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ENDOTHELIAL DYSFUNCTION IN HYPERCHOLESTEROLEMIC RATS EFFECT OF BEZAFIBRATE ON ENDOTHELIUM–DERIVED SUBSTANCES.

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A B S T R A C T

The present study was done on sixty male albino rats. They were randomly divided into four groups: the first group (n=10) was fed a normal diet (control). The second group (n=10) fed on normal diet and bezafibrate at a dose of 100 mg/kg B. wt. /day. The third group (n=10) was fed normal diet enriched with 1% cholesterol and 5% coconut oil (cholesterol-fed group). The fourth group (n=30) was fed same as the cholesterol-fed group but supplemented with bezafibrate at concentration 50, 100, 200 mg/kg B. wt. /day. Feeding was continued daily for 8 weeks. Biochemical investigation involved the measurement of total cholesterol, triacylglecerol, high density lipoprotein (HDL), low density lipoprotein (LDL), apolipoprotein B, endothelin-1, histamine, nitric oxide (NO), IL-6, creatinine and alanine amino transferase (ALT).The results of the present study indicate that the total cholesterol, triacylglecerol, apolipoprotein B, and low density lipoprotein (LDL) concentration were significantly elevated in the cholesterol–fed rats compared with the bezafibrate and control rats. Plasma endothelin-1, histamine and IL-6 concentration were significantly elevated in the cholesterol-fed rats compared with the bezafibrate and control rats. Plasma nitric oxide and high density lipoprotein (HDL) concentration was significantly lowered in the cholesterol fed rats compared to those of bezafibrate treated rats.

KEY WORDS: Endothelial dysfunction, Hypercholesterolemia, Rat

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1. INTRODUCTION

Problem of hypercholesterolemia is being of much interest because an elevated concentration of lipoproteins can develop chest pain, heart attack, and accelerate the development of atherosclerosis with its dual sequel of thrombosis and infraction. Hyperlipidemia, particularly hyper-cholesterolemia is a major cause of atherosclerosis and atherosclerosis associated conditions including coronary heart disease, ischemic cerebrovascular disease and peripheral vascular disease [1, 8]. In general, mono-therapy with a pharmacologic agent should be attempted first, together with dietary adjustments. Combination treatment may be required for refractory severe hypertriglyceridemia, but should be attempted only with caution and frequent monitoring of serum concentrations of creatine kinase, transaminase and creatinine.

Fibric acid derivatives such as bezafibrate are a mainstay of hypertriglyceridemia treatment. These fibrates can reduce plasma triglyceride levels by up to 50% and raise plasma HDL-C concentrations as much as 20% (although these percentages vary). The complex mechanism of action of fibrates includes modulation of the activity of peroxisome proliferator-activated receptor-α in the liver, with reduced hepatic secretion of VLDL and increased lipolysis of plasma triglycerides [16]**.** Fibrates reduce the quantity of small, dense LDL particles and increase HDL-C.

Accordingly, this work was designed evaluate the hypolipidemic effect of bezafibrate as hypolipidemic drugs on endothelium derived substances in addition the essential changes produced by lipid lowering drugs. Bezafibrate and used various amount to find most effective hypolipidemic amount with any side-effect or at least cause the minimum side-effect on other organs (liver, kidney and aorta)

The investigated Biochemical parameters were measurement of plasma total cholesterol, triacylglecerol, high density lipoprotein (HDL), low density lipoprotein (LDL), apolipoprotein B, endothelin -1, histamine, nitric oxide (NO), IL-6, creatinine and alanine amino transferase (ALT).

2. MATERIALS AND METHODS

2.1. *Animals and experimental design*

Sixty male white albino rats; aged 6 weeks and weighting 140-150 gram were housed in separated metal cage, fresh and clean water was supply ad libitum. Rats were kept under constant and nutritional environmental condition throughout the experiment. Rats were left for one week before beginning of experiment for acclimatization [9]**.** Rats were divided into the following groups:

Group 1 (n=10) fed on normal diet and served as control group

Group 2 (n=10) fed on normal diet and Bezafibrate at a dose of 100 mg/kg/day.

Group 3 (n=40) fed on high fat diet for about (14 weeks) at the end of the periods. Rats were divided into 4 equal subgroups

Subgroup (3A): Hyperlipidemic: fed high fat diet only.

Subgroup (3B): Hyperlipidemic and Bezafibrate**:** fed high fat diet and were given Bezafibrate at a dose level of 50mg/kg/day

Subgroup (3C): Hyperlipidemic and Bezafibrate received high fat diet and were given Bezafibrate at a dose level 100 mg/kg/day.

Subgroup (3D): Hyperlipidemic an Bezafibrate**:** received high fat diet and were given Bezafibrate at a dose level 200 mg/kg/day.

2.2. *Ration and additives*

The animals were fed on constant ration throughout the course of the experiment in the form of pelleted diet (Atmeda for Investment Co., Dakahlia) in accordance to NRC [12]. Data of the present study revealed that hyperlipidemia, induced by continuous supplementation of high fat (coconut oil 2% wt/wt) and high cholesterol (1% wt/wt) (El-Gomhoria Co. for Trading Chemicals, Medicines and Medical Appliances, Egypt) diet.

2.3. *Preparation of bezafibrate*:

Bezafibrate powder (EIPICO Pharmaceutical, Egypt) was dissolved in 20% ethanol, where (0.7), (1.4) and (2.8) mg of Bezafibrate were dissolved firstly in 5 ml absolute alcohol, and then the alcoholic Bezafibrate solution was completed to 25 ml by distilled water. Each rat within the target group received 0.5 ml of the prepared solution which is equivalent to a dosage rate of 50, 100 and 200 mg/kg. Body weight, orally and once daily

2.4. *Blood sampling*:

Heparinized blood samples (20 IU/ ml) were collected from animals after 14 weeks for detection of hypercholestrolemai, then blood samples collected after 2, 4 and 6 weeks from the beginning of Bezafibrate administration. The samples were collected in the morning after overnight fasting from the retro-orbital plexus of eyes. In the dry, clean and screw capped tubes and plasma was separated by centrifugation at 3000 rpm for 10 minutes. The clear plasma were aspirated carefully by Pasteur pipettes and transferred into dry, clean and sterile labeled tubes and kept in deep freezer at -20°c until used for subsequent biochemical analysis Then the following Biochemical analysis were performed for the following

parameters: Total cholesterol, triacylglycerol (TG), high-density lipoproteins cholesterol (HDL-ch), low-density lipoproteins cholesterol (LDL-ch), apolipoprotein B , endothelin-1 , histamine, nitric oxide (NO), IL-6, creatinine and ALT.

2.5. *Statistical analysis*:
Statistical analysis was done using SPSS software version 15. The inter-group variation was measured by one way analysis of variance (ANOVA) followed by Post Hoc LSD test. Results were expressed as mean± S.E. The mean difference is significant at the 0.05 level [18].

3. RESULTS AND DISCUSSSION

Hypercholesterolemia, defined as excessively high plasma cholesterol levels, has emerged as a strong risk factor for cardiovascular disease (CVD). As high total cholesterol levels are considered to be a major independent risk factor for development of PVD and CAD, considerable attention has been directed toward evaluating the impact and mechanisms of cholesterol lowering therapies and interventions for cardiovascular outcomes **[17]**.
The obtained results demonstrated in table (1, 2, 3) revealed that rats on hyperlipidemic diet show a significant increase of plasma lipid profile concentration including total cholesterol, triglyceride, low density lipoprotein (LDL) and apolipoprotein-B (APOB), and significant decrease high density lipoprotein (HDL) compared with control group. An increased content of cholesterol in the liver despite the fact that the diet produced a cessation of endogenous cholesterol synthesis has been reported formerly [17]. The significant rise in serum triglycerides level, similar with that was reported previously by Huijgen et al. [10] who investigated those rats with high serum lipid concentration developed intimal lesions similar to those of human atherosclerosis. The dramatic rise in serum total cholesterol (free cholesterol more than esterified cholesterol) observed in this study was due to increased up taken of exogenous cholesterol .This rise was mainly reflected on the cholesterol level of LDL fraction [11]. Also, These findings were in agreement with Ros [16] recorded that, both dietary fat and cholesterol changes the lipoprotein content of serum and affect specific classes of lipoprotein of LDL content (Apo B) and HDL and increased the content of cholesterol VLDL. Saturated fats mostly increase the concentration of cholesterol, LDL, and to a less extent VLDL levels. The increase in LDL levels produced by saturated fats seems to be related mainly to reduce catabolic rate. Moreover, Csont et al. [3] demonstrated that, elevated level of LDL, appearing in the circulation upon feeding the hyperlipidemic diet, is mainly derived from LDL is up taken by the receptor in liver an extra hepatic tissue. The production of LDL exceeds the capacity of LDL receptors i.e. efflux of cholesterol from the liver is more than influx. This could explain the elevated serum LDL level observed in our study.
The presented data in tables revealed that, Bezafibrate administration significant decrease in plasma total cholesterol after 2, 4 and 6 weeks, with significant decrease in Triglyceride, low density lipoprotein and apolipoprotein B with significant increase in high density lipoprotein after 2, 4 and 6 week, when compared to hyperlipidemic non-treated group. These findings were in agreement with Palmieri et al. [14] who found that, Bezafibrate, a second-generation fibrate drug, is used clinically as a hypolipidemic agent. Bezafibrate treatment lowers serum triglyceride and cholesterol levels by more than 25% and 10%, respectively, in patients with hyperlipidemia. The Bezafibrate infarction prevention study demonstrated a relationship between the lipid-lowering effects of bezafibrate and a reduction of the risk of cardiovascular events in

dyslipidemic patients with coronary artery disease. The molecular mechanism underlying the triglyceride-reducing effect of bezafibrate is due in part to the induction of lipoprotein lipase activity mediated by the activation of peroxisome proliferators-activated receptor α (PPARα), a member of the nuclear receptor super family. Also, the result are in accordance with Choonjans et al. [2] who found that, The mechanism of the action of Bezafibrate on lipoprotein metabolism appears to involve the activation of transcription factors, known as PPAR, principally PPAR which are expressed in the liver. PPAR modulate the expression of genes involved in lipid metabolism through PPAR response elements. Specifically, PPAR-α activators stimulate the oxidation of fatty acids in the liver resulting in a reduced availability of fatty acids for triglyceride synthesis. Furthermore, Pennacchio et al. [15] demonstrated that, the activation of PPAR-α by Bezafibrate induces lipoprotein lipase in the liver, which plays a key role in triglyceride-rich lipoprotein catabolism. It also affects the binding and clearance in the liver of remnant lipoprotein particles by LDL-related receptors. The fibrate-induced increased lipoprotein catabolism may also be related to a PPAR mediated lower hepatic Apo CIII synthesis. It is well known that Apo CIII delays the catabolism of triglyceride rich lipoproteins, since it inhibits their binding to the endothelial surface and lipolysis by lipoprotein lipase and interferes with Apo E-mediated receptor clearance of remnant particles from plasma Finally, a new additional mechanism contributing to the fibrate-induced reduction in triglyceride rich-lipoproteins was also proposed is a recently discovered lipoprotein that influences plasma triglyceride levels. Specifically, the over expression of Apo AV results in a significant reduction in serum triglycerides human hepatocytes treated with fibrate display a significant induction of this lipoprotein,this effect is mediated by PPAR A-II activation. The present results were affirmed by Vu-Dac et al. [23] who stated that, The improvement of serum lipolytic activity may account for the improvement in postprandial dyslipidaemia noted with fibrate The decrease in plasma concentrations of triglyceride-rich lipoproteins could be responsible for the decreased chlolesteryl ester transfer protein (CETP) activity observed after Bezafibrate administration, leading to increased HDL-C levels and to reduced concentrations of small dense LDL particles Fibrates also induce the expression of the human Apo AI and Apo AII genes leading to elevated HDL levels Moreover, Fruchart et al. [6] demonstrated that, fibrates also affect HDL metabolism by other ways. In fact, the increase in HDL-C may be related to accelerate triglyceride-rich lipoprotein catabolism leading to an increase in pre-β1 HDL, which is the key acceptor of cholesterol for peripheral cells during reverse cholesterol transport. The obtained data showed that, in table (1, 2 and 3) rats on hyperlipidemic diet showed a significant decrease of nitric oxide (NO) and a significant increase endothelin-1 when compared with control group. The results of the present work agreed with Huijgen et al. [10] who demonstrated that, cholesterol has been shown to interrupt and alter vascular structure and function as it builds within the lining of the vascular wall, and can interfere with endothelial function leading to lesions, plaques, occlusion, and emboli, along with a reduction in healing, recovery, and appropriate management of ischemia/ reperfusion injury with specific relevance to the microcirculation. It has been clearly demonstrated that evolution of hypercholesterolemia is associated with endothelial cell dysfunction. Additionally, Jiang et al. [11] reported a near-complete abrogation in vascular NO bioavailability, elevated oxidant stress, and the creation of a strongly pro-inflammatory condition.

Table (1): Effect of two weeks administration of Bezafibrate on some biochemical blood parameters of hyperlipidemic rats

	Cholesterol (mg/dl)	TG (mg/dl)	HDL (mg/dl)	LDL (mg/dl)	Apo(B) (mg/dl)	NO (nmol/L)	Endothelin-1 (ng/dl)	Histamine (ng/dl)	IL-6 (pg/ml)	ALT (IU/ml)	Creatinine (mg/dl)
Control	147.8±0.01^{c}	82.7±0.0^{a}	40.1±0.0^{a}	133.3±0.0^{c}	105.5±0.0^{d}	0.20± 0.01^{a}	1.86±0.01^{d}	0.60±0.00^{d}	9.33±0.01^{c}	11.66±0.00^{b}	0.85±0.02^{d}
Hyperlipidemic	218.4±0.01^{a}	198.5±0.0^{a}	23.5±0.01^{d}	207.4±0.0^{a}	204.3±0.0^{a}	0.17±0.01^{a}	2.30±0.00^{d}	2.20±0.00^{a}	18.64±0.00^{a}	20.00±0.01^{a}	2.06±0.08^{a}
Control +Beza100	150.7±0.01^{c}	75.3±0.0^{a}	35.2±0.00^{b}	124.6±0.0^{c}	108.3±0.0^{d}	0.19±0.01^{a}	1.38±0.00^{a}	0.58±0.00^{d}	9.37±0.00^{c}	10.0^{0}±0.01^{b}	0.85±0.02^{d}
Hyperlipidemic + Beza 50 mg/kg/day	194.8±0.01^{b}	182.4±0.0^{a}	23.1±0.0^{d}	155.2±0.0^{c}	167.2±0.0^{b}	0.17±0.01^{a}	1.01±0.00^{b}	2.00±0.00^{b}	18.20±0.01^{a}	19.66±0.00^{a}	1.93±0.02^{a}
Hyperlipidemic + Beza 100 mg/kg/day	196.2±0.01^{b}	335.8±0.0^{a}	26.1±0.0^{c}	158.2±0.0^{c,b}	149.5±0.0^{c}	0.18±0.00^{a}	1.01± 0.01^{b}	2.00±0.00^{b}	15.30±0.01^{ab}	18.33±0.00^{a}	1.70±0.05^{b}
Hyperlipidemic + Beza 200 mg/kg/day	182.4±0.0^{ab}	157.3±0.0 ^{a}	33.1±0.0 ^{b}	144±0.0^{a,c}	111.0±0.0^{d}	0.19±0.00^{a}	1.01±0.01^{c}	1.70±0.01^{c}	14.25±0.00^{b}	16.00±0.00^{a}	1.40±0.09^{c}

Values (mean ± S.E.) with different superscripts within each column indicate statistical significant differences between groups at 0.05

Table 2 Effect of four weeks administration of Bezafibrate on some biochemical blood parameters of hyperlipidemic rats

	Cholesterol (mg/dl)	TG (mg/dl)	HDL (mg/dl)	LDL (mg/dl)	Apo(B) (mg/dl)	NO (nmol/L)	Endothelin-1 (ng/dl)	Histamine (ng/dl)	IL-6 (pg/ml)	ALT (IU/ml)	Creatinine (mg/dl)
Control	152.4±0.0^{c}	89.8±0.0^{a}	43.3±0.0^{a}	133.2±0.0^{cd}	102.2±0.0^{c}	0.20±0.01^{a}	1.30±0.01^{d}	0.60±0.02^{e}	9.85±0.00^{d}	11.60±0.00^{d}	0.85±0.02^{d}
Hyperlipidemic	246.8±0.1^{a}	207.8±0.0^{a}	19.8±0.0^{e}	21.6±0.0^{a}	207.4±0.0^{a}	0.17±0.01^{d}	2.90±0.01^{a}	2.30±0.07^{a}	20.61±0. 00^{a}	25.66±0.00^{ab}	2.27±0.01^{a}
Control +Beza100	148.0±0.1^{c}	71.3±0.0^{a}	40.5±0.0^{b}	126.9±0.0^{d}	106.1±0.0^{c}	0.24±0.01^{a}	1.20±0.01^{d}	0.50±0.01^{e}	8.65±0.00^{d}	19.00±0.01^{bc}	0.84±0.06^{d}
Hyperlipidemic + Beza 50 mg/kg/day	186.8±0.0^{b}	168.2±0.0^{a}	28.1±0.0^{d}	153±0.0^{b}	139.5±0.0^{b}	0.18±0.00^{cd}	1.00±0.00^{b}	2.00±0.01^{b}	15.30±0.01^{b}	20.00±0.00^{c}	1.80±0.06^{b}
Hyperlipidemic + Beza 100 mg/kg/day	183.0±0.0^{b}	168.2±0.0^{a}	30.2±0.0^{d}	143.4±0.0^{cd}	134.3±0.0^{b}	0.19±0.00^{c}	1.80±0.00^{c}	1.60±0.07^{c}	14.25±0.00^{bc}	17.66±0.00^{bc}	1.50±0.01^{c}
Hyperlipidemic + Beza 200 mg/kg/day	167.0±0.0^{bc}	137.5±0.0^{a}	34.9±0.0^{c}	133.5±0.0^{cd}	113.6±0.0^{c}	0.23±0.00^{b}	1.20±0.01^{c}	1.50±0.01^{d}	11.96±0.01^{c}	19.33±0.01^{a}	1.30±0.09^{c}

Values (mean ± S.E.) with different superscripts within each column indicate statistical significant differences between groups at 0.05

Table 3 Effect of six weeks administration of Bezafibrate on some biochemical blood parameters of hyperlipidemic rats

	Cholesterol (mg/dl)	TG (mg/dl)	HDL (mg/dl)	LDL (mg/dl)	Apo(B) (mg/dl)	NO (nmol/L)	Endothelin-1 (ng/dl)	Histamine (ng/dl)	IL-6 (pg/ml)	ALT (IU/ml)	Creatinine (mg/dl)
Control	145.0±0.0^{cd}	84.7±0.0^{d}	41.3±0.0^{a}	127.3±0.0^{c}	101.1±0.0^{d}	0.20±0.01^{b}	1.40±0.00^{a}	0.60±0.02^{e}	9.85±0.30^{cd}	11.66±0.00^{c}	0.85±0.02^{e}
Hyperlipidemic	260.8±0.0^{a}	230.3±0.0^{a}	18.2±0.0^{a}	224.8±0.0^{a}	209.2±0.0^{a}	0.14±0.00^{c}	2.20±0.00^{c}	2.40±0.09^{a}	22.34±0.17^{a}	25.66±0.00^{b}	2.27±0.00^{a}
Control +Beza100	124.0±0.0^{d}	65.7±0.0^{e}	42.3±0.0^{a}	125.9±0.0^{c}	105.1±0.0^{c}	0.24±0.01^{a}	2.00±0.00^{c}	0.60±0.01^{e}	8.70±0.24^{d}	13.66±0.01^{c}	0.85± 0.02^{e}
Hyperlipidemic + Beza 50 mg/kg/day	173.8±0.0^{b}	155.3±0.0^{b}	33.2±0.0^{a}	143.4±0.0^{b}	136.3±0.0^{b}	0.19±0.01^{b}	1.40±0.01^{a}	1.50±0.04^{b}	14.25±0.11^{b}	16.66±0.00^{b}	1.40±0.09^{b}
Hyperlipidemic + Beza 100 mg/kg/day	161.6±0.0^{bc}	148.1±0.0^{b}	35.6±0.0^{a}	133.5±0.0^{bc}	128.6±0.0^{c}	0.20±0.00^{b}	1.60±0.00^{bc}	1.30±0.01^{c}	11.96±0.06^{bc}	19.33±0.01^{a}	1.23±0.00^{c}
Hyperlipidemic + Beza 200 mg/kg/day	142.4±0.0^{cd}	127.0±0.0^{c}	37.9± 0.0^{a}	124.6±0.0^{c}	115.3±0.0^{d}	0.23±0.00^{a}	1.20±0.00^{c}	1.10±0.02^{d}	10.13±0.01^{cd}	13.33±0.01^{c}	1. 40±0.01^{d}

Values (mean ± S.E.) with different superscripts within each column indicate statistical significant differences between groups at 0.05

Such symptoms can culminate in profound impairments to vascular reactivity development of atherosclerotic lesions is often preceded by abnormalities in vascular wall reactivity. Also, Verma et al. [22] reported that, in many ways, this alteration in arterial function stems from changes in endothelial cells, highlighting one of many examples that have re-defined the endothelium as a dynamic, biologically-active organ rather than just a passive arterial lining. The importance of the endothelium in vessel reactivity and subsequent abnormalities of arterial responses has fostered the use of the term endothelial dysfunction. Importantly, endothelial dysfunction includes alterations in any of the functional roles the endothelium plays in vivo, including maintenance of normal tone, limiting thrombosis, and protecting against leukocyte adhesion. Reactivity of the arterial wall is controlled in part by biomechanical inputs, including blood flow and blood pressure. Vessel wall tone is a carefully controlled parameter regulated in part by ECs and their production and regulation of opposing signals. Endothelin-1 (ET-1) promotes blood vessel constriction, as evident with the decrease in blood flow after endothelial ET-1 release. ET-1 also induces smooth muscle cells (SMCs) proliferation. These ET-1 responses are countered by endothelial release of nitric oxide (NO), which stimulates vasodilatation, thus increasing blood flow. Endothelial nitric oxide synthase (eNOS) is the key enzymatic step in producing NO, a secondary messenger produced by EC that can inhibit NFκB activation and attenuate endothelial inflammatory responses, including adhesion molecule expression. Current models suggest that cardiovascular risk factors, including mechanical forces like hypertension and stress, shift the balance between these opposing forces, increasing ET-1 production and decreasing NO production, resulting in increased vasoconstriction, abnormal vasomotor responses and promotion of atherosclerosis.

The current data revealed that, Bezafibrate administration caused significant decrease in endothelin-1 after 2, 4 and 6 weeks, and significant increase in nitric oxide concentration after 2, 4 and 6 week when compared to hyperlipidemic non treated group. Similarly Delerive et al. [4] showed that, peroxisome proliferator-activated receptors (PPARα) had effects on both these countering endothelial limbs involving ET-1 and NO. By inhibiting the AP-1 signaling pathway noted earlier, PPARα activation has been reported to inhibit thrombin-mediated induction of ET-1. In addition, in EC the induction of ET-1 release by oxidized low-density lipoprotein (ox-LDL) is inhibited by PPARα agonists. In terms of NO, PPARα agonists reportedly enhance eNOS expression and NO release .The same results were observed by Omura et al. [13] in their study excessive NO production may enhance formation of peroxynitrite, possibly promoting oxidative stress PPARα involvement in other NO pathways has also been suggested, including inhibition of inducible nitric oxide synthase (iNOS) expression by murine effects on ET-1 expression and NO release suggest that PPARα activation may confer a vasoprotective effect to the endothelium, limiting one component of endothelial dysfunction. These responses may contribute to improvements in vascular reactivity reported in hypertriglyceridemic human subjects in response to fibrate treatment.

The present results revealed that, rats fed on hyperlipidemic diet showed a significant increase in (IL-6) and histamine as compared with control group. This results agreed with Stokes et al. [20] demonstrated that, hypercholesterolemia leads to an inflammatory response within the microvasculature, reflected by endothelial cell activation, leukocyte recruitment, rolling and adherence, as well as platelet activation and adhesion characterized.

Platelet activation can initiate leukocyte recruitment to lesion prone areas as evidenced by an increased surface CD40 expression indicative of cellular activation in hypercholesterolemia. The decreased bioavailability of NO in hyper-cholesterolemia also diminishes the anti-inflammatory properties of the endothelial cell, permitting the activity of growth factors on the cell surface and platelet activation to act as chemo attractants to parade of inflammatory events. Leukocytes begin to roll along the lumen and adhere to the cell wall, extravagating due to an increase in vascular permeability, and residing within the initial space. Monocyte chemo tactic protein-1 (MCP-1) interleukin-6 and histamine both have been found to be important in hyper-cholesterolemia patients, acting to increase monocyte recruitment and adherence which leads to wall remodeling. Also, Stapleton et al. [19] stated that macrophages, derived from monocytes, begin to accumulate LDL and oxidized LDL (oxLDL) which develops into foam cells between the basal lamina of the endothelium and the smooth muscle layer. These foam cells lead to the production of numerous inflammatory and oxidative stress markers, cytokines, chemokine, and growth factors which aggravate the balance of endothelial equilibrium leading to vascular dysfunction. The presented data revealed that, Bezafibrate administration caused significant decreased in interlukine-6 and histamine concentration after 2, 4 and 6 week when compared with hyperlipidemic group the results of the present work agreed with previous studies. These findings were in agreement with Gervois et al. [7] reported an increased plasma concentration of, bezafibrate was found to reduce IL-6and histamine an effect being attributable to the activation of the peroxisome proliferator-activated receptor (PPAR)-α with a consequent reduction of NF-κβ activation.. These discrepancies may be due to the differences in inflammatory status at baseline, duration of the study period, or the lack of control group.

Current results showed that rats on hyperlipidemic diet show a significant increase ALT activity and creatinine compared with control group. These findings were in agreement with Dohmen et al. [5] recorded that the activity of ALT was highly significantly increased in hyperlipidemic diet. Also of kidney functions (creatinine) highly significantly increased, these results may be due to increase in LDL level which is regulated by LDL receptors. We observed after bezafibrate administration in tables (1, 2 and 3) revealed that, a significant increase in ALT activity and creatinine concentration after 2, 4 and 6 week when compared to hyperlipidemic non treated group. The results of the present work agreed with Dohmen et al. [5].

The results in the current study showed that Bezafibrate administration caused Bezafibrate is a member of such fibrate class agents work as a ligand of PPARα, and also shows a potent triglyceride-lowering effect. The elevation of aminotransferase levels has been frequently observed after the administration of Bezafibrate and this phenomenon is considered to be non-pathological because Bezafibrate activates the gene expression of the aminotransferases. Recently, fibrate has been used not only for hypercholesterolemia but also for primary biliary cirrhosis (PBC). Also, the obtained are in accordance with Tsimihodimos et al. [21] recorded that, there is convincing evidence that fibrates, with the possible exception of gemfibrozil, significantly increase serum urea and creatinine levels. A significant increase in serum creatinine levels occurred after Bezafibrate (by 12%, and ciprofibrate (by 17%, administration another study [46] increase (by 6%) in serum creatinine after taking Bezafibrates. The increase in serum urea and creatinine levels were evident at the' first follow-up (mean: 6 weeks of therapy) and remained

unchanged or slightly elevated during a follow-up period of 8 months (3-18 months).

CONCLUSION AND RECOMMENDATIONS

These data suggest that Bezafibrate may act as a mixed blessing drug; therefore it must be used carefully and under physician supervision to get its therapeutic benefits and guard against its adverse

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مجلة بنها للعلوم الطبية البيطرية
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الخلل الوظيفى فى الاوعية الدموية الناتج عن أرتفاع الكوليسترول وتأثير مادة البيزافيبرات على المواد الناتجة من بطانة الاوعية الدموية

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الملخص العربى

يعتبر ارتفاع نسبة الكوليستيرول في الدم وما يصاحبه من أمراض للقلب مثل تصلب الشرايين وارتفاع ضغط الدم سمة من سمات العصر الحديث ومع التطور الحديث والسريع للحياة الذي غاب فيه ممارسة الرياضة مع الإقبال على تناول الوجبات السريعة الدسمة والتي تحتوى على نسبة عالية من الدهون والتي بدورها تسبب ارتفاع نسبة الكوليستيرول في الدم. هدفت الدراسة الحالية إلى توضيح التحويلات البيوكيماوية والهيستولوجية المحتملة ف جانب أيض الدهون وجانب وظائف الاعضاء والتي قد تنتج عن المعالجة المستمرة بالبيزافيبرات للفئران البيضاء الصحيحة وتلك التي تتميز بزيادة نسبة الدهون ف دمها عن طريق تغذيتها على مدى طويل بعليقة غنية بالدهون ومضافا إليها الكوليسترول. لقد أجريت هذه الدراسة على عدد (60) ستون من ذكور الفئران البيضاء والتي تتراوح أعمارها بين شهر وشهر ونصف وأوزانها بين 140–150 جرام، وضعت فى أقفاص حديدية مفصولة وتعايشت في نفس الظروف البيئية وظروف التربية والتغذية لمدة أسبوع قبل بدأ التجربة حيث تم تغذيتها على نفس نوع العليقة دون تمييز قسمت إلى مجموعتين: المجموعة الأولى: احتوت على مجموعتين فرعيتين بعدد (20) من ذكور الفئران البيضاء قسمت إلى: مجموعة ضابطة سلبية. مجموعة ضابطة إيجابية تم تجريعها البيزافيبرات 100مج/ كجم /اليوم. المجموعة الثانية: احتوت على أربع مجاميع فرعية بعدد (40) من ذكور الفئران البيضاء. قسمت إلى مجموعة الكوليستيرول. مجموعة الكوليستيرول + 50مج/كجم/اليوم البيزافيبرات. مجموعة الكوليستيرول + 100مج/ كجم /اليوم البيزافيبرات. مجموعة الكوليستيرول+ 200مج/ كجم /اليوم البيزافيبرات. تم تجميع العينات على ثلاث فترات بعد الأسبوع الثاني والرابع والسادس من بداية تناول البيزافيبرات وقد أوضحت الدراسة ما يلى: حدث نقص معنوى فى كل من الكوليستيرول الكلى، الكوليستيرول المنخفض الكثافة في حين حدث زيادة معنوية فى الكوليستيرول العالى الكثافة و فى تركيز النيترك أو كسيد وجد أيضا نقص معنوي فى(APO–B) وتركيز الجليسريدات الثلاثية و في (endothelin–1) والهيستامين و إنترلوكين 6 و في تركيز أنزيم الALT و في تركيز الكرياتنين بالمقارنة بمجموعة الكولسترول.

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