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Research Article

Examining the Impact of Maternally Administered Bisphenol-A on Rat Kidney Development

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Abstract

Aim: Bisphenol-A (BPA) is an estrogenic chemical used today in the production of epoxy resin and as an additive in other non-polymer plastics. Due to the widespread use of BPA today, human exposure is inevitable. This exposure causes harmful effects on various body systems. The aim of this study is to investigate the effects on the development of the kidneys of the offspring of mother rats exposed to BPA during pregnancy and lactation, as a result of the offspring being exposed to BPA through the placenta and milk.
Material and Methods: In this study, 13 adult Wistar albino female rats were divided into 3 groups. In Group 1 (Control group), rats were only administered 1 ml/kg/day corn oil intraperitoneally. Group 2 (25 mg BPA group) rats were administered 25 mg/kg/day BPA; Group 3 (50 mg group) rats were administered 50 mg/kg/day BPA intraperitoneally for 5 weeks. At the end of the experiment, the intracardiac blood and kidney tissues of the offspring rats were taken and examined for urea, total protein, creatinine, TAS, TOS, MDA values.
Results: At the end of the study, it was determined that BPA increased serum urea, creatinine and total protein levels, induced the formation of reactive oxygen species causing oxidative damage in kidney tissue, and caused serious structural damages
Conclusion: Only mother rats exposed to BPA. BPA transferred to pups via placenta and milk, causing structural damage: narrowing in Bowman's space of renal corpuscle, dilatation in proximal/distal tubules and collecting ducts, occasional cell loss, vacuolization in tubule epithelia.

Keywords: Bisphenol-A, urea, protein, creatinine, oxidative stress

INTRODUCTION

The kidney is a vital organ in the human body. Its primary functions include the excretion of metabolites and harmful substances, maintaining water balance, preserving electrolyte and acid-base balance, regulating blood pressure, promoting red blood cell production, and encouraging Vitamin D activation to ensure internal stability. Any structural or functional abnormalities in the kidney are defined as chronic kidney disease (CKD). Numerous chemical and environmental factors we encounter in daily life can trigger chronic kidney disease by affecting various systems, primarily the endocrine system. The main substances affecting the endocrine system include Bisphenol-A (BPA), polychlorines, biphenyls, phthalates, pesticides, and phytoestrogens. One of these endocrine disruptors, widely used today, is a synthetic compound known as BPA. BPA, an estrogenic chemical with the formula 2,2-bis(4-hydroxyphenyl) propane, is used as an additive in the production of epoxy resins and other non-polymer plastics. BPA can act as a selective estrogen receptor modulator by binding to the estrogen receptor in some tissues to trigger a response, while in other tissues, it prevents the estrogen receptor from binding, thus inhibiting a response. The widespread use of BPA in the plastic industry leads to its extensive distribution in the environment (1,2).

The harmful effects of BPA on human health arise from

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the community's continuous exposure to low doses, especially during fetal development and subsequent periods. Maternal exposure to BPA increases the risk of adverse outcomes such as liver tumors, breast cancer, birth defects, lung inflammation, Parkinson's disease, diabetes, and reproductive anomalies in offspring (2,3). It has been reported by Rezg et al. in 2014 that BPA exposure affects the physiology of the central nervous system (CNS), especially during the brain's development stage, and due to its lipophilic structure, it can easily cross the blood-placenta and blood-brain barriers, making its effect more pronounced during the lactation period (4,5). The aim of our study is to investigate the histological and biochemical effects on the early development of the kidneys of offspring indirectly exposed to BPA through placental and milk transfer as a result of maternal exposure during pregnancy and lactation periods. BPA, which has an extremely widespread production and usage area, is also defined as an endocrine disruptor.

MATERIAL AND METHOD

In this study, a total of 13 adult female Wistar Albino rats and 60 newborn rats were used. Female rats were mated with male rats during their estrus cycle to ensure pregnancy. Pregnant female rats were randomly divided into three separate groups: control (n:3), 25 mg BPA group (n:5), and 50 mg BPA group (n:5). Starting from the 6th day of pregnancy, 1 ml/kg/day of corn oil was administered intraperitoneally to the mother rats in the control group (Group 1), while 25 mg/kg/day (Group 2) and 50 mg/kg/day (Group 3) BPA were given to the mother rats in the non-control groups until the 21st day of the postnatal lactation period. A total of 10 randomly selected offspring rats from different mothers in each group were sacrificed on the 21st day (n=30) and 45th day (n=30) by intraperitoneal injection of Xylazine hydrochloride at a dose of 10 mg/kg and Ketamine hydrochloride at a dose of 90 mg/kg. The abdominal anterior wall of the anesthetized subjects was opened by incision to reach the heart from the diaphragm, and their intracardiac blood was collected. Kidney tissues were taken for pathological examination. From the serum samples, urea (OttoScientific, OttoBC157, Türkiye), total protein (OttoScientific, OttoBC154, Türkiye), creatinine (OttoScientific, OttoBC139, Türkiye), Total Antioxidant Levels (TAS) (Rel Assay, RL0017, Türkiye), Total Oxidant Levels (TOS) (Rel Assay, RL0024, Türkiye), and Malondialdehyde (MDA) values were determined using a colorimetric method with the MINDRAY-BS400 device, strictly adhering to the protocol provided by the manufacturer. The kidney tissues taken from the subjects were rinsed with 0.9% cold saline. The tissues were fixed in containers with a 10% neutral formalin solution labeled to indicate which group they belonged to. The Hematoxylin-Eosin (H&E) staining method, one of the most commonly used methods for staining sections, and the Masson-Trichrome staining method were used to show the difference in fibrous tissue formation in the experimental and control groups due to possible kidney toxicity. The tissues were examined under a microscope to determine which experimental groups had damage areas.

Histopathological findings were evaluated by measuring Bowman's space. The ratio of Bowman's capsule area to glomerular area was used in the assessment of Bowman's space. A decrease in this ratio indicates a reduction in the space, whereas an increase indicates an enlargement. One-way analysis of variance (ANOVA) was employed to assess the differences between groups. Sidak's multiple comparison test was used for post hoc analysis. A significance level of $p<0.05$ was considered for all tests. GraphPad Prism version 8.0.2 for Windows, GraphPad (Software, Boston, Massachusetts, USA) was utilized for statistical analyses.

RESULTS

Histopathological Findings

In our study, the kidney tissues of 21 and 45-day-old offspring born to mother rats administered with 25 mg and 50 mg BPA were examined at the light microscope level and the statistical analysis results given at Table 1.

Table 1 Statistical results of histopathological findings

	Mean 1	Mean 2	SE of diff,	Summary	Adjusted P Value
21th day Control vs. 21th day 25mg	72.15	82.4	1.575	****	<0.0001
21th day Control vs. 21th day 50mg	72.15	90.9	1.638	****	<0.0001
21th day 25mg vs. 21th day 50mg	82.4	90.9	1.548	****	<0.0001
45th day Control vs. 45th day 25mg	71.71	87.62	2.644	****	<0.0001
45th day Control vs. 45th day 50mg	71.71	93.19	2.919	****	<0.0001
45th day 25mg vs. 45th day 50mg	87.62	93.19	2.535	ns	0.2331
21th day Control vs. 45th day Control	72.15	71.71	2.435	ns	>0.9999
21th day 25mg vs. 45th day 25mg	82.4	87.62	1.883	ns	0.0535
21th day 50mg vs. 45th day 50mg	90.9	93.19	2.297	ns	0.9689

Histopathological findings of 21-day-old rats

Findings related to the control group (Group 1)

Upon examining the kidney tissues of the 21-day-old Control group at low magnification with a light microscope, it was observed that the renal corpuscles located in the cortex exhibited normal histological features when examined at high magnification. This included the Bowman's capsule located on the outer part, the parietal leaf epithelial cells, the Bowman's space where the filtrate is filtered and sent to the urine, and the glomerular capillary tuft structure. The proximal and distal tubules and the macula densa cells appeared normal. No deformation was observed in the structure and cells of the proximal and distal tubules located in the medulla, the thin part of the Henle's loop with flat epithelial cells, and the collecting ducts (Figure 1).

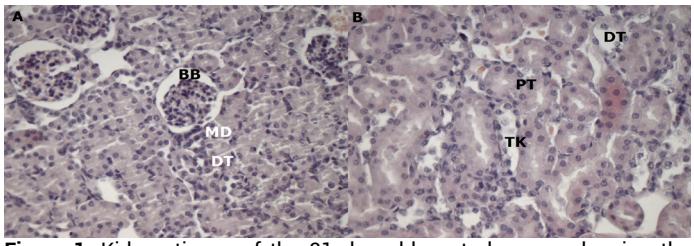

Figure 1. Kidney tissue of the 21-day-old control group, showing the structure of the renal corpuscle (G), Bowman's space (BB), macula densa cells 17, proximal (PT) and distal (DT) tubules, and collecting ducts (CD) (H&E, 40x)

Findings related to the 25 mg BPA group (Group 2)

When tissue samples taken from the kidneys of newborn rats in the group administered with 25 mg BPA on the 21st day were examined at low magnification under a light microscope, it was observed that there were numerous renal corpuscles and nephron tubules in the cortex of the kidney tissue, and collecting ducts and tubules in the medulla. Upon examination at high magnification, it was observed that in many renal corpuscles located in the cortex, narrowing occurred in the Bowman's space as a result of the expansion of capillary tufts in the glomerulus due to BPA. No serious deformation was observed in the cells and epithelia of the proximal and distal tubules located in the medulla. It was observed that the cuboidal epithelial cells of the collecting ducts transformed into squamous epithelial cells. When sections examined with Masson's trichrome staining, it was seen that there were small amounts of connective tissue areas between the renal corpuscles and tubules (Figure 2).

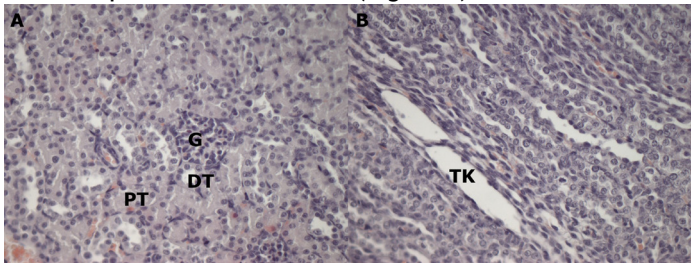

Figure 2. In the renal cortex of the 21-day-old 25 mg BPA group, the renal corpuscle (G), narrowing in the Bowman's space (*), proximal (PT) and distal tubules (DT), and dilation in the collecting duct (CD) located in the medulla are shown (H&E, 20x)

Findings related to the 50 mg BPA group (Group 3)

When tissue samples taken from the kidneys of newborn rats in the group administered with 50 mg BPA on the 21st day were examined at low magnification under a light microscope, it was observed that the general appearance of the kidney tissue had a clear distinction between the cortex and medulla; numerous renal corpuscles were located in the cortex, and collecting ducts and tubules were in the medulla. Upon examination at high magnification, it was found that there were deformations in the capillary tuft in some of the renal corpuscles located in the cortex as a result of BPA exposure. As a result of the expansions in the capillary tuft, narrowing occurred in the Bowman's space; no serious disruption was observed in the cells and epithelia of the proximal and distal tubules located in the medulla. It was observed that the cuboidal epithelial cells of the collecting ducts transformed into squamous epithelial cells, and there was tubular dilation in some. When sections examined with Masson's trichrome staining, it was seen that there were connective tissue areas between the renal corpuscles and tubules and around the blood vessels (Figure 3).

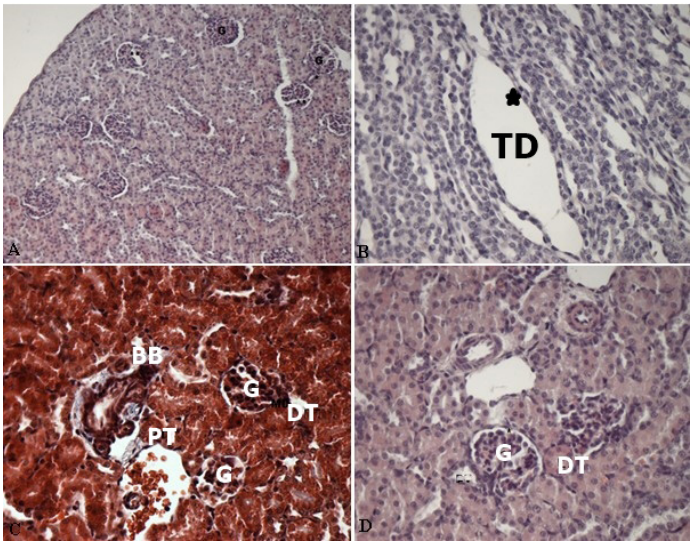

Figure 3. Kidney tissue of the 21-day-old 50 mg BPA group; A) Renal corpuscle (G) in the renal cortex, deformation in the capillary tuft (**) (H&E, 20x); B) Renal medulla; tubular dilation (TD) in the collecting duct, squamous transformation in epithelia(*) (H&E, 40x); C) Glomeruli (G), macula densa cells 17, proximal tubule (PT), distal tubule (DT) and connective tissue (BD) (MTK, 40x) in the renal cortex; D) Structures located in the renal cortex are shown (H&E, 40x)

Histopathological findings of 45-day-old rats

Findings related to the control group (Group 1)

In the 45-day-old Control group, light microscopic examinations at low magnification revealed the presence of numerous renal corpuscles and nephron tubules in the cortex, and collecting ducts and tubules in the medulla. Upon high magnification examination of the renal corpuscles located in the cortex, the Bowman's capsule located on the outer part, parietal leaf epithelial cells, the Bowman's space where the filtrate is sieved and sent to urine, the glomerular capillary tuft formed by the convergence of capillaries, and the macula densa

cells were observed to be normal. No deformation was observed in the cells and structures of the proximal, distal tubules, Henle's loop, and collecting ducts located in the medulla. No pathological findings were encountered in the collecting ducts. Sections examined with Masson's trichrome staining revealed a small amount of connective tissue around the blood vessel (Figure 4).

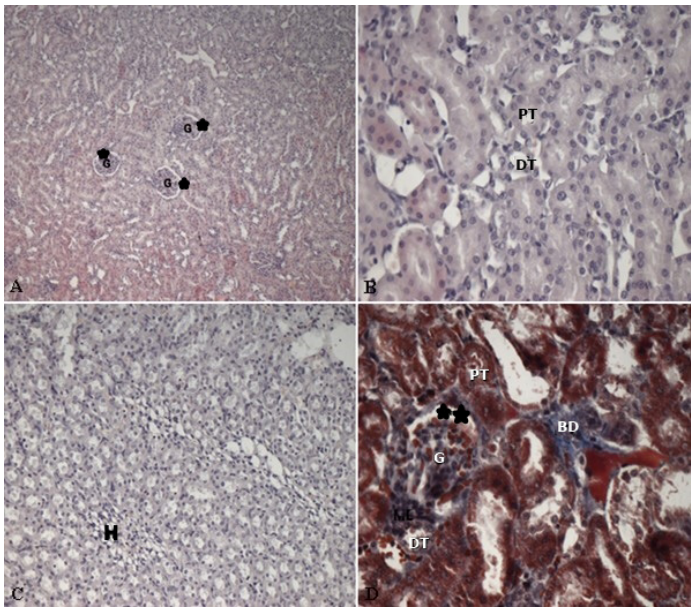

Figure 4. Kidney tissue belonging to the 45-day-old control group; A) Renal corpuscles (G) located in the renal cortex, Bowman's space (*) (H&E, 10x). B) Renal medulla; proximal tubule (PT) and distal tubule (DT) (H&E, 40x). C) Henle's loop (H) (H&E, 20x); D) Glomerule (G), Bowman's space (**), Macula densa cells 17, proximal tubule (PT), distal tubule (DT), and connective tissue (BD) in the renal cortex are shown (MTK, 40x)

Findings related to the 25 mg BPA group (Group 2)

In the high magnification examinations of tissue samples taken from the adult rat kidneys of the 45-day-old 25 mg BPA group, it was observed that due to BPA exposure, there was a narrowing in the Bowman's space in the renal corpuscles in the renal cortex, and in some, this space was completely closed; there were occasional cell sloughing in the cells and structures of the proximal and distal tubules located in the medulla. Dilatation in the collecting ducts and a decrease in epithelial cells were detected (Figure 5).

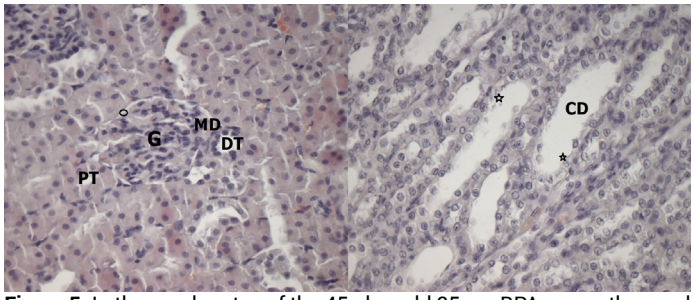

Figure 5. In the renal cortex of the 45-day-old 25 mg BPA group, the renal corpuscle (G), narrowed Bowman's space (•), Macula densa cells 17, proximal (PT) and distal tubule (DT), and dilatation in the collecting duct (CD) and decrease in epithelial cells (*) are shown (H&E, 40x)

Findings related to the 50 mg BPA group (Group 3)

In the high magnification examinations of tissue samples taken from the adult rat kidneys of the 45-day-old 50 mg BPA group, it was observed that in most of the renal corpuscles in the cortex, due to BPA-induced expansion in the capillary tuft, there was a narrowing in the Bowman's space, and in the majority, this space was completely closed. Destruction of epithelial cells in the tubules and the formation of vacuoles were also observed. Serious damages such as cell loss and deformation in the cells and epithelium of the distal, proximal tubules located in the medulla were observed; it was seen that the cuboidal epithelial cells of the collecting ducts were transformed into squamous epithelial cells in places, some epithelial cells decreased, and dilatation was observed in some collecting ducts (Figure 6).

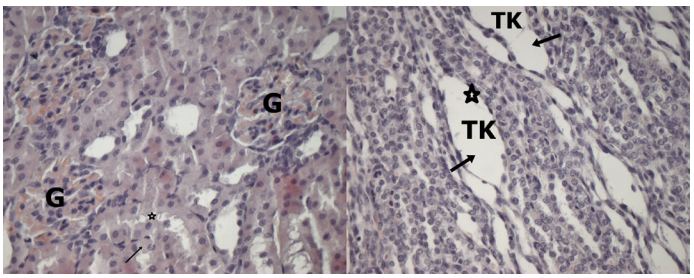

Figure 6. In the renal cortex of the 45-day-old 50 mg BPA group, renal corpuscles (G), vacuolization in proximal tubules (left picture-arrow) and cell loss (*); flattening (*) in the cells of the collecting duct (TK) in the renal medulla and tubule dilatation (arrow marks) (H&E, 40x)

Biochemical Findings

Total antioxidant level results

Upon analyzing the TAS values studied from the sera, it was found that the highest TAS value belonged to the 21-day 50 mg BPA group (4.5150 mmol/L), while the lowest TAS value belonged to the 21-day 25 mg BPA group (1.4833 mmol/L). A significant difference was detected between the control group (Group 1, 21-day) and Group 3 (50 mg BPA, 21-day); between Group 2 (25 mg BPA, 21-day) and Group 3 (50 mg BPA, 21-day); and between the 50 mg BPA groups (Group 3, 21-day-45-day) ($p<0.0001$) (Table 2).

Total oxidant level results

Upon analyzing the TOS values studied from the sera, it was found that the highest TOS value belonged to the 21-day 50 mg BPA group (54.5900 µmol/L), while the lowest TOS value belonged to the control group (Group 1, 21-day) (3.8163 µmol/L). A low degree of significant difference was found between the control group (Group 1, 21-day) and Group 2 (25 mg BPA, 21-day); a significant difference was found between Group 1 (Control, 21-day) and Group 3 (50 mg BPA, 21-day); between 25 mg BPA (Group 2, 21-day) and 50 mg BPA (Group 3, 21-day); and between the 50 mg BPA groups (Group 3, 21-day-45-day) ($p<0.0001$) (Table 2).

Oxidative stress index results

Upon analyzing the OSI values studied from the sera, it was found that the highest OSI value belonged to the 25 mg BPA group (Group 2, 21-day) (1.224) and the 50 mg BPA group (Group 3, 21-day) (1.207), while the lowest

Oxidative Stress Index (OSI) value belonged to the control group (Group 1, 21-day) (0.1519). A significant difference was found between the control group (Group 1, 21-day) and Group 2 (25 mg BPA, 21-day); between the control group (Group 1, 21-day) and Group 3 (50 mg BPA, 21-day); between the 25 mg BPA groups (Group 2, 21-day-45-day) and the 50 mg BPA groups (Group 3, 21-day-45-day) ($p<0.0001$) (Table 2).

Malondialdehyde level results

Upon analyzing the MDA values studied from the sera, it was found that the highest MDA concentration value belonged to the 50 mg BPA group (Group 3, 21-day) (178.6 mmol/L), while the lowest MDA value belonged to the 25 mg BPA group (Group 2, 45-day) (5.213 mmol/L). A low level of significant difference was found between the 25 mg BPA group (Group 2, 45"-day) and the 50 mg BPA group (Group 3, 45-day); a significant difference was found between the control group (Group 1, 21-day) and Group 3 (50 mg BPA, 21-day); between the 25 mg BPA group (Group 2, 21-day) and the 50 mg BPA group (Group 3, 21-day); and between the 50 mg BPA groups (Group 3, 21-day-45-day) ($p<0.0001$) (Table 3).

Table 2. Comparative analysis of TAS, TOS, and OSI values across different groups

Test details	TAS		TOS		OSI	
	Summary	P Value	Summary	P Value	Summary	P Value
(21 day) Control vs. 25 mg BPA	Ns	0.3423	*	0.026	****	<0.0001
(21 day) Control vs. 50 mg BPA	****	<0.0001	****	<0.0001	****	<0.0001
(45 day) Control vs. 25 mg BPA	Ns	>0.9999	Ns	>0.9999	Ns	>0.9999
(45 day) Control vs. 50 mg BPA	Ns	>0.9999	Ns	>0.9999	Ns	0.5599
(21 day) 25 mg BPA vs. 50 mg BPA	****	<0.0001	****	<0.0001	****	<0.0001
(45 day) 25 mg BPA vs. 50 mg BPA	Ns	>0.9999	Ns	>0.9999	****	<0.0001
25 mg BPA (21 day) vs. 25 mg BPA (45 day)	Ns	0.0536	Ns	0.6426	Ns	>0.9999
50 mg BPA (21 day) vs. 50 mg BPA (45 day)	****	<0.0001	****	<0.0001	Ns	>0.9999

Table 3. Comparative analysis of MDA, TP, UREA, creatinin values across different groups

Test details	MDA		Total Protein		UREA		Creatinin	
	Summary	P Value	Summary	P Value	Summary	P Value	Summary	P Value
(21 day) Control vs. 25 mg BPA	ns	>0.9999	ns	0.1893	ns	0.1851	*	0.0389
(21 day) Control vs. 50 mg BPA	****	<0.0001	****	<0.0001	ns	0.7596	****	<0.0001
(45 day) Control vs. 25 mg BPA	ns	>0.9999	ns	>0.9999	ns	>0.9999	ns	>0.9999
(45 day) Control vs. 50 mg BPA	ns	0.2962	ns	>0.9999	ns	>0.9999	ns	0.3589
(21 day) 25 mg BPA vs. 50 mg BPA	****	<0.0001	ns	>0.9999	ns	>0.9999	****	<0.0001
(45 day) 25 mg BPA vs. 50 mg BPA	**	0.0048	****	<0.0001	**	0.0014	ns	>0.9999
25 mg BPA (21 day) vs. 25 mg BPA (45 day)	ns	>0.9999	****	<0.0001	*	0.0234	***	0.0004
50 mg BPA (21 day) vs. 50 mg BPA (45 day)	****	<0.0001	ns	>0.9999	ns	>0.9999	****	<0.0001

Total protein level results

Upon analyzing the Total Protein (TP) values studied from the sera, it was found that the highest TP concentration value belonged to the 50 mg BPA group (Group 3, 21-day) (15.41 g/dL), while the lowest TP value belonged to the control group (Group 1, 21-day) (4.412 g/dL). A significant difference was found between the control group (Group 1, 21-day) and Group 3 (50 mg BPA, 21-day); between the 50 mg BPA groups (Group 3, 21-day-45-day); and between the 25 mg BPA group (Group 2, 21-day) and the 50 mg BPA group (Group 3, 21-day) ($p<0.0001$) (Table 3). The highest total protein concentration level in the 50 mg BPA group supports the notion that BPA causes proteinuria.

Urea level results

Upon analyzing the urea values studied from the sera, it was found that the highest urea concentration value belonged to the 25 mg BPA group (Group 2, 45-day) (74 mg/dL), while the lowest urea value belonged to the 25 mg BPA group (Group 2, 21-day) (56.67 mg/dL). A low level of significant difference was found between the 25 mg BPA group (Group 2, 21-day) and the 50 mg BPA group (Group 3, 21-day); a low level of significant difference was found between the 25 mg BPA groups (Group 2, 21-day-45-day) ($p<0.0001$) (Table 3).

Creatinine level results

Upon analyzing the creatinine values studied from the sera, it was found that the highest creatinine level belonged

to the 50 mg BPA group (Group 3, 21-day) (3.083 mg/L), while the lowest creatinine value belonged to the 25 mg BPA group (Group 2, 21-day) (0.5767 mg/L). A low level of significant difference was found between the 25 mg BPA group (Group 2, 21-day) and the control group (Group 1, 21-day); a medium level of significant difference was found between the 25 mg BPA groups (Group 2, 21-day-45-day); a high level of significant difference was found between the control group (Group 1, 21-day) and the 50 mg BPA group (Group 3, 21-day); between the 25 mg BPA groups (Group 2, 21-day) and the 50 mg BPA group (Group 3, 21-day); and between the 50 mg BPA group (Group 3, 21-day) and the 50 mg BPA group (Group 3, 45-day) ($p<0.0001$) (Table 3).

The question with the lowest score in this study was "The lack of face-to-face interaction make learning difficult (Figure 2). This question was reverse-coded and scored. While 10 students in the female group and 13 students in the male group answered completely agree (1 point), 13 students in the female group and 11 students in the male group answered agree (2 points).

DISCUSSION

After oral intake, BPA is rapidly absorbed from the intestines into the body. In cases where glomerular filtration rate is low, BPA accumulates in the body. The accumulated BPA undergoes elimination through conjugation with glucuronic acid in the liver and is excreted from the body through urine by the kidneys (6-8).

Due to its estrogenic activity, BPA exhibits sensitivity in developing organs towards abnormal endocrine signals caused by this chemical. Therefore, BPA particularly affects developing organs during the prenatal period. Studies have shown that even at low concentrations, BPA binds to nuclear receptors and affects the physiological functions of cells and tissues. BPA is also known to interact with thyroid hormone receptors, androgen receptors, peroxisome proliferator-activated receptors, and other endocrine system receptors. It has been shown to have adverse effects on the CNS, cardiovascular system, respiratory system, excretory system, and immune system. Additionally, BPA exposure has been reported to cause changes in the endogenous cannabinoid system of the liver (ECS), decrease sperm quality and quantity indices, lead to neuroendocrine disruptions, birth defects, and diseases such as breast cancer (9).

BPA, an endocrine-disrupting chemical, interacts with estrogen receptors (ERα) by mimicking the synthesis of endogenously produced estrogens, and exhibits estrogenic effects. As a result, it disrupts endocrine functions, leading to decreased fertility and congenital malformations in the reproductive system and increased cancer risk in tissues that interact with estrogen. BPA also has toxic effects on the cardio-renal system, causes changes in the structure of cardiac and renal tissues, affects the activities of redox enzymes, and alters gene expression. It is known to induce oxidative stress and contribute to hypotension, along with various adverse effects on the CNS, cardiovascular system, respiratory system, excretory system, and immune system (6,10,11).

With the increase in industrialization today, various chemicals caused by environmental pollution adversely affect human health. These chemicals we are exposed to in daily life affect many systems, especially the endocrine system, leading to the emergence of chronic diseases. Bisphenol-A (BPA), which is industrially produced and the most common environmental pollutant, comes first. Bisphenol-A is one of the phenolic compounds known as endocrine disruptors with estrogenic activity. BPA accumulating in the body first undergoes elimination in the liver, is conjugated with glucuronic acid, and is excreted from the body by the kidneys through urine (6-8). As it is a chemical with estrogenic activity, developing organs are quite sensitive to abnormal endocrine signals caused by this chemical. Therefore, BPA has an effect especially on organs developing in the prenatal period. BPA affects the function of many vital organs, including the kidney, testis, brain, heart, liver, and pancreas, by accumulating in them (3,12).

In most of the experimental studies on BPA, evaluations have generally been made with the findings obtained on the animals to which BPA was applied (13,14). As a result of these studies, the most observed morphological findings were structural damages such as narrowing in the Bowman's space in the renal corpuscle, dilatation in the proximal, distal tubules and collecting ducts, cell loss in tubule epithelia, and vacuolization. Shin et al. have examined the spread of Bisphenol A with placental transfer to the placenta, fetus, maternal serum, and amniotic fluid. As a result of the study, they determined that the distribution of BPA to the placenta, fetus, and amniotic fluid occurred rapidly, the accumulation of BPA in the amniotic fluid was less than the other placenta, fetus, maternal serum, and the maximum concentration level was reached within 0.6 hours (36 minutes) after intraventricular (iv) injection (15).

In the study where Edres et al. investigated whether BPA causes kidney damage, they determined that after BPA application, there was an increase in serum urea, creatinine levels, formation of reactive oxygen species, degenerative changes in kidney tubules, narrowing in the Bowman's space in the renal corpuscle with hydronephrosis, significant expansions in cortical renal blood vessels and the emergence of intertubular hemorrhagic areas, and concluded that BPA causes serious damage in kidney tissues. In our study, we found that the serum urea levels increased in the BPA group compared to the control group in the analysis results of the 50 mg/kg/day BPA group rats, and as a result of the TAS, TOS, MDA tests we performed, BPA caused oxidative stress and caused damage in the kidney tissue. In addition, as a result of our histopathological examinations, we detected degeneration in the kidney tubules, especially cell loss with vacuolization in the proximal tubules, structural disorders in the renal corpuscle with narrowing in the

Bowman's space, expansions in renal blood vessels, and hemorrhagic areas between the tubules. Therefore, this study we conducted supports the hypothesis put forward by Edres et al. (14).

During the embryonic/fetal period and infancy, BPA exposure leads to developmental impairments in certain organs, including the reproductive system, due to oxidative stress (OS) and lipid peroxidation in tissues. Maternal exposure to BPA limits the fetus's ability to metabolize this chemical component, leading to significant complications. There is also evidence linking BPA exposure in adults and children to proteinuria. BPA-induced damage is associated with OS and can disrupt the oxidative balance directly or indirectly, affecting mitochondrial activity, modulation of antioxidant enzymes, and increased levels of thiobarbituric acid-reactive substances. Studies by Kovacic in mice showed that BPA administration increased the levels of thiobarbituric acid-reactive substances, which are considered markers for ROS-OS. Additionally, embryonic/fetal and infancy exposure induced tissue OS and peroxidation, resulting in developmental impairments in the brain, kidneys, and testes. In rats, BPA was found to reduce the activities of superoxide dismutase, catalase, GSH reductase, and GSH peroxidase while increasing hydrogen peroxide and lipid peroxidation levels, supporting the hypothesis proposed by Esplugas et al. (11).

Studies related to BPA are generally conducted on rats directly exposed to BPA. However, studies investigating the harmful effects of BPA on the kidneys of newborn rats indirectly exposed to BPA are limited. Therefore, in this study, we focused on the effects of BPA exposure through milk and placenta on the development of the kidneys in newborn rats. We investigated the impact of BPA administered to the mother through the placenta during the intrauterine period and through lactation on the development and structure of the newborn rat kidneys, as well as its effects on protein, creatinine, and urea levels. Pregnant rats were identified for this study. The pregnant rats were exposed to BPA during the gestational and lactation periods. After weaning, blood samples and kidney tissues were collected from some of the 21-day-old newborn rats, while the remaining rats were allowed to reach adulthood. At 45 days of age, the adult rats were sacrificed, and blood samples and kidney tissues were collected for histological examination. The analysis and examinations conducted in this study revealed that maternal exposure to BPA through milk and placenta induced oxidative stress and resulted in kidney damage. Microscopic examination of the kidney tissue showed narrowing or complete closure of Bowman's space in the renal corpuscles, loss of epithelial cells in the proximal and distal tubules, and tubular dilatation, supporting the findings of the study conducted by Kabuto et al. (16).

CONCLUSION

In this study we conducted, we compared the degrees of BPA impact on pups exposed to BPA through the mother, on the 21st day, which is the end of the exposure period, and on 45-day-old rats that survived the exposure and entered adolescence. According to the results we obtained, we determined that the damage seen on the 45th day continued even without exposure to BPA and the damage did not show recovery during this period. When we closely examined the structure and biochemical values of the kidney tissues on the 21st and 45th days, we obtained the following results:

1. BPA increased serum urea, creatinine, and total protein levels,
2. As a result of our TAS, TOS, MDA analyses, we found that BPA induced the formation of reactive oxygen species, causing oxidative damage in the kidney tissue,
3. Although only mother rats were exposed to BPA, we determined that BPA was transferred to the pup rats through the placenta and milk, causing serious structural damages such as narrowing in the Bowman's space of the renal corpuscle located in the kidneys of the pup rats, dilatation in the proximal, distal tubules and collecting ducts, and occasional cell loss, vacuolization in tubule epithelia.

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