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The role of galectine-3 in disruption of ovarian during diabetes mellitus and stress

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The objective: **to study the role of galectin-3 (Gal-3) in ovarian function under conditions of diabetes mellitus (DM), chronic stress, and their combination in rats.**
Materials and methods**. The study used 20 six-month-old female albino laboratory rats, which were equally divided into 4 groups: Group 1 – control animals, Group 2 – rats with simulated streptozotocin-induced DM (SIDM) and chronic immobilization stress (CIS), Group 3 – rats with SIDM, Group 4 – rats with CIS. Glucose and cortisol levels were determined in blood plasma. Morphological study of ovarian tissue was conducted. The material was taken on the 28th day from the beginning of the experiment. Histological, immunohistochemical, biochemical and statistical research methods were used.**
Results**. Against the background of elevated glucose and *HbA1c* levels in the experimental Groups 2 and 3, congestion of blood vessels in the ovarian medulla is observed, which was caused by erythrocyte sludges and microthrombi formation. The general morphology of the ovaries of rats in the Groups 2–4 was similar to that of rats with polycystic ovary syndrome (PCOS). In particular, the appearance of numerous cystic follicles and an increased number of atretic follicles confirm this. Moreover, we detected different levels of Gal-3 expression in cells of different layers of primary, secondary and tertiary follicles. Follicular cells of rats with SIDM showed particularly pronounced Gal-3 expression. In all experimental Groups, Gal-3 expression increased in ovarian tissue. In the ovaries of rats with SIDM, Gal-3 expression was more pronounced in the cells of the outer layer of primary, secondary, and tertiary follicles compared to rats with comorbid pathology and CIS. Most luteocytes of the corpus luteum intensively expressed Gal-3. In primary follicles, Gal-3 was expressed only in the cells of the theca interna, while in secondary follicles it was expressed in small or moderate amounts in the cells of all layers – the granulosa layer, theca interna and theca externa. Atrophic follicles showed varying Gal-3 expression intensity across different pathological Groups.**
Conclusions**. Our study showed that DM and stress lead to the development of PCOS, which is morphologically confirmed by the appearance of numerous cystic follicles in the ovarian tissue and an increased number of atretic and destruction of primary and secondary follicles.**
DM and stress lead to increased expression of Gal-3 in follicular cells at different stages of ovarian development compared to control values. At the same time, Gal-3 expression was highest in the Group of animals with DM. Based on the results, it can be concluded that stress in animals with DM reduces Gal-3 expression in the cells of primary, secondary and tertiary follicles, but not in the corpus luteum and atretic follicles. It should be noted that ovarian oocytes remained insensitive to Gal-3 expression.
Keywords: *diabetes mellitus, stress, polycystic ovary syndrome, reproduction system, ovary, galectin-3.*

Значення галектину-3 у патогенезі функціональних розладів яєчників на тлі цукрового діабету та стресу

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Мета дослідження: вивчення ролі галектину-3 (Gal-3) у функції яєчників щурів на тлі цукрового діабету (ЦД), хронічного стресу та їх поєднання.
Матеріали та методи. У дослідженні було використано 20 6-місячних білих лабораторних щурів-самок, яких було рівномірно розподілено на 4 групи: група 1 – контрольні тварини, група 2 – щурі з індукованим стрептозотоциновим ЦД (СЦД) та хронічним іммобілізаційним стресом, група 3 – щурі із СЦД, група 4 – щурі з хронічним іммобілізаційним стресом. У плазмі крові визначали рівні глюкози, кортизолу. Проводили морфологічне вивчення тканини яєчника. Матеріал забирали на 28-й день від початку експерименту. Використовували гістологічний, імуногістохімічний, біохімічні та статистичні методи дослідження.
Результати. На тлі підвищеного рівня глюкози та *HbA1c* в експериментальних групах 2 та 3 спостерігалося повнокрів'я судин мозкової речовини яєчників унаслідок еритроцитарних сладжів та мікротромбів. Загальна морфологія яєчників щурів у групах 2–4 була схожою з морфологією яєчників щурів із синдромом полікістозних яєчників (СПКЯ). Зокрема, це підтверджується появою численних кістозних фолікулів та збільшенням кількості атретичних фолікулів. Крім того, виявлено різні рівні експресії Gal-3 у клітинах різних шарів первинних, вторинних і третинних фолікулів. Фолікулярні клітини щурів із СЦД демонстрували особливо виражену експресію Gal-3. У всіх експериментальних групах експресія Gal-3 збільшилася в тканині яєчників. В яєчниках щурів із СЦД експресія Gal-3 була більш вираженою в клітинах зовнішнього шару первинних, вторинних і третинних фолікулів порівняно зі щурами з коморбідною патологією та хронічним іммобілізаційним стресом. Більшість лютеоцитів жовтого тіла інтенсивно експресували Gal-3. У первинних фолікулах Gal-3 експресувався тільки в клітинах внутрішньої оболонки, тоді як у вторинних фолікулах він експресувався в невеликих або помірних кількостях у клітинах усіх шарів – гранульозного шару, внутрішньої та зовнішньої теки. Атрофічні фолікули інтенсивно експресували Gal-3 у різних досліджуваних групах.

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Висновки. Наше дослідження показало, що ІЦД та стрес призводять до розвитку СПКЯ, що морфологічно підтверджується появою численних кістозних фолікулів у тканині яєчника й зростанням кількості атретичних і деструкцією первинних та вторинних фолікулів.

ІЦД і стрес призводять до збільшення експресії Gal-3 у фолікулярних клітинах на різних стадіях розвитку яєчників, порівняно з контрольними показниками. При цьому експресія Gal-3 була найвищою в групі тварин із ІЦД. Враховуючи результати, можна стверджувати, що стрес у тварин із ІЦД знижує експресію Gal-3 у клітинах первинних, вторинних і третинних фолікулів, але не в жовтому тілі та атретичних фолікулах. При цьому слід зазначити, що овоцити яєчників залишалися нечутливими до експресії Gal-3.

Ключові слова: *цукровий діабет, стрес, синдром полікістозних яєчників, репродуктивна система, яєчники, галектин-3.*

Diabetes mellitus (DM) type 1 and 2 are commonly medico-social diseases worldwide due to prevalence, development of complications and mortality [1]. The most frequent complications of DM are cardiovascular diseases [2, 3], retinopathies [4], neuropathies [5, 6], nephropathies [7] and other [8, 9]. However, in addition to these noticeable complications, diabetes is also associated with reproductive dysfunction. These disorders appear to occur in 40% of women with diabetes and include delayed menstruation, all types of menstrual disorders such as amenorrhea, oligomenorrhea, menstrual cycle disorders, as well as menorrhagia, infertility, characteristics of polycystic ovary syndrome (PCOS), and early (or rarely late) menopause [10–14].

Galectin-3 (Gal-3) is a member of soluble protein that bind with β-galactoside containing glycans [15]. Intracellular Gal-3 plays a crucial role in cell growth, anti-apoptosis, controlling of RNA (Ribonucleic Acid) splicing [16], meanwhile extracellular Gal-3 takes a part of inflammation response [15]. Multiple studies have reported that Gal-3 associate with different types of cancers doe to involved in the regulation of different tumor suppressor genes and oncogenes [17]. Gal-3 is also involved in the production of the hormone progesterone and is expressed in mature mouse ovaries during the luteolytic and atretic stages [18]. Individual works showed that Gal-3 has been found to be related with insulin resistance and reported as a potential biomarker for early detection of prediabetes and diabetes [15, 19].

Stress is one of the most common and underestimated causes of reproductive dysfunction in women and girls. The stress system leads to adaptive reactions through the mobilization of hormonal systems, in particular the hypothalamic-pituitary-ovarian axis [20]. In women with chronic psychogenic stress, ovulatory dysfunction leads to abnormal uterine bleeding, which is diagnosed three times more often than in women without stress [21]. Unfortunately, we were unable to find any studies in the literature that addressed the impact of stress on changes in reproductive function in women with DM. Moreover, changes in Gal-3 expression in this context remain unknown.

The objective of our study is to examine the role of Gal-3 in the functioning of the ovarian under conditions of DM, chronic stress and their combination in rats.

MATERIALS AND METHODS

In this study, we used a total of 20 six-month-old female albino laboratory rats, equally divided into four groups (five rats per group): Group 1 (Control) consisted of healthy rats; Group 2 included rats with comorbid pathology – streptozotocin-induced DM (SIDM) combined with chronic immobilization stress (CIS); Group 3 included rats with SIDM only; and Group 4 included rats subjected to CIS only. In Groups 2 and 3, SIDM was simulated by a single intraperitoneal injection of streptozotocin (Sigma-Aldrich, USA), which was diluted in 0.1 M citrate buffer with a pH of 4.5 (at the rate of 6 mg per 100 g of body weight). In Groups 2 and 4, CIS was simulated by placing the animals in a closed plastic container for 5 hours a day. In Group 2, SIDM was simulated and starting from the 14th day of the experiment, CIS was added.

The experiment on animals was conducted in the vivarium of the Ivano-Frankivsk National Medical University (IFNMU). The rat cages were kept in a room with a controlled environment, in the following standard conditions (12/12 light/dark cycle with 22 ± 3 °C room temperature). All rats were provided with standard laboratory chow and water ad libitum. At the end of the experiment, the animals were euthanized under ketamine anesthesia. Immediately after euthanasia, blood samples were collected into test tubes for further analysis. Glucose levels were measured using the glucose oxidase method at the Center of Bioelementology of IFNMU. The levels of glycated hemoglobin (*HbA1c*) and cortisol were determined in the clinical diagnostics laboratory "Medlux". The levels of glucose and cortisol were measured in blood plasma. Tissue samples (ovaries and blood) were collected on the 28th from the beginning of the experiment in Groups 1–3. In Group 4, the materials were collected on the 14th days from the beginning of CIS induction. Material collection was performed in the morning (between 7:00 and 8:00 am), before feeding, to exclude the influence of daily rhythm and biological activity on rat metabolism. The estrous cycle stage was determined via vaginal cytology and monitored for at least 7 days before experiments involving the natural estrous cycle [22].

For light microscopic observation, samples (ovaries) were fixed 24 hours in 10% paraformaldehyde in phosphate buffer solution (PBS) with pH 7.4, dehydrated and embedded in paraffin. In addition to routine histological examination (hematoxylin-eosin staining). For detection Gal-3 we used antibodies to Gal-3 (clone EP2775Y, 1:250, Abcam, United Kingdom) according to the manufacturer's instructions which allows to provide semiqualitative measurements in section samples. Gal-3 expression intensity of follicular cells were measured by a histological score (HSCORE) method: 0 – no staining; 1 (+) – weak staining; 2 (++) – moderate staining; 3 (+++) – intense staining [23].

The quantification of the immunoreactivity intensity in both right and left ovarian tissues was included in the analysis. To evaluate ovarian architecture and follicle number, we conducted samples stained by hematoxylin-eosin. Ten fields from three randomly selected sections of each ovary were examined at an original magnification of × 200 to calculate the number of follicles at different stages of maturation [24].

All sections were evaluated with an optical microscope (Leica DM750, Leica Microsystems, Switzerland)

and monitored with an attached digital camera (ToupCam 5.2M UHCCD C-Mount Sony sensor, ToupTek Photonics, China). Statistical analysis was performed using the Statistica 12 software (StatSoft Inc., Tulsa, OK, USA). To assess differences between Groups, the Mann–Whitney U test was used. The sample parameters presented in the text are denoted as M ± SD, where M represents the sample mean, SD the standard deviation, and p the achieved level of statistical significance.

RESULTS AND DISCUSSION

On the 28th day of the experiment, the level of glucose and *HbA1c* in the blood of rats in Group 2 was the highest, compared to Group 1, and was 18.72 ± 2.09 mmol/L ($p < 0.001$) and 9.35 ± 0.53% ($p < 0.001$), respectively; in Group 3 – 16.09 ± 1.86 mmol/L ($p < 0.001$) and 8.06 ± 0.41% ($p < 0.001$); in Group 4 – 5.07 ± 0.73 mmol/L ($p > 0.05$) and 2.45 ± 0.32% ($p > 0.05$); while in Group 1 the above indicators were 4.57 ± 0.63 mmol/L and 2.29 ± 0.26%. The level of cortisol in experimental Groups 2–4 was probably higher than that of control rats and was: in Group 2 – 28.69 ± 2.43 ng/mL, in Group 3 – 24.63 ± 2.28 ng/mL, in Group 4 – 24.39 ± 1.76 ng/mL (in all cases $p < 0.01$), in control animals (Group 1) it was 10.12 ± 1.09 ng/mL. Such biochemical changes in Groups 2 and 3 indicate the development of decompensated DM, and in Group 4 – the development of stress.

At the light microscopic examination, the ovaries of sexually mature female rats consist of a cortex, medulla and capsule. The epithelium of the ovarian surface consists of a single layer of flattened cells lying on the basement membrane that separates it from the lower protein membrane. The histological structure of the ovaries of the Control rats is characterised by the presence of different

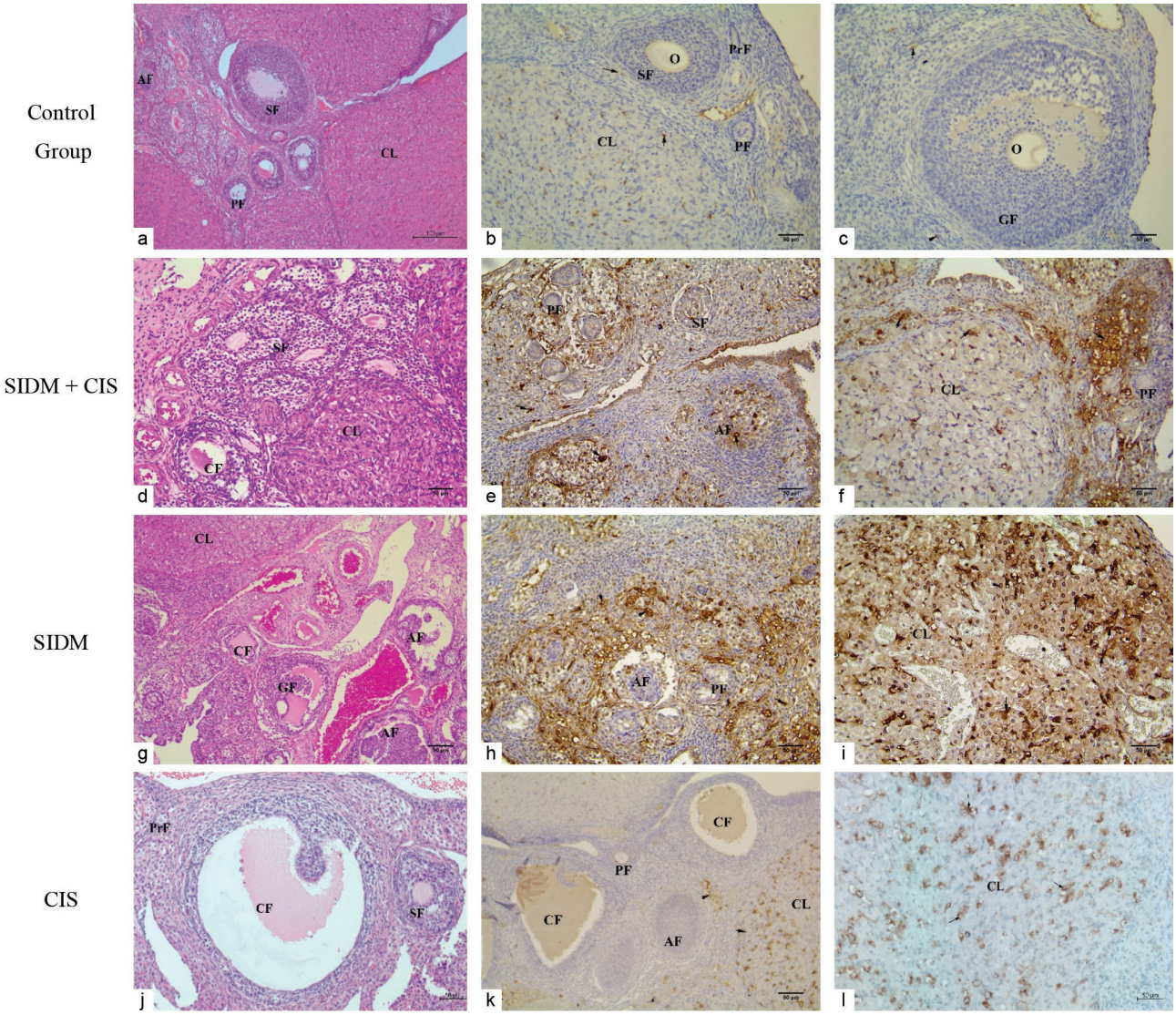

Fig. 1. Histopathological alterations and representative Gal-3 immunoreactivity in ovarian sections of the control (a–c) and the experimental (d, e) Groups. Control Group exhibited normal ovarian morphology, whereas experimental Groups showed many cystic and atretic follicles. CF indicates cystic follicle; AF – atretic follicle; CL – corpus luteum; PrF – primordial follicle; PF – primary follicle; SF – secondary follicle; GF – Graafian follicle; O – oocyte; arrow – expressing Cal-3; H & E – hematoxylin-eosin staining

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types of follicles at different stages of development (primordial follicles, primary follicles, secondary follicles and mature follicles) and corpus luteum. The ovaries of adult females contain 3 to 5 corpora lutea and 0–2 atretic follicles of normal structure, while cystic follicles are absent. Granulosa and theca cells had a typical structure and intact structure. Oocytes and zona pellucida were clearly contoured (Fig. 1a). In the Control Group of rats, Gal-3 expression was found to be moderate in the corpus luteum and in isolated granulosa cells of secondary follicles (Fig. 1b, c). However, we were unable to detect Gal-3 expression in the oocytes of any follicles (Fig. 1b, c).

In rats in Groups 2 and 3, sections revealed noticeable atrophic and degenerative changes in both the ovarian cortex and the medulla, with thinning of the white matter (Fig. 1d, g). The blood vessels were dilated and full-blooded due to erythrocyte sludge and microthrombi. Numerous atretic follicles were found in the ovarian cortex, the average number of which per 0.05 mm^2 increased to 4.40 ± 1.43 in Group 2 and to 4.1 ± 1.2 in Group 3, compared to the Control Group (0.90 ± 0.74; $p < 0.05$ in all cases) (Fig. 2). These follicles were of various sizes and were characterised by degenerated oocytes without zona pellucida or, more often, without any membrane at all. The granulosa cells of such follicles were characterised by pyknosis of nuclei and severe degenerative changes. In all follicles at different stages of folliculogenesis, pronounced degeneration was observed in the form of ruptures and fragmentation of granulosa cells, their desquamation into the lumen of the follicles, and an increase in cell debris in the antral cavities in the form of clusters. Many granulosa cells and inner theca cells had vacuolated cytoplasm with pyknotic nuclei (Fig. 1d, e, g–i).

The number of cystic follicles in Groups 2 and 3 increased from 1 to 3 in the vision of these Groups of animals, compared to the Control values where such follicles were completely absent (Fig. 2). Thus, the number of cystic follicles in Group 2 was 2.50 ± 1.78, and in Group 3 it was 2.10 ± 1.19, whereas no cystic follicles were observed in the Control Group (in all cases $p < 0.001$). Thinning of the granulosa cell layer and its disorganisation were observed in the cystic follicles. Moreover, many granulosa cells were found in the filled antrum of the cystic follicles. Apoptotic granulosa cells with pyknotic nuclei, indicating follicle atresia, were particularly noticeable in secondary follicles in Groups 2 and 3 (Fig. 1d, e, g, h). The corpora lutea had an irregular shape and volume with vacuolated granulosa lutein cells (Fig. 1f, i). In the ovarian medulla of these animal Groups, thick connective tissue septa extending from the capsule to the cortex were clearly visualised. The interstitium had areas of hyaline and hydropic degeneration. Despite the pronounced changes in the ovaries, no significant difference in the number of atretic and cystic follicles between experimental Groups 2 and 3 was found (in all cases $p > 0.05$), while in the Control Group their number increased significantly (in all cases $p < 0.05$).

The general morphology of the ovaries of rats in Group 4 with CIS showed numerous cystic and atretic follicles and several corpora lutea (Fig. 1j–l). At the same time, the number of both cystic and atretic follicles was significantly higher than in the Control Group, amounting to 1.60 ± 1.07 and 3.30 ± 1.25, respectively (Fig. 2, in all cases $p < 0.05$), but lower than in experimental Groups 2 and 3 (Fig. 2, in all cases $p < 0.05$). In cystic follicles, the number of layers of granulosa cells undergoing pronounced destructive changes decreased. Oocytes

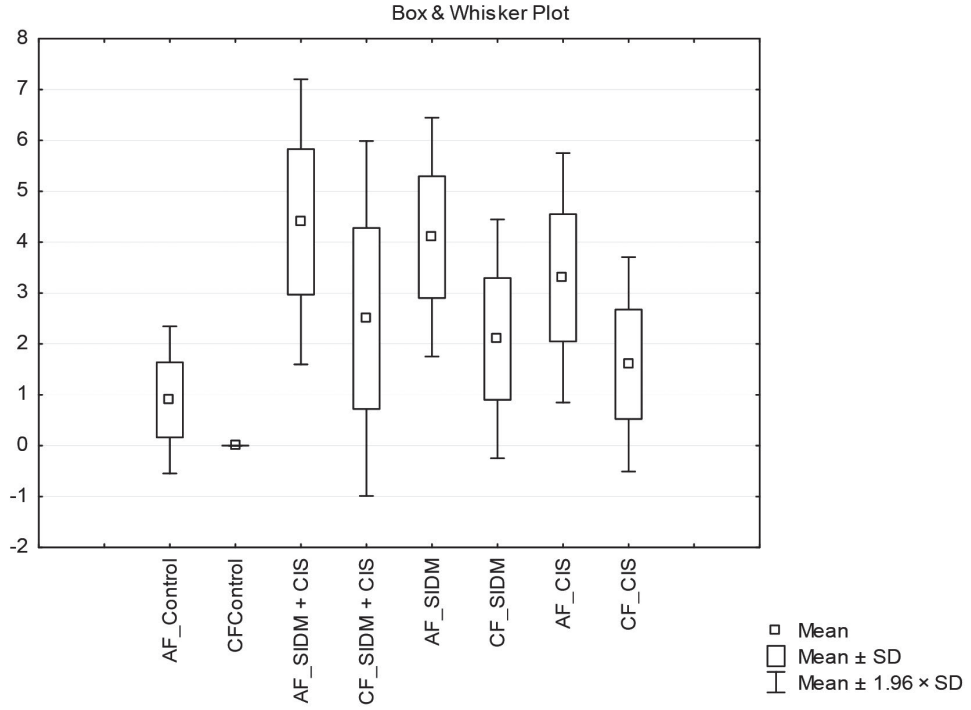

Fig. 2. Increase number of atretic and cystic follicles in the ovaries during the pathologies studied (AF – atretic follicle; CF – cystic follicle)

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were absent in atretic follicles. Degenerative oocytes and a complete absence of the transparent membrane were often observed in Graafian follicles. Moreover, apoptotic, vacuolated and destructively altered granulosa cells underwent desquamation and exfoliate into the lumen of the antrum (Fig. 1j, k). Such a restructuring of the follicle indicates its atresia. The architecture of the corpora lutea in the ovaries of this experimental Group was preserved. It should also be noted that luteocytes with signs of vacuolar dystrophy appeared in the corpora lutea.

In all experimental Groups, Gal-3 expression increased in ovarian tissue (Table). Thus, in the ovaries of rats with SIDM, Gal-3 expression was more pronounced in the cells of the outer layer of primary, secondary, and tertiary follicles compared to rats with comorbid pathology and CIS (Fig. 1h). Most luteocytes of the corpus luteum intensively expressed Gal-3 (Fig. 1i). In primary follicles, Gal-3 was expressed only in the cells of the theca interna, while in secondary follicles it was expressed in small or moderate amounts in the cells of all layers – the granulosa layer, theca interna and theca externa (Table). Atrophic follicles did not differ in Gal-3 expression intensity from those with comorbid pathology.

In rats with CIS, the immunoreactivity of follicular cells at different stages of ovarian development to Gal-3 is slightly increased compared to control values. In particular, we see the expression of this marker in granulosa cells and cells of theca interna and theca externa of primary, secondary and tertiary follicles (Fig. 1k). Increased expression of Gal-3 is also found in luteocytes of the corpus luteum (Fig. 1l). In general, Gal-3 expression in the ovarian tissue of rats with CIS is higher than in the Control Group, but lower than in rats with diabetes (Table).

In rats with comorbid pathology, cells in different follicles show different reactivity to Gal-3. Thus, unlike Group 3 of rats and the Control Group, in Group 2, weak expression of Gal-3 is observed in the follicular cells of primordial follicles and corresponds to that in Group 4. As for secondary and tertiary follicles, weak Gal-3 expression is observed in all their layers, but it is less pronounced compared to Group 3 (Fig. 1e, Table). In atretic follicles and the corpus luteum, cells are intensively marked with Gal-3 (Fig. 1f, Table).

Currently, there is ongoing debate regarding the involvement of Gal-3 in folliculogenesis, as most studies demonstrate its involvement in the processes of carcinogenesis and metastasis of gynaecological tumours, particularly ovarian cancer [17].

Some studies have shown that Gal-3 is involved in the immunoreactivity of follicular cells at different stages of ovarian development [25]. A study by Seung-Dam Heo et al. showed that Gal-3 promotes early egg development in prenatal ontogenesis, but not postnatal ontogenesis [25]. It was detected in the follicular squamous cells of primary ovarian follicles, after which a gradual decrease in Gal-3 levels was observed during the multilaminar formation stage. Moreover, during the prenatal period of ontogenesis, age is expressed on the oocytes of primordial and primary follicles. The controversial role of Gal-3 in apoptosis requires further study, since many primary follicles are eliminated during development and Gal-3 was not expressed in the granulosa cells of multilayered ovarian follicles (primary to tertiary). The same authors have shown that Gal-3 is involved in cell death in atretic follicles, while in the corpus luteum it is involved either in the maintenance of luteal cells, luteolysis or their apoptosis [25].

Immunohistochemical evaluation of Gal-3 in the ovary

Follicular development	Cell type	Research Groups			
		Control Group	SIDM + CIS	SIDM	CIS
Primordial	Oocyte	ND	ND	ND	ND
	Follicular cells	–	+	–	+
Primary	Oocyte	–	–	–	–
	Granulosa cells	–	–	–	+
	Theca cells	–	+	++	+
Secondary	Oocyte	ND	ND	ND	ND
	Granulosa cells	–	+	++	+
	Theca interna	–	+	+	+
	Theca externa	+	+	++	++
Graafian	Oocyte	ND	ND	ND	ND
	Granulosa cells	–	++	++	+
	Theca interna	–	+	+	+
	Theca externa	–	+	++	+
Atretic	Oocyte	ND	ND	ND	ND
	Granulosa cells	–	++	++	–
	Fibrous theca	–	+++	+++	++
Corpus luteum	Luteal cells	+	+++	+++	++

Notes: Gal-3 expression in each structure of the ovary is as follows: – negative; + positive (1 (+) – weak; 2 (++) – moderate; 3 (+++) – intense); ND – not detected.

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It is known that cytoplasmic Gal-3 binds to various anti-apoptotic proteins, such as Bcl-2, activated K-Ras, Alix / AIP1, and synnexin, to inhibit intrinsic apoptotic pathways, functioning as an inhibitor of apoptosis [26]. Intracellular Gal-3 is also capable of modulating external apoptotic signaling pathways triggered by death receptors, including Fas, TNFR-1, and TRAIL, a TNF / Apo2-related apoptosis-inducing ligand [26]. Based on the literature data, we can conclude that in our studies, the pronounced expression of Gal-3 in luteocytes of the corpus luteum is aimed at their elimination, which is especially pronounced in rats with diabetes and comorbid pathology.

The general morphology of the ovaries of rats in Groups 2–4 was similar to that of rats with PCOS [19]. In particular, the appearance of numerous cystic follicles and an increase in atretic follicles confirm this. Moreover, we detected different levels of Gal-3 expression in cells of different layers of primary, secondary and tertiary follicles. Follicular cells of rats with SIDM showed particularly pronounced Gal-3 expression. According to the literature, hyperglycaemia leads to the development of oxidative stress and increases the level of advanced glycation end products (AGEs) in the body [27]. AGEs have been shown to play an important role in reproduction by regulating the functions of granulosa cells in the ovary. On the one hand, modifications in protein assembly and subsequent loss of function caused by AGEs in diabetes lead to apoptosis of these cells [28]. On the other hand, DM provokes apoptosis of glycemic cells by causing a significant induction of oxidative stress, increasing the expression of the P53 gene and activating kinases 1 and 2, which ultimately causes DNA (Deoxyribonucleic Acid) damage and endoplasmic reticulum stress. Glycemic cell apoptosis inhibits oocyte maturation and is considered a key molecular mechanism of follicular atresia [29]. Accelerated follicular degeneration and subsequent follicular atresia caused by glycemic cell apoptosis lead to a decrease in serum anti-Müllerian hormone levels, which are considered one of the best determinants of ovarian reserve and fertility, especially in DM, and are closely correlated with Gal-3 levels [24].

Furthermore, other studies have shown that elevated serum Gal-3 levels correlate with the severity of type 2 diabetes and its complications. Several human studies have provided evidence that Gal-3 levels are markedly elevated in individuals with obesity and type 2 diabetes. Thus, Gal-3 may be useful in the diagnosis and prognosis of microvascular and macrovascular complications in patients with type 2 DM. Gal-3 has been shown to be involved in inflammation, apoptosis, and angiogenesis, and is also associated with the development of insulin resistance in patients with type 2 diabetes. It has been proven that there is a relationship between serum Gal-3 levels and various complications and biochemical parameters in patients with type 2 diabetes, in particular, positive significant correlations were found between serum Gal-3 levels and body mass index, *HbA1c*, cholesterol, triglycerides, urinary albumin-to-creatinine ratio, and age [30].

CONCLUSIONS

Our study showed that DM and stress lead to the development of PCOS, which is morphologically confirmed by the appearance of numerous cystic follicles in the ovarian tissue and an increase in the number of atretic and destructive primary and secondary follicles.

Diabetes and stress lead to increased expression of Gal-3 in follicular cells at different stages of ovarian development compared to control values. At the same time, Gal-3 expression was highest in the Groups of animals with diabetes. Based on the results, it can be concluded that stress in animals with diabetes reduces Gal-3 expression in the cells of primary, secondary and tertiary follicles, but not in the corpus luteum and atretic follicles. It should be noted that ovarian oocytes remained insensitive to Gal-3 expression.

Prospects for further research. To understand the effect of Gal-3 on folliculogenesis processes in rat ovaries under conditions of DM and stress, it is necessary to study the mechanisms of apoptosis using various immunohistochemical markers, which will allow us to understand what kind of apoptotic or anti-apoptotic effect the latter has on follicle cells.

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REFERENCES

1. International Diabetes Federation. Diabetes Atlas [Internet]. Brussels: IDF. Available from: https://diabetesatlas.org/.
2. Rajbhandari J, Fernandez CJ, Agarwal M, Yeap BXY, Pappachan JM. Diabetic heart disease: A clinical update. World J Diabetes. 2021;12(4):383-406. doi: 10.4239/wjd.v12.i4.383.
3. Vasyliuk VM, Zhurakivska OYa, Kondrat AIV, Khabchuk VS. Morphological characteristics of the endocrine function of the heart in comorbid pathology. Pol Merkuriusz Lek. 2023;51(3):194-200. doi: 10.36740/Merkur202303102.
4. American Diabetes Association Professional Practice Committee. 12. Retinopathy, Neuropathy, and Foot Care: Standards of Care in Diabetes-2024. Diabetes Care. 2024;47(1):231-43. doi: 10.2337/dc24-S012.
5. Vinelli-Arzubiaga D, Suasnabar Campos CE, Laso-Salazar MC, Abarca-Barriga H. Polymorphic variants and risk of diabetic peripheral neuropathy in patients with type 2 diabetes mellitus: systematic review and meta-analysis. BMC Endocr Disord. 2025;25(1):69. doi: 10.1186/s12902-025-01897-1.
6. Zhurakivska OYa, Koshkin OYe, Tkachuk YL, Rudyak OM, Knyazevych-Chorna TV. Age characteristics of morphogenesis of diabetic myopathies. Probl Endocrine Pathol. 2020;74(4):115-23. doi: 10.21856/j-PEP.2020.4.15.
7. Van Raalte DH, Bjornstad P, Cherney DZI, de Boer IH, Fioretto P, Gordin D, et al. Combination therapy for kidney disease in people with diabetes mellitus. Nat Rev Nephrol. 2024;20(7):433-46. doi: 10.1038/s41581-024-00827-z.
8. Mishriky BM, Cummings DM, Powell JR. Diabetes-Related Microvascular Complications – A Practical Approach. Prim Care. 2022;49(2):239-54. doi: 10.1016/j.pop.2021.11.008.
9. Zhurakivska OY, Bodnarchuk YV, Kostitska IO, Kindrativ EO, Andriiv AV, Zhurakivskyi VM, et al. Morpho-functional characteristics liver of rats in early development of streptosotocin diabetes mellitus using cluster analysis. Probl Endocrine Pathol. 2021;75(1):84-96. doi: 10.21856/j-PEP.2021.1.11.
10. Zaimi M, Michalopoulou O, Stefanaki K, Kazakou P, Vasileiou V, Psaltopoulou T, et al. Gonadal dysfunction in women with diabetes mellitus. Endocrine. 2024;85(2):461-72. doi: 10.1007/s12020-024-03729-z.
11. Thong EP, Codner E, Laven JSE, Teede H. Diabetes: a metabolic and reproductive disorder in women. Lancet Diabetes Endocrinol. 2020;8(2):134-49. doi: 10.1016/S2213-8587(19)30345-6.
12. Pakharenko LV, Zhylka NYa, Shcherbinska OS, Kravchuk IV, Lasytchuk OM, Zhurakivskyi VM, et al. The modern pathogenetic challenges of polycystic ovary syndrome. Reprod Health Woman. 2024;(2):75-80. doi: 10.30841/2708-8731.2.2024.304662.
13. Pakharenko L, Vorobii V, Kurtash N, Basiuha I. Association of ace gene polymorphism with the development of premenstrual syndrome. Georgian Med News. 2019;(294):37-41.
14. Pakharenko LV, Vdovichenko YP, Kurtash NY, Basiuha IO, Kravchuk IV, Vorobii VD, et al. Estradiol blood level and ESR1 gene polymorphism in women with premenstrual syndrome. Wiad Lek. 2020;73(12):2581-85.
15. Nikolić VN, Stefanović M, Mitić D, Sunarić S, Stojiljkovic V, Trajković H, et al. Metformin dosage and galectin-3 levels: insights from PCOS patients preparing for IVF. Front Pharmacol. 2025;15:1505022. doi: 10.3389/fphar.2024.1505022.
16. Di Lella S, Sundblad V, Cerliani JP, Guardia CM, Estrin DA, Vasta GR, et al. When galectins recognize glycans: from biochemistry to physiology and back again. Biochemistry. 2011;50(37):7842-57. doi: 10.1021/bi201121m.
17. Chetry M, Thapa S, Hu X, Song Y, Zhang J, Zhu H, et al. The role of galectins in tumor progression, treatment and prognosis of gynecological cancers. J Cancer. 2018;9(24):4742-55. doi: 10.7150/jca.23628.
18. Nio-Kobayashi J, Iwanaga T. Galectin-1 and galectin-3 in the corpus luteum of mice are differentially regulated by prolactin and prostaglandin F2α. Reproduction. 2012;144(5):617-24. doi: 10.1530/REP-11-0495.
19. Alves MT, de Souza IDP, Ferreira CN, Cândido AL, Bizzi MF, Oliveira FR, et al. Galectin-3 is a potential biomarker to insulin resistance and obesity in women with polycystic ovary syndrome. Gynecol Endocrinol. 2020;36(9):760-63. doi: 10.1080/09513590.2020.1739267.
20. Valsamakis G, Chrousos G, Mastorakos G. Stress, female reproduction and pregnancy. Psychoneuroendocrinology. 2019;100:48-57. doi: 10.1016/j.psyneuen.2018.09.031.
21. Fedosiuk KV, Pakharenko LV, Chaika KV, Zhurakivskyi VM, Lasytchuk OM, Kusa OM. The causes of abnormal uterine bleeding in women with chronic psychogenic stress. Zaporozhye Med J. 2023;25(1):30-4.
22. Ajayi AF, Akhigbe RE. Staging of the estrous cycle and induction of estrus in experimental rodents: an update. Fertil Res Pract. 2020;6:5. doi: 10.1186/s40738-020-00074-3.
23. Guzel E, Basar M, Ocak N, Arici A, Kayisli UA. Bidirectional interaction between unfolded-protein-response key protein HSPA5 and estrogen signaling in human endometrium. Biol Reprod. 2011;85(1):121-7. doi: 10.1095/biolreprod.110.089532.
24. Ali EMT, Abdallah HI, El-Sayed SM. Histomorphological, VEGF and TGF-β immunoexpression changes in the diabetic rats' ovary and the potential amelioration following treatment with metformin and insulin. J Mol Histol. 2020;51(3):287-305. doi: 10.1007/s10735-020-09880-x.
25. Heo SD, Park C, Kim J, Ahn M, Shin T. Unilaminar follicular cells transiently express galectin-3 during ovarian folliculogenesis in pigs. Tissue Cell. 2017;49(1):106-11. doi: 10.1016/j.tice.2016.11.003.
26. Nangia-Makker P, Nakahara S, Hogan V, Raz A. Galectin-3 in apoptosis, a novel therapeutic target. J Bioenerg Biomembr. 2007;39(1):79-84. doi: 10.1007/s10863-006-9063-9.
27. Babel RA, Dandekar MP. A review on cellular and molecular mechanisms linked to the development of diabetes complications. Curr Diabetes Rev. 2021;17(4):457-73. doi: 10.2174/1573399816666201103143818.
28. Merhi Z. Advanced glycation end products and their relevance in female reproduction. Hum Reprod. 2014;29(1):135-45. doi: 10.1093/humrep/det383.
29. Hamdan M, Jones KT, Cheong Y, Lane SIR. The sensitivity of the DNA damage checkpoint prevents oocyte maturation in endometriosis. Sci Rep. 2016;6:36994. doi: 10.1038/srep36994.
30. Kumar S, Ranawat CS, Bhandiwad C, Arya H, Mali M, Singh CP, et al. Galectin-3 as a potential biomarker of microvascular complications in patients with type 2 diabetes. Indian J Endocrinol Metab. 2022;26(5):490-7. doi: 10.4103/ijem.ijem_270_22.

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