LEVEL OF LIPID PROFILE AND LIVER ENZYME OF DIABETIC MALE RATS INDUCED BY STREPTOZOTOCIN TREATED WITH FORXIGA

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ABSTRACT

The present study including study Level of lipid profile and liver enzyme of diabetic male rats induced by streptozotocin The study was carried out in the animal house of the Biology Department, College of Science, University of Thi-Qar ,Iraq. Thirty lab male rats were used in this study, and divided into five groups (6 rats for each group).

Thirty male rats (190-210 gm) were randomly divided into five groups and placed in cages according to the groups, containing 6 rats per group as following. Group1, considered as the negative control group, given food and water for a period of 30 days. Group 2, served as the diabetic positive control, given streptozotocin were injected I.P. 60 mg/kg b.w. as a single dose with food and water for 15 days. Group 3, received streptozotocin were injected I.P (60 mg/kg) with food and water for 15 days, then treated with forxiga 1mg/kg administrated orally every day for a period of 15 days. Group 4, given were injected I.P streptozotocin (60 mg/kg) with s food and Water for 30 days. Group 5, received streptozotocin were injected I.P (60 mg/kg) with food and water. Then treated with forxiga1mg/kg administrated orally every day for a period of 15 day. At the end of experimental, all rats were euthanized, blood sample were obtained for bio chemical parameters.

KEYWORDS

Lipid profile, liver enzyme ,Streptozotocin, Diabetic rats, forxiga

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PAPER INDEX

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1. INTRODUCTION

Diabetes mellitus (DM), a disarray of carbohydrate metabolism, is a medical and endocrinological set of symptoms characterized by hyperglycemia, high glycated hemoglobin, and a high risk of morbidity and humanity (1). It is caused by absence or diminish efficiency of endogenous insulin or the inappropriate use of insulin by goal cells, and is characterized by unbalanced metabolism, hypertension, and squeal principally distressing the vasculature (2). Experimental models in animals are used to study a variety of aspects associated to the disease, such as its symptom, development, and complication. They have also been second-hand in pharmacological tests in the exploration for more successful drugs and treatments.

The diabetes model most often use absorb the supervision of a single high dose of streptozotocin(STZ) or alloxan (ALX) to fully developed animals, which lead to the damage of pancreatic β cells and reason hyperglycemia as a express consequence of undersupplied insulin production (3). Forxiga exerts its glucose-lower property through awkwardness of the SGLT2 protein in the kidney proximal tubule, resultant in the excretion of glucose and calories into the urine(4). This lackluster energy balance consequences in dapagliflozin treatment-associated weight loss, as has been confirmed in a number of clinical Studies(5,6). Diabetic patients recurrently display a progressive decline in muscle mass and impair muscle serviceable quality(7), which are caused by concentrated insulin sensitivity and decreased mitochondrial role payable underline pathogenesis of T2DM(8).Regarding SGLT2i induced weight reduction, clinical concern has been raise over the event of sarcopenia(decrease in muscle mass)(9 ,10) and clinical studies are therefore needed to establish the weight loss efficacy and any belongings on muscle mass of dapagliflozin treatment in T2DM patients(11).

Aim of this study to elevated Level of lipid profile and liver enzyme of diabetic male rats induced by streptozotocin Treated with Forxiga.

2. MATERIAL AND METHODS

2.1. INDUCTION OF DIABETES MELLITUS

The male rats intraperitoneally injected by a single dose STZ (Sigma, Chemical), 60 mg/kg body wt, dissolved in sodium citrate buffer (0.1 mol/liter, pH 4.5) at a concentration of 20 mg/ml immediately before use. In order to prevent the onset of severe hypoglycemia they have received a solution of 10% glucose instead of normal drinking water over the 24 hours following the treatment. Streptozotocin induces diabetes within 3 days by destroying the beta cells and a mean blood glucose > 250 mg/dL. Diabetic animals and non-diabetic control group were kept in metabolic cages individually and separately and under feeding and metabolism control. Glucose in the blood of diabetic rats exceeded that of the non-diabetic control ones. Diabetes rats were treatment were with Forxiga drug (1mg /1kg/day) orally for 15 day. Animals used

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as normal control received standard rat pellet with ad libitum, distilled water till the end of the experiment.

2.2. EXPERIMENTAL DESIGN

Thirty male rats (190-210 gm) were randomly divided into five groups and placed in cages according to the groups, containing 6 rats per group as following.

1-Group1 :(Control group) considered as the negative control group, given food and water for a period of 30 days.

2-Group 2: (DM group for 15 day) served as the diabetic positive control, given streptozotocin were injected I.P.60 mg/kg b.w. as a single dose with food and water for 15 days.(12).

3-Group 3: (DM+ forxiga group for 15) received streptozotocin were injected I.P(60 mg/kg) with food and water for 15 days, then treated with forxiga 1mg/kg administrated orally every day for a period of 15 days. (13).

4-Group4:(DM group for 30 day) given were injected I.P streptozotocin(60 mg/kg) with s food and Water for 30 days

5- Group 5: (DM+ forxiga group for 30) received streptozotocin were injected I.P (60 mg/kg) with food and water. Then treated with forxiga1mg/kg administrated orally every day for a period of 30 day.

At end of experiment measured body weight of animals and then sacrificed.

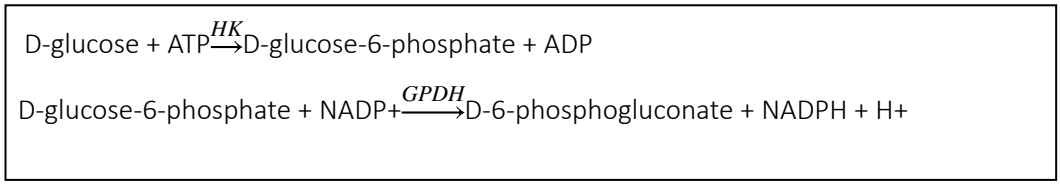
2.3. BLOOD SAMPLES

Blood were drawn from each animal in the experimental groups, by heart puncture method after 12 hours fast and sacrificed by inhalation milddiethyl ether. Blood samples were obtained by means of heart puncture. Using 5cc sterile syringes, the sample was transferred into clean tube, left at room temperature for 15 minutes for clotting, centrifuged at 3000 rpm for 15 minutes, and then serum was separated and kept in a clean tube in the refrigerator at (-20$_o$C) until the time of assay.

2.4. MEASUREMENT OF GLUCOSE LEVEL (MG/DL)

Test principle

Enzymatic situation method through hexokinase.4,5 Hexokinase (HK) catalyzes the Phosphorylation of glucose through ATP to formglucose-6-phosphate and ADP. To follow the response, a second enzyme, glucose-6-phosphate dehydrogenase (G6PDH) is use to catalyze oxidation of glucose-6-phosphate by NADP+ to form NADPH (Titetz, 2006).



https://doi.org/10.17993/3cemp.2023.120151.273-288

The attentiveness of the NADPH formed is directly proportional to the glucose concentration. It is determined by measuring the raise in absorbance at 340 nm.

Reagents - working solutions

R1	MES buffer: 5.0 mmol/L; pH 6.0; Mg2+: 24 mmol/L; ATP: ≥ 4.5 mmol/L; NADP+: ≥ 7.0 mmol/L
SR	HEPES buffer: 200 mmol/L; pH 8.0; Mg2+: 4 mmol/L; HK (yeast):≥ 300 µkat/L; G6PDH (microbial): ≥ 300 µkat/L

2.5. MEASUREMENT OF LIPID PROFILE

2.5.1. TOTAL CHOLESTEROL LEVEL (TC) (MG/DL)

Enzymatic, colorimetric technique Cholesterol esters are cleave by the action of cholesterol esterase to yield free cholesterol and fatty acids. Cholesterol oxidize then catalyzes the oxidation of cholesterol to cholest-4-en-3-one and hydrogen peroxide. In the attendance of peroxides, the hydrogen peroxide formed effects the oxidative coupling of phenol and 4-aminoantipyrine to form a red quinone-imine dye.

Cholesterol esters + H2O $\xrightarrow{CE}$ cholesterol + RCOOH

Cholesterol + O2 $\xrightarrow{CHOD}$ cholest-4-en-3-one + H2O2

2 H2O2 + 4-AAP + phenol $\xrightarrow{POD}$ quinone-imine dye + 4 H2O

The color concentration of the dye formed is directly proportional to the cholesterol concentration. It is determined by measuring the increase in absorbance at 512 nm.

Reagents - working solutions

R	PIPESa) buffer: 225 mmol/L, pH 6.8; Mg2+: 10mmol/sodium cholate: 0.6 mmol/L; 4-aminoantipyrine: ≥ 0.45 mmol/L; phenol: ≥ 12.6 mmol/L; fatty alcohol polyglycol ether: 3 %; cholesterol esterase (Pseudomonas spec.): ≥ 25 µkat/L (≥ 1.5 U/mL); cholesterol oxidase (E. coli): ≥ 7.5 µkat/L (≥ 0.45 U/mL); peroxidase (horseradish): ≥ 12.5 µkat/L (≥ 0.75 U/mL); stabilizers; preservativea) PIPES = Piperazine-1,4-bis(2-ethanesulfonic acid.

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Pipetting parameters

Diluent (H2O)

R 47 µL70 µL

Sample 2 µL23 µL

Total volume 142 µL

Calculation

$$Result = \frac{Abs(Assay)}{Abs(standard)} x Standard\,concentration\left(\frac{mmol}{L}\right)$$

2.5.2. TRIGLYCERIDES LEVEL(TG) (MG/ML)

Test principle

Enzymatic colorimetric test (sidelet al .,1993).

triglycerides + 3 H2O $\xrightarrow{LPL}$ glycerol + 3 RCOOH

glycerol + ATP $\xrightarrow{GK}$ glycerol-3-phosphate + ADP

glycerol-3-phosphate + O2 $\xrightarrow{GPO}$ dihydroxyacetone phosphate + H2O2

H2O2 + 4-aminophenazone + 4-chlorophenol $\xrightarrow{Peroxidase}$

4-(p-benzoquinone-monoimino)-phenazone + 2 H2O + HCl

Reagents - working solutions

R	PIPES buffer: 50 mmol/L, pH 6.8; Mg2+: 40 mmol/L;sodium cholate: 0.20 mmol/L; ATP: ≥ 1.4 mmol/L; 4-aminophenazone: ≥ 0.13 mmol/L; 4-chlorophenol: 4.7 mmol/L; LPL (microbial): ≥ 83 µkat/L; GK (microbial): ≥ 3 µkat/L; GPO (microbial): ≥ 41 µkat/L; POD (horseradish): ≥ 1.6 µkat/L; preservative; stabilizers

R is in position B

Pipetting parameters

Diluent (H2O)

R 120 µL

Sample 2 µL28 µL

Total volume 150 µL

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Calculation

$$\text{Result} = \frac{Abs(Assay)}{Abs(standard)} x Standard\ concentration(200) mg/dl$$

2.5.3. HIGH DENSITY LIPOPROTEIN LEVEL (HDL) (MG/ML)

Test principle

Homogeneous enzymatic colorimetric assay. In the attendance of magnesium ions and dextran sulfate, water-soluble complexes with LDL, VLDL, and chylomicrons are form which are resistant to PEG-modified enzymes. The cholesterol special management of HDL cholesterols single-minded enzymatically by cholesterol esterase and cholesterol oxides couple with PEG to the amino groups (approximately40 %). Cholesterol esters are busted down quantitatively into gratis cholesterol and fatty acids by cholesterol esterase. In the presence of oxygen, cholesterol is oxidized by cholesterol oxides to Δ4cholestenoneand hydrogen peroxi.

HDL-cholesterol esters + H2O $\xrightarrow{PEG - cholesteol\ esterase}$ HDL-cholesterol+ RCOOH

HDL-cholesterol + O2 $\xrightarrow{PEG - cholesteol\ oxidase}$ Δ4-cholestenone + H2O2

2 H2O2 + 4-aminoantipyrine + HSDA a) + H+ + H2O $\xrightarrow{peroxidase}$ purple blue pigment + 5 H2O

a) Sodium N-(2-hydroxy-3-sulfopropyl)-3,5-dimethoxyaniline.The color intensity of the blue quinoneimine dye formed is directly proportional to the HDL-cholesterol concentration. It is determined by measuring the increase in absorbance at 583 nm.

Reagents - working solutions

R	HEPES buffer: 10.07 mmol/L; CHES: 96.95 mmol/L, pH 7, sulfate: 1.5 g/L; magnesium nitrate hexahyd rat> 11.7 mmol/L; HSDA: 0.96 mmol/L; as corbate oxides (Eupenicillium sp., recombinant): > 50 µ/L; per oxides (horseradish): > 16.7 µt/L; preservative
RS	HEPES buffer: 10.07 mmol/L, pH 7.0; PEG cholesterol esterase(Pseudomonas spec.): > 3.33 µ /L; PEG cholesterol oxides (Streptomycin sp., recombinant): > 127 µ/L; per oxidize(horseradish): > 333 µ/L; 4-amino-antipyrine: 2.46 mmol/L; preservative

R1 is in position B and SR is in position C.

Pipetting parameters

Diluent (H2O)

R1 150 µL

https://doi.org/10.17993/3cemp.2023.120151.273-288

Sample 2.5 µL7.0 µL

SR 50 µL

Total volume 209.5 µL

Calculation

$$Result = \frac{Abs(sample)}{Abs(Stander)} \times 50 \times 2$$

2.5.4. LOW DENSITY LIPOPROTEIN LEVEL (LDL) (MG/DL)

Serum LDL concentration can be calculated by the following equation (Ram,1996).

L D L = Cholesterol con. – (HDL +TG/5) = $(mmol/L)$

2.5.5. VERY LOW DENSITY LIPOPROTEIN (MG/ML)

By the following function:

VLDL= (TG\5)

2.6. MEASUREMENT OF LIVER ENZYME

2.6.1. ALANINE AMINOTRANSFERASES LEVEL (ALT)(U/L)

Test principle

Method according to the International Federation of Clinical Chemistry (IFCC), but without pyridoxal-5'-phosphate.3,4ALT catalyzes the reaction between L-alanine and 2-oxoglutarate(Schumann et al .,2002). The pyruvate formed is reduced by NADH in a reaction catalyzed by lactatedehydrogenase (LDH) to form Lactate and NAD+ Lalanine + 2-oxoglutarate$ALT \rightarrow$ pyruvate + Glutamate

pyruvate + NADH + H+$LDH \rightarrow$ Lactate + NAD+

The rate of the NADH oxidation is directly proportional to the catalytic ALT activity. It is determined by measuring the decrease in absorbance at340 nm.

Reagents - working solutions

R1	TRIS buffer: 224 mmol/L, pH 7.3 (37 °C); Lalanine: 1120mmol/L; albumin (bovine): 0.25 %; LDH (microorganisms): 45µkat/L; stabilizers; preservative
RS	2Oxoglutarate: 94 mmol/L; NADH: ≥ 1.7 mmol/L;preservate

R1 is in position B and SR is in position C.

https://doi.org/10.17993/3cemp.2023.120151.273-288

Pipetting parameters

Diluent (H2O)

R1 59 µL10 µL

Sample 11 µL26 µL

SR 17 µL9 µL

Total volume 132µL

2.6.2. ASPARTATE AMINOTRANSFERASES LEVEL(AST) (U/L)

Test principle

Method according to the International Federation of Clinical Chemistry(IFCC), but without pyridoxal-5'-phosphate.3,4AST in the sample catalyzes the transfer of an amino group between Aspartame and 2-oxoglutarate to form oxaloacetate and Glutamate. The oxaloacetate then reacts with NADH, in the presence of malatedehy drogenase (MDH), to form NAD+

Aspartate + 2oxoglutarate$\xrightarrow{AST}$ oxaloacetate + Glutamate
Oxaloacetate + NADH + H+$\xrightarrow{MDH}$ malate + NAD+

The rate of the NADH oxidation is directly proportional to the catalytic AST activity. It is determined by measuring the decrease in absorbance at 340 nm.

Reagents - working solutions

R1	TRIS buffer: 264 mmol/L, pH 7.8 (37 °C); L-aspartate: 792 mmol/L;MDH (microorganism): ≥ 24 µ/L; LDH (microorganisms):≥ 48 µkat/L; albumin (bovine): 0.preservative
RS	NADH: ≥ 1 .7 mmol/L; 2-oxoglutarate: 94 mmol/L; preservative

R1 is in position A and SR is in position B and C.

Pipetting parameters

Diluent (H2O)

R140 µL29 µL

Sample 11 µL26 µL

SR 17 µL9 µL

Total volume 132µL

https://doi.org/10.17993/3cemp.2023.120151.273-288

2.6.3. ALKALINE PHOSPHATASE LEVEL(ALP) (U/L)

Test principle

Colorimetric assay in accordance with a standardized method. In the presence of magnesium and zinc ions, pnitrophenyl phosphate is cleaved by phosphatase into phosphate and pnitrophenyl.

pnitrophenyl phosphate + H2O$ALP \rightarrow$ phosphate + pnitrophenyl

The pnitrophenyl released is directly proportional to the catalytic ALP activity. It is determined by measuring the increase in absorbance at409 nm.

Reagents - working solutions

R1	2-amino-2-methyl-1-propanol: 1.724 mol/L, pH 10.44 (30 °C)magnesium acetate: 3.83 mmol/L; zinc sulfate: 0.766 mmol/L; N-(2-hydroxyethyl)-ethylenediaminetriacetic acid: 3.83 mmol/L
RS	p-nitrophenyl phosphate: 132.8 mmol/L, pH 8.5 (25 °C); preservatives

R1 is in position B and SR is in position C.

Pipetting parameters

Diluent(H2O)

R1 75 µL16 µL

Sample 2.75 µL20 µL

SR 17 µL10 µL

Total volume 140.75 µL

$$ALP = \frac{Abs\ sample - Abs\ blank}{Abs\ standard} \times \mathbf{n}$$ N=141,8 u/l

3. RESULTS

3.1. EFFECT OF FORXIGA ON GLUCOSE LEVEL OF DIABETIC MALE RATS

The results as presented in table 1 indicated a significant increase (P≤ 0.05) of glucose concentration in DM and DM +forxiga groups (2,3,4and5)compared with control group, while no significant different were recorded in STZ treated group for 15 days compare with group that treated for 30 days . However a significant (P≤ 0.05) increase in glucose level of group DM and DM +forxgia groups for 15 days. In addition, significant (P≤ 0.05) increase in glucose level of group DM and DM +forxgia groups for 30 days.

https://doi.org/10.17993/3cemp.2023.120151.273-288

Table 1. Effect of forxiga on glucose level of diabetic male rats.

Parameters Groups	Glucose (mg/dl)
Group 1 Control group	88.16 ± 8.75[c]
Group 2 DM group (15 days)	329.33 ± 62.25[a]
Group 3 DM +Forxiga (15 days)	150.50 ± 14.23[b]
Group 4 DM group (30 days)	427.33 ± 230.02[a]
Group 5 DM +Forxiga (30 days)	277.0 ± 42.70[b]
L.S.D	146.57

*Values expressed as Mean ± SD(n=6)

*Different small letters denote significant deference (P ≤ 0.05) between experimental groups.

3.2. EFFECT OF FORXIGA ON LIPID PROFILE LEVEL OF DIABETIC MALE RATS

The results of lipids profile that found in the present study showed a significant (P≤0.05) increase in serum concentrations of CHOL and TG level in groups(2,3,4and5) compared with control group. There was significant decrease in serum concentrations CHOL and TG in DM group compared with DM (group 2) + forxiga group for 15 days (group 3). The serum concentrations of CHOL and TG was significant decrease in STZ administration group(group 4)compared with DM+forxiga group(5).

In the table 2 the results indicated no significant changes in the serum concentration of HDL in group(2,3 and 5) compared with control group. There was no significant change in level of HDL in group(2)compared with group(3). While there was significant(P≤0.05) increase of HDL level in group(5) compared with group(4).

In same table 2 the results indicated a significant increase (P≤0.05) in the serum concentration of groups(2,3,4 and 5) compared with control group. The serum concentration LDL was no significant change in group(2) compared with group(3). But there was no significant change in group (4) compared with group (5).

https://doi.org/10.17993/3cemp.2023.120151.273-288

Lastly a significant increase (P≤0.05)of the serum concentration of VLDL in DM and DM+ forxiga groups(2, 3, 4, 5) compared with control group (1). The serum concentration of VLDL a significant decrease in DM group compared with DM + forxiga group for 15 days .A significant decrease (P≤0.05)of the serum concentration of VLDL in group administration of STZ (group 4) than those of administration of STZ and treated with forxiga for 30 days(group 5) .

Table 2. Effect of forxiga on lipid profile level of diabetic male rats

Parameters Group	Cholesterol (mg/dl)	TGs (mg/dl)	HDL (mg/dl)	LDL (mg/dl)	VLDL (mg/dl)
Group 1 Control group	88.0 ± 5.54^{a}	60.0 ± 8.80^{d}	33.33 ± 6.80^{ab}	41.55 ± 4.42^{c}	11.66 ± 1.52^{d}
Group 2 DM group (15 days)	128.83 ± 4.70^{b}	165.50 ± 6.09^{b}	31.50 ± 5.0^{ab}	64.23 ± 7.49^{ab}	33.10 ± 1.21^{b}
Group 3 DM +Forxiga (15 days)	122.50 ±4.59^{c}	140.0 ± 8.46^{c}	35.0 ± 6.44^{a}	60.50 ± 9.88^{b}	28.0 ± 1.69^{c}
Group 4 DM group (30 days)	138.83 ± 3.48^{a}	185.50 ± 8.50^{a}	29.66 ± 5.60^{b}	72.05 ± 6.50^{a}	37.11 ± 1.70^{a}
Group 5 DM +Forxiga (30 days)	133.66 ± 6.28^{b}	167.16 ± 5.94^{b}	36.0 ± 7.0^{a}	63.40 ± 13.98^{ab}	33.43 ± 1.18^{b}
L.S.D	4.94	7.56	6.24	8.94	1.46

*Values expressed as Mean ± SD (n=6)

*Different small letters denote significant deference (P ≤ 0.05) between experimental groups.

3.3. EFFECT OF FORXIGA DRUG ON LEVEL OF LIVER ENZYME OF DIABETES MALE RATS

The results represented in Table 3 revealed a significant increase (P≤0.05) in serum concentration of ALT, AST groups (2, 3, 4 and 5)compared with control group. A significant decrease (P≤0.05)in DM group(2) compared with DM +forxiga treated group for 15 days (group 3).

On the other hand, ALT and AST concentrations in were significant decrease(P≤0.05)in group(4) compared with group(5).

In same table 3, A significant increase (P≤0.05) in ALP concentration was recorded in serum of the groups (2, 3, 4 and 5) compared with control group. There was no significant change in group DM(group 2) compared with DM + forxiga treated group

https://doi.org/10.17993/3cemp.2023.120151.273-288

for 15 days(group 3) and no significant change in DM (group 4) compared with DM + forxiga treated group (group 5) for 30 days.

Table 3. Effect of forxiga drug on level of liver enzymes of diabetes male rats.

Parameters Groups	ALT(U/L)	AST(U/L)	ALP(U/L)
Group 1 Control group	46.83±6.24^{d}	31.83±2.13^{e}	47.0±4.56^{c}
Group 2 DM group (15 days)	123.33±5.53^{b}	62.16±7.62^{c}	70.33±4.41^{b}
Group 3 DM +Forxiga (15 days)	102.83±13.10^{c}	52.16 ±6.96^{d}	67.48±0.87^{b}
Group 4 DM group (30 days)	139.83±6.21^{a}	89.66±10.57^{a}	92.16±9.90^{a}
Group 5 DM +Forxiga (30 days)	126.16 ±4.79^{b}	74.0 ±12.31^{b}	88.80±1.14^{a}
L.S.D	7.67	8.53	5.22

*Values expressed as Mean ± SD (n=6)

*Different small letters denote significant deference(P ≤ 0.05) between experimental groups.

4. CONCLUSION AND DISCUSSION

Data in the present study showed administration of STZ alone cause significant increase in the glucose as compared to the control group while When use forxiga, glucose return to normal or close to normal compared with control groups.

Uncontrolled blood glucose levels cause conditions of high(hyperglycaemia) or low (hypoglycaemia) blood sugar (14). Diabetes symptoms identify by raised blood glucose, change lipids, carbohydrate, and enhance opportunity for diabetic difficulties and oxidative stress (15,16). Low dosage streptozotocin is known to induce rapid obliteration of pancreatic β-cells lead to impaired glucose-stimulated insulin make public and insulin resistance, both of which are marked features of type 2 diabetes. The result showed significant increase in serum concentration of CHOL, TG, VLDL and LDL in diabetic groups compared with control group, while there was a significant decrease in level of HDL. Forxiga drug lead to significant improvement of serum

https://doi.org/10.17993/3cemp.2023.120151.273-288

concentration of CHOL, TG, VLDL and LDL , but there was significant increase in level of HDL compared with diabetic groups.

Lipid and lipoprotein abnormality are frequent in the diabetic inhabitants due to the effects of insulin shortage and insulin resistance on key metabolic enzymes (17). Glucose tolerance, insulin resistance and plasma an insulin levels have been implicate in abnormal plasma lipoprotein levels and hyperinsulinemia has been associated with the development of atherosclerotic vascular complications in diabetic patients . The result showed a significant increase in levels of (AST ,ALT and ALP) in diabetic groups compared with control group but DM group which treated with forxiga drug caused a significant improvement and return of serum AST and ALT to normal, while no significant changes in serum ALP concentration compared with diabetic group.

The analysis of the activities of these enzymes in the serum was used to observe the condition of liver tissue and any damage might occur after being exposed to a certain pharmacological agent such as STZ. Liver as an insulin-dependent tissue plays a vital role in the metabolism of glucose and other substances. The damage of liver cells cause a leakage of the contents out of the tissue into the blood stream (18). reported that increased activities of serum AST, ALT and ALP level indicated that hepatic dysfunction may be induced due to hyperglycemia in diabetic rats(19-20).

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