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Effect of hypo- and hyperthyroidism on kidney morphology in experimental prostate hyperplasia in rats

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Abstract. ***Introduction.*** The influence of thyroid status on the morphogenesis of obstructive nephropathy, which develops against the background of benign prostatic hyperplasia, remains unexplored, despite the presence of contradictory clinical data on the relationship of hypo- and hyperthyroidism with the risk of developing benign prostatic hyperplasia. There are no experimental studies on this issue. ***The aim*** — to evaluate the effect of experimental hypo- and hyperthyroidism on the morphological characteristics of the kidneys in conditions of testosterone-induced benign prostatic hyperplasia and concomitant obstructive uropathy in rats. ***Materials and methods.*** Benign prostatic hyperplasia was modeled on 32 male Wistar rats using daily injections of testosterone propionate (5 mg/kg). The animals were divided into 4 groups (n=8): intact control, “pure” benign prostatic hyperplasia, benign prostatic hyperplasia + hyperthyroidism (L-thyroxine, 10 mcg/100 g/day) and benign prostatic hyperplasia + hypothyroidism (propylthiouracil, 0.05% with drinking water). On day 36, macro- and micromorphometry of the kidneys was performed using light microscopy, hematoxylin and eosin staining, and digital image analysis (ImageJ). The mass of the organ, the thickness of the cortical substance, the area of the glomeruli, the diameter of the lumen of the proximal and distal tubules, the density of capillaries were evaluated, and a semi-quantitative assessment of hydronephrosis (0–4 points) and inflammatory infiltrate (0–3 points) was performed. The thyroid status was confirmed by measuring the levels of thyroxine and thyroid-stimulation hormone using the ELISA method. ***Results.*** Hyperthyroidism on the background of benign prostatic hyperplasia led to the maximum severity of obstructive changes: the relative mass of the kidneys increased by 38.1% compared to the control ($p < 0.05$), the mass of residual urine exceeded the control value by 10.25 times ($p < 0.05$), and the thickness of the cortical substance decreased by 36.7% (to 0.95±0.12 mm, $p<0.05$). Micromorphometry revealed pronounced dilation of the distal tubules (diameter 48.2±5.9 microns versus 21.0±2.8 microns in the control, $p < 0.001$), an increase in glomerular area by 15% ($p<0.05$), an increase in capillary density by 50% ($p < 0.05$), as well as the development of grade 3 hydronephrosis and moderate inflammation (2 points). In the “benign prostatic hyperplasia + hypothyroidism” group, all parameters were much closer to the control: tubule dilation was minimal (25.3±3.2 microns), cortical thickness was preserved (1.40±0.17 mm), inflammatory infiltrate was absent, and hydronephrosis was estimated at 1 point. ***Conclusion.*** experimental hyperthyroidism potentiates structural kidney damage in obstructive uropathy, while hypothyroidism, on the contrary, exhibits a pronounced protective effect.

Keywords: kidney, obstructive nephropathy, hypothyroidism, hyperthyroidism, benign prostatic hyperplasia, rats

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Оригинальная статья
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Влияние гипо- и гипертиреоза на морфологию почек при экспериментальной гиперплазии предстательной железы у крыс

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Резюме. ***Введение.*** Влияние тиреоидного статуса на морфогенез обструктивной нефропатии, развивающейся на фоне доброкачественной гиперплазии предстательной железы, остается неизученным, несмотря на наличие противоречивых клинических данных о взаимосвязи гипо- и гипертиреоза с риском развития гиперплазии предстательной железы. Экспериментальные исследования, посвященные этому вопросу, отсутствуют. ***Цель*** — оценить влияние экспериментального гипо- и гипертиреоза на морфологические характеристики почек в условиях тестостерон-индуцированной гиперплазии предстательной железы и сопутствующей обструктивной уропатии у крыс. ***Материалы и методы.*** На 32 самцах крыс линии Wistar смоделирована гиперплазия предстательной железы с помощью ежедневных инъекций тестостерона пропионата (5 мг/кг). Животные были разделены на четыре группы (n=8): интактный контроль, «чистая» гиперплазия предстательной железы, гиперплазия предстательной железы + гипертиреоз (L-тироксин, 10 мкг/100 г/сут) и гиперплазия предстательной железы + гипотиреоз (пропилтиоурацил, 0,05% с питьевой водой). На 36-е сутки проведена макро- и микроморфометрия почек с использованием световой микроскопии, окрашивания гематоксилином и эозином и цифрового анализа изображений (ImageJ). Оценивали массу органа, толщину коркового вещества, площадь клубочков, диаметр просвета проксимальных и дистальных канальцев, плотность капилляров, а также выполняли полуколичественную оценку гидронефроза (0–4 балла) и воспалительного инфильтрата (0–3 балла). Тиреоидный статус подтвержден измерением уровня тироксина и тиреотропного гормона методом иммуноферментного анализа. ***Результаты.*** Гипертиреоз на фоне гиперплазии предстательной железы привел к максимальной выраженности обструктивных изменений: относительная масса почек увеличилась на 38,1% в сравнении с контролем ($p < 0,05$), масса остаточной мочи превысила контрольный показатель в 10,25 раза ($p < 0,05$), а толщина коркового вещества уменьшилась на 36,7% (до 0,95±0,12 мм, $p < 0,05$). Микроморфометрия позволила выявить выраженную дилатацию дистальных канальцев (диаметр 48,2±5,9 мкм против 21,0±2,8 мкм в контроле, $p < 0,001$), увеличение площади клубочков на 15% ($p < 0,05$), повышение плотности капилляров на 50% ($p < 0,05$), а также гидронефроз III степени и умеренное воспаление (2 балла). В группе «гиперплазия предстательной железы + гипотиреоз» все параметры были значительно ближе к контролю: дилатация канальцев была минимальной (25,3±3,2 мкм), толщина коры сохранена (1,40±0,17 мм), воспалительный инфильтрат отсутствовал, а гидронефроз оценивался в 1 балл. ***Заключение.*** Экспериментальный гипертиреоз потенцирует структурное повреждение почек при обструктивной уропатии, а гипотиреоз, напротив, проявляет выраженный протективный эффект.

Ключевые слова: почка, обструктивная нефропатия, гипотиреоз, гипертиреоз, доброкачественная гиперплазия предстательной железы, крысы

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INTRODUCTION

Benign prostatic hyperplasia (BPH) is a morphologically heterogeneous condition leading to lower urinary tract obstruction and secondary obstructive nephropathy [1, 2]. In addition to the key role of androgens, systemic hormonal and metabolic disorders, including thyroid dysfunction, are attracting increasing attention as a contributing factor to BPH and its complications [3–5]. Recent epidemiological studies demonstrate a close association between thyroid dysfunction and renal pathology. For example, a large population-based NHANES study (2007–2012) identified a U-shaped relationship between levels of free triiodothyronine (T3), thyroxine (T4), and chronic kidney disease. Both hypothyroidism and hyperthyroidism are associated with an increased risk of developing and progressing renal dysfunction [5]. These findings are particularly relevant for patients with benign prostatic hyperplasia (BPH), since obstructive uropathy may exacerbate renal complications, and thyroid status may act as a critical modifier of pathogenesis.

AIM

The aim of this study was to evaluate how experimental hypothyroidism and hyperthyroidism affect renal morphological characteristics in a model of testosterone-induced prostatic hyperplasia and concomitant obstructive uropathy in rats.

MATERIALS AND METHODS

The experiment was conducted on 32 sexually mature male Wistar rats (weighing 220–250 g). The animals were housed under standard vivarium conditions at a temperature of 22±2 °C, relative humidity of 50–60%, and a 12-hour light cycle (from 8:00 a.m. to 8:00 p.m.) . All procedures complied with the principles of European Convention for the Protection of Vertebrate Animals (Strasbourg, 1986) and were approved by the local ethics committee.

Overall, the study lasted 35 days. All animals, except for intact controls, underwent total bilateral orchiectomy under thiopental sodium anesthesia (40 mg/kg) to induce androgen deprivation. Seven days after surgery, the animals began receiving testosterone propionate (5 mg/kg) to induce prostatic hyperplasia and model obstructive uropathy [1].

Group 1 (intact control): sham surgery + subcutaneous administration of olive oil (0.1 mL/100 g body weight) from day 7 through day 35. Group 2 (hyperplasia model, BPH): daily subcutaneous injections of testosterone propionate (5 mg/kg) in olive oil from day 7 to day 35. Group 3 (BPH + hyperthyroidism): 7 days prior to orchiectomy and continuously thereafter — L-thyroxine (dry substance, Belmedpreparaty State Unitary Enterprise, Republic of Belarus) at a dose of 100±10 μg per 100 g of body weight once daily + testosterone propionate according to the regimen for Group 2. Group 4 (Castration + Hypothyroidism): 7 days prior to orchiectomy and continuously thereafter — propylthiouracil (dry substance, Merck Selbstmedikation GmbH, Germany) at a dose of 2.0±0.15 mg per 100 g of body weight once daily, administered intragastrically via an atraumatic polyurethane tube + testosterone propionate according to the Group 2 regimen.

To ensure biochemical verification that the model corresponded to the planned endocrine status, blood was collected from the retroorbital sinus 24 hours prior to euthanasia in 4 randomly selected rats from each group under light ether anesthesia. Serum was obtained by centrifugation at 3,000 rpm for 15 minutes. Concentrations of free thyroxine (T4) and thyroid-stimulating hormone (TSH) were determined by solid-phase enzyme-linked immunosorbent assay (ELISA) using commercial kits manufactured by NVO Immunotech CJSC for the detection of T_4 (Immuno-FA-free T_4) and TSH (ImmunoFA-TSH).

On day 36, the animals were euthanized with an overdose of sodium thiopental (100 mg/kg, intraperitoneally). A total laparotomy was performed, and the kidneys were removed. The organs were weighed on analytical balances accurate to 0.1 mg, the thickness of the cortical substance (mm) was measured, and the organs were fixed in 10% neutral buffered formalin (pH 7.4) for 24 hours. After standard histological processing, the material was embedded in paraffin, and serial sections 3–4 μm thick were prepared. The sections were stained with hematoxylin and eosin. Morphometric analysis was performed on digital images of the sections obtained using a Carl Zeiss Axio Scope A1 light microscope equipped with a digital camera. Before measurements, the system was calibrated using an objective micrometer scale. ImageJ software (USA) was used.

For each parameter, 10 randomly selected fields of view were analyzed from a single animal. The following parameters were assessed: cortical thickness (mm; ×100); glomerular area (μm²), 30 randomly selected glomeruli in the cortical region of the section (×400); hemocapillary density (units/mm²), number of capillary profiles in 10 fields of view of the cortical substance (×400); height of the proximal tubule epithelium (μm), measured as the height of 30 epithelial cells with a distinct nucleus and basement membrane (×1000, immersion); lumen diameter of the proximal and distal tubules (μm), minimum internal diameter of 30 transverse tubule sections (×400).

In addition, a semi-quantitative assessment of hydronephrosis was performed (0–4 points): 0 — normal; 1 — slight dilatation of the renal pelvis; 2 — moderate dilatation of the renal pelvis, flattening of the papillae; 3 — marked dilatation of the renal pelvis, blurring of the pyramid borders; 4 — severe dilatation of the renal pelvis, thinning of the cortical and medullary layers. Semi-quantitative assessment of inflammatory infiltrate (0–3 points): 0 — absence of infiltrates; 1 — isolated lymphohistiocytic cells in the interstitium; 2 — moderate multifocal infiltrates; 3 — dense diffuse infiltrates.

The normality of quantitative data distribution was tested using the Shapiro–Wilk test. Data following a normal distribution are presented as the arithmetic mean and standard deviation (M±SD). One-way analysis of variance (ANOVA) with Tukey's post hoc test was used to compare parameters between groups. Semi-quantitative scores are presented as the median and interquartile range [Me (Q_{25}; Q_{75})]. To compare these scores between groups, the nonparametric Kruskal–Wallis test was used, followed by pairwise comparisons using the Mann–Whitney U test with Bonferroni correction. Differences were considered statistically significant at p <0.05. Morphometric results were recorded in tables and subsequently analyzed using STATISTICA 10.0, specifically the Nonparametric, ANOVA, and Discriminant Analysis modules.

RESULTS

Throughout the experiment, the animals in all groups remained in satisfactory condition. Weekly body weight measurements revealed no statistically significant differences between the groups prior to euthanasia (F=1.12; p=0.364), indicating that the drugs used had no toxic effect on the animals' general somatic condition. Biochemical analysis of blood serum confirmed that the target endocrine states had been achieved. The T4 level in the "PH + hyperthyroidism" group was significantly increased by 2.8-fold compared to controls (p <0.001), accompanied by a decreased TSH level (p <0.01). The "PH + hypothyroidism" group showed a 65% decrease in T_4 levels (p <0.001) and a compensatory 3.2-fold increase in TSH levels (p<0.001).Controls and the PH group did not significantly differ from each other in terms of T_4 and TSH levels (p >0.05).

Macromorphometric analysis revealed significant differences between the groups in parameters associated with obstructive uropathy (Table 1).

Table 1

The effect of experimental hypo- and hyperthyroidism on the macromorphometric characteristics of the kidneys

Таблица 1

Влияние экспериментального гипо- и гипертиреоза на макроморфометрические характеристики почек

Параметр Parameter	n	Группа Group					
		масса тела, г weight, g (M±SD)	почки kidneys			мочевой пузырь bladder	
			абсолютная масса, мг absolute weight, mg	относительная масса, мг/100 г relative weight, mg/100 g	толщина коркового вещества, мм thickness of the cortical substance, mm	относительная масса опорожнения, мг/100г relative weight of emptying, mg/100g	остаточная моча, мг residual urine, mg
Контроль Control	8	312,0±35,4	11 207±137,3	359,2±37,3	1,50±0,18	58,2±6,1	1,2±0,4
ГПЖ BPH	8	302,5±32,8	1347,8±131,2*	445,6±31,2*	1,25±0,15*	72,8±8,3*	8,5±2,1*
ГПЖ + T_4 BPH + T4	8	294,5±31,5	1583,5±130,1*#	537,8±30,1*#	0,95±0,12*#	85,4±9,7*#	12,3±3,5*#
ГПЖ + ПТУ BPH + PTU	8	290,5±31,9	1190,5±129,8†	409,8±29,8†	1,40±0,17†	65,1±7,2*†	3,8±1,2*†
ANOVA		F=1,12 (p =0,364)	F=15,45 (p <0,001)	F=18,90 (p <0,001)	F=22,30 (p <0,001)	F=15,43 p <0,001	F=28,91 (p <0,001)

Notes. * — differences with the control group are significant (p <0.05); # — differences with the "BPH" group are significant (p <0.05); † — differences with the "BPH group + hyperthyroidism" is significant (p <0.05). BPH — benign prostatic hyperplasia

Примечания. * — различия с группой контроля достоверны (p <0,05); # — различия с группой «ГПЖ» достоверны (p <0,05); † — различия с группой «ГПЖ+ + гипертиреоз» достоверны (p <0,05). ГПЖ — гиперплазия предстательной железы.

Table by the authors of this article
Таблица авторов данной статьи

As shown in Table 1, modeling testosterone-induced PH led to a statistically significant 20.4% increase in relative kidney mass compared to controls (p <0.05), which was accompanied by a significant increase in residual urine mass (7-fold; p <0.05). The most pronounced changes in macroparameters were observed in the "PH + + hyperthyroidism" group: relative kidney mass was highest (a 38.1% increase relative to the control group; p <0.05), and residual urine mass exceeded the control value by more than 10.25-fold (p <0.05).At the same

Table 2

The effect of experimental hypo- and hyperthyroidism on micromorphometric and semi-quantitative kidney parameters in rats with benign prostatic hyperplasia compared with the control group

Таблица 2

Влияние экспериментального гипо- и гипертиреоза на микроморфометрические и полуколичественные показатели почек у крыс с гиперплазией предстательной железы по сравнению с контрольной группой

Параметр Parameter	Группа Group				Статистическая значимость (основные сравнения) Statistical significance (main comparisons)
	группа 1 (контроль) group 1 (control)	группа 2 (ГПЖ) group 2 (BPH)	группа 3 (ГПЖ + гипертиреоз) group 3 (BPH + hyperthyroidism)	группа 4 (ГПЖ+ гипотиреоз group 4 (BPH + hypothyroidism)	
Толщина коркового вещества, мм (M±SD) Thickness of the cortical substance, mm (M±SD)	1,50±0,18	1,25±0,15*	0,95±0,12*#	1,40±0,17†	Гр. 3–Гр. 2: <0,05 Gr. 3–Gr. 2: <0.05; Гр. 4–Гр. 3: <0,00 Gr. 4–Gr.3: <0.001
Площадь клубочка, мкм² (M±SD) Glomerular area, mm² (M±SD)	8250±950	9100±1050	10 500±1200*#	8600±980	Гр. 3–Гр. 2: <0,05 Gr. 3–Gr. 2: <0.05; Гр. 3–Гр. 4: <0,01 Gr. 3–Gr. 4: <0.01
Плотность капилляров коры, шт/мм² (M±SD) Density of cortical capillaries, pcs/mm² (M±SD)	320±45	380±50*	480±60*#	290±40†	Гр. 3–Гр. 2: <0,01 Gr. 3–Gr. 2: <0.01; Гр. 4–Гр. 3: <0,001 Gr. 4–Gr. 3: <0.001
Высота эпителия проксимальных канальцев, мкм (M±SD) Height of the epithelium of the proximal tubules, microns (M±SD)	8,2±1,1	9,5±1,3*	10,8±1,5*#	7,8±1,0†	Гр. 3–Гр. 2: <0,05 Gr. 3–Gr. 2: <0.05; Гр. 4–Гр. 3: <0,001 Gr. 4–Gr. 3: <0.001
Диаметр просвета проксимальных канальцев, мкм (M±SD) Diameter of the lumen of the proximal tubules, microns (M±SD)	28,5±3,5	32,0±4,1	35,5±4,8*	29,2±3,7†	Гр. 3–Гр. 2: <0,05 Gr. 3–Gr. 2: <0.05; Гр. 4–Гр. 3: <0,01 Gr. 4–Gr. 3: <0.01
Диаметр просвета дистальных канальцев, мкм (M±SD) Diameter of the lumen of the distal tubules, microns (M±SD)	21,0±2,8	35,5±4,5*	48,2±5,9*#	25,3±3,2*†	Гр. 3–Гр. 2: <0,001 Gr. 3–Gr. 2: <0.001; Гр. 4–Гр. 3: <0,001 Gr. 4–Gr. 3: <0.001
Степень гидронефроза, баллы [Me (Q_{25}; Q_{75})] Degree of hydronephrosis, points [Me (Q_{25}; Q_{75})]	0 [0; 0]	2 [1,5; 2,5]*	3 [3; 4]*#	1 [0,5; 1]*†	Гр. 3–Гр. 2: <0,01 Gr. 3–Gr. 2: <0.01; Гр. 4–Гр. 3: <0,001 Gr. 4–Gr. 3: <0.001
Воспалительный инфильтрат, баллы [Me (Q_{25}; Q_{75})] Inflammatory infiltrate, scores [Me (Q_{25}; Q_{75})]	0 [0; 0]	1 [1; 2]*	2 [2; 3]*#	0 [0; 1]†	Гр. 3–Гр. 2: <0,05 Gr. 3–Gr. 2: <0.05; Гр. 4–Гр. 3: <0,001 Gr. 4–Gr. 3: <0.001

Notes. * — differences with the control group are significant (p <0.05); # — differences with the "BPH" group are significant (p <0.05); † — differences with the "BPH group + hyperthyroidism" is significant (p <0.05). The data are presented as mean±standard deviation (M±SD) or median and interquartile range [Me (Q25; Q75)]. BPH — benign prostatic hyperplasia.

Примечания. * — различия с группой контроля достоверны (p <0,05); # — различия с группой «ГПЖ» достоверны (p <0,05); † — различия с группой «ГПЖ + гипертиреоз» достоверны (p <0,05). Данные представлены как среднее±стандартное отклонение (M±SD) или медиана и интерквартильный размах [Me (Q25; Q75)]. ГПЖ — гиперплазия предстательной железы.

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time, cortisol thickness in this group was the lowest (0.95±0.12 mm). Compared to the control group, there was a 36.7% decrease ($p < 0.05$). Despite the presence of the PH model in the "PH + hypothyroidism" group, all measured parameters (kidney weight, residual urine volume, cortical thickness) differed significantly from those of the hyperthyroidism group ($p < 0.05$) and were closer to the values of the "pure" PH group or controls, indicating that the obstruction was less severe.

Histological examination and subsequent morphometric analysis of kidney sections stained with hematoxylin and eosin allowed for a detailed description of structural changes.

The architecture of the cortical substance was preserved in intact controls. Glomeruli were of normal size and had well-defined contours. The proximal and distal tubules were lined with tall columnar and cuboidal epithelium, respectively; their lumens were uniform and not dilated. The stromal connective tissue layers were thin, with no signs of edema or cellular infiltration.

The "HP" group showed a pattern of early obstructive damage. Against a background of relatively intact glomeruli, focal dilation of distal tubules and collecting ducts was noted, with their lumens unevenly dilated. The epithelium of proximal tubules appeared flattened in some areas. Moderate edema and isolated lymphohistiocytic infiltrates, predominantly perivascular, were identified in the stroma.

The most pronounced and complex changes were observed in the "HP + hyperthyroidism" group. The cortical substance was thinned. The glomeruli often appeared enlarged, with well-vascularized loops. Another characteristic finding was marked, widespread dilation of the tubules, especially in distal segments, many of which were markedly dilated and lined with flattened epithelium. At the same time, hypertrophy of the proximal tubule epithelium was noted in unaffected areas. The stroma was moderately edematous, with multifocal, fairly dense inflammatory infiltrates. The microcirculatory bed (peritubular capillaries) appeared visually well-perfused and branched.

As for "HP + hypothyroidism" group, the histological picture of the cortex differed significantly. Signs of obstructive tubular dilatation were minimal and focal. The glomeruli and tubular epithelium were structurally closer to controls, although the stroma could appear somewhat denser, with signs of mild diffuse basophilic staining (edema). Inflammatory infiltration was generally absent. The capillary network did not appear well-perfused.

A quantitative assessment of the described histological changes is presented in Table 2.

Based on the results of morphometric analysis (see Table 2), a clear correlation was identified between structural changes in the kidneys and thyroid status during obstruction. Histological features of the kidneys in the intact control group were normal. The glomeruli had a standard area (8250±950 μm²), tubular lumens were uniform (distal tubule diameter 21.0±2.8 μm), and stroma was unremarkable; there was no inflammatory infiltrate.

The HP model group showed signs of early obstructive nephropathy: a statistically significant 69% increase in the diameter of the distal tubule lumen (to 35.5±4.5 μm; $p < 0.05$) and a moderate increased density of peritubular capillaries by 19% (to 380±50 per mm²; $p < 0.05$) compared with the control group. Semi-quantitative assessment revealed grade II hydronephrosis [2 (1.5; 2.5)] and a mild inflammatory infiltrate [1 (1; 2)].

Hypothyroidism was not only associated with a lower degree of obstruction (as confirmed by macroscopic parameters) but also exerted a suppressive effect on the vascular and proliferative components of renal tissue, preventing the development of hyperplastic and angiogenic reactions that are typical for obstruction. The "HP + hyperthyroidism" group exhibited the most pronounced and complex structural changes. In comparison with the "pure" HP group, this group demonstrated increased tubular dilation. First of all, the lumen diameter of the distal tubules was 36% larger than in the "HP" group (48.2±5.9 vs. 35.5±4.5 μm; $p < 0.05$), exceeding the control value by 2.3 times. Secondly, there was an increase in glomerular and vascular changes. The glomerular area expanded by 15% compared to the "HP" group (10,500±1,200 vs. 9,100±1,050 μm²; $p<0.05$), and cortical capillary density increased by 26% (480±60 vs. 380±50 per mm²; $p < 0.05$), which was 50% higher than the control level. Finally, there was progression of hydronephrosis and inflammation. The median hydronephrosis score (in points) was significantly higher than in the "HP" group [3 (3; 4) vs. 2 (1.5; 2.5); $p < 0.05$], and the inflammatory infiltrate reached a moderate degree [2 (2; 3)].

By contrast, the "PH + hypothyroidism" group showed the least pronounced changes in most parameters. Compared with the "HP + hyperthyroidism" group, distal tubule dilation was 48% lower (25.3±3.2 vs. 48.2±5.9 μm; $p < 0.05$), while remaining 20% higher than the control group ($p < 0.05$). The density of renal cortical capillaries was 40% lower (290±40 vs. 480±60 per mm²; $p < 0.05$), which was even 9% lower than control levels ($p < 0.05$). There was no glomerular or tubular epithelial hypertrophy: glomerular area and proximal tubular epithelial height did not differ statistically from control values ($p > 0.05$). Minimal signs of obstructive damage were noted: hydronephrosis was assessed at 1 point [1 (0.5; 1)], which was significantly

lower than in the “PH” group ($p < 0.05$). The inflammatory infiltrate was insignificant or absent [0 (0; 1)].

DISCUSSION OF THE RESULTS

Clinical data on associations between thyroid status and benign prostatic hyperplasia (BPH) are contradictory. Some studies indicate an association between hyperthyroidism and increased prostate volume [4], whereas others, using Mendelian randomization, show that hypothyroidism may be associated with a reduced risk of PH [6]. These contradictions underscore the complex nature of thyroid hormones influencing urinary system development. Current research demonstrates that experimental hypothyroidism and hyperthyroidism exert divergent effects on structural changes in the kidneys in the context of testosterone-induced obstructive uropathy in rats.

Hyperthyroidism potentiated, while hypothyroidism significantly reduced the severity of hydronephrosis, tubular dilatation, inflammation, and glomerular changes.The changes observed in hyperthyroidism may be associated with several interrelated mechanisms [7, 8]. First, this is linked to an increase in hemodynamic load. Excess thyroid hormones stimulate renal blood flow and glomerular filtration [9, 10], which, under conditions of obstruction, places an additional burden on the nephrons, contributing to glomerulomegaly and sclerosis. Second, they may be associated with oxidative stress [11, 12]. Hyperthyroidism is related to increased production of reactive oxygen species through NOX4 activation [13], which exacerbates damage to the tubular epithelium. Third, it is associated with modulation of the inflammatory response: thyroid hormones modulate NF-κB-dependent inflammation [14], enhancing the production of proinflammatory cytokines (interleukin-1β, tumor necrosis factor-α).

Macroscopic and microscopic parameters in the “PH + hypothyroidism” group were similar to those in the intact control group or the “pure” PH group. The protective effect of hypothyroidism may be associated with three factors. The macroscopic and microscopic parameters in the “PH + hypothyroidism” group were similar to those in intact controls or the “pure” PH group. The protective effect of hypothyroidism may be associated with three factors. First, there is a reduction in metabolism. Hypothyroidism decreases renal blood flow and the metabolic load on the nephrons [10], thereby slowing the rate of their damage and sclerosis. Second, there is a shift in the balance toward antioxidant factors. A reduction in the generation of reactive oxygen species [13] protects tubulocyte mitochondria from apoptosis. Finally, T3 deficiency in hypothyroidism attenuates TGF-β/SMAD signaling (transforming growth factor beta / Sma and Mad — a family of proteins), a key pathway in fibrogenesis [15, 16]. This may explain the preservation of cortical architecture and less severe tubular dilation in the “PH + hypothyroidism” group [17].

The results underscore importance of assessing thyroid status in patients with BPH as a potential risk factor for renal complications. Correction of hyperthyroidism can be considered an additional strategy to slow the progression of nephropathy.

CONCLUSION

Experimentally induced hyperthyroidism in the PH model potentiates structural kidney damage due to obstructive uropathy against a background of more pronounced prostatic hyperplasia and lymphogenic infiltration of the renal parenchyma, despite an increase in glomerular surface area and capillary density. In contrast, when hypothyroidism is induced, a pronounced protective effect occurs due to a reduction in signs of obstructive damage to the renal parenchyma and the absence of lymphogenic infiltration. When extrapolating these findings to clinical practice, it underscores the need for a comprehensive endocrinological approach for managing patients with PH.

ADDITIONAL INFORMATION

Author contribution. R.I. Glushakov — concept of the experiment, writing the original text; Z.V. Pachuliya — collection of material, preparation of histological preparations; A.L. Semenov — conducting the experimental study; V.V. Krishtop — description of morphological preparations, analysis of the obtained data, statistical analysis; A.R. Iskalieva — writing the text of the article, scientific and technical editing.

All authors made a substantial contribution to the conception of the study, acquisition, analysis, interpretation of data for the work, drafting and revising the article, final approval of the version to be published and agree to be accountable for all aspects of the study.

Competing interests. The authors declare that they have no competing interests.

Experiments with animals. All manipulations complied with the principles of the European Convention for the Protection of Vertebrate Animals (Strasbourg, 1986) and were approved by the local ethics committee.

ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

Вклад авторов. Р.И. Глушаков — концепция эксперимента, написание исходного текста; З.В. Пачулия — сбор материала, изготовление гистологических препаратов; А.Л. Семенов — проведение

экспериментального исследования; В.В. Криштоп — описание морфологических препаратов, анализ полученных данных, выполнение статистического анализа; А.Р. Искалиева — написание текста статьи, научное и техническое редактирование.

Все авторы внесли существенный вклад в разработку концепции, проведение исследования и подготовку статьи, прочли и одобрили финальную версию перед публикацией.

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

Эксперименты с животными. Все манипуляции соответствовали принципам Европейской конвенции о защите позвоночных животных (Страсбург, 1986) и были одобрены локальным этическим комитетом.

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