovial venules and capillaries, reducing the barrier function for at least 16 hours after hemorrhage, which is an important factor in the development of the inflammatory response [39]. Hypervascularization due to high iron concentrations in posttraumatic hemarthrosis leads to expansion of the synovial lining and subsynovial membrane tissue resulting in a fourfold increase in synovial cell mitotic activity and endothelial cell pinocytosis. Mature collagen between endothelial

cells, pericytes and layers of pericytes, iron-containing mononuclear cells appear after 8-24 hours [39]. VEGF (vascular endothelial growth factor), PDGFB (platelet derived growth factor subunit B) and neovascularization at the site of injury contribute to an increased oxygen concentration in the cartilage causing degenerative processes. The occasional oxygenation impairs the metabolism of cartilage tissue [65].

The increased intracapsular pressure caused by bleeding ultimately exceeds capillary perfusion pressure and leads to repeated hypoxic-reperfusion injuries, generation of ROI (reactive oxygen intermediates) and superoxide radicals by synoviocytes [39].

Complications and possible causes from the view of the inflammation theory

Common complications of post-traumatic hemarthrosis include osteoarthritis, synovitis and ankylosis. Osteoarthritis as a monoarticular disease develops with post-traumatic hemarthrosis [66]. It is not only a trauma that determines the risk of osteoarthritis. Mitochondrial dysfunction, molecular patterns associated with damage, cytokines, metabolites, bioactive lipids, prostaglandins, tricarboxylic acid cycle intermediates, and crystals in the synovium activate synovial cells and mediate synovial inflammation. Overweight, type 2 diabetes mellitus, activation of the aging program play an important role in the pathogenesis of osteoarthritis [67]. Osteoarthritis is associated with the reaction of molecular proteins of synovial fluid to acute knee injury, most pronounced for MCP-1 (monocyte chemoattractant protein) and IL-6 at 2 months of injury. Changes in the concentrations of IL-6, IL-8, MMP-1, MMP-2, and MMP-3 in the synovial fluid are also among the factors in the development of osteoarthritis [68]. Trauma induces the formation of a heterogeneous microenvironment rich in immune cells, consisting of T-lymphocytes with multiple Th phenotypes (T-helper, T-helper). Of all CD4 subsets, Th1, Th2, and Th17 are becoming the dominant populations, these phenotypes are similar to those of Th cells found in patients with progressive osteoarthritis [69]. Considering osteoarthritis as a complication of post-traumatic hemarthrosis, the condition can develop in patients with mechanism of low-intensity chronic systemic inflammation being present in the body at the time of injury including cases of atherosclerosis, type 2 diabetes mellitus, autoimmune disease, aging programs. In this case, the acute course of classical (canonical) inflammation is transformed into chronic systemic inflammation, leading to the gradual destruction of the cartilage. Synovitis is another complication of post-traumatic hemarthrosis [70]. The synovial fluid is predominantly represented by neutrophilic granulocytes, rarely by lymphocytes, in specific and nonspecific arthritis/synovitis. Purulent arthritis may occur with the articular cavity being infected with infectious agents [71]. The predominance of polymorphonuclear cells in the synovial fluid is accompanied by severe leukocytosis in septic arthritis[72]. Objective information about the activity of the process, an infectious agent, the results of the selection of antibiotic therapy, and the assessment of the need for surgical intervention can be obtained with laboratory examination of synovial fluid using arthrocentesis [73]. Signs of low-grade inflammation, the chronic course of classical inflammation and pre-systemic inflammation (purulent arthritis) must be differentiated for synovitis in view of the inflammation theory and adequate treatment tactics. Ankylosis is a rare complication of post-traumatic hemarthrosis with the bone neoplasm being pathological, since osteogenesis replaces the normal articular structure without remodeling processes. Osteoblasts derived from mesenchymal stem cells are the only bone-forming cells at the site of injury. Similar signaling molecules and pathways are used for ankylosis and for physiological remodeling including BMP (bone morphogenic protein) and Wnt (combination Wg + Int without decoding, established expression). Fibrous ankylosis is associated with a prolonged phase of hematoma and impaired formation of the cartilaginous tissue. In fibrotic ankylosis, there are significantly lower levels of expression of mRNA (matrix ribonucleic acid), HIF-1α (hypoxia-inducible factor, hypoxia-induced factor), VEGF (vascular endothelial growth factor), VEGFR-2 (receptor VEGF, vascular endothelial growth factor receptor), SDF-1 (stromal cell-derived factor, stromal cell factor), Ang-1 (angiopoietin, angiopoietin), Tie-2 (tyrosine kinase, tyrosine kinase), vWF (von Willebrand factor, von Willebrand factor), CYR-61 (cysteine-rich angiogenic inducer), FGF-2 (fibroblast growth factor), TIMP-1 (tissue inhibitor of metalloproteinase), MMP-2 and MMP-9 than with bone. Angiogenesis and osteogenesis are closely integrated: VEGF, produced by osteoblast progenitor cells, stimulates osteoblast differentiation through an intracrine mechanism. Angiogenesis determines the outcome of injury: increased neovascularization in the joint space promotes osteogenesis and leads to bone ankylosis [74]. Interaction of hemarthrosis with cells of the proliferative zone or chondrocytes is another reason for ankylosis. Proliferation zone cells and articular chondrocytes can secrete cytokines and growth factors into the hematoma. Or osteoporosis precursor cells under the fibrous layers may migrate into the joint space through hematoma. These factors will contribute to the development of ankylosis [18]. Ankylosis of the joint may be a consequence of chronic systemic inflammation of low intensity with the involvement of degeneration processes from the view of the inflammation theory.

Main therapeutic approaches to treatment

Oral use of iron chelators after the onset of hemarthrosis does not bring significant results in reducing pathological reactions [59], and there have been no reports to evaluate the potential of an iron chelator administered intravenously or locally. However, there is a reason to believe that limiting the role of iron, which is one of the triggers of inflammation, may prevent long-term damage to the joint when it comes into contact with blood. Albumin, the most common plasma protein, is a physiological iron chelator, have been explored with peripheral blood plasma for intra-articular injections. Potassium ferricyanide addition reactions to oxidize hemoglobin to methemoglobin produced the desired result [75]. A question arose concerning the understanding of why albumin of one's own blood does not bind free iron in post-traumatic hemarthrosis, and if binding occurs, then at an insufficient rate? Intra-articular plasma injections have also shown to be effective in preventing the complications of hemarthrosis due to the fact that they lead to a decrease in extracellular DNA and DNA elastase [76]. The frequent use of blood components, and bone marrow in some cases, for the articular treatment is an important reason for studying the effect of hemarthrosis on the dynamics of metabolic changes in large joints [77].

Intra-articular injections of vitamin E and corticosteroids, inhibitors of inflammation have been found to be useful in preventing the articular cartilage changes observed in hemarthrosis. An experiment showed that intra-articular injections of 20 ng of vitamin E led to the normalization of proteoglycan levels in articular cartilage, in contrast to the high values found in patients with hemarthrosis, and histopathological assessment showed the identity of the cartilagenous structure in intact animals and those who had vitamin E administered after simulating post-traumatic hemarthrosis [44]. Intra-articular administration of 10 mg of the synthetic glucocorticoid TCA (triamcinolone acetonide) in the experiment showed no significant changes in the levels of proteoglycans, and the histopathological assessment demonstrated identical cartilage structure in intact limbs and in the joints after TCA administration [44]. A single administration of dexamethasone led to a significant decrease in the expression of mRNA of destructive and inflammatory molecules (MMP-3, ADAMTS-4 and SOD-2 – superoxide dismutase) in the menisci at 2 days and 9 weeks [78]. In general, most of the therapeutic approaches based on anti-inflammatory therapy give a positive result in the rehabilitation of post-traumatic hemarthrosis. although there is evidence on the harm of intra-articular bleeding for cartilage tissue, there is no consensus on the need to aspirate blood from the joint after hemarthrosis [47]. The patient may not seek medical help in a timely manner, and the aspiration may not be performed. Another reason may be the fact that destructive processes become clinically evident after a few years in the absence of aspiration. A number of studies are performed in vitro and it is suggested that aspiration of blood from the joint should be performed as soon as possible, at least within 48 hours after a joint hemorrhage, in order to prevent or reduce long-term effects on the cartilage [79]. The dependence of exposure time and/or dose of hemorrhage into the joint on side effects suggests that the sooner aspiration occurs, the better [47]. The examination of aspirated fluid can provide useful diagnostic information in terms of the degree of inflammation and the nature of hemarthrosis [80]. Immobilization, recommended for hemarthrosis, can lead to articular cartilage degeneration, which is recorded as a decrease in the number of chondrocytes on the functional surface [22].

DISCUSSION

The generally accepted view of post-traumatic hemarthrosis as a hemorrhage into the joint can be re-thought from the view of the inflammation theory. Other important aspects of the pathological process open up the possibility for a more accurate assessment of the patient's condition determining probable prognosis of the outcome. Using the previous theory of the process being based on cellular and tissue inflammatory stress [31], it is possible to analyze the previous data recorded in patients with posttraumatic hemarthrosis. The typical pathological process is realized at the tissue level with the participation of the vascular bed. The combined action of exogenous (trauma) and endogenous (hemorrhage) phlogogens leads to a rapid reaction consisting in the expansion of the capillary network with increased vascular permeability, decreased lymph flow, edema compressed tissues, disengaged oxidation and phosphorylation and formation of hypoxia. Signs of the classical (canonical) inflammation observed in post-traumatic hemarthrosis include appearance of a voluminous pool of leukocytes, activation of cytokine reactions, changes in the hemostasis, dysproteinemia with greater synthesis of acute phase proteins, increased activity of lysosomal enzymes, greater synthesis of antibodies with their binding into immune complexes. Also, a sign of canonical inflammation is the presence of a zone of delimitation of the process from other tissues of the body [29]. Types of inflammatory reactions and the manifestations in post-traumatic hemarthrosis and complications are presented in Table 2.

Table 2

Types of inflammatory reactions and the manifestations in post-traumatic hemarthrosis and complications

Type of stress	Manifestations of stress reactions	Possible manipulations (external and internal)	Instance
Cellular stress	Daily life activities	Management of necrosis, apoptosis, transformation	Daily response to changing physico-chemical and biological pressures
Tissue stress	Low grade inflammation	Removal of the source of pathologically altered cells to ensure the survival of less impaired cells to maintain the function	Substantial injuries that do not lead to the occurrence of post-traumatic hemarthrosis
	Canonical (classic) inflammation	Removal of the source of damage even due to the destruction of own tissues (inflammation trigger and secondary injured tissues) with the ability to return to the physiological norm; increased synthesis of anti-inflammatory mediators; activation of the receptor apparatus	Actually post-traumatic hemarthrosis in the acute course of inflammation or synovitis in the chronic course of inflammation
	Presystemic inflammation	Stabilized condition to prevent the transition of the process to the systematic level	Purulent arthritis with infection of the joint
	Chronic systemic inflammation of low intensity	Reducing inflammation of microvessels and microcirculation disorders at the system level; microthrombosis; activation of factors of innate immunity; synthesis of pro-inflammatory cytokines, chemonkins, growth factors	Osteoarthritis as a remote consequence of post-traumatic hemarthrosis, ankylosis of the joint with the involvement of degenerative processes
	Acute systemic inflammation	Support for the functioning of inflammation tissues with simultaneous activation of buffer systems that prevent the release of aggressive biofactors from the inflammation focus into the systemic circulation	Not encountered in post-traumatic hemarthrosis

Mechanical damage to the joint causes migration of immune cells from the bloodstream through the synovial membrane into the synovial fluid. Trauma leads to the death of cells at the site causing the formation of injury-associated DAMPs (danger-associated molecular patterns), which are detected on cellular surfaces by TLR proteins (toll-like receptor). This potentiates the implementation of inflammatory cascades and the infiltration of synovial fluid by cells. Thus, a damaging feedback loop is established. Activation of the NLRP-3 inflammasome in macrophages, followed by the production of IL-1β is the main mechanism of DAMP promoting inflammation in the joint [55]. The key points in post-traumatic hemarthrosis include oxidative stress through the Fenton reaction in the presence of iron as a metal with variable valence, the formation of the antioxidant properties of the haptoglobin-hemoglobin complex and the activation of the receptors of the complex CD163 (SR-I1, scavenger receptor) for formation of M2 macrophages associated with Hb (M-(Hb)), which have pronounced anti-inflammatory properties [50]. Inflammation can either resolve quickly or take on a more severe course depending on the extent of injury and concomitant factors. Conjugation of several variants of inflammation can lead to complications of post-traumatic hemarthrosis and osteoarthritis can develop in cases with the mechanism of low-intensity chronic systemic inflammation having been implemented at the time of injury. The acute course of classical inflammation is transformed into chronic systemic inflammation, leading to the gradual destruction of the cartilaginous tissue. Synovitis may have signs of low-grade inflammation that involves the activation of TLR with molecular patterns being the end products of glycation and oxidation of lipoproteins in addition to the main molecular mechanisms of inflammatory polarization and oxidation of lipoproteins [33], a chronic course of the classical inflammation and presystemic inflammation (purulent arthritis). Ankylosis can be considered as a consequence of chronic systemic inflammation of low intensity with degeneration processes from the view of the inflammation theory.

CONCLUSION

An analysis of modern literature has shown the complexity and versatility of the inflammation aspects in post-traumatic hemarthrosis. The lack of emphasis on the assessment of the inflammatory response during the rehabilitation of patients with post-traumatic hemarthrosis can lead to complications including osteoarthritis, ankylosis, synovitis. A personalized approach to the problem of restoring the function of a damaged joint, taking into account low-intensity inflammatory processes, can be more effective for rehabilitation of the patient. A detailed analysis of the mechanisms of the inflammatory response in patients with post-traumatic hemarthrosis is the main perspective of the study.

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Information about the authors:

1. Olga V. Berdiugina – Doctor of Biological Sciences, berolga73@rambler.ru;
2. Valery A. Chereshnev – Doctor of Medical Sciences, Professor, Academician of the Russian Academy of Sciences, v.chereshnev@iip.uran;
3. Kirill A. Berdiugin – Doctor of Medical Sciences, Professor of the Russian Academy of Sciences, kiralber1973@rambler.ru.

Contribution of the authors*:*

Berdiugina O.V. – conceptualization; collection and processing of material; writing the original text; scientific editing; final conclusions.
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