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Morphofunctional changes in the kidneys of rats during acute respiratory distress syndrome and its treatment with human umbilical cord-derived mesenchymal stem cells



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ABSTRACT

Acute respiratory distress syndrome (ARDS) is a severe pathological condition often accompanied by kidney injury. It is known that mesenchymal stem cells (MSCs) have high potential for treating various diseases due to their ability to paracrinely stimulate the regeneration of damaged cells and tissues and restore impaired organ functions.

PURPOSE – to investigate the nephroprotective effect of human umbilical cord MSCs in a model of ARDS induced in rats by intranasal administration of lipopolysaccharide (LPS).

MATERIALS AND METHODS. Seventy-two sexually mature male Wistar rats were randomly divided into nine groups: intact animals, 3 days, 7 days, and 28 days of ARDS development, MSC control, and four treatment groups: 24 hours LPS + 2 days MSCs, 4 days LPS + 3 days MSCs, 14 days LPS + 14 days MSCs, 21 days LPS + 7 days MSCs. MSCs were administered intraperitoneally at a dose of 10^6 cells/kg body weight. Levels of structural kidney damage were assessed using histological analysis of sections stained with hematoxylin and eosin. The expression of the fibrosis marker TGF- β 1 in kidney tissues was evaluated by immunohistochemistry technique. Creatinine, urea, and uric acid levels in blood serum were measured using a kinetic method.

RESULTS. The conducted studies revealed the presence of significant damage to the kidney parenchyma, signs of fibrosis, and impaired nephron function in rats with modeled ARDS. The severity of pathological changes increased with the duration of the experiment. The use of human umbilical MSCs as a treatment factor significantly reduced the severity of coagulopathy, tubular necrosis, and destruction of renal corpuscles, inhibited the development of interstitial fibrosis, and improved the levels of renal blood markers. The best nephroprotective effect of MSCs was observed on the 28th day of the experiment in the group 14 days LPS + 14 days MSCs. This is likely due to the earlier use and longer duration of action of the stem cells compared to the group 21 days LPS + 7 days MSCs.

CONCLUSION. Human umbilical MSCs have regenerative, antifibrotic, and nephroprotective effects in an animal model of kidney injury caused by ARDS. This may indicate the therapeutic potential of umbilical MSCs for the treatment of nephropathies of various origins.

KEY WORDS: kidney injury; human umbilical cord mesenchymal stem cells; histological analysis; immunohistochemical analysis; renal blood markers

Acute respiratory distress syndrome (ARDS) is a rapidly progressing form of respiratory failure that arises due to excessive inflammation, accounting for 10 % of hospitalizations in intensive care units [1, 2]. ARDS was not described in the scientific literature until 1967, but by that time it had already made an impact on the medical community [3]. Documented mortality rates for ARDS patients range from 34-46 % depending on the

severity of the disease [4]. Due to the rapid increase in incidence, severity, wide range of manifestations and complications, and the public attention caused by the COVID-19 pandemic, ARDS currently draws significant interest from biomedical researchers seeking effective treatment methods.

ARDS is considered a multifaceted syndrome characterized by dysregulation of systemic inflammation, increased endothelial and epithelial

permeability, and diffuse alveolar damage leading to parenchymal edema, fibrosis, necrosis, and lung proteinosis [5-7]. The disease progresses through three overlapping stages: acute (exudative), subacute (fibroplasia), and chronic (fibrosis or resolution stage) [8, 9], although not all patients necessarily go through each stage.

The pathophysiological mechanisms of ARDS development primarily include an uncontrolled and intense inflammatory process, with the release of large amounts of inflammatory mediators from damaged cells (IL-1 α , IL-1 β , IL-6, IL-8, IFN- γ , TNF- α , TGF- β 1) [10]. This cytokine storm can lead to sepsis and multiple organ failure [11]. One of the most common ARDS complications is the development of acute kidney injury (AKI) [12, 13]. In a single-center trial by Pilarczyk et al. (2022), it was found that almost two-thirds of ARDS patients developed stage 2-3 AKI and/or required renal replacement therapy [14].

AKI involves a complex interaction between renal parenchyma and the immune system, leading to inflammation at the site of tissue damage and impaired kidney function [15, 16]. Renal ischemia is a significant cause of AKI and is characterized by reduced tissue perfusion, leading to acute tubular injury. The restoration of blood flow after prolonged ischemia activates endothelial cells of blood vessels and enhances the formation of reactive oxygen species (ROS). This causes the release of inflammatory mediators and induces apoptosis of tubular epithelial cells [17]. Ischemia-reperfusion AKI is marked by increased oxidative stress and immune system activation in response to ischemic tissue damage [18].

The pathogenesis of AKI includes acute tubular injury, ROS formation, activation of the inflammatory response, apoptosis of tubular epithelial cells, infiltration of inflammatory cells, and extensive release of pro-inflammatory cytokines [15, 19-22]. Thus, reducing the immune response and decreasing the extent of kidney tissue damage are potential therapeutic approaches for AKI.

Traditional treatments for AKI are not highly effective, hence the search for innovative methods to treat kidney parenchyma inflammation is of heightened interest. In some preclinical studies, stem cells have proven to be quite effective in treating nephropathies. One of the significant mechanisms of the positive therapeutic effects of stem cells is their ability to interact with immune cells in the inflammatory micro-environment, exhibiting anti-inflammatory effects [23, 24]. Additionally, stem cells can minimize tissue damage through the secretion of soluble cytoprotective factors [25, 26].

It has been proven that mesenchymal stem cells (MSCs) possess immunomodulatory, anti-inflammatory, antioxidant, anti-apoptotic, and reparative properties [27, 28]. MSCs from human umbilical cords do not cause rejection in recipients due to reduced expression of major histocompatibility complex class I molecules and the complete absence of class II proteins and co-stimulatory molecules CD80 and CD86. This suggests that they can evade innate immune responses, such as NK-cell-mediated cytotoxicity, and lack the pathway for antigen presentation necessary for activating the adaptive immune system [29, 30].

The purpose of our study was to determine the nephroprotective potential of human umbilical cord MSCs in an animal model of ARDS induced by lipopolysaccharide (LPS).

MATERIALS AND METHODS

For this study, we used 72 sexually mature male Wistar rats weighing 200-220 grams. The rats were kept under standard vivarium conditions with a controlled temperature of 24 °C, a 12-hour light/dark cycle, and free access to food and water. All procedures involving animals were conducted in accordance with the European Convention for the Protection of Vertebrate Animals used for Experimental and Other Scientific Purposes (Strasbourg, 1986; Oslo, 2018) and the Law of Ukraine No. 3447-IV "On the Protection of Animals from Cruelty" (February 21, 2006).

The study was conducted as a part of the state-funded research work "Investigation of the Regenerative Potential of Cell Therapy Agents in Acute Respiratory Distress Syndrome" (2021-2023, state registration number 0121U100159), with approval obtained from the bioethics committee of Ternopil National Medical University, protocol No. 60 dated September 1, 2020.

For the experiment, the rats were randomized into nine groups (n = 8 per group):

1. Intact rats.
2. 3 days after LPS administration.
3. 7 days after LPS administration.
4. 28 days after LPS administration.
5. Control-MSCs – intact rats euthanized 3 days after intraperitoneal MSC injection.
6. 1 day LPS + 2 days MSCs – rats that received an MSC injection 24 hours after LPS and were euthanized 2 days later.
7. 4 days LPS + 3 days MSCs – rats that received an MSC injection 4 days after LPS and were euthanized 3 days later.
8. 14 days LPS + 14 days MSCs – rats that received an MSC injection 14 days after LPS and were euthanized 14 days later.
9. 21 days LPS + 7 days MSCs – rats that received an MSC injection 21 days after LPS and were euthanized 7 days later.

ARDS was induced via intranasal administration of LPS from *E. coli* (*Sigma-Aldrich*, USA) at a dose of 5 mg/kg of rat body weight. To treat the pathological condition, a suspension of MSCs was administered intraperitoneally at a dose of 1 million cells per kg of body weight.

The frozen suspension of human umbilical cord MSCs was kindly provided by Professor Lavrenchuk H. Y. from the National Scientific Center of Radiation Medicine of the National Academy of Sciences of Ukraine. The umbilical cord tissue was obtained from a healthy donor with an informed consent following normal childbirth. The primary culture of MSCs from Wharton's jelly was obtained using an enzymatic method with 0.1 % type I collagenase (*Sigma-Aldrich*, USA). The cells were cultured in DMEM/F12 Advanced medium (*Gibco*, USA) supplemented with 2 % fetal bovine serum (FBS) (*Gibco*, USA) at 37 °C and 5 % CO₂. Passaging was performed when 80-90 % confluence was reached using TrypLE Express Enzyme (*Gibco*, USA). Cultured cells were cryopreserved at passage 4 using a cryoprotective medium composed of 30 % DMEM/F12 Advanced, 40 % FBS, 20 % conditioned medium, and 10 % dimethyl sulfoxide (*Sigma*, USA).

The immunophenotyping of MSCs was performed using a BD Accuri™ C6 Plus flow cytometer (*Becton Dickinson*, USA) with mouse monoclonal antibodies against human markers CD73, CD90, CD105, CD34, and CD45 (*Invitrogen*, USA). Thawed MSCs were cultured in DMEM/F12 Advanced medium with an initial FBS concentration of 10 %, which was reduced to 2 % after 2 days, under standard CO₂ incubator conditions (temperature 37 °C and CO₂ concentration 5 %). MSCs at passage 5 were used for cell therapy in the experimental model.

For the accurate comparison of the nephroprotective effect of MSCs over different time intervals post-administration, our data were divided into three comparative groups:

1. Intact animals, 3 days LPS, and 1 day LPS + 2 days MSCs.
2. Intact animals, 7 days LPS, 4 days LPS + 3 days MSCs, and MSC control (3 days post-injection).
3. Intact animals, 28 days LPS, 14 days LPS + 14 days MSCs, and 21 days LPS + 7 days MSCs.

These experimental timeframes were determined according to different stages of ARDS progression [28]. In groups treated with MSCs, rats were sacrificed at various intervals post-MSC administration (2 days in group 6, 3 days in group 7, 14 days in group 8, and 7 days in group 9) to enable comparative analysis with corresponding groups of animals (2-4) that did not receive MSC therapy. Rats in the MSC control group were euthanized 3 days post-MSC injection to assess MSC medium-term effects.

Terminal anesthesia was performed via intraperitoneal injection of an overdose (150 mg per rat) of sodium thiopental (*Arterium*, Ukraine).

Cardiac puncture was performed to obtain blood samples, and pieces of the left kidney were fixed for subsequent histological analysis. Levels of creatinine, urea, and uric acid in the serum were measured using the kinetic method with a semi-automatic biochemical analyzer Master T (*Hospitex*, Italy) and commercial kits (*Spinreact*, Spain).

Kidney samples were fixed in 10 % formalin. Further dehydration of kidney fragments and embedding in paraffin were performed using the LOGOS One processor (*Milestone Medical*, USA). Histological sections of 5 μm thickness were obtained using an AMR 400 rotary microtome (*Amos Scientific*, Australia) and stained with hematoxylin and eosin (H&E). For the comparative microscopic assessment of morphofunctional changes in the rat kidneys, 24 histological sections were analyzed for each comparison group.

To investigate the expression of transforming growth factor-beta 1 (TGF- β 1) as a marker of fibrosis in kidney samples, the histological sections were deparaffinized, rehydrated, and subjected to heat-induced antigen retrieval. Endogenous peroxidase activity was blocked using 3 % hydrogen peroxide. For TGF- β 1 detection, recombinant rabbit monoclonal primary antibodies against rat TGF- β 1 (Cat. No. ab215715, *Abcam*, USA) and the Mouse/Rabbit PolyVue™ HRP/DAB detection system (*Diagnostic BioSystems*, USA) were utilized. The sections were additionally counterstained with Mayer's hematoxylin. For immunohistochemical analysis, 8 sections were used per comparison group. All samples were examined under a light microscope Eclipse Ci-E (*Nikon*, Japan) and documented using an M3CMOS 14000 camera (*Sigeta*, Ukraine) and Toup View software (*ToupTek Photonics*, China).

For the quantitative assessment of the area of immunoprecipitate obtained after staining with TGF- β 1 antibodies, 144 fields of view (FOV) at 100 \times magnification were analyzed. The images were processed using ImageJ software (*Wayne Rasband*, USA) with the "Analyze particles" plugin. For each dataset, the mean value (M), standard error (m), and standard deviation (σ) were calculated. The significance of differences between groups was determined using Student's t-test for normally distributed data. Differences were considered significant at $p < 0.05$.

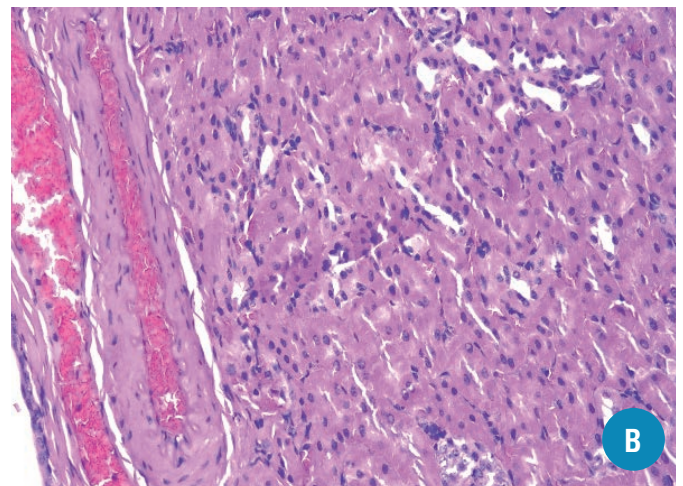
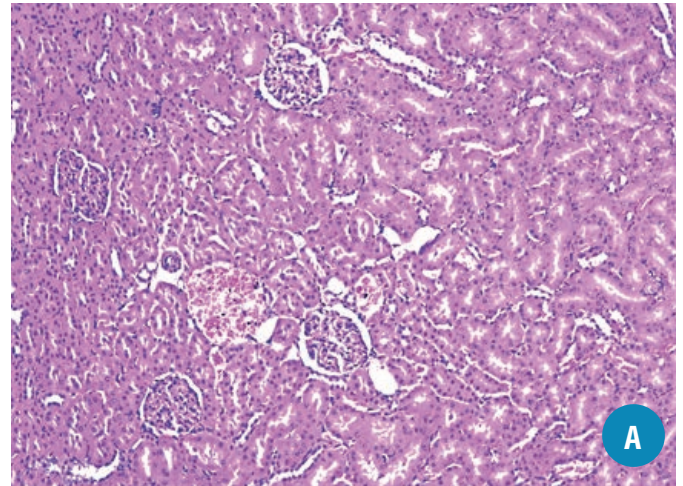
The obtained biochemical blood analysis data were processed using Statistica 10.0 software (*Statsoft Inc.*, USA). Further data visualization was performed using box plots. For the assessment of differences between the obtained data, which did not fit normal distribution, the Kruskal-Wallis test was used. A p-value < 0.05 was considered statistically significant. Changes in the concentrations of creatinine, urea, and uric acid were presented in box plots with non-centered medians, providing additional evidence of the abnormal distribution of experimental data.

RESULTS AND DISCUSSION

Histological analysis of intact rat kidneys did not reveal any specific structural abnormalities of the organ (**Fig. 1 A**). Three days after modeling ARDS, blood-filled arteries and veins with signs of disseminated intravascular coagulation (DIC) were observed. Epithelial cells in nephron tubules were swollen, with occasional signs of desquamation. The urinary lumen of renal corpuscles was narrowed, indicating reduced kidney filtration capacity (**Fig. 1 B**). Signs of DIC syndrome persisted in some microcirculatory vessel branches one week after the start of the experiment. Malpighian bodies exhibited various sizes and shapes. Some vascular glomeruli were wrinkled with damaged structural components, and the urinary lumen of Bowman's capsule was either greatly expanded or excessively narrowed. Desquamated epithelium was frequently observed in proximal and distal nephron tubules (**Fig. 1 C**). By day 28 of the experiment, vascular lesions were less pronounced, but parenchymal edema and stromal compaction due to peritubular connective tissue growth were noted. Vascular glomeruli were significantly denser due to mesangial proliferation, and the urinary lumen of renal corpuscles was not visualized (**Fig. 1 D**).

In the control-MSc group (**Fig. 1 E**), no significant changes in kidney structures compared to intact rats were observed. In animals from the 1-day LPS + 2-day MSCs group (**Fig. 1 F**), dilated interstitial vessels were observed without signs of DIC syndrome. Desquamated epithelial cells continued to be present in some proximal nephron tubules. Most renal corpuscles maintained their shape, although some remained compacted. In animals from the 4-day LPS + 3-day MSCs group (**Fig. 1 G**), peritubular capillaries were significantly dilated and blood-filled; however, the epithelium in most proximal nephron tubules showed no signs of damage. Malpighian bodies appeared normal, and no edema or connective tissue stromal proliferation was observed. In the group 14 LPS + 14 days MSCs (**Fig. 1 H**), renal parenchyma appeared preserved. Renal corpuscles had well-defined urinary lumens of Bowman's capsule with moderately blood-filled glomerular capillaries. The epithelium of nephron tubules showed no signs of desquamation. No interstitial edema was observed, and no signs of coagulopathy were detected in the vascular system. The microscopic examination of kidneys of the 21-day LPS + 7-day MSCs group (**Fig. 1 I**) indicated their better preservation compared to the kidneys of the animals from the 28-day LPS group. However, hypertrophied renal corpuscles, densely packed blood-filled vascular glomeruli with narrowed Bowman's capsule lumens were observed. Desquamated epithelial cells were occasionally observed in the proximal nephron. Some venous vessels showed signs of stasis and DIC syndrome.

Thus, comparative histological analysis of structural changes in rat kidneys with modeled ARDS, both without and with MSC treatment, demonstrated the ability of stem cells to reduce parenchymal and stromal edema, decrease the frequency of circulatory disorders, and restore damaged epithelium in nephron tubules.



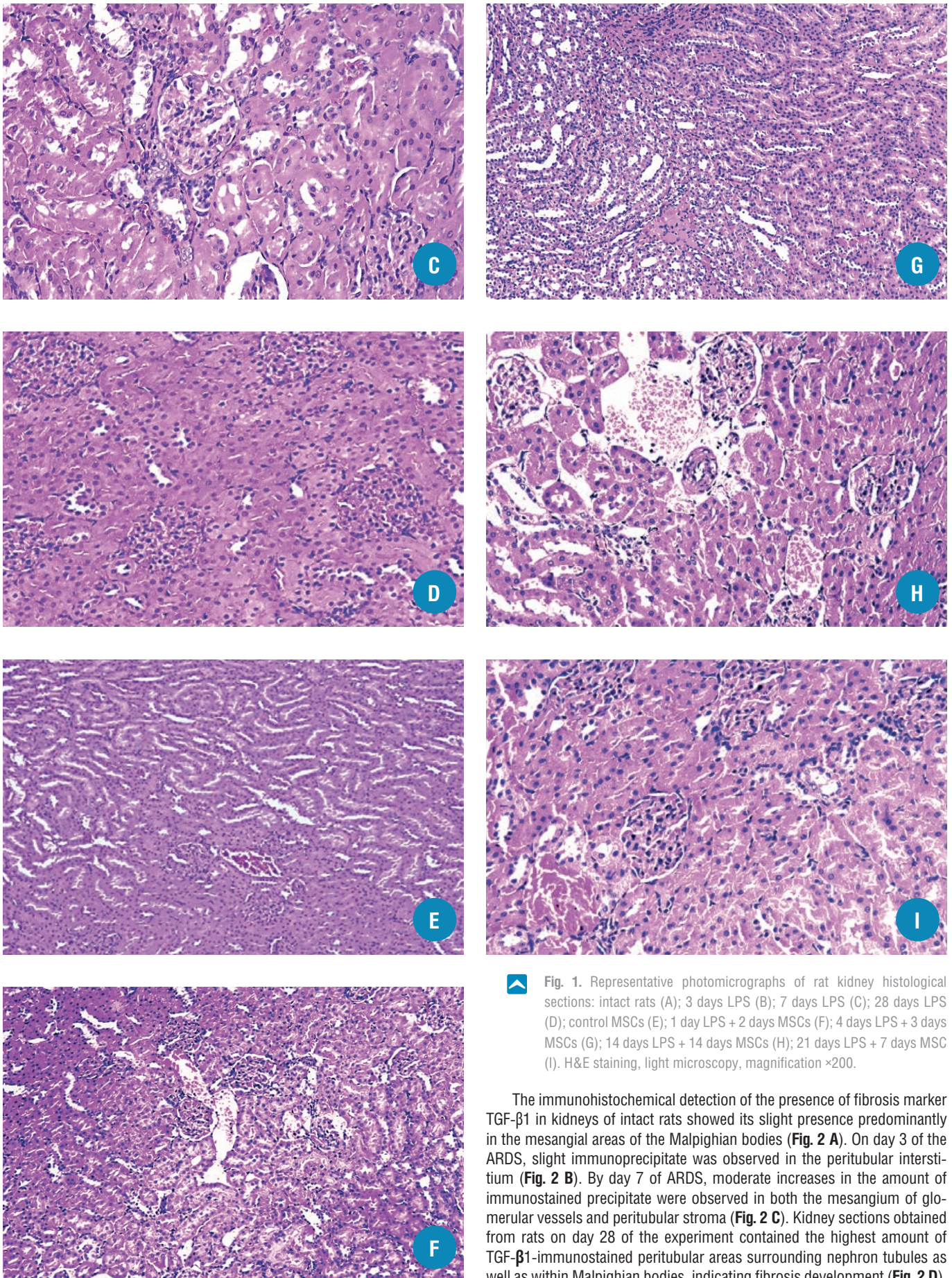
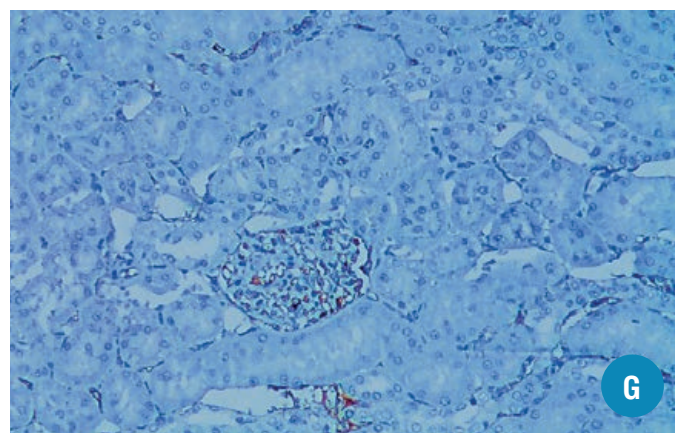
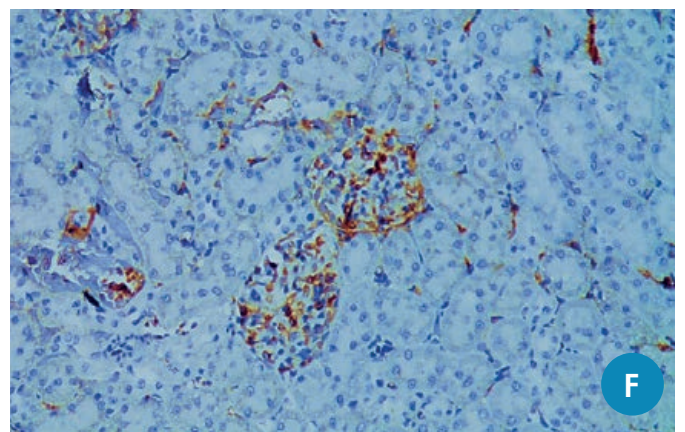
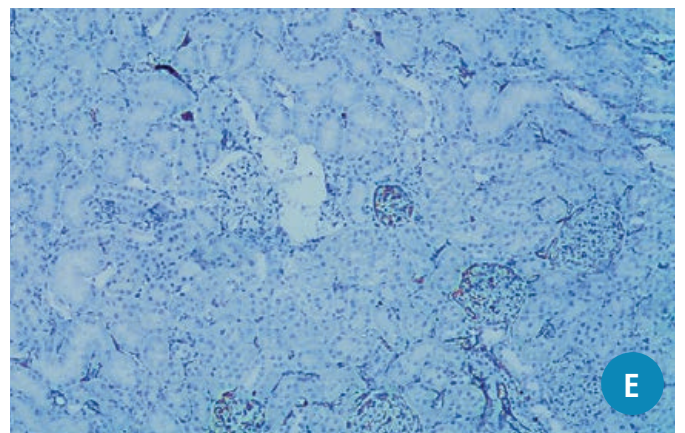
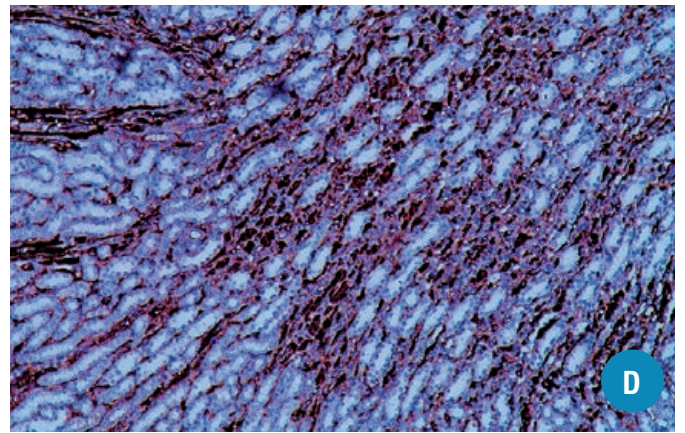
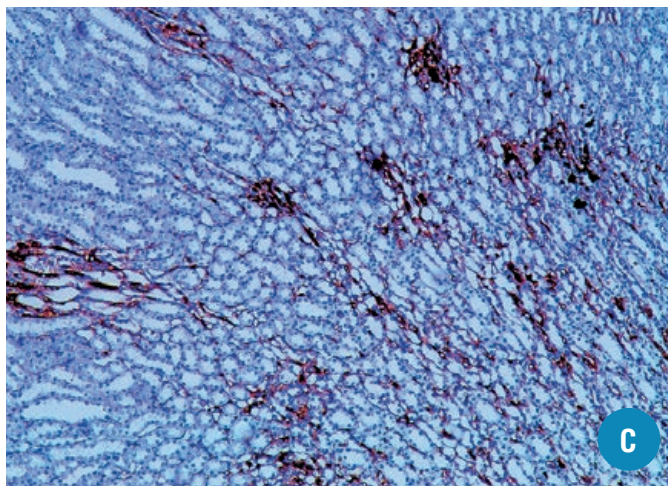
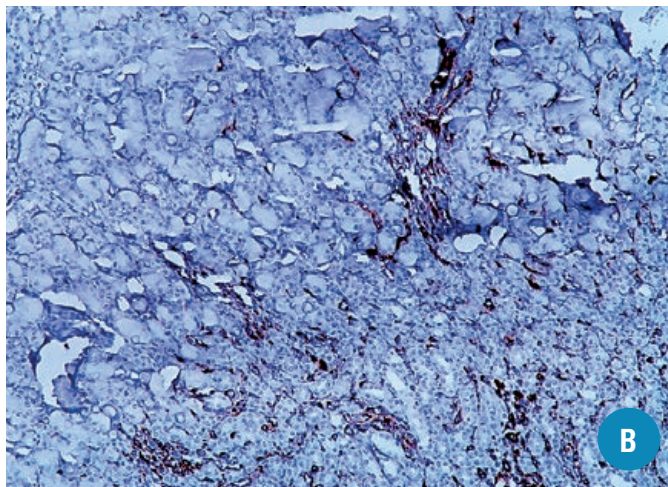
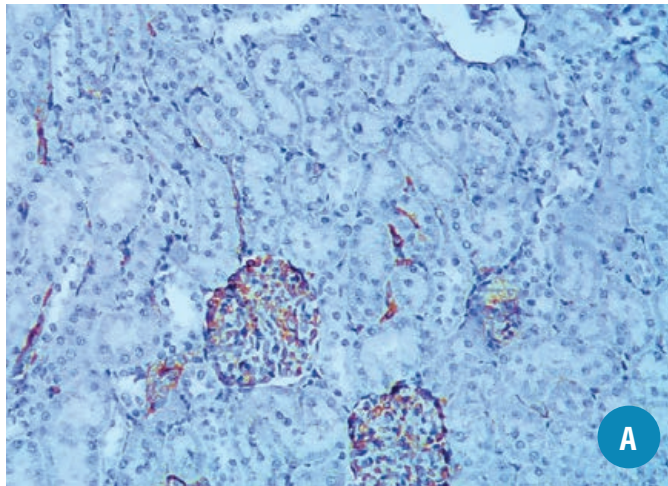


Fig. 1. Representative photomicrographs of rat kidney histological sections: intact rats (A); 3 days LPS (B); 7 days LPS (C); 28 days LPS (D); control MSCs (E); 1 day LPS + 2 days MSCs (F); 4 days LPS + 3 days MSCs (G); 14 days LPS + 14 days MSCs (H); 21 days LPS + 7 days MSC (I). H&E staining, light microscopy, magnification $\times 200$.

The immunohistochemical detection of the presence of fibrosis marker TGF- $\beta 1$ in kidneys of intact rats showed its slight presence predominantly in the mesangial areas of the Malpighian bodies (Fig. 2 A). On day 3 of the ARDS, slight immunoprecipitate was observed in the peritubular interstitium (Fig. 2 B). By day 7 of ARDS, moderate increases in the amount of immunostained precipitate were observed in both the mesangium of glomerular vessels and peritubular stroma (Fig. 2 C). Kidney sections obtained from rats on day 28 of the experiment contained the highest amount of TGF- $\beta 1$ -immunostained peritubular areas surrounding nephron tubules as well as within Malpighian bodies, indicating fibrosis development (Fig. 2 D).

The comparative analysis of immunohistochemical detection of TGF- β 1 in the groups of untreated rats and rats treated with MSC showed a significant decrease in immunostaining intensity in the later groups. Brown precipitate was observed in small amounts predominantly in the areas of renal corpuscles and occasionally in the interstitial and large vessel areas (Fig. 2 F-I). The reduction in TGF- β 1 expression in renal stroma indicates the ability of MSCs to exert an anti-fibrotic effect.



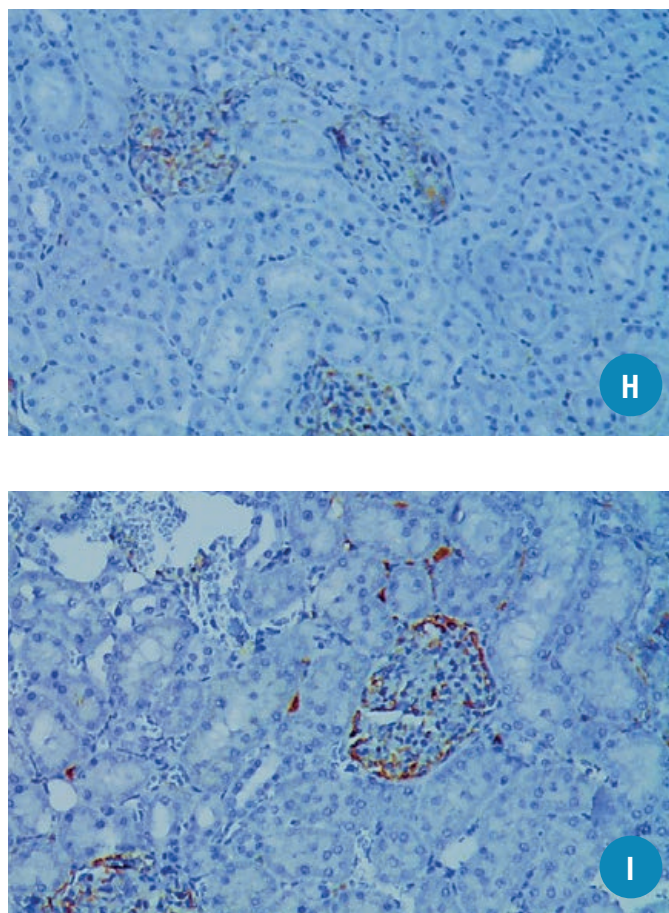


Fig. 2. Representative photomicrographs of rat kidney sections stained for TGF- β 1: intact rats (A); 3 days LPS (B); 7 days LPS (C); 28 days LPS (D); control MSCs (E); 1 day LPS + 2 days MSCs (F); 4 days LPS + 3 days MSCs (G); 14 days LPS + 14 days MSCs (H); 21 days LPS + 7 days MSC (I). Sections counterstained with Mayer's hematoxylin, light microscopy, magnification $\times 100$ (B-E), $\times 200$ (A, F-I).

The comparative analysis of the percentages of area occupied by immunoprecipitate showed that on day 3 of ARDS, the area of precipitate increased by 1.4 times compared to intact animals. By day 7 from the start of the experiment, it increased by 2.5 times compared to the control. On day 28 of modeled ARDS, the intensity of the immune reaction with TGF- β 1 antibodies was the highest, reaching 5.6 times higher than the control value. In the control MSC group of rats, the percentage of precipitate area did not statistically differ from intact animals. In all groups of rats with ARDS treated with MSCs, the amount of TGF- β 1 immunoprecipitate was statistically significantly lower than in the respective groups of animals with untreated ARDS. In 1 day LPS + 2 days MSCs and 14 days LPS + 14 days MSCs groups it approached the control values.

On day 3 of ARDS, the acute stage of ARDS persists, during which TGF- β 1 starts to be secreted by damaged kidney cells, so the influence of MSCs, although short (2 days in the 1 day LPS + 2 days MSCs group), was sufficiently effective to suppress the expression of this cytokine. In the 4 days LPS + 3 days MSCs group, the level of TGF- β 1 expression decreased by 1.9 times compared to 7 days LPS group, but remained 1.3 times higher than the control value. One week after ARDS modeling in rats, the second stage of ARDS (fibroplasia) begins, when the production of the fibrosis marker becomes more intense, and a longer action of MSCs is needed to more fully exert their anti-fibrotic effect. In animals of the 14 days LPS + 14 days MSCs group, a pronounced anti-fibrotic effect of MSCs was observed, characterized by a 4.6-fold decrease in

immunostaining intensity compared to the 28 days LPS group (ARDS without treatment). In 21 days LPS + 7 days MSCs group, TGF- β 1 levels were statistically significantly higher than control values (1.6 times), but significantly decreased compared to the 28 days LPS group (3.6 times) (see **Fig. 3**). When comparing the quantitative results of TGF- β 1 expression in the 14 days LPS + 14 days MSCs and 21 days LPS + 7 days MSCs groups, it can be concluded that the anti-fibrotic action of MSCs depends on the stage at which treatment was performed and the duration of action of stem cells.

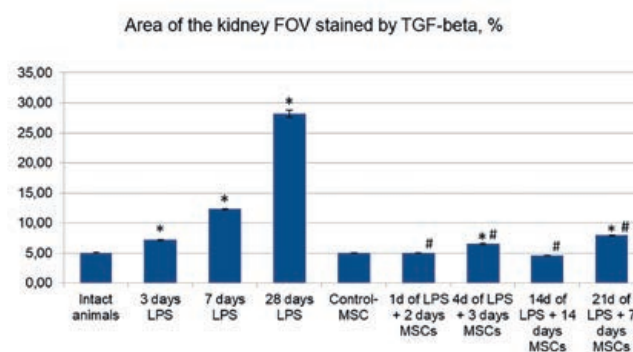


Fig. 3. Quantitative analysis of the area of TGF- β 1 immunoprecipitate in rat kidney sections.

Notes: * – statistically significant difference in results compared to the intact animal group;

– statistically significant difference in results compared to corresponding experiment terms in untreated groups.

Analyzing the levels of creatinine, urea, and uric acid in the serum of the experimental animals, their statistically significant increase ($p < 0.05$) was found in all rats at the early stage of ARDS development. The level of creatinine significantly increased on day 3 of ARDS (by 2.2 times), slightly decreased on day 7 (1.6 times higher than intact animals), and increased again on day 28 (1.8 times higher than the control value) (**Fig. 4 A**). This indicates the development of kidney damage.

The concentration of urea in the blood significantly increased on day 3 of ARDS (by 1.7 times) compared to the control value, slightly decreased on day 7 (1.4 times higher than control), and remained consistently elevated until day 28 of the experiment (1.6 times) (**Fig. 4 B**). The concentration of uric acid in the serum increased on day 3 of the experiment (by 1.33 times) and significantly decreased on days 7 and 28 of LPS (1.4 times and 1.3 times lower than the control value, respectively). Pathological decreases in uric acid levels on days 7 and 28 (**Fig. 4 C**) indicate concurrent liver damage (leading to decreased uric acid formation). This may also be a sign of impaired kidney ability to reabsorb uric acid in renal tubules due to their damage. This leads to increased excretion of uric acid in the urine and subsequently lower blood levels. Another reason for low levels of uric acid in the blood may be the development of oxidative stress as a result of inflammation caused by ARDS. Increased consumption of antioxidants during inflammation could lead to decreased levels of uric acid, which acts as an antioxidant itself.

The levels of kidney tests in the blood of rats in the control MSC group did not show deviations from intact animals ($p > 0.05$). In the MSC treatment groups (6, 7, and 9), creatinine levels were higher than in the intact animal group but statistically significantly lower ($p < 0.05$) than the indicators in the corresponding untreated ARDS groups (groups 2-4) (**Fig. 4 A**). The lowest and closest to the control value was the creatinine level in the 8th group, 14 days LPS + 14 days MSCs. These data are consistent with the previously described most pronounced regenerative and anti-fibrotic effects of stem cells administered at this term of the experiment.

The urea levels in the groups of rats treated with MSCs (groups 6-9) were also significantly lower ($p < 0.05$) compared to the respective groups of untreated animals (2-4) and statistically significantly different from the values of intact animals only in the 1 day LPS + 2 days MSCs group (Fig. 4 B). Obviously, a two-day treatment with stem cells was insufficient to preserve kidney function at the early acute stage of the disease.

The uric acid levels in all groups of treated animals reached the level of control values (Fig. 4 C). These data indicate a positive effect of MSCs on kidney function restoration.

Our research results indicate that modeled ARDS leads to the development of pathological changes in the kidneys of the experimental animals. The systemic inflammatory response associated with ARDS not only induces lung damage but also significantly affects the morphofunctional state of the kidneys, leading to the development of AKI [31]. The mutual negative impact of injured lungs and kidneys leads to the development of multi-organ failure and is a major cause of high mortality in ARDS [32].

During the early stages of renal ischemia, circulating neutrophils and monocytes quickly infiltrate the organ parenchyma and release lysosomal enzymes, leading to damage to the epithelial cells of nephron tubules [17]. Further cross-interactions between damaged epitheliocytes, activated endothelial cells, and tissue macrophages induce oxidative stress and complement activation, contributing to cell damage processes such as mitochondrial dysfunction and lipid peroxidation [33].

Molecules secreted by damaged cells activate pro-inflammatory transcription factors, leading to the release of cytokines and chemokines with subsequent leukocyte infiltration into the renal parenchyma, which culminates in endothelial dysfunction, mitochondrial dysfunction, oxidative-reductive imbalance, epithelial apoptosis, and necrosis. Once these pathological changes reach a threshold, kidney function is impaired, clinically evidenced by oliguria, as well as increased levels of creatinine and urea nitrogen in serum [34]. The above-mentioned data align with the results of our studies on the destruction and desquamation of nephron epithelium, leukocytic infiltration of stroma, or microvascular damage in the kidneys of rats after modeling ARDS, indicating the development of AKI in the experimental animals

A number of scientific studies have investigated the safety, efficacy, and appropriateness of using MSCs for the treatment of kidney injuries of various etiologies.

The regenerative effect of allogeneic MSCs has been demonstrated in the study by Kim et al., who induced ischemia-reperfusion injury of the left kidney in mice and used allogeneic bone marrow MSCs administered via the tail vein at a dose of 5 million cells as treatment [35].

Allinson et al. (2023), in their review article, summarized the results of some preclinical studies assessing the therapeutic effects of MSCs in AKI models [36]. Particularly, Changizi-Ashtiyani et al. (2020) demonstrated on a rat model of AKI that allogeneic adipogenic MSCs at a dose of 2×10^6 cells per rat fully or partially protected the kidneys from ischemia-reperfusion injury [37]. Condor et al. (2016) investigated the treatment of nephropathy caused by cecal ligation and puncture model of sepsis in rats. Human Wharton's jelly-derived MSCs at a dose of 1 million cells per rat, improved glomerular filtration rate, tubular function, reduced the expression of pro-inflammatory cytokines, attenuated apoptosis in the kidneys, and increased survival rate [38].

Xu et al. (2020) in their studies demonstrated that in a rat model of cisplatin-induced AKI, serum levels of creatinine and urea nitrogen were reduced after the intravenous administration of human umbilical cord MSC suspension at a dose of 2 million cells. Additionally, there were significantly lower levels of renal tubular damage in rats treated with MSCs [39]. As in the aforementioned studies, we also observed a reduction in parenchymal damage and restoration of kidney functional capacity in groups treated with MSCs.

Tseng et al. (2021), in their study on the impact of allogeneic bone marrow-derived hypoxic MSCs at a dose of 500,000 cells in a rat model of acute kidney ischemia-reperfusion injury, demonstrated the ability of MSCs to modulate macrophage phenotypes, reduce glomerular apoptosis, and enhance tubular proliferation in kidney tissues [40].

Additionally, Missoum et al. (2020) showed in an animal model of ischemia-reperfusion kidney injury that human umbilical cord MSCs improve glomerular filtration rate and nephron tubular function better than human adipose-derived MSCs [41].

In their meta-analysis, Zhou et al. (2020) found that MSC therapy can reduce serum creatinine levels at 1 day, 2 days, 3 days, 5 days, and >7 days in animal models of AKI. Moreover, stem cell therapy also reduced serum urea nitrogen levels at 1 day, 2 days, 3 days, and 5 days. They

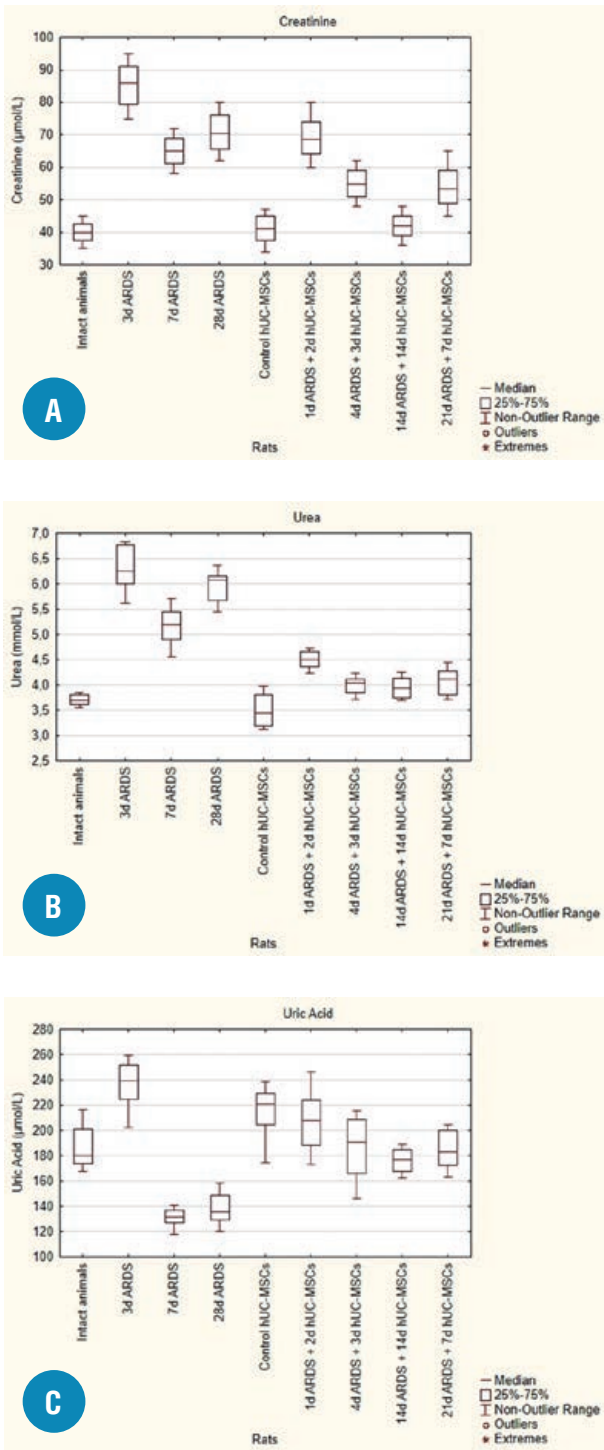


Fig. 4. Levels of creatinine (A), urea (B), and uric acid (C) in the blood serum of rats with modeled ARDS and its treatment with MSCs at different terms of experiment.

also assessed kidney damage and found that MSC usage significantly mitigated kidney injury in animal models of AKI [42]. Overall, the results of the analyzed studies demonstrate the nephroprotective effects of MSCs on kidney injuries of various etiologies [42].

Fawzy et al. (2023) showed in their study that the injection of adipogenic MSCs significantly improved kidney function in rats with cisplatin-induced nephrotoxicity, as evidenced by significant reductions in serum levels of creatinine, urea nitrogen, and uric acid. These results were further supported by reversion of all pathological changes confirmed by histological examination of the kidneys [43]. The described effects of adipogenic rat MSCs coincide with the results of our experiments which indicate the normalization of renal blood marker values and the reduction of pathological changes in the kidneys of rats with ARDS treated with human umbilical cord MSCs.

The development of tubulointerstitial renal fibrosis is a complex process involving inflammatory cell infiltration, epithelial cell damage, epithelial-to-mesenchymal transition (EMT), accumulation of myofibroblasts, and excessive deposition of extracellular matrix (ECM) [44]. A key mediator in renal fibrogenesis is TGF- β [45, 46]. TGF- β has 3 isoforms, with TGF- β 1 identified as the most potent mediator of kidney fibrosis [47]. It is known that the increased TGF- β 1 expression causes renal parenchymal cells transform into myofibroblasts (both EMT and monocyte-mesenchymal transitions), leading to ECM production and fibrosis development [48, 49]. Experimental inhibition of TGF- β 1 has been shown to significantly reduce the expression of epithelial transition markers and decrease fibrosis. Therefore, interventions that block or inhibit EMT may be potential therapeutic strategies for treating chronic progressive renal fibrosis [44].

In their study, Huang et al. (2022) found that levels of TGF- β 1 expression in serum and kidney tissues were significantly reduced in a murine lupus nephritis model following treatment with human umbilical cord MSCs, indicating the ability of umbilical MSCs to promote kidney recovery through the TGF- β 1 pathway [50]. These data are consistent with the results of our studies on the normalization of TGF- β 1 expression levels in an animal model of AKI after the use of human umbilical cord-derived MSCs.

Ullah et al. (2020) investigated the impact of bone marrow-derived MSCs in combination with focused pulsed ultrasound on acute kidney injury induced by cisplatin. While untreated groups showed glomerular and tubular cylinders and signs of kidney fibrosis, MSCs combined with ultrasound significantly reduced the presence of these pathological changes on histological examination [51].

Renal fibrosis manifests as an excessive deposition of ECM in renal parenchyma, leading to renal failure. Under normal conditions, ECM is degraded by metalloproteinases, but imbalance between metalloproteinases and their tissue inhibitors (TIMPs) results in ECM accumulation. MSCs have the ability to suppress expression of TIMPs, thereby alleviating fibrosis [52, 53].

The nephroprotective effect of MSCs in kidney injury lies in their anti-inflammatory capabilities (production of IL-10), angiogenic abilities (production of erythropoietin, insulin-like growth factor, fibroblast growth factor-2, and vascular endothelial growth factors), stimulation of endogenous cell precursors (vascular endothelial growth factor, insulin-like growth factor, leukemia inhibitory factor, hepatocyte growth factor, and stromal cell-derived factor-1), anti-apoptotic effects (insulin-like growth factor and hepatocyte growth factor), anti-fibrotic abilities (hepatocyte growth factor, matrix metalloproteinases, and TIMPs), antioxidant actions (erythropoietin and heme oxygenase-1), and stimulation of cell reprogramming (exosomes) [54].

CONCLUSION

The results of the conducted studies indicate that the severity of kidney damage increases with the progression of ARDS. Human umbilical cord-derived MSCs exert regenerative, anti-inflammatory, and anti-fibrotic effects, which manifest in the restoration of damaged renal parenchyma, reduction of fibrosis marker expression, and normalization of serum renal biomarkers. It has been found that the effectiveness of stem cell therapy depends on the stage of ARDS development and the duration of MSCs action. It has been demonstrated that the use of MSCs on the 14th day of ARDS development provides a better nephroprotective effect on the 28th day of the experiment compared to MSC administration on the 21st day of ARDS, which is explained by the longer impact of administered stem cells on the damaged kidney. Thus, our study complements existing understandings of the therapeutic potential of MSCs in kidney injury and highlights the advantages of this approach for treating AKI.

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Морфофункціональні зміни у нирках щурів за умов гострого респіраторного дистрес-синдрому та його корекції мезенхімальними стовбуровими клітинами пуповини людини



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РЕЗЮМЕ

Гострий респіраторний дистрес-синдром (ГРДС) – важкий патологічний стан, що часто супроводжується ураженням нирок. Відомо, що мезенхімальні стовбурові клітини (МСК) мають високий терапевтичний потенціал для багатьох захворювань завдяки своїй здатності паракринно стимулювати регенерацію пошкоджених клітин і тканин та відновлювати порушені функції органів.

МЕТА: дослідити нефропротекторний вплив МСК з пуповини людини на моделі ГРДС, індукованого у щурів інтраназальним введенням ліпополісахариду (ЛПС).

МАТЕРІАЛИ І МЕТОДИ. 72 статевозрілих самця щурів Вістар рандомізовано поділили на дев'ять груп: інтактні тварини, 3 дні, 7 днів і 28 днів розвитку ГРДС, контроль-МСК та чотири групи корекції: 24 години ЛПС + 2 дні МСК, 4 дні ЛПС + 3 дні МСК, 14 днів ЛПС + 14 днів МСК, 21 день ЛПС + 7 днів МСК. МСК вводили інтраперитонеально в дозі 10^6 клітин/кг маси тіла. Рівні структурного пошкодження нирок досліджували за допомогою гістологічного аналізу зрізів, зафарбованих гематоксилином та еозином. Експресію маркера фіброзу TGF- β 1 у тканинах нирок оцінювали імуногістохімічним методом. Рівні креатиніну, сечовини та сечової кислоти у сироватці крові вимірювали за допомогою кінетичного методу.

РЕЗУЛЬТАТИ. Проведені дослідження виявили значне ураження паренхіми нирки, фіброгенез та порушення функції нефронів у щурів зі змодельованим ГРДС. Патологічні зміни наростали з тривалістю експерименту. Застосування МСК з пуповини людини як коригуючого чинника значно зменшило ознаки коагулопатії, тубулярного некрозу і деструкції ниркових тілець, загальмувало розвиток інтерстиційного фіброзу та покращило ниркові показники крові. З'ясовано, що кращий нефропротекторний ефект МСК проявляли на 28 добу експерименту у групі щурів 14 днів ЛПС + 14 днів МСК, що, очевидно, пов'язано з більш раннім застосуванням та тривалішим терміном дії стовбурових клітин, порівняно з групою 21 день ЛПС + 7 днів МСК.

ВИСНОВОК. Мезенхімальні стовбурові клітини з пуповини людини мають регенеративну, антифібротичну та нефропротекторну дію на тваринній моделі ниркового ураження, спричиненого ГРДС. Це може свідчити про терапевтичний потенціал МСК пуповини для лікування нефропатій різного генезу.

КЛЮЧОВІ СЛОВА: ураження нирок; мезенхімальні стовбурові клітини пуповини людини; гістологічний аналіз; імуногістохімічний аналіз; ниркові маркери в крові