

The Dyslipidemic and Hyperglycemic Effects of L-arginine in Alloxan-Induced Diabetic Albino Rats

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Abstract: Diabetes is a dangerous condition that poses a substantial risk to worldwide health care. The augmentation of lipolysis caused by persistent hyperglycemia, which eventually results in dyslipidemia, is a major contributing component to its systemic negative effects. Most diabetic people have dyslipidemia, which is a major risk factor for all cardiovascular disorders. When combined with its antioxidant properties, L-arginine can significantly help control and prevent diabetes and its associated complications. The goal of the study was to identify new applications for L-arginine in the treatment of diabetes. In this investigation, 21 adult male albino rats weighing 240-290 g were employed. After their blood sugar and lipid profiles were checked, animals were randomly divided into three groups of seven respectively. One group was maintained as the Normal Control Group (NC), while the other two groups were treated with only intraperitoneal (IP) dose of alloxan (140 mg/kg body weight) to create a quasi-analogue Type II diabetic model. All of the rats in the two groups had blood sugar levels above 200 mg/dl after 48 hours, and they were diagnosed with diabetes. One was used as the treatment group, DM+L-ARG, and the other was used as a positive control, using Type II diabetic rats (DM). While the DM+L-ARG group received L-arginine (200 mg/kg daily) by oral gavage, the NC and Type II diabetic DM groups were fed a conventional diet and clean drinking water. Blood tests were performed to compare their lipid profile and fasting blood sugar after 30 days of treatment. Group III (DM+L-ARG) demonstrated a substantial enhancement with a p-value of less than 0.001 in terms of fasting blood sugar (FBS), total cholesterol (T-Chol), triglycerides (TG), low density lipoprotein (LDL), and high-density lipoprotein (HDL). We conclude from this experimental animal study that the antioxidant L-arginine, with an excellent safety profile and few side effects, has anti-hyperglycemia and anti-lipidemia properties in the alloxan-induced diabetic model.

Keywords: Alloxan, Dyslipidemia, Hyperglycemia, Diabetes Mellitus, L-arginine

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Introduction

The chronic metabolic condition known as diabetes mellitus (DM) impairs the body's ability to manufacture or respond to insulin, which regulates level of sugar inside body. This leads to elevated blood and urine glucose levels, as well as an abnormal carbohydrate metabolism [1]. According to recent World Health Organization (WHO) reports, 415 million people globally are impacted. With diabetes. The number of people with diabetes is expected to rise by 2045, when 48% of people worldwide are expected

to have the condition [2]. The most prevalent signs of diabetes mellitus include weight loss in spite of having a healthy appetite and heightened vulnerability to infections, especially skin and urinary tract infections [3]. However, if left untreated, diabetes mellitus can result in serious side effects such as nerve damage, hearing loss, cardiovascular disease (CVDs), and chronic kidney disease (CKD). Obesity, poor consumption customs, a sedentary routine, and little physical activity are common risk factors for diabetes mellitus. diabetes mellitus is classified into three different categories: type 1 DM (T1DM), type 2 DM (T2DM) and gestational diabetes, since 90% of cases stated are of T2DM [4].

The primary risk factors for long-term complications of DM are the duration of diabetes, the degree of dyslipidemia, and hyperglycemia. Higher plasma glucose levels can cause a relative rise in reactive oxygen species (ROS) and a decrease in nitric oxide (NO) bioavailability, leading to an increase in diabetic dyslipidemia [5]. Atherosclerotic cardiovascular disease (ASCVD), neuropathy, nephropathy, retinopathy, metabolic disorders, weakened antioxidant defense system, dyslipidemia, and chronically and persistently elevated blood glucose are typically linked to abnormalities in fat, carbohydrate, and protein metabolism in Type II DM [6].

Since antioxidants have been shown to be an effective substitute for diabetes problems, including dyslipidemia, research into compounds and associated strategies to address hyperglycemia, dyslipidemia, and the associated consequences of diabetes mellitus. Degenerative disorders like diabetes and its consequences have been improved by natural compounds with hypoglycemic and antioxidant qualities [7].

E. Schulze and E. Steiger extracted L-arginine, also known as L-Arg, from lupin seeds for the first time in 1886. They named it “ἀργυρος” (argiros), meaning silver in Greek, because of the crystal's white-silver color. One necessary or conditionally essential amino acid is L-arginine. L-arg. is considered an important amino acid for tissue healing, synthesis of protein, the urea cycle, and functions of immune system. The antioxidant properties of L- arginine may be the result of reduced superoxide anion, which is typically generated by endothelial cells and reduces oxidative stress, or they may be ascribed to decreased radical processes [8].

According to research conducted in vivo and in vitro, as well as in healthy and diabetic humans, L-arginine is a precursor of NO that influences insulin release. Numerous studies have also suggested different ways that NO effects glucose homeostasis [7]. L-Arg's primary effects on lipid metabolism included raising NO levels and controlling the expression of genes involved in lipid metabolism. L-Arg benefits the cardiovascular system in several ways. Thus, giving L-Arg may help the endothelium in atherosclerotic disorders and promote NO formation [9]. Moreover, L- arginine, with its antioxidant properties, can help control dyslipidemia, lower oxidative stress, and preserve glucose homeostasis [10]. In order to help medical experts reconstruct the diabetic regimen in a more beneficial way, the study has been aimed at developing new uses for this amino acid.

Methodology

Study design

The research commenced in lab. Animal house of college of veterinary medicine The College of Medicine's ethical committee for experimental studies at the University of Baghdad approved this research.L- arginine/ Germany. While Sigma-Aldrich supplied alloxan.

Animals: A total of 21 adult male albino rats weighing 240-290 g were employed. The animals were sourced from the animal facility at the Iraqi Center for Cancer Research and Medical Genetics in Baghdad, Iraq, where they were kept. They were housed in polyethylene cages topped with stainless steel

covers and elevated to avoid coprophagy. Animals were acclimated for 1 week prior to the study. They were kept under standard laboratory environments (21-25 °C, 12-hour light-dark cycle) and had unrestricted access to chow pellets and tap water.

Type two diabetes mellitus Induction: Alloxan in sodium citrate buffer was used to induce DM in rats. To do this, 2g of sodium citrate was dissolved in 100ml of distilled water to create 0.1 mol of citrate buffer. 0.6g of alloxan was dissolved in 1 ml of citrate buffer to create 60 mg of alloxan. After a single intraperitoneal injection of alloxan (140 mg/kg body weight in solution form) in rats, the animals were induced, and their Blood glucose levels were tested during fasting. 72 hours later using an active blood glucose meter. Blood glucose levels in diabetic rats exceeded 200 mg/dl. In accordance with the study plan, Rats in the control group were not given DM [11].

At the beginning and end of the experiment, blood samples were taken for biochemical analysis. The samples were collected from the tail vein of the rats prior to DM induction and after an 8-hour fast. The animals were kept fasting for 12 hours at the conclusion of the trial, which took place 30 days after the start. After that, under anesthesia using 90mg/kg of ketamine and 40mg/kg of Xylazine within the muscle. A heart puncture was then used to acquire the sample. After being extracted from the drawn blood, the serum was utilized to measure biochemical markers. After a week of acclimation, these rats were divided into three equal-sized groups, each consisting of seven rats. The following individuals were among the participants in the experimental groups:

Table 1. The Intervention procedures

Group	Intervention Procedure
Group I: Control Group (NC)	Rats given clean drinking water and fed on a standard diet
Group II: DM Group (DC)	DM rats were given clean drinking water and fed on a standard diet
Group III: DM+ L-ARG Group	DM rats were treated with L-arginine (200 mg/kg/day) given by oral gavage for 30 days.

Assessment of antioxidant properties of L-arginine in alloxan-induced diabetic rats.

The animals were put under anesthesia using 90mg/kg of ketamine and 40mg/kg of Xylazine within the muscle at the end of the experiment, which was day 30 [12]. Blood samples were collected by executing a direct puncture of the heart using plastic syringes holding 5 milliliters, after which they were transferred into a gel tube. These tubes were ultimately centrifuged for 10 minutes at 3000 revolutions per minute throughout the entire process investigation. After the blood was completely separated, the serum was extracted, transferred into 2 mL plastic tubes, and kept at -20 °C until analysis [13]

Statistical analysis:

The Statistical Package for the Social Sciences (SPSS) Version 25 was used to analyze the data. The mean + SD was used to summarize the quantitative variables. To determine significance at multiple time points within the group, a paired-samples t-test was used. Tukey's post hoc correction for multiple comparisons was applied after a One-Way Analysis of Variance (ANOVA) was used to assess differences across all groups [14].

Results

Comparing Groups Using Different Criteria Parameters: How different groups behave in each of the mean values of each category of parameters can be summed together as follows:

Fasting Blood Sugar (FBS): L-Arginine Group (L-Arg) exhibits a notable improvement in the FBS test results. The findings have a statistically significant value of $p < 0.001$. The following appendix contains the tabular data:

Table 2. Comparison of mean values of fasting blood sugar (FBS)*

Comparative Analysis	(Mean Values)	(Mean Values)	(Mean Values)
Parameters	NC	DC	DM+L-Arg
Pre Alloxan Infusion	105.7	108.4	109.4
PostTreatment (mg/dL)	112.2	384.1	151.7

p value <0.001 * * Significant p value < 0.05

Lipid Profile: The L-Arg group showed a notable improvement in T Chol, TG, HDL, and LDL. The outcome was statistically significant when the p-value was less than 0.001. Below are the tabulated data:

Table 3. Comparison of mean values of lipid profile

Comparative Analysis	(Mean Values)	(Mean Values)	(Mean Values)
Parameters	NC	DC	DM+L-Arg
Pre Alloxan Infusion			
T Chol. (mmol/L)	1.35	1.40	1.44
Post treatment			
T Chol. (mmol/L)	1.42	3.66	1.62
Pre Alloxan Infusion			
TG	0.74	0.71	0.73
Post treatment TG			
(mmol/L)	0.76	2.74	0.80
Pre Alloxan Infusion			
HDL	1.44	1.39	1.35
Post Treatment HDL			
(mmol/L)	1.48	1.85	1.19
Pre Alloxan Infusion			
LDL	0.25	0.24	0.25
Post treatment LDL			
(mmol/L)	0.24	0.81	0.39

p value <0.001 * * Significant p value < 0.05

Discussion

Today's world is greatly impacted by the rising prevalence of diabetes mellitus (DM). Hostilely anywhere in the world. Currently, more than 150 million people have diabetes, and according to World Health Organization predictions, that number will probably quadruple by 2025, reaching 783.2 million in 2045 , reaching an alarming 300 million cases. Neuropathy, nephropathy, metabolic diseases, retinopathy,

compromised immune function, and lipid abnormalities are some of these consequences. Profile and atherosclerosis, the majority of which are brought on by high blood glucose levels [15], [16].

Diabetes's complex etiology has therefore affected care patterns and drug strategies, ranging from monotherapy to a suite of composite and combination medications. Numerous empirical studies have demonstrated that the combined use of synthetic and antioxidant medications outperforms each treatment alone [17].

Chronic hyperglycemia is associated with Reactive oxygen species (ROS) and oxidative stress, which alter the cellular redox state. Additionally, it decreases the tissues' capacity to use carbs, which can lead to a range of illnesses and issues with the metabolism of proteins and fats [18]. Empirical data indicate that prolonged elevated blood glucose levels aggravate oxidative stress by oxidizing proteins and promoting glucose autooxidation. They also contribute to ROS generation [19]. Numerous recent studies have demonstrated that increasing antioxidant intake and supplementation lowers oxidative stress and protects tissues from ROS damage, thereby reducing the incidence of various degenerative diseases, including diabetes and its consequences [20].

Because L-arginine has antioxidant, hypoglycemic, and dyslipidemic properties, this study was designed to evaluate its effects in an Alloxan-induced diabetic animal model. The study's findings showed that giving antioxidants to diabetics reduced their hyperglycemia [21]. The decrease in both TG and LDL levels may be linked to improved glycaemic management, even though the increase in HDL is mainly driven by improved insulin function, supported by antioxidants. The protective membrane-bound lipoprotein lipase against lipid peroxide may be linked to the effectiveness of antioxidants in reducing blood LDL and TG [22], [23]. Reduced VLDL and LDL levels may result from antioxidants' antihyperglycemic properties, which improve diabetic function [24]. Under normal circumstances, the antioxidant defense mechanisms eliminated sufficient ROS, but the additional ROS produced increased lipid peroxidation and reduced the activities of glutathione peroxidase (GSH-Px) and superoxide dismutase (SOD). All of this highlights oxidative stress, which is primarily controlled by hyperglycemia [25].

Glycation of the enzyme, which occurs at persistently elevated blood glucose levels, may be linked to reduced antioxidant enzyme activity in diabetes. As previously noted by Teixeira and Alves, glycation of SOD reduces its mobility, leading to insufficient dismutation of superoxide anions (O_2^-). This has led to a correlation between improved glycemic control and reduced protein glycation, resulting in increased SOD activity [26].

Oxidative stress results from a redox imbalance between ROS production and the compensatory response of the endogenous antioxidant network. It is important to note that there is still disagreement among researchers about how different antioxidant enzymes function in diabetic rats [27]. These enzymes decreased in some studies on SOD activity in diabetes; however, a few others found that they rose. Activity in rats with DM caused by Alloxan. H_2O_2 acting as an inducer of tissue SOD and, accordingly, increased superoxide generation could be the cause of this increase in SOD activity [28]. Because chronic hyperglycemia in diabetes is linked to increased oxidative stress, taking antioxidant supplements helps control In DM, glycaemia acted as a protective factor against lipid peroxidation [29]. According to earlier research, L-arginine administration decreased plasma glucose, triglycerides, and cholesterol, as well as biochemical markers associated with diabetes. Furthermore, L-arginine enhanced glucose tolerance and insulin levels [30]. To summarize the previous discussion, giving antioxidants to Alloxan-induced diabetic rats improved their hyperglycemia and dyslipidemia. Therefore, the imbalance between ROS production and enzyme activity in diabetic rats must be managed.

Study limitations

The study's small sample size and brief duration prevent it from examining the interactions between L-arginine and other dietary fats or carbs, which are important components of human dyslipidemia.

Conclusion

In an alloxan-induced diabetic animal, this work shows that L-arginine supplementation has notable anti-hyperglycemic and anti-lipidemic benefits. L-arginine is a powerful metabolic regulator that dramatically lowers fasting blood sugar (FBS), total cholesterol, LDL, and triglycerides while concurrently raising "good" HDL cholesterol.

L-arginine's antioxidant qualities, which probably lessen the oxidative stress and systemic lipolysis usually brought on by persistent hyperglycemia, are mostly responsible for its therapeutic success in this study. L-arginine offers a promising supplemental treatment for controlling diabetes and lowering the risk of related cardiovascular problems due to its outstanding safety profile and few adverse effects.

Author Contributions: Study conception (Jalal A. Al-Saedi and Faris Kadhim Khadir) , Study design, and critical revision: (Jalal A. Al-Saedi)). Acquisition of data and analysis (Faris Kadhim Khadir), Drafting of the manuscript, and interpretation of data: (Jalal A. Al-Saedi and Faris Kadhim Khadir) .

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