Original Article

The Protective Effect of L-arginine in Cisplatin-induced Nephrotoxicity in Streptozotocin-induced Diabetic Rats

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Abstract

Background: Cisplatin (CP) is accompanied with a nephrotoxicity. L-arginine (LA) plays an important role in the regulation of renal function. The present study was designed to investigate the protective role of LA supplementation in CP-induced nephrotoxicity in a diabetic rat's model. **Materials and Methods:** Sixteen adult female and male Wistar rats were used and they received a single dose of streptozotocin (STZ) (60 mg/kg i.p.). Diabetic female and male rats were arranged as groups 1–5 and groups 6–10, respectively. Groups 1 and 6 (LA groups) received LA alone. Groups 2 and 7 (CP groups) received CP alone. Groups 3 and 8 (CP + LA [PT] groups) received LA as prophylaxis and then treated with LA and CP. Groups 4 and 9 (CP + LA [T] groups) were treated with LA and CP simultaneously. Groups 5 and 10 (CP + LA [P] groups) received LA as prophylaxis and then treated with CP. **Results:** The serum creatinine (Cr) level of males in Groups 8 and 9 was significantly increased when compared with LA and CP ($P < 0.05$), whereas no differences were observed in Cr level in female groups. Blood urea nitrogen/Cr ratio and kidney weight were reduced in all CP-receiving male rats. Such observation was not seen in female rats. Different results related to weight loss were obtained between male and female animals. The kidney tissue damage score in CP + LA (PT) male group was significantly greater than CP group ($P < 0.05$). **Conclusion:** Our findings indicate that administration of LA in female and male rats has no protective effect on the severity of nephrotoxicity induced by CP in diabetic rats.

Keywords: *Cisplatin, diabetes, L-arginine, nephrotoxicity, rat*

Introduction

L-arginine (LA) is a semi-essential amino acid that is converted into nitric oxide (NO) via NO synthase (NOS).[1] LA plays an important role in the regulation of renal function.[2] Kidney has a key role in arginine metabolism and synthesis. Liver arginine destruction is increased in diabetic animals and thus reduced plasma arginine levels were observed in diabetic animals.[3] Although serum levels of internal inhibitor of NOS have risen in both Type 1 and Type 2 diabetes mellitus in diabetic patients, the plasma levels of LA is reduced, so LA supplementation may be effective to improve the endothelial and renal function in diabetic patients.[4] Diabetes is related to an increased risk of several types of cancers.[5] Studies have shown that uncontrolled streptozotocin (STZ)-induced diabetic rats could protect renal tissue against cisplatin (CP)-induced damage.[6]

Cis-diamminedichloroplatinum (II) (CP) as the most popular potent chemotherapeutic drug is used in the treatment of different solid cancers in clinic. Nephrotoxicity induced by CP may limit therapeutic uses of CP in clinic.[7,8] Nephrotoxicity decreases renal blood flow and glomerular filtration rate (GFR), and it is accompanied with increased blood urea nitrogen (BUN) and creatinine (Cr)[9] and changes in nitrite (NO stable metabolite) levels.[10,11] The toxicity of CP is due to increase in the production of oxygen free radicals and it reduces the antioxidants activity.[12] The three NOS isoforms are expressed in the kidney.[13] Recent evidence shows that both endothelial NO synthesis (eNOS) and inducible NOS (iNOS)-derived NO vasodilators decrease nephrotoxicity, restoring normal glomerular functions and hemodynamic stability.[14] It is reported that LA has a protective role against reactive oxygen species (ROS) through interaction with superoxide anion.[10,11] Some studies indicate that NO plays a role in CP-induced nephrotoxicity.

How to cite this article: Gharibi F, Soltani N, Maleki M, Talebi A, Nasiri M, Shirdavani S, *et al*. The Protective Effect of L-arginine in Cisplatin-induced Nephrotoxicity in Streptozotocin-induced Diabetic Rats. Adv Biomed Res 2017;6:100.

Received: November, 2015. **Accepted:** January, 2016.

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Access this article online

Website: www.advbiores.net

DOI: 10.4103/2277-9175.212928

Quick Response Code:

Administration of NOS inhibitor exacerbates CP-induced nephrotoxicity.[11]

Recent studies have shown that LA supplementation significantly reduces oxidative stress.[15,16] LA deficiency causes endothelial inflammation and cardiovascular disorders, and dietary LA supplementation can reverse these disorders, and also it has a protective effect against CP-induced nephrotoxicity. Therefore, we hypothesized that LA dietary supplementation will alter preserving renal function in diabetic Wistar rats treated by CP.

Materials and Methods

Chemicals

CP was purchased from EBEWE Pharma Ges.m.b.H (Austria), STZ and LA were purchased from Sigma-Aldrich (St. Louis, MO, USA).

Animals

Sixteen adult female (weight: 163.3 ± 3.2 g) and male (weight: 193.8 ± 4.0 g) Wistar rats (Animal Center, Isfahan University of Medical Sciences, Isfahan, Iran) were used in this study. Animals were housed at a room temperature of 23–25°C. Rats had free access to water and rat chow. The experimental procedures were approved in advance by the Ethics Committee of Isfahan University of Medical Sciences.

Experimental protocol

Diabetes was induced with a single intraperitoneal injection of STZ (60 mg/kg).[17,18] Three days later, blood glucose level was measured using glucometer (Accu-Chek Active, GC Model, Germany) and the rats with blood glucose levels above 250 mg/dl were considered as diabetic. The thirty adult female and thirty male diabetic rats were randomly assigned to 10 groups (female and male rats as groups 1–5 and groups 6–10, respectively, $n = 6$):

- Groups 1 or 6 (named, LA): Diabetic male and female rats received LA (150 mg/kg i.p.)[19] for consecutive 12 days
- Groups 2 or 7 (named, CP): Diabetic male and female rats received CP (2.5 mg/kg i.p.)[20] for 6 days
- Groups 3 or 8 (named, CP + LA [PT]): Diabetic male and female rats received LA (150 mg/kg i.p.) for 12 days, and from the 6th day, the animals were also treated with CP (2.5 mg/kg/day i.p.) by the end of experiment
- Groups 4 or 9 (named, CP + LA [T]): Diabetic male and female rats received LA (150 mg/kg i.p.) accompanied with CP (2.5 mg/kg/day i.p.) for 6 days
- Groups 5 or 10 (named, CP + LA [P]): Diabetic male and female rats received LA (150 mg/kg i.p.) for 6 days as prophylaxis and from the 6th day, animals received CP [Figure 1].

All rats were killed after blood sampling via direct intracardiac puncture under chloral hydrate anesthesia. The serum samples were kept at −20°C for measurement. The kidney, testis, and uterus were removed and weighed. The left kidney was fixed in 10% formalin for histological examination and right kidney was homogenated and centrifuged at 15000 rpm for 2 min. The supernatant was used for the measurement of malondialdehyde (MDA) activity and NO level.

Measurements

The serum levels of Cr and BUN were determined using kits (Pars Azmoon Co., Tehran, Iran) and device analyzer (TechniconRA-1000, Ireland). The serum and renal levels of nitrite (NO stable metabolite) were measured using assay kit (Promega Croatian, Madison, WI, USA). The serum and renal levels of MDA were measured by manual method using (trichloroacetic acid and thiobarbituric acid).

Kidney histology

For histopathological investigations, the excised right kidney was embedded in paraffin. Then, hematoxylin and eosin stain was used to assay the tubular damage. The tubular damage was evaluated by an expert pathologist who was blind to the study. According to the intensity of

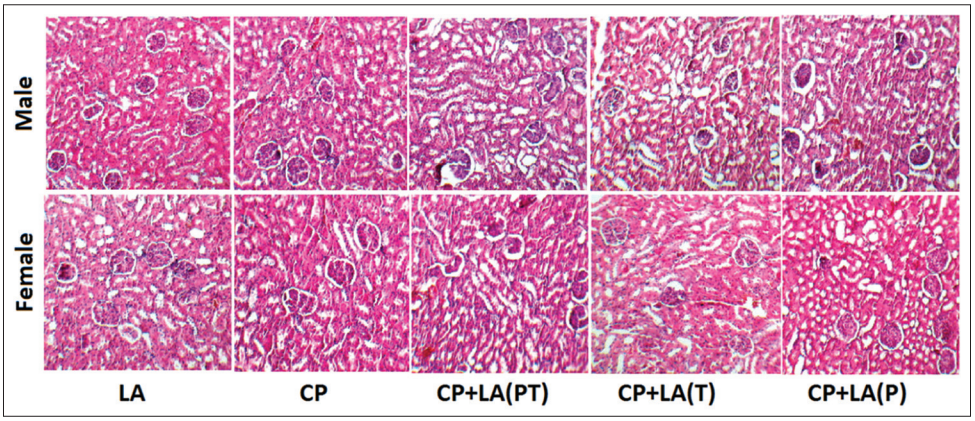

Figure 1: The images (×100) of kidney tissue in five experimental groups in male and female streptozotocin-induced diabetic rats. LA group received LA alone. CP group received CP alone. CP + LA (PT) group received LA as prophylaxis and then treated with both LA and CP. CP + LA (T) group treated with LA and CP simultaneously. CP + LA (P) group received LA as prophylaxis and then treated with CP alone. CP: Cisplatin, LA: L-arginine

tubular injuries, the kidney tissue damage score (KTDS) was graded from I to IV, based on the intensity of tubular lesions (hyaline cast, debris, vacuolization, flattening and degeneration of tubular cells, and dilatation of tubular lumen), while zero was assigned to normal tubules without any damage.

Data analysis

Data are expressed as mean ± standard error of the mean. The levels of BUN, Cr, MDA, nitrite, kidney weight (KW), and UW were analyzed by one-way ANOVA followed by the least significant difference test for multiple comparisons of significance. Comparison of the KTDS between groups was assessed using Mann–Whitney test. $P < 0.05$ was considered significant.

Results

Effect of L-arginine and hyperglycemia on serum level of creatinine, blood urea nitrogen, and blood urea nitrogen/creatinine ratio

The serum levels of Cr were not significantly different in female rats, whereas the serum levels of Cr were significantly increased in male CP + LA (PT) and CP + LA (T) groups in comparison to CP or LA alone groups ($P < 0.05$) [Figure 2]. The serum level of BUN did not indicate significant differences in male ($P < 0.15$) and female ($P < 0.71$) groups. However, no significant differences were in the BUN/Cr ratio in female groups, whereas in male groups, BUN/Cr ratio was significantly decreased in CP, CP + LA (PT), and CP + LA (P) groups when compared with treated animals with LA alone ($P < 0.05$) [Figure 2].

Effect of L-arginine and hyperglycemia on the level of nitrite and malondialdehyde

In hyperglycemic male rats, the serum nitrite level of CP, CP + LA (PT), CP + LA (T), and CP + LA (P) groups was significantly lower than LA-treated group ($P < 0.05$). However, no significant differences were in the serum levels of nitrite between female groups ($P = 0.45$) and also in the tissue level of nitrite between the groups neither in male ($P = 0.40$) nor in female ($P = 0.58$) rats [Table 1]. The serum levels of MDA were significantly decreased in female CP + LA (PT), CP + LA (T), and CP + LA (P) groups in compared with CP group ($P < 0.05$) [Table 1]. However, no significant differences were observed in the serum levels of MDA in male rats and kidney tissue level of MDA in two genders.

Effect of L-arginine and hyperglycemia on body weight, kidney weight, uterus weight, and kidney tissue damage score

The body weight loss in LA received as treatment was significantly greater than CP received male animals ($P < 0.05$). The body weight losing female groups in LA received as treatment or prophylaxis was greater than LA received alone, and body weight loss significantly was

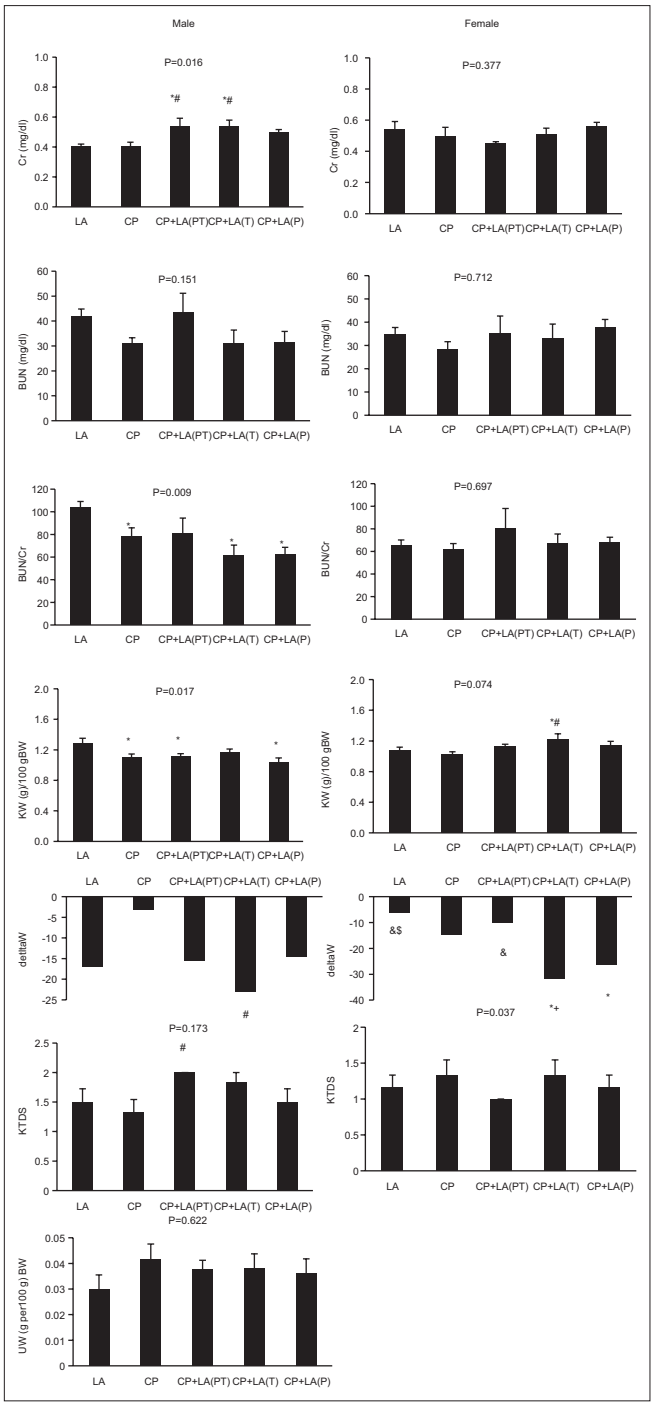

Figure 2: Serum levels of creatinine, blood urea nitrogen and blood urea nitrogen/creatinine ratio, kidney weight per 100 g of body weight body weight change (delta BW), uterus weight per 100 g of body weight, and kidney tissue damage score in five experimental groups in male and female streptozotocin-induced diabetic rats. LA: Group received LA alone. CP group received CP alone. CP + LA (PT) group received LA as prophylaxis and then treated with both LA and CP. CP + LA (t) group treated with LA and CP simultaneously. CP + LA (p) group received LA as prophylaxis and then treated with CP alone. *,#,+, and,$ means significant difference from LA, CP, CP + LA (PT), CP + LA (t), and CP + LA (p) groups, respectively ($P < 0.05$). CP: Cisplatin, LA: L-arginine

Table 1: Level of nitrite and malondialdehyde in serum and kidney in all experimental groups

Gender	Group	Serum nitrite (µmol/L)	Kidney nitrite (µmol/g tissue)	Serum MDA (µmol/L)	Kidney MDA (nmol/g tissue)
Male	LA	13.9±1.9	0.14±0.01	4.03±0.74	9.4±1.4
	CP	7.9±1.0*	0.17±0.01	4.59±0.15	10.1±1.1
	CP + LA (PT)	7.4±1.1*	0.16±0.02	4.12±0.49	8.6±0.8
	CP + LA (T)	7.3±0.4*	0.15±0.01	5.02±0.55	8.7±1.5
	CP + LA (P)	8.6±2.7*	0.13±0.01	4.41±0.19	9.2±0.4
	P	0.04	0.41	0.62	0.88
Female	LA	12.3±3.4	0.12±0.01	6.1±1.3	11.9±1.1
	CP	16.9±5.6	0.13±0.01	8.2±0.8	11.0±1.3
	CP + LA (PT)	8.2±0.4	0.13±0.02	4.6±0.5#	9.1±0.9
	CP + LA (T)	12.0±0.7	0.14±0.01	5.8±0.6#	11.0±1.3
	CP + LA (P)	11.0±2.9	0.13±0.03	5.0±0.3#	12.7±1.6
	P	0.46	0.58	0.02	0.38

*,#Significant difference from LA, CP, and CP + LA (T) groups, respectively ($P<0.05$). LA: Group received LA alone, CP: Group received cisplatin alone, CP + LA (PT): Group received LA as prophylaxis and then treated with both LA and CP, CP + LA (T): Group treated with LA and CP simultaneously, CP + LA (P): Group received LA as prophylaxis and then treated with CP alone. MDA: Malondialdehyde, LA: L-arginine, CP: Cisplatin

decreased in CP + LA (PT) group when compared with CP + LA (T) group ($P < 0.05$). The KW was increased significantly in female CP + LA (T) group and it did not demonstrated significant change in male rats in comparison to CP group, while in male CP, CP + LA (PT) group and CP + LA (P) group were significantly less than treated animals with LA alone ($P < 0.05$). Uterus weight was not significantly different in female groups ($P < 0.05$). KTDS in CP + LA (PT) group was significantly greater than CP group ($P < 0.05$) [Table 2 and Figure 2].

Discussion

The main objective of this study was to determine the effect of LA on CP-induced nephrotoxicity in hyperglycemic rat model.

Our results showed that serum levels of BUN and Cr in both female and male hyperglycemic rats treated with CP were within normal range. This data were confirmed by pathology and KW findings. It is proven that CP causes nephrotoxicity and increases parameters of renal function in normal rats[21] by inflammatory processes.[22] In addition, studies demonstrate that diabetic patients are resistant against CP-induced nephrotoxicity,[23] due to increased urinary CP excretion and decrease of OCT2 (transport regulator gene platinum in the kidney cells) expression in diabetic rats.[20,23] Accordingly, it is shown that high blood glucose level has protective effect against CP-induced nephrotoxicity. The decline was rapid with decreased OCT2 expression by more than 50% within 7 days after induction of diabetes.[24] It is recommended to CP-nephrotoxicity in hydrated patients, especially with saline before and after CP administration as urine output reaches to 100 cc/h.[25-27] It is likely that in the current study, urine output increased in diabetic rats declined CP-nephrotoxicity. Hydration allowed the increase of the dose to achieve therapeutic levels[25] indicating that decrease of CP-nephrotoxicity in both Type 1 and Type 2 diabetes,[23] probably intensity of CP-nephrotoxicity is related to decreased blood sugar by LA.

It is reported that LA reduces the serum level of BUN and Cr in treated male rats with CP,[19] but in our research, such observation was not documented in Cr level in male and female when LA was accompanied with CP. The decreased resistance against CP-nephrotoxicity was demonstrated in insulin-treated diabetic rats that have high level of BUN than nontreated diabetic rats.[23] Of course, in this study, all the above parameters were in normal range. However, LA caused vasodilation through NO production and GFR increase,[28] while decreasing GFR in diabetic rats caused increased BUN and Cr levels.[29] The research demonstrates LA decreased blood glucose level in diabetic rats, but the mechanism of this action is not clear some studies believed that this mechanism mediated via blockade of RAS or the inhibition of oxidative stress.[30] The present study demonstrated that LA has not positively affected the level of BUN and Cr in diabetic CP-treated rats. It was also shown that LA has no effect on Cr clearance in diabetic rats.[31]

BUN/Cr ratio is an index for renal function. Probably, main characteristic of renal failure is elevating plasma Cr levels, but in the early stages of renal failure, the kidneys can enhance Cr secretion and reduce its serum.[31] In these early stages, the index of BUN/Cr that we used for renal function indicates reduction in renal perfusion and GFR. Our results show that pretreatment and treatment (Groups 4, 5 male) with LA prevent the toxicity of CP by reduction of the Bun/Cr ratio. Asna *et al*.indicated reduction of the Bun/Cr ratio in CP-treated animals by amifostine treatment.[32]

The serum level of nitrite did not demonstrate significant changes. In this study, probably, decreasing eNOS, nNOS, and increasing iNOS in CP-induced nephrotoxicity were

Table 2: The kidney tissue damage score in experimental groups

Group		Kidney tissue damage score					*n*
Gender	Treat	0	1	2	3	4	
Male	LA		6				6
	CP		3	3			6
	CP + LA (PT)		4	2			6
	CP + LA (T)	1		5			6
	CP + LA (P)		1	5			6
Female	LA		5	1			6
	CP		4	2			6
	CP + LA (PT)		6				6
	CP + LA (T)		4	2			6
	CP + LA (P)		5	1			6

Grading scale is as follows: 0=Normal, 1=Minimal damage (5-25%), 2=Mild damage (25-50%), 3=Moderate damage (50–75%), 4=Severe damage (>75%). LA: L-arginine, CP: Cisplatin

the factors for increasing CP-induced toxicity.[10] Elevating arginase enzyme activity in the diabetic rat's kidney inhibits NOS activity and increases oxidative stress.[33] Some studies reported that iNOS was decreased in both the renal cortex and medulla in LA-treated diabetic rats compared to untreated diabetic rats.[28] Thus, the mechanism involved is not well elucidated. Study showed that the amounts of nitrate and nitrite increased due to oxidative stress in diabetes.[34] Our results confirmed previous studies.

In the present study, LA accompanied by CP treatment in male and female rats decreased kidney and serum levels of MDA that approved pervious finding. It is reported that LA plays a protective role against ROS through interaction with superoxide anions.[10,26] MDA as an end-product of lipid peroxidation is increased in diabetic rats.[35,36] In diabetic rats, LA supplementation increased NO concentration and ameliorate antioxidant status.[37] Renal function of diabetic rats was significantly lower than diabetic rats with antioxidant diet, so it seems that oxidative stress may be due to increased production of peroxynitrite via iNOS causing cell death.[38] It is demonstrated that LA increased antioxidant enzymes both in liver and kidney of diabetic rats that operate via increasing NOS activity declining ROS formation.[31,39] It was previously demonstrated that there are increased oxidative stress and ROS and induced serum SOD concentrations in diabetic rats.[40] On the other hand, CP increased oxidative stress and reduced the level of antioxidant enzymes such as SOD. SOD has a protective effect on renal function.[19]

For the duration of the present study, LA also did not decrease CP toxicity on KW and body weight in male and female rats. However, both in diabetic rats[31,41] and CP-treated rats, there were body weight loss and KW gain, which is related to gastrointestinal disturbances.[19] LA is also similar to the administration of magnesium-intensified weight loss induced by CP in diabetic rats.[20] In another study, LA decreased the body weight of diabetic rats.[31] Hence, LA administration did not prevent the weight loss and did not change KW in diabetic animals. Our finding is in agreement with these studies. KW gain can be owing to retention of water and salt in the kidney tubule or even renal blood flow changes and reduction of GFR by CP.[42,43] LA accompanied with CP treatment has not changed uterus weight significantly that was likely due to estrogen protective effect.

Conclusion

Our findings indicate that the administration of LA in female and male rats has no protective effect on the onset or severity of nephrotoxicity induced by CP in STZ-induced diabetic rats, although previous reports indicated that LA has a protective effect on diabetes or CP-nephrotoxicity in rats. Of course, LA showed antioxidant effect in the present study. Probably, using antioxidants with no hypoglycemic effect is more preferable because of the declined resistance against CP-nephrotoxicity in groups with lower level of glucose.

Financial support and sponsorship

This study was supported by Hormozgan University of Medical Science

Conflicts of interest

There are no conflicts of interest.

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