The Effect of L-Arginine on Diabetic Male Sex Organs

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ABSTRACT

L-arginine is the substrate for the enzyme nitric oxide synthase (NOS), which is responsible for the production of nitric oxide (NO), an endogenous messenger molecule involved in many metabolic processes. The purpose of this work was to evaluate the effect of L -arginine on male sex organs under diabetic conditions. In this study three groups of adult male rats were used, the first as control, the second was alloxan – induced diabetic rats under control by insulin and the third was like the second but was treated with L-arginine for four weeks. At the end of the experiment , the rats were killed . The serum level of glucose, testosterone, body weight, serum cholesterol, penile nitric oxide synthase (NOS) activity, arginase activity in (seminal vesicle and prostate gland), lag time and erection time were estimated. The glucose level was significantly increased in both second and third groups due to effect of alloxan and was less significantly increased in the third group due to the effect of L– arginine. There was also significant decrease in serum testosterone in the second and the third groups in relation to the control group, with no significant change between the second and third groups. There was a significant increase in the level of serum cholesterol and in the lag time in both groups 2 and 3, with significant decrease in the third group in relation to the second group. The other remaining parameters showed a significant decrease in both second and third groups in relation to the control group with significant improvement in the third group when compared with the second group due to the effect of giving L-arginine . We suggest that these findings due to the beneficial effect of L- arginine on the sexual functions of the male sex organs that were affected by diabetes.

INTRODUCTION

L-Arginine is an important amino acid that participates in multiple biochemical processes in mammals. In addition to its role in the urea cycle and protein synthesis, it serves as a precursor for the synthesis of amino acids , nitric oxide , polyamines, creatine, agmatine and other guaridino compounds[(1)]. In most mammalian species, arginine is not considered an essential amino acid for healthy adult , since it can be synthesized in the tubular cells of the kidney from the citrulline generated in the small intestine[(2)].

However arginine may be considered a conditionally essential amino acid for adult animals under certain stressful conditions, and for young growing animals, when the endogenous synthesis is inadequate to accomplish arginine requirements[(3)]. In addition, it has been reported that supplemental arginine may have

beneficial effects since it enhances wound healing and angiogenesis, improves protein anabolism, stimulates the immune functions and ameliorates cardiovascular Homeostasis of L- arginine in plasma is regulated by dietary arginine intake , protein turnover , transport , arginine synthesis and catabolism[5]. The relative importance of these processes may be dependent on different factors such as age, animal species or dietary salt intake[6]. Thus, while endogenous synthesis of arginine plays an important role in regulating arginine homeostasis in neonatal and growing pigs[7]. dietary arginine intake appears to be the main regulator of arginine levels in adult human[8]. In rodents, it has been reported that feeding adult animals an arginine – deficient diet decreased arginine concentration in plasma[9]. In a recent study, it was found that there is a marked gender dimorphism in the levels of arginine in plasma, kidney and skeletal muscle in female mice having higher levels than males[10]. Moreover, the restriction of dietary arginine produced a marked decrease of arginine in plasma and tissues that almost abolished the sexual dimorphism found in the levels of this amino acid. This dietary restriction also affected the activities of enzymes related to the metabolism of arginine and ornithine that are regulated by sex hormones, suggesting the existence of interaction between dietary arginine and hormone action[10].

In the present study we have investigated the influence of the beneficial effect of L-arginine on the disturbed sexual function of the male sex organs of the diabetic rats, by estimating the level changes of serum glucose, testosterone, cholesterol. Body weight, penile nitric oxide synthase (NOS) activity, arginase activity in both seminal vesicle and prostate gland. Lag time and erection time in both normal and diabetic male rats.

MATERIAL & METHODS

In this study 21 adult male albino rats of average body weight 300 ± 10 gm were kept under optimal environmental conditions of diet , water , light, temperature … etc for accommodation for one week, then the animals were divided into three groups:

1. Group (1):Control (7 rats).
2. Group (2):Alloxane induced insulin – dependent diabetes mellitus group (7rats).
3. Group (3): Was like the second group but was injected i. p. (intraperitoneally) with L-arginine 5 mg / kg (Aldrich, U.K) solubilized in saline beginning from the day of diabetes induction and the solution was adjusted to pH 7[11] (7 rats) .

Diabetes induction:

Both groups 2 and 3 were administered alloxan (mesoxotyl urea) (C_4 H_2 N_2 O_2H_{20}M.Wt.160 from lab Rasyan) via the intraperitoneal route at a dose of 200 mg/kg body weight of rat and after 10 days the rats were readministered 1/10 th of the initial dose[12]. Both groups 2 & 3 was treated by ultra-lint insulin at dose of 1-3 u/kg rat body weight/day via subcutaneous injection into the axillary fold to minimize polyuria and aviod clinical hypoglycaemic crises,

as well as to maintain glucose blood level between 260 – 270 mg %[13].

The animals were weighed every week (for weight loss) and initial glycosuria was determined by test tape to identify the first day of onset of diabetes at glucose serum level > 180 mg %.

Papaverine test

After 4 weeks of the onset of diabetes all rat groups were placed on their back (non anaesthesized). The four limbs were firmly fixed to table and were injected papaverine directly into the corpora cavernosa of penis at a dose of 0.3 mg /kg to measure the lag time (the time between papaverine injection and appearance of penile erection) and to measure the erection time. The rat was left for a period up to 15 minutes to elicit erection[14].

N.B.: As not all rats develop erection so a bigger number of rats were used and only the potent (erectile) rats were used (7 for each group)

At the end of the study (4 weeks after the onset of diabetes mellitus) the rats were decapitated by cervical dislocation, then weighed, blood sample were obtained for serum glucose and radio– immuno –essay of testosterone according to Stlay et al[15]. Measurements of cholesterol by colorimetric method of Tinder[16], using the kit supplied by Human. The penis was surgically excised and stored rapidly in deep freeze until analysis of penile tissue nitric oxide synthase (NOS) activity as described by Italaeno et al[17]. Prostate gland and seminal vesicles were removed , freed from adjacent tissues , and placed in saline , the glands were homogenized (1:5) in 0.04 M Tris – Hcl , pH 8.7 containing 0.2 m M Mn cl_2[18]. Arginase activity was measured by the method of Bond et al[19].

Data were collected, analyzed statistically and put in tables and columns [mean value ± SD , F (ANOVA) test and Scheffe test to compare the affected groups and locate the site of significance]

RESULTS

The results of this work were presented in table 1 also in figures 1–9.

- *Serum glucose:* Showed significant increase in both groups (2&3) on comparison with control group 1 and significant decrease in group 3 in relation to group 2 (tab . 1 and fig . 1).
- *Serum testosterone:* Showed significant decrease in groups 2and 3 when compared with control group 1. There is no significant change between group 2 and group 3 (tab. 1 and fig. 2).
- *Body weight:* It gave significant decrease in groups 2 and 3 when compared with control group 1. There is significant increase in group 3 in relation to group 2 . (tab .1 and fig . 3) .
- *Serum cholesterol:* Showed significant increase in groups 2 and 3 when compared with control group 1. There is significant decrease in group 3 in relation to group 2. (tab. 1 and fig 4).

Tab (1): The effect of L-arginine on serum glucose (mg %), serum testosterone (ng/ ml), body weight (gm), serum cholesterol (mg/dI), Penile nitric oxide synthase (NOS) activity (μ mole/ min /gm tissue), arginase activity in seminal vesicle (arg. act. in s.v.) in (μ mole/ min /gm tissue), arginase activity in prostate gland (arg. act. in prost) (μ mole/ min /gm tissue), lag time (sec) and erection time (min) in normal and diabetic rats.

	(1) Control		(2) Diabetic		(3)Diabetic+ L-argnine		F	P	Scheffe test
	Mean	SD±	Mean	SD±	Mean	SD±			
Serum glucose	101.2	1.89	261.5	11.1	233.1	10.28	660.4	<0.001*	All significant
Serum testosterone	6.04	9.05	4.97	0.16	5.21	0.35	41.49	<0.001*	(3=2)<1
Body weight	302.1	7.55	242.8	21.57	271.4	22.11	18.24	<0.001*	All significant
Serum cholesterol	166.2	12.37	280.1	25.82	209.8	25.65	46.88	<0.001*	All significant
Penile NOS act.	0.56	5.67	0.27	6.29	0.42	7.99	32.54	<0.001*	All significant
Arg.act.in s. v.	0.43	0.10	0.11	3.83	0.29	8.36	27.55	<0.001*	All significant
Arg.act.in prost.	0.71	0.11	0.28	5.71	0.48	7.22	44.63	<0.001*	All significant
Lag time	76.1	16.83	155.2	34.91	115.4	32.46	12.86	<0.001*	All significant
Erection time	11.07	2.99	2.50	1.23	6.22	1.98	26.8	<0.001*	All significant

**Significant*

Graphic presentation of the effect of L-arginine on serum glucose (mg %), serum testosterone (ngm/ ml), body weight (gm) and serum cholesterol (mg/dI)

Fig. (1) Serum glucose in the studied groups

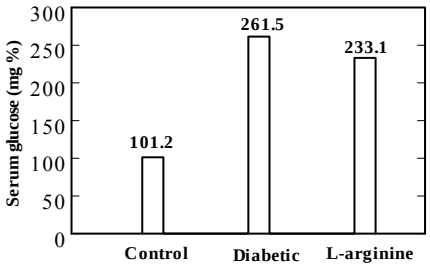


Fig. (2): Serum testosterone in the studied groups

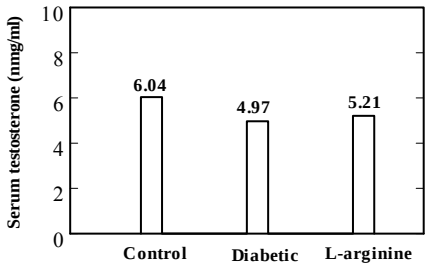


Fig. (3) Body weight in the studied groups

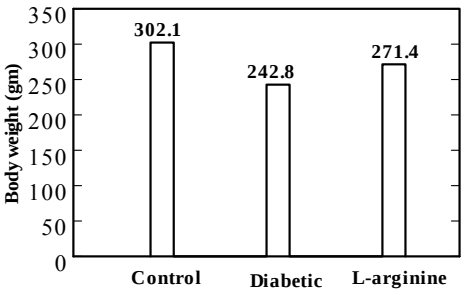
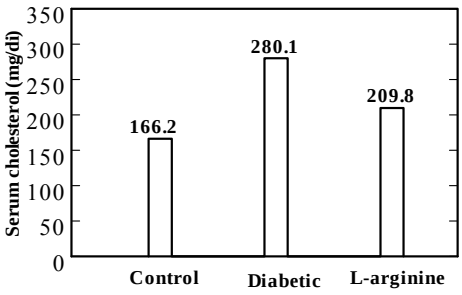


Fig. (4): Serum Cholesterol in the studied groups



Graphic presentation of the effect of L-arginine on penile nitric oxide synthase (NOS) activity (μ mole/ min /gm tissue), arginase activity in seminal vesicle (arg. act. in s.v.) in (μ mole/ min /gm tissue), arginase activity in prostate gland (arg. act. in prost) (μ mole/ min /gm tissue), lag time (sec) and erection time (min) in normal and diabetic rats.

Fig. (5) Penile NOS act. in the studied groups

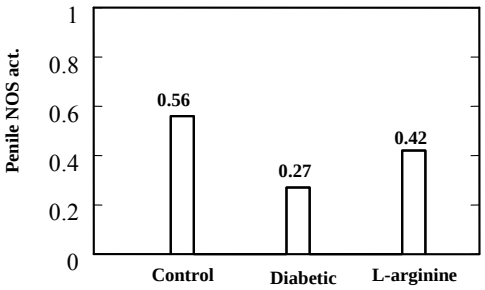


Fig. (6) Arg. act. in S.V. in the studied groups

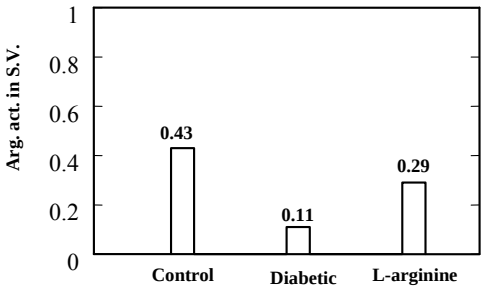


Fig. (7) Arg. act. in Prost. in the studied groups

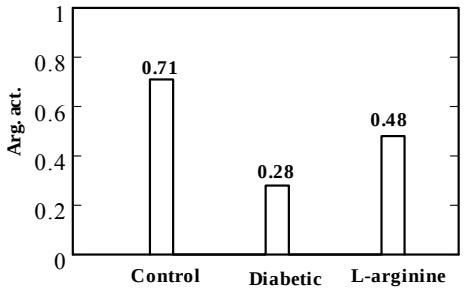


Fig. (8) Lag time in the studied groups

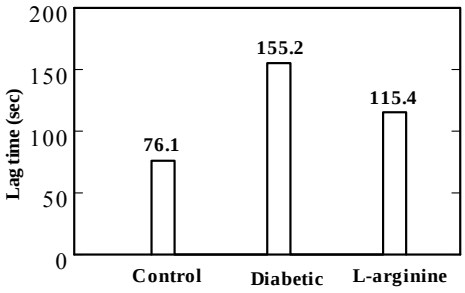
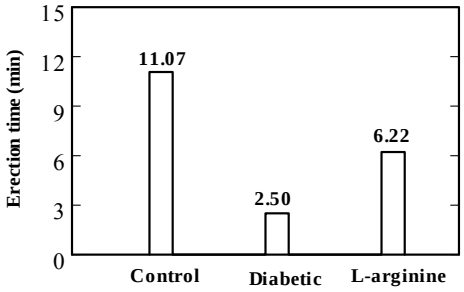


Fig. (9) Erection time in the studied groups



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- Penile nitric oxide synthase activity, rginase activity in seminal vesicle and in prostate gland: Showed significant decrease in groups 2 and 3 when compared with control group 1. There is significant increase in group 3 in relation to group 2 (tab. 1 and fig 5, and 7).
- Lag time: Showed significant increase in groups 2 and 3 when compared with control group 1. There is significant decrease in group 3 in relation to group 2. (tab. 1 and fig. 8)
- Erection time: Showed significant decrease in groups 2 and 3 when compared with control group 1. There is significant increase in group 3 in relation to group 2. (tab. fig . 9).

DISCUSSION

The choice of alloxan-induced diabetes in rats as experimental models was preferred to demonstrate similar reproductive, immune, metabolic and clinical findings of diabetic cases[20]. as it can show also the complications of eye[21], kidney[22] and nerves[20]. Alloxan (mesoxatyl urea) can destroy selectively the B-cells of islets of Langerhans leading to impaired glucose utilization and an induced-diabetic state similar to the clinical condition[23].

Papaverine test for erection was chosen because it is easy rapid and can be applied to both man and experimental animals, where animals were not anaesthetized because of absence of the psychic factor opposite to that of man[14] . Under the effect of papaverine {which is smooth muscle relaxant that can affect corpora cavernosa and it is an inhibitor that blocks adenosine 3,5 cyclic monophosphate and cGMP hydrolysis}[24]. So, impotence in rats had developed because diabetes mellitus lead to smaller cGMP penile pool than in control as shown in experimental studies and lead to no smooth muscle relaxation due to decrease nitric oxide synthesis[25] .

Glucose:

There was a significant increase in glucose blood level in groups 2 and 3 than the control due to diabetes induction, by alloxan that destroyed B cells of pancreas leading to disturbed utilization of glucose[23]. Glucose blood level is the diagnostic marker for diabetes, but not for impotence as impotence has been proved to occur in diabetic male patients at rate between 10-33% sooner or later without a clear relation to control by insulin[26]. The significant decrease in serum glucose in group (3) in relation to group 2 is due to administration of L- arginine, as L- arginine is one of the most potent insulin secretagogues[27] Also L- arginine administration at the time of diabetic induction results in only moderate hyperglycemia in comparison with diabetic animals in which sever hyperglycemia had developed[20] .

Testosterone:

It was significantly decreased in both groups 2 and 3 when compared with control, with no significant change between groups 2 and 3. This was attributed to the effect of diabetes on the genital organs (affecting their nervous and arterial blood supply by endartritis obliteranas). This was

supported by Hassan et al.[29] who showed a marked drop in serum testosterone level in experimental diabetic rat models, as well as the evident drop of testosterone decreased level in impotent old diabetic human males of organic origin 50-75% of control level that was related to a severe affection of penile reflexes and copulatory behavior[30]. The reduced testosterone secretion was explained by Cameron et al. [31], due to diminished formation in endoplasmic reticulum in Leydig cells of testis, as well as an increased lipid deposits, that accompanied diabetic state. Another study had described testicular morphological change in diabetic men, in addition to a reduced human chorionic gonadotrophic (HCG) binding sites when compared with control[32]. L-arginine has no effect on testosterone level, but L-arginine is required for the anabolic action of androgens [33].

Body weight:

There was a significant decrease in body weight in both groups 2 and 3 when compared with the control group . This decrease can be attributed to the direct diabetic metabolic errors and indirectly by the androgenic hormonal level decrease[30] .

There was a significant increase in group 3 in relation to group 2 due to treatment with L- arginine . Feeding mice an arginine deficient diet, decreased plasma concentration of arginine in both sexes. This produce marked decrease in body weight, this decrease was not associated with decrease in the circulating levels of testosterone. Dietary arginine restriction that prevented the body weight gain and not corrected by giving testosterone, indicate that arginine is required for the anabolic action of androgens[33]. L- arginine may be considered an essential amino acid for animal under certain stressful conditions e . g diabetes when endogenous synthesis is inadequate to accomplish arginine requirements[3]. Also , L- arginine increases body weight because it increase insulin and growth hormone secretion [28] .

Serum cholesterol:

There was a significant increase in both groups 2 and 3 when compared with the control group due to the effect of diabetes . In diabetic patients , the plasma cholesterol level is usually elevated and this may play a role in the accelerated development of the atherosclerotic vascular disease that is a major long term complication of diabetes in human . The rise in plasma cholesterol level is due to an increase in the plasma concentration of very low density lipoproteins (VLDL) and low density lipoproteins (LDL), which may be due to increased hepatic production of VLDL or decreased removal of VLDL and LDL from the circulation[34]. There was significant decrease in group 3 in relation to group 2 due to administration of L- arginine.

Acute and chronic administration of L- arginine has been shown to improve endothelial function in animal model of hypercholesterolemia and atherosclerosis. Also, L-arginine supplementation can augment nitric oxide production in human and thereby improve vascular health[28]. Even small concentration increase of L-arginine within the physiological range will lead to increased NOS activity and thus improve the

antioxidant effect of L- arginine . So , L – arginine has direct antioxidant effects due to the alpha–amino group and may scavenge super oxide or restore the cofactor tetrahydrobiopterin ($B H_4$) [28]. In patient with peripheral arterial occlusive disease (PAOD); L-arginine significantly improved flow dependent vasodilation and reduced oxidative stress as reflected by decreased urinary levels of established biomarker of oxidative stress of 8–iso–prostaglandin F2 . Another interesting possible mechanism is that oxidized LDL and lysophosphatidycholin decrease L-arginine transport into endothelial cells , this may be the reason for the beneficial effects of L-arginine in patients with hypercholesterolemia [28].

In animal with hypercholesterolemia, L- arginine appears to inhibit the progression of atherosclerotic plaques and preserve endothelial function. In addition, L-arginine affect other mediators of atherosclerosis including inflammatory cells and platelets[28].

Penile nitric oxide synthase (NOS) activity:

Nitric oxide (NO) is formed in the endothelium from the amino acid L- arginine by endothelial isoform of NO synthase (eNOS) , this enzyme may be stimulated to increase NO synthesis by a variety of physiological agonists and pharmacological agents including acetylcholine.

In many vascular disorders, including essential hypertension , diabetes mellitus , cigarette smoking , aging and hypercholesterolemia ; the endothelium is a direct , sensitive target for the damaging effects of atherogenic risk factor . In these conditions, there is a loss of bioactive endothelial NO . There are two fundamental mechanisms for the loss of NO bioactivity: reduced synthesis and increased oxidative inactivation by reactive oxygen species (ROS)[28] .

There was significant decease in penile (NOS) activity in both groups 2 and 3 in relation to the control group . These results could be explained by the effect of diabetic pathogenesis on the neurovascular supply of penis in form of disease in the putative penile endothelial NOS[35]. Some authors related NOS decreased activity in part to the decreased serum testosterone[36]. Through the recycling of citrulline (a co–product of NOS)[37]. Arginine may play an important role in maintaining the availability of arginine for NOS in endothelial cells [38].

A straightforward approach to increase NO synthesis is to provide additional substrate to the endothelial cells. The semi – essential amino – acid L- arginine serves as the substrate for the enzyme e NOS[39].

Arginase activity in both seminal vesicle and prostate gland:

Arginase (L-arginine amidinohydrolase, E.C. 3.5.3.1), which catalyzes the hydrolysis of L-arginine to form L- ornithine and urea, is one of the polyamine biosynthetic enzymes .Arginase produces ornithine for the subsequent formation of putrescine. Arginase activity has been detected in the prostate gland, where it provides L- ornithine for polyamine biosynthesis. lower levels of arginase activity also have been identified in other accessory sex glands [40].

Arginase activity is hormone – dependent, stimulated in intact or castrated male rats by testosterone, prolactin and decreased by estradiol[41].

Our results showed that arginase activity in both seminal vesicle and prostate gland was significantly decreased in both groups 2 and 3. This decrease could be explained by the fact that the diabetic state decreased androgen – binding capacity in the rats[42]. Since arginase activity is an androgen–dependent enzyme,[41] experimental diabetes may decrease arginase activity, mediated by androgen deficiency or poor response to androgens in accessory glands[27] .

The results also showed that there was significant increase in group 3 in relation to group 2 , which is due to administration of L-arginine which stimulate arginase activity when administered for a long period of time[43].

L–arginine may act as a secrtagogue of growth hormone and insulin in human and other mammals and enhance testosterone action in kidney, skeletal muscle and other tissues[28].

Lag time and erection time:

The results showed that induction of diabetes in male rats produce significant increase in the lag time in both groups 2 and 3 at the same time there is significant decrease in erection time in both groups 2 and 3 when compared with the control group. This is because diabetes millitus lead to smaller c GMP penile pool, produces a decrease in testosterone, arginase and NOS activities in the sexual organs which leads to decreased production of nitric oxide, which produce abnormal endothelial function in insulin dependent diabetes millitus [27] .

Administration of L-arginine produce significant improvement in lag time and erection time in group 3 in relation to the group 2. This is because L-arginine improve the activity of arginase[43]and NOS[39] which could improve NO production, which could be the active agent in erection. Acute and chronic administration of L-arginine has been shown to improve endothelial function in animal models of hypercholesterolemia and atherosclerosis.[28]**.** Also L-arginine enhance effect of testosterone , so increase the response to testosterone in accessory sex glands . This help in improving of lag time and erection time[46].

CONCLUSION

This study suggest that L-arginine increase the responsiveness of male sexual function in diabetic rats. this effect appears to improve the lag time and the erection time in diabetic male rats

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تأثير إل أرجنين على الأعضاء الجنسية في ذكور الفئران المصابة بالسكر

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يهدف هذا البحث إلى دراسة تأثير مادة أل أرجنين على ذكور الفئران البيضاء المصابة بالسكر وذلك على الاعضاء التناسلية وبعض الوظائف الحيوية وكذلك وزن الفئران . وقد أجرى هذا البحث على ٢١ فأر أبيض من الذكور قسمت إلى ثلاث مجموعات .

(١) المجموعة الأولى : قابضة ومكونة من ٧ فئران .

(٢) المجموعة الثانية : مصابة بمرض السكر عن طريق حقن الألوكسان وتعطى عقار الانسولين ومكونة من ٧ فئران .

(٣) المجموعة الثالثة : مثل المجموعة الثانية وتعطى مادة أل أرجنين لمدة أربع أسابيع ومكونة من ٧ فئران.

وفي نهاية التجربة بعد أربع أسابيع تم قتل الفئران ووزن كل فأر وتحليل الدم لتحديد مستوى السكر وهرمون التستوستيرون والكوليسترول . وقد تم قياس مستوى نشاط أنزيم أكسيد النيتريك المخلق بالقضيب وكذلك مستوى نشاط أنزيم الأرجيناز في البروستاتا والحوصلة المنوية هذا وقد تم قياس وقت الانتصاب في القضيب والمدة السابقة للانتصاب بعد حقن مادة (بابا فرين) قبل ذبح الفئران .

وقد أظهرت النتائج زيادة الجلوكوز والذي كان مرتفعاً بأهمية إحصائية في المجموعتين الثانية والثالثة بسبب مرض السكر بالنسبة للمجموعة الأولى ولكنه أنخفض بنسبة ذو دلالة إحصائية في المجموعة الثالثة بالنسبة للمجموعة الثانية بسبب تأثير مادة أل أرجنين .

وجد أيضاً انخفاض ذو دلالة إحصائية في مستوى هرمون التستوستيرون في المجموعتين الثانية والثالثة عن المجموعة القابضة مع عدم وجود تغيير ذو دلالة إحصائية بين المجموعة الثانية والثالثة . وقد وجد زيادة ذو دلالة إحصائية في المجموعتين الثانية والثالثة في مستوى الكوليستيرول في الدم وكذلك في الزمن قبل انتصاب القضيب . هذا وقد حدث انخفاض ذو دلالة إحصائية في المجموعة الثالثة بالنسبة للمجموعة الثانية وذلك بسبب أعطاء مادة أل

أرجنين . وكان هناك هبوط بأهمية إحصائية في المجموعتين الثانية والثالثة في بقية القياسات ولكن بعد الحقن بمادة أل أرجنين وجد تحسن (زيادة) ذو أهمية إحصائية في هذه القياسات وذلك في المجموعة الثالثة بالمقارنة بالمجموعة الثانية .

ونحن نتوقع أن هذا التحسن في معظم هذه القياسات نتيجة التأثير المفيد لمادة أل أرجنين على ذكور الفئران البيضاء المصابة بمرض السكر .