

Inhibition of c-Jun N-Terminal Kinase Attenuates Diabetic Testicular Damage via Endoplasmic Reticulum Stress Reduction

La Inhibición de la Cinasa N-Terminal de c-Jun Atenúa el Daño Testicular Diabético Mediante la Reducción del Estrés del Retículo Endoplasmático

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SUMMARY: The underlying causes of many diabetes-related complications are well known. However, the reasons for the complication related to male reproductive health remain unclear. Hyperglycemia disrupts the balance between oxidants and antioxidants, causing damage to cells, especially ER stress. ER stress triggered by the proteins accumulating in the ER lumen causes apoptosis by activating various pathways. c-Jun N-terminal kinase (JNK) is a key protein in systemic diseases like diabetes, and SP600125 is a widely used JNK inhibitor. This study focuses on whether JNK inhibition by SP600125 prevents diabetic testicular damage by reducing ER stress. In our study, animals were divided into three groups: Control group, the diabetes group, and the JNK inhibition group. Blood glucose level, body and testicular weights, and seminiferous tubule diameters were measured. Seminiferous tubules were evaluated by the Johnsen score in Hematoxyline and Eosin stained sections. Protein expressions of caspase 3, phospho (p)-JNK, caspase 12, and CHOP were evaluated. The Inhibitor group had significantly decreased active caspase-3, (p)-JNK, caspase-12, CHOP values, and blood glucose levels, increased body and testicular weights, seminiferous tubule diameter, and Johnsen score values compared to the diabetes group. JNK inhibition significantly ameliorated the histopathological damage in testicular tissue by preventing diabetes-induced ER stress and apoptosis.

KEY WORDS: Diabetes mellitus; Protein Kinase Inhibitors; Endoplasmic Reticulum Stress; Apoptosis; Testis.

INTRODUCTION

Diabetes mellitus (DM) is a metabolic disease that threatens public health all over the world. It is known that the prevalence of diabetes is increasing rapidly in the world (Saeedi *et al.*, 2019). A great amount of research indicated the correlation between diabetes and the male infertility. It has been emphasized in many recent studies that biochemical and histopathological changes occur in the male genital system and that they may result in infertility (Nna *et al.*, 2021; Buhur *et al.*, 2023; Kumar *et al.*, 2023; Huang *et al.*, 2024). The mitogen-activated protein kinase (MAPK) family plays a role in the regulation of many cell signals related to embryogenesis, cell proliferation and apoptosis (Li *et al.*, 2022). c-Jun N-terminal kinase (JNK), a member of MAPKs, is an important transcription factor. JNK is an important transcription factor involved in the transmission of signals such as proliferation, differentiation and apoptosis from the cell cytoplasm to the cell nucleus (Grynberg *et al.*, 2017; Li

et al., 2022). It has been shown in some studies that JNK inhibition reduces apoptosis (Yu *et al.*, 2024; Gagnani *et al.*, 2025). One of the important pathways in the regulation of apoptosis is activated by "endoplasmic reticulum (ER) stress". Misfolding of some proteins produced in ER that results in accumulation of proteins and ER stress stimulates apoptosis via C/EBP homologous protein (CHOP), JNK, and caspase 12 (Kizilay *et al.*, 2021; Sun *et al.*, 2024). Although there is an increased number of studies to understand increasing apoptosis in diabetic testicular tissue, we are of the opinion that there is still a need for many studies to elucidate all the details. The purpose of this study is to evaluate the effects of JNK inhibition on the mechanism of apoptosis caused by ER stress and the expression of some key proteins in diabetic male rat testes. Thus, we aim to expand our current knowledge of the literature by creating new perspectives on the treatment of diabetes complications.

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MATERIAL AND METHOD

This study was approved by the Animal Experiments Ethics Committee of Trakya University (TUHADYEK 2018/13). The animals were fed standard rat chow (21 % protein) and water ad libitum. The environment was maintained at 22.1 °C with a 12-hour light/12-hour dark cycle. All procedures followed ethical standards, and informed consent was obtained from all animal handling personnel. Three-month-old male Wistar albino rats weighing 250–350 g were split into 3 groups: Group C (control group treated with 0.1M citrate buffer; n=9), group D (type I diabetes group treated with a single dose of 55 mg/kg streptozotocin (STZ); n=9) (Buhur *et al.*, 2023), and group I (inhibition group; after 55 mg/kg STZ injection, 15 mg/kg SP600125 administered once daily for 4 days n=9). All animals were sacrificed on the 30th day. In our study, blood glucose levels were measured with a glucometer (IME-DC, Oberkotzau, Germany) to confirm type I diabetes (above 250 mg/dl). Blood samples were taken from the tail vein at the beginning of the experiment, on the 2nd day, and the 30th day (sacrifice day) following STZ administration. Body weights were weighed and recorded at specific times (at the beginning of the experiment and the end of the experiment). At the end of the experiment, the testis of animals were removed under anesthesia (10 mg/kg xylazine and 50 mg/kg ketamine) and then all animals were sacrificed. For light microscopy examinations, the testes were fixed in 10 % formalin, passed through a graded series of alcohols, and embedded in paraffin (Merck Millipore, Darmstadt, Germany) and hematoxylin and eosin (H-E) staining was performed. Mean seminiferous tubule diameter (MSTD) was measured using an ocular micrometer (Sun *et al.*, 2024) Johnsen scoring was performed to evaluate the damage to the seminiferous tubules in the testicular tissue (Fu *et al.*, 2024).

Immunohistochemistry

After antigen retrieval in citrate buffer pH 6.0 (Invitrogen Carlsbad, CA) using microwave, sections were incubated in H₂O₂ (Abcam, Cambridge, UK) and blocking solution (Invitrogen). Antibody dilution solution (Invitrogen) prepared with rabbit polyclonal active caspase-3 (NB100-56113) and caspase-12 antibodies (NBP2-24518) (diluted at 1:300, 1:500, respectively; Novus Biologicals, Colorado, USA) and rabbit polyclonal phospho-SAPK/JNK (Thr183/Tyr185) (81E11) and CHOP (D46F1) antibodies (diluted at 1:100, 1:300, respectively; Cell Signaling Technology, Massachusetts, USA) was kept at 25 °C for 1 h. Sections were incubated with secondary antibodies (Invitrogen) and HRP-streptavidin for 10 min. DAB (Invitrogen) was used as chromogen, and hematoxylin counterstaining was

performed. Active caspase-3 and p-JNK immunoreactivities were scored as the number of immunopositive cells/1000 cells/ per slide (Li *et al.*, 2014). The data of this study were evaluated as a double blinded randomized controlled trial.

Western Blotting

Testis samples were incubated in RIPA lysis buffer (ChemCruz, Netherlands) for 30 min and centrifuged. The amount of protein in the supernatant was measured using a nanodrop device (Optizen NanoQ, Mecasy, Korea). Protein samples were run on NuPAGE Novex 4-12 % Bis-Tris gel (Invitrogen). The gel was transferred to the nitrocellulose membrane using an iBlot 2 Gel Transfer Device (Life Technologies Inc.). Rabbit polyclonal caspase-12 (1:1000 dilution, Abcam), CHOP (1:500 dilution, Novus Biologicals), β -actin (1:10000 dilution, Novus Biologicals), and secondary antibodies were incubated for 2 h on the iBind™ Flex Western device (Thermo Fisher Scientific, MA, USA). Membranes were exposed to chemiluminescence (SuperSignal West Pico Plus, Thermo Scientific) for 5 min. Quantification of the immunoblot bands was performed using the Chemidoc™ MP Imaging System Biorad device. All band profiles were normalized to the β -actin band using Image J 1.48v software (Wayne Rasband, NIH, USA).

Statistical analysis

Statistical analyses of our study were performed using SPSS. Body weights, testicular weights, MSTD, and immunohistochemical data were compared by one-way ANOVA. Caspase-12 and CHOP western blot and Johnsen score results were evaluated by one-way ANOVA. In the case of a significant difference between the groups, the Tukey test was used to determine this difference.

RESULTS

At the end of the experiment, group D and group I had higher blood glucose levels than group C ($p < 0.001$, Fig. 1a). Group I blood glucose values decreased compared to group D ($p < 0.05$, Fig. 1a). When the body weights of all groups were measured before the sacrifice, the body weight values of group D and group I values were significantly decreased compared to group C ($p < 0.001$, Fig. 1b) The comparison body weight values of group D and group I revealed no significant difference ($p = 0.170$, Fig. 1b). After sacrifice, testes were weighed. Testicular weights in group D and group I were found to be statistically significantly decreased compared to group C ($p < 0.05$, Fig. 1c). Furthermore, the testicular weights of group D were found to be significantly decreased compared to group I ($p < 0.05$, Fig. 1c).

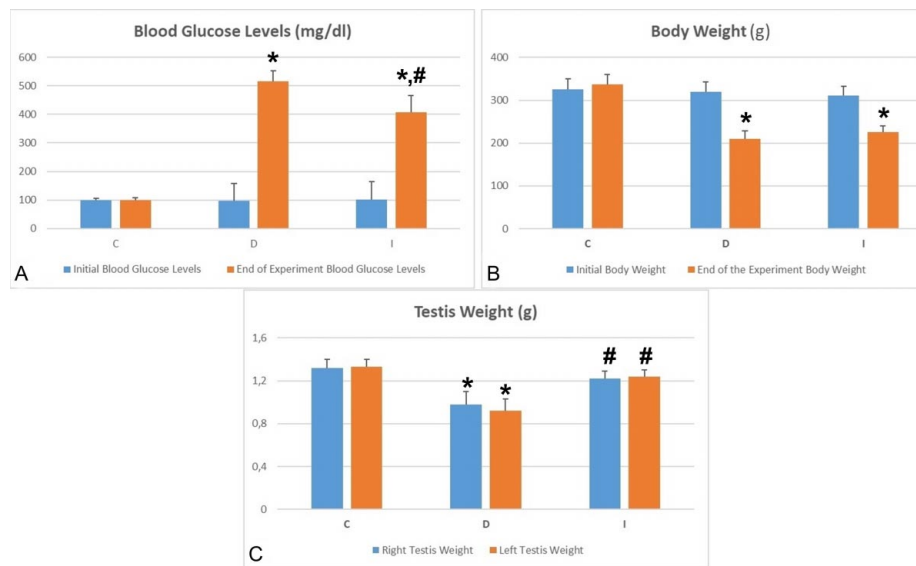


Fig. 1. Blood glucose levels (a), body weight (b), and testicular weight (c). *: Compared to group C, #: compared to group D, p: value <0.05 was considered significant.

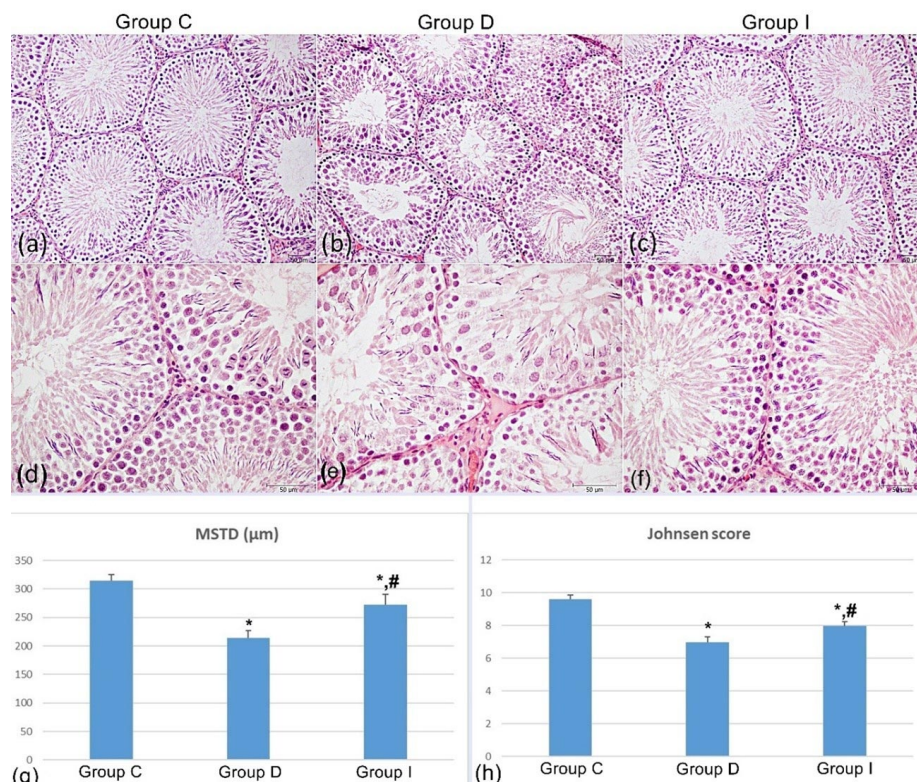


Fig. 2. Sections with H-E staining. MSTD and Johnsen score chart. Sections with H-E staining. MSTD and Johnsen score chart. Normal testicular structure is observed in group C. Control group x200 (a), Control group x400 (d). Testicular sections of group D showed arrested spermatogenesis, loss of germinal cells, reduced tubular diameter, and degenerated seminiferous tubules. Diabetic group x200 (b), Diabetic group x400 (e). The histological structure of group I testis was found to be similar to group C. Inhibitor group x200 (c), Inhibitor group x400 (f). Scale bar: 50 μm. MSTD chart (g) and Johnsen score chart (h). *: compared to group C, #: compared to group D, p-value <0.05 was considered significant.

Histological Results

The normal testicular structure characterized by group C showed regular seminiferous epithelium, interstitial areas, and spermatogenesis (Figs. 2a,d). Testicular sections of group D showed arrested spermatogenesis, loss of germinal cells, reduced tubular diameter, and degenerated seminiferous tubules. There was also vacuolization and atrophy in tubules (Figs. 2b,e). The histological structure of group I testis was found to be similar to group C (Figs. 2c,f). The MSTD values of group D and group I were statistically decreased compared to group C (both $p < 0.001$; Fig. 2g). However, the MSTD value of group I was statistically higher than that of group D ($p < 0.001$; Fig. 2g). We used the Johnsen scoring method to evaluate the histopathological changes in the seminiferous tubules. The Johnsen scores of group D and group I were significantly lower than those of group C (both, $p < 0.001$; Fig. 2h). In addition, group I values were significantly higher than group D values ($p < 0.001$; Fig. 2h). These results are parallel to our histopathological findings.

Endoplasmic Reticulum Stress-Induced Apoptosis Results

To understand the ER stress-related mechanism of cell death through apoptosis, we performed immunohistochemistry and western blotting analysis. Caspases are critical mediators of apoptosis in mammalian cells. One of the caspase family of proteases, caspase-12, is exclusive to the endoplasmic reticulum (ER) and is triggered by stress. It was found that during ER stress-induced apoptosis, activation of active caspase-3 rather than mitochondria-related caspase-9 causes activation of ER resident caspase-12 (Spencer & Finnie, 2020; Kizilay *et al.*, 2021; Li *et al.*, 2022). In our present study, active caspase-3 expression was significantly increased in group D and group I compared to group C ($p < 0.001$, $p = 0.021$, respectively), but group I values were statistically decreased compared to group D values ($p < 0.001$; Fig. 3g).

These results suggest that JNK inhibitors may be effective against ER stress-induced apoptosis. The results of p-JNK immunohistochemistry activite showed that the values in group D and I were higher than group C values (both, $p < 0.001$; Fig. 3h). However, p-JNK expression was significantly decreased in group I compared to group D ($p < 0.001$, Fig. 3h). Caspase-12 and CHOP immunopositive cells were significantly increased in group D and group I compared to group C (for caspase-12, Figs. 4a-c and for CHOP, 4d-f). Caspase-12 and CHOP immunopositive cells were statistically decreased in group I compared to group D (for caspase-12, Figs. 4a-c and for CHOP, Figs. 4d-f). Caspase-12 and CHOP immunoblotting expressions were statistically decreased in group I compared to group D (for caspase-12 and CHOP $p < 0.001$; Figs. 4i,j). These data show that our immunoblotting and immunohistochemistry caspase-12 and CHOP results are consistent with each other.

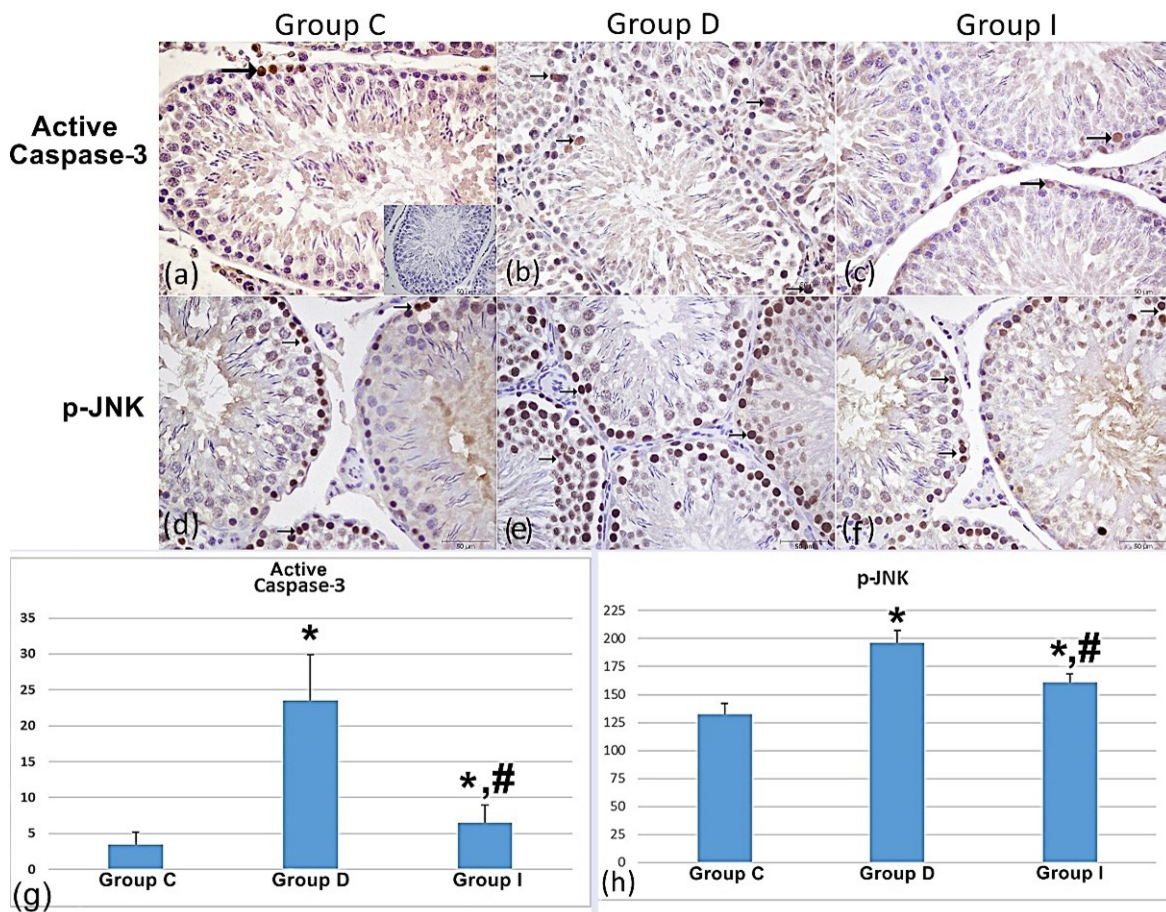


Fig. 3. Active caspase 3 and p-JNK immunohistochemical staining and scores. Control group x200 (a), Diabetic group x200 (b), Inhibitor group x200 (c), Control group x400 (d), Diabetic group x400 (e), Inhibitor group x400 (f), The small square depicts negative control. Active caspase 3 immunoreactivity (a-c) and P-JNK immunoreactivity (d-e). Active caspase 3 (g) and p-JNK (h) immunoscore. *: compared to group C, #: compared to group D, p-value < 0.05 was considered significant.

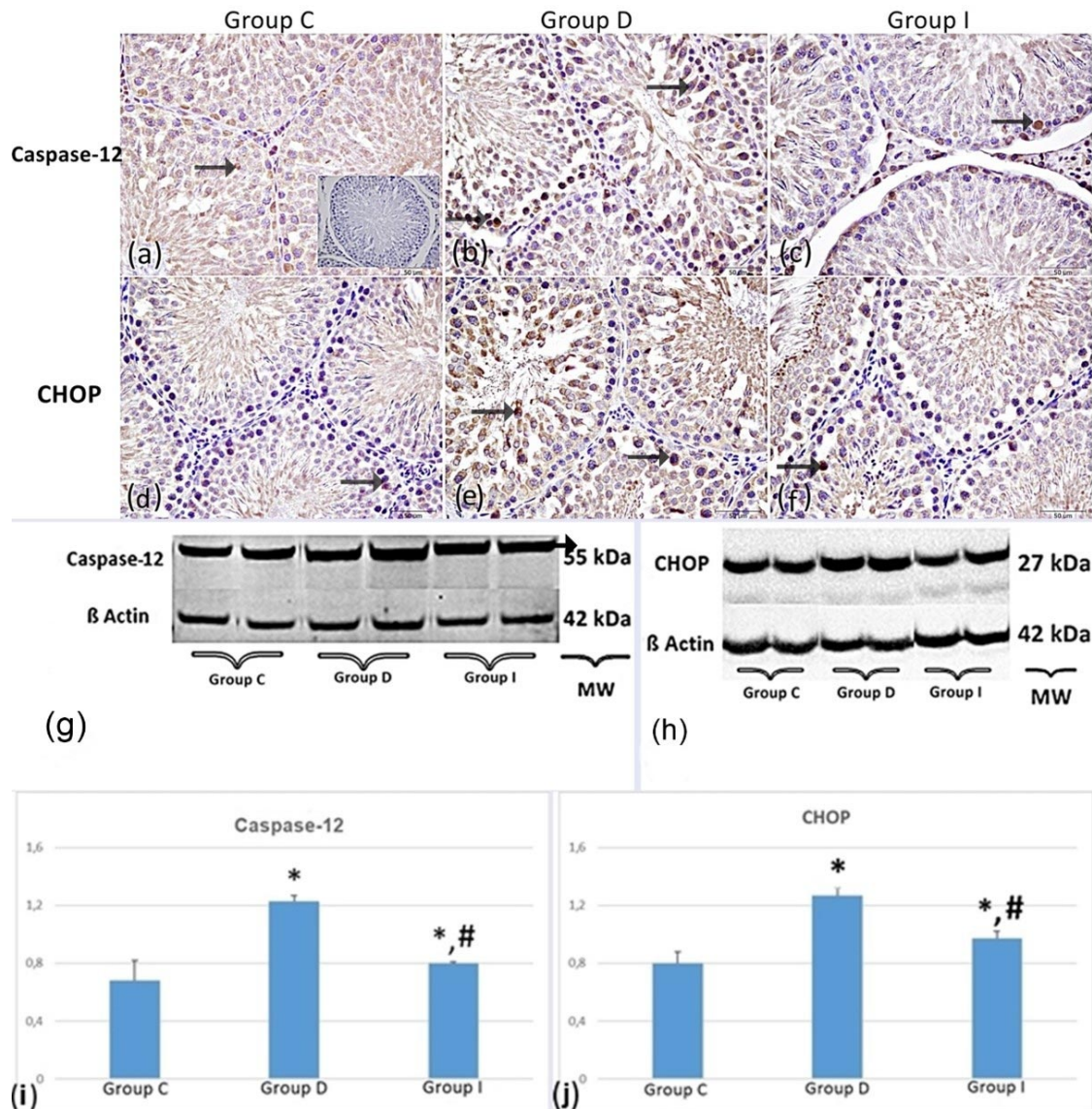


Fig. 4. Caspase 12 and CHOP immunohistochemical staining and western blotting. Control group x400 (a,d), Diabetic group x400 (b,e), Inhibitor group x400 (c,f). Caspase 12 immunoreactivity (a-c) and CHOP immunoreactivity (d-f). Counterstained with hematoxylin. Immunopositive reactivity (Æ). Scale bar: 50 µm. Caspase 12 western blot bands and graph of analysis (g, i). CHOP western blot bands and graph of analysis (h, j). *: Compared to group C, #: compared to group D, p-value <0.05 was considered significant.

DISCUSSION

Diabetes is a major systemic disease with many complications and is well-known to cause male infertility in diabetic men (Graziani *et al.*, 2024). In our study, increased blood glucose levels in the diabetic group were also observed to decrease in the inhibition group. Zhang *et al.* (2018) reported that SP600125 administration to diabetic subjects did not change blood glucose levels. We believe that this difference is due to the dosage and duration of application. In parallel with our study, many studies have found that

diabetes causes weight loss in the body (Hein *et al.*, 2019; Sun *et al.*, 2024). In our study, JNK inhibition with SP600125 did not cause a statistically significant decrease in body weight. Another study also reported that JNK inhibition did not prevent body weight loss caused by diabetes (Lim *et al.*, 2011). In our study, histopathological sections of diabetic testicular tissues showed undulations in the basal membranes, germinal cells in the tubular lumen, cellular vacuolization, narrowing of the seminiferous tubules, and disorganization

of the germinal epithelium. These histopathological findings are consistent with previous studies (Li *et al.*, 2014; Kizilay *et al.*, 2021; Buhur *et al.*, 2023; Fu *et al.*, 2024). Our study demonstrated that the histopathological changes in the testicular tissue were greatly reduced in group I sections and that JNK inhibition had a positive effect on the MSTD and Johnsen scores. This study is the first in the literature to demonstrate the effects of JNK inhibition on diabetic testicular tissue. However, JNK inhibition has been shown in other studies to improve various diabetes-induced damages (Wang *et al.*, 2023). A previous study reported that JNK inhibition prevented many histopathological changes in diabetic kidney tissue, and JNK inhibitors may be a new therapeutic agent for diabetic nephropathy (Zhang *et al.*, 2018). Salah *et al.* (2022) reported that active caspase-3 expression was increased by diabetes, which is consistent with our findings of increased active caspase-3 levels in the diabetic group. There was a significant decrease in active caspase-3 activation in the group I compared to the group D. It is known that increased oxidative stress caused by diabetes is responsible for JNK-mediated cell death. In our study, p-JNK expression was significantly increased in group D compared to group C. In addition, p-JNK activation was significantly decreased in group I compared to group D. Pan *et al.* (2013), found that JNK inhibition reduced diabetic renal pathological findings. ER stress increases the expression of caspase-12 and CHOP in diabetic testis tissue (Shi *et al.*, 2020; Kizilay *et al.*, 2021). A previous study reported that JNK inhibition reduced caspase-12 and CHOP activations in ER stress induced by myocardial ischemia-reperfusion (Zhang *et al.*, 2017). In our study, the expression of caspase-12 and CHOP decreased significantly in group I.

CONCLUSION

In our study, the decreased expression of caspase-12 and CHOP in group I suggests that JNK inhibition is an effective target against ER stress, effectively mitigating the severity of diabetes-induced testicular damage. This study focused on the effect of the JNK inhibitor SP600125 on ER stress in diabetic testis tissue. Administration of the JNK inhibitor significantly prevented diabetes-induced ER stress and apoptosis. Recent studies have shown that there is a link between increased JNK activation and the development of various diseases and that JNK inhibitors may be effective in preventing disease. We believe that this study, which is the first to use a JNK inhibitor against ER stress-induced apoptosis in diabetic testis tissue, will make a significant contribution to the literature.

Conflict of interest. The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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BAYRAM, S.; ERSOY, O.; DEVECI, E. & KIZILAY, G. La inhibición de la cinasa N-terminal de c-Jun atenúa el daño testicular diabético mediante la reducción del estrés del retículo endoplasmático. *Int. J. Morphol.*, 44(2):683-689, 2026.

RESUMEN: Las causas subyacentes de muchas complicaciones relacionadas con la diabetes son bien conocidas. Sin embargo, las razones de las complicaciones relacionadas con la salud reproductiva masculina aún no están claras. La hiperglucemia altera el equilibrio entre oxidantes y antioxidantes, causando daño celular, especialmente estrés del retículo endoplasmático. El estrés del retículo endoplasmático, desencadenado por la acumulación de proteínas en su lumen, provoca apoptosis mediante la activación de diversas vías. La cinasa N-terminal de c-Jun (JNK) es una proteína clave en enfermedades sistémicas como la diabetes, y SP600125 es un inhibidor de JNK ampliamente utilizado. Este estudio se centra en determinar si la inhibición de JNK mediante SP600125 previene el daño testicular diabético al reducir el estrés del retículo endoplasmático (RE). En nuestro estudio, los animales se dividieron en tres grupos: grupo control, grupo diabético y grupo de inhibición de JNK. Se midieron los niveles de glucosa en sangre, el peso corporal y testicular, y el diámetro de los túbulos seminíferos. Los túbulos seminíferos se evaluaron mediante la escala de Johnsen en secciones teñidas con hematoxilina y eosina. Se evaluó la expresión proteica de caspasa 3, fosfo-JNK (p-JNK), caspasa 12 y CHOP. El grupo de inhibición presentó una disminución significativa de los valores de caspasa-3 activa, p-JNK, caspasa-12 y CHOP, así como de los niveles de glucosa en sangre, y un aumento del peso corporal y testicular, del diámetro de los túbulos seminíferos y de la puntuación de Johnsen, en comparación con el grupo diabético. La inhibición de JNK mejoró significativamente el daño histopatológico en el tejido testicular al prevenir el estrés del RE y la apoptosis inducidos por la diabetes.

PALABRAS CLAVE: Diabetes mellitus; Inhibidores de la proteína quinasa; Estrés del retículo endoplasmático; Apoptosis; Testículo.

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