

## The Effects of Leptin Hormone Concentrations and Some Immunological and Biochemical Parameters in Alloxan Induced Diabetic Male Rabbits and Diabetic Treated with Alpha Lipoic Acid and L-Carnitine

Mohanad Hasan Mahmood Humadi<sup>1</sup>, Zaid Mohamad Mubarak<sup>1</sup>, Ismat Jamal Jamil<sup>2</sup>

<sup>1</sup> Department of Biology, Science College, Tikrit University, Tikrit, Iraq

<sup>2</sup> Veterinary Medicine College, Kirkuk University, Kirkuk, Iraq

### Abstract

This study was designed in order to estimate the effect of alloxan induced diabetes mellitus on leptin concentration and some immunological and biochemical parameters of male domestic rabbits. The study involved (20) blood samples which divided into 4 groups : group one : adult normal healthy male rabbits as control group , group two: adult male rabbits with alloxan induced diabetes mellitus, group three: adult male rabbits with alloxan induced diabetes mellitus treated with alpha lipoic acid (100 mg/kg) , group four: adult male rabbits with alloxan induced diabetes mellitus treated with L-carnitine (100 mg/kg).The results of this study showed a significant increase in leptin concentrations ( $P \leq 0.05$ ) of second group in comparison with control group; while significant decrease in leptin concentrations at levels ( $P \leq 0.05$ ) of third and fourth groups compared with diabetic group, and there is significant increase in proinflammatory cytokine Interleukin 6 (IL-6) concentrations ( $P \leq 0.05$ ) of second group in comparison with control group, There was a significant decrease in IL-6 concentrations ( $P \leq 0.05$ ) of third and fourth groups in comparison with diabetic group; also there is a significant increases in both urea and creatinine concentrations ( $P \leq 0.05$ ) of second group in comparison with control group, while significant decreases in both urea and creatinine concentrations ( $P \leq 0.05$ ) of third and fourth groups in comparison with diabetic group.

**Keywords:** Diabetes mellitus , Alloxan , Leptin , IL-6 , Urea , Creatinine.

### Introduction

Diabetes mellitus is a combination of heterogeneous disorders commonly presenting with episodes of hyperglycemia and glucose intolerance, as a result of lack of insulin , defective insulin action, or both [1]. Such disorders occur due to derangements in the regulatory systems for storage and mobilization of metabolic fuels, including the catabolism and anabolism of carbohydrates, lipids and proteins arising from such defects in insulin secretion, insulin action, or both with disturbances of carbohydrate, fat and protein metabolism [2]. There are 5 types of diabetes the main types of them are type 1 and type 2; Type 1 diabetes mellitus is caused mainly by the autoimmune destruction of the insulin-producing  $\beta$  cells of the pancreas. The destruction process is marked by infiltration of the pancreatic islets by mononuclear cells, and activated CD4+ and CD8+ lymphocytes, antibodies and components of the complement system [3].

Alloxan (2,4,5,6-tetraoxypyrimidine; 2,4,5,6-pyrimidinetetrone) is an oxygenated pyrimidine derivative found as alloxan hydrate in aqueous solution effects on beta cells of pancreas mediated by reactive oxygen species (ROS) formation , by which alloxan causes diabetes type 1 by rapid complete or partial depletion of pancreatic beta cells by DNA alkylation and accumulation of cytotoxic free radicals resulted from initial islet inflammation, followed by infiltration of activated macrophages and lymphocyte ; and these harmful effects of alloxan cause reduction in plasma insulin concentration leading chronic hyperglycemia state [4].

Leptin is a 16 kDa soluble protein hormone of 146 amino acids belonging to the class-1 helical cytokine family of proteins [5]. Leptin acts as an anorexigenic

signal through a negative feedback loop to the appetite centre in the hypothalamus causing long term and short-term effects on feed uptake and energy homeostasis [6]. The hypothalamus is the major connection between the central nervous system (CNS) and leptin action to regulate feeding behavior and energy balance by which the area known as the arcuate nucleus (ARC) in the hypothalamus has the highest amount of leptin receptors [7].

Increased level of serum leptin considered as a component of metabolic syndrome; suggested that resistance to leptin in  $\beta$ -cells might prevent the inhibitory effect of leptin on insulin secretion resulting in hyperinsulinemia, which might exhaust pancreatic  $\beta$ -cells leading to development of type 2 diabetes mellitus reflected in increasing or unchanging of leptin levels in diabetic patients [8]. Blood leptin concentrations increase in chronic inflammation; also leptin levels are rapidly increased by many acute phase cytokines which raised in diabetes mellitus, such as TNF- $\alpha$ , IL-1  $\beta$  and IL-6 [9]. Moreover C-reactive protein (CRP) bind competitively to leptin, thus decreasing leptin's interactions with its receptors and decreasing its cellular effects, suggesting a pathway for leptin resistance which contribute to development of diabetes mellitus [10].

### Materials and Methods

#### 1. Animals :

The experiment was performed on 40 adult male domestic rabbits (*Oryctolagus cuniculus*) weighing between (1300-1500) g and their age ranges between (6 -9) months obtained from the animals market in Kirkuk city. The experiment period was from

beginning of april till mid of july (2015) in Kirkuk city.

## 2. Induction of Diabetes:

Diabetes was induced by single dose (150 mg/kg) of freshly prepared intraperitoneal injection of alloxan (BDH company). It has dissolved by 1.5 g of alloxan in 10 ml of normal saline [11]. After alloxan injection, the rabbits were allowed to drink 5% glucose solution for 24 hours to overcome the drug induced hypoglycemia. Each rabbit of the normal control group was injected with 1 ml of normal saline. The induction of diabetes was confirmed by collecting blood from the external ear vein for glucose analysis by using portable blood glucose monitor and its strips (Rossmax company) every day, for 10 days, and then rabbits with fasting blood glucose levels above 150 mg/dl were considered diabetic [12].

## 3. Experimental Design:

Twenty adult male rabbits were used, divided randomly into eight groups. Five male rabbits were included in each group, Equal weight of each group was taken into consideration as much as possible before the start of the study:

**Group 1:** (control group) normal control male rabbit were given water and food for 30 days.

**Group 2:** (Diabetic group): they have been injected alloxan 150 mg/kg body weight intraperitoneal injection then given food and water for 30 days.

**Group 3:** (Diabetic +Alpha-lipoic acid group): they have been injected alloxan 150 mg/kg body weight intraperitoneally then given 100mg/kg body weight alpha-lipoic acid orally concomitantly for 30 days.

**Group 4:** (Diabetic +L-Carnitine group): they have been injected alloxan 150 mg/kg body weight intraperitoneally then given 100mg/kg body weight L-carnitine orally concomitantly for 30 days.

## 4. Determination of Parameters:

Adiponectin and IL-6 were determined using its kit (my bioscience, USA) of ELISA technique; while the concentrations of serum urea were determined using kit from

Spinreact company (Spain); and the concentrations of serum creatinine were determined by using kit from BIOLABO -France- [13].

## Results and Discussion

This study showed high significance increase in blood glucose concentration ( $p \leq 0.05$ ) in diabetic group during the experiment period Figure (1) ( $192.00 \pm 17.72$  mg/dl) as compared with control group.

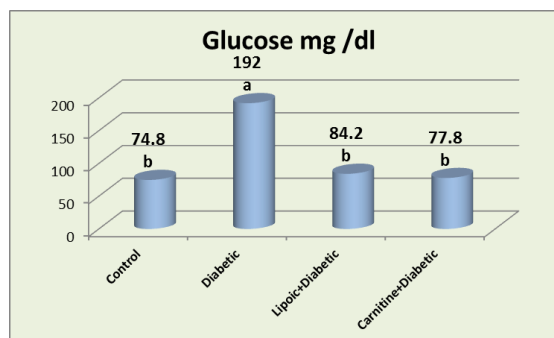


Figure (1): Concentrations of Blood Glucose (mg/dl) in the study groups

These results were in agreement with the studies of Mir (2016) [14]; Ikram and Hussain (2014) [12]; they found that there was a significant increase in blood glucose concentration in alloxan induced diabetic rabbits in comparison with control group.

While there was a significance increase in blood serum leptin concentrations ( $p \leq 0.05$ ) in diabetic group during the experiment period Figure (2) ( $7.682 \pm 4.069$  ng/ml) as compared with control group.

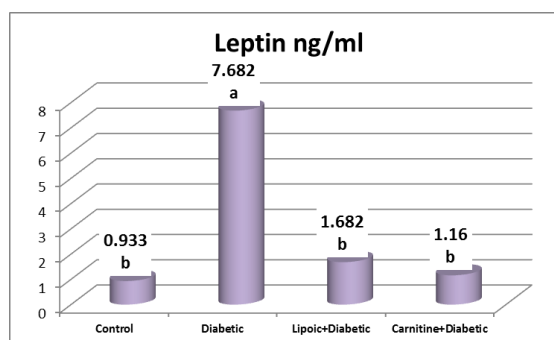


Figure (2): Concentrations of Leptin (mg/dl) in the study groups

These results were in agreement with the study of Lin *et al.* (2014) [15], who showed significant increase of leptin serum concentrations in diabetic mice.

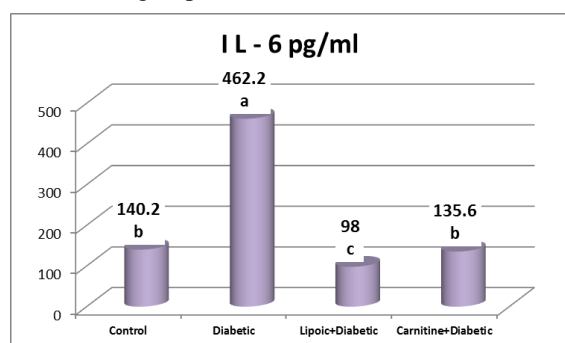
Increased level of serum leptin is considered as a component of metabolic syndrome, it was suggested that resistance to leptin in  $\beta$ -cells might prevent the inhibitory effect of leptin on insulin secretion resulting in hyperinsulinemia, which might exhaust pancreatic  $\beta$ -cells leading to development of diabetes mellitus [8], and this lead to increase of blood leptin concentrations due to leptin resistance in beta cells of pancreas, also in diabetes mellitus, endoplasmic reticulum stress of adipocytes participates in the dysregulation of adipokine secretion [16], and this lead to increase secretion of leptin; in addition leptin increases natural killer (NK) cells and macrophages activation and cytokines release such as tumor necrosis factor (TNF)- $\alpha$  and IL-6 [17], additionally leptin has a role in the pathogenesis of autoimmune inflammatory conditions, such as experimental type 1 diabetes mellitus [18]; furthermore leptin has proinflammatory properties and several actions similar to those of the acute phase reactants, and

upregulates the secretion of inflammatory cytokines like TNF- $\alpha$ , IL-6, and IL-12; and in return, TNF- $\alpha$  and IL-1 $\beta$  increase the expression of leptin mRNA in the adipose tissue, creating a loop whose components influence each other in promoting inflammation [19]. This study showed a significant decrease in blood serum leptin concentration ( $p \leq 0.05$ ) of male rabbits in diabetic group treated with alpha lipoic acid in comparison with diabetic group and this was in agreement with the study of Huerta *et al.* (2015) [20], who showed such significant decrease in serum leptin after oral administration of alpha lipoic acid to overweight and obese women during weight loss.

Alpha lipoic acid has inhibitory effect on leptin production and secretion; additionally alpha lipoic acid inhibits Akt phosphorylation, and stimulating Sp1 phosphorylation and inhibited Sp1 transcriptional activity reducing DNA-binding activity which mediated in part by the abrogation of the PI3K/Akt pathway; thus all these effects inhibit both leptin gene expression and leptin secretion [21].

The study showed a significant decrease in blood serum leptin concentration ( $p \leq 0.05$ ) of male rabbits in diabetic group treated with L-carnitine in comparison with diabetic group and this supported by the study of Barzegar *et al.* (2013) [22], who reported such significant decrease in blood serum leptin followed oral administration of L-carnitine to obese type 2 diabetic patients; because L-carnitine partly reduces the leptin resistance, and improves ATP production in skeletal muscle mitochondria through an increase in mitochondrial protein content [23]; in addition to L-carnitine protective effects against oxidative stress of diabetes mellitus reducing its inflammatory condition including adipose tissue and also L-carnitine inhibits TNF- $\alpha$  and this may lead to decrease leptin production [24].

There was a significant increase in blood serum IL-6 concentration ( $p \leq 0.05$ ) of male rabbits in alloxan induced diabetic group during the experiment period Figure (3) ( $462.20 \pm 186.90$  pg/ml) as compared with control group.



**Figure (3): Concentrations of blood serum IL-6 concentrations in the study groups.**

These results were coincided with the study of Sun *et al.* (2015) [25], who reported a significant increase of blood serum IL-6 levels in type 2 diabetic patients.

Hyperglycemia in diabetes mellitus contribute to the glycation of proteins and lipids, resulting in the formation of advanced glycated end products (AGE), the binding of AGEs to receptors of AGE (RAGE) which are expressed in many different tissue and cell types leads to intracellular generation of reactive oxygen species (ROS) which in turn activate NF- $\kappa$ B, and as a consequence of NF- $\kappa$ B activation expression of a variety of cytokines is increased including tumor necrosis factors (TNF- $\alpha$  and TNF- $\beta$ ), interleukins IL-1, IL-6, IL-8 and I N F- $\gamma$  [27]; additionally leptin upregulates the secretion of these proinflammatory cytokines thus leptin increasing their serum concentrations [19].

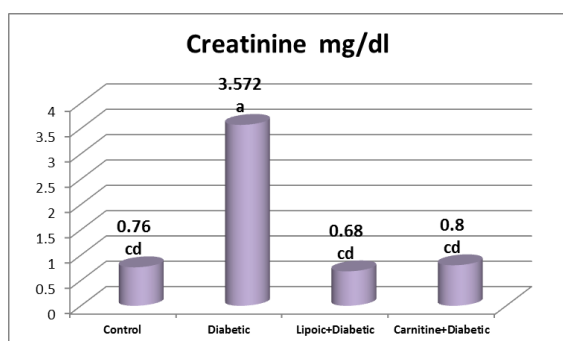
In diabetic alpha lipoic acid treated group there was a significant decrease of blood serum IL-6 concentrations ( $p \leq 0.05$ ) in comparison with diabetic group which were in agreement with the study of Zhang *et al.* (2011) [26], who showed that in impaired glucose tolerance patients after intravenous injection of alpha lipoic acid.

Alpha lipoic acid has anti-inflammatory properties which can inhibit the NF- $\kappa$ B pathway due to the inhibitory effect on degradation of I $\kappa$ B through the mitogen-activated protein kinases (MAPK) pathway; furthermore, alpha lipoic acid can help regenerate vitamin E, thereby inhibiting protein kinase C that can phosphorylate I $\kappa$ B. All these effects of alpha lipoic acid lead to suppression of proinflammatory cytokines production including IL-6 [28]; moreover alpha lipoic acid inhibits expression of proinflammatory cytokines [29]; in addition alpha lipoic acid can augment the induction of endogenous PPAR- $\gamma$  centrally and peripherally, repressing Th1 and Th17 responses and enhancing systemic Th2 and T regulatory cells [30].

There was a significant decrease in blood serum IL-6 concentrations ( $p \leq 0.05$ ) of male rabbits in diabetic group treated with L-carnitine in comparison with diabetic group and this agree with the study of Barzegar *et al.* (2013) [22], who showed a significant decrease after oral administration of L-carnitine to obese type 2 diabetic patients.

L-carnitine characterised by antioxidant properties which participated in its immunosuppressive capacity; by which L-carnitine suppress immune responses by either quenching reactive oxygen species (ROS), and thereby inhibiting the third signal for T cell activation, or by activating GR- $\alpha$  translocation directly and mimicking the known immunosuppressive properties of glucocorticoids, this lead to suppression of proinflammatory cytokines production including IL-6 [31].

This study revealed significance increase in blood serum creatinine concentrations ( $p \leq 0.05$ ) of male rabbits in alloxan induced diabetic group during the experiment period Figure (5) ( $3.5720 \pm 1.1135$  mg/dl) as compared with control group.



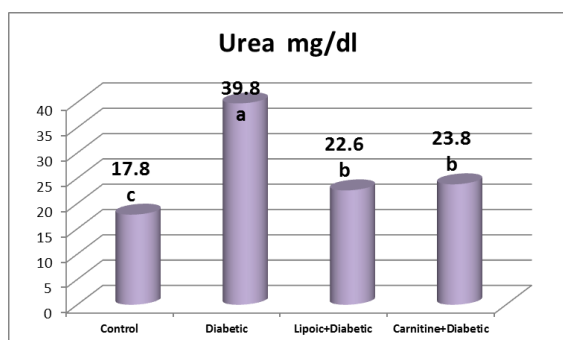
**Figure (4): Concentrations of blood serum Creatinine concentrations in the study groups**

These results were in agreement with the study of Hundekari *et al.* (2012) [32], who found a significant increase of blood serum creatinine concentrations in alloxan induced diabetic rabbits in comparison with control group.

There was a significant decrease in blood serum creatinine ( $p \leq 0.05$ ) of male rabbits in diabetic group treated with alpha lipoic acid in comparison with diabetic group and this was in agreement with the study of Wang *et al.* (2013) [30], who reported that there was a significant decrease in blood serum creatinine after intraperitoneal injections of alpha lipoic acid to streptozotocin induced diabetic rats.

The study showed a significant decrease in blood serum creatinine concentrations ( $p \leq 0.05$ ) of male rabbits in diabetic group treated with L-carnitine in comparison with diabetic group which were in agreement with those of Bashi and Al-Farha (2010) [33], who showed that oral L-carnitine decrease blood serum creatinine significantly after oral administration of L-carnitine to type 2 diabetic patients.

The study revealed a significance increase in blood serum urea concentrations ( $p \leq 0.05$ ) of male rabbits in alloxan induced diabetic group during the experiment period Figure (5) ( $39.800 \pm 7.950$  mg/dl) as compared with control group.



**Figure (5): Concentrations of blood serum Urea concentrations in the study groups**

These results were in agreement with other studies on

rabbits such as studies of Mir (2016) [13], and Hundekari *et al.* (2012) [32], they found a significant increase of blood serum urea concentrations in alloxan induced diabetic rabbits in comparison with control group.

There was a significant decrease in serum levels of urea ( $p \leq 0.05$ ) in diabetic alpha lipoic acid treated group in comparison with diabetic group which was agreed with the study of Wang *et al.* (2013) [30], who found a significant decrease of blood serum urea concentrations after intraperitoneal injections of alpha lipoic acid to streptozotocin induced diabetic rats.

There was a significant decrease in blood serum urea ( $p \leq 0.05$ ) of male rabbits in diabetic group treated with L-carnitine in comparison with diabetic group and this coincide with the study of Bashi and Al-Farha (2010) [33], who revealed a significant decrease in blood urea concentrations in type 2 diabetic patients followed oral administration of L-carnitine.

Diabetes mellitus causes renal damage due to abnormal glucose regulation including elevated glucose and glycosylated protein tissue level, changes within the kidney and oxidative stress. Both negative balance of nitrogen and lowered protein synthesis leads to increased level of serum creatinine and urea that indicates progressive renal damage in diabetic animals like basement membrane injury; furthermore the increased urea and creatinine production in diabetes might be due to accelerated catabolism of both liver and plasma proteins [34]; in addition to lose the kidneys in diabetes mellitus their ability to remove wastes products, such as creatinine and urea from the blood due to reduction of glomerular filtration rate [35].

Alpha lipoic acid treatment provided renal protection in diabetic rabbits with decreased blood urea because alpha lipoic acid is potent antioxidant can effectively reduce the generation of reactive oxygen species (ROS), and protecting mitochondrial function [30]; in addition alpha lipoic acid lower NF-kb which play an important role in diabetic kidney dysfunction also alpha lipoic acid increase antioxidative systems such as reduced glutathione (GSH), and also prevent lipid peroxidation [36].

L-carnitine increases the level of nitric-oxide synthase (NOS) and Hemeoxygenase (HO-1), which are known as antiproliferative and anti-inflammatory agent and these enzymes are protective against oxidative stress of diabetes mellitus in kidney; in addition L-carnitine enhances activity of pyruvate dehydrogenase by decreasing acetyl-CoA to coenzyme A proportion in mitochondria of kidney cells which lead to increase of glucose catabolism [37].

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## تأثيرات هرمون اللبتين وبعض المعايير المناعية والكيموحيوية في ذكور الارانب المصابة بداء السكر المستحث بالالوكسان والمصابة بداء السكر المعالجة بحامض اللبويك والكارنتين

مهند حسن محمود حمادي<sup>1</sup> ، زيد محمد مبارك<sup>1</sup> ، عصمت جمال جميل<sup>2</sup>

<sup>1</sup>قسم علوم الحياة ، كلية العلوم ، جامعة تكريت ، تكريت ، العراق

<sup>2</sup>كلية الطب البيطري ، جامعة كركوك ، كركوك ، العراق

### الملخص

جرى تصميم هذه البحث لمعرفة تأثير داء السكر المستحث بالالوكسان على تركيز هرمون اللبتين (Leptin Hormone) وبعض المتغيرات المناعية والكيموحيوية في ذكور الارانب المحلية ، وشملت الدراسة (20) عينة دم قسمت الى 4 مجاميع: المجموعة الاولى : ذكور ارانب بالغه سليمة كمجموعة سيطرة ، المجموعة الثانية : ذكور ارانب بالغه مصابة بداء السكر المستحث بالالوكسان ، المجموعة الثالثة : ذكور ارانب بالغه مصابة بداء السكر المستحث بالالوكسان معالجة بحامض اللبويك ( Alpha Lipoic Acid ) ( 100 ملغم/كغم) ، المجموعة الرابعة : ذكور ارانب بالغه مصابة بداء السكر المستحث بالالوكسان معالجة بالكارنتين ( L-Carnitine ) ( 100 ملغم/كغم) ، ولقد أظهرت نتائج الدراسة الحالية ارتفاع تركيز هرمون اللبتين معنويًا عند مستوى ( $P \leq 0.05$ ) في المجموعة الثانية (مجموعة داء السكر) مقارنة مع مجموعة السيطرة ، بينما كان هناك انخفاض معنوي في تركيز هرمون اللبتين عند مستوى ( $P \leq 0.05$ ) في المجاميع الثالثة والرابعة مقارنة مع مجموعة داء السكر ، ولوحظ ارتفاع معنوي في تركيز الحركي الخلوي انترلوكين ستة ( Interleukin-6 [IL-6] ) عند مستوى ( $P \leq 0.05$ ) في المجاميع الثالثة والرابعة مقارنة مع مجموعة السيطرة ، بينما كان هناك انخفاض معنوي في تركيز الحركي الخلوي IL-6 عند مستوى ( $P \leq 0.05$ ) في المجاميع الثالثة والرابعة مقارنة مع مجموعة داء السكر ، كما وجدت الدراسة الحالية ارتفاعات معنوية في تراكيز كلا من اليوريا والكرياتنين عند مستوى ( $P \leq 0.05$ ) في المجموعة الثانية مقارنة مع مجموعة السيطرة ، بينما كان هناك انخفاضات معنوية في تراكيز كلا من اليوريا والكرياتنين عند مستوى ( $P \leq 0.05$ ) في المجاميع الثالثة والرابعة مقارنة مع مجموعة داء السكر .