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Role of Adiponectin Hormone Concentrations and Some Immunological and Biochemical Parameters inAlloxan Induced Diabetic Male Rabbits and Diabetic Treated with Alpha Lipoic Acid and L-Carnitine

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Abstract
This study was designed in order to estimate the effect of alloxan induced diabetes mellitus on adiponectin hormone concentration and some immunological and biochemical parameters of male domestic rabbits. The study involved (20) blood samples were 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 found significant decrease in adiponectin hormone concentrations at levels ($P\leq 0.05$) in second group as compared with control group; while significant increase in adiponectin hormone concentrations at levels ($P\leq 0.05$) in third and fourth groups in comparison with diabetic group, and there is significant increase in proinflammatory cytokine Interleukin 1 β (IL-1β) concentrations at levels ($P\leq 0.05$) of second group in comparison with control group, while significant decrease in IL-1 β concentrations at levels ($P\leq 0.05$) of third and fourth groups in comparison with diabetic group; and there are significant increases in the activity of enzymes: Alanine amino transferase (ALT), and Aspartate amino transferase (AST) at levels ($P\leq 0.05$) of second group in comparison with control group, while significant decrease in the activity of enzymes: Alanine amino transferase (ALT), and Aspartate amino transferase (AST) at levels ($P\leq 0.05$) of third and fourth groups in comparison with diabetic group.

Keywords: Diabetes mellitus, Alloxan, Adiponectin, IL-1 β, ALT, AST.

Introduction
Diabetes mellitus is a complex metabolic disorders occur with hyperglycemia and glucose intolerance, resulted from lack or deficiency of insulin, defective insulin action, or both[1]; which causing disturbances in the metabolism of carbohydrates, proteins, and lipids [2].

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 pancreatic beta cells mediated by formation of reactive oxygen species (ROS), 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 Langerhans islets inflammation, after that infiltration of the inflammatory site occurs by activated macrophages and lymphocytes causing decreasing in blood insulin level resulting from that chronic hyperglycemia condition [3].

Adiponectin is an adipokine abundantly produced and secreted by adipose tissue characterized by its antidiabetic, anti-inflammatory, antiatherogenic effects playing an important role in the metabolism of glucose and lipids [4]. Adiponectin enhances insulin-sensitivity, decreases free fatty acids (FFAs) influx, increases β-oxidation in liver and muscle; Adiponectin receptor can sensitize and increase the extent of insulin signaling on target cells, facilitating glucose uptake and energy homeostasis [5]; also adiponectin enhances insulin sensitivity in liver via promoting phosphorylation of insulin receptor and insulin receptor substrate-1 (IRS-1). In pancreas, adiponectin acts on cell proliferation stimulating insulin secretion [6]. Another potential mechanism for adiponectin's protective effect is counteract proinflammatory cytokines and fatty acids induced cell dysfunction [7]. Low blood adiponectin concentrations are noticed in several forms of diabetes mellitus with insulin resistance, including type 2 diabetes, gestational diabetes, and diabetes associated with lipodystrophy [8].

Pro-inflammatory cytokine IL-1β is secreted mainly from adipose tissue and macrophages and play a role in autoimmune condition of type 1 diabetes mellitus , and in type 2 diabetes mellitus the decreasing of pancreatic beta cells is linked with glucotoxicity mediated by IL-1 β, IFN- γ and TNF- α induced apoptosis [9]; in addition advanced glycated end products (AGEs) in diabetes mellitus stimulate the production of IL-1β by macrophages and monocytes[10], by which hyperglycemia contribute to the glycation of proteins and lipids, resulting in the formation of advanced glycated end products (AGE) which lead to intracellular generation of reactive oxygen species (ROS) which activate NF-KB and this lead to increase the expression and production of different pro-inflammatory cytokines including tumor necrosis factors (TNF-α and TNF-β), interleukins IL-1β, IL-6, IL-8 and INF-ɣ [11]; furthermore inflammatory processes occur in the liver in response to fatty infiltration and lipoproteins accumulation in liver artery walls during diabetes mellitus due to hypercholestermia stimulate hepatic pro-inflammatory cytokines productions including IL-1β, IL-6, and Tumor Necrosis Factor (TNF-α) [12];

additionally reactive oxygen species (ROS) mediate the expression of the pro-inflammatory cytokines including IL-1β by activating oxidant-sensitive transcription factors, such as nuclear factor kappa light chain enhancer of activated B lymphocytes (NF-kB) , activator protein- 1 (AP-1) , janus kinase signal transducers, and activators of transcription - Jak/Stat- [13].

Alanine transaminase (ALT) and aspartate transaminase (AST) are present in blood and in different body tissues, but they most abundant in liver. Serum Alanine transaminase (ALT) and serum aspartate transaminase (AST) levels, and AST/ALT ratio are usually measured clinically as liver healthbiomarkers[14].Liver enzymes Alanine transaminase (ALT), Aspartate transaminase (AST) increased significantly in association with insulin resistance, metabolic syndrome and diabetes mellitus as markers of hepatocellular injury [15]; reflecting both hepatic injury and enhanced oxidative stress [16].The excess free fatty acids (FFAs) found in the insulin resistant state is directly toxic to hepatocytes by mechanisms include cell membrane disruption at high concentration of FFAs, lipid peroxidation, mitochondrial dysfunction, toxin formation, and activation and inhibition of key steps in the metabolism regulation [17]. The insulin resistant conditionis also involve an elevation in pro-inflammatory cytokines such as TNF-α, which also participate in liver cells injury[18].

Material and Methods

1.Animals

The experiment is performed on 40 adult male domestic rabbit (*Oryctolaguscuniculus*) of weighing between (1300-1500) g and age ranges between (6-9) months obtained from the animals market in Kirkuk city, the animals stayed for 2 weeks for adapted the place and to make sure they are free of disease before began the experiment. The experiment period was from end of march (2015) to 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 (british BDH company). It has dissolved by 1.5 g of alloxan in 10 ml of normal saline. After alloxan injection, the rabbits were allowed to drink 5% glucose solution as proper concentration for 24 hours to overcome the drug induced hypoglycemia. Each rabbit of the normal control group was injected with 1 ml of normal saline [19]. 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 [20].

3. Experimental Design

In the present experiment, 20 adult male rabbit were used. The rabbits were divided randomly into eight groups. Five male rabbit were included in each group, Equal weights 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 alloxan150 mg/kg body weight intraperitoneal injection then given food and water for 30 days [19].

Group 3: (Diabetic +Alpha-lipoic acid group): they have been injected alloxan150mg/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 alloxan150 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-1β were determined by using its kit from (my bioscourse) company (USA) of ELISA technique; and the activity of enzymes Aspartate amino transferase (AST) , Alanine amino transferase (ALT) were determined by using Their kits from biolabo company (France) [21].

Result 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 ±17.72 mg/dl) as compared with control group.

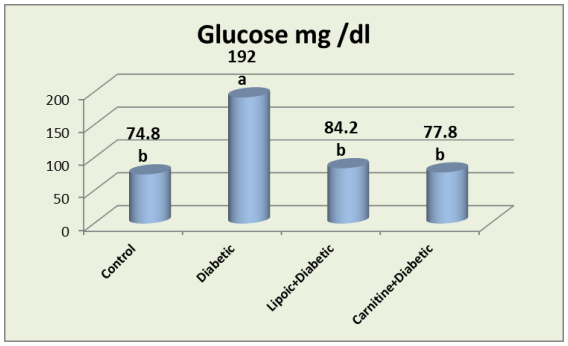

Figure (1): Concentrations of Blood Glucose (mg/dl) in the study groups.

These results coincide with the studies [22]; and [20]; they found significant increase of blood glucose in alloxan induced diabetic rabbits in comparison with control group.

The current study showed high significance decrease in blood serum adiponectin concentrations ($p \leq 0.05$) in diabetic group during the experiment period Figure (2) (3.088 ± 2.026 ng/ml) as compared with control group.

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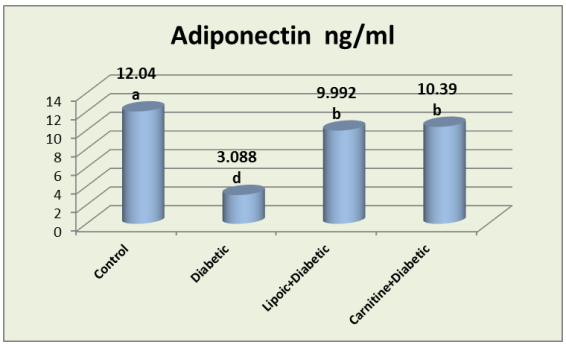

Figure (2): Concentrations of Adiponectin (mg/dl) in the study groups.

These results supported by other studies such as the study of Hemmati*et al.*, 2015 [23]; and the study Esposito *et al.*, (2003) [24]; this significant decrease in blood serum adiponectin concentrations take place because in diabetes mellitus stress of adipocytes endoplasmic reticulum participates in the dysregulation of adipokine secretion, with reduced secretion of adiponectin[25]; also significantly, serum adiponectin levels are inversely correlated with pro-inflammatory cytokine TNF-α concentration; by which increased TNF-α in diabetes mellitus significantly decrease adiponectin expression and secretion; TNF-α also decreases adiponectin promoter activity in adipocytes; furthermore TNF-α induces production of inhibitory transcription factor IGFBP-3, which suppresses adiponectin transcription and induces insulin resistance [26].

This study revealed significant increase in blood serum adiponectin concentrations ($p \leq 0.05$) of male rabbits in diabetic group treated with alpha lipoic acid in comparison with diabetic group and this agree with the study of Lopina and Zhuravlyova (2012) [27] , who reported significant elevation of adiponectin in type 2 diabetic patients after oral administration of alpha lipoic acid .

Alpha lipoic acid increase Peroxisome Proliferator-Activated Receptor-γ2 (PPARγ2) mRNA expression levels in white adipose tissue, PPARγ plays a significant role in the transcriptional activation of adiponectin via a functional PPAR-responsive element (PPRE) in its promoter; PPARγ2 is highly expressed in white adipose tissue; thus alpha lipoic acid induce the secretion of adiponectin [28].

This study reported significant increase in blood serum adiponectin 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 [29], who found such significant raising after oral administration of carnitine in high fructose fed rats.

L-carnitine increase the fat oxidationrate act as fat burner; adiponectin concentrations are inversely related to the body fat mass; thus increased oxidation of free fatty acids by L-carnitine is associated with raising of adiponectin expression, also L-carnitine decrease TNF-α production which is an important cause related to decreasing adiponectin secretion [30]; in addition to positive role of L-carnitine in controlling hyperglycemia in diabetes mellitus which inversely associated with adiponectin.

This study showed High significance increase in blood serum pro-inflammatory cytokine IL-1 β concentrations ($p \leq 0.05$) in diabetic group during the experiment period Figure (3) (408.60 ±68.76pg/ml) as compared with control group.

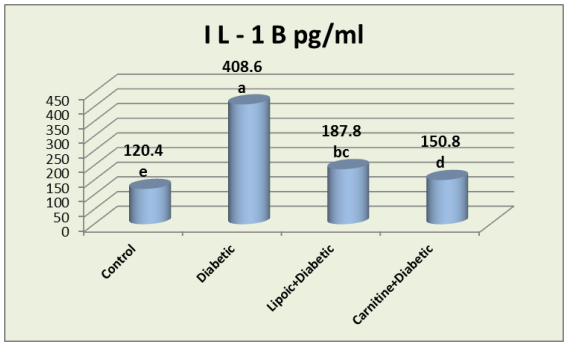

Figure (3): Concentrations of blood serum IL-1 β concentrations in the study groups.

These results agree with the studyof Ozkanlar*et al.*, (2016) [31]; who revealed significant elvation of IL-1 β in streptozotocin induced diabetic rats .

While significance decrease in blood serum IL-1 β concentrations ($p \leq 0.05$) in both diabetic alpha lipoic acid and diabetic L-carnitine treated groups as compared with diabetic group.

Pro-inflammatory cytokine such as IL-1β , IFN-γand TNF-α are secreted mainly from macrophages and adipose tissue participate in autoimmune reactions of diabetes mellitustype 1, and in type 2 diabetes mellitus the lowering in pancreatic beta cells is associated with glucose toxicity mediated by IL-1β, IFN-γ and TNF-α inducingapopotosis[9]; in addition advanced glycated end products (AGEs) in diabetes mellitus stimulate the production of IL-1β by macrophages and monocytes [10].

Alpha lipoic acid has anti-inflammatory properties which can inhibits the NF-kBpathway due to the inhibitory effect on degradation of IkB through the mitogen-activated protein kinases (MAPK) pathway; these effects of alpha lipoic acid lead to suppression of pro-inflammatory cytokines production [32]; additionally alpha lipoic acid exhibits a non-redox anti-inflammatory role via modulation of various signaling cascades and that in turn inhibit pro-inflammatory cytokines including IL-1 β [33].

L-carnitinecharacterised by antioxidant properties which participate in itsimmunosuppressive capacity; by which L-carnitinecan cause suppression of immune responses by either quenching reactive oxygen species (ROS), and thereby inhibiting the third signal for T cell activation, or by activating GR-a translocation directly and mimicking the immunosuppressive properties of glucocortocoids, this lead to suppression of pro-inflammatory cytokines production [34].

This study showed high significance increase in blood serum Alanine Transaminase (ALT) enzyme

activity (p≤0.05) in diabetic group during the experiment period Figure (4) (75.40 ±18.12U/L) as compared with control group.

The current study showed high significance increase in blood serum Aspartate Transaminase (AST) enzyme activity (p≤0.05) in diabetic group during the experiment period Figure (4) (98.40 ±6.54U/L) as compared with control group.

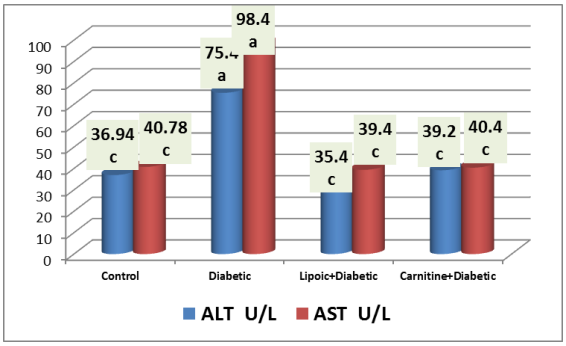

Figure (4): Concentrations of blood serum Alanine Transaminase (ALT) and Aspartate Transaminase (AST) enzymes activities in the study groups.

These results agree with other studies on rabbits such as study of [35], who found significant increase of blood serum Alanine Transaminase (ALT) enzyme activity in alloxan induced diabetic rabbis in comparison with control group.

This study found significant decrease in blood serum Alanine Transaminase (ALT) enzyme activity (p≤0.05) of male rabbits in diabetic group treated with alpha lipoic acid in comparison with diabetic group and this agree with the study of [36], who revealed such significant decrease after intraperitoneal injection of L-carnitine to alloxan induced diabetic rats.

This study revealed significant decrease in blood serum AlanineTransaminase (ALT) enzyme activity (p≤ 0.05) of male rabbits in diabetic group treated with L-carnitine in comparison with diabetic group and this agree with the study of [37], who reported significant decrease in blood serum Alanine Transaminase (ALT) enzyme activity after intraperitoneal injection of L-carnitine to alloxan induced diabetic rats.

These results agree with other studies on rabbits such as study of [23], who found significant increase of blood serum Aspartate Transaminase (AST) enzyme activity in alloxan induced diabetic rabbis in comparism with control group.

This study revealed significant decrease in blood serum Aspartate Transaminase (AST) enzyme activity (p≤0.05) of male rabbits in diabetic group treated with alpha lipoic acid in comparison with diabetic group and this agree with the study of [36].

This study found significant decrease in blood serum Aspartate Transaminase (AST) enzyme activity (p≤ 0.05) of male rabbits in diabetic group treated with L-carnitine in comparison with diabetic group and this agree with the study of [37], who reported such significant decrease after intraperitoneal injection of L-carnitine to alloxan induced diabetic rats.

The aspartate transaminase and alanine transaminase (AST and ALT) are important liver marker enzymes acting as indicators of liver function which are increased in alloxan induced diabetes mellitus, and this occur due leaking out of ALT and AST enzyme from hepatocytes into the circulation by the hepatotoxic effect of alloxanby which alloxan can induce the liver injury or dysfunction via free radical mechanism [38]; also alloxan increased the activities of transaminases in both liver and serum of diabetics, this elevated levels of transaminases, which is actived in the absence of insulin because of the availability of amino acids in the blood of diabetics is responsible for the increased gluconeogenisis and ketogenisis metabolism in diabetes mellitus[35], diabetes mellitus is also characterized by raising in pro-inflammatory cytokines such as TNF-α, which also involved in hepatic cellsdamage[18].

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دور تراكيز هرمون الاديبونيكتين وبعض المتغيرات المناعية والكيموحيوية في ذكور الارانب المصابة بداء السكر المستحث بالالوكسانو المصابة بداء السكر المعالجة بحامض اللبويك والكارنتين

مهند حسن محمود حمادي العزي[1] ، زيد محمد مبارك المهداوي[1] ، عصمت جمال جميل[2]

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[2]كلية الطب البيطري ، جامعة كركوك ، كركوك ، العراق

الملخص

جرى تصميم هذه البحث لمعرفة تأثير داء السكر المستحث بالالوكسان على تركيز هرمون الاديبونيكتين(Adiponectin Hormone) وبعض المتغيرات المناعية والكيموحيوية في ذكورالارانب المحلية, وشملت الدراسة (20) عينة دم قسمت الى 4 مجاميع: المجموعة الاولى: ذكور ارانب بالغة سليمة كمجموعة سيطرة, المجموعة الثانية: ذكورارانب بالغة مصابة بداء السكر المستحث بالالوكسان, المجموعة الثالثة: ذكورارانب بالغة مصابة بداء السكر المستحث بالالوكسان معالجة بحامض اللبويك (Alpha Lipoic Acid) (100 ملغم/كغم), المجموعة الرابعة: ذكور ارانب بالغة مصابة بداء السكر المستحث بالالوكسان معالجة بالكارنتين (L-Carnitine) (100 ملغم/كغم), ولقد أظهرت نتائج الدراسة الحالية انخفاض تركيز هرمون الاديبونيكتين معنويا عند مستوى ($P\leq0.05$) في المجموعة الثانية (مجموعة داء السكر) مقارنة مع مجموعة السيطرة, بينما كان هناك ارتفاعا معنويا في تركيز هرمون الاديبونيكتين عند مستوى ($P\leq0.05$) في المجاميع الثالثة والرابعة مقارنة مع مجموعة داء السكر , ولوحظ ارتفاع معنوي في تركيز الحركي الخلوي انتيرلوكين واحد بيتا (Interleukin-1 β[IL-1β]) عند مستوى ($P\leq0.05$) في المجموعة الثانية مقارنة مع مجموعة السيطرة, بينما كان هناك انخفاضا معنويا في تركيز الحركي الخلوي IL-1βعند مستوى ($P\leq0.05$) في المجاميع الثالثة والرابعة مقارنة مع مجموعة داء السكر , كما وجدت الدراسة الحالية ارتفاعات معنوية في الفعاليات الانزيمية لانزيمي ناقل امين الالنين (ALT) وناقل امين الاسبارتيت (AST) عند مستوى ($P\leq0.05$) في المجموعة الثانية مقارنة مع مجموعة السيطرة, بينما كان هناك انخفاضات معنوية في الفعاليات الانزيمية لانزيمي ناقل امين الالنين (ALT) وناقل امين الاسبارتيت (AST)عند مستوى ($P\leq0.05$) في المجاميع الثالثة والرابعة مقارنة مع مجموعة داء السكر .