ORIGINAL ARTICLE

CONTENTS

Experimental evidence of kidney damage following oral administration of gadolinium nanoparticles $GdYVO_4:Eu^{3+}$

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ABSTRACT

Aim: To study the effect of native and UV-activated GdYVO4:Eu3+ nanoparticles in different concentrations on the histological and biochemical indicators of kidney function.

Materials and Methods: Male rats (6 groups) were orally administered a colloidal solution of nanoparticles at doses of 50, 100, and 200 μg/kg body weight (native and UV-activated). An intact animal group was included. Each group contained 6 individuals. Pathohistological examination of kidney tissue and biochemical analysis of blood and kidney tissue homogenate were performed. Statistical analysis was done using the Mann-Whitney test.

Results: Yellow granules were found in the glomerular tissue and tubular epithelium of rats. Volume voids were seen in the renal cortex with a medium-sized renal artery. As nanoparticle doses increased, the number of functioning glomeruli decreased, and both atrophic and hypertrophic glomeruli with hyperplasia of capillaries appeared. Higher doses were associated with increased transamidinase activity, von Willebrand factor, creatinine, and urea levels in blood serum, along with a decrease in ATP and total protein in kidney tissue. UV pre-irradiation of nanoparticles enhanced dystrophy, tissue death, and glomerular atrophy, with more pronounced biochemical shifts.

Conclusions: Pathohistological and biochemical analysis showed that oral administration of GdYVO4:Eu3+ nanoparticles caused kidney damage, worsening with increased doses. UV-activated nanoparticles exacerbated renal damage.

KEY WORDS: nanoparticles, kidneys, damage, pathohistology, biochemistry

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INTRODUCTION

The advancement of nanotechnology in biology and medicine facilitates the development and application of nanomaterials for diagnosing, treating, and monitoring pathological processes. Nanotechnology has improved early cancer diagnosis and treatment, reducing the need for toxic drugs [1]. The development of nanoparticles (NPs) of various types has enhanced targeted drug delivery and tumor cell destruction due to their electrical, magnetic, and optical properties [2–4]. Additionally, the use of NPs as contrast agents for in vivo molecular imaging is actively being explored.

Gadolinium-based nanocomplexes are of particular interest. Studies have shown that gadolinium orthovanadate doped with europium exhibits both antioxidant and prooxidant properties depending on conditions [5], while its administration may induce toxic organ damage [6–9]. Kidney diseases represent a significant medical and social problem, affecting over 500 million adults worldwide [10]. Given the toxic effects of GdYVO4:Eu3+ NPs, their use in cancer diagnosis and therapy may pose a potential risk to kidney health [11,12].

Since NPs are excreted and can accumulate in the kidneys, their impact requires thorough investigation. Due to identified risks, the European Medicines Agency has restricted the use of certain linear gadolinium-based contrast agents for MRI (Abu-Alfa AK, 2020) [13]. However, the mechanisms underlying GdYVO4:Eu3+ nephrotoxicity remain insufficiently understood.

To assess this impact, an experimental study funded by Ukraine was conducted on animals, involving the administration of a colloidal solution of GdYVO4:Eu3+ NPs. Histological changes in the kidneys were analyzed, along with biochemical markers reflecting their functional state.

AIM

To study the cumulative effect of native and *UV*-activated nanoparticles of the complex substance $GdYVO_4:Eu^{3+}$ in different concentrations on the histological picture of the kidneys and biochemical indicators of their functional state.

MATERIALS AND METHODS

In the experimental study, an artificially synthesized colloidal solution of GdYVO4:Eu3+ nanoparticles was used according to the method described by Klochkov V.A. [12]. The solution administered to experimental animals contained spherical NPs with a predominance of sizes of 8–25 nm. In half of basic groups GdYVO4:Eu3+ was activated by UV exposure. The administration of the colloidal substance was carried out orally using an automatic dispenser.

GROUPS OF ANIMALS

Experiments were conducted on male rats of the WAG population weighing 180-200 g, which were kept in standard vivarium conditions under natural lighting, on a balanced diet. Rats were randomly divided into 7 groups, 6 animals in each:

- control group (group C), animals received 0.18-0.20 ml of drinking water orally;
- three main groups that received gadolinium solution in doses of 50, 100 and 200 mcg/kg of body weight (group G-50, group G-100, group G-200) for 14 days;
- three main groups that received *UV*-activated gadolinium solution at doses of 50, 100 and 200 mcg/kg body weight (group GUV-50, group GUV-100, group GUV-200) for 14 days .

Thus, each of the three doses used contained gadolinium NPs in two versions – native or activated by *UV* irradiation.

MATERIAL COLLECTION

After the end of the NP solution administration, the next day the rats were removed from the experiment by decapitation using a guillotine, blood was collected, and during autopsy the right kidney was isolated for morphological study. Blood serum and the left kidney were used for biochemical studies. The right kidney was fixed in 10% neutral formalin for morphological study.

When working with experimental rats, the provisions of the European Convention for the Protection of Vertebrate Animals (Strasbourg, 18.03.1986, revised and supplemented in 2006), the Law of Ukraine No. 3447-IV, Articles 26, 31 «On the Protection of Animals from Cruelty», «General Ethical Principles of Experiments on Animals», adopted by the Fifth National Congress on Bioethics (Kyiv, 2013), were adhered too.

BIOCHEMICAL METHODS

Serum creatinine and urea levels were determined by spectrophotometric methods using commercial reagent kits from «Filisit-Diagnostics». Serum transamidinase activity was determined by spectrophotometric method [14]. Measurements were performed on a Scular PV spectrophotometer. The amount of protein in kidney tissue was determined by the Lowry spectrophotometric method [15] to assess the state of blood vessels endothelium in experimental rats we determined the content of von Willibrandt factor (vWF) in the blood serum of rats. The determination was carried out by immunoenzymatic method using the reagent kit Elabscience VWF ELISA KIT of Elabscience Biottchnology (USA). Measurements were performed on a Stat Fax semi-automatic immunoenzyme analyzer (USA). The ATP content in tissue homogenates was determined by spectrophotometric method [16], expressed in mmol/g of tissue.

MORPHOLOGICAL METHODS

Sections were stained with hematoxylin-eosin, Van Gieson's picrofuchsin, and Einarson's halocyanine-chromium alum for total nucleic acids, and the PAS-reaction was performed. Microscopy was performed on an Axiostar plus microscope (Zeiss, Germany), and the images of the micropreparations were analyzed with subsequent morphometry using Photoshop CS6. The optical density [15] of the cytoplasm of the proximal tubules of the kidneys was determined using digital images of kidney tissue stained with Einarson's halocyanine-chromium alum for total nucleic acids. In addition, to assess the degree of development of glomerular capillaries on microphotographs, the average number of capillary epithelial cells in one glomerulus was counted.

Statistical processing of the data obtained in the studies was carried out using the Graph Pad Prizm 5 program (Grath Pad Soflware, USA) using the non-parametric Mann-Whitney *U*-test.

RESULTS

HISTOLOGICAL EXAMINATION OF THE KIDNEYS

In intact animals (group C), glomeruli were evenly distributed in the renal cortex and had uniform size.

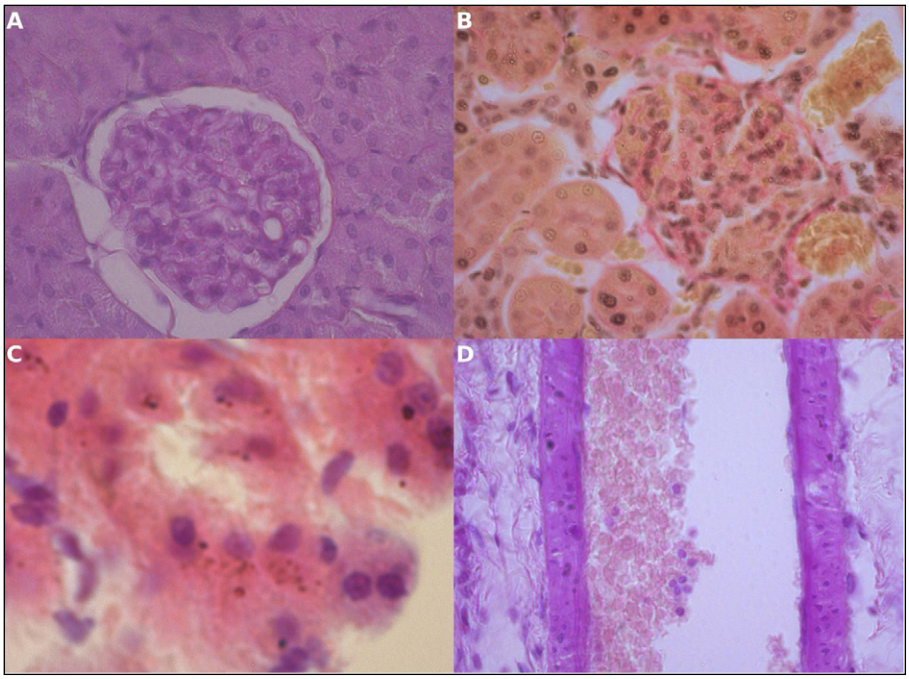

Fig. 1. A – well-preserved glomerulus and tubular epithelium in the kidney of an animal of group C; B – irregularly shaped glomerulus with yellow shallow inclusions in the mesangium (group G-50); C – significantly damaged tubular epithelium with shallow yellow inclusions in the cytoplasm (group G-200); D – absence of endothelium in the intima over a significant area with the formation of a thrombus (group GUV-100). Staining: A, D – PAS, B – according to Van Gieson, C – hematoxylin-eosin. Magnification: A, B, D – 400, C – 1000

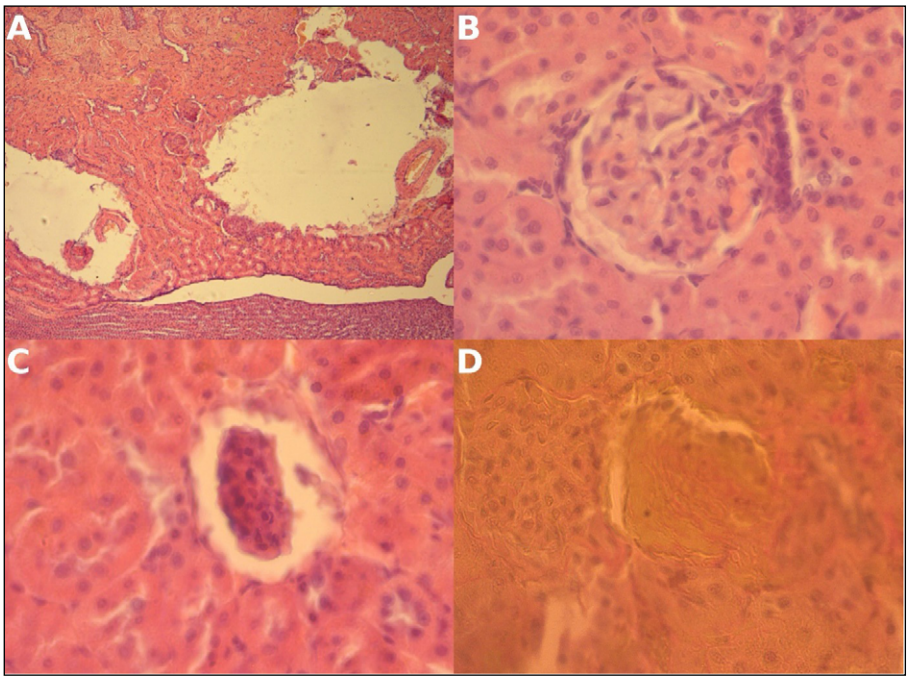

Fig. 2. A – cysts appearing in the cortical substance of the kidneys in group G-50; B - hyperplastic juxta-glomerular apparatus, reduced number of endothelial cells of the glomerular capillaries, expanded mesangium, додати group GUV-50; C - atrophied glomerulus of the kidney in group G-100; D – completely fibrotic glomerulus with the appearance of mature fuchsinophilic collagen in the kidney of an animal in group GUV-200. Staining: A, B, C – hematoxylin-eosin, D – picrofuchsin according to Van Gieson. Magnification: A – 50, B, C, D – 400

Capillaries appeared collapsed, with a thin PAS-positive basement membrane. Juxtaglomerular apparatus cells were small with rounded nuclei. Tubular epithelium was preserved, with moderately euchromatic nuclei. The brush border in convoluted tubules was narrow and fuchsinophilic. The interstitium consisted of narrow layers with few fibrocytes (Fig. 1A).

All groups (Fig. 1B-D; Fig. 2 A-D) exhibited cystic spaces with a single medium-sized artery. Both hypertrophied and atrophied glomeruli were observed. Increasing nanoparticle doses led to a rise in atrophied glomeruli and a reduction in compensatory hypertrophied ones, though their hypertrophy became more pronounced.

Atrophying glomeruli displayed fuchsinophilic deposits in the mesangium (Van Gieson). Active glomeruli contained serous and hemorrhagic exudates in Bowman's capsule. Small yellow granules (presumably gadolinium) were visible in the mesangium under ×1000 magnification. In some areas, swelling of the tubular epithelium led to glomerular compression and deformation of Bowman's capsule. Many tubular epithelial cells lacked nuclei; tubules with necrotic epithelium formed relatively large foci. Small yellow granules were also present in the cytoplasm of epithelial cells. The interstitium was thickened, with increased cellularity.

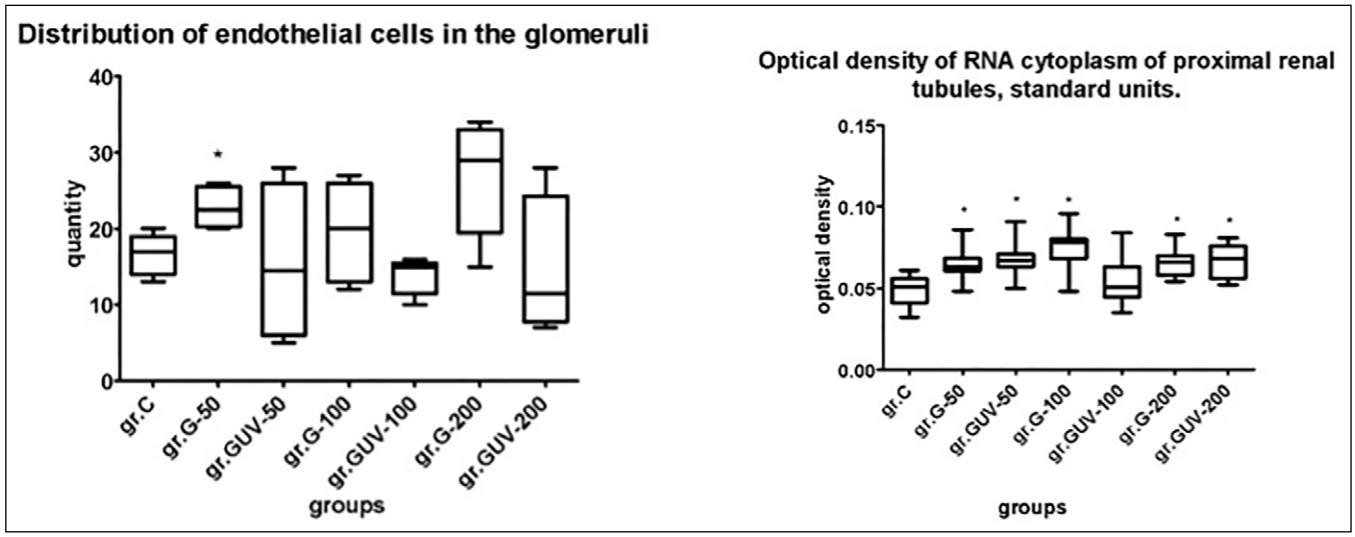

Fig. 3. The number of capillary endothelial cells in the glomeruli.
* - $P < 0.001$, the probability of differences between the control and experimental groups.

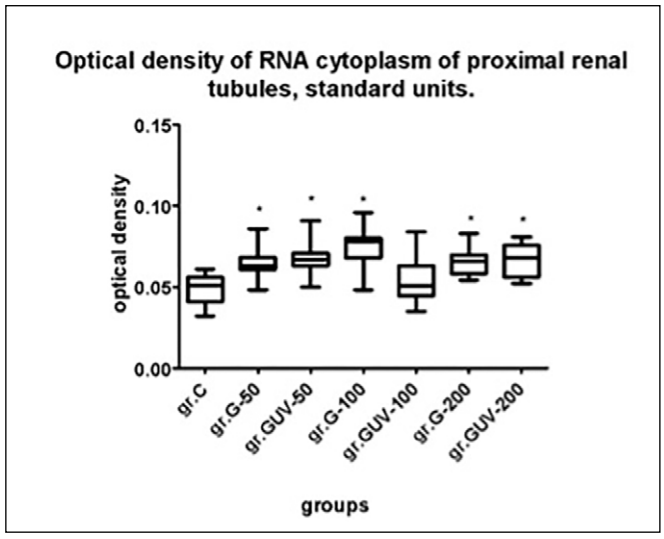

Fig. 4. Optical density of epithelial cytoplasm in proximal tubules *$P < 0.001$, probability of differences between the control and experimental groups

Endothelial cell counts confirmed vascular-origin glomerular atrophy and compensatory hypertrophy of intact glomeruli (Fig.3). In group C, capillary endothelial cells ranged from 13 to 20, whereas in G-50, endothelial hyperplasia reached 20–26 cells with minimal glomerular atrophy. Higher nanoparticle doses increased glomerular atrophy and hypertrophy severity. At the highest dose, glomeruli with 32–34 endothelial cells appeared alongside severely atrophied ones (7–12 cells). Pre-irradiation of nanoparticles exacerbated glomerular atrophy and reduced the number of endotheliocytes.

Analysis of the optical density of tubular epithelial cytoplasm (Einarson staining, Fig.4) showed a wide range of values, reflecting both reduced morphofunctional activity in damaged cells and compensatory increases in unaffected or minimally affected cells. Mean values in all groups (except GUV-100) exceeded those in C, peaking in G-100. At 50 µg/ml, UV treatment increased cytoplasmic density, whereas at 100 µg/ml, it reduced it to C levels. In G-200, this parameter significantly decreased, with UV pre-treatment having no effect.

Hyperplasia of the juxtaglomerular apparatus was observed in all groups, most prominently at the highest gadolinium dose.

BIOCHEMICAL EXAMINATION OF THE KIDNEYS

When rats were administered a colloidal solution of GdYVO4:Eu3+ nanoparticles, an organ-specific renal enzyme, transamidinase (Table 1), was detected in the blood, indicating a pathological process in renal tissue. At the minimum nanoparticle dose, enzyme activity was found only in the GUV-50 group, meaning native nanoparticles at 50 µg/kg did not cause renal damage. At 100 and 200 µg/kg doses, enzyme activity was detected in all groups, more pronounced with irradiated nanoparticles and with higher doses.

To assess endothelial damage, the concentration of vWF was measured. Only non-irradiated nanoparticles at 50 µg/kg did not cause an increase in vWF concentration. In all other experimental conditions, vWF concentration significantly increased, indicating endothelial damage. The increase in vWF concentration was directly proportional to nanoparticle dose, and higher with irradiated nanoparticles. This suggests that administering nanoparticle preparations in doses above the minimum disrupts kidney function.

Analysis of the concentration of end products of protein metabolism (urea and creatinine) in blood serum revealed that their content was increased in rats of all groups, except group G-50 (Table 2). The increase of concentration of urea and creatinine were proportional to increasing dose, within one dose - higher with the introduction of activated NPs

Table 1. Transamidinase activity and content of von Willibrandt factor, in the blood

groups	Transamidinase, µmol/hour/L	vWF , ng/ml
gr.C	is missing	4,79 [4,62; 4,94]
gr. G-50	is missing	5,04 [4,89; 5,35]
gr. GUV-50	7,21 [6,74; 7,67]	6,05* [5,84; 6,19]
gr. G-100	33,72*# [33,04,5; 34,21]	13,97* [13,72; 14,06] #
gr. GUV-100	44,21#p* [43,59; 45,04]	17,16 *[17,13; 17,46]#
gr. G-200	63,52#* [62,16; 64,14]	34,50*# [34,41; 34,72]
gr. GUV-200	70,06*# [66,82; 74,31]	49,08 *[48,97; 49,31]#

Note: * - P1 < 0.05, probability of differences between the control and experimental groups; # - P2 < 0.05, probability of differences between groups (native and irradiated) within one dose

Table 2. Creatinine and urea content in the blood serum of rats, [Me (25,75)]

groups	Creatinine, µmol/l	Urea, mmol/l
gr.Control	91,48 [90,1; 92,63]	6,93 [6,77; 7,07]
gr. G-50	92,33 [91,21; 93,38]	7,09 [6,97; 7,20]
gr. GUV-50	93,87* [93,23; 94,50]	7,4*# [7,31; 7,49]
gr. G-100	103,9* [101,5; 106,2]	7,71* [7,54; 7,91]
gr. GUV-100	108,0* [104,9; 110,4]	8,29*# [8,21; 8,38]
gr. G-200	112,8* [110,6; 114,6]	9,01* [8,99; 9,16]
gr. GUV-200	126,0*# [124,1; 127,7]	9,65*# [8,91; 10,19]

Note: * - P1 < 0.05, probability of differences between the control and experimental groups; # - P2 < 0.05, probability of differences between groups (native and irradiated) within one dose

Table 3. ATPh and protein content in rat kidney tissue after oral administration of a colloidal solution of GdYVO4:Eu3+ nanoparticles (in native and irradiated forms), [Me (25, 75)]

groups	ATPh, mmol/g of tissue	Total protein, mg/g of tissue
gr.Control	2,53 [2,46; 2,61]	158,7 [154,9; 162,1]
gr. G-50	2,09* [2,05; 2,15]	150,9* [149,0; 152,9]
gr. GUV-50	1,95*# [1,9; 2,0]	141,8*# [140,3; 143,5]
gr. G-100	1,82* [1,77; 1,88]	129,4* [127,0; 131,7]
gr. GUV-100	1,7*# [1,67; 1,74]	107,7*# [106,0; 109,5]
gr. G-200	1,6* [1,56; 1,65]	116,0* [113,7; 118,7]
gr. GUV-200	1,48*# [1,44; 1,53]	97,5*# [96,2; 98,6]

Note: * - P1 < 0.05, probability of differences between the control and experimental groups; # - P2 < 0.05, probability of differences between groups (native and irradiated) within one dose

(Table 2). The increase in urea and creatinine concentrations indicates a decrease in glomerular filtration rate.

Analysis of the content of ATPh and total protein in kidney homogenates after oral administration of NPs revealed that there was a dose-dependent decrease in the concentration of ATPh and total protein in the kidneys of rats (Table 3).

DISCUSSION

As a result of biochemical studies, it was found that when rats were orally administered a colloidal solution of GdYVO4:Eu3+ nanoparticles in both native and irradiated forms, the concentration of the organ-specific renal enzyme transamidinase increased. This indicates a violation of nephrocyte membrane permeability and the release of the enzyme into the blood. This is likely related to the development of oxidative stress under the influence of GdYVO4:Eu3+ nanoparticles, as confirmed by many authors [8, 19, 20]. The consequence of oxidative stress is structural and functional changes in the kidneys, with tubular epithelial cell death and glomerular fibrosis, as well as the appearance of transamidinase in blood serum. Microscopic examination revealed dystrophy of the tubular epithelium with inclusion of small yellow particles in the cytoplasm (presumably gadolinium) and mass epithelial cell death leading to cyst formation. The toxicity of gado-

linium nanoparticles was also observed in the endothelium of large arteries and glomerular capillaries, which leads to thrombosis in arteries and death of glomerular capillaries (yellow inclusions were also found in the mesangium).

It was found that the increase in transamidinase activity in serum is dose-dependent, with the highest activity observed at a dose of 200 µg/ml. This coincides with a dose-dependent decrease in ATP levels in tissues, a reduction in protein mass in the kidneys, and an increase in the concentration of urea and creatinine in blood serum, indicating impaired kidney function. The changes in these concentrations are also dose-dependent, being more pronounced with irradiated nanoparticles. These results directly indicate a decline in kidney function upon administration of gadolinium nanoparticles, especially irradiated ones.

Morphological diagnostics revealed cysts in the kidneys and pronounced glomerular fibrosis, particularly at the highest dose of gadolinium and when nanoparticles were UV-irradiated before administration, which supports these conclusions.

Derrick J. Todd and Jonathan Kay [18], analyzing clinical data, concluded that in people with significant renal dysfunction, severe nephrogenic systemic fibrotic lesions occur after the use of gadolinium nanoparticles for diagnostic purposes, although the mechanism is unknown. Most commonly, these were systemic skin lesions [19-21]. It can be hypothesized that gadolinium, as demonstrated in this experiment, significantly affects the vascular endothelium, which may lead to a reduction in the capillary bed and thrombosis both in the skin and in systemic vessels, ultimately causing ischemia and fibrosis. Furthermore, since gadolinium is primarily excreted from the blood through the kidneys, and the kidneys significantly reduce their function under the direct influence of gadolinium, nanoparticles remain in the blood for longer periods and at higher concentrations. It is also evident that pre-existing kidney disease accelerates and exacerbates these effects.

CONCLUSIONS

Experimentally, in laboratory rats, using biochemical and histological methods, it was found that oral administration of gadolinium nanoparticles at doses of 50, 100, and 200 µg/kg causes significant damage to kidney tissue, including tissue lysis and glomerular fibrosis. The appearance of transamidinase in the blood serum, along with a decrease in ATP and protein levels, and an increase in creatinine and urea concentrations in the blood, also indicates kidney atrophy. Yellow microgranules (gadolinium) accumulate in the vascular endothelium, leading to the death of glomerular capillaries and the formation of fibrous glomeruli. Microgranules are filtered in functioning glomeruli, appear in the urine and in the cytoplasm of tubular epithelium, leading to its destruction. The use of UV-activated gadolinium nanoparticles exacerbates kidney damage.Keywords: nanoparticles, kidneys, damage, pathohistology, biochemistry

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CONFLICT OF INTEREST
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