Effect in of L-Arginine on Some Biochemical and pathological parameter in diabetes mellitus induced by Alloxan-monohydrate in Rats

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Abstract

The present study was designed to investigate the effect of the amino acid (L-Arginine-Hcl) on serum (glucose, lipid profile and lipid peroxidation) and determine the protective effect of (L-Arginine-Hcl) on pathological changes in some body organs (Liver, Kidney) in alloxan induced diabetes rats. Forty eight mature male rats aged 10 weeks ,were randomly divided into four equal groups as follows 1st group diabetic group; 2nd group diabetic group treated with (L-Arginine-Hcl), 3ed group treated with (L-Arginine-Hcl) and 4th control group. After verifying the occurrence of diabetes in rats, the rats in second and third groups were daily injectedwith L-Arginine-Hcl (200mg/kg B.W) intraperitonealy, while first and fourth groups were daily injected with sterile distilled water intraperitonealy. All experimental parameters were carried out at days 20, 40 and 60 were the blood samples were collected from heart to make serological parameters (glucose level, lipid profile and MDA concentration) and section from Liver and Kidney were taken to observe the histopathological changes in different period. The diabetic signs were clearly observed in first group characterized by excessive thirst, frequent urination, and increase appetite, also first group showed significant increase ($P<0.05$) in serum glucose, lipid (TC, TG, LDL-C and VLDL-C) and lipid peroxidation (MDA) concentration. With significant decrease ($P<0.05$) in HDL-C concentration. Histopathological changes in first group showed mild to severe fatty changes with congestion in the liver. The kidney showed glomeruloseclerosis with increase thickness of mesangial cells compared with control group. In the other hand the second group showed normal signs compared with first group with a significant decrease ($P<0.05$) in serum glucose level at day 40, significant decrease ($P<0.05$) in serum TC and LDL-C at day 40. Also showed significant decrease ($P<0.05$) in TG and VLDL-C concentration at day 60 and showed significant increase in HDL-C at day 60 compared with first group, meanwhile the second group showed significant decrease ($P<0.05$) in lipid peroxidation (MDA) at day 60.While the histopathological study showed that the (Liver and Kidney) showed almost normal structures. In conclusion the L-Arginine has beneficial effect on normalization the hyperglycemia, regulate the dyslipemia and decrease the level of lipid peroxidation, also L-Arginine has a protective role to reduce the pathological complication accompanied with diabetic state.

تأثير الـــ(أرجينين) على بعض المعايير الكيميائية الحيوية والتغيرات المرضية في الجرذان المعاملة بالألوكسان كعامل محدث للداء السكري

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الخلاصة

أجريت هذه الدراسة لمعرفة تأثير الحمض الأميني (ال-أرجينين هدروكلوريد) على وزن، مستوى السكر، الدهون وأكسدة الدهون في مصل الدم ولمعرفة ألتأثير الأنتقائي على بعض أعضاء الجسم (الكبد والكلية) نســجياً ووظيفياً في الجرذان المصابة بالداء السكري تجريبياً. تم استخدام (48) ذكراً بالغاً من الجرذان بعمر 10 أسابيع

تم تقسيمها عشوائياً إلى أربعة زمر كل مجموعة 12 جرذ كالأتي الزمرة الاولى: زمرة مصابة بالداء السكري، الزمرة الثانية: زمرة مصابة بالداء السكري ومعالجة بـــ(أرجينين هدروكلوريد)، الزمرة الثالثة: زمـــرة ســـليمة ومعالجة بـــ(ال-أرجينين هدروكلوريد) والزمرة الرابعة: زمرة سليمة كحيوانات سيطرة. بعد التحقق من حدوث الداء السكري تم البدء بحقن الـــ(ال-أرجينين هدروكلوريد 200 ملغم/ كغم) بشكل يومي في غشاء الخلب الـــى الزمرة الثانية والثالثة أما الزمرتان الأولى والرابعة فقد تم حقنهما بشكل يومي في غشـــاء الخلـــب بـــــ(المـــاء المعقم). أن معايير الدراسة أجريت في المدد 20، 40 و60 حيث تم سحب الدم من الجرذان التي سيتم التضحية بها (4 جرذان من كل زمرة) من اجل حساب كمية السكر، الدهون (TC,TG,LDL-C,HDL-Cو VLDL-C) وتركيز أكسدة الدهون (MDA) كما وتم رفع (الكبد، الكلية) من اجل تسجيل التغيرات المرضية الحاصلة فـــي كل فترة. أظهرت النتائج ان الجرذان المصابة بالداء السكري والغير المعالجة (المجموعـــة الأولـــى) أعطـــت علامات سريرية اشتملت على: العطاش، البوال والنهم وكما أظهرت ارتفاع معنوي ($P<0.05$) بمستوى ســـكر الدم، الدهون (TC,TG,LDL-C and VLDL-C) وانخفاض معنوي ($P<0.05$) في (HDL-C) بالإضـــافة إلى حدوث ارتفاع معنوي ($P<0.05$) في تركيز بروكسيد الدهن (MDA) خلال جميع فترات التجربـــة، أمـــا الفحص المرضي فقد أوضح عدم وجود تغيرات مرضية عيانيا، أما نسجياً فقد شملت التنكس الدهني والاحتقـــان في الكبد في مختلف مراحل التجربة، أما بالنسبة للكلية فقد أظهرت تثخناً وتصلباً في جدران اللمـــة الشـــعيرية. أظهرت النتائج عودة العلامات السوية في الجرذان المصابة بالـــداء الســـكري والمعالجـــة بـــــ(ال-أرجينـــين هدروكلوريد) ابتداءاً من اليوم 20 من التجربة، كما أظهـــرت النتـــائج ان للحمـــض الامينـــي (ال-أرجينـــين هدروكلوريد) ذا تأثير معنوي ($P<0.05$) في انخفاض مستوى سكر الدم أبتدءاً من اليوم 40 للتجربة مقارنة مع الزمرة المصابة بالداء السكري، كما كان له دور فعال في الانخفاض المعنوي ($P<0.05$) لمستوى (TC and LDL-C) أبتدءاً من اليوم 40 وذا تأثير معنوي($P<0.05$) في انخفاض مســـتوى (TG and VLDL-C) فـــي اليوم 60 من التجربة، أما تركيز (HDL-C) فقد اظهر ارتفاعاً ملحوظاً غير معنوي ($P<0.05$) في اليـــوم 60 من التجربة مقارنة مع المجموعة المصابة بالسكري، كما أن الـــ(ال-أرجينين هدروكلوريد) أظهر تأثيرا معنويا ($P<0.05$) في خفض مستوى أكسدة الدهون (MDA) في اليوم 60 من التجربة مقارنة مع المجموعة المصابة بالسكري، أن الدراسة النسجية للأعضاء (الكبد، الكلية) لم تظهر أي تغيرات مرضية في اليوم 60 من التجربة. تم ألأستنتاج بأن الحامض الاميني (ال-أرجينين هدروكلوريد) له تأثير فعال في خفض مستوى سكر مصل الدم وارجاعه الى المستويات الطبيعية، كم كان لة تأثير في خفض مستوى الدهون في مصل الدم (TC,TG,LDL-C and VLDL-C) ورفع مستوى (HDL-C)، كما كان للـــ(ال-أرجينين هدروكلوريد) دور مهم في عمليـــة خفض مستوى أكسدة الدهون في مصل الدم، كما كان له دور مهم وفعال وقائياً في التغيرات المرضية لـــبعض الأعضاء (الكبد، الكلية) حيث أظهرت الصورة النسجية أنها اقرب للنسيج الطبيعي.

Introduction

Diabetes mellitus is a chronic metabolic disorder characterized by a high blood glucose concentration due to insulin deficiency and/or insulin resistance (1). Diabetes mellitus is one of the most challenging health problems in the 21st century (2) Approximately 246 million people worldwide is currently estimated to have diabetes, a global prevalence of 5.9% (3). These high risks are increasing especially in the growing countries due to the new life style and lowered sports in these countries the prevalence may reach to 75 %(4). In Iraq, WHO, in 2000 indicated the number of diabetics was estimated at more than 600 thousand, which is approximately 3% of the entire population (5). Diabetes mellitus syndrome classify into four types: Type 1 or insulin

dependent diabetes mellitus (IDDM), type II or non-insulin dependent diabetes mellitus (NIDDM) (6), type III is Gestational diabetes or gestational diabetes mellitus (7), while Type IV of diabetes may occur due to specific causes include (Chronic pancreatitis and cystic fibrosis) (8). The morbidity associated with long-standing diabetes results from complications such as microvascular including retinopathy, nephropathy and neuropathy and macrovascular complications including coronary artery disease, Peripheral vascular disease and cerebrovascular events (9). The basis of the chronic long-term complications is a subject of a great deal of research, most of the available experimental and clinical evidence suggest that the complications of diabetes mellitus are a consequence of the metabolic derangements, mainly hyperglycemia (10). Hyperglycemia, dyslipidemia and oxidative stress are main cause of major diabetic complication (11), L -Arginine is a semi-essential amino acid in most mammals and can increases insulin secretion (12). The goal of the diabetes mellitus treatment is to control hyperglycemia and dyslipidemia as well as oxidative stress. In this investigation we use amino acid (L-Arginine) to control diabetes or decrease the level of glucose, lipid (TC, TG, LDL and VLDL) and lipid peroxidation as well as the effect of L-Arginine supplementation on histopathological change which may occur due to diabetics complication.

Materials and Methods

- **Animals of experiment:** A total number of 48 albino mature male rats were used in this investigation. The rats were 10 weeks old, body weight (125g-280g with range 195g). Animals in all stage of the experiment were maintained under uniform environmental conditions, The rats were kept at a temperature between 21-28 C° and kept in plastic cages (56, 40, 17 cm), The light and dark cycle was (12:12hr). Rat had free access to fed ordinary pellet diet and water. The animals were adapted for 2 weeks and allocated randomly.
- **Experimental set up:** Forty eight of albino male rats were divided into 4 groups and treated for 60 day as follow:

1. Control group (CG). Consists of 12 animals. They were receiving daily a single dose of sterile distal water intraperitonealy.
2. L-Arginine-HCl control group (AG).This group consists of 12 animals. They were receiving daily a single dose of L-Arginine-HCl intraperitonealy (200mg/Kg B.W).
3. Diabetics group (DG). This group consist of 12 animals were receiving single dose of Alloxan monohydrate (150 mg/kg) to induce diabetic. After (5 days) they were received daily sterile distal water (0.5 cc /animal) intraperitonealy after indication of diabetic.
4. Diabetics with L-Arginine-Hcl group (DAG): This group consists of 12 animals. They received single dose of Alloxan monohydrate (150 mg/ kg) to induce diabetic, after (5 days) they were received daily single dose of L-Arginine-Hclintraperitonealy (200 mg/Kg B.W).

- **Induction of experimental diabetes:** Diabetes was induced by a single ip injection of alloxanmonohydrate (Sigma Chemical Co, United State of America), (150 mg/kg dissolved in sterile normal saline) after fasting the rats for 12 hours (13) After 72 hours of alloxan injection, the diabetic rats (glucose level >135 mg/dl) were separated andused for the study as diabetic rats.
- **L-Arginine preparation:** L-Arginine was obtained from BDH Chemical Company (ENGLAND). Prepared immediately before use by dissolving (1 gm) of L-Arginine Hcl in 10 ml sterile distilled water (10%).
- **Biochemical analysis:** Blood samples were taken from heart of rats by cardiac puncture under ether anesthesia by inhalation at the 20, 40 and 60 day of the study.

After centrifugation at 3000 rpm for 15 min, serum was separated. Serum samples were analyzed for determination of the concentration of (glucose, TC, TG, HDL-C) spectrophotometrically by using commercial kits, according to the BioLinear chemicals kits company (SPAIN), the serum VLDL-C and LDL-C concentration was calculated by friedewald formula (14), the Serum MDA concentration was measured by the thiobarbituric acid (TBA) assay. All biochemical tests will done by Unico spectrophotometer (Germany).

- **Histopathological examination:** After longitudinal abdominal opening of animals, carefully dissected some organ include (Liver and Kidney). All tissue samples were collected out and stored immediately and fixed in formalin (10%), the fixed tissue samples were dehydration by passing the tissue blocks through ascending grades of ethanol (70, 80, 90 and 100%) (1^{st} run) and 100% (2^{nd} run) then clearing by passing the tissue through xylene then embedded in paraffin, mounted on glass slidesand stained with haematoxylin-eosin (15).
- **Statistical analysis:** The statistical analysis was done by using the SAS system v. 6.11. Results are expressed as means ± SE. Differences between groups were analyzed by one-way ANOVA, and if significant paired *t*-test or also called (LSD)least significant differences was used between individual data points. *P*-values are two-sided and considered significant when $P < 0.05$ (16).

Results

- **Serum Glucose concentration:** The statistical analysis for Serum Glucose concentration (mg/dl) revealed that the DG showed a significant increase ($P<0.05$) in serum glucose concentration at the 20, 40 and 60 days compared with CG in the same period, Meanwhile DAG showed significant ($P<0.05$) decrease in serum glucose concentration at days 40 and 60 (compared with DG in the same period. On the other hand, the DAG showed significant decrease in serum glucose concentration at day 60compared within day 20, as shown in (Table 1).
- **Serum Cholesterol Concentration:** Our results showed significant increase ($P<0.05$) in total serum cholesterol (mg/dl) in DG at days 20, 40 and 60 respectively compared with CG and AG at the same period. Meanwhile DAG showed significant decrease ($P<0.05$) in total serum cholesterol at days 40 and 60 compared with DG in the same time, also DAG showed significant decrease ($P<0.05$) in total serum cholesterol at days 40 and 60 compared within 20 day, (Table 2).
- **Serum TG Concentration:** The serum TG mg/dl concentration for theDG showed significant increased ($P<0.05$) at days 20, 40 and 60 compared with CG and AG at the same time. On the other hand the DAG group showed significant decrease ($P<0.05$) serum TG concentration in day 60compared with DG at the same time. Also the DAG showed significant decrease ($P<0.05$) in TG serum concentration during days 40 and 60 Compared with day 20, (Table 3).
- **Serum HDL-C. Concentration:** It was clear that animal inDG revealed significant decrease ($P<0.05$) in serum HDL-C concentration at days 40 and 60 compared with CG and AG at the same time. Also there is no significant ($P<0.05$) in DG during days 20, 40 and 60 respectively. Moreover non-significant ($P<0.05$) increase in HDL-C concentration was observed of DAG at days 40 and 60 compared with DG at the same time, but these results are non-significant ($P<0.05$).While DAG showed significant increase ($P<0.05$) in serum HDL-C concentration at day 60 compared with it at day 40, (Table 4).
- **Serum LDL-C Concentration:** Our results showed that the DG has a significant increase ($P<0.05$) in serum at 20, 40 and 60 days compared with CG and AG at the same, meanwhile the DG showed no significance ($P<0.05$) difference during 20, 40

and 60. Also, the DAG was showed a significant decrease (P<0.05) in a concentration of the LDL-C concentration in serum at days 40 and 60 compared with DG at the same time. Moreover the DAG showed significant decrease (P<0.05) at days 40 and 60 compared with day 20, as shown in (Table 5).

- **Serum VLDL-C. Concentration (mg/dl):** In DAG group a significant decrease (P<0.05) in VLDL-C serum concentration at day 60 (19.60 mg/dl ±1.50 mg/dl) was observed compared with DG at the same time. Also the DAG showed significant decrease (P<0.05) in VLDL-C serum concentration at days 40 and 60 compared with day 20, as shown in (Table 6).
- **Serum MDA Concentration (µmol/d):** The results revealed that the DG has significant increase (P<0.05)in the concentration of the serum MDA concentration **(**µmol/d) compared with other groups DAG, AG and CG. Table (7)
- **Histopathological study**

- **Liver:** The gross appearance of liver of DG at day 20 showed slightly paleness, it become pale to yellow at days 40 and 60 (Fig1).
- Microscopically: at day 20 the histopathological examination of DG showed degenerative changes characterized by fatty changes (Fig 2), at days 40 and 60 the liver showed severe fatty change with acute cellular degeneration with congestionofsinosoides with inflammatory cell infiltration mostly lymphocytic cuffing (Fig 3, 4 and 5). In DAG treated with L-Arginine, the liver architecture appears more or less like CG with the exception of some congestion areas in the blood sinusoids (Fig. 6, 7).
- **Kidney:** Histopathological section of kidney in DG group at day 20 and 40 showed degenrative changes in kidney tubule with shrinkage in glomerula tuft and congestion (Fig. 8, 9). At day 60, the histopathological changes in kidney indicate hyper cellular of glomerula tuft and increase in the amount of mesangialmarix cell and increase thickness of basement membrane of the glomeruli with hyalinization of the arterioles of kidney showed hyperplasia in the tunica intema and tunica media with observation of foam cell in tunica intema and tunica media (Fig. 10, 11). The kidney architecture of DAG treated with L-Arginine, appeared more or less like CG with the exception of some inflammatory infiltration that appeared in the interstitum (Fig. 12, 13).

Table (1) Effect of L-Arginine on serum glucose (mg/dl) concentration in normal and diabetes rats groups at different periods

DAYS / GROUPS	20 Days	40 Days	60 Days
DG	230.75±23.71 A a	215.50±9.59 A a	188.75±11.24 A a
DAG	196.00±14.33 A a	160.25±27.24 B ab	112.00±2.88 B b
AG	118.25±4.47 B a	126.00±0.40 BC a	120.00±3.57 B a
CG	108.00±10.23 B a	97.00±5.73 C a	116.00±3.53 B a

Table (2) Effect of L-Arginine on serum cholesterol (mg/dl) concentration in normal and diabetes rats groups in different periods

DAYS / GROUP	20 Days	40 Days	60 Days
DG	204.25±21.25 A a	148.00±19.81 A a	159.00±15.64 A a
DAG	202.75±14.34 A a	120.00±9.75 B b	96.00±6.00 B b
AG	106.00±9.68 B a	111.00±0.00 B a	116.25±1.75 B a
CG	92.00±2.44 B a	111.75±19.43 B a	116.75±1.97 B a

Values are expressed as mean ± SE, n= 4/group, Capital letters denote significant difference (P<0.05) within a column, Small letters denote significant differences (P<0.05) within a row, DG: Diabetic group, DAG: Diabetic arginine group, AG:-Arginine group, CG:-Control group.

Table (3) Effect of L-Arginine on serum TG (mg/dl) concentration in normal and diabetes rats groups at different periods

DAYS / GROUP	20 Days	40 Days	60 Days
DG	156.50±15.83 A a	106.50±4.71 A b	189.75±16.89 A a
DAG	191.25±16.05 A a	101.50±6.99 AB b	98.00±7.51 B b
AG	116.25±6.48 B a	86.00±2.67 B b	109.50±8.41 B ab
CG	108.25±6.93 B a	79.75±7.33 B b	93.50±2.90 B ab

Table (4) Effect of L-Arginine on serum HDL-C (mg/dl) concentration in normal and diabetes rats groups at different periods

DAYS / GROUP	20 Days	40 Days	60 Days
DG	45.75±4.58 A a	23.00±2.82 C b	26.50±2.72 C b
DAG	48.75±5.76 A a	31.75±2.59 BC b	50.75±4.88 BC a
AG	52.25±2.28 A a	41.00±2.97 B a	59.25±2.21 AB a
CG	42.75±3.90 A a	55.00±4.70 A a	67.25±3.63 A a

Values are expressed as mean ± SE, n= 4/group, Capital letters denote significant difference (P<0.05) within a column, Small letters denote significant differences (P<0.05) within a row, DG: Diabetic group, DAG:- Diabetic arginine group, AG: Arginine group, CG: Control group.

Table (5) Effect of L-Arginine on serum LDL-C (mg/dl) concentration in normal and diabetes rats groups at different periods

DAYS / GROUP	20 Days	40 Days	60 Days
DG	119.70±20.96 A a	81.25±3.57 A a	96.55±17.13 A a
DAG	115.75±18.40 A a	59.45±9.32 B b	25.65±4.98 B c
AG	35.55±8.81 B b	70.47±2.49 AB a	34.50±0.77 B b
CG	27.60±5.03 B b	40.30±2.64 C a	30.90±1.96 B ab

Table (6) Effect of L-Arginine on serum VLDL-C (mg/dl) concentration in normal and diabetes rats groups at different periods

DAYS / GROUP	20 Days	40 Days	60 Days
DG	31.30±3.16 A ab	23.00±1.51 A b	45.95±9.29 A a
DAG	38.25±3.21 A a	20.30±1.39 AB b	19.60±1.50 B b
AG	23.25±1.29 B a	17.27±0.53 B ab	20.30±1.50 B a
CG	21.65±1.38 B a	15.20±0.82 B ab	18.60±0.57 B a

Values are expressed as mean ± SE, n= 4/group, Capital letters denote significant difference (P<0.05) within a column, Small letters denote significant differences (P<0.05) within a row, DG: Diabetic group. DAG: Diabetic arginine group, AG: Arginine group, CG: Control group.

Table (7) Effect of L-Arginine on serum MDA (µmol/d) concentration in normal and diabetes rats groups at day 60

DAYS / GROUP	60 Days
DG	0.11±0.009 A
DAG	0.072±0.002 B
AG	0.071±0.010 B
CG	0.06±0.004 B

Values are expressed as mean ± SE, n= 4/group, The letters denote significant difference (P<0.05), DG: Diabetic group, DAG: Diabetic arginine group, AG: Arginine group, CG: Control group.

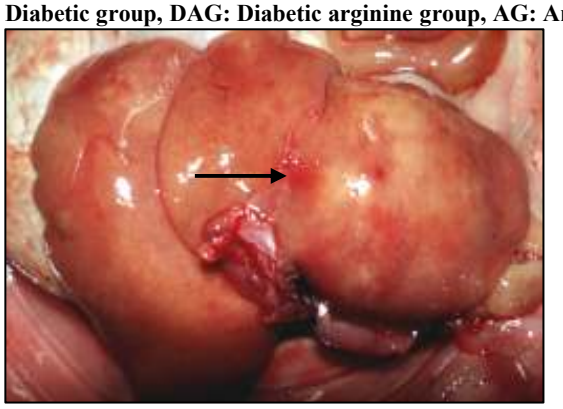

Fig. (1) Showed the paleness to yellowish in color (fatty change) (→)

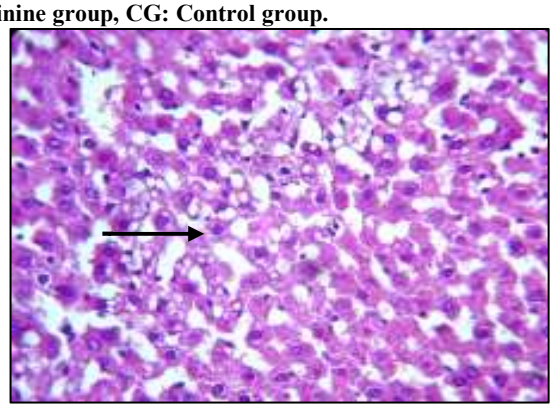

Fig. 2: Histopathological section in the liver of DG at days 20 showed mild fatty change (→) (H and E, X40).

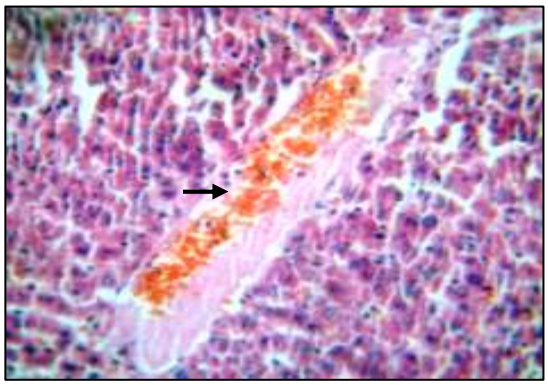

Fig (3) Histopathological section in the liver of DG at days 40 showed congestion of the portal blood vessel (→) (H and E, X40).

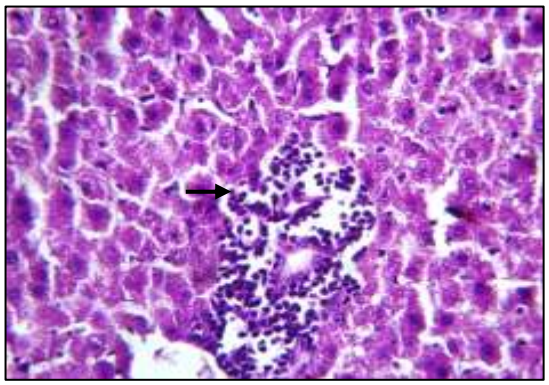

Fig (4) Histopathological section in the liver of DG at days 40 showed inflammatory cell infiltration (→) (H and E, X40).

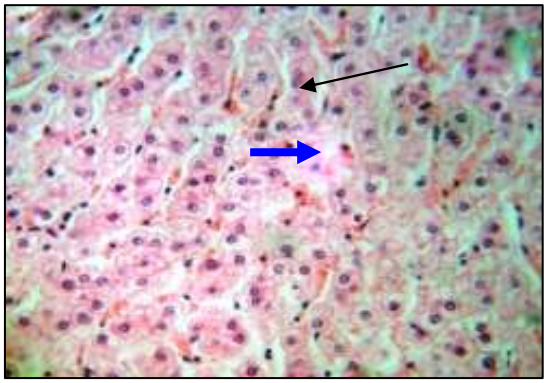

Fig. (5) Histopathological section in the liver of DG at days 60 showed severe fatty change (⟶) and hemorrhage in sinusoid (⟶) (H and E,X40).

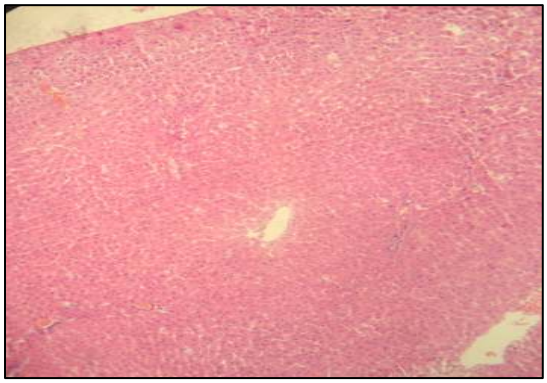

Fig. (6) Histopathological section in the liver of DAG in days 60 (H and E, X10).

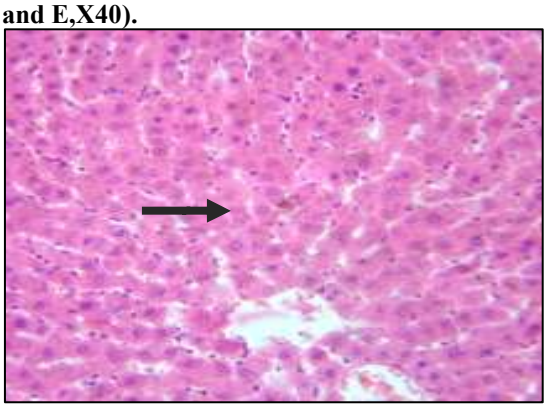

Fig. (7) Histopathological section in the liver of DAG in days 60 showed normal liver architecture (⟶) (H and E, X40).

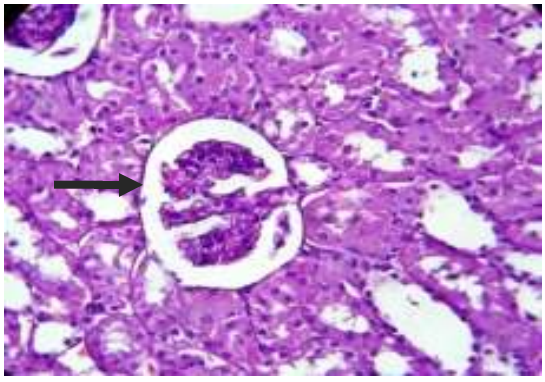

Fig. (8) Histopathological section in the kidney of DG in day 20 showed atrophy of glumerular tuft with widening of urinary space (⟶) (H and E, X40).

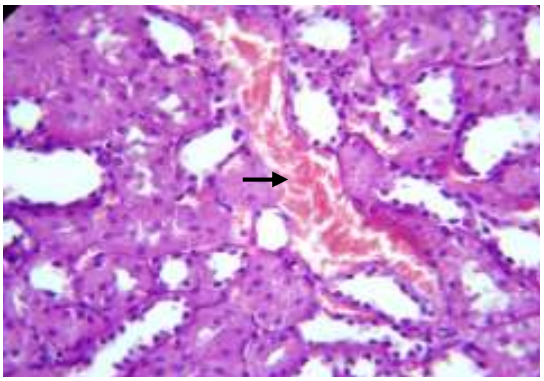

Fig. (9) Histopathological section in the kidney of DG at day 40 showed congestion (⟶) (H and E, X40).

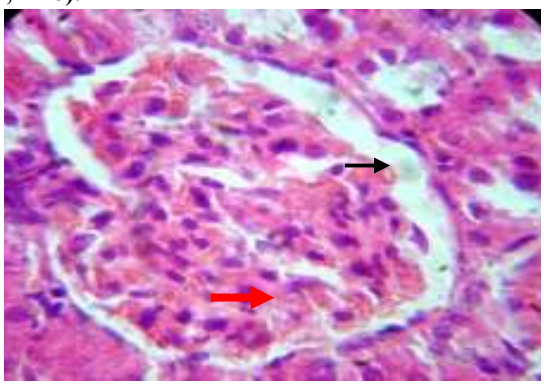

Fig. (10) Histopathological section in the kidney of DG at day 60 showed hyalinization of the arterioles of glomerular tuft (⟶) and thickness in basement membrane (⟶) (H and E, X100).

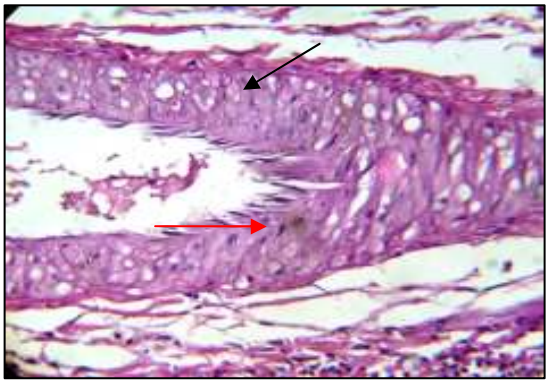

Fig. (11) Histopathological section in the kidney of DG in day 60 showed hyperplasia of endothelial cell (➡) and presece of foam cell (⟶) (H and E, X40).

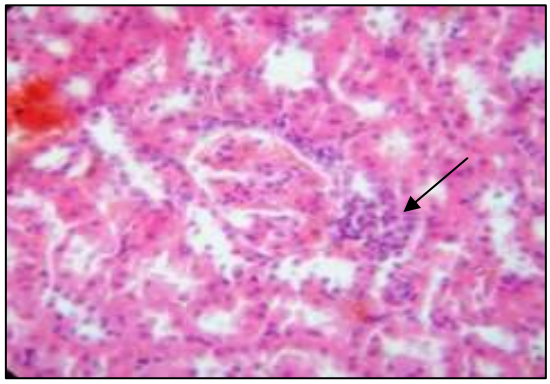

Fig. (12) Histopathological section in the kidny of DAG at day 40 showed inflammatory cell infiltration (⟶) (H and E, X40).

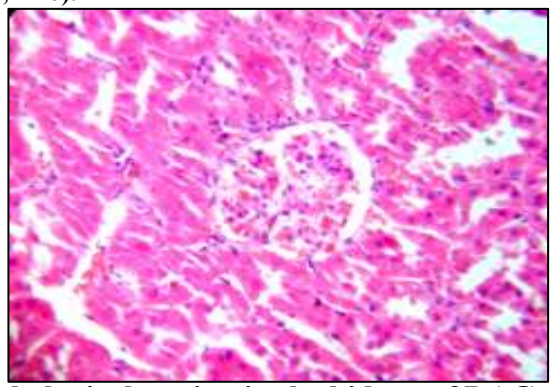

Fig. (13) Histopathological section in the kidney of DAG at day 60 (H and E, X40).

Discussion

Significant increase (P<0.05) in serum glucose concentration in DG of blood glucose concentration thatmay be due to destruction of the ß-cells in pancreas by Alloxan and absent of insulin secretion (17). Our results demonstrate that administration of L-Arginine to the DAG showed significant (P<0.05) decrease in the serum glucose concentration at days 40 and 60 compared with DG in the same period. This is a very significant finding, may due to the following cause: The L-Arginine stimulates glucose uptake and utilization by skeletal muscle by increasing GLUT-4 translocation to the plasma membrane (18). Also (19, 20) reported that the NO donors increase basal skeletal muscle glucose uptake in rats. Also the hypoglycemic effect of L-Arginine may leads to β cell neogenesis (21). The result showed significantly increase (P<0.05) in serum TC, TG, VLDL-C and LDL-C (mg/dl) and significant decrease (P<0.05) of serum HDL-Cconcentration in DG group compared with CG at the same time. In the diabetic state insufficiency of insulin leads to lipogenesis inhibition, increased lipolysis which lead to increased efflux of free fatty acids from adipose tissue and impaired insulin-mediated skeletal muscle uptake of free fatty acids which lead to increase hepatic free fatty acid concentrations (22). In response, the liver will increase VLDL production and cholesteryl ester synthesis (23). Free fatty acids combine with a cholesterol molecule to form a cholesteryl ester. Cholesteryl ester concentrations may regulate VLDL production, with increased concentrations of cholesterol ester that lead to elevated the VLDL synthesis (24) .The increase of T.G , LDL-C particles results from increased VLDL secretion (25). Also the elevation of TG may be due to impaired of lipoprotein lipase (24). The lipoprotein lipase activity is markedly impaired due to insulin deficiency (26, 27). While insulin increases the number of LDL receptor, so chronic insulin deficiency might be associated with a diminished concentration of LDL

receptor (28). The hepatic TG lipase become more active and catabolizes the TG resulting a reduction in HDL particle size and an increase in HDL-C clearance, which leads to decreased HDL-C concentration in diabetic case (24, 29). These results agree with the studies of (30, 31, 32, 33).These studies reported that diabetic rats had marked elevated concentration of plasma T.G, total cholesterol and LDL-C but decreased concentration of plasma HDL-C. The DAG showed significant decreased in total serum cholesterol and LDL-C,TG and VLDL-C and significant increase in HDL-C these result reveal theability L-Arginine can normalizes dyslipidemia may involve: The hypocholesterolemic effect of L-Arginine might be due to decreased activity of its synthesis by the liver. It has been shown that L-Arginine administration into diabetic rats decreased the activity of HMG-CoA reductase in the liver (34). Our results showed that hyperglycemic associated with significant increase in the concentration of the serum MDA concentration in DG and this may be due to the abnormal lipid metabolism (35), also oxidative stress arises because of excessive production of reactive oxygen species and impaired antioxidant defense mechanisms (36) could be suggested. The damages that occurred in the liver of DG may be due to oxygen free radicals (37). The imbalance between Oxygen free Radicals production and cellular defense mechanisms could be critical in influencing vascular injury (38). The excessive fatty change in liver of DG may be due to the glycogenolysis, lipolysis and proteolysis that may occur as a result to hyperglycemia and insulin insufficiency and defect in lipid metabolism (39). The histopathological changes that occurred in the Kidney like the liver of DG may be due to oxygen free radicals production (41). The histopathological changes observed in DG group may be also due to increase of total protein excreted, albuminuria, glycosuria, and urinary urea levels, indicating impaired renal function of diabetic rats (42). The DAG normalized the histological abnormalities caused by diabetes. This improvement may due to its antioxidant effects of L-Arginine that protect against oxidative stress. Antioxidant-based therapy is promising to minimize the complications associated with oxidative stress in diabetes mellitus (43, 44). The protective mechanism of L-Arginine also by normalizing of dislipedimia and hyperglycemia (21).

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