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BIOCHEMICAL BASIS FOR THE INTERPRETATION OF CHANGES IN PLATELET INDICES UNDER CONDITIONS OF ALIMENTARY PROTEIN DEFICIENCY AND TOXIC INJURY INDUCED BY ACETAMINOPHEN

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The work is devoted to elucidating the biochemical mechanisms and patterns of changes in platelet indices under conditions of dietary protein deficiency and acetaminophen-induced toxic injury. The relevance of the study is determined by the prevalence of nutrient-associated disorders and drug-induced hepatopathies, which are accompanied by systemic alterations in hemostasis, particularly of the primary platelet component. Particular attention is paid to platelet indices as integral markers of the morphofunctional state of platelets, the activity of thrombocytopoiesis, and platelet reactivity. The study was conducted on white outbred rats aged 2.5–3 months, in which alimentary protein deficiency was modeled by maintaining them on a semi-synthetic low-protein diet for 28 days, as well as acute acetaminophen-induced toxic injury at a dose of 1250 mg/kg body weight. Platelet count was determined in peripheral blood smears stained according to the Romanowsky–Giemsa method, whereas mean platelet volume, platelet distribution width, and plateletcrit were assessed using a hematological analyzer. The results of the study demonstrated the development of pronounced thrombocytopenia in all experimental groups, most intense under conditions of acetaminophen-induced toxic injury. The decrease in platelet count was accompanied by a significant reduction in plateletcrit against the background of an increase in mean platelet volume and platelet distribution width. Morphological analysis of blood smears confirmed the presence of giant platelet aggregates and increased platelet heterogeneity, indicating platelet activation and disturbances in the thrombocytopoiesis process. The obtained results allow us to conclude that acetaminophen-induced injury is a key factor in the imbalance of the platelet component of hemostasis, while dietary protein deficiency enhances the extent of these changes. The identified pattern of alterations in platelet indices has a clear biochemical basis and may be used for an in-depth laboratory assessment of the hemostatic state under metabolically unfavorable conditions.

Keywords: platelets, plateletcrit, mean platelet volume, platelet distribution width, hemostasis, low-protein diet, acetaminophen, toxic injury

Introduction. The hemostatic system is one of the key components in maintaining the organism's homeostasis, responding sensitively to metabolic, nutritional, and toxic influences. A special place in its regulation belongs to platelets, which, in addition to their participation in primary hemostasis, play an important role in the processes of inflammation, immune response, angiogenesis, and tissue regeneration. The morphofunctional state of platelets is to a large extent reflected by platelet indices – platelet count (PLT), plateletcrit (PCT), mean platelet volume (MPV), and platelet distribution width (PDW), which are currently regarded as sensitive markers of changes in thrombocytopoiesis, platelet activation, and functional heterogeneity of platelets (Tokgöz Çakır et al., 2025, Budak et al., 2016; Zhu et al., 2018; Eisinger et al., 2018).

Dietary protein deficiency is a widespread manifestation of nutrient imbalance, accompanied by impaired synthesis of structural and enzymatic proteins, alterations in the course of energy and plastic metabolism, and a negative impact on the functional state of hematopoietic organs. A deficiency of amino acids required for the synthesis of cytoskeletal proteins, membrane receptors, and enzymatic systems may lead to disturbances in megakaryocytopoiesis, changes in the morphological characteristics of platelets, and a reduction in the efficiency of primary hemostasis. At the same time, the biochemical mechanisms underlying alterations in platelet indices under conditions of protein deficiency remain insufficiently elucidated (Manary et al., 2024; Hastreiter et al., 2021; Cunha et al., 2013; Uner et al., 2001).

Particular attention is attracted by the toxic effects of acetaminophen, one of the most widely used analgesics and antipyretic agents, which, in cases of overdose or prolonged use, is capable of inducing pronounced liver injury. The biotransformation of acetaminophen in hepatocytes involving the cytochrome P450 system, particularly the CYP2E1 isoform, is accompanied by the formation of reactive metabolites and excessive generation of reactive oxygen species, leading to the

development of oxidative stress (Ramachandran & Jaeschke, 2019; Kopylchuk et al., 2022).

Given the central role of the liver in the synthesis of hemostatic factors and the regulation of platelet homeostasis, toxic damage to this organ may indirectly affect the quantitative and qualitative characteristics of platelets. The combination of dietary protein deficiency with acetaminophen-induced toxic injury creates conditions that may potentially exacerbate the negative impact on the platelet component of hemostasis, leading to complex metabolic and biochemical disturbances. Changes in platelet indices under such conditions may reflect not only impairments in thrombocytopoiesis, but also platelet activation, alterations in their morphological heterogeneity, and the formation of prerequisites for dysfunction of primary hemostasis (Ramachandran & Jaeschke, 2019; Eisinger et al., 2018; Thomas et al., 2024; Korniluk et al., 2019). In this regard, the biochemical substantiation and interpretation of changes in platelet indices under conditions of dietary protein deficiency and acetaminophen-induced toxic injury are relevant, which will make it possible to deepen the understanding of the mechanisms of interaction between nutritional status, xenobiotic load, and the functional state of the hemostatic system, as well as to increase the informativeness of laboratory assessment of platelet disorders under metabolically unfavorable conditions.

Considering the above-mentioned information, the aim of the work was to study the indicators of the platelet-vascular component of the hemostatic system of rats under conditions of dietary protein deficiency and acetaminophen-induced injury.

Materials and methods. The study subjects were white outbred rats, aged 2.5–3 months and weighing 160–180 g. During the performance of the experimental studies, ethical standards for the handling of laboratory animals were observed in accordance with the key provisions of the "European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes," documented in Strasbourg (1986), Law of Ukraine No. 3447-IV "On the Protection of Animals from Cruel Treatment" (2006), and the recommendations of the Sixth National Congress of Ukraine on Bioethics (2006).

Throughout the entire experiment, the rats were fed a semi-synthetic AIN-93 diet, as approved by the American Institute of Nutrition (Reeves et al., 1993). To model the state of alimentary protein deficiency, a group of rats daily received a semi-synthetic low-protein diet for 28 days. Standardization of the daily ration was performed in accordance with the principle of pair-feeding. After four weeks of maintaining the animals on the experimental diet, acute toxic injury induced by acetaminophen was modeled. Administration of the toxin was performed at a calculated dose of 1250 mg/kg of body weight in the form of a suspension in a 2% starch gel solution once daily for 2 days using a specialized probe (Kopylchuk et al., 2025).

In the course of the experimental studies, the rats were divided into four groups: 1 – animals that received a semi-synthetic diet containing all macro- and micronutrients for 28 days – the control group (C); 2 – animals that were maintained on a semi-synthetic low-protein diet for 4 weeks (1/3 of the standardized daily protein requirement) (LPD); 3 – animals in which acetaminophen-induced injury was modeled after 28 days of consumption of a complete semi-synthetic diet (TI); 4 – animals to which, after being maintained on a low-protein diet for 28 days, toxic doses of acetaminophen were administered (LPD/TI). Blood sampling was carried out in accordance with regulated bioethical norms and rules on days 29 (groups C and LPD) and 31 (groups TI and LPD/TI) of the experiment.

Counting of the quantitative platelet content (PLT) was performed on peripheral blood smears fixed with 96% ethyl alcohol and stained with an azure-eosin solution, according to the Romanowsky-Giemsa method, using the XS-2610 LED MICROmed light microscope with a 100× objective and immersion oil (Dhakar et al., 2018). Assessment of the indicators of mean platelet volume (MPV), platelet distribution width (PDW), and plateletcrit (PCT) was performed on a KT-40 hematological analyzer (Genrui Biotech Inc.) on the basis of the CNE "Chernivtsi City Polyclinic No. 2".

Statistical analysis was performed using GraphPad Prism (version 8.0.1). Group differences were assessed by one-way analysis of variance (ANOVA), followed by Tukey's multiple comparison post hoc test. Results were considered statistically significant at $p < 0.05$. Data are expressed as mean ± standard error of the mean (SEM).

Results and Discussion. The study's results showed a decrease in platelet count in all experimental rat groups compared to control values. In animals consuming a low-protein diet (LPR group), quantitative platelet values were 40.5% lower compared to those in rats that received a semi-synthetic complete diet throughout the experimental period (control group). At the same time, the entry into the organism of toxic doses of the medicinal xenobiotic acetaminophen, regardless of the amount of protein in the diet (experimental animal groups TI and LPD/TI), led to the maximum decrease (by 77–78% compared with control indicators) in platelet count in the blood of experimental rats (Fig. 1).

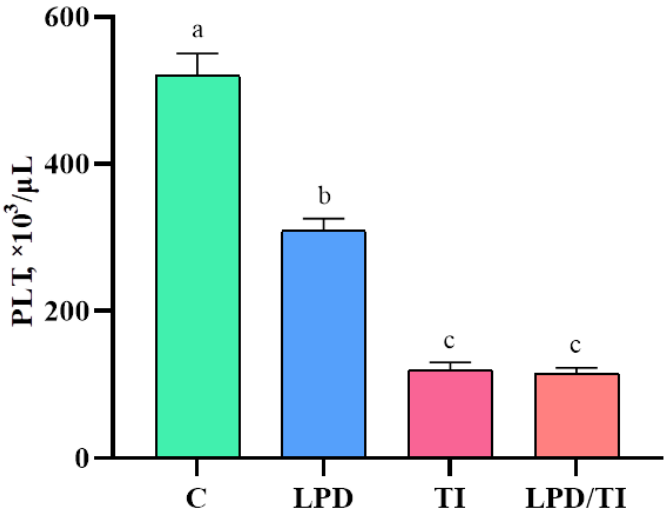

Fig. 1. Platelet levels (PLT) in the blood of rats under conditions of alimentary protein deficiency and acetaminophen-induced injury

Note (here and hereinafter):C – rats that received a complete semi-synthetic diet for 28 days (control group); LPD – animals that were maintained on a semi-synthetic low-protein diet for 4 weeks; TI – rats in which acute acetaminophen-induced toxic injury was modeled after 28 days on a complete semi-synthetic diet; LPD/TI – animals that were administered toxic doses of acetaminophen after being maintained on a low-protein diet for 28 days; values marked with different letters indicate statistically significant differences (a, b, c).

The results obtained in our study indicate the development of thrombocytopenia in the experimental groups of rats, in which two key mechanisms may be involved: increased platelet destruction or impaired platelet production. The rapid development of thrombocytopenia may be mediated by enhanced platelet clearance and/or destruction. Platelets can be activated by antigen–antibody immune complexes or host inflammatory responses; activated platelets are more readily removed from the circulation by the reticuloendothelial system (Assinger, 2014). Platelets are actively involved in the propagation of inflammatory signaling and play a significant role in host defense during infectious challenges. Through the integration of thrombotic and immunological functions, platelets contribute to the coordinated activation of hemostasis and immune responses, thereby limiting microbial dissemination and tissue invasion. These effects are mediated by platelet interactions via multiple surface receptors, including Toll-like receptors, which enable direct recognition of pathogen-associated molecular patterns (Rainger et al., 2015).

latelets contribute to the recruitment and activation of circulating leukocytes at the endothelial interface, thereby facilitating leukocyte adhesion and subsequent transendothelial migration. The coordinated interactions between endothelial cells, platelets, and leukocytes represent a key mechanism underlying the procoagulant milieu associated with the development and progression of pathological conditions. Thrombocytopenia, platelet secretion, and interaction with leukocytes may exert detrimental or protective immune effects under the given experimental conditions (Rainger et al., 2015; Rossaint & Zarbock, 2018). Platelets are essential mediators of primary hemostasis, as they rapidly adhere to the site of vascular injury and undergo aggregation, thereby arresting bleeding. Following endothelial disruption, platelets bind to immobilized von Willebrand factor through the platelet glycoprotein (GP) Ibα complex, as well as to exposed collagen via integrin α2β1 and the immunoglobulin receptor GPVI. These adhesive interactions trigger platelet activation, which is accompanied by granule secretion, cytoskeletal reorganization with a characteristic change in cell shape, and activation of the fibrinogen receptor GPIIb/IIIa. The release of granule components, particularly adenosine diphosphate (ADP), promotes rapid amplification of platelet activation and recruitment. Platelet shape change and spreading further enhance surface coverage of the damaged area, effectively limiting blood loss and supporting stable platelet aggregation (Armant, 2002; Nieswandt et al., 2011; Tuna et al., 2024).

Previously, it was believed that the main mechanism underlying the appearance of thrombocytopenia was the active destruction of these cells under the influence of autoantibodies. However, at present, in addition to the traditional

pathogenetic theory of thrombocytopenia development, great importance is attributed to impaired platelet production in the bone marrow, as well as to T-cell mechanisms of their destruction. The current concept of etiopathogenesis assumes the simultaneous presence of several complex mechanisms that provoke the occurrence of the disease, including the production of autoantibodies against platelet membrane receptors; enhanced destruction of antigen–antibody complexes in the spleen; complement-mediated platelet lysis; T-lymphocyte-mediated platelet lysis; and inadequate platelet production (Koupenova et al., 2018; Maouia et al., 2020). The main cytokine that stimulates platelet production is thrombopoietin. The absence of a compensatory increase in thrombopoietin levels in response to pronounced immune-mediated thrombocytopenia represents an important pathophysiological mechanism of thrombocytopenia development (Kuter, 2013; Gernsheimer, 2008; Thomas et al., 2024). It is known that acetaminophen toxicity directly and/or indirectly causes the development of inflammatory reactions in the body, which promotes the progression of drug-induced liver injury, as a result of which the initiation of the coagulation cascade may be disrupted. In addition, in cases of overdose with the specified xenobiotic, a decrease in the concentration of fibrinogen in blood serum is observed, as well as in the levels of certain coagulation system factors, reflecting alterations in both primary and secondary hemostasis (Sivagurunathan & Calivarathan, 2025; Ramachandran & Jaeschke, 2019; Ganey et al., 2007; Kerr et al., 2003).

At the same time, a decrease in platelet count in the blood of animals from all experimental groups is characterized by a simultaneous increase in mean platelet volume compared with control values (LPD – 26%, TI – 51%, LPD/TI – 55%). It should be noted that in the rat groups with toxic injury, TI and LPD/TI, the studied indicator reaches its maximum values (Fig. 2). Clinically, this parameter reflects the size of circulating platelets in the blood at the time of sampling. The larger the platelet volume, the higher its coagulation capacity. It is likely that the findings obtained by us are associated with enhanced platelet aggregation, resulting in a decrease in their total number at the expense of an increase in the mean volume (Korniluk et al., 2019; Budak et al., 2016; Zhu et al., 2018; Tokgöz Çakır et al., 2025). It is likely that the obtained results are associated with enhanced platelet aggregation, resulting in a decrease in their total number at the expense of an increase in the mean volume.

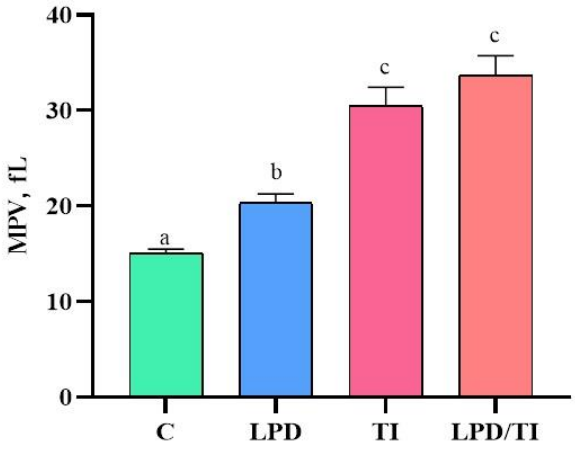

Fig. 2. Mean platelet volume (MPV) in the blood of rats under conditions of alimentary protein deficiency and acetaminophen-induced injury

For example, the literature (Balduini et al., 2011) indicates that patients with Bernard–Soulier syndrome exhibit thrombocytopenia with giant platelets, in addition to functional defects such as impaired platelet adhesion to the subendothelium and reduced platelet aggregation. These processes are associated with structural and functional alterations of the platelet membrane glycoprotein complex GPIb–IX–V, which harbors the binding site for von Willebrand factor–a key plasma glycoprotein mediating platelet adhesion to the endothelial surface. Consequently, the GPIb–IX–V complex is considered to be essential for effective platelet biogenesis and function. Supporting this concept, in vitro studies have demonstrated that the application of antibodies targeting GPIb–IX–V markedly suppresses proplatelet formation. These studies demonstrate that one of the mechanisms by which macrothrombocytopenia may arise is defective proplatelet formation.

The initial phases of platelet adhesion and activation are followed by the recruitment of

additional circulating platelets and the assembly of three-dimensional platelet aggregates through multiple molecular mechanisms. Platelet recruitment, activation, and aggregation are primarily driven by the synthesis of platelet-derived thromboxane A_2 and the release of adenosine diphosphate (ADP) from dense (δ) granules. Furthermore, platelet–platelet interactions during thrombus formation are mediated and stabilized by the fibrinogen receptor GPIIb/IIIa. Notably, the emergence of hyperreactive platelet subpopulations is associated with enhanced adhesive and aggregatory responses, which in turn promote increased thrombin generation and contribute to a prothrombotic state (Levin, 2019; Nieswandt et al., 2011; Heemskerk et al., 2013; Khodadi, 2020). Therefore, as can be observed, certain changes occur already at the initial stage of the blood coagulation system functioning.

During the counting of platelet numbers in the field of view of a light microscope, we recorded certain morphological changes in platelets in different experimental groups of rats, as evidenced by photographs of blood smear micropreparations (Fig. 3).

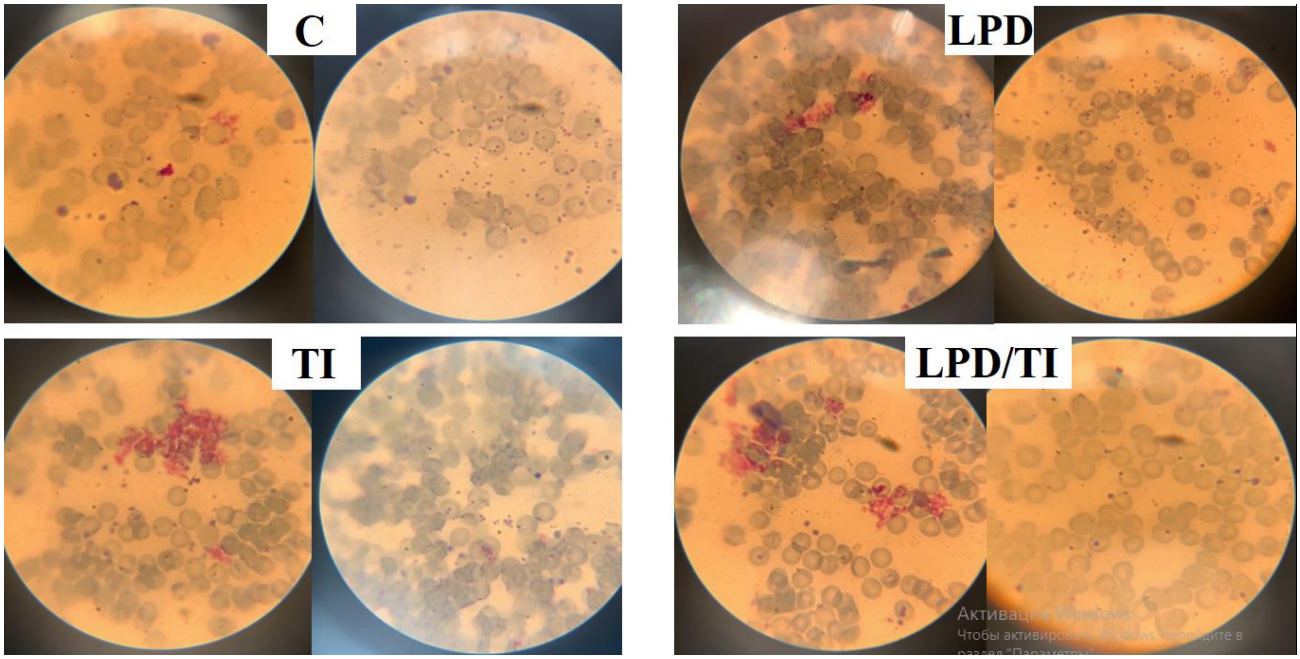

Fig. 3. Photographs of blood smear micropreparations from rats under conditions of alimentary protein deficiency and acetaminophen-induced injury

As shown in Fig. 3, in blood smear micropreparations from rats of the control group (group C), predominantly single platelets are observed, with platelet aggregates occasionally detected. This is likely related to the adhesive functions of platelets under physiological conditions. At the same time, in the group of rats that consumed a low-protein diet (LPD group), a significantly greater number of such aggregates is observed, which is consistent with the increase in the mean platelet volume under these experimental conditions (Fig. 2). Under conditions of administration of toxic doses of acetaminophen (TI and LPD/TI groups), we observed a minimal number of single platelets, in contrast to a substantial proportion of platelet aggregates. It should be emphasized that even during blood sampling in experimental animals of the TI and LPD/TI groups, practically almost immediate blood coagulation occurs.

During the assessment of platelet indices, we found an increase in the platelet distribution width index in all experimental groups of rats (LPD – 29%, TI – 41%, LPD/TI – 45%), with the maximum values recorded under conditions of administration of toxic doses of acetaminophen (Fig. 4). Platelet distribution width (PDW) is an indicator of heterogeneity, that is, the non-uniformity of cells of the same type. It reflects which platelet forms predominate in the total population. An increase in this parameter may be observed under conditions of enhanced platelet aggregation and the presence of microclots (Budak et al., 2016; Rong et al., 2024; Eisinger et al., 2018), as confirmed by photographs of blood smear micropreparations (Fig. 3).

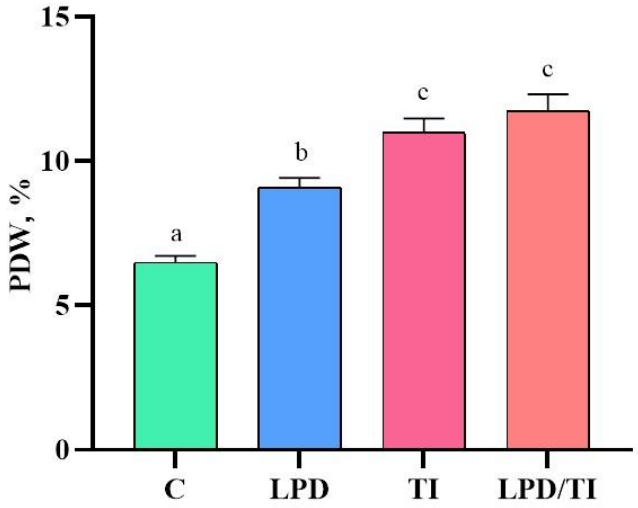

Fig. 4. Platelet distribution width (PDW) in the blood of rats under conditions of alimentary protein deficiency and acetaminophen-induced injury

The transformation of preplatelets into proplatelets involves microtubules and is determined by two primary biophysical properties: the diameter of the microtubule coil and the thickness of the microtubule coil. Interestingly, these parameters regulate and predict the size of circulating platelets formed from proplatelets, explaining a platelet diameter of approximately 2 μm. This supports a model in which ring-shaped preplatelets are released into the bloodstream and rapidly and spontaneously convert into proplatelets, leading to the formation of mature platelets. Additionally, preplatelets may enter the microcapillaries of the bone marrow, lungs, or spleen, where intravascular shear forces stimulate the production of platelets from proplatelets. Therefore, platelet size (Fig. 2) correlates with platelet reactivity; larger platelets exhibit a greater prothrombotic potential. An increased platelet size (mean platelet volume) is associated with enhanced platelet aggregation, increased expression of adhesion molecules, and an elevated risk of peripheral arterial injury, which may be assumed under conditions of exposure to toxic doses of acetaminophen (Leysi-Derilou et al., 2012; Korniluk et al., 2019; Khodadi, 2020; Eisinger et al., 2018; Tian et al., 2025; Machlus & Italiano, 2013; Thon et al., 2012).

Interestingly, studies in patients with acute coronary disease have revealed a direct relationship between the expression of the integrin α2 chain and mean platelet volume, indicating that the expression levels of integrin α2β1 are involved in regulating platelet size. This was recently confirmed by the generation of a conditional megakaryocyte-specific integrin α2 chain-deficient mouse model, in which the resulting platelets exhibit a significantly reduced mean volume (Khodadi, 2020; Thon et al., 2012; Machlus & Italiano, 2013).

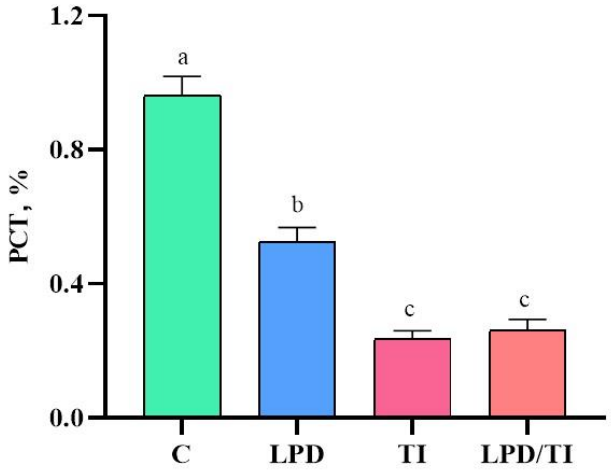

Fig. 5. Plateletcrit (PCT) indicator in the blood of rats under conditions of alimentary protein deficiency and acetaminophen-induced injury

In contrast, a decrease in the plateletcrit indicator (Fig. 5), that is, the ratio of platelet volume to the volume of the liquid fraction of blood under these experimental conditions (LPD – 45%, TI – 75.5%, LPD/TI – 73%), is unequivocally a consequence of thrombocytopenia (Fig. 1). This may occur for three reasons. First, the body retains platelets in the spleen. Under normal conditions, the spleen filters undesirable substances and aged, damaged cells from the blood, including platelets. However, under certain pathological conditions, the spleen enlarges and begins to retain and actively sequester platelets. Therefore, their number in the blood decreases. Second, the body produces fewer platelets than required. Third, the body consumes or destroys platelets more rapidly than usual. This may occur in bacterial infections, autoimmune diseases, hemolytic–uremic syndrome, and as a result of the use of certain medications, including sulfur-containing antibiotics, anticonvulsants, and anticoagulants (Kuter, 2013; Gernsheimer, 2008; Provan et al., 2010; Smock & Perkins, 2014; Budak et al., 2016).

Conclusions. Thus, acetaminophen-induced injury acts as a key factor in reducing the platelet count in the blood and plateletcrit, with an increase in their mean volume and a simultaneous increase in platelet distribution width in the presence of giant platelet aggregates. The identified complex of changes in platelet indices indicates disturbances in the processes of thrombocytopoiesis, platelet activation, and morphofunctional heterogeneity, which reflects the development of an imbalance in the primary platelet link of hemostasis. The obtained results confirm that under conditions of alimentary protein deficiency and acetaminophen-induced toxic injury, changes in platelet indices have a clear biochemical basis associated with metabolic stress, oxidative disturbances, and damage to the functional state of the megakaryocytic–platelet system.

Interests disclosure. *The authors declare no conflict of interest.*

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БІОХІМІЧНІ ОСНОВИ ІНТЕРПРЕТАЦІЇ ЗМІН ТРОМБОЦИТАРНИХ ІНДЕКСІВ ЗА УМОВ АЛІМЕНТАРНОЇ НЕСТАЧІ ПРОТЕЇНУ ТА ТОКСИЧНОГО УРАЖЕННЯ АЦЕТАМІНОФЕНОМ

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Робота присвячена з'ясуванню біохімічних механізмів та закономірностей змін тромбоцитарних індексів за умов аліментарної нестачі протеїну та ацетамінофен-індукованого токсичного ураження. Актуальність дослідження зумовлена поширеністю нутрієнтно-асоційованих порушень і медикаментозних гепатопатій, які супроводжуються системними змінами гемостазу, зокрема первинної тромбоцитарної ланки. Особливу увагу приділено тромбоцитарним індексам як інтегральним маркерам морфофункціонального стану тромбоцитів, активності тромбоцитопоезу та тромбоцитарної реактивності. Дослідження проведено на білих безпородних щурах віком 2,5–3 місяці, яким моделювали аліментарну нестачу протеїну шляхом утримання на напівсинтетичному низькопротеїновому раціоні протягом 28 днів, а також гостре токсичне ураження ацетамінофеном у дозі 1250 мг/кг маси тіла. Кількість тромбоцитів визначали у мазках периферичної крові, забарвлених за Романовським–Гімза, а показники середнього об'єму тромбоцитів, ширини їх розподілу та тромбокриту – за допомогою гематологічного аналізатора. Результати досліджень засвідчили розвиток вираженої тромбоцитопенії в усіх дослідних групах, найбільш інтенсивної за умов токсичного ураження ацетамінофеном. Зниження кількості тромбоцитів супроводжувалося достовірним зменшенням тромбокриту на тлі зростання середнього об'єму тромбоцитів та ширини їх розподілу. Морфологічний аналіз мазків крові підтвердив наявність гігантських тромбоцитарних скупчень та підвищену гетерогенність тромбоцитів, що свідчить про їх активацію та порушення процесів тромбоцитопоезу. Отримані результати дозволяють зробити висновок, що ацетамінофен-індуковане ураження є ключовим чинником дисбалансу тромбоцитарної ланки гемостазу, а аліментарна нестача протеїну посилює вираженість цих змін. Виявлений комплекс змін тромбоцитарних індексів має чітке біохімічне підґрунтя та може бути використаний для поглибленої лабораторної оцінки стану гемостазу за метаболічно несприятливих умов.

Ключові слова: тромбоцити, тромбокрит, середній об'єм тромбоцитів, ширина розподілу тромбоцитів, гемостаз, низькопротеїновий раціон, ацетамінофен, токсичне ураження

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