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CHANGES IN FOLLICULAR APOPITOSIS IN OVARIAN TORSIONS

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ABSTRACT- Ovarian torsion can be given as an example of ischemia/reperfusion (I/R) injuries. It is likely to be encountered in young women who apply to the emergency department. Reactive oxygen radicals (ROS) formed as a result of I/R are an important damaging mechanism in this mechanism. Here, apoptotic mechanisms are also triggered and lead to cell death. **Material and method** Sixteen rats were equally divided into two groups (n=8). In Group 1, only laparotomy was applied to the control group (n=8), and ovarian torsion was applied to the experimental group (n=8) in Group 2. **Results** In the rats in the control group, the difference in bcl-2 and P53 staining scores in the primordial follicle, secondary follicle, antral follicle was found to be statistically significant ($p<0.001$, $p=0.007$, $p=0.007$, respectively). For bcl-2 and p53 in the Corpus Luteum tissue, the difference between the groups was found to be statistically significant ($P=0.007$, $p=0.007$, respectively) **Conclusion:** It is thought that total loss may not occur in ovarian ischemia and preventive surgery can be performed. These results should be supported by hormonal levels and rat studies at different ages.

Keywords: Ovary, Ischemia/reperfusion, Apoptosis, Age.

Introduction Ovarian torsion is a surgical emergency that is often associated with pre-existing ovarian masses, such as functional cysts or neoplasms. It is more commonly observed in young and adolescent females. Immediate intervention is required to preserve fertility in cases of ovarian torsion. The primary pathophysiology of torsion involves ischemia followed by reperfusion. Thus, ovarian torsion is one of the ischemia/reperfusion (I/R) injuries. As a result of I/R, reactive oxygen species (ROS) are released in tissues. Another pathogenic mechanism involves the migration and activation of neutrophils, which release ROS during the reperfusion phase, exacerbating tissue damage. These mechanisms also trigger apoptotic pathways, leading to cell death.1-3 When ischemic cell damage becomes irreversible, restoring blood flow can help heal the cells. However, in some cases, the re-establishment of blood flow can accelerate the injury process and lead to further tissue damage. Ischemia/reperfusion (I/R) injury is associated with several clinical conditions, including myocardial infarction, stroke, vascular diseases, organ transplantation, and shock. During I/R injury, ROS are released, the complement system is activated, and leukocyte-endothelial cell adhesion increases, contributing to tissue damage.4-6 Ovarian torsion occurs when the arterial and venous blood vessels

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of the ovary twist around the pedicle, partially or completely obstructing blood flow. Ovarian torsion occurs in 2.7% of gynecological emergencies and can affect all age groups, from female fetuses to postmenopausal women, but is most commonly observed in women of reproductive age. The exact etiology of ovarian torsion is not fully understood, but functional cysts or neoplasms are present in most cases. Delayed or incorrect diagnosis can result in the loss of the ovary or a decrease in follicular reserve. When acute abdomen (peritoneal irritation) symptoms are present, most cases undergo diagnostic laparotomy or laparoscopy. However, in most cases of torsion, clinical symptoms are unclear, which leads to delays in diagnosis and treatment.6-9 The delicate balance between cell survival and apoptosis maintains tissue homeostasis. Apoptosis is an active, genetically and biologically programmed process. Various molecules play a role in determining whether a cell survives or undergoes apoptosis. Survival molecules, such as the Bcl-2 protein, are important in this process. Bcl-2, originally identified for its role in B-cell lymphomas, is a survival molecule expressed in both fetal and adult ovarian granulosa cells.8-11 The p53 gene is a tumor suppressor factor that maintains genomic integrity by halting the cell cycle or inducing apoptosis. It encodes a 53 kDa nuclear protein that is activated in response to stress. p53 accumulates in the cytoplasm during the G1 phase of the cell cycle and migrates to the nucleus at the beginning of the synthesis (S) phase. The mechanisms it activates are antagonistic to those of Bcl-2. When needed, p53 activates apoptosis by inducing the Bax gene, which initiates apoptotic cell death. In the ovary, p53 expression has been observed in apoptotic granulosa cells of follicles undergoing atresia.8-11 Ischemic injury is associated with changes in survival and apoptosis-related molecules (such as Bcl-2 and p53 proteins) in various organs. However, it is not yet fully understood how these molecules change in ovarian tissues subjected to ischemia. This study aims to investigate how the expression of Bcl-2 and p53 proteins is altered in ovarian tissues as a result of ischemia/reperfusion injury following ovarian torsion. Materials and Methods Experimental Model Sixteen rats were equally divided into two groups (n=8). In Group 1 (the control group, n=8), only laparotomy was performed, while in Group 2 (the experimental group, n=8), ovarian torsion was induced. All rats were anesthetized with intramuscular injections of 50 mg/kg ketamine hydrochloride (Ketalar®; Eczacıbaşı, Istanbul, Turkey) and 10 mg/kg xylazine hydrochloride (Rompun®; Bayer, Istanbul, Turkey). Following anesthesia, a longitudinal incision of 2,5 cm was made in the lower abdominal region where the adnexa were located. In the experimental group, the right adnexa was rotated 1080° counterclockwise, and the twisted adnexa were fixed to the anterior abdominal wall using 4/0 silk sutures. The abdominal wall was closed in two layers using 3/0 silk sutures. In Group 1, the adnexa were palpated and left in their anatomical position without rotation, and only laparotomy was performed. In Group 2, ischemia was applied for 3 hours. After the ischemic period, the torsion was relieved by untwisting the adnexa, and then a 3-hour ovarian ischemia/reperfusion (I/R) protocol was applied. After the experimental procedure, ovaries were surgically excised from all rats for histopathological analysis. Histopathological Evaluation Histopathological evaluation was

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performed to assess apoptosis in primordial, primary, and secondary follicles, corpus luteum, germinal epithelium, and stroma. The apoptotic cells were graded both within the groups and for differences in staining intensity. For this purpose, apoptosis-associated markers, such as Bcl-2 and p53, were used. The tissue slides were stained immunohistochemically and evaluated under a light microscope. The staining intensity was graded as 0 (no staining), 1 (mild), 2 (moderate), or 3 (severe) (Figures 1, 2). As positive controls, the spleen was used for Bcl-2 staining, and squamous cell carcinoma was used for p53 staining. For p53 staining evaluation, both nuclear and cytoplasmic staining were considered positive. Bcl-2 protein was considered positive if diffuse golden-yellow cytoplasmic staining was present in the mitochondria region.10

STATISTICAL ANALYSIS Data Analysis The study variables were described by frequency (n) and percentage (%), and the Fisher's Exact Test or Fisher-Freeman-Halton Exact Test was used to analyze. SPSS v30 (IBM Corporation, Amork, NY, USA) statistical package program was used in data analysis. The statistical significance level was considered as 5% (two-tailed). Table 1. Comparison of staining results of Bcl-2 and P53 markers obtained from different tissues in the Control and Sham-Experimental groups. Results When the staining scores obtained from the germinal epithelium were examined, no significant difference was found between the distribution of Bcl-2 and P53 staining scores in the control group (p=0.203). Bcl-2 staining was scored as 1 in all patients (100%), while P53 was scored as 1 in more than half of the patients (62.5%). Similarly, in the Sham-Experiment group, no significant difference was observed between the distribution of Bcl-2 and P53 staining scores (p=0.608). Bcl-2 staining was scored as 0 in half of the patients (50%), and as 1 in the other half (50%). When the staining scores from primordial follicles were examined, in the control group, all patients had a Bcl-2 staining score of 0, while P53 staining scored 1 in all patients. This difference was statistically significant (p=0.608).

Comparison of Groups Based on Bcl-2 Marker Results: When comparing the groups in terms of Bcl-2 staining results, no statistically significant difference was found in the germinal epithelium (p=0.077). In the control group, all patients (100%) had a staining score of 1, whereas in the Sham-Experiment group, half of the patients (50%) had a score of 0, and the other half (50%) had a score of 1. In primordial follicles, secondary follicles, and antral follicles, all patients in both the control and Sham-Experiment groups had a staining score of 0. In the corpus luteum tissue, 25% of patients in the control group had a score of 0, and 75% had a score of 1, whereas all patients in the Sham-Experiment group had a staining score of 0. This difference between the groups was statistically significant (p=0.007). In the stroma tissue, 25% of patients in both groups had a staining score of 0, and 75% had a score of 1 (p=0.999). Comparison of Groups Based on P53 Marker Results: 7 When comparing the groups based on P53 staining results, no statistically significant difference was found in the germinal epithelium (p=0.063). In the control group, 12.5% of patients had a score of 0, 62.5% had a score of 1, and 25% had a score of 2. In the Sham-Experiment group, 75% of patients had a score of 0, and 25% had a score of 1. There were no patients in the

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Sham Experiment group with a score of 2. In primordial follicles, all patients in the control group (100%) had a staining score of 1, while in the Sham-Experiment group, 25% of patients had a staining score of 1, and the majority (75%) had a score of 0. This difference between the groups was statistically significant (p=0.007). In secondary follicles, antral follicles, and corpus luteum tissue, 75% of patients in the control group had a staining score of 1, while 75% of patients in the Sham-Experiment group had a staining score of 0. No significant difference between the groups was found in these tissues (p=0.132). In the stroma tissue, 37.5% of patients in the control group had a score of 0, and 62.5% had a score of 1. In the Sham-Experiment group, half of the patients (50%) had a score of 0, and half (50%) had a score of 1. There was no statistically significant difference between the groups (p=0.999).

Results for Bcl-2 and P53 Markers: In the control group, the results for Bcl-2 (staining scores 0, 1, and 2) showed significant changes across tissues (p<0.001), whereas the results for P53 showed no significant variation across tissues (p=0.390). In the Sham-Experiment group, Bcl-2 staining results (scores 0, 1, and 2) also showed significant differences across tissues (p<0.001), but P53 staining results did not show significant variation (p=0.936).

Discussion Apoptosis is defined as programmed cell death occurring in multicellular organisms. It plays a key role in tissue homeostasis, embryonic growth, and immune response. The Bcl-2 protein family regulates apoptosis by controlling both pro-apoptotic and anti-apoptotic proteins. The balance between the expression of these anti-apoptotic and pro-apoptotic proteins determines whether apoptosis is promoted or inhibited. Bcl-2 is an anti-apoptotic protein, and when expressed, it prevents the release of cytochrome c from the mitochondria, thus inhibiting apoptosis.12,13 Studies suggest that apoptosis is a dynamic process, with the duration of ischemia and reperfusion affecting the amount of free radicals and the apoptosis rate. Additionally, the response of epithelial cells in follicles to apoptosis varies according to hormonal stages. A failure to achieve pregnancy has been linked to higher rates of apoptosis in granulosa-lutein cells.11 While there are studies indicating that Bcl-2 is upregulated during ischemia, others suggest ischemia triggers apoptosis via Bcl-2's cytoprotective effects.10 A gradual increase in Bcl-2 positive follicles with prolonged ischemia, along with fluctuations in the cell cycle, tissue damage due to reactive oxygen species (ROS), and the consequent induction of Bcl-2 expression, could explain this mechanism. The strong antioxidant properties of Bcl-2 might provide cytoprotection to ovarian follicles after ischemic events. Furthermore, Bcl-2's cytoprotective role could be attributed to its inhibition of cytochrome c release and delay in caspase activation.14 In this study, Bcl-2 expression was not affected in primordial, primary, and secondary follicles in either group. However, apoptosis was triggered in the corpus luteum. Ovarian torsion, characterized by the interruption of blood flow to the ovaries, is a common gynecological problem that can lead to infertility if diagnosed late. Historically, the only available treatment was oophorectomy. With recent advances in early diagnosis and medical intervention, the primary approach now focuses on

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restoring proper ovarian circulation. Ovarian ischemia/reperfusion (I/R) stimulates the release of pro-inflammatory cytokines by inflammatory cells. These cytokines enhance the affinity of circulating neutrophils for the endothelium, promote the production of reactive oxygen species (ROS), intensifying neutrophil infiltration, and worsening ischemic injury. This process activates apoptotic pathways by initiating the formation of an apoptosome protein complex and activating caspases.14,15 Ischemic injury is associated with changes in molecules related to cell survival and apoptosis, such as Bcl-2 and P53 proteins. Whether ovarian tissue ischemia is linked to similar changes in these molecules remains unclear.11 Hussein et al reported higher Bcl-2 expression in healthy follicles compared to atretic follicles, with secondary follicles showing the highest impact in ischemic tissues, followed by primary, primordial, and atretic follicles.10 In their study, they demonstrated that ischemia of ovarian tissues could alter the expression of Bcl-2 and P53 proteins. They indicated that apoptosis plays a critical role in follicular atresia, with Bcl-2 and P53 being key players in this process. This effect was more pronounced for Bcl-2, while P53 expression was nearly absent in healthy primordial, primary, and secondary follicles, corpus luteum, germinal epithelium, and stromal cells exposed to warm ischemia.11 In a study by Han et al., they analyzed I/R in the heart and observed increased Bax expression and decreased Bcl-2 expression in the I/R group compared to controls.17 In ischemic conditions, the lack of P53 expression in healthy follicles and most atretic follicles can be explained by genetic integrity preservation mechanisms after ischemic damage. The decrease in P53 expression in the experimental group in this study can similarly be interpreted. Recent studies have suggested that after transient brain ischemia, P53 might protect against brain injury instead of exacerbating it. This effect occurs through mechanisms unrelated to its apoptotic properties.9,10,18 P53 has been proposed to mediate apoptosis through interactions with various influential genes, such as those in the Bcl-2 family, found in granulosa cells of ovarian tissues.9,10,18 In this study, the decrease in P53 levels during the ischemic process compared to the control group may indicate that, while P53 plays a role in supporting developmental processes in the control group, its support may have been diminished in ischemic conditions. Several studies on I/R and Bcl-2, particularly in the cardiac system, have been conducted. In one such study, Xie et al. examined heart ischemia/reperfusion (I/R) injury and observed Bcl 2/Bax ratios in cardiomyocytes. They found that while Bcl-2 and Bax increased in the I/R group, the Bcl-2/Bax ratio decreased, with Bcl-2 levels reducing after reperfusion. They suggested that the marked increase in Bcl-2 in areas outside the reperfused region might act as a mechanism to protect surviving cardiomyocytes.[18-20]

In this study, it appears that P53 might have decreased through a similar mechanism, which warrants further detailed investigation. In this study, the control group showed signs of apoptosis in the germinal epithelium and corpus luteum, which correlated with a decrease in Bcl-2 levels. However, Bcl-2 expression was not observed in primary, secondary, or antral follicle cells in both the control and ischemic groups. The decrease in P53 levels suggests that ischemia/reperfusion may influence follicular tissues through different

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mechanisms. Stromal cells in both groups did not show significant differences. P53 levels being higher in the control group and lower in the experimental group may be related to the stage of ovarian development. To clarify this, further research including ovarian developmental stages and serum hormone levels could provide more insight. These variables were not included in this study.

Conclusion This study highlights that primordial, primary, secondary, and antral follicular structures were not significantly affected by ischemic processes. The application of protective methods in I/R injury could be beneficial for maintaining ovarian function.

Table 1. Comparison of staining results of Bcl-2 and P53 markers obtained from different tissues in the Control and Sham-Experimental groups.

			Control			Sham- experi mental		
			Bcl-2	**P53**	**p**	**Bcl-2**	**P53**	**p**
Germinate- ve layer	0	n	0	1	0.203[a]	4	6	0.608[b,c]
		%	0.0	12.5		50.0	75.0	
	1	n	8	5		4	2	
		%	100.0	62.5		50.0	25.0	
	2	n	0	2		0	0	
		%	0.0	25.0		0.0	0.0	
Primordial Follicle	0	n	8	0	**<0.001**[b]	8	6	0.467[b]
		%	100.0	0.0		100.0	75.0	
	1	n	0	8		0	2	
		%	0.0	100.0		0.0	25.0	
Secondary Follicle	0	n	8	2	**0.007**[b]	8	6	0.467[b]
		%	100.0	25.0		100.0	75.0	
	1	n	0	6		0	2	
		%	0.0	75.0		0.0	25.0	
Antral Follicle	0	n	8	2	**0.007**[b]	8	6	0.467[b]
		%	100.0	25.0		100.0	75.0	
	1	n	0	6		0	2	
		%	0.0	75.0		0.0	25.0	
Corpus Luteum	0	n	2	2	0.999[b]	8	6	0.467[b]
		%	25.0	25.0		100.0	75.0	
	1	n	6	6		0	2	
		%	75.0	75.0		0.0	25.0	
Stroma	0	n	2	3	0.999[b]	2	4	0.608[b]
		%	25.0	37.5		25.0	50.0	
	1	n	6	5		6	4	

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		%	75.0	62.5		75.0	50.0

[a]: Fisher-Freeman-Halton Exact Test; [b]: Fisher's Exact Test; [c]: The last row was not used in the test.

Table 2.

Changes in staining results obtained in each tissue for Bcl-2 and P53 markers according to groups

			Control		Sham-experimental		p
			n	%	n	%	
Bcl-2	Germinative Layer	0	0	0.0	4	50.0	0.077[a]
		1	8	100.0	4	50.0	
	Primordial Follicle	0	8	100.0	8	100.0	-
		1	0	0.0	0	0.0	
	Secondary Follicle	0	8	100.0	8	100.0	
		1	0	0.0	0	0.0	-
	Antral Follicle	0	8	100.0	8	100.0	-
		1	0	0.0	0	0.0	
	Corpus Luteum	0	2	25.0	8	100.0	**0.007**[a]
		1	6	75.0	0	0.0	
	Stroma	0	2	25.0	2	25.0	0.999[a]
		1	6	75.0	6	75.0	
P53	Germinative Layer	0	1	12.5	6	75.0	0.063[b]
		1	5	62.5	2	25.0	
		2	2	25.0	0	0.0	
	Primordial Follicle	0	0	0.0	6	75.0	**0.007**[a]
		1	8	100.0	2	25.0	
	Secondary Follicle	0	2	25.0	6	75.0	0.132[a]
		1	6	75.0	2	25.0	
	Antral Follicle	0	2	25.0	6	75.0	0.132[a]
		1	6	75.0	2	25.0	
	Corpus Luteum	0	2	25.0	6	75.0	0.132[a]
		1	6	75.0	2	25.0	
	Stroma	0	3	37.5	4	50.0	0.999[a]
		1	5	62.5	4	50.0	

-: Could not be calculated; [a]: Fisher's Exact test; [b]: Fisher-Freeman-Halton Exact Test

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Table 3.

Changes in staining results of Bcl-2 and P53 markers according to tissues in the Control and Sham-Experimental groups.

			0		1		2		p
			n	%	n	%	n	%	
Control	Bcl-2	Germinative Layer	0	0.0	8	100.0	0	0.0	**<0.001**[a,b]
		Primordial Follicle	8	100.0	0	0.0	0	0.0	
		Secondary Follicle	8	100.0	0	0.0	0	0.0	
		Antral Follicle	8	100.0	0	0.0	0	0.0	
		Corpus Luteum	2	25.0	6	75.0	0	0.0	
		Stroma	2	25.0	6	75.0	0	0.0	
	P53	Germinative Layer	1	12.5	5	62.5	2	25.0	0.390[a]
		Primordial Follicle	0	0.0	8	100.0	0	0.0	
		Sekondary Follicle	2	25.0	6	75.0	0	0.0	
		Antral Follicle	2	25.0	6	75.0	0	0.0	
		Corpus Luteum	2	25.0	6	75.0	0	0.0	
		Stroma	3	37.5	5	62.5	0	0.0	
Sham- experimental	Bcl-2	Germinative Layer	4	50.0	4	50.0	0	0.0	**<0.001**[a,b]
		Primordial Follicle	8	100.0	0	0.0	0	0.0	
		Sekondary Follicle	8	100.0	0	0.0	0	0.0	
		Antral Follicle	8	100.0	0	0.0	0	0.0	
		Corpus Luteum	8	100.0	0	0.0	0	0.0	
		Stroma	2	25.0	6	75.0	0	0.0	
	P53	Germinative Layer	6	75.0	2	25.0	0	0.0	0.936[a,b]
		Primordial Follicle	6	75.0	2	25.0	0	0.0	
		Sekondary Follicle	6	75.0	2	25.0	0	0.0	
		Antral Follicle	6	75.0	2	25.0	0	0.0	
		Corpus Luteum	6	75.0	2	25.0	0	0.0	
		Stroma	4	50.0	4	50.0	0	0.0	

[a]: Fisher-Freeman-Halton Exact Test; [b]:

The last column was not used in the test.

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Data availability

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Consent for publication

Not applicable.

Contributors HE contributed to the conception, design, acquisition, analysis, drafting, final approval of this paper and is the guarantor. AK, YKA, DK and OY, IK, KK contributed to the conception, acquisition, drafting and final approval of this paper. OY, IK, KK, YKA and HA contributed to the analysis, interpretation of data for the work, drafting and final approval of this paper. All authors agree to be accountable for all aspects of the work.

FIGURE LEGENDS

1- Normal appearance in the upper right control group. Upper left: bcl2 expression in the control group. Lower right and lower left: expression rate of p53 in the control group in follicles and other areas.

2- Normal appearance in the upper right sham group. Upper left: bcl2 expression in the sham group. Lower right and lower left: expression rate of p53 in the sham group in follicles and other areas.