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Protective Effect of Curcumin Against Pancreatic Islet Injury in Streptozocin Induced Type 2 Diabetic Rats: An Experimental Study

Tip 2 Diyabetik Sıçanlarda Kurkuminin Streptozosin Kaynaklı Pankreatik Adacık Hasarına Karşı Koruyucu Etkisi: Deneysel Bir Çalışma

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ABSTRACT Objective: The aim of study of was to determine the damage caused by streptozocin (STZ)-induced Type 2 diabetes in pancreatic islet in rats and the effect of curcumin on this damage. **Material and Methods:** A total of 32 (250-320 g) Wistar albino male rats were used. Rats were randomly divided into 4 groups as Control (C), Diabetes (DM), Curcumin (CUR), and Diabetes+Curcumin (DM+CUR) (n=8). Histopathological, stereological and immunohistochemical analyzes were used to determine the damage caused by type 2 diabetes in the pancreatic tissue and the effect of curcumin on this damage. **Results:** In the histopathological evaluation of pancreatic tissues, in pancreatic sections of DM group rats, the islets were smaller and their borders were irregular, and degenerative and necrotic changes were observed in the cells. In the DM+CUR group, it was determined that these degenerative changes in the islets of Langerhans and cells were alleviated. In the stereological analysis, it was determined that the islet volume, the ratio of islets to the pancreas and the number of beta cells in the DM group were statistically significantly decreased compared to the other groups, and it was found to be higher in the DM+CUR group than in the DM group ($p<0.05$). In the immunohistochemical evaluation, the C and CUR groups showed similar staining with Ki67, whereas the staining was less in the diabetic group. In the diabetes group treated with curcumin, it was found that curcumin attenuated the diabetes-related Ki67 reduction. **Conclusion:** In this study, it was determined that curcumin reduced the damage in the islets and beta cells in the pancreas of rats with diabetes mellitus with STZ and provided a significant protection in the pancreatic tissue.

Keywords: Type 2 diabetes mellitus; curcumin; islets of Langerhans

ÖZET Amaç: Bu çalışmanın amacı, sıçanlarda streptozosin (STZ) ile indüklenmiş Tip 2 diyabetin, pankreas dokusunda oluşturduğu hasarı ve kurkuminin bu hasar üzerindeki etkisini belirlemektir. **Gereç ve Yöntemler:** Çalışmada toplamda 32 (250-320 g) Wistar albino erkek sıçan kullanıldı. Sıçanlar rastgele Kontrol (K), Diyabet (DM), Kurkumin (KUR) ve Diyabet+Kurkumin (DM+KUR) olmak üzere 4 gruba ayrıldı (n=8). Tip 2 diyabetin, pankreas dokusunda oluşturduğu hasar ve kurkuminin bu hasar üzerindeki koruyucu etkisini belirlemek için histopatolojik, stereolojik ve immünohistokimyasal analizler kullanıldı. **Bulgular:** Pankreas dokularında yapılan histopatolojik değerlendirmede, DM grubu sıçanlarının pankreatik kesitlerinde adacıkların küçüldüğü ve sınırlarının düzensiz olduğu, hücrelerde dejeneratif ve nekrotik değişiklikler olduğu görüldü. DM+CUR grubunda ise langerhans adacıklarında ve hücrelerde meydana gelen bu dejeneratif değişikliklerin hafiflediği belirlendi. Yapılan stereolojik analizlerde, DM grubundaki adacık hacminin, adacıkların pankreasa oranının ve beta hücrelerinin sayısının diğer tüm gruplara göre istatistiksel olarak anlamlı azaldığı, DM+CUR grubunda ise DM grubuna göre daha fazla olduğu tespit edildi ($p<0,05$). İmmunohistokimyasal değerlendirmede, K ve KUR grubunun Ki67 ile benzer boyanma gösterdiği, diyabetli grupta ise boyanmanın az olduğu gözlendi. Kurkumin ile tedavi edilen diyabet grubunda ise kurkuminin diyabetle ilişkili Ki67 azalmasını hafiflettiği tespit edildi. **Sonuç:** Bu çalışmada, STZ ile diyabet oluşturulmuş sıçanların pankreaslarındaki adacıklarda ve beta hücrelerinde meydana gelen hasarı kurkuminin indirgediği ve pankreas dokusunda önemli bir koruma sağladığı tespit edildi.

Anahtar Kelimeler: Tip 2 diabetes mellitus; kurkumin; Langerhans adacıkları

Diabetes mellitus (DM) is a chronic illness arising from a hereditary and/or acquired deficiency in insulin production that is increasing at an alarming rate and becoming a major health burden worldwide.[1] Type 2 DM (T2DM) is accompanied by chronically elevated blood glucose levels associated with disrup-

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tion of the inflammatory and oxidative state and dyslipidemia.[2] Although it is accepted as one of the most studied diseases, the search for an effective treatment continues for both pathophysiological mechanisms and complications.

It's critical to concentrate on specific medication targets when researching a novel diabetic treatment. The primary focus should be on regenerating pancreatic β-cells so that enough insulin can be released to keep blood glucose levels stable.[1] Herbal products that are effective in preventive β-cells from any injury can be used for this purpose.[3] Through various processes, numerous herbal medications, including their bioactive origines, have been proven to have a glucose-lowering impact.[4-6] These products can be assessed as therapeutic alternatives for diabetes therapy. It should be noted that many of these products have only been assessed for their preliminary efficacy, and more in-depth research is needed to evaluate them.

It is stated that many medicinal plants such as cinnamon, coriander, ginger, anise, cloves, turmeric, fenugreek, garlic, cumin, black pepper, curry and mustard, which are included in our daily diet are effective in blood glucose management.[3] Among these, one of the most studied in recent years is curcumin (CUR), which is obtained from the turmeric (*Curcuma longa*) plant. Many studies have shown that CUR has many biological activities such as antioxidant, anti-inflammatory, anticancer, anti-aging, antidiabetic, antimicrobial, wound healing.[7-10] In addition, in vivo and in vitro studies on curcumin and its derivatives have reported that although curcumin and its derivatives do not show cytotoxic effects for normal cells, they are cytotoxic for many cancer cell types.[11-13]

CUR has been demonstrated in numerous studies to be a natural antioxidant and anti-inflammatory agent that can diminish the effect of streptozocin (STZ) on oxidative stress in rats with experimental diabetes.[14,15] However, in order for CUR to be used clinically, more studies are needed to provide a clearer understanding of its mechanism of action, especially on the pancreas, which is directly related to DM.

Accordingly, in the present study, we aimed to investigate the damage caused by STZ-induced T2DM in pancreatic tissue in rats and the protection of CUR on this damage by using histopathological, stereological and immunohistochemical analyzes.

MATERIAL AND METHODS

ANIMALS

In this study, animal rights were protected by doing it in line with the Guidelines for the Care and Use of Laboratory Animals. This study was carried out with the permission of Ondokuz Mayıs University Animal Experiments Local Ethics Committee (date: April 20, 2018, no: 218/27). This study was carried out in conformity with the principles of the Helsinki Declaration. In the study, a total of 32 Wistar albino male rats (250-320 g) were taken from Ondokuz Mayıs University Experimental Animals Research and Application Center. During the study, rats were fed with ad libitum water under conventional conditions at 24±1°C ambient temperature for 12 hours in light and dark conditions.

EXPERIMENTAL PLAN

The rats were put into 4 groups at random as Control (C), Diabetes (DM), Curcumin (CUR), and Diabetes+Curcumin (DM+CUR) (n=8). In order to induce diabetes in rats in DM and DM+CUR groups, a single dose of 50 mg/kg STZ (BioShop STR 201.1) was dissolved in 0.01 M citrate buffer (pH: 4.5) and administered intraperitoneally (ip).[16] Three days later, fasting blood glucose values were measured in blood samples taken from the tail vein of these rats with a glucometer (Contour TS Bayer). Animals with a fasting blood glucose level of 250 mg/dL and above were included in the study.[17] CUR and DM+CUR groups were given 60 mg/kg/day curcumin (Sigma Aldrich, Australia) dissolved in corn oil by oral gavage once a day during the 14-day experiment.[18] The selection was applied according to the dose that was informed to have a protecting effect via examining studies that curcumin has an effect on DM. No treatment was applied to the C groups. At the end of the 14-day experiment, pancreatic tissues were removed by intracardiac perfusion under ketamine anesthesia in all rats. The removed pancreas was placed in cold saline solution and weighted after freeing from adi-

pose tissue. Tissues were fixed in 10% buffered neutral formalin.

HISTOPATHOLOGICAL STUDIES

After the removed pancreases were fixed, they were passed through a graded series of ethanol and xylol and embedded in paraffin. Hematoxylin-Eosin (H&E) staining was performed by taking 5 µm thick sections from the blocks. Samples were stained with aldehyde fuchsin to reveal the β-cell effect of DM. Sections stained with the aldehyde fuchsin were counterstained with hematoxylin and light green/orange G. The histopathological evaluation of the samples was done semi-quantitatively under the light microscope. According to the severity of the damage; it was scored as 0 (normal), 1 (mild), 2 (moderate), and 3 (severe) (Table 1).

STEREOLOGICAL STUDY

From the obtained paraffin blocks, the first section was randomly selected, and approximately 10-15 sections of 5 micron thickness were taken from each piece at certain intervals, every 1/100. Sections were stained with H&E. In volume measurement, using the modified method of Cavalieri's principle, the volume ratio in the sections was measured with a dotted area ruler. Photographs were taken at x20 objective magnification using a Leica, DFC 450C & DM 2500 model light microscope, and their volumes and areas were calculated.

Formulas used in Cavalieri Volume Calculation:

Volume=Area x Thickness

Area=Total number of points x The area represented by the point

Ratio of Langerhans Islets volume to pancreatic volume=Total number of points per Langerhans Islets/Total number of points per pancreatic tissue.

The number of β-cells in an islet β-cells of the pancreas were counted in sections stained with aldehyde fuchsin in a 40 lens. The number of β-cells was evaluated by counting the nuclei of all positive cells within an islet in the area. A total of 30 islets were counted for each group.

IMMUNOHISTOCHEMISTRY STUDIES

Sections of 4 µm thickness were taken for immunohistochemical study from the samples, which were subjected to routine follow-up and later embedding. Monoclonal primary anti-Ki67 antibodies (1:100; Abcam, ab15580) were used for the detection of cellular proliferation of pancreatic islet cells. Staining was performed using the Ventana BENCHMARK GX automated immunohistochemistry staining device. Afterwards, the samples were washed in detergent water, passed through alcohol and xylol series, and covered with entellan. Immunohistochemical evaluation was performed under the light microscope.

STATISTICAL EVALUATION

The statistical analysis was carried out using the SPSS for Windows version 22.0. (IBM Corp., Armonk, New York, USA). The Kruskal-Wallis test, which is non-parametric, was employed to compare the groups. The non-parametric Mann-Whitney U-test was used to compare the 2 groups. When the results had a 95% confidence interval and a p 0.05, they were considered statistically significant.

RESULTS

HISTOPATHOLOGICAL EVALUATION

According to the results of histopathological studies performed in all groups, pancreatic sections of the C group were found to be large and the borders of Langerhans islets were regular (Figure 1A). No sig-

TABLE 1: Histopathological parameters scored in pancreatic tissue.*

	C (n=8)	DM (n=8)	CUR (n=8)	DM+CUR (n=8)
Contour irregularity in islets	0	3	0	1
Cytoplasmic vacuole	0	3	0	2
Pycnotic cells	0	3	0	2

*According to the severity of the damage; it was scored as 0 (normal), 1 (mild), 2 (moderate), and 3 (severe); C: Control; DM: Diabetes; CUR: Curcumin; DM+CUR: Diabetes+curcumin.

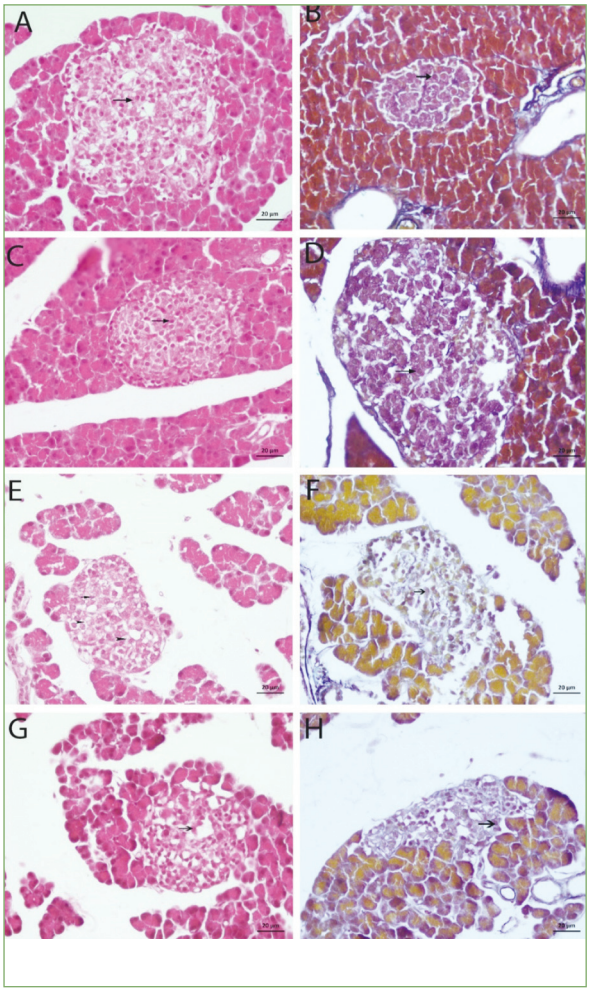

FIGURE 1: C group H&E **(A)**. Aldehyde fuchsin **(B);** C CUR group H&E **(C)**. The aldehyde fuchsin **(D);** DM group H&E **(E).** Aldehyde fuchsin **(F);** DM+CUR group H&E **(G).** The aldehyde Fuchsin **(H).** β cell (black arrow). Picnotic nucleus (short black arrow). Hydropic degeneration (arrow head).

nificant change was detected in the CUR group and was similar to the C group (Figure 1C). In the pancreatic sections of DM group rats, it was determined that the islets got smaller and there was a decrease in the number of β cells. Degenerative and necrotic changes were observed in the cells, and hydropic degeneration and degranulation were found in the cell cytoplasms (Figure 1E). In the diabetic group treated with CUR, improvement in Langerhans islet structures and an increase in cell number were detected. Degenerative and necrotic changes were observed to decrease in this group (Figure 1G) (Table 1).

According to the results of aldehyde fuchsin staining, the granules of β cells in the control group were strongly stained in blue-violet color (Figure 1B). Similar staining was observed in the CUR group with the control (Figure 1D). In the DM group, however, the staining was weak and indistinct, with a decrease in β cells (Figure 1F). On the other hand, an increase in purple-stained granules was observed in diabetic rats treated with curcumin compared to the diabetes group (Figure 1H).

STEREOLOGICAL EVALUATION

When pancreatic wet weights and pancreatic volumes of rats in all groups were compared, no statistically significant difference was observed between the groups in terms of these 2parameters ($p>0.05$) (Table 1). When the groups were compared in terms of islet volume, it was found that the islet volume in the DM group was less than in the other groups and this difference was statistically significant ($p<0.05$). There was a significant increase in islet volume in the DM+CUR group compared to the DM group ($p<0.05$). There was no difference in islet volume in the pancreas of the rats in the C, CUR and DM+CUR groups ($p>0.05$). When the groups were compared in terms of the ratio of islets to pancreas, it was observed that the volume reduction in the DM group was significant compared to all other groups ($p<0.05$). There was no difference between C, CUR and DM+CUR groups ($p>0.05$). There was a significant increase in the ratio of islets to pancreas in the DM+CUR group compared to the DM group ($p<0.05$). It was determined that the number of beta cells stained with aldehyde fuchsin in the pancreatic islets of rats in the DM group decreased significantly compared to the C group ($p<0.05$) (Table 1). On the other hand, there was a significant increase in the mean number of β-cells in the DM+CUR group compared to the DM group ($p<0.05$). There was no significant difference between C, CUR and DM+CUR groups ($p>0.05$) (Table 2).

IMMUNOHISTOCHEMISTRY EVALUATION

In the present study, nuclei staining was achieved by using the replication marker Ki67. The control and curcumin groups showed similar staining, whereas the staining was less in the diabetic group (Figure 2A, Figure 2B, Figure 2C). In the diabetes group treated with CUR, it was found that CUR attenuated diabetes-related Ki67 reduction (Figure 2D).

TABLE 2: Stereological parameters of rats in all groups.*

	C (n=8)	DM (n=8)	CUR (n=8)	DM+CUR (n=8)
Pancreas wet weight (g)	1.12±0.02	1.06±0.02	1.11±0.02	1.09±0.02
Pancreas volume (cm^3)	2.02±0.03	1.98±0.05[a]	2.02±0.05	2.01±0.04
Total islet volume (mm^3)	56.3±2.0	28.4[a]±2.3	57.2±1.5	51.3±1.8[b]
Volume density islets/pancreas (%)	2.75±0.08	1.33[a]±0.09	2.68±0.08	2.56±0.08[b]
β-cells/islet	87.6±2.5	24.4[a]±1.8	87.5±1.9	89.6±1.5[b]

*Values are mean ±S.E. "n" refers to the number of rats in each group. Coefficient error (CE) in each measurement are less than 0.05, [a]p<0.05 compared to control group, [b]p<0.05 compared to diabetic; C: Control; DM: Diabetes; CUR: Curcumin; DM+CUR: Diabetes+curcumin.

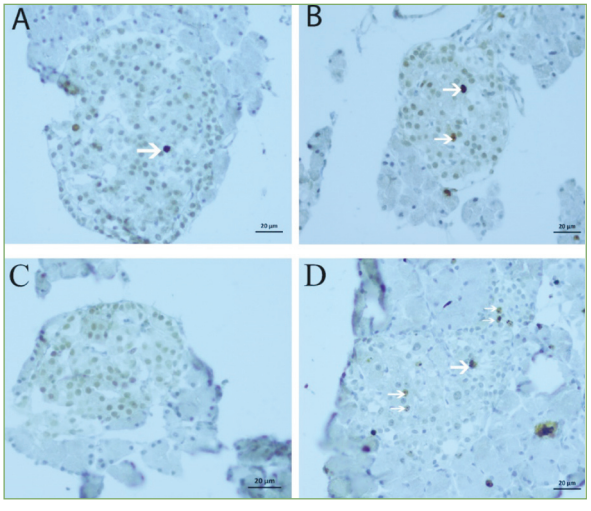

FIGURE 2: Control group *(A)*. Curcumin group **(B).** Diabetes group **(C)** Curcumin+diabetes group **(D).** Ki 67 positive cell (white arrow).

DISCUSSION

In this study, it was determined that CUR reduced the damage in the islets and beta cells in the pancreas of rats with DM with STZ.

STZ is one of the toxic agents used to create a diabetes model in experimental animals.[7] An animal model of STZ-induced DM was also used in the present study. Many studies have reported that STZ has selective toxicity for pancreatic β-cells.[19]

In the stereological and histochemical results obtained from the study, it was determined that the volume of the islets decreased, the proliferation ability of β cells decreased, and the number of beta cells decreased in the pancreas of the rats in the DM group. In addition, semiquantitative histopathological evaluation. Degenerative and necrotic changes in cells, hydropic degeneration and degranulation in cell cytoplasm were observed.

The generation of reactive oxygen species (ROS), reactive nitric oxide (NO) species, and inflammatory reactions are thought to be involved in STZ's cytotoxicity.[20] Overproduction of ROS and/or insufficient antioxidant neutralization contribute to the onset and progression of DM problems by damaging cell membranes and vessel walls.[21]

Oxidative stress is considered an important mediator of apoptosis.[19] STZ enters the pancreatic β-cell via the glucose transporter-2, causes abundant production of ROS and NO, which leads to oxidative stress and also causes inflammation by increasing inflammatory cytokines.[22] Hyperglycemia also causes greater oxidative stress due to protein glycation, glucose auto-oxidation, and the production of advanced glycation products, all of which induce tissue damage.[23] These results that were informed support our study findings. Therefore we can say that STZ, which we used in the current study, causes oxidative stress and/or inflammation in the pancreas, primarily reducing proliferation in beta cells and causing apoptosis, leading to a decrease in their number, which in turn causes shrinkage in islets and damage to the pancreas in general.

In the current study, the general histological structure of the pancreas in rats given CUR was similar to the rats in the control group. It was determined that the damage in islets and beta cells in the DM group regressed in rats in the DM+CUR group. The volume of the islets, the number of beta cells, and necrotic changes in the cells were less compared to the diabetes group. In addition, in the immunohisto-

chemical evaluation performed with Ki67 staining, it was determined that the proliferation abilities of beta cells were increased compared to the DM group.

CUR is an antioxidant with proven protective effect against oxidative damage. CUR reduces lipid peroxidation by normalizing antioxidant enzyme levels such as catalase, superoxide dismutase and glutathione peroxidase.[24] Administration of tetrahydrocurcumin (80 mg/kg body weight), a derivative of CUR, for a period of 45 days has been reported to reduce fasting blood glucose (~55%) and increase antioxidant defenses of STZ-induced diabetic rats.[25] Rashid and Sil reported that CUR can reduce the oxidative stress caused by STZ, endoplasmic reticulum stress and related inflammation, and protect pancreatic beta cells from apoptotic damage under hyperglycemic conditions in rats whose diabetes model was created with STZ.[26] According to Ganugula et al. reported that nano-CUR (300 nm particle size. p.o. application) could prevent STZ-induced inflammation and apoptosis in pancreatic islet cells, and decrease glucose level, proinflammatory cytokines and oxidative stress.[27] Al-Ali and et al., stated that because CUR is a potent antioxidant, it protects pancreatic islet cells by preventing apoptosis.[28] Qihui et al. showed that CUR inhibited inflammation and apoptosis in pancreatic islet β cells of diabetic rats.[29] Moreover, there are scientific reports that CUR may be neglected even in high concentrations in human and animals regarding its toxicity.[30-32] Our results match up with the study results that CUR is a great antioxidant.

CONCLUSION

The current study has shown that CUR is a significant protection in pancreatic tissue, consistent with previous study results that have shown exceptional protection of β-cell function and proliferation. In conclusion we can say that CUR provides protection in experimental DM with the results of this study and previous studies by reducing oxidative stress, increasing proliferation and cell survival and preserving pancreatic β-cell integrity.

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Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Bilge Bal Özkaptan, Dilek Sağır;* ***Design:*** *Bilge Bal Özkaptan, Dilek Sağır;* ***Control/Supervision:*** *Bilge Bal Özkaptan, Dilek Sağır;* ***Data Collection and/or Processing:*** *Bilge Bal Özkaptan, Dilek Sağır, Fatma Aksoy;* ***Analysis and/or Interpretation:*** *Bilge Bal Özkaptan, Dilek Sağır, Fatma Aksoy;* ***Literature Review:*** *Bilge Bal Özkaptan;* ***Writing the Article:*** *Bilge Bal Özkaptan, Dilek Sağır, Fatma Aksoy;* ***Critical Review:*** *Bilge Bal Özkaptan;* ***References and Fundings:*** *Bilge Bal Özkaptan, Dilek Sağır, Fatma Aksoy;* ***Materials:*** *Bilge Bal Özkaptan, Dilek Sağır, Fatma Aksoy.*

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