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EFFECT OF CLOFIBRATE ON BLOOD GLUCOSE AND GLUCOSE TOLERANCE IN STREPTOZOTOCIN - DIABETIC RATS

Salah A. Ghareib, Hassan M. El-Fayoumi and Mohamed N. M. Zakaria

Department of Pharmacology, Faculty of Pharmacy, Zagazig University , Egypt

ABSTRACT

The effects of clofibrate (120 mg/kg) on the blood levels of glucose, lactate, pyruvate, free fatty acids (FFA) , triglycerides (TG), cortisol, triiodothyronine (T3) , tetraiodothyronine (T4) , calcium and potassium of adult male diabetic rats were studied for four weeks . Moreover, the effects of four weeks treatment with clofibrate on the oral glucose tolerance were investigated. Results showed that administration of clofibrate significantly decreased the blood glucose levels to 190 , 165 and 160 mg/dl after the 2nd 3rd and 4th week of treatment vs 230 mg/dl of control. Moreover, clofibrate improved the glucose tolerance in STZ - diabetic rats after four weeks of treatment in comparison with the control diabetic rats . There is a reduction in the area under the glucose curve recording 59550± 3440 vs 79200 ± 5060 mg. min/ dl of control value . Clofibrate decreased the blood levels of FFA , TG , T4 , whereas, it increased that of cortisol. The plasma levels of both lactate and pyruvate were reduced all over the time course of treatment. Potassium blood levels were significantly increased to 26.9, 25.8, 27.6 and 28.4 mg/dL after the 1st , 2nd , 3rd and 4th week of treatment respectiviely. In conclusion, the capability of the antihyperlipidemic agent , clofibrate, to reduce the blood glucose levels and to improve glucose tolerance in STZ- diabetic rats may be in part due to its ability to reduce the blood levels of FFA,TG , lactate and pyruvate and in part to the increasing of potassium plasma levels . All these changes could play a major role in reduction of the rate of gluconeogenesis and consequently reducing the hepatic glucose production (HGP) that may participate in the above actions of clofibrate on blood glucose .

INTRODUCTION

Non-insulin dependent diabetes mellitus (NIDDM) is characterized by decreased insulin sensitivity of liver[1,2] and musucle [3-5] . This abnormality is mostly marked in obese patients [6] Although plasma insulin levels are frequently normal or increased in absolute terms, the regulation of both carbohydrate and fat metabolism is clearly abnormal[7,8] . Hyperglycemia is accompanied by raised plasma levels of free fatty acids [8-10] and increased fatty acid oxidation rate [10] .

Hypertriglyceridemia is a common finding in patients with NIDDM . It has been reported by several investigators that treatment with clofibrate reduces the glucose blood levels in normal individuals [11], NIDDM[12] and in insulin dependent diabetic patients IDDM [13,14] . Clofibrate was found to improve glucose tolerance in man [11,12] . However, it did not change the insulin sensitivity both in-vitro [15] and in-vivo [16] nor insulin action [17].

The present study was undertaken to study the effects of clofibrate on the blood glucose levels as well as on glucose tolerance in STZ-diabetic rats. Moreover, the role of the changes in plasma levels of FFA, TG, cortisol, T_3, T_4, Ca^{2+}, K^+ and some glucose metabolites e.g. lactate and pyruvate on the above effects of clofibrate was investigated.

MATERIALS AND METHODS

Adult male albino rats obtained from the animal house and laboratories of the National Information and Documentation Center (NIDOC), Doky, were used in the present study . Rats were kept in our animal house and left on access food and water ad libitum for more than one week before starting the experiment for accommodation. Rats became diabetic and were divided into groups (8-10 animals of each) and received drugs and solvents according to the following protocol :

1-Determinaion of the weekly effects of clofibrate for four weeks on blood glucose , lactate , pyruvate , cortisol, T_3, T_4 , free fatty acids, triglycerides, calcium and potassium:

A) **Group 1** : diabetic rats received clofibrate (Cairo Pharm. Co., Egypt) intraperitoneally in a dose of 120 mg/kg for four weeks. These animals were divided into three subgroups as follows ;
   a) Rats were used to study the effect of clofibrate on blood glucose levels and glucose metabolites , lactate and pyruvate.
   b) Animals of this subgroup were used to study the effect of clofibrate on FFA , TG, k^+ and Ca^{2+}.
   c) Rats were used to study the effect of clofibrate on blood levels of cortisol, T_3 and T_4 .

B) **Group 2 :** Thirty diabetic rats were used as control and received propylene glycol intraperitoneally as a solvent in a dose of 0.1 ml/100 g.b.w. rat. These rats were divided into three subgroups and were used parallel to the above treated subgroups.

Blood samples were withdrawn from the orbital sinus of rats on fluoride from both treated and control rats on the 7th , 15th , 21st and 28th days of starting the study and were centrifuged at 3000rpm for 15 min for separation of plasma . Plasma was used immediately for determination of blood glucose and the other biochemicial parameters. The remaining portions of plasma were kept at -20C untill the time of hormonal assay.

II-Glucose tolerance test :

a) Control Group ; Eight diabetic rats of this group were injected intraperitoneally with propylene glycol and used as control.

b) Clofibrate treated group ; animals of this group received clofibrate for four weeks and used for studying the effect of clofibrate on glucose tolerance at the 29th day of treatment.

Glucose tolerance test :

The test was carried out as follows; at the night of the 28th day of treatment with clofibrate, the food was completely removed from the animal's cages and animals were fasted at least for 15 hours before the test. Glucose powder (BDH) was dissolved in distilled water and was given orally by gavage in dose of 6.75 g/kg b.wt. rat . About 200 μl blood was collected from the rat orbital sinus on fluoride at -30, 0.0, 30, 60, 90, 120, 150, and 180 min , after glucose administration . Rats were returned back to their cages after each sample and left on access water during the intervals of sampling . The collected blood samples were rapidly centrifuged at 3000 rpm for 15 min and the separated plasma was used for determination of blood glucose.

Induction of diabetes :

Diabetes was induced in rats by intraperitoneal injection of streptozotocin , STZ (Sigma Co. USA), in a dose of 38 mg/kg dissolved in citrate buffer, pH 4.5 (18). Animals which had blood glucose levels range 10-15 mM and had stable body weight after the initial weight loss that followed STZ injection were considered diabetic and were used in this study while the other rats with severe hyperglycemia were canceled.

Assay and determinations :

Blood glucose levels were determined by oxidase method (19) using Bio0Analytical kits. Potassium blood levels were measured by turbidimetric method of Henery (20) using QCA, kits. Plasma calcium levels were determined colourmetrically using Diamond Diagnostic kit following the method of Tietz (21). Blood lactate levels were measured chemically according to the method of Barker and Sammerson (22) . Pyruvate blood levels were determined using Boehringer Mannheim GmbH Diagnostica kit (23). Hormonal blood levels of T3, T4 and cortisol were determined using DELFIA fluoroimmmnoassay kits and pharmacia fluorometer (LKB, Wallac, Mod. No. 1230) . Blood triglyceride levels were determined according to the method of Bucolo and David(24). Free fatty acids were determined according to the method of Soloni and Sardina (25).

Calculation and statistical analysis of data :

Data of the present study are presented as mean value $\pm$ SEM . The test of significance was carried out using both paired and unpaired Student"t" test . For all tests, the differences were considered to be statisticially significant at $P<0.05$, Area under the glucose curves was calculated for both control and treated animals using treapezoidal method.

RESULTS

1- Effect of clofibrate on blood glucose levels :

As shown in Fig. (1), administration of clofibrate to STZ-diabetic rats significantly reduced the blood glucose levels after the 2nd, 3rd and 4th week of treatment to 190 , 180 and 165 mg/dl vs 235, 220 and 223 mg/dl of control diabetic rats respectively.

2- Effect of clofibrate on glucose tolerance :

The effect of four weeks treatment with clofibrate on glucose tolerance in STZ - diabetic rats was determined and constructed in Fig. (2) . The results showed that the clofibrate-treated diabetic rats had significantly ($P<0.01$) lowered glucose blood level compared with the control rats and the area under the glucose curve was 59550 $\pm$ 3440 vs 79200 $\pm$ 5060 mg . min./dl for both clofibrate-treated and control rats respectively. The recorded reduction in the area under the glucose curves was 24.8% from the control group. Taking in mind that all rats were with blood glucose of 260 $\pm$ 14.6 mg/dl before their distribution between groups , the existed difference between the fasting blood glucose levels of both control and treated groups may be due to the treatment with clofibrate.

3- Effect of clofibrate on both free fatty acids and triglycerides :

Administration of clofibrate for four weeks significantly reduced the blood levels of both free fatty acids and triglycerides. This effect started after two weeks of treatment recording 510, 460 and 430 μM/L in case of FFA vs 800 , 785 and 760 μM/L of the control rats respectively (Fig.3) and 180, 175 and 170 mg/dl in case of triglycerides vs 217, 230 and 213 mg/dl of control respectively (Fig. 4).

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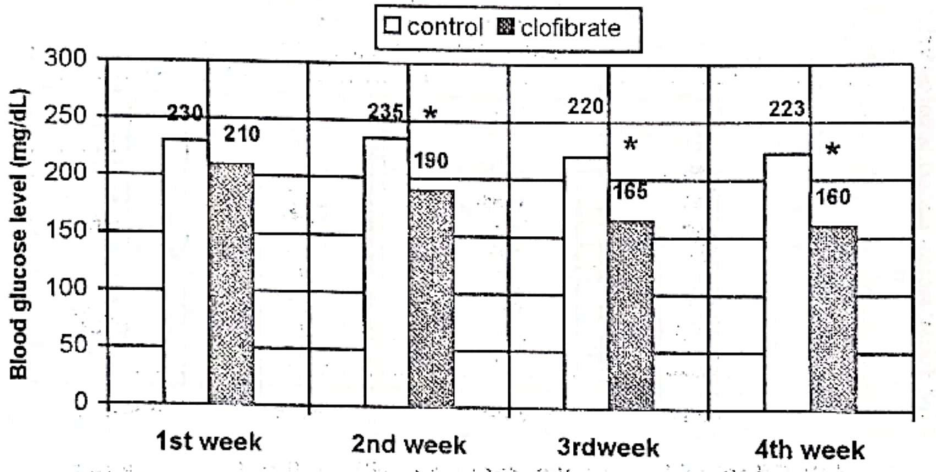
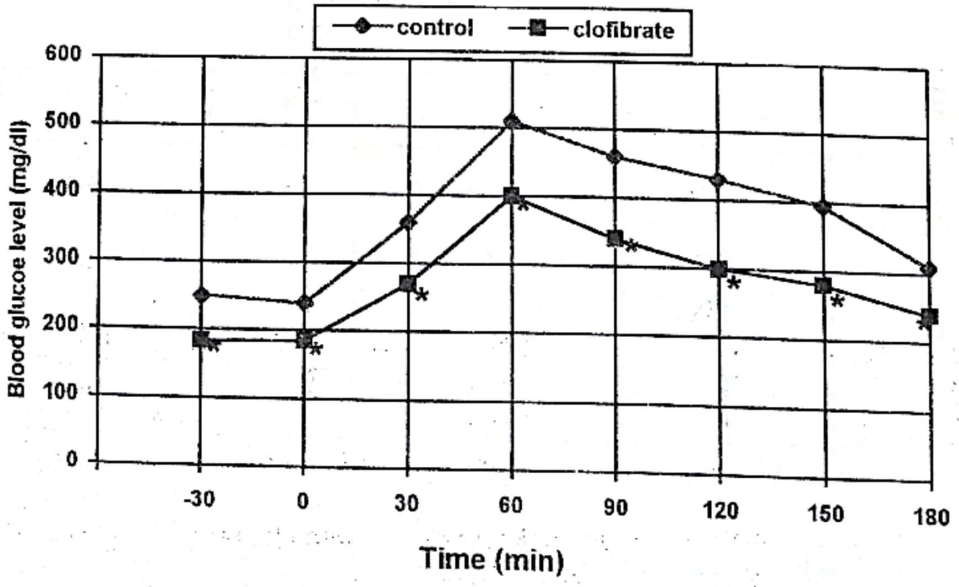


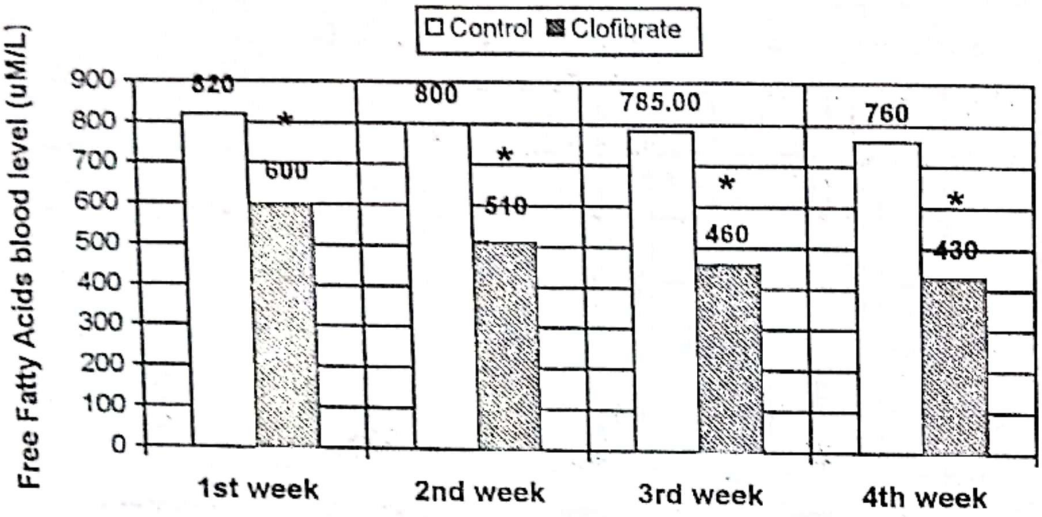
Fig(1): Effect of four weeks treatment with clofibrate on glucose blooc level in STZ-diabetic rats.

* Significntly different from control value at P< 0.05.



Fig(2): Changes in blood glucose levels during oral glucose tolerance testing (OGTT) in response to 6.75 gm/kg oral glucose challenge after four weeks treatment with clofibrate in STZ-diabetic rats.

* Significantly different from control value at P< 0.05.



Fig(3): Effect of four weeks treatment with clofibrate on free fatty acids blood level in STZ-diabetic rats.

* Significantly different from control value at P<0.05.

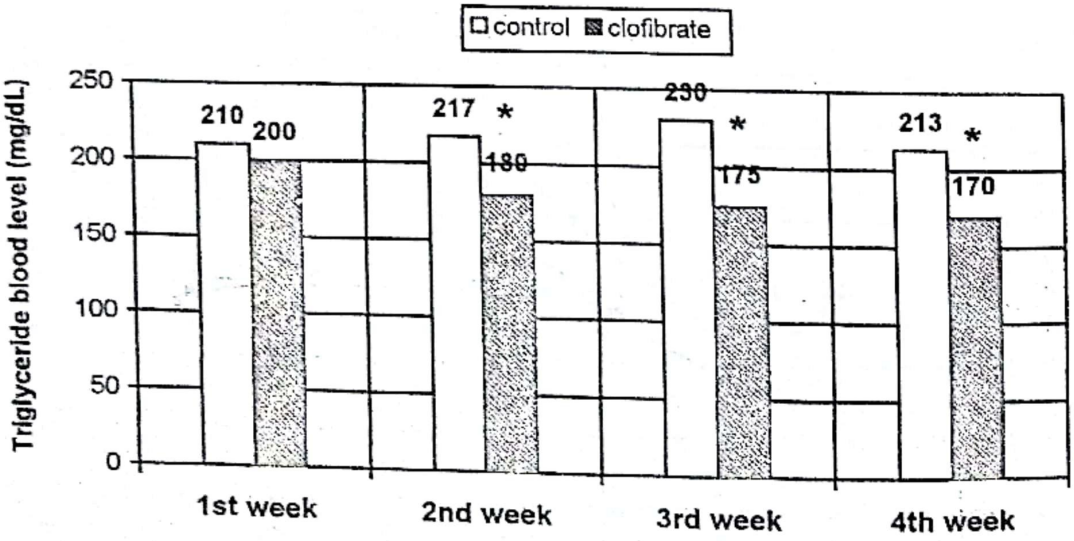


Fig (4) : Effect of four weeks treatment with clofibrate on triglyceride blood level in STZ- Diabetic rats.

* Significantly different from control value at P<0.05.

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4- Effect of clofibrate on cortisol and thyroid hormones :

As shown in Fig. (5,6), clofibrate for four weeks significiantly decreased the plasma levels of both T_3 and T_4 . The redution of T_3 started after the second week of treatment recording 0.59, 0.41 and 0.32 ng/dl after the 2nd , 3rd and 4th week vs 0.91 , 0.78 and 0.74 ng/dl of control respectively. In case of T4 clofibrate reduced its plasma levels to 1.6 , 1.4 and 1.5 ng/dl after the 2nd, 3rd and 4th week of treatment vs 2.4, 1.9 and 2.1 ng/dl of control group respectively. Clofibrate administration significantly increased the cortisol plasma levels to 490, 625 and 647 μM/L after the 2nd , 3rd and 4th week of treatment respectively vs 425, 440 and 463 μM/L of the control diabetic rats (Fig. 7).

5- Effect of colfibrate on lactate and pyruvate blood levels :

The recorded results showed that clofibrate administration significantly reduced the blood levels of both lactate and pyruvate in STZ-diabetic rats (Table 1). Lactate blood levels were decreased to 4.6, 3.4 and 3.1 mg/dl after the 2nd , 3rd and 4th week of treatment vs 6.9, 6.1 and 5.8 mg/dl of control respectively . Pyruvate blood levels were decreased to 0.85 , 0.8 and 0.61 mg/dl after the 2nd , 3rd and 4th week of treatment with clofibrate respectively.

6-Effect of clofibrate on potassium and calcium blood levels :

In table (2) clofibrate did not significantly affect the blood levels of calcium all over the time of treatment. Potassium blood levels were significantly increased to 26.9, 25.8, 27.6 and 28.4 mg/dl after the 1st, 2nd , 3rd and 4th week of treatment vs 18.3, 18.7, 19.1 and 19.7 mg/dl of control rats recording 47%, 38%, 45% and 44% increase respectively.

Table (1) : Effect of clofibrate (120mg/kg) on lactate and pyruvate blood levels in adult male diabetic rats.

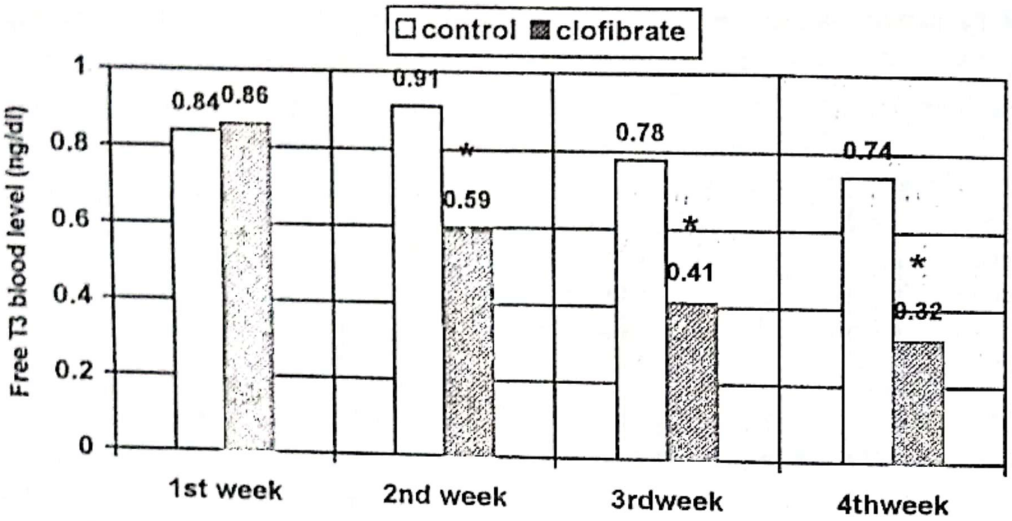
Period of treatment	Lactate (mg/dl)			Pyruvate (mg/dl)		
	Control	Clofibrate	% change	Control	Clofibrate	% change
1st Week	6.3 ± 0.43	4.1 * ± 0.53	- 35	1.6 ± 0.15	1.3 * ± 0.11	- 18.75
2nd Week	6.9 ± 0.63	4.6 *± 0.34	- 33.33	1.45 ± 0.14	0.95 *± 0.07	- 34.48
3rd Week	6.1 ± 0.58	3.4 *± 0.26	- 44.26	1.49 ± 0.13	0.81 *± 0.06	- 45.64
4th Week	5.8 ± 0.55	3.1 *± 0.23	- 46.55	1.5 ± 0.12	1.01* ± 0.08	- 32.67

* Significantly different from control values at P<0.05. - Values are expressed as the mean ± SEM.

Table (2) : Effect of clofibrate (120mg/kg) on potassium and calcium blood levels in adult male diabetic rats.

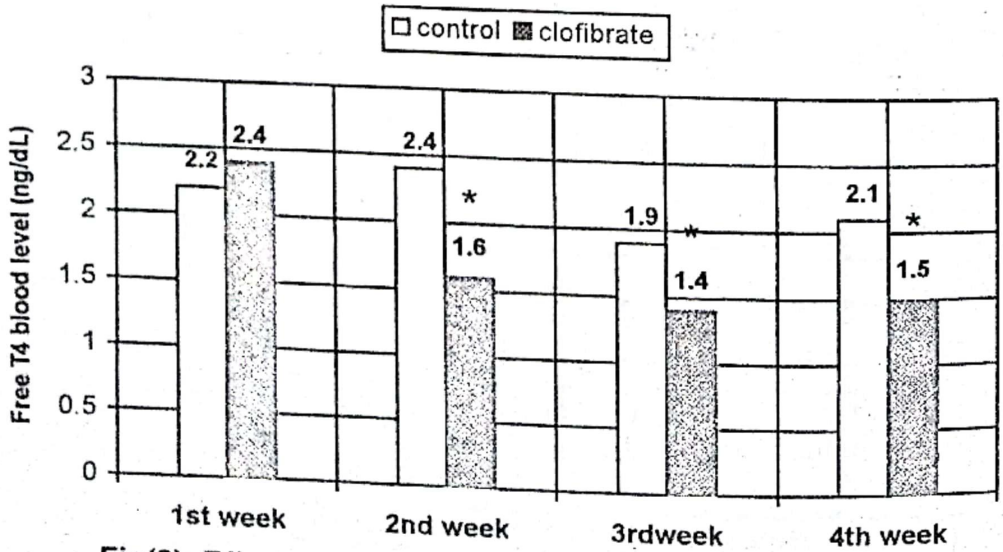
Period of treatment	Potassium (mg/dl)			Calcium (mg/dl)		
	Control	Clofibrate	% change	Control	Clofibrate	% change
1st Week	18.3 ± 1.65	26.9 *± 1.73	+ 47	10.25 ± 0.95	10.9 ± 0.85	+ 6.34
2nd Week	18.7 ± 1.33	25.8 *± 1.89	+ 38	10.8 ± 0.98	11.3 ± 1.12	+ 4.63
3rd Week	19.1 ± 1.71	27.6 *± 2.11	+ 45	10.6 ± 0.87	11.8 ± 1.22	+ 11.32
4th Week	19.7 ± 1.52	28.4 *± 2.01	+ 44	11.1 ± 1.01	12.1 ± 1.19	+ 9.00

* Significantly different from control values at P<0.05. - Values are expressed as the mean ± SEM.



Fig(5): Effect of four weeks treatment with clofibrate on the blood level of free triiodothyronine (T3) in STZ- diabetic rats.

* Significantly different from control value at P <0.05.



Fig(6): Effect of four weeks treatment with clofibrate on free tetraiodothyronine (T4) blood level in STZ-diabetic rats.

* Significntly different from control value at P<0.05.

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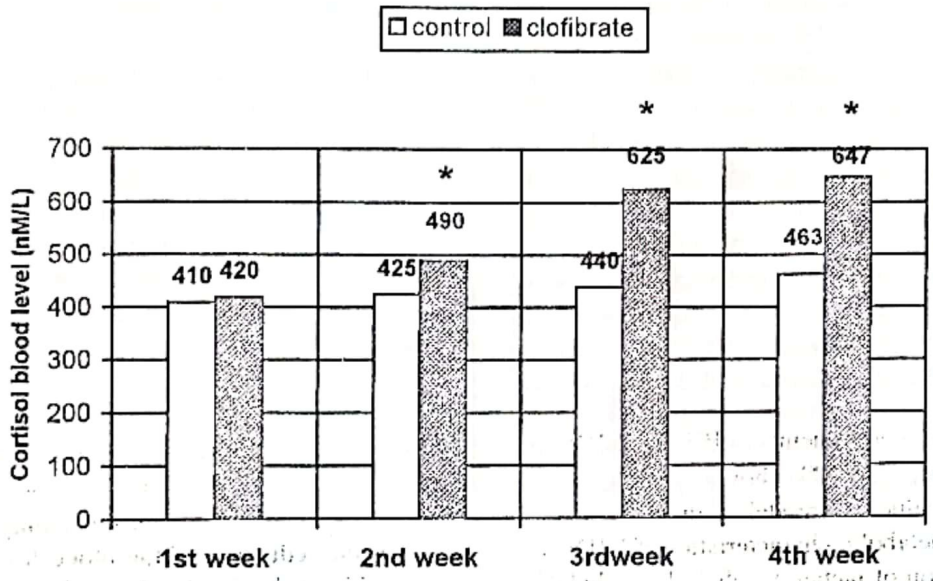

Fig(7):Effect of four weeks treatment with clofibrate on cortisol blood level in STZ-diabetic rats.

* Significantly different from control value at P< .05.

DISCUSSION

Clofibrate is the first derivative of fibric acid and is widely used in the treatment of hypertriglyceridemia . Clofibrate characteristically reduces the plasma levels of triglycerides by lowering the concentration of VLDL- within 2-5 days after initiation of therapy (26) . The antihypertriglyceridemic effect of clofibrate is due to the increasing of the activity of lipoprotein lipase in hyperlipidemic patients, whereas, hepatic lipase activity is not affected (27,28).

Results of the present study showed that clofibrate treatment for four weeks significantly reduced the plasma glucose levels of STZ-diabetic rats. An effect which started after 2 weeks and lasted all over the time course of treatment. The intensity of this reduction was increased with the prolonged administration . These results are in accordance with that reported in NIDDM(12). IDDM patients(13,14) and normal individuals (11) . Moreover, clofibrate treatment for 4 weeks improved glucose tolerance in STZ-diabetic rats, which indicated by the significant reduction of blood glucose levels after oral glucose challenge compared with control diabetic rats , all - over the time intervals . Similar findings were reported by Murakami et al., (29) & Kobayashi et al., (15) .

The ability of clofibrate to decrease the blood glucose levels may be in part due to the reduction of hepatic gluconeogenesis and consequently decreasing the HGP. It was previously reported that a significant direct relationship exists between fasting plasma glucose (FPG) concentration and endogenous glucose production in NIDDM patients (30), leading to the view that the elevated FPG levels in NIDDM patients is secondary to hepatic overproduction of glucose , which is primary attributable to enhancement of hepatic gluconeogenesis(31) .

There are three proposed mechanisms for HGP and its regulation which are relevant to our findings.

Firstly, clofibrate was reported to increase the affinity and to enhance the binding of insulin to insulin receptors in skeletal muscle, adipose tissues and liver(29) . So it can increase hepatic insulin sensitivity and decrease hepatic insulin resistance in NIDDM patients (15) an effect that may reduce hepatic gluconeogenesis and consequently the HGP . It was previously reported that the ability of insulin to inhibit HGP is reduced in NIDDM patients (1,3,5) and the increased rate of gluconeogenesis is secondary to hepatic insulin resistance in diabetic patients .

Secondly, in the present study clofibrate reduced the blood levels of both lactate and pyruvate. This effect was in a significant correlation with the induced reduction in blood glucose ($r = 0.82$ at $P<0.05$) and may also play an important role in the reduction of the basal rate of gluconeogenesis and HGP and consequently glucose blood levels. Similar observations were reported by Mondon et al.(32) who mentioned that the increase in lactate shift to liver could contribute to the enhancement of gluconeogenesis and could have a profound effect on

increasing HGP and consequently FPG in NIDDM patients[33], Weiland et al. [18] showed that low dose (38 mg/kg) of STZ induced a model of diabetes which shares many of the metabolic characteristics of NIDDM and in special elevation of lactate levels in both skeletal muscles and adipose tissues. This elevation in lactate levels is accompanied by reduction in pyruvate dehydrogenase (PDH) enzyme activities in these tissues [32]. Whereas, we prepared the same model of diabetic rats, so the elevated blood lactate levels in our model is accompanied by elevated lactate levels in tissues, increased rate of gluconeogenesis and HGP . Under these circumstances, it is perthaps not surprising that HGP was reduced after clofibrate, an effect which has some sort on the reduction of blood glucose affter clofibrate treatment.

Thirdly, the results of the present study showed that clofibrate reduced the plasma levels of FFA all over the time course of treatment. These results are in agreement with that reported by other researchers [34-36] who claimed that clofibrate reduces fasting plasma levels of FFA in human by inhibiting their mobilization from adipose tissues. Moreover, clofibrate inhibits the De novo synthesis of fatty acid [37] , displaces fatty acids in albumin, reduces the amount of fatty acids available to the liver for TG synthesis and enhances their mitochondrial and peroxysomal oxidation [38] . Clofibrate was reported to increase the activity of acyl- and acetyl- carnitine transferase as well as the total coenzyme A content indicating an enhanced capacity of the liver for beta-oxidation of long-chain acyl-coenzyme A [39].

Also, the results show that clofibrate significantly reduced the plasma levels of triglycerides all over the time intervals of treatment . This effect was correlated with the reduction in blood glucose levels induced by clofibrate ($r = 0.93$ at $P<0.01$) . These results are in accordance with that reported by Wulfert, [40] . These effects may be due to the increased activity of lipoprotein lipase, whereas hepatic lipase activity was not affected resulting in the increased rate of TG catabolism [27,28]. Morover, reduction in the levels of circulating FFA should decrease the availability of FFA to the liver to serve as a substrate for the synthesis of TG for VLDL [35] . Suppression of triglyceride synthesis and very low - density lipoprotein output together with acceleration of the removal of TG - rich lipoproteins are the mechanisms whereby the drug exerts a potent triglyceride lowering effect in diabetic rats [41]. Clofibrate was reported to decrease the hepatic synthesis and secretion of VLDL and increase the blood levels of HDL, indirectly as a result of the decreased concentrations of VLDL - TG [42] . Normally, VLDL exchanges lipids with HDL , which plays a role as making as FFA scavenger [43] . The catabolism of triglyceride and its mobilization between VLDL and HDL with different proportions may also play major role in the reduction of the blood levels of FFA in our study . The reduction in plasma levels of both FFA and TG induced by clofibrate may play a part in the reduction of blood glucose levels and improvement of glucose tolerance after clofibrate treatment. This finding is in agreement with that reported by Kabayashi et al. [15]. Good correlation was obtained in- vivo between the elevated fasting plasma levels of FFA , rate of lipid oxidation and basal HGP [4,8,44] . In healthy human , experimental elevation of serum FFA enhances HGP [44] and blunts the inhibitory effect of insulin on HGP in obese individuals[45]. Conversely, acute lowering of serum FFA augments the insulin - mediated suppression of HGP in NIDDM patients [46] .

Results of the present study showed that clofibrate reduced the plasma levels of T3 and T4 while increasing that of cortisol. The reduction in the levels of both T3 and T4 are in accordance with the finding of Ganong , W. F. [47] , who reported that clofibrate increases thyroid binding globulin (TBG) content and consequently increases the binding of both T3 and T4 resulting in reduction of their blood levels . On the other hand , cortisol was reported to inhibit secretion of the thyroid stimulating hormone (TSH), and consequently the rate of synthesis and release of thyroid hormones[47] . The reduction in serum levels of both T3 and T4 under the influence of clofibrate may be due in part to the increased plasma levels of cortisol rather than increasing their binding to TBG. However, the little increase in plasma levels of cortisol may result from the initial increase of the cholesterol blood levels after clofibrate treatment, which may result from the mobilization of cholesterol and cholesterol esters from HDL to other lipoproteins [48] . Since the reduction of cholesterol synthesis needs period of treatment longer than four weeks [49].

It was previously reported that thyroid , cortisol, glucagon and growth hormones as well as catecholamines are counter - regulatory hormones for glucose homestasis [50] . T3 and T4 were reported to increase blood glucose levels and lead to experimental diabetes by increasing intestinal absorption and hepatic production of glucose [47] . Cortisol was found to increase the blood glucose levels through increasing hepatic glycogenolysis and gluconeogenesis as well as increasing the blood lactate and pyruvate levels which have a profound effects on hepatic production of glucose in NIDDM and accounts 60-70% of gluconeogenesis [33] . So the reduction of both T3 and T4 may mask the effect of increased serum cortisol levels on blood glucose .

In addition to the above actions, hyperkalemia induced by clofibrate may also play a role in the reduction of blood glucose and improvement of glucose tolerance by partial increase of insulin release. It was reported that potassium , in absence of any other secretagogue , stimulates insulin release (51) . .The mechanisms involved in this action through depolarizing the plasma membrane, opening voltage-sensitive Ca^{2+} channels, and allowing Ca^{2+} , to enter the cell(52) . Moreover, potassium stimulates somatostatin release from the islets (53) and neurohypophysis(54). Somatostatin consequently inhibits glucagon release(55) and hence enhances insulin secretion.

In conclusion , results of the present study showed that clofibrate treatment significantly reduced the blood glucose levels and improved glucose tolerance in STZ - diabetic rats. This effect of clofibrate may be induced by the reduction of the rate of gluconeogenesis and consequently the basal rate of hepatic glucose production. This may result from the reduction of plasma levels of FFA , TG, lactate and pyruvate and increased potassium blood levels . Finally, a word of caution should be mentioned that upon using clofibrate in combination with other antidiabetics for treatment of diabetic hyperlipidemic patients, care should be taken to avoid the occurrence of severe hypoglycemia. Otherwise , if there is a bad need for this combination, monitoring of blood glucose should be carried out from time to time.

Further research should be carried out for the determination of glucose oxidation rate, basal rate of HGP and energy expenditure after clofibrate treatment for longer time.

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تأثير الكلوفيبرات على مستوى الجلوكوز فى الدم واحتمالية الجلوكوز فى الجرذان المصابة بالداء السكرى المستحدث بالاستربتوزوتوسين

صلاح عبدالمنعم غريب ، حسن محمود الفيومى ، محمد نجيب محمد زكريا
قسم الفارماكولوجى - كلية الصيدلة - جامعة الزقازيق - مصر

فى هذا البحث تمت دراسة تأثير التجرع الفمى (١٢٠ مجم/كجم) من الكلوفيبرات للجرذان البالغة والمصابة بالداء السكرى تجريبياً يومياً ولمدة أربعة أسابيع ، على مستويات الجلوكوز ، اللكتات ، البيروفات ، الأحماض الدهنية ، الجلسريدات الثلاثية ، الكورتيزول ، الثيروكسين ، رباعى يوديد الثيرونين ، الكالسيوم والبوتاسيوم فى الدم. وكذلك تمت دراسة تأثير التجرع المسبق لمدة أربعة أسابيع بالكلوفيبرات على تحمل الجلوكوز المجرع بالفم فى الجرذان المصابة بالداء السكرى.

وقد أثبتت النتائج أن الكلوفيبرات قد خفض مستويات الجلوكوز فى الدم لتصل إلى ١٩٠ ، ١٦٥ ، ١٦٠ مجم/دسل من الدم وذلك بعد الأسبوع الثانى والثالث والرابع على التوالى من تجرع الكلوفيبرات وهذا الأنخفاض ذات دلالة احصائية بالمقارنه بمجموعة الجرذان الضابطة. علاوة على ذلك ، فأن الكلوفيبرات قد حسن من تحمل الجسم للجلوكوز المعطى عن طريق الفم ، وذلك بعد أربعة أسابيع من التجرع الفمى للكلوفيبرات ، حيث أنه قلل من المساحة المسجلة تحت منحنى الجلوكوز لتصل إلى ٥٩٥٥٠ مجم دقيقة / دسل مقابل ٧٩٢٠٠ مجم دقيقة / دسل فى الجرذان الغير معالجة بالكلوفيبرات . والجدير بالذكر أن الكلوفيبرات قد خفض مستويات الأحماض الدهنية ، الجلسريدات الثلاثية ، الثيروكسين ، ورباعى يوديد الثيرونين - بينما أدى إلى ارتفاع مستوى الكورتيزول فى دم الجرذان المصابة بالداء السكرى . وفى الوقت الذى انخفض مستوى اللكتات والبيروفات فى الدم فقد أرتفعت مستويات البوتاسيوم ارتفاعاً ذات دلالة احصائية كبيرة مسجلا ٢٦٫٩ ، ٢٥٫٨ ، ٢٧٫٦ و ٢٨٫٤ مجم / دسل.

فى الخلاصة وبناء على ماسبق ، أن نتائج هذا البحث قد دلت على أن قدرة الكلوفيبرات على خفض مستويات الجلوكوز فى الدم وكذلك تحسين تحمل الجسم للجلوكوز المعطى بالفم فى الجرذان المصابة بالداء السكرى قد يرجع ولو جزئياً إلى قدرته على خفض مستوى الأحماض الدهنية ، الجلسريدات الثلاثية ، اللكتات والبيروفات من ناحية ، وإلى زيادة مستوى البوتاسيوم فى الدم من ناحية أخرى ، وأن جميع هذه التغيرات ربما لعبت دوراً كبيراً فى خفض معدل تكوين الجلوكوز فى الجسم " الجلوكونيوجنزيس " وعلى ذلك يتم تقليل تكوين وانتاج الجلوكوز فى الجسم بواسطة الكبد - كل هذا ادى إلى تأثير الكلوفيبرات الخافض لمستوى الجلوكوز فى الدم.