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Effects of Captopril on Cell Damage and Liver Damage

Kaptoprilin Hücre Hasarı ve Karaciğer Hasarı Üzerine Etkileri

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ABSTRACT Objective: To evaluate the effects of captopril (CAP), an angiotensin converting enzyme inhibitor (ACEI), on oxidative stress, liver enzymes, cardiovascular damage, and micronucleus (MN) frequency in streptozotocin-induced diabetes mellitus (STZ-DM). **Material and Methods:** A total of 24 young Sprague-Dawley male rats were divided into three groups as control, STZ, and STZ+CAP. The rats with DM, induced by way of a single dose injection of STZ (45 mg/kg), received CAP 50 mg/L/day for eight weeks. At the end of this period, liver and cardiovascular damage was evaluated from the level of creatine kinase (CK), creatine kinase isoenzyme-MB (CK-MB), alanine aminotransferase (ALT), aspartate aminotransferase (AST), and lactate dehydrogenase (LDH) and the level of lipid peroxidation was evaluated using the thiobarbituric acid reactive substances (TBARS), glutathione (GSH), and total thiol content (T-SH). The MN frequency was also examined. **Results:** STZ was found to cause significant increases in the TBARS and LDH levels, ALT and AST activity, and MN frequency and a decrease in the GSH levels, while CAP increased T-SH production and decreased LDH activity and MN frequency. However, CAP increased the activities of ALT and AST. **Conclusion:** Our study results suggest that CAP produces antioxidant effects in rats with STZ-induced DM and long-term use of CAP can correct the complications of diabetes at the cellular level, such as cell and tissue damage, as well as causing liver damage. Based on these results, diabetes seems to affect the liver, kidneys, and heart to varying degrees, although the liver is the most extensively affected organ.

Keywords: Diabetes mellitus; captopril; oxidative stress; angiotensin converting enzyme inhibitor; liver damage

ÖZET Amaç: Bir anjiyotensin dönüştürücü enzim inhibitörü (ACEİ) olan kaptopril (CAP)'in streptozotosin kaynaklı diyabetes mellitusta (STZ-DM) oksidatif stres, karaciğer enzimleri, kardiyovasküler hasar ve mikronükleus (MN) frekansı üzerindeki etkilerini değerlendirmek. **Gereç ve Yöntemler:** Toplam 24 genç Sprague-Dawley erkek sıçan kontrol, STZ ve STZ+CAP olmak üzere üç gruba ayrıldı. Tek doz STZ enjeksiyonuyla (45 mg/kg) indüklenen DM'li sıçanlar, sekiz hafta boyunca 50 mg/L CAP aldı. Bu sürenin sonunda, karaciğer ve kardiyovasküler hasar, kreatin kinaz (CK), kreatin kinaz izoenzim-MB (CK-MB), alanin aminotransferaz (ALT), aspartat aminotransferaz (AST) ve laktat dehidrojenaz (LDH) seviyeleri değerlendirildi. Lipit peroksidasyon seviyesi, tiobarbitürik asit reaktif maddeler (TBARS), glutatyon (GSH) ve toplam tiol içeriği (T-SH) kullanılarak değerlendirildi. MN frekansı incelendi. **Bulgular:** STZ'nin TBARS ve LDH seviyeleri, ALT ve AST aktivitesi ve MN frekansında önemli artışa ve GSH seviyesinde azalmaya neden olduğu, CAP'in T-SH üretimini artırdığı, LDH aktivitesini ve MN frekansını azalttığı bulundu. Ancak CAP, ALT ve AST'nin aktivitelerini artırdı. **Sonuç:** Çalışma sonuçlarımız, CAP'in STZ ile indüklenen DM'li sıçanlarda antioksidan etki sağladığı ve CAP'in uzun süreli kullanımı diyabetin hücre ve doku hasarı gibi hücresel düzeydeki komplikasyonlarını düzeltirken karaciğerde de hasara yol açabileceğini düşündürmektedir. Bu sonuçlara dayanarak, diyabet karaciğer, böbrek ve kalbi değişen derecelerde etkilemekte, ancak karaciğer en çok etkilenen organdır.

Anahtar Kelimeler: Diabetes mellitus; kaptopril; oksidatif stres; anjiyotensin dönüştürücü enzim inhibitörü; karaciğer hasarı

Hyperglycemia in diabetes causes cellular damage by increasing the level of reactive oxygen species (ROS) and triggering oxidative stress.[1,2] Free radical damage in diabetes causes extensive damage to the genetic material, thereby, leading to deoxyribonucleic acid (DNA) strand breakage and the formation of micronucleus (MN) which are associated with carcinogenesis and teratogenesis.[3] Therefore, patients with diabetes are not only subjected to complications related with oxidative stress, but there is also the risk of

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passing nuclear defects onto the next generations.[4] In both animal models and studies of human subjects, diabetes has been shown to be characterized by increased angiotensin converting enzyme (ACE) activity.[5] Angiotensin II, which is an important hormone in the renin-angiotensin system (RAS), can produce a large number of harmful effects at a microvascular level in diabetes, resulting in end-organ damage.[6] ACEIs protect pancreatic beta-cells by inhibiting the vasoconstrictive effects of angiotensin II on the pancreas, increasing blood flow to the pancreatic islet blood flow, thereby increasing insulin secretion from the beta-cells.[7] Also, ACEIs have been shown to provide cardiovascular benefits by preventing protein glycosylation and to inhibit angiotensin II and exert antioxidant effects by increasing the activity of antioxidant enzymes.[5,8-10] Captopril (CAP) has been found to be considerably effective in clearing free radicals, and it is though that its antioxidant effects derive from the unblocked sulfhydryl group in the drug molecule.[11] Interestingly, only a certain quantity of CAP binds to ACE in the organism, while the remaining amount is found in an adsorbed form in the form of disulfides, by reacting with sulfhydryl-containing compounds such as glutathione (GSH) and plasma proteins.[12] In the present study, we aimed to investigate the effects of CAP, an ACEI, on oxidative stress and antioxidant capacity; the biochemical parameters indicating cardiovascular or liver damage, such as creatine kinase (CK), creatine kinase isoenzyme MB (CK-MB), lactate dehydrogenase (LDH), alanine aminotransferase (ALT) and aspartate aminotransferase (AST) activity, and MN frequency indicating DNA damage in rats with streptozotocin STZ-DM.

MATERIAL AND METHODS

In the study, a total of 24 young male Sprague-Dawley rats were divided into three groups, each consisting of eight rats: Group I was administered intraperitoneal (i.p.) physiological saline (0.5 ml/100g) as the control group; Group II was administered with a single dose of STZ (45 mg/kg) i.p.; and Group III received a single dose of STZ (45 mg/kg) i.p. and CAP 50 mg/L/day through an oral gavage for eight weeks. Following the STZ administration, the development of diabetes was followed through the measurements of blood glucose levels twice a week. The rats with a fasting blood glucose level of ≥300 mg/dL or ≥16.7 mmoL/L were considered to have developed diabetes.[13] The ethical approval for the study was obtained from the Laboratory Animals Local Ethics Committee of İnönü University (Ethical approval number: 15.02.2009-2009/02). The research related to animal use has complied with all the relevant national regulations, institutional policies and is in accordance with the tenets of the Helsinki Declaration. The rats were sacrificed at the end of eight weeks. Blood samples collected from the vena cava inferior were centrifuged at 3000xg for 10 min to separate the plasma and serum, and biochemical tests were performed. Tissue samples were harvested from the heart, liver and kidneys for the measurement of thiobarbituric acid reactive substances (TBARS), GSH, and total thiol content (T-SH) levels and stored at -80°C until analysis. The method developed by Ohkawa et al. and modified by Jamall and Smith was used to determine the level of TBARS in the tissues.[14,15] This method requires measuring the amount of colored product at 532 produced by thiobarbituric acid (TBA) that reacts with substances that reacts with end-products of peroxidized lipids and TBA. 1,1,3,3-tetraethoxypropane (TEP) was used as the standard for calibration, and the results were expressed in (malondialdehyde) MDA/g. The levels of GSH and T-SH in the tissues were determined using the method proposed by Sedlak and Linsay, which is based on the determination of the amount of 5-Mercapto-2-Nitro-Benzoic Acid at 412 nm that forms as a result of the reaction between 5.5′-Dithiobis (2-nitrobenzoic acid) (DTNB; Ellman reactive) and the thiol groups.[16] Reduced GSH was used as a standard for calibration, and the T-SH and GSH results were expressed as µmol/g. The CK and CK-MB levels, and LDH, ALT, and AST activity were measured in the serum samples using the enzyme-linked immunosorbent assay (ELISA) method in an Olympus AU 2700 autoanalyzer (Beckman-Coulter, Inc., Fullerton, CA), according to the manufacturer's instructions. The MN was determined by the Cytokinesis-Block (CB) method developed by Fenech and Morley, which involves arresting cytokinesis in cell

that undergoes mitosis by cytochalasin-B (Cyt-B) – a fungal metabolite.[17] The number of MN counted on light microscope was recorded.

STATISTICAL ANALYSIS

Statistical analysis was performed using the INSTAT automated software (GraphPad Prism Inc., San Diego, CA, USA). The results were expressed in mean±standard error (SE). One-way analysis of variance (ANOVA) was used to compare the differences between the groups, and a Tukey *post-hoc* test was used for the comparison of paired groups. A *p* value of<0.05 was considered statistically significant.

RESULTS

There was an increase in the TBARS levels of the liver (1.2-fold, p<0.05) and kidney (1.3-fold, p<0.001) tissues in the STZ group than in the control group, whereas there was a decrease in the levels of the heart tissue that was not found to be significant (Table 1). The group which received CAP showed no tissue changes related to oxidative stress. There was a decrease in GSH levels of the liver due to the effect of STZ (1.6-fold, p<0.001) compared to the control group, while there was no significant increase in the GSH content of the kidney and heart tissues (Table 1). The administration of CAP had no effect on the GSH content. The administration of STZ had no effect on the T-SH of the tissues (Table 1). The CAP administration increased the thiol content of the liver by 19.4% (p<0.05) and of the heart by 26.1% (p<0.01). The T-SH of the kidney remained unchanged. The biochemical parameters of all study groups are summarized in Table 1. Neither STZ nor CAP affected CK and CK-MB levels. The STZ administration increased LDH activity 1.2-fold (p<0.05), ALT activity 2.9-fold (p<0.001), AST activity 2.4-fold (p<0.01), and MN frequency 5.4-fold (p<0.001). After CAP treatment, ALT activity increased by 78.7% (p<0.001) and AST activity increased by 90.9% (p<0.001). CAP decreased LDH levels by 17.7% (p<0.05) and MN frequency by 25.1% (p<0.01). STZ has been found to increase TBARS and LDH levels, ALT and AST activity, and MN frequency levels, and in addition to this cause glutathione consumption. The positive effects of CAP, such as an increase in T-SH production, a decrease in LDH activity and the frequency of MN,

TABLE 1: Effect of captopril on oxidative stress and biochemical parameters in diabetic rats.

Parameter		Control	STZ	STZ + CAP
TBARS (nmol/g)	Liver	421.0±16.9	489.1±11.9*	451.8±9.9
	Kidney	519.6±9.9	656.2±39.9***	660.4±26.1
	Heart	274.8±18.5	271.6±14.9	274.8±4.7
GSH (µmol/g)	Liver	5.7±0.2	3.5±0.4***	4.2±0.2
	Kidney	3.7±0.3	3.8±0.5	3.9±0.1
	Heart	2.0±0.1	2.3±0.3	2.5±0.1
TSH (µmol/g)	Liver	14.3±0.4	12.9±0.9	15.4±0.5*
	Kidney	11.4±0.4	10.5±1.0	11.4±0.3
	Heart	6.9±0.2	6.5±0.5	8.2±0.3**
CK (U/L)	Serum	402.9±26.2	401.6±43.2	306.9±41.1
CKMB (U/L)		426.1±38.7	477.0±53.7	378.9±46.8
LDH (U/L)		474.1±26.0	563.3±13.2*	463.4±29.4+
ALT (U/L)		44.6±2.7	131.5±13.4***	235.0±20.4+++
AST (U/L)		73.1±5.5	175.0±23.2**	334.1±27.8+++
MN%	Blood	0.7±0.2	3.5±1.9***	2.6±0.2++

Values are represented as mean; * Significant change in comparison with control at p<0.05; ** Significant change in comparison with control at p<0.01; *** Significant change in comparison with control at p<0.001; +Significant change in comparison with STZ group at p<0.05; ++Significant change in comparison with STZ group at p<0.01; +++Significant change in comparison with STZ group at p<0.001.

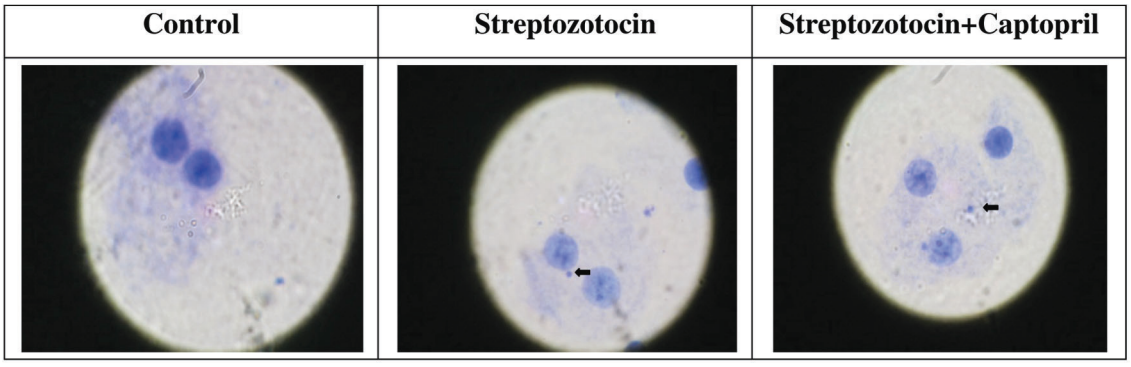

FIGURE 1: Effect of captopril treatment on micronucleus formation in streptozotocin-induced diabetic rats.

were found. However, in addition to these positive effects, it increased the activities of ALT and AST, which are indicators of liver damage.

The number of MN was examined using light microscopy and recorded (Figure 1) to calculate the total MN frequency (MN%).

DISCUSSION

Captopril exerts its anti-oxidant and anti-inflammatory effects through two mechanisms. First, it inhibits ACE and decreases the blood and tissue levels of angiotensin II; and second, it possesses antioxidant features due to its thiol content and protects against free radicals. Increasing pancreatic angiotensin II levels induces oxidative stress, inflammation and apoptosis in pancreatic ß-cells.[18] The oxidation of glucose in the Langerhans islet cells increases due to increased lipid peroxidation in relation to free radicals, and insulin secretion is suppressed.[3] An increase is observed in the TBARS levels in STZ-DM, indicating that an increased TBARS level in diabetes is an indirect indication of free radical production.[19] In the present study, TBARS levels were found to be increased in the liver and kidney tissue. Similarly, previous studies found that STZ-induced oxidative stress in the liver and kidney tissue of rats.[20-22] One study reported that six- and 12-week therapy with CAP reduced kidney MDA levels, and there have been numerous studies reporting significantly decreased MDA levels in the plasma and kidneys in association with CAP therapy.[5,18,23] The present study found that increases in TBARS levels were not reversed by CAP therapy.[19,20] The present study observed increased lipid peroxidation in the liver and kidney tissue of rats with STZ-DM, and this was accompanied by a decreased GSH level in the liver. In a study by Chen et al., it was suggested that CAP could prevent oxidative stress while regulating blood pressure, and it was also concluded that the beneficial effects of CAP on the endothelium is related with antioxidation.[24] In a study by Fiordaliso et al., lisinopril, an ACEI, was found to reduce oxidative stress in the heart and aorta of rats with STZ-DM.[6] In parallel to our study, previous studies reported decreased GSH levels in the liver and kidney tissue of animals with DM induced by chemical agents.[20-22] Increased lipid peroxidation and decreased GSH levels in the liver are typical features of diabetes. CAP has been reported to have no stimulatory effects on GSH production. It can be speculated that liver and kidney tissues are affected by oxidative stress to the same extent. It was observed that CAP caused greater increases in T-SH levels in the heart than in the liver. The increased T-SH levels in the tissues after CAP administration suggest that CAP exerts antioxidant effects, although its antioxidant effect was not found to be significant to the extent reported in literature, and it was found to have a more potent effect on the heart. The increases in ALT and AST enzymes can be regarded as a limitation of its use for cardioprotective purposes. On the other hand, considering an eight-week course of CAP therapy, and the fact that CAP is largely metabolized in the liver, an increase in transaminase enzyme levels is an expected finding in relation to an increase in liver TBARS levels and increased GSH consumption.

Captopril is widely used in the treatment of hypertension, being an effective and safe antihypertensive agent, although it is also used in cases of heart failure and myocardial infarction.[24,25] In the present study, we found that CAP had no effect on either CK or CK-MB levels. The higher levels of LDH, ALT and AST in the STZ group than in the control group indicate that STZ can induce myocardial damage. In a study by Gao et al., CAP was found to reduce increased LDH, AST, CK and CK-MB levels in STZ-induced cardiomyopathy.[26] Similarly, we found that the administration of CAP significantly reduced LDH, AST, and ALT activity in diabetic rats, and the decreases in these markers support the cardioprotective effect of CAP. An increase in the number of MN is regarded as an indirect indicator of numeric or structural chromosomal irregularities.[27] In our study, an increased frequency of MN was found in diabetic rats. This finding suggests that CAP can regulate blood pressure and decrease the MN formation which is found to be increased in diabetes. The increased frequency of MN may be the result of the cytotoxic effect that is observed in association with the STZ-induced destruction of beta-cells and the induction of hyperglycemia. A decrease in the frequency of MN, the increased thiol content of the heart and liver, and the decrease in LDH activity indicate the protective effect of CAP in diabetes. Although previous studies report that as a thiol-containing compound, CAP possesses strong antioxidant activity and prevents lipid peroxidation by clearing various types of ROS, the findings of the present study did not support this finding.

CONCLUSION

Our study results suggest that CAP has no effect on increased lipid peroxidation in tissues and it causes an increase in ALT and AST activity. Based on these results, CAP seems to prevent diabetic complications through various independent mechanisms.

Source of Finance

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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: *Göknur Aktay;* ***Design:*** *Göknur Aktay, Şule Öner Gürsoy;* ***Control/Supervision:*** *Göknur Aktay;* ***Data Collection and/or Processing:*** *Murat Ceritli;* ***Analysis and/or Interpretation:*** *Şule Öner Gürsoy, Murat Ceritli;* ***Literature Review:*** *Songül Ünüvar;* ***Writing the Article:*** *Songül Ünüvar;* ***Critical Review:*** *Göknur Aktay;* ***References and Fundings:*** *Göknur Aktay, Songül Ünüvar, Şule Öner Gürsoy, Murat Ceritli;* ***Materials:*** *Şule Öner Gürsoy, Murat Ceritli.*

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