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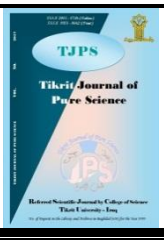

The effect of different concentrations of metformin drug on the concentration of glucose and lipid profile in the male rats induced diabetes by alloxan.

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ABSTRACT

The present study aimed to find out the effect of Metformin drug on some of biochemical parameters, including Glucose and lipid profile: Cholesterol, Triglycerides, High density lipoprotein HDL-CH, and low density lipoprotein LDL-C Male albino rats were used in this study.

The results showed that the development of diabetes induced by alloxan led to a significant increase in the levels of glucose, cholesterol, triglycerides, and low-density lipoprotein cholesterol (LDL-C) compared with the control group. Treatment of animals in the third and fourth groups with metformin at two different concentrations of (500,850) mg led to a significant decrease in glucose and cholesterol levels, compared with the aloxan group, the results were similar to the control group, and the treatment resulted in a significant decrease in triglycerides and low-density lipoproteins (LDL-C) compared with the alloxan group and gave results comparable to the control group (healthy controls).

Introduction

Diabetes mellitus is a chronic disease that occurs as a result of an imbalance in the metabolism, and is mainly characterized by an increase in the concentration of glucose in the blood, insulin resistance and dysfunction in beta cells[1]. It was considered one of the most common metabolic diseases with a rate of 6.4% in people aged from 20-79 years[2], and diabetes is one of the leading causes of death worldwide[3,4]. There are two different types of diabetes, type 1 and type 2, which are guaranteed to have gestational diabetes, and this type of diabetes occurs during pregnancy[5].

many treatments have appeared that reduce blood glucose and have recently spread a drug that has been approved by the World Health Organization, the World Food, and the drug Association, which is metformin. Metformin is the first line of treatment for people with T2DM who have been newly diagnosed by the American Diabetes Association (2017). This drug primarily prevents the liver from gluconeogenesis the glucose, thus reducing fasting glucose levels[6]. It was also found that the effect of metformin on the liver occurs by suppressing the excessive glucose synthesis process by stimulating the effect of insulin, reducing the production of glucose by the liver, and reducing the effects of the glucagon hormone[7]. Metformin also has positive effects on blood lipid disorders, inflammation and clotting, which benefit vascular function[8]. Studies indicate that metformin lowers total cholesterol, triglycerides, and low-density lipoprotein (LDL), as well as metformin in its effect on lowering lipid concentrations by improving insulin and leptin sensitivity[9].

Or by activating the AMP- protein kinase (AMPK) and thus suppressing the fatty acid desaturase (FADS) genes, which leads to a decrease in the levels of lipid metabolism and the concentration of harmful cholesterol[10].

Materials and Methods

Materials used in the experiment

Alloxan was used which is prepared according to the method used by [11] before injection directly into the Citrate Buffer at a concentration of (0.1 mol) and pH 0.5, which was prepared from a dissolution of (21.0g /L) of Citric acid, and 35. 6 g / l of disodium phosphate, then the prepared alloxan was filtered with 0.7m filter paper prepared by (Whatman International Ltd. Maidston, England). The metformin solution was

prepared by taking a tablet for each concentration and dissolving it with (100) ml of distilledwater.

Animals of study

Albino males rats were used in this study, the age of rats ranged between (3-4) months, then they were placed in clean plastic cages prepared previously,the necessary cages were prepared for shelter and sterilized with (ethanol alcohol 99% concentration), then the shelter cages were furnished with sawdust wood, and the animals were left for a period of two weeks to settle and adapt in their new location with starting to work according to the diet and water for the specified period of sixty days, The animals were fed by a mixture of feed, which consisted of (25% wheat, 45% yellow corn, 20% soybean, 1% powdered milk, 10% animal protein, 50 g / 100 kg of vitamins and preservatives with anti-fungal substances)[12] .Likewise, water feedings were monitored daily and to ensure that water did not leak into the cage, as well as taking into account the provision of temperature between (23-25) ° C and the rate of humidity ranged between (10-30%), throughout the study period, the time for changing the mulch and the date and time Dose with drugs,. These animals were given water and food continuously and in sufficient quantities throughout the study period.

Experience design:

Male rats were used in this study by (42) animals, and they were divided into four groups, each group includes (6) animals with similar weights The dose is calculated as follows, where the average human weight is equal to 70 kg and the daily dose that patients consume is 500.850 mg of the drug regulating diabetes, and the dose is a result of multiplying the amount of the drug with the weight of the animal to divide the result by 70,000 grams (the average human weight in grams The drugs, and in order to obtain the concentration of one dose per day for one group of male rats, each according to the drug taken, 0.038265 x 6 = 0.0214285 grams is multiplied, after taking 10 tablets of the drug and grinding them with a special ceramic mortar For medicines, and taking the required amount after weighing it with a sensitive scale, to be dissolved in 42 ml of distilled water and give each animal an amount of one milliliter, as shown below :

The first group (control group): - Included of 6 animals and were exempted from any dose or test (treatment), and normal food (diet) was provided to them and water was placed in special bottles freely throughout the study period and it was sixty daily.

The second group (the second control group): - Included 36 animals with experimental diabetes was exempt from any dose, but was injected with alloxan at a concentration of 150 mg / kg once and for more than one sub-cutaneous area and left on the diet and water throughout the study period, which was sixty days.

with experimental diabetes by alloxan.

The third group (treatment group with Alloxan + 500mg of metformin): this group included 18 animals,and it was divided into three under sub-groups according to the number of times of dosing. Each group included 6 animals. They were injected with Alloxan at a concentration of 150 mg / kg once and for more than one cutaneous sub area Then she was dosed with metformin at a concentration of mg500, where it was ground and took a concentration of (0.021485) and dissolved in 20 ml of distilled water, put in the feeding bottles and give each animal one ml per day) in addition to the feed for a period of sixty days. which are as follows:

1. Sub- group that was dosed twice in the morning and noon.
2. Sub- group that was dosed once in the morning.
3. Sub- group that was dosed three times in the morning, noon and evening.

The fourth group (group treated with Alloxan +850 mg of metformin): - this group included 18 animals, and it was divided into three sub- groups according to the times of dosing. Each group included 6 animals. They were injected with Alloxan at a concentration of 150 mg / kg for one time and for more than one area under the skin cutaneous Sub and then dosed with metformin at a concentration of mg850, where it was ground and took its concentration (0.03285) and dissolved in 20 ml of water Distilled, and put in the feeding bottles and given to each animal one ml per day) in addition to the diet for a period of sixty days, which are as follows:

1. Sub- group that was dosed once in the morning.
2. Sub- group that was dosed twice in the morning and noon.
3. Sub- group that was dosed three times in the morning, noon and evening.

1- Determination of glucose concentration:

The concentration of glucose in the blood serum was determined by using a ready-made measuring kit from the (Spanish company, Bio Systems)[13].

2- Determination of cholesterol concentration

The concentration of glucose in the blood serum was determined by using a ready-made measuring kit from the (Spanish company, Bio Systems) [14]

3- Determination of triglyceride concentration

The concentration of TG in serum was determined by the enzymatic method by using a ready-made measurement kit from the Spanish company Bio Systems.[15]

4-Determination of Blood Serum (LDL-C)

The (LDL-c) concentration was estimated in light of the following equation:

LDL-c (mg / dl) = Total cholesterol- (HDL-c + VLDL-c) [16].

Statistical Analysis

ANOVA One-way system was using to analyze the results and estimated the significant differences between more than two averages from the experiment groups with an emphasis on these differences by

extracting the Standard Error (SE), where the statistical analyzes were performed at a significant level (P≤0.05)[17] .

Results and discussion

1- The effect of metformin on blood glucose concentrations of Glucose

The results in Table (1) showed an increase in the blood glucose concentration in the second group (Alloxan), which was given aloxan significantly at (P ≤0.05) compared with the other study groups from the first week to the eighth week of the study, and the fourth group gave Glucophage (Alloxan + 850metformin) mg, the lowest blood glucose concentration, and the significant differences were at (P≤0.05) compared to the third group (Alloxan + 500mg metformin), especially from the sixth week to the eighth week. It was also observed from the same table and figure (1) that the control group gave the lowest concentrations. The results showed significant improvement in (P ≤ 0.05) in the third and fourth groups in blood glucose concentrations compared to the second group that was given alloxan only. Also, there was no significant difference between the control group and the fourth group which treated with metformin three times daily, as shown in figure (1). These results are in agreement with a previous study[18], which was confirmed when administering alloxan to rats, and as expected, it led to an increase in blood glucose, by destroying beta cells in Langerhan Islands in the pancreas and the resulting inactivation of the insulin hormone Responsible for regulating blood glucose levels. These results also agree with previous studies on the idea that metformin has an anti- hyperglycemia effect [19'20]. Metformin has been shown to reduce blood glucose concentrations by reducing glucose production rates in the liver; metformin also has affect the liver's relative contribution to gluycogen breakdown and glucose formation. As proved by previous study by [21]. Metformin reduces blood glucose gradually and the glucose concentration does not fall below the normal range, so it is difficult to prove the effect of the drug in other than in the event of induced diabetes with Alloxan in rats as metformin does not stimulate insulin secretion and doesn't cause hypoglycemia below the normal range in controls group.It has been shown that a blood sugar lowering effect due to metformin can be linked to more than one mechanism. These mechanisms include: a - improvement of peripheral sensitivity to insulin, b - inhibitor of gastrointestinal absorption of glucose c - reduced production of glucose in the liver [18]. In addition to a parallel study in which diabetic mice treated with metformin-rich yogurt for 30 days recorded a significant reduction in blood sugar levels[24].

Table (1) shows the effect of metformin administration on blood sugar concentrations

Mean ± Standard div				Transactions	
Week (7-8)	Week (5-6)	Week (3-4)	Week (1_2)		
112.0±9.54 b	104.2±11.30 f	98.75±11.5 f	109.5±9.26 h	Control	Glucose mg/d l
605.0±14.25 a	543.0±20.65 a	513.5±23.6 a	568.0±6.97 a	Alloxan	
101.0±10.28 c	196.8±8.1 b	190.1±12.1 b	510.0±16.9 b	Alloxan+500mg 1	
96.50±11.51 c	175.1±10.37 c	181.1±15.8 bc	460.3±11.66 d	Alloxan+500mg 2	
82.63±10.61 d	154.3±8.33 e	172.0±14.5 cd	312.2±15.28 e	Alloxan+500mg 3	
92.75±9.63 c	166.6±8.00 d	181.0±17.1 bc	476.6±25.82 c	Alloxan+850mg 1	
82.75±8.58 d	146.5±8.33 e	165.0±14.88 d	286.0±9.09 f	Alloxan+850mg 2	
81.75±5.50 d	103.0±6.14 f	152.0±12.1 e	197.8±10.33 g	Alloxan+850mg 3	

Vertically different letters mean significant differences with a probability level (P ≤ 0.05).

2-The effect of metformin on blood cholesterol concentration

Table (2) shows an increase in the concentration of blood cholesterol in the second group, which was given alloxan, a significant increase at (P ≤ 0.05) compared to the other study groups. The fourth group which was treated with metformin (Alloxan + 850 mg) causes the lowest of blood cholesterol concentration. The differences were significant at (P≤0.05) compared to the third group (Alloxan + 500mg metformin), especially from the sixth week to the eighth week. the results showed a significant improvement (P≤ 0.05) in the third and fourth group of blood cholesterol concentrations compared to the second group given alloxan only. The significant difference also exists between the control group and the fourth group, treatment with metformin three times a day. These results are in agreement with a previous study [22] where it was explained that the occurrence of type II diabetes leads to harmful to the cells of the pancreas producing insulin and the resulting results. It reduces the secretion of insulin, which reduces the tissue's use of glucose, which leads to various metabolic effects, including

hypercholesterolemia. It has been shown that these effects on the action of insulin causing diabetes are associated with harmful changes in risk factors for cardiovascular disease, such as hyperlipidemia and Blood hypertension. [23]

Table (2) shows the effect of metformin administration on cholesterol concentrations

.Mean ± Standard div				Transactions	
Week (7-8)	Week (5-6)	Week(3-4)	Week(1-2)		
84.50±7.43 c	76.50±4.44 f	74.38±10.39 e	72.50±9.83 e	Control	mg/dl Cholesterol
154.6±5.24 a	142.6±6.99 a	123.5±12.46 a	135.5±10.70 a	Alloxan	
96.75±6.09 b	109.7±11.16 b	111.7±13.54 b	131.7±7.91 ab	Alloxan+500mg 1	
87.75±4.80 c	98.75±7.96 c	101.6±11.16 c	127.6±9.55 ab	Alloxan+500mg 2	
80.38±7.41 de	91.38±8.07 d	97.38±9.86 c	118.3±10.17 cd	Alloxan+500mg 3	
82.38±3.34 cd	92.50±7.23 d	98.38±8.14 c	124.3±9.80 bc	Alloxan+850mg 1	
76.88±2.90 e	83.88±6.33 e	86.75±7.54 d	115.8±10.95 cd	Alloxan+850mg 2	
71.38±3.58 f	74.38±4.50 f	80.63±7.91 de	110.5±9.74 d	Alloxan+850mg 3	

Vertically different letters mean significant differences with a probability level($P \leq 0.05$).

3-The effect of metformin on blood triglyceride concentrations

Table (3) shows the high concentration of triglycerides in the second group, which was given alloxan significantly at ($P \leq 0.05$) compared to the other study groups, and the fourth group which treated with (Alloxan + 850mg metformin) caused the lowest of blood triglycerides concentration Triglyceride and there was significant difference at ($P \leq 0.05$) compared to the third group (Alloxan +500mg metformin), especially from the sixth week to the eighth week.

The results showed significant improvement ($P \leq 0.05$) in the third and fourth group in the blood triglyceride concentrations compared to the second group given alloxan only. The results obtained in this study are in agreement with [24], who showed that treating diabetic rats with metformin partially restored the dyslipidemia represented by triglyceride. Another study conducted by researchers [25] confirmed that metformin as an insulin stimulator is often associated with a significant decrease in plasma triglycerides, especially with large doses of metformin, which lead to a significant reduction in triglyceride levels in rats.

Table (3) shows a comparison of the effect of metformin administration on Triglycerides

Mean ± Standard div				Transactions	
Week (7-8)	Week (5-6)	Week(3-4)	Week(1-2)		
105.3±7.19 c	105.3±7.19 c	44.50±6.05 e	96.50±9.84 d	Control	mg/dl Triglyceried
123.5±4.99 a	97.38±5.48 d	112.6±9.61 b	145.5±18.91 a	Alloxan	
110.2±6.23 b	107.6±8.55 c	133.6±11.54 a	140.6±13.56 ab	Alloxan+500mg 1	
103.7±6.27 c	132.2±7.83 a	126.3±9.55 a	138.6±10.10 ab	Alloxan+500mg 2	
96.25±5.06 c	128.7±7.81 a	110.7±13.83 b	130.6±7.17 bc	Alloxan+500mg 3	
102.3±5.50 c	114.1±6.31 b	109.5±10.16 b	140.6±13.63 ab	Alloxan+850mg 1	
93.75±6.63 de	108.7±5.55 c	97.75±8.48 c	132.6±9.83 bc	Alloxan+850mg 2	
89.63±4.47 e	97.63±4.87 d	86.38±8.81 d	125.5±11.26 c	Alloxan+850mg 3	

Vertically different letters mean significant differences wi th a probability level ($P \leq 0.05$).

4-Effect of metformin on low-density lipoprotein (LDL) concentration

Table (4) shows an increase in the blood low-density lipoprotein LDL concentration in the second group, which was given alloxan significantly at (P≤ 0.05) compared with the other study groups, and the fourth group gave (Alloxan + metformin 850 mg) result in lowest concentration for low-density lipoprotein in the blood, the differences were significant at (P≤0.05) compared with the third group (Alloxan + 500mg metformin), especially from the sixth week to the eighth week. The results showed significant improvement at (P≤ 0.05) in the third and fourth groups of the concentrations of low-density lipoprotein LDL in the blood compared to the second group given alloxan only, there were also significant differences between the control group and the fourth group treated with metformin three times daily.

Research shows that factors that affect glucose metabolism are also responsible for increased lipid metabolism[26]. In addition to altered glucose balance in the diabetic mice, dyslipidemia was evident through increased triglycerides and low-density lipoprotein (LDL) blood concentrations [27]. Metformin may act as cholesterol and biosynthesis inhibitors by inhibiting an enzyme such as CoA reductase[28]. Researchers[29] have observed that there is no appropriate treatment after two weeks to improve lipid levels, particularly for low-density lipoprotein (LDL-Cholesterol), by treatment with metformin alone.

Table 4: shows the effect of metformin on low-density lipoprotein LDL concentrations

Mean ± Standard div				Transactions	
Week (7-8)	Week (5-6)	Week(3-4)	Week(1-2)		
27.25 ± 5.04 e	24.25 ± 2.605 f	22.25 ± 2.96 g	21.38 ± 7.80 d	Control	LDL mg/dl
83.38 ± 5.73 a	78.38 ± 5.26 a	72.38 ± 8.67 a	75.50 ± 9.87 a	Alloxan	
41.88 ± 5.96 b	51.8 ± 5.19 b	63.75 ± 10.99 b	70.88 ± 8.95 ab	Alloxan+500mg 1	
35.63 ± 4.00 c	46.63 ± 4.63 c	57.50 ± 6.78 c	73.6 ± 11.13 ab	Alloxan+500mg 2	
26.75 ± 3.62 e	39.75 ± 6.78 d	52.75 ± 5.95 cd	65.75 ± 11.76 bc	Alloxan+500mg 3	
31.25 ± 2.49 d	41.38 ± 5.24 d	49.50 ± 7.86 d	72.38 ± 10.65 ab	Alloxan+850mg 1	
21.63 ± 3.42 f	31.63 ± 4.47 e	42.38 ± 6.05 e	66.50 ± 12.62 bc	Alloxan+850mg 2	
22.38 ± 3.50 f	22.38 ± 2.825 f	36.63 ± 5.04 f	60.50 ± 8.77 c	Alloxan+850mg 3	

Vertically different letters mean significant differences with a probability level (P ≤ 0.05).

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تأثير تراكيز مختلفة من عقار منظم سكر الدم Glucophage على تركيز الكلوكوز والكلسترول والكلسريدات الثلاثية والمركب الدهني واطئ الكثافة في ذكور الجرذان المصابة بداء السكر المحدث بالالوكسان

ايناس معجل نايف الجنابي ، وهبي عبد القادر سلمان الحمداني

قسم علوم الحياة .كلية التربية للبنات ، جامعة تكريت . تكريت ، العراق

الملخص

هدفت الدراسة الحالية إلى معرفة تأثير مخفض داء السكر Metformin في عدد من المعايير الكيموحيوية ومنها سكر الكلوكوز في الدم Glucose وبعض المركبات الدهنية: الكولسترول Cholesterol, الكلسريدات الثلاثية Triglycerides TG, وكذلك البروتينات الدهنية واطئة الكثافة High density lipoprotein - cholesterol LDL-C. أستخدمت في هذه الدراسة ذكور الجرذان البيضاء. أضهرت نتائج الدراسة ان استحداث داء السكر بالالوكسان ادى الى ارتفاعاً معنويا في مستويات الكلوكوز والكلسترول ,والكلسريدات الثلاثية ,كوليسترول البروتينات الدهنية واطئة الكثافة (LDL-C) مقارنة مع مجموعة السيطرة.حيث ادت معاملة الحيوانات بالمجموعتين الثالثة والرابعة بعقار الميتفورمين بتركيزين مختلفين mg 500,850 الى انخفاض معنوي في مستويات الكلوكوز والكلسترول مقارنة مع مجموعة الالوكسان وكانت نتائج مماثلة للمجموعة السيطرة (الاصحاء), كما ادت المعاملة الئ انخفاض معنوي في الكلسريدات الثلاثية, والبروتينات الدهنية واطئة الكثافة (LDL-C) مقارنة مع مجموعة الالوكسان واعطت نتائج مقاربة للمجموعة السيطرة (الاصحاء.) .