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Research

Assessment of Liver Damage in an Experimental Model of Streptozotocin-Induced Diabetes in Sprague Dawley Rats: Focusing on Morphological and Oxidative Stress Status

Sprague Dawley Sıçanlarında Streptozotosin ile İndüklenmiş Deneysel Diyabet Modelinde Karaciğer Hasarının Değerlendirilmesi: Morfolojik ve Oksidatif Stres Durumuna Odaklanma

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ABSTRACT

Objective: Diabetes mellitus (DM) is a widespread metabolic disorder that causes severe complications, including damage to various organs. The liver, a pivotal organ involved in metabolic regulation, is particularly vulnerable to diabetic injury. This study aimed to investigate the effects of diabetes on the liver, using streptozotocin (STZ)-induced diabetic model in Sprague Dawley rats.

Methods: Twelve male rats were divided into control and diabetic groups. Diabetes was induced via intraperitoneal injection of a single dose of STZ (55 mg/kg), and after eight weeks, the rats were sacrificed, and the liver tissues were collected for analysis of histological changes, apoptosis, and oxidative stress markers.

Results: Histological evaluations demonstrated significant alterations in diabetic liver tissue, characterized by hepatocyte degeneration, fibrosis, and cellular swelling. Immunohistochemical analysis revealed elevated active caspase-3 expression, indicating increased apoptosis in diabetic livers. Additionally, the analysis of oxidative stress markers revealed a significant increase in H_2O_2 levels, while superoxide dismutase activity remained unchanged, suggesting an oxidative imbalance.

Conclusion: These findings confirm that diabetes leads to liver damage through mechanisms including apoptosis, fibrosis, and oxidative stress, emphasizing the significance of therapeutic approaches targeting these pathways. In this respect, future research should focus on these mechanisms in other DM models and include additional liver injury biomarkers to better understand the progression of diabetic liver disease.

Keywords: Diabetes, liver damage, morphologic evaluation, apoptosis, oxidative stress

ÖZ

Amaç: Diabetes mellitus (DM), çeşitli organ hasarları da dahil ciddi komplikasyonlara neden olan yaygın bir metabolik hastalıktır. Metabolik aktivitelerin düzenlenmesindeki rolüyle önemli bir organ olan karaciğer, diyabetik hasara karşı oldukça hassastır. Bu çalışmada, Sprague Dawley sıçanlarında streptozotosin (STZ) ile indüklenen diyabet modeli kullanılarak diyabetin karaciğer üzerindeki etkilerinin araştırılması amaçlandı.

Gereç ve Yöntem: On iki erkek sıçan kontrol ve diyabetik gruplara ayrıldı. İntraperitoneal tek doz STZ (55 mg/kg) enjeksiyonu ile diyabet oluşturuldu ve sekiz hafta sonunda hayvanlar sakrifiye edildi ve sonrasında karaciğer dokuları histolojik değişiklikler, apoptoz ve oksidatif stres belirteçleri açısından değerlendirildi.

Bulgular: Histolojik değerlendirmeler diyabetik karaciğer dokusunda hepatosit dejenerasyonu, fibrozis ve hücresel şişme ile karakterize önemli değişikliklerin olduğunu göstermiştir. İmmünohistokimyasal analiz, aktif kaspaz-3 ekspresyonunun dolayısıyla diyabetik karaciğerlerde apoptozun arttığını ortaya koymuştur. Ek olarak, oksidatif stres belirteçlerinin analizi, H_2O_2 düzeylerinde önemli bir artış olduğunu diğer taraftan süperoksit dismutaz aktivitesinin değişmediğini göstermiştir. Bu durum oksidatif stres durumunda bir dengesizlik olduğunu düşündürtmüştür.

Sonuç: Bu sonuçlar, diyabetin apoptoz, fibrozis ve oksidatif stres gibi mekanizmalar yoluyla karaciğer hasarına yol açtığını ve bu yolları hedef alan terapötik yaklaşımların önemini vurgulamaktadır. Bu bağlamda, gelecekteki araştırmalar diğer DM modellerinde bu mekanizmalara odaklanarak diyabette karaciğer patolojilerine bağlı hastalıkların ilerleyişini daha iyi anlamak ve takip etmek için yeni hepatik hasar biyobelirteçleri içermelidir.

Anahtar Kelimeler: Diyabet, karaciğer hasarı, morfolojik değerlendirme, apoptoz, oksidatif stres

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INTRODUCTION

Diabetes mellitus is a significant global health issue, affecting millions worldwide and leading to serious complications in multiple organ systems (1). The disease is characterized by chronic hyperglycemia, which stems from either insufficient insulin production or the inability of cells to respond properly to insulin (2). One key mechanism linking diabetes to cellular and tissue damage across multiple organs is oxidative stress (3). Oxidative stress is the result of disruption of the balance between the antioxidant defence of the body and the production of reactive oxygen species (ROS). In diabetes, hyperglycemia contributes to increased ROS production through several mechanisms, such as glucose autoxidation, activation of protein kinase C, and the buildup of advanced glycation end products (3). These processes bring about mitochondrial dysfunction and an overproduction of free radicals, overwhelming the body's natural antioxidant defenses (4). This oxidative imbalance is not merely a consequence of diabetes but is a driving force behind its complications. ROS can bring about destructive effects on DNA, proteins, and lipids, leading to cellular malfunction, apoptosis, inflammation, and morphological damage (4). These effects are evident in several organs and contribute to the progression of diabetic complications. For example, in the kidneys, oxidative stress plays a key role in diabetic nephropathy, where increased ROS causes glomerular injury, podocyte apoptosis, and tubulointerstitial fibrosis (5). Similarly, oxidative stress leads to vascular damage in diabetic patients, promoting endothelial dysfunction, smooth muscle cell proliferation, and the formation of atherosclerotic plaques, which increase the cardiovascular disease risk (6).

The liver is one of the organs most significantly affected by diabetes, playing a vital role in glucose regulation, lipid metabolism, and detoxification. It is essential to understand the extent of liver damage caused by diabetes, as it not only disrupts these vital functions but also contributes to the progression of systemic complications associated with the disease (7). In diabetic individuals, liver dysfunction is linked to several pathological processes, including insulin resistance, increased fatty acid accumulation, inflammation, and fibrosis. These alterations can further disrupt metabolic regulation, increase the risk of developing non-alcoholic fatty liver disease (NAFLD), cirrhosis, and hepatocellular carcinoma in diabetic patients (8). However, despite its pivotal role in maintaining metabolic balance, the liver is often underrepresented in research on diabetic complications. Elucidating the mechanisms underlying diabetes-induced liver damage, including histological changes, apoptosis, and oxidative stress, is critical for developing therapeutic strategies to mitigate these harmful effects.

In this research, our main aim is to investigate the effects of diabetes on the liver using an experimental model of streptozotocin (STZ)-induced diabetes in Sprague Dawley rats. STZ is a compound that selectively destroys pancreatic β-cells, resulting in hyperglycemia and is commonly employed in experimental diabetes models (9). We explore the liver's response to hyperglycemia by administering a single intraperitoneal injection of 55 mg/kg STZ, focusing on histological changes, apoptosis, and oxidative stress markers. Understanding these hepatic alterations is crucial for identifying the cellular and molecular pathways involved in liver damage caused by diabetes and may ultimately assist in developing targeted therapies to reduce liver-related complications in diabetic patients.

METHODS

This study was conducted using experimental animals, and no patient-related biological material was utilized. Therefore, patient approval was not required.

Animal Model of Diabetes Mellitus

Animal experiments were carried out after obtaining the necessary ethical approval from the Bezmialem Vakıf University Animal Experiments Local Ethics Committee (approval no: 1294-1, date: 21.10.2024). Twelve male Sprague Dawley rats, aged 10-12 weeks and weighing between 350-450 grams, were kept in a controlled environment with a temperature of 20±2 °C, humidity levels of 45-55%, and a 12-hour light-dark cycle. They had free access to standard laboratory chow and water. Six randomly selected rats were given intraperitoneal injections of 55 mg/kg STZ (STZ; Sigma S0130) dissolved in sodium citrate buffer (SCB) (SCB; pH 4.5, 0.1 M) to induce type 1 diabetes (T1D), while the other six rats received SCB alone and served as the control group. Blood glucose levels (BGLs) were regularly monitored with a glucometer, and the rats with BGL exceeding 250 mg/dL were considered diabetic. At the end of the 3rd day following the STZ injection, all the rats were hyperglycemic (BGL >250 mg/dL). After 8 weeks, all rats were euthanized under general anesthesia induced by ketamine and xylazine.

Histological Analysis

After the animals were sacrificed, liver samples were collected, cut into small pieces, and prepared for light microscopic evaluations. The tissues were placed in 10% neutral buffered formalin for fixation and after 24 hours, they were dehydrated through the increasing alcohol series (70%, 90%, 96%, and 100%) before being cleared in toluene.

The samples were then embedded in paraffin, and 4 µm-thick sections were cut. These sections were deparaffinized, rehydrated through a descending alcohol series (100%, 96%, 90%, and 70%), and placed in distilled water. The slides were stained with hematoxylin and eosin (H&E) and Masson's trichrome stains to assess morphological changes and fibrosis in the tissue, respectively. The preparations were evaluated with the Olympus BX43 microscope, and photographed with the Olympus SC100 camera system (10).

Immunohistochemical Analysis

Following rehydration, antigen retrieval was executed with citrate buffer (6.0 pH) in a microwave for 20 min. The sections were washed with phosphate buffered saline (PBS) and the sections were treated with 3% hydrogen peroxide for 10 min at room temperature. After another round of PBS wash, a blocking agent (Thermo Scientific TP-125-HL) was applied for 6 min. Subsequently, the sections were incubated overnight at 4 °C with 1 µg/mL active caspase-3 (Thermo Fisher, MS-1123). After washing with PBS, biotinylated secondary antibody solution (Thermo Scientific TP-125-HL) was applied to the preparations for 10 minutes. After washing again with PBS, they were incubated with streptavidin peroxidase solution (Thermo Scientific TP-125-HL) for 10 minutes. Finally, the immune reaction was made visible with 3-amino-9-ethylcarbazole chromogen application (Thermo Scientific TA-125-HA). The preparations were investigated with the Olympus BX43 microscope and photographed with the Olympus SC100 camera system. To quantify the immune reaction, a 4-point scoring system was used, where 0 indicated no staining, 1 represented positive staining in less than 30% of cells per high-power field (40X), 2 indicated positive staining in 30% to 70% of cells, and 3 represented positive staining in more than 70% of cells per high-power field (11).

Evaluation of Oxidative Stress Status

The liver samples weighing approximately 20 mg were rinsed with cold PBS and homogenized in 180 uL PBS with a tissue lyser at 4 °C for 2.5 minutes at 50 oscillations. Then the samples were centrifuged at 4000 revolutions per minute for 10 min at 4 °C to remove insoluble material. The supernatant was collected and kept on ice for detection. At this point, the protein concentrations of the supernatant were assessed with a bicinchoninic acid assay (Thermo Scientific, 23225 and 23227). For analysis of total-superoxide dismutase (T-SOD) activity, 1 mL of working buffer solution was mixed with 0.07 mL of sample, and double distilled water, to set sample and control tubes, respectively. Then, 0.1 mL of nitrosogenic agent, 0.1 mL of substrate solution, and 0.1 mL of enzyme stock working solution were added into each tube, fully mixed with a vortex mixer, and incubated at 37 °C for 40 min. In the following stage, 2 mL of chromogenic agent was added into each tube and fully mixed, and kept for 10 minutes at room temperature. Optical density (OD) values of each tube were measured at 550 nm in a quartz cuvette with a 1 cm optical path, following setting zero with double distilled water. SOD concentration was calculated using the following formula: T-SOD activity (U/mL)=i/50% x V1/V2 x f; where i is the inhibition ratio calculated by the formula (ODcontrol-ODsample)/ODcontrol x 100%; V1 is the total volume of reaction solution (mL); V2 is the volume of sample added (mL); f is the dilution factor of concentration of protein (Cpr) is the concentration of protein in the sample (g prot/L).

For determination of the concentration of H_2O_2, 1 mL of buffer solution was added to 5 mL Eppendorf tubes and incubated at 37 °C for 10 min. In the following: 0.1 mL of double distilled water, 0.1 mL of 60 mmol/L H_2O_2, and 0.1 mL of sample were separately added to the tubes to prepare the blank, standard and sample tubes, respectively. 1 mL of ammonium molybdate reagent was added to each tube prepared in the previous step, and the contents were mixed thoroughly. The spectrophotometer was set to zero with double-distilled water, and then the OD value of each tube was measured at 405 nm with a 1 cm optical path quartz cuvette. H_2O_2 content of the sample was calculated by using the following formula: H_2O_2 content (mmol/L)=ΔA1/ΔA2 x C x f ÷ Cpr. Where ΔA1: ODsample-ODblank; ΔA2: ODstandard-ODblank; C: The concentration of H_2O_2 standard, 60 mmol/L; f: The dilution factor of the sample before the test; Cpr: the concentration of protein in the sample (g prot/L).

Statistical Analysis

Statistical analyses were executed using SPSS version 20.0 (IBM Corp., Armonk, NY, USA). Data were presented as mean ± standard error. The Shapiro-Wilk test was performed to assess normality. For data that are normally distributed, one-way ANOVA and post hoc Tukey tests were performed to compare group means. For non-normally distributed data, the Kruskal-Wallis test was used. A p-value of less than 0.05 ($p<0.05$) was considered statistically significant.

RESULTS

Histological Evaluations

H&E staining of liver sections from control rats showed that the liver has a normal lobular architecture, characterized by a central vein with hepatic cords extending from it, separated by well-defined blood sinusoids. The portal tracts, located

at the periphery of the hepatic lobules, were composed of the typical triad: branches of the portal vein, hepatic artery, and bile duct. Hepatocytes appeared large and polyhedral, with slightly eosinophilic granular cytoplasm. They had rounded euchromatic nuclei with prominent nucleoli, and some cells were observed to be binucleated (Figure 1a). In contrast, liver sections from diabetic rats revealed significant histopathological alterations. The hepatic parenchyma was disorganized, with evident dilation and congestion of the central veins and hepatic sinusoids. Hepatocytes exhibited degenerative changes including cellular disorganization and vacuolization. In some sections, there were focal areas of fibrosis accompanied by cellular proliferation. Furthermore, shrunken pyknotic nuclei were noted in some of the hepatocytes along with intense eosinophilic cytoplasm in diabetic conditions, all of which indicate apoptosis (Figure 1b). On the other hand, Masson's trichrome staining, which highlights collagen deposition in light blue, demonstrated that liver sections from diabetic rats displayed notable fibrosis, particularly prominent around the central veins and at the peripheries of the portal triads (Figure 1c and 1d).

The liver samples of two diabetic rats displayed cystic dilations of ductules which are characterized by biliary-like epithelium, surrounded by increased dense fibrotic tissue (Figure 2).

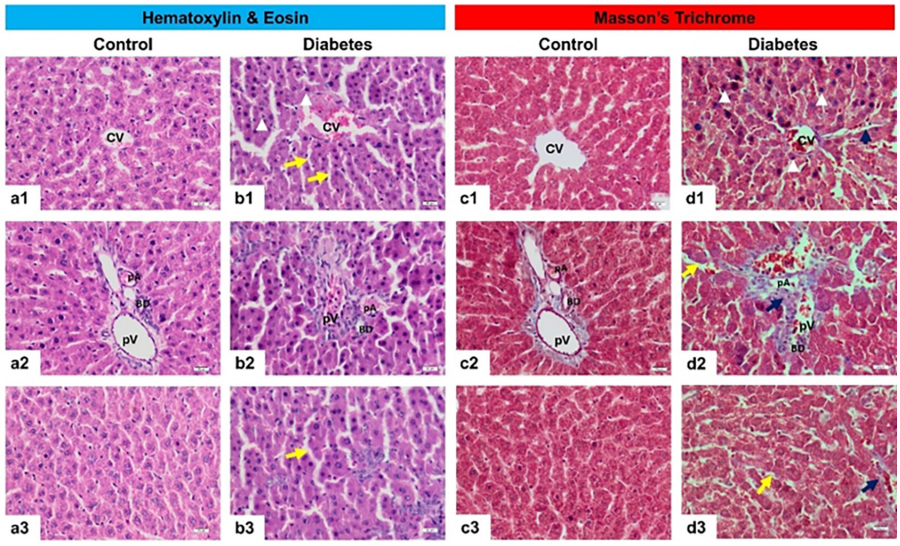

Figure 1. **(a,b)** Representative figures for hematoxylin & eosin and **(c,d)** Masson's trichrome staining. Central vein (CV), portal artery (pA), portal vein (pV), bile duct (BD), dilated sinusoidal capillaries (yellow arrow), pyknotic nuclei (white arrowhead) and fibrosis (purple arrow)

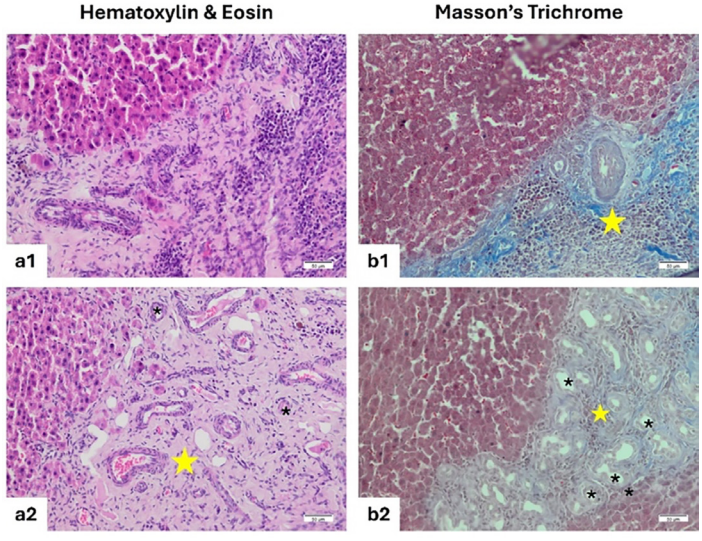

Figure 2. **(a)** Representative figures for the cystic dilations of ductules stained with hematoxylin & eosin and **(b)** Masson's trichrome. Cystic dilations of ductules (asterisk) were surrounded by increased dense fibrotic tissue (yellow star)

Immunohistochemical Analysis

Active caspase-3 expression was determined with immunohistochemical analysis. Semi-quantitative scoring of active caspase-3 staining showed that diabetes significantly increased the apoptotic death of hepatocytes in comparison to the control group (Figure 3).

Evaluation of Oxidative Stress Status

The oxidative stress status of the obtained liver tissue samples was determined by the spectrophotometric analysis of SOD activity and H_2O_2 concentration. It was found that there was no statistical difference for the SOD activity between the control and diabetes groups, while there was a statistically significant increase noted for the H_2O_2 level of the diabetes group, compared to that of the control group (Figure 4).

DISCUSSION

The findings of this study contribute to an increasing body of evidence on the role of diabetes in liver damage, with a particular emphasis on oxidative stress, histopathological alterations, and apoptosis using an STZ-induced diabetes model in Sprague Dawley rats. Our results showed that diabetes led to significant histopathological alterations in the liver, increased apoptosis as evidenced by active caspase-3 expression, and increased oxidative stress, particularly reflected by elevated H_2O_2 levels. These results are well aligned with the previous research on diabetic hepatopathy and further reinforce the detrimental impact of hyperglycemia and oxidative stress on hepatic tissue.

Histologically, liver sections from diabetic rats exhibited notable alterations, including hepatocyte degeneration, cellular swelling, and fibrotic changes. These observations are consistent with earlier studies that have shown structural disorganization of liver tissue and fibrosis in diabetic models (7,12). Fibrosis, a recognized outcome of chronic liver injury and a key feature of diabetic liver damage, was observed in focal areas, particularly around central veins and portal triads. These results support the idea that hyperglycemia accelerates fibrotic processes via pro-inflammatory and

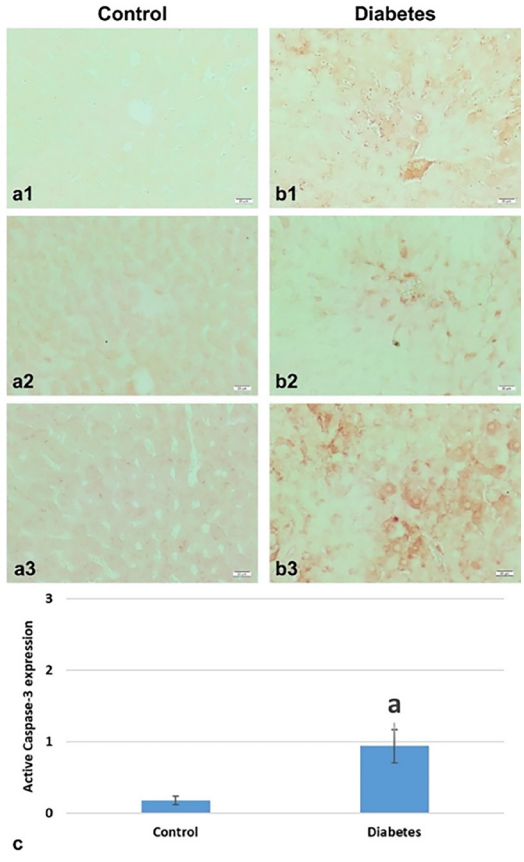

Figure 3. Representative figures for the immunohistochemical staining of active caspase-3 for control **(a)** and diabetes **(b)** groups. Graphical expression of semi-quantitative evaluation of active caspase-3 expression **(c)**. aP<0.005

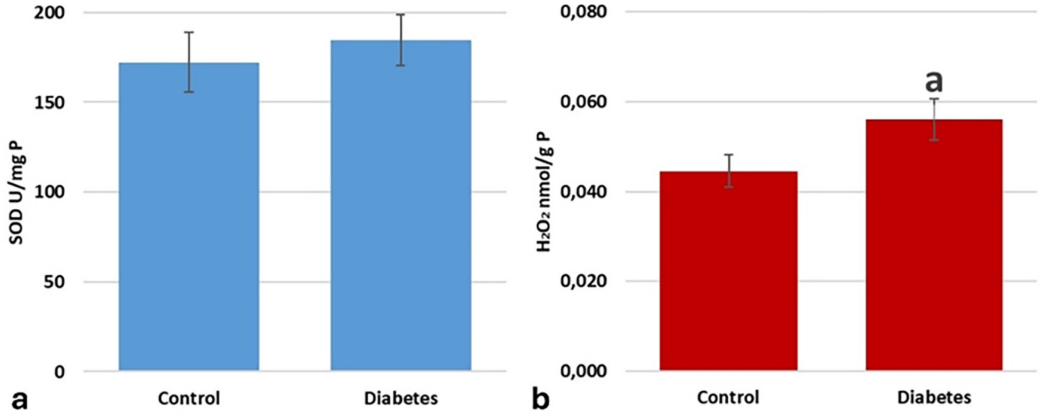

Figure 4. **(a)** Graphical representation for evaluation of superoxide dismutase activity (SOD) and **(b)** concentration of hydrogen peroxide (H_2O_2). aP<0.05

fibrogenic pathways (8,13). The presence of fibrosis in diabetic rats emphasizes the progression of liver injury, with potential implications for the occurrence of conditions such as NAFLD and cirrhosis (14). At this point, investigation of biochemical parameters including the levels of plasma alanine transaminase (ALT) and aspartate transaminase (AST) would have been complementary, where it was noted that ALT level was higher than that of AST in most of the NAFLD patients, while it was reversed in patients with alcoholic fatty livers (15). Additionally, the presence of cystic dilatations of ductules in certain diabetic liver samples, characterized by biliary-like epithelium and surrounding fibrosis, represents a novel finding that suggests early involvement of bile ducts in diabetic liver damage, warranting additional investigation.

Immunohistochemical analysis revealed increased active caspase-3 expression in diabetic liver samples, pointing to enhanced hepatocyte apoptosis. This is in line with previous research showing that oxidative stress induced by hyperglycemia triggers mitochondrial dysfunction, leading to apoptosis (6,16). In diabetic liver damage, it was shown that apoptosis has a significant role in the loss of functional hepatocytes and further impairment of liver function (17). The increased apoptotic activity noted in our study emphasizes the importance of targeting apoptosis in therapeutic strategies to alleviate liver damage in diabetic patients.

In terms of oxidative stress markers, the marked increase in the level of H_2O_2 in the diabetic group, along with unchanged SOD activity, suggests a persistent oxidative imbalance in diabetic liver tissue. As SOD is a crucial antioxidant enzyme that is responsible for converting superoxide radicals into less harmful species, however, stable SOD activity may indicate that antioxidant defences are insufficient to counteract the excessive production of ROS, including H_2O_2. This imbalance could explain the ongoing oxidative damage observed in liver tissue, resulting in apoptosis and fibrosis, as seen in this study. Previous studies have similarly reported increased oxidative stress markers in diabetic liver tissue, further supporting the idea that oxidative damage plays a central role in the pathogenesis of diabetic liver injury, including the promotion of collagen deposition and extracellular matrix remodelling (4,5).

Overall, our findings provide valuable insights into the mechanisms of liver damage in diabetes. The observed histopathological changes, fibrosis, increased apoptosis, and oxidative stress in diabetic rats underscore the complex nature of liver injury in diabetes. These results highlight the importance of targeting oxidative stress and apoptosis in therapeutic interventions to prevent or mitigate liver damage in diabetic patients. Future research should investigate the molecular pathways linking hyperglycemia, oxidative stress, and liver fibrosis, with the goal of developing targeted therapies to protect the liver from the detrimental effects of diabetes.

Study Limitations

A limitation of this study is the use of a single model of STZ-induced diabetes, which primarily mimics T1D. Future studies should include models of type 2 diabetes to assess whether similar hepatic alterations occur in the context of insulin resistance and metabolic syndrome, which are more common in the general population. Additionally, while we measured oxidative stress markers, a broader assessment of other ROS and antioxidant enzymes could provide a clearer picture of the oxidative balance in diabetic liver tissue. Furthermore, evaluation of certain liver injury biochemical markers like AST and ALT would provide a more comprehensive understanding of the pathophysiology of diabetes-associated hepatopathy.

CONCLUSION

In conclusion, this study demonstrated that diabetes leads to notable histopathological changes, increases apoptosis, and elevates oxidative stress in liver tissue, all of which contribute to fibrosis and hepatic dysfunction. These findings highlight the liver's vulnerability to diabetic injury and underscore the need for further research into therapeutic strategies to counteract oxidative stress and prevent diabetes-related liver complications.

ETHICS

Ethics Committee Approval: Animal experiments were carried out after obtaining the necessary ethical approval from the Bezmialem Vakıf University Animal Experiments Local Ethics Committee (approval no: 1294-1, date: 21.10.2024).

Informed Consent: Animal experimentation

FOOTNOTES

Authorship Contributions

Surgical and Medical Practices: S.Ö., Concept: S.Ö., Design: S.Ö., Data Collection or Processing: S.Ö., Analysis or Interpretation: S.Ö., M.K., Literature Search: S.Ö., Writing: S.Ö., M.K.

Conflict of Interest: No conflict of interest was declared by the authors.

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