



The effect of different concentrations of metformin in the liver and kidney functions for diabetic induced male rats.

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ABSTRACT

The aimed of the study to determination the effects of reducing diabetes drug "Metformin" on the liver and kidney function by number of biochemical parameters, including two liver enzymes: Alanine Transaminase (ALT), Alkaline phosphatase (ALP), and concentration of kidney function in the blood serum urea, and uric acid. male albino rats, which were used in this study. The results showed an increase in ALT activity, as well as the status of ALP activity. The concentrations of urea, and uric acid increase significantly ($P \leq 0.05$) in serum of rats the animals that were given alloxan compared to the control group. The concentrations of these enzymes decreased in the third and fourth groups of animals that were dosed with metformin at a concentration of 500,850 mg compared with the alloxan group. The group treated with metformin at a concentration of 850 mg was revealed three times the lower activities of all enzymes throughout the study period.

Introduction

Metformin is considered an anti-diabetes drug from the Biguanides category, which is used by people who develop hyperglycemia and infected with T2DM (Type 2 diabetes mellitus), especially people who are overweight as well as obesity, and the drug is taken orally and works to reduce levels of cumulative sugar (HbA1c) in Non-insulin dependent diabetes mellitus[1]. Evidence from epidemiological studies indicates that long-term treatment with metformin significantly reduces the average activity of transaminase (ALT), improves liver cell viability and prevents nonalcoholic steatohepatitis, and metformin reduces the activity ALT, AST, ALP, and all pro-inflammatory symptoms.[2,3,4].

Metformin can protect kidney tissues from injuries caused by diabetes. Metformin has been shown to improve several types of kidney diseases such as renal cell injury and nephrotoxicity[5]. Metformin leads to a significant decrease in uric acid concentrations in the blood and a decrease in urinary excretion[6,7,8]. It was found that the prophylactic use of metformin significantly facilitates the course of urinary nephropathy, confirming a shift in pH value of urine to alkaline trend.[9]. It reduces the activity of lactate dehydrogenase (LDH) which reverses damage to the kidney epithelium, and a decrease in free radicals in the blood. and kidneys[10].

Metformin is contraindicated in men and women with serum creatinine concentrations of 1.5 mg / dl or higher and 1.4 mg / dl or higher, respectively, and there are other factors that lead to lactic acidosis, including severe dehydration (decreased tissue perfusion), congestive heart failure, and hypoxia, oxygenation, liver impairment, advanced age, and excessive alcohol intake may also increase the risk of metformin-associated lactic acidosis [11,12].

Materials and Methods

Chemicals Materials

Alloxan was used and prepared prior to injection directly into the Citrate Buffer at a concentration of 0.1 mol and pH 0.5, prepared from dissolution of 21.0 g/L citric acid and 35.6 g/l disodium phosphate, based on the process used by[13]. Filter paper (Whatman International Ltd. Maidston, England) 0.7 m was used to filter alloxane prepared by the preparation of the filter paper. Tablet of metformin drug for each concentration was dissolved it with 100 ml of distilled water to reaper drug solution.

Experimental Animals:

Male albino rates, aged between (3-4) months, were used in this experiments, Then they were housed in clean plastic cages that were prepared for shelter and sterilized with (99 ethanol alcohol). Then the cages were covered with wood shavings. The animals were

left to settle for a period of two weeks and to adapt to their new position with the start of the tap water and standar forage for a specified period of sixty days. The animals were fed a diet mix consisting of (25% wheat, 45% yellow maize, 20% soybeans, 1% powdered milk, 10% animal protein, 50 g/100 kg) [14].

Experimental 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, $0.038265 \times 6 = 0.0214285$ 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 (Negtive 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 postive control group): - Included 36 rats 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:

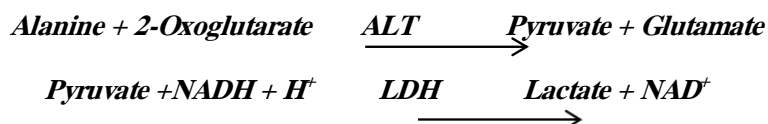
1. Sub- group that was dosed twice in the morning and noon.
2. Sub- group that was dosed once in the morning.
3. Sub- group that was dosed three times in the morning, noon and evening.

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.
- Sub- group that was dosed three times in the morning, noon and evening

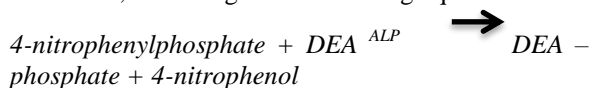
1-Determination the activity of ALT enzyme

A ready-made package from the Spanish company Bio Systems was used to test the efficacy of the ALT enzyme concentration. [15]. This approach is focused on catalysis for the conversion of the amine group from alanine to 2-oxoglutarate and pyruvate and glutamate formation., For the rate of decrease of NADH, the catalyst concentration is calculated and measured at a wave length (340 nm) through the LDH lactate cleaning process with the reaction as shown in the following equation:-



2- Determination the activity of (ALP) enzyme:

The concentration of ALP activity was estimated by using a ready-made kit from the Spanish company Bio Systems[15]. This method is based on stimulation in an alkaline medium by transferring the phosphate group 4-nitrophenol phosphate to the diethanol amine DEA and thus releasing 4-Nitrophenol, and then Measuring by a Spectrophotometer with a wavelength of 405 nm, according to the following equation:



3- Determination of total serum urea concentration:

The concentration of urea in the blood serum was determined using an enzymatic method (Urease – Modified Berthelot Reaction), as the method includes the use of ready-made solutions. The ready-made kit contains the enzyme urease, which works to release ammonia in the basic environment, as ammonia reacts with salicylate, and hypochlorite to be 2,2, dicarboxy indophenol green in color, whose intensity is measured at a wavelength of (580) nanometers Spectrophotometer .[16]

4- Determination of serum uric acid concentration:

Determine the concentration of uric acid in the blood serum using the BIOLABO SA, France kit [18’17]. This method is based on the activity of the enzyme Uricase, which interacts with uric acid to produce a compound (Allantoin, CO₂ and hydrogen peroxide) in the presence of the peroxidase enzyme.

Statistical Analysis

The results were analyzed statistically using the ANOVA One-way system to extract Standard Error (SE), where the statistical tests were conducted at a significant level ($P \leq 0.05$), The significant differences between more than two averages from the experiment groups with a focus on these differences were made[19].

Results and discussion

1- The effect of metformin on serum ALP activity

Table (1) shows an significantly at ($P \leq 0.05$) increase in the concentrations of serum ALP activity in the second group, which treated with alloxan s compared with the other groups, the fourth group gave the lowest concentrations of blood ALP enzyme in and

the differences were Significant at ($P \leq 0.05$) compared to the third group, Especially in comparison to the third group, from the sixth week to the eighth week in particular. As noted in a same table, the findings showed a substantial increase in blood concentrations of the enzyme ALP in the third and fourth classes, relative to the second group treated with alloxan-only There are also significant differences between the healthy group and the fourth group, given metformin three times a day. A previous study [20] showed that there are histological changes in the liver due to insulin deficiency in diabetes. And after treatment with metformin in a group of diabetes patients partially reduced to degenerative changes occurred in the liver. The hepatic enzymes, ALP, AST and ALT, are involved in biological processes. These enzymes were catalyzed the transfer the amino acids into a-keto acid, which is directed to main total metabolism through the Krebs cycle and electron chain transfer. The increased glucose and ketone formation accrue through diabetes diseases may be results from the high of activity of these transaminases[21].

Table 1: The effect of metformin administration on serum ALP enzyme activity during te study weeks

ALP IU/L	Transactions	Mean ± Standard div			
		Week(1-2)	Week(3-4)	Week (5-6)	Week (7-8)
	NegativeControl group	95.63 ± 11.80 f	101.6 ± 9.50 g	98.88 ± 8.77 g	102.5 ± 9.59 F
Postive control Group alloxan	816.50 ± 12.02 a	801.3 ± 34.1 a	789.4 ± 31.8 a	938.5 ± 15.79 A	
Alloxan+500mg 1	809.38 ± 11.88 a	671.3 ± 28.18 b	606.3 ± 18.49 b	232.3 ± 7.17 C	
Alloxan+500mg 2	790.38 ± 12.76 b	632.2 ± 23.60 c	543.6 ± 27.29 c	264.6 ± 7.76 B	
Alloxan+500mg 3	750.38 ± 13.27 c	592.3 ± 38.8 d	498.4 ± 29.1 d	176.3 ± 5.97 D	
Alloxan+850mg 1	755.38 ± 11.76 c	599.6 ± 30.0 d	424.6 ± 29.5 e	231.3 ± 8.23 C	
Alloxan+850mg 2	710.38 ± 12.67 d	513.2 ± 18.43 e	343.4 ± 28.6 f	123.3 ± 9.50 E	
Alloxan+850mg 3	683.50 ± 15.78 e	432.1 ± 20.91 f	98.88 ± 8.77 g	13.63 ± 4.14 G	

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

2-The effect of metformin on serum ALT concentrations

Table (2) showed a significant increase in the concentrations of the enzyme alanine aminotransferase AST in the blood serum in the second group, that is treated with alloxan ($P \leq 0.05$) related to the other groups, and the fourth group which was gave (Alloxan + metformin 850 mg) causes reduction in AST concentrations in the blood, the differences were significant at ($P \leq 0.05$) compared to the third group (Alloxan + 500mg metformin), especially from the sixth week to the eighth week. Results showed significant benefit ($P \leq 0.05$) of the AST enzyme in the third and fourth groups in which

metformin was administered to rats at different concentrations compared to the second group in which alloxan alone was administered. There were also major variations between the control group and the fourth group, who were handled three times daily with metformin. his result is in agreement with a previous study[22], which showed significant elevations in blood ALT (93%) in diabetic patients, and it was noted that treatment with metformin led to a significant decrease in ALT concentration (46%) in the blood was marked instead of individual level metformin and mono pitavastatin treatment two weeks after the start of treatment [20].

Table 2: The effect of metformin administration on ALT enzyme concentrations during the study weeks

ALT IU/L	Transactions	Mean \pm Standard div			
		Week(1-2)	Week(3-4)	Week (5-6)	Week (7-8)
	NegativeControl group	63.50 \pm 12.40 f	73.38 \pm 9.68 g	68.38 \pm 6.84 h	74.38 \pm 8.25 g
	Postive control Group alloxan	552.3 \pm 12.65 a	615.3 \pm 19.69 a	513.3 \pm 26.12 a	465.2 \pm 9.05 a
	Alloxan+500mg 1	529.8 \pm 13.71 b	443.7 \pm 22.02 b	432.6 \pm 13.50 b	312.8 \pm 5.96 b
	Alloxan+500mg 2	510.2 \pm 10.42 c	398.3 \pm 21.07 c	364.2 \pm 8.07 c	234.2 \pm 12.00 c
	Alloxan+500mg 3	490.7 \pm 13.58 d	367.6 \pm 19.57 d	302.6 \pm 8.93 d	103.7 \pm 8.75 e
	Alloxan+850mg 1	508.5 \pm 10.76 c	387.5 \pm 18.97 c	265.5 \pm 9.37 e	165.5 \pm 9.37 d
	Alloxan+850mg 2	492.2 \pm 12.67 d	312.2 \pm 19.27 e	201.2 \pm 13.40 f	87.38 \pm 7.11 f
	Alloxan+850mg 3	440.5 \pm 13.51 e	265.3 \pm 17.01 f	183.5 \pm 14.48 g	61.38 \pm 7.03 h

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

3- The effect of metformin on serum urea concentrations

The finding of this study indicate increasing of urea concentrations in the blood of the second group, which was treated with alloxan ($P \leq 0.05$) related to the other study groups from the first week to the eighth week of the study (table 3), lowest serum urea concentrations found in the fourth group since the differences were significant at ($P \leq 0.05$) compared with the third group, in particular, from the sixth week to the 8th week. It was also noticed from the same table that the control group gave the lowest concentrations of urea in the blood compared with other groups over the length of the study. The results

showed significant improvement at ($P \leq 0.05$) in the third and fourth group, in which the rats were given metformin at different concentrations in the serum urea concentrations in, compared to the second group, which was given alloxan only. This finding is in agreement with [23], which explained Diabetic Nephropathy in Type 2 Diabetes Mellitus is the most common cause of kidney disease at end-stage, and one of the leading causes of morbidity and mortality worldwide. Preventing the development of diabetic nephropathy has been a challenge in biomedical research. Increased levels of blood glucose, serum creatinine, urea, and uric acid are signs of impaired kidney function associated with diabetes [24].

Table 3: The effect of metformin administration on serum urea concentrations during the study weeks

Urea mmol/L	Transactions	Mean \pm Standard div			
		Week(1-2)	Week(3-4)	Week (5-6)	Week (7-8)
	NegativeControl group	132.2 \pm 14.93 g	143.2 \pm 11.04 g	138.2 \pm 8.60 g	141.2 \pm 10.98 ef
	Postive control Group alloxan	455.7 \pm 12.53 a	476.8 \pm 35.4 a	476.7 \pm 23.6 a	467.7 \pm 19.15 a
	Alloxan+500mg 1	430.7 \pm 13.56 b	386.7 \pm 24.92 b	312.3 \pm 15.8 b	308.2 \pm 7.96 b
	Alloxan+500mg 2	420.7 \pm 11.39 bc	326.1 \pm 14.74 c	264.7 \pm 7.61 c	236.7 \pm 12.88 c
	Alloxan+500mg 3	409.7 \pm 13.48 de	287.5 \pm 18.0 d	211.6 \pm 7.85 d	145.6 \pm 9.46 e
	Alloxan+850mg 1	418.7 \pm 11.11 cd	298.2 \pm 16.6 d	198.2 \pm 16.60 e	169.2 \pm 8.36 d
	Alloxan+850mg 2	403.7 \pm 9.77 e	213.7 \pm 16.64 e	165.2 \pm 17.6 f	134.2 \pm 9.25 f
	Alloxan+850mg 3	387.7 \pm 11.37 f	176.3 \pm 10.56 f	133.7 \pm 15.5 g	102.8 \pm 8.22 g

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

4-The effect of metformin on serum uric acid concentrations:

Table (4) indicate the significant increases of serum uric acid concentrations in the second group, which was treated with alloxan ($P \leq 0.05$) compared with the other study groups from the first week to the eighth week of the experiment, fourth group was given less

serum uric acid concentrations, and the differences were significant at ($P \leq 0.05$) compared with the third group, especially from the sixth week to the eighth week. It was also noticed that the control group gave the lowest concentrations of uric acid in the blood compared to the other groups.

The results showed a significant improvement in the concentrations of serum uric acid at ($P \leq 0.05$) in the third and fourth group, in which the rats were given metformin with different concentrations, compared to the second group given alloxan only. There were also slight significant differences between the control

group, and the fourth group which treated with metformin three times a day. These results are consistent with a last study, (25), which showed that metformin alone has a beneficial effect on renal impairment and elevation of uric acid level in the blood.

Table 4: The effect of metformin administration on uric acid concentrations during the study weeks

URIC ACID $\mu\text{mol/l}$	Transactions	Mean \pm Standard div			
		Week(1-2)	Week(3-4)	Week (5-6)	Week (7-8)
	NegativeControl group	4.675 \pm 1.035 e	5.463 \pm 0.984 f	5.25 \pm 1.165 cd	5.25 \pm 1.669 b
Postive control Group alloxan	10.25 \pm 2.550 a	12.438 \pm 2.165 a	9.37 \pm 1.353 a	11.250 \pm 1.832 a	
Alloxan+500mg 1	8.875 \pm 1.642 b	7.138 \pm 0.578 b	7.750 \pm 0.475 b	3.50 \pm 1.690 c	
Alloxan+500mg 2	8.625 \pm 1.302 bc	6.725 \pm 1.018 b	6.125 \pm 0.539 c	3.250 \pm 1.035 c	
Alloxan+500mg 3	8.125 \pm 1.55 b	6.425 \pm 0.812 bc	5.963 \pm 0.593 c	2.875 \pm 0.991 cd	
Alloxan+850mg 1	7.750 \pm 1.98 c	5.787 \pm 0.491 cd	4.862 \pm 0.814 d	2.250 \pm 0.886 d	
Alloxan+850mg 2	7.875 \pm 1.727 c	5.32 \pm 0.518 d	3.875 \pm 0.585 e	2.125 \pm 0.991 d	
Alloxan+850mg 3	7.500 \pm 1.60 d	4.475 \pm 0.555 e	2.450 \pm 0.504 e	2.125 \pm 0.991 d	

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

Conclusions

1-Treatment with metformin led to a significant increase in the activity of the ALT enzyme, and the

occurrence and decrease in the efficacy of ALP concentrations.

2- Decreased concentrations of Urea, Uric acid, and Creatinine creatinine when dosed with metformin-updated animals with metformin.

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تأثير تراكيز مختلفة من الميتفورمين على وظائف الكبد والكلية في ذكور الجرذان المصابة بداء السكر المستحث بالالوكسان

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الملخص

الهدف من الدراسة معرفة تأثير مخفض داء السكر الميتفورمين في وظائف الكبد والكلية بواسطة عدد من المعايير الكيموحيوية ومنها بعض انزيمات الكبد: انزيم ناقل امين الالانين (ALT) وانزيم الفوسفاتيز القاعدي (ALP) , وتركيز اليوريا , وحامض اليوريك ووظائف الكلية في مصل دم ذكور الجرذان البيض المستخدمة في هذه الدراسة. وظهرت النتائج ارتفاع معنوي ($P \leq 0.05$) في فعالية انزيم ناقل امين الالانين ALT , وكذلك الحال للأنزيم الفوسفاتيز القاعدي ALP وتركيز اليوريا وحامض اليوريك في مجموعة الجرذان التي تم اعطائها الالوكسان مقارنة مع مجموعة السيطرة. فقد انخفضت فعالية هذه الانزيمات في مجموعتي الحيوانات الثالثة والرابعة التي تم تجريعها بعقار الميتفورمين بتركيز 850,500ملغم /كغم من وزن الجسم بالمقارنة مع مجموعة الالوكسان. واعطت المجموعة المعاملة بعقار الميتفورمين بتركيز 850ملغم /كغم من وزن الجسم بثلاث مرات تراكيز منخفضة لكل من الانزيمات على طيلة فترة الدراسة.