Research Article

Proceeding of 8th International Scientific Conference, College of Veterinary Medicine University of Basrah, Dec. 7-8, 2022,Iraq.

BASRAH JOURNAL OF VETERINARY RESEARCH, 2022, 21(S1):162-176
https://bjvr.uobasrah.edu.iq/

The Protective Effect of Alpha-Lipoic Acid on Oxidative Stress and Proinflammatory cytokines in L-Arginine-Induced Acute Pancreatitis Male Rats

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Accepted: Nov. 2022

Abstract

Acute pancreatitis (AP) is a common serious stirring disease of the pancreas characterized by strict abdominal twinge that lasts for days to weeks. Rats were injected with high dose of the amino acid L-arginine (500 mg/kg B.W.). The study has been done to induce acute pancreatitis (AP) by L-Arginine (Arg) and to investigate the effect of AP on body weight, body weight gain, serum amylase, lipase, oxidative stress and proinflammatory cytokine parameters. In addition, some histopathological changes in pancreas and intestine were examination in male rats.

Serum amylase, lipase, IL-6, and TNF-α levels, and MDA levels significantly increased in rats with L-Arginine induced AP. However, the boy weight and body weight gain, serum GPx, SOD and CAT activity significantly reduced. In addition, some histological changes in pancreas and intestine were identified, reversed and improved with ALA treatment.

Key words: α-Lipoic acid, oxidative stress, Proinflammatory cytokines, L-Arginine, Acute Pancreatitis.

Introduction

Acute pancreatitis (AP) represents confront to the health society since: (i) it can lead to systemic irritation and numerous organs dysfunction syndromes; (ii) high mortality rate that can reach 50% in severe AP form and (iii) there is no available drug of choice to treat pancreatitis (1,2). In AP, activation of digestive proteinases caused auto digestion and inflammation of the pancreas, which can lead in severe cases to diffuse pancreatic necrosis and bleeding, leukocyte penetration, necrosis and apoptosis of pancreatic acinar cells (3). Additionally, it is supposed that many etiological factors supply to this disease like the gallstone overcrowding the common bile duct, direct trauma, unpleasant drug effects, virus, sepsis and shock (4). Experimental AP using animal models of the disease is very useful to thoroughly understand the pathophysiology of the disease and to test potential drugs and compounds to treat acute pancreatitis (5). L-arginine-induced acute pancreatitis in rats and mice is reported following an injection (i.p. injections) of two doses (2.5 - 4 gm/kg) of the amino acid (6, 7).

L-Arginine (Arg) is a semi-essential amino acid that can be synthesized from glutamine, glutamate, and proline via the urea cycle (the intestinal-renal axis in humans and most other mammals (including pigs, sheep and rats)). Arg is involved in protein synthesis and is the substrate for nitric oxide synthase (NOS) to create the vascular protective nitric oxide (NO) released from the endothelial cells (8) Since decreased bioavailability of NO or deficiency of NO production promote development of kidney diseases and is exceedingly associated with aging (9, 10). A current Mendelian randomization study proposed that soaring L-Argin levels are associated with elevated risk of ischemic heart disease, which further indicates that chronic L-Arg supplementation may cause destructive effects. Unfavorable effects seemed dependent on the dosage regime (11).

Alpha-Lipoic Acid (ALA) is a naturally taking place composite that is formed endogenously by plants and animals, acting as a cofactor for enzyme complexes such as pyruvate dehydrogenase and α-ketoglutarate dehydrogenase. In addition, LA acts as an antioxidant in both oxidized (LA) and reduced (dihydrolipoic acid; DHLA) forms (12). Beside its role in direct radical scavenging and metal chelating activity. There are reports that LA may act indirectly to maintain the cellular antioxidant status by regeneration reduced forms of essential intracellular antioxidants. The current study aimed to determine whether potential role of ALA on oxidative stress and proinflammatory cytokines in L-Argin-Induced AP male rats.

Materials and Methods

All experimental measures were accepted by the health check explore principled team at University of Basrah and according to the Guide for the care and use of animal's house. Wistar rats (total 50 rats) weighing 200-250 g were used for these studies. All rats were housed at temperatures of 23 ± 1 °C and a 12 h light: 12 h dark cycle. Rats had free access to tap water and fed standard foodstuff during the adaptation period.

Experimental design. After a one-week adaptation period, rats were randomly assigned into 3 groups (n = 10; each) and distributed in their corresponding cages and classified as follows: Control group (Control): non treated rats that were injected

i.p with vehicle. Group two: L-Argin-treated the model group (L-Arg): rats were injected i.p on day 21with 500 mg/kg L-Argin, they received no treatment (vehicle) in the first three weeks The protective group (ALA+L-arg): rats were treated with ALA (50 mg/kg) from day 1 – day 14 and injected on day 15 with 500 mg/kg L-Argin. At the end of experimental period (on day 21), blood samples were collected by cardiac puncture under anesthesia (chloroform at 40 mg/kg body weight) Animals were then culled and tissues were harvested. Blood samples were collected without anticoagulant and allowed to stand for 10 min, centrifuged at 4000 r/ min for 10 min to obtain serum, which was stored at –20 °C until further biochemical analysis. Histological examination. Pancreas and intestine from all rats were collected and fixed in formol saline (10 %) for 24 h prior to dehydrate with alcohols and paraffin embedding using standard methods. Blocks were processed, sectioned in 5mm thickness and subjected to H&E staining to observe the morphological changes (13). Measurement of body weight, body weight gain and weight of pancreas. The animals were weighed before starting the experiment and at the end of the experiment (14). Determination of blood levels of Calprotectin, TNF-α, IL-6. MDA, SOD, GPx and Catalase were done. Amylase and Lipase were also measured. At day 21, animals were sacrificed and serum levels of TNF-α (Abcam, Cambridge, UK) and IL-6 (RayBio, GA, USA) were determined using ELISA kits according to the manufacturer's instructions.

Statistical and morphometric analysis: The data were expressed as mean standard deviation (SD). Data were processed and analyzed using the SPSS version 10.0 (SPSS, Inc., Chicago, Ill., USA). One-way ANOVA was performed followed by Tukey's post hoc test. Quantitative data were tabulated as a means and standard deviations (SD) and compared using analysis of variance (ANOVA) followed by post-hoc analysis (Tukey test). A significant difference was considered when P-value ≤ 0.05. Calculations were made on SPSS software (version 23)

Result

1-Effect of α-Lipoic Acid on Body Weight, Body Weight Gain and Weight of Pancreas in Acute Pancreatitis Male Rats Induced by L-Arginine. The current study revealed a significant decrease (P≤0.05) in final body weight and body weight gain in acute pancreatitis male rats' group(+ve) compared with (-ve) control group (Table 1). While, the result of final body weight and body weight gain in acute pancreatitis male treated with α-lipoic (50 and 100 mg/kg dose) and treated α-lipoic (100mg/kg alone significant (P≤0.05) revealed increased compared with control Positive. The present study revealed a significant increase (P≤0.05) in weight of pancreas in acute pancreatitis male rats induced by L-Arginine (+ve) control compared with control (-ve) and treated with α-lipoic (50 and 100 mg/kg dose) (Table 1). While, the results showed non-significant change (P>0.05) in weight of pancreas in acute pancreatitis male rats treated with α-lipoic (100 mg/kg dose) compared with control (-ve) group.

2-Effect of α-Lipoic Acid on Amylase and Lipase Concentrations in serum of Acute Pancreatitis Male Rats Induced by L-Arginine. The obtained results revealed a significant increase (P≤0.05) amylase in

serum of acute pancreatitis male rats induced by L-Arginine (+ve) control compared with (-ve) control group and another treated (Table 2). While, the results showed a non-significant change (P≤0.05) amylase in serum of acute pancreatitis male rats treated with α-Lipoic acid (50 and 100mg/Kg B.W.) and treated with α-Lipoic acid (100mg/Kg B.W.) alone compared with (-ve) control. The obtained results) revealed a significant increase (P≤0.05) lipase in serum of acute pancreatitis male rats induced by L-Arginine (+ve) control compared with (-ve) control group and another treated (Table 2). While, the results showed a non-significant change (P≤0.05) lipase in serum of acute pancreatitis male rats treated with α-Lipoic acid at dose (50 and 100mg/Kg B.W.) and treated with α-Lipoic acid at dose 100mg/Kg B.W. alone compared with (-ve) control.

3-Effect of α-Lipoic Acid on Antioxidative Stress Concentrations in serum of Acute Pancreatitis Male Rats Induced by L-Arginine. The present study revealed a significant increase (P≤0.05) MDA in serum of acute pancreatitis male rats induced by L-Arginine (+ve) control compared with (-ve) control group and another treated (Table 3). While, the results showed a significant increase (P≤0.05) MDA in serum of acute pancreatitis male rats treated with α-Lipoic acid at dose (50and 100mg/kg) and α-Lipoic acid alone group compared with (-ve) control group. The results of SOD revealed a significant decrease (P≤0.05) in acute pancreatitis male rats induced by L-Arginine (+ve) control compared with (-ve) control and treated with α-Lipoic acid at dose (50and 100mg/kg). While, the results showed a non-significant change (P≥0.05) SOD in serum of male rats treated with α-Lipoic acid alone compared with (+ve) control. The results of Gpx revealed a significant increase (P≤0.05) in acute pancreatitis male rats induced by L-Arginine (+ve) compared with (-ve) control and treated α-Lipoic acid at dose (50and 100mg/kg). While, the results showed a non-significant change (P≤0.05) Gpx in serum of male rats treated with α-Lipoic acid alone compared with (+ve) control. The results of CAT revealed a significant decrease (P≤0.05) in acute pancreatitis male rats induced by L-Arginine (+ve) control compared with (-ve) control and treated with α-Lipoic acid at dose (50and 100mg/kg). While. the results showed a non-significant change (P≥0.05) CAT in serum of male rats treated with α-Lipoic acid alone compared **with (+ve) control.**

4-Effect of α-Lipoic Acid on Proinflammatory Cytokine Concentrations in serum of Acute Pancreatitis Male Rats Induced by L-Arginine. The current study showed a significant increase (P≤0.05) of serum calprotectin (Cal), TNF-α and IL-6 concentrations in acute pancreatitis male rats group compared with control group (Table 4). The present results revealed a significant increase (P≤0.05) Cal in serum of acute pancreatitis male rats induced by L-Arginine (+ve) control compared with (-ve) control group and another treated (Table 5). While, the results showed a significant increase (P≤0.05) Cal in serum of acute pancreatitis male rats treated with α-Lipoic acid at dose (50and 100mg/kg) and α-Lipoic acid alone group compared with (-ve) control group. The results of TNF-α revealed a significant increase (P≤0.05) in acute pancreatitis male rats induced by L-Arginine (+ve) control compared with (-ve) control and treated with α-Lipoic acid at dose (50and 100mg/kg). While, the results showed a non-significant change (P≥0.05) TNF-α in serum of male rats treated with α-Lipoic acid alone

compared with (+ve) control. The results of IL-6 revealed a significant increase (P≤0.05) in acute pancreatitis male rats induced by L-Arginine (+ve) compared with (-ve)control and treated α-Lipoic acid at dose (50and 100mg/kg). While, the results showed a non-significant change (P≤0.05) IL-6 in serum of male rats treated with α-Lipoic acid alone compared with (+ve) control.

Histological Examination 1 -Pancreas The pancreases of negative control group rats appeared to be divided into two different types of glandular tissue, exocrine and endocrine, embedded between the exocrine units lie clusters of endocrine cells called pancreatic islets (Fig 1) and (6) normal of Langerhans islets. Control rat pancreas showed closely packed lobules of pancreatic acini. The acini are formed of pyramidal cells with basal nuclei and apical acidophilic cytoplasm. Islets of Langerhans were embedded within the exocrine portions and alpha cells (arrows) located on the peripheral. While, the AP male rats induced by L-Arginine positive control group revealed histopathological changes including both exocrine and endocrine part of the pancreas represented by vacuolation (v) and degeneration marked decrease of b-cells. Some exocrine acini revealed focal acinar damage represented by cytoplasmic vacuolation and pyknotic nuclei of some acinar cells obvious (Fig 2 and7). The rat treated with L-arginine injected lead to pancreas marked atrophy of islets of Langerhans and severe congestion in other sections. In addition to proliferation of the fibrous connective tissue (fibrosis), within the pancreatic lobules causing pressure atrophy of the pancreatic tissue. In contrast to result that injected of L-arginine in male rats combination with α-lipoic acid at dose (50mg/Kg B.W.), the histological changes revealed ameliorate damage areas in pancreatic structure composed from several rounded or tubular groups of pancreatic cells called acini and congested blood vessels in other sections (Fig 3 and 8). Moreover, the pancrease of rabbits treated with 50 mg /B.W. of α-Lipioc acid showed clear revealed histopathological changes. Furthermore, the pancrease of acute pancreatitis male rats treated with (100mg/kg B.W.) α-Lipioc acid showed amelioration of architecture of islets langerhan's compared with pancreas treated with L-arginine alone (Fig 4 and 9). The pancreas of rats treated with 100mg/kg B.W. α-Lipioc acid showed nearly normal structure of islets of Langerhans embedded within the exocrine portions which are formed of pyramidal cells with basal nuclei. After treated with (100mg/kg B.W.) α-Lipioc acid, the pancreas appeared similar to the control and most of the islets of Langerhans (Fig 5 and 10).

2- Intestine: The male rat treated with L-Argin i.p. revealed congestion of blood vessels of glandular region with perivascular lymphocytic infiltrations and plasma cells (Fig. 17). However, L-Arginine with lipoic acid(50mg/kgB.W.) revealed egrease perivascular lymphocytic infiltrations (Fig 18). In other sections in group treated by L-arginine with 100mg lipoic acid showed mononuclear aggregation (Fig 19). In contrast to result that i.p. of L-Arginine in combination with 100mg α-lipoic acid showed marked hyperplasis (Fig.15). Intestinal crypts extend downward to the deepest tunica mucosa and blood congestion was also seen (Fig 20).

Table (1): Effect of α-Lipoic Acid on Body Weight, Body Weight Gain and Weight of Pancreas in Acute Pancreatitis Male Rats Induced by L-Arginine. (Mean±SD) (N=10)

Parameters Treatments	Initial Body Weight (g)	Final Body Weight (g)	Body Weight Gain (g)	Weight of Pancreas (g)
Control (-ve) Normal Saline (0.9% NaCl)	200.07± 1.77 NS	210.47± 2.75 a	9.6±0.33 a	16.39±0.64 b
Control (+ve) L-arginine(500mg/kg)	201.61 ± 1.01 NS	160.67 ± 2.36 b	-40.94±0.11 c	43.07±0. 21 a
L-arginine +α-Lipoic acid (50mg/kg)	205.63 ± 3.01 NS	211.67 ± 8.01 a	6.04±0.26 b	18.40±0. 41 b
L-arginine +α-Lipoic acid (100mg/kg)	207.73 ± 2.23 NS	212.73 ± 5.23 a	5.00±0.01 b	19.09±0. 18 b
α-Lipoic acid(100mg/kg)	209.23±3.48 NS	219.21±3.04 a	9.00±0.17 a	16.76±0. 28 b

N=number of animals, Small letters denote differences between groups, P≤0.05 vs. control, NS=non-significant.

Table (2) Effect of α-Lipoic Acid on Amylase and Lipase Concentrations in Serum of Acute Pancreatitis Male Rats Induced by L-Arginine. (Mean±SD) (N=10)

Parameters Treatments	Amylase U/L	Lipase U/L
Control (-ve) Normal Saline(0.9% NaCl)	329.14±32.31 b	224.81± 6.98 c
Control (+ve) L-arginine(500mg/kg)	631.84±36.91 a	552.81 ±7.43 a
L-arginine +α-Lipoic acid (50mg/kg)	367.02±22.10 b	373.15±32.62 b
L-arginine +α-Lipoic acid (100mg/kg)	257.72±12.48 c	225.34± 16.17 c
α-Lipoic acid(100mg/kg)	323.47±24.79 b	221.23±8.66 c

N=number of animals, small letters denote differences between groups, P≤0.05

vs. control, NS=non-significant.

Table (3): Effect of α-Lipoic Acid on Antioxidative Stress Concentrations in Serum of Acute Pancreatitis Male Rats Induced by L-Arginine. (Mean±SD) (N=10)

Parameters Treatments	MDA mg/dl	SOD mg/dl	GPx mg/dl	CAT mg/dl
Control (-ve) Normal Saline(0.9% NaCl)	103.67± 14.70 c	1.97±0.03 c	60.53±19.33 b	569.45±3.38 a
Control (+ve) L-Arginine(500mg/kg)	215.63±29.37 a	0.62±0.14 d	47.83 ±12.92 c	337.43±6.49 b
L-Arginine +α-Lipoic acid (50mg/kg)	149.93±5.51 b	1.84±0.79 c	55.80 ±9.12 b	506.67±9.27 a
L-Arginine +α-Lipoic acid (100mg/kg)	127.61±18.28 c	2.65±1.27 b	57.00±7.96 b	519.78±2.32 a
α-Lipoic acid(100mg/kg)	110.67±8.58 c	4.61±0.65 a	78.43±14.58 a	565.37±7.6 a

N=number of animals, small letters denote differences between groups, P≤0.05 vs. control, NS=non-significant.

Table (4): Effect of α-Lipoic Acid on Proinflammatory Cytokine Concentrations in Serum of Acute Pancreatitis Male Rats Induced by L-Arginine. (Mean±SD) (N=10)

Parameters Treatments	Cal µg/mg	TNF-α ng/L	IL-6 pg/ml
Control (-ve) Normal Saline (0.9% NaCl)	350.92 ± 10.01 b	120.12 ± 36.43 c	1.85±0.37 d
Control (+ve) L-Arginine(500mg/kg)	3000.34 ± 36.89 a	200.60 ± 45.23 a	5.56±0.09 a
L-Arginine +α-Lipoic acid (50mg/kg)	377.41± 18.41 b	160.17 ± 14.21 b	2.26±0.27 c
L-Arginine +α-Lipoic acid (100mg/kg)	360.52 ± 24.39 b	140.11 ± 30.25 b	4.05±0.35 b
α-Lipoic acid(100mg/kg)	347.68 ± 15.33 b	126.02 ± 23.29 c	5.49±0.67 a

N=number of animals, small letters denote differences between groups, P≤0.05 vs. control, NS=non-significant.

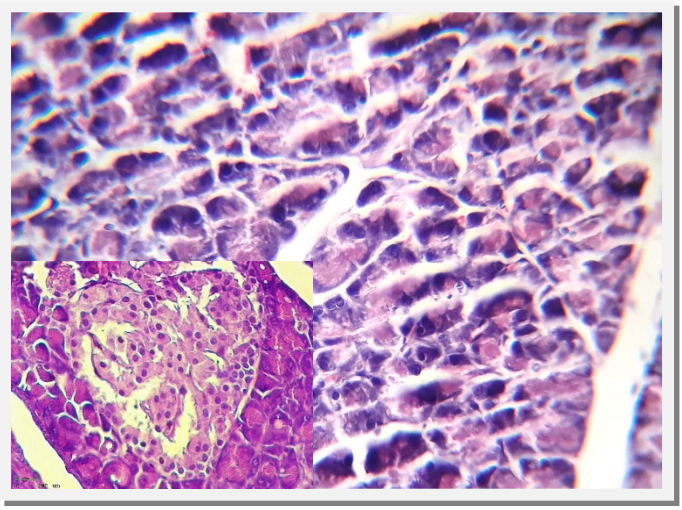


Fig. (1) Cross section of rat's pancreas control group showing normal acini were pear shaped pancreatic cells. 400X. H&E.

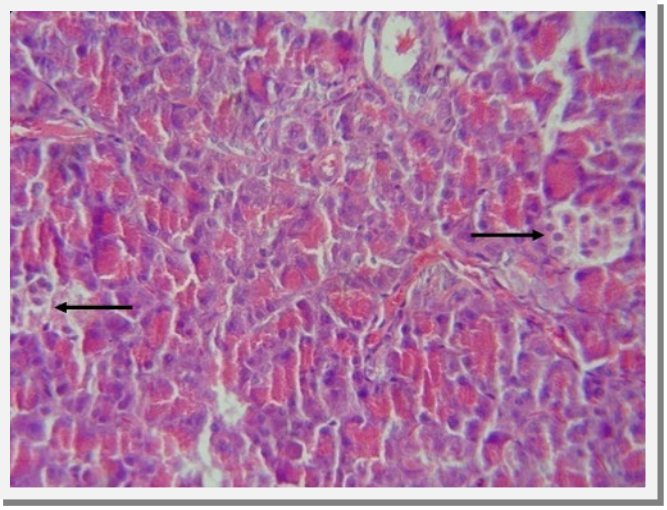


Fig. (2): Cross section of pancreas rat treated with Arginine induced acute pancreatitis shows mar atrophy of islets of Langerhans (arrow). 200X H&I

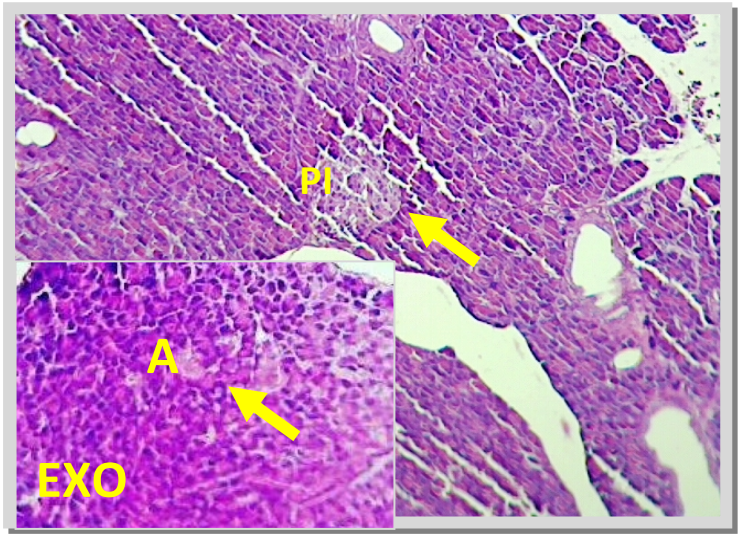


Figure (3): Cross section of pancreas of AP) male rats treated with ALA (50mg/kg)showed marked normal structure of acini (A) and Islet of pancreatic Langerhans (arrow). 200X ,400 XH&E.

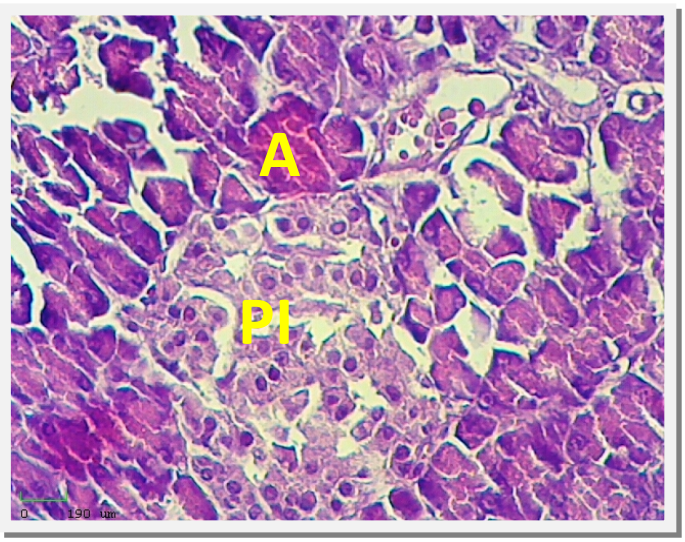


Figure (4): Cross section of pancreas of (AP) male r treated with ALA (100mg/kg), showing normal a (A)were pear shaped and normal islet of pancreas. 40(H& E.

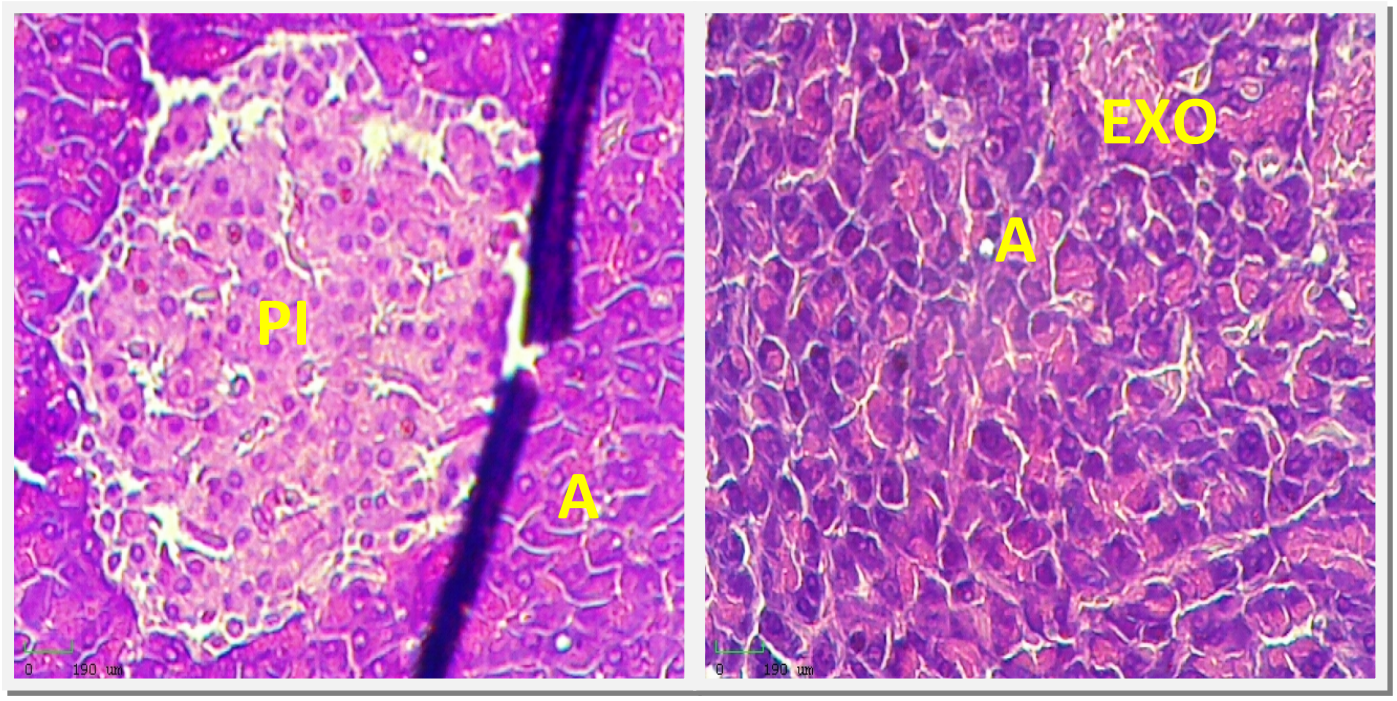


Figure (5):-Cross section of pancreas of male rats treated with ALA alone(100mg/KgB.W.)

showing normal acini (A) were pear shaped and normal islet of pancreatic langerhans(PI).400X, H&E.

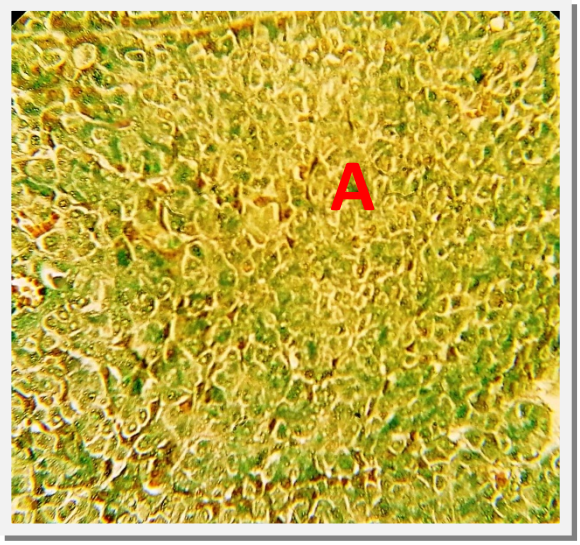


Figure (6):- Cross section of the pancreas of a rat (control group (-ve)), showing present normal acini (A), stained with Gomoroi aldehyde fucshion. (400X).

Figure (7):-Cross section of the pancreas of a rat injected L-arginine (500mg/kg B.W.) induced AP, showing some necrotic acinar nuclei (N), edematous (O) fluid within and around dilated ducts (D) and some extravasated blood cells (↑).Stained with Gomoroi aldehyde fucshion. (400X).

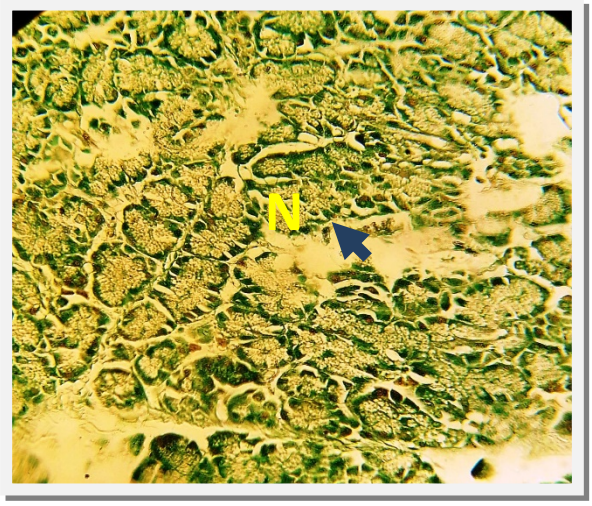


Figure (8):-Cross section of the pancreas of of acute pancreatitis male rat induced by L-Arginine and treated with α-Lipoic acid at dose (50mg/kgB.W.) showing some normal acinar nuclei (N), and normal ducts (D) and some extravasated blood cells (↑),Stained with Gomoroi aldehyde fucshion. (400X).

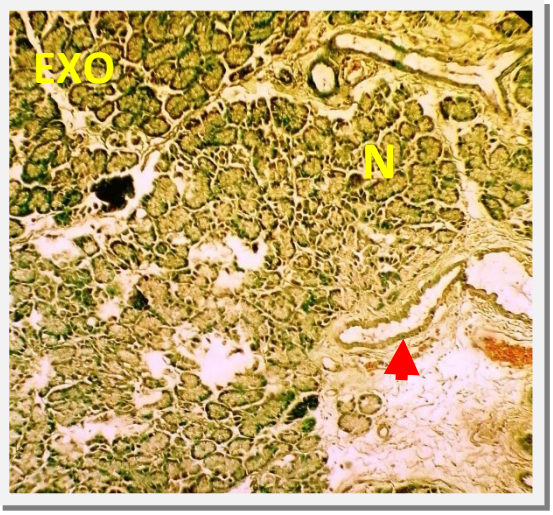


Figure (9):-Cross section of the pancreas of acute pancreatitis male rat induced by L-Arginine and treated with α-Lipoic acid at dose (100mg/kgB.W.) showing normal acinar nuclei (N), normal ducts (D) and normal blood vessels, Stained with Gomoroi aldehyde fucshion. (400X).

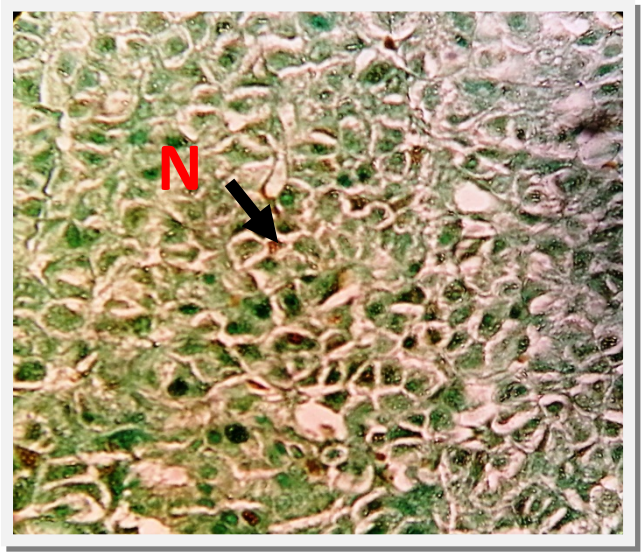


Figure (10):-Cross section of the pancreas of a rat treated with α-Lipoic acid alone at dose(100mg/kgB.W.), showing normal acinar nuclei (N), Stained with Gomoroi aldehyde fucshion. (400X).

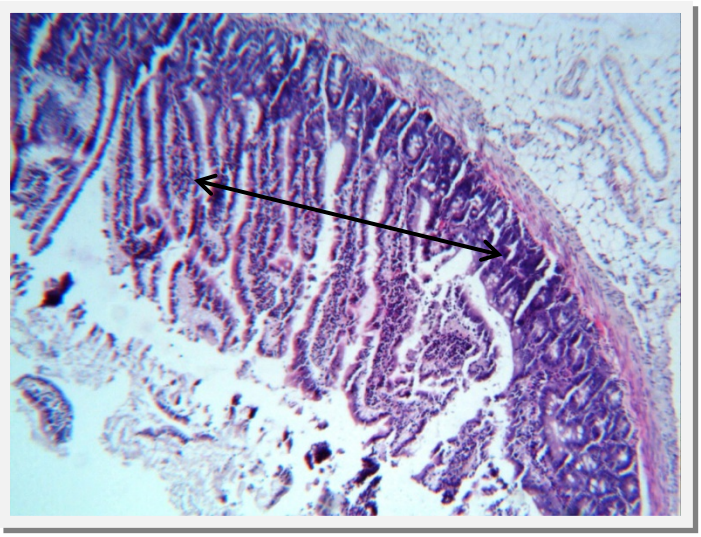
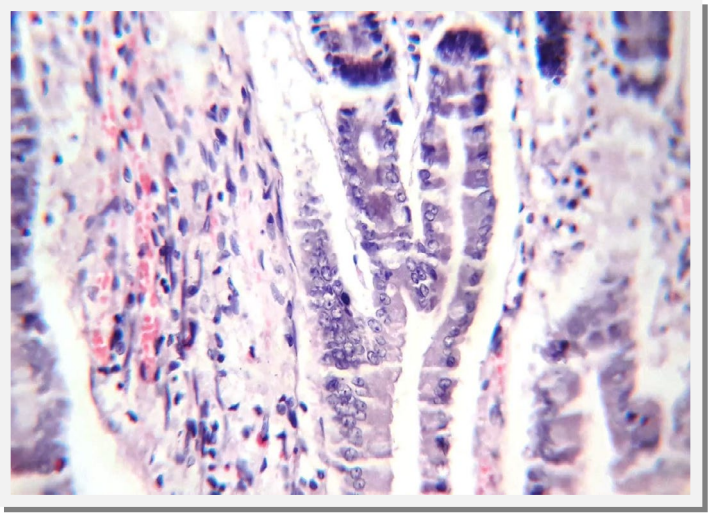
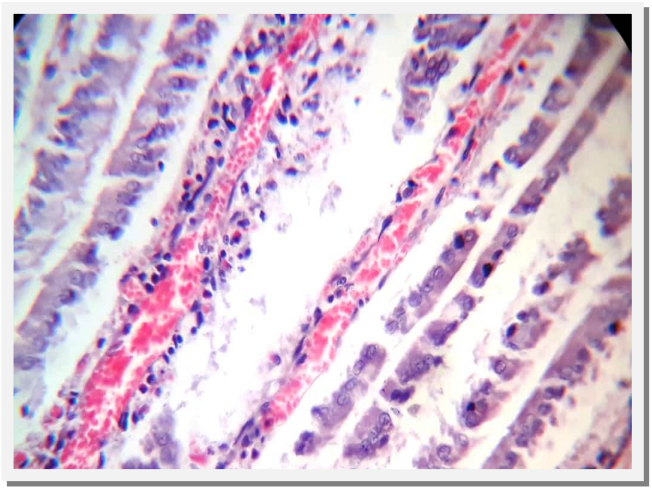


Figure (11):-Cross section of rat's intestine con showing downward to the villi and deepest tur mucosa (arrow).200X, stain with H&E.



Figure(12):- Cross section of intestine of (AP) male induced by L-Arginine showing perivascu lymphocytic infiltrations and plasma cells. 400X, st with H&E.



Figure(13): Cross section of (AP)rat's intes induced by L-Argin and treated with (50 mg/kg A showing degrease perivascular lymphoc infiltrations.400X,

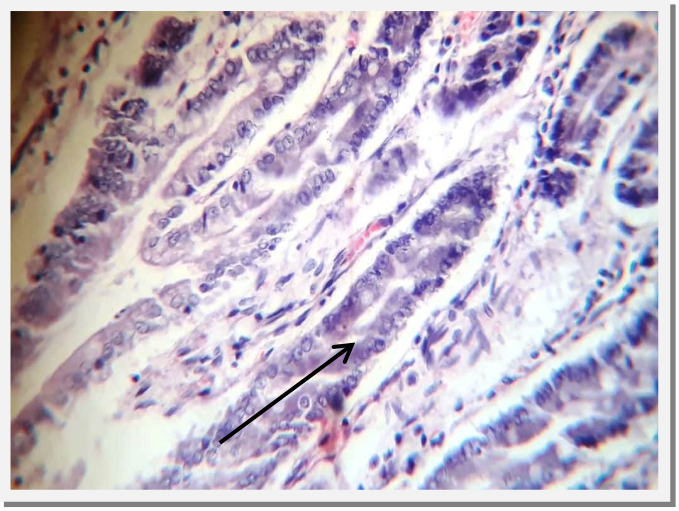


Figure (14) Cross section of (AP) rat's intestine induced by byL-Arginand treated with (100mg/kg) ALA showing mononuclear aggregation (arrow).

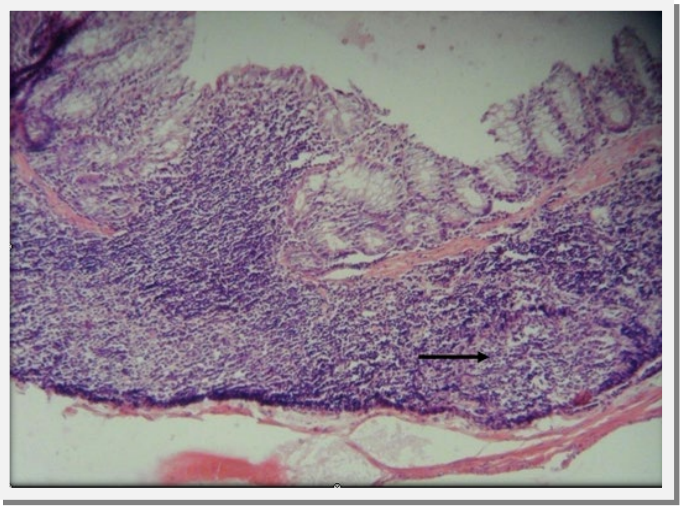


Figure (15): Cross section of rat's intestine treated ALA alone (100 mg/kg), showing normal tissue (arrc 200X H&E.

Discussion

This study has demonstrated that L-Argin induced AP provokes decrease body weight and body weight gain. The changes in body weight provide information about the effects of a substance administration (15). Because of the adverse side effects and restricted outcomes of the traditional treatments being used, it is necessary to study new product lines with more desirable therapeutic profiles to improve the outcomes. The AP increases in weight of pancreas, serum lipase, amylase, calprotectin, MDA and histopathological in pancreas and intestine indicate that related closely to physiological and microscopic measured of pancreatitis. This finding is in a agreement with previous studies (24 - 28). Unlike TNF-α and IL-6, which increased after the AP, this marker remained increased with persistent inflammation in the intestinal tube. Calprotectin is a Toll-like receptor-4 (TLR4) ligand expressed by neutrophils, monocytes, and early differentiated macrophages (16). These cell populations are all prominent in the peripheral blood of patients with ulcerative colitis (UC), secrete pro-inflammatory cytokines and correlate with levels of pancreatic inflammation (17, 18). Serum levels of calprotectin are increased in some inflammatory conditions and selective removal of peripheral blood activated granulocytes and monocytes/macrophages leads to a decrease in fecal calprotectin levels in patients with UC (19, 20). In previous years, TNF-α and IL-6 have been attributed increasingly important roles in the physiopathology of inflammatory diseases (21). It is believed

that increased levels and excessive synthesis of these mediators result in a loss of bowel homeostasis, which leads to significant disequilibrium and directly contributes to disease development. The results of the present study have confirmed the participation of TNF-α and IL-6 in TNBS-induced inflammation, which has been previously described (22) However, we have demonstrated that both cytokines decline by day 12 in this model, despite on-going evidence of histologic and endoscopic inflammation. α-lipoic acid (ALA) is a natural antioxidant which acts as a cofactor of bioenergetic mitochondrial enzymes. Along with its mitochondrial action, ALA and its reduced form have many biological functions resulting in a wide variety of actions such as anti-inflammation and antioxidant protection, scavenging reactive oxygen species, regenerating other antioxidant agents, such as vitamins C and E, and cytosolic glutathione, chelating the transitional metal ions (e.g., iron and copper), and modulating the signal transduction of nuclear factor (23).

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التأثير الوقائي لحامض ألفا ليبويك على الإجهاد التأكسدي والسيتوكينات المنشطة لالتهابات في التهاب البنكرياس الحاد المستحث بواسطة إل-أرجينين

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الخلاصة

التهاب البنكرياس الحاد (AP) هو مرض خطير شائع يصيب البنكرياس ويتسم بوخز شديد في البطن يستمر من ايام إلى أسابيع. تم حقن الجرذان بجرعة من الحمض الأميني L-arginine (500 مجم / كجم من وزن الجسم). أجريت الدراسة للحث على التهاب البنكرياس الحاد (AP) باستخدام L-Arginine (Arg) واستقصاء تأثير AP على وزن الجسم والزيادة الوزنية ومستوى انزيم الامايليز واللايبيز في مصل دم الجرذان والإجهاد التأكسدي ومعايير السيتوكين المسببة للالتهابات وكذلك على بعض التغيرات النسيجية المرضيةفي نسيجي البنكرياس والامعاء في ذكور الجرذان. زادت مستويات الأميلاز والليباز وIL-6 وTNF-α ومستويات MDA بشكل ملحوظ في الجرذان مع AP المستحث بـ L-Arginine، مما أدى إلى انخفاض نشاط GPx,SOD,CATفي مصل الدم بشكل كبير وتغيرات مرضية في نسيجي البنكرياس والامعاء. تم عكس كل هذه التغييرات وتحسينها باستخدام علاج ALA.