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Effect Of Atorvastatin And Fenofibrate Versus Mononuclear Cells On Histopathology And Oxidative Markers In Liver Of Streptozotocin Induced Diabetic Rats.

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ABSTRACT

Diabetes mellitus is a major concern to the public health, it causes serious life-threatening complications on body organs including the liver. In this study we evaluate and compare the effects of atorvastatin, fenofibrate and human umbilical cord derived mononuclear cells on the liver of streptozotocin induced diabetic rats. The study included 35 rats divided into 5 groups included normal control group, diabetic control group, atorvastatin treated diabetic group, fenofibrate treated diabetic group, mononuclear cells treated group. Several investigations were done at the different time intervals including body weight, blood pressure, blood sugar, lipid profile and after sacrifice liver histopathology and glutathione level. The results of the study showed that mononuclear cell injection caused significant improvement of all parameters measured compared to diabetic control and drug treated groups (p value<0.5) concluding that human umbilical cord blood mononuclear cells can be a promising treatment to liver injury caused by diabetes mellitus.

Keywords: fenofibrate, atorvastatin, mononuclear cells, liver, rats, diabetes mellitus.

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INTRODUCTION

Diabetes mellitus is a major concern to the public health all over the world, its prevalence is increasing day by day. By the end of 2030, diabetes mellitus will be the seventh leading cause of death in the world [1]. it is the cause of severe tissue damage and has long term complications on body tissues and organs as liver and kidney [2]. High blood sugar causes glucose auto-oxidation with formation of reactive oxygen species (ROS). Hyperlipidemia may speed production of reactive oxygen species (ROS) by increasing level of nicotinamide adenine dinucleotide phosphate (NADPH) oxidases and through stimulating breakdown of the transport chain of mitochondria of the cell [3]. The structure of Fenofibrate is fibric acid which is linked to an ester of isopropyl... It decreases level of blood lipids through activation of peroxisome proliferator activated receptor alpha (PPARα). The PPARα in turn causes active of the enzyme lipoprotein lipase and decreases apoprotein CIII, this causes increase lipid breakdown through the process of lipolysis together with decrease level of triglycerides in blood [4].

Atorvastatin is an inhibitor of 3-hydroxy-3-methylglutaryl coenzyme A reductase, it decreases the level of cholesterol in blood and prevent coronary heart disease [5].

Human umbilical cord blood mononuclear cells (hUCBMNCs) have various types of stem cells however they have no or little immunogenic cells, and they can be separated from the blood of umbilical cord of human in a convenient and easy way [7]. They have been studied and reported for their effect on many diseases as renal fibrosis [8].

The deterioration of liver injury and failure is caused by severe inflammatory processes caused by many factors such as hyperglycemia, whether hUCBMNCs treatment is a promising method that can be used in case of liver injury in diabetes needs to be studied.

In this study we studied and compared effect of fenofibrate and atorvastatin versus human umbilical cord blood mononuclear cells transplantation on the liver and metabolic parameters of rats with streptozocin induced diabetes.

MATERIALS AND METHODS

Animals

A 35 adult male albino rats were included in this study which were further subdivided into 5 groups. Weight of each rat approximately 150 grams ±20 and were purchased from Research Centre in Cairo. All animals were fed standard animal diet and water and were housed in spacious wire mesh cages in suitable room temperature and humidity.

Drugs

- Citrate buffer saline (the vehicle for streptozotocin) intraperitoneal injection.
- Human umbilical cord blood (HUCB) mononuclear cells 150 x 10^6 cells/rat via tail vein.
- Streptozotocin 65 mg/kg intraperitoneal injection.
- Fenofibrate and atorvastatin, the vehicle is distilled water.

All drugs were purchased from Sigma pharmaceuticals

Experimental design

Type of the study: An experimental study.

Study site: Suez Canal University, Faculty of medicine, Pharmacology department.

Mode of induction of diabetes in rats

Type I diabetes was induced by a single dose of streptozotocin via intraperitoneal injection (65 mg/Kg of body weight) in 0.15 ml. saline together with 1 ml. Na citrate buffer.

Rats fasted for 12-h before induction of diabetes by streptozotocin. Streptozotocin was freshly prepared in 0.05 M citrate buffer, pH 4.5. rats with fasting blood sugar exceeding 200 mg/dl measured one week after induction of diabetes were considered diabetic and were included in the study.

Collection and preparation of human cord blood (8)

Human cord blood was collected from placentas of full-term neonate after delivery and after consent of the mother. Samples of blood were collected in a 50 ml sterile test tube which contain 5 ml of citrate phosphate dextrose which was used as anticoagulant in this experiment. Volume of blood collected from every placenta range from 20 to 40 ml. blood samples were stored at 4 °C in a blood bank refrigerator. Blood samples were placed in a 15 ml disposable centrifuge test tube and the mononuclear cells were separated from the whole cord blood by Ficoll–Hypaque density gradient centrifugation.

After separation of mononuclear cells, the viability and counting of the cells were done, 0.2 ml of phosphate buffer saline solution was added for final dilution preparing for injection into the tail vein of rats.

Study groups

The rats (35 rat) were divided into the following study groups, each group included 7 rats.

Group 1: Control group: Normal rats which received only the vehicle citrate buffer via intraperitoneal injection once.

Group 2: Diabetic untreated group: Diabetic untreated rats.

Group 3: Diabetic group treated with fenofibrate;(9) Diabetic rats received fenofibrate (100mg/kg/day) oral (by gavage) starting one week after induction of diabetes. Treatment continued for 8 weeks.

Group 4: Diabetic group treated with atorvastatin. Diabetic rats received atorvastatin (10 mg/kg/day) oral one week after induction of diabetes.

Group 5: Diabetic group treated with mononuclear stem cells after induction of diabetes: Diabetic rats received human umbilical cord blood (HUCB) 150 x 10^6 cells/rat) via tail vein one week after the STZ injection.

Methods

After eight weeks from induction of diabetes, all rats of all study groups were killed under ether anesthesia.

Liver and kidney were removed and weighed then fixed in formalin for further histopathological studies.

Metabolic data

All the following investigations were done at the start of the study then after one week,4 and 8 weeks from induction of diabetes:

- The weights of the rats were measured and recorded.
- Then blood samples were taken via the tail vein of rats after 12 hours fasting,
- Blood glucose level was measured using glucose oxidase method
- The following were measured at the beginning of the study, after 4 weeks and after 8 weeks:Lipid profile.
- Systolic BP (SBP) was measured by tail-cuff plethysmography in conscious prewarmed rats.

The following was done at the end of the study

Liver histopathology After sacrifice and dissection, livers of the rats were removed and fixed in 10% neutral phosphate-buffered formalin for 24 hours. For proper examination of the liver, the sections of the liver were mounted on slides, dewaxed, and stained with hematoxylin and eosin (H&E) [11]. The examinations were carried out using a light electric microscope.

Determination of GSH-Px One small section (200 mg) of liver was removed from the rats and weighed. Subsequently, saline was added according to the tissue weight: Saline volume=1:9 (w/v). then homogenization was done at 4°C by a DY89-I electric homogenate (Ningbo Scientz Biotechnology Co., Ltd., Ningbo, China), the homogenates were then centrifuged at 1,100xg for 15 min at room temperature., GSH-Px (glutathione perioxidase) levels were determined by using commercially available kits, according to manufacturer's protocol..

Ethical approval

The protocol of research study and steps of handling experimental animals was approved by research ethical committee in faculty of medicine portsaid university and was done corresponding to the "Guide for the care and use of Laboratory Animals" for handling and use of animals in research experiments, which was published in the US National Institutes of Health (NIH publication No. 85–23, 1996) and in the Ethics considering the animal experiments [10].

Statistical analysis

Statistics and mathematical calculations will be carried out using SPSS 22. The findings and results of the data will be shown as means ± SD. Oneway ANOVA with Tukey-Kramer tests can be used to compare between different groups of the study.

RESULTS

Body weight in mononuclear cells treated group was significantly higher than diabetic untreated group and groups treated with either fenofibrate or atorvastatin which were significantly lower than normal group as shown in table 1.

Table 1: Comparison between the effect of fenofibrate, atorvastatin and mononuclear cells on body weight of diabetic rats (mg)

Study group	0 week	4 weeks	8 weeks
normal	170±20	220±32	260±30
Diabetic untreated	170±20	140±10 (a ,c)	110±14 (a ,c)
Fenofibrate treated	170±20	177±13(a,c,b)	180±22(a,b,c)
Atorvastatin treated	170±20	180±10(a,b,c)	185±15(a,b,c)
Mononuclear cells treated	170±20	230±32(b)	265±25(b)

(a) $P < 0.05$ significantly different from Normal group.
(b) $P < 0.05$ significantly different from Diabetic group.
(c) $P < 0.05$ significantly different from Diabetic +Mononuclear cells group.
*Each value represents the mean± SD (standard deviation)

Blood glucose level (mg/dl)measured in the diabetic groups treated with either fenofibrate 0r atorvastatin was significantly lower than in the control diabetic group, but it was significantly higher than normal group or mononuclear cell treated group which showed non significant difference compared to normal (Table 2).

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Table 2: comparison between blood glucose level in study groups(mg/dl)

Studied groups	After 4 weeks	After 8 weeks
Normal	90±10	90±10
Diabetic	255±15a	280±10a
Diabetic + Fenofibrate	220±10 a, b,c	220±15 a, b,c
Diabetic + atorvastatin	210±15 a,b, c	225±20 a,b, c
Diabetic +mononuclear cells	100±10 b	90±10 b

(a) P < 0.05 significantly different from Normal group.
(b) P < 0.05 significantly different from Diabetic group.
(c) P < 0.05 significantly different from Diabetic +Mononuclear cells group.
*Each value represents the mean± SD (standard deviation)

The control diabetic group had significantly higher systolic blood pressure than normal control and treated groups. However the group treated with mononuclear cells had significantly lower systolic blood pressure than the groups treated with either fenofibrate or atorvatstin (Table 3).

Table 3: comparison between systolic blood pressure in study groups(mg Hg)

Studied groups	Systolic blood pressure after 4 weeks(mmHg)	Systolic blood pressure after 8 weeks(mmHg)
Normal	116±10	115±8
Diabetic	149±20 a	155±10a
Diabetic +fenofibrate	136±11a, b ,c	133±8 a, b ,c
Diabetic + arorvastatin	135±9a, b ,c	130±12 a, b ,c
Diabetic + mononuclear cells	110±5 b	111±8 b

(a) P < 0.05 significantly different from Normal group.
(b) P < 0.05 significantly different from Diabetic group.
(c) P < 0.05 significantly different from Diabetic +Mononuclear cells group.
*Each value represents the mean± SD (standard deviation)

All the diabetic treated groups (either fenofibrate or atorvastatin or mononuclear cells) had significantly lower cholesterol than the untreated control diabetic group. However the group treated with mononuclear cells had significantly lower cholesterol than other treated groups and nonsignificant difference compared to normal group (Table 4).

Table 4: Comparison between total cholesterol level in study groups(mg/dl)

Studied groups	Total cholesterol (mg/dL)	Total cholesterol (mg/dL)
Normal	133±11	135±10
Diabetic	235±22a ,c	250±15 a ,c
Diabetic + fenofibrate	153± 10a, b ,c	150±11 a, b ,c
Diabetic + atorvastatin	152±12 a, b,c	150±11 a, b,c
Diabetic + mononuclear cells	130±11 b	132±11 b

(a) P < 0.05 significantly different from Normal group.
(b) P < 0.05 significantly different from Diabetic group.
(c) P < 0.05 significantly different from Diabetic + Mononuclear cells group.
*Each value represents the mean± SD (standard deviation)

Groups treated with either fenofibrate, atorvastatin or mononuclear cells had significantly lower serum triglycerides than the control diabetic group as shown in table 4.

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Table 5: comparison between serum triglycerides in study groups (mg/l)

Studied groups	Triglycerides (mg/L)	Triglycerides (mg/L)
Normal	140±5	146±5
Diabetic	230±20 a ,c	250±15 a ,c
Diabetic + fenofibrate	140±11 b	140±10 b
Diabetic + atorvastatin	144±12 b	145±15 b
Diabetic + mononuclear cells	140±10 b	145±10 b

(a) P < 0.05 significantly different from Normal group.
(b) P < 0.05 significantly different from Diabetic group.
(c) P < 0.05 significantly different from Diabetic +Mononuclear cells group.
*Each value represents the mean± SD (standard deviation)

All the study treated groups had significantly lower level of low-density lipoprotein and significantly higher high density lipoprotein than the control diabetic group and non significant difference treated with normal group (Table 5 and 6).

Table 6: Comparison between LDL level in study groups(mg/dl)

Studied groups	LDL after 4 weeks (mg/L)	LDL after 8 weeks(mg/dL)
Normal	73±7	75±5
Diabetic	165±11 a	180±10 a
Diabetic + fenofibrate	88±5 a, b	80±15 a, b
Diabetic + atorvastatin	86±9 a, b	82±10 a, b
Diabetic + mononuclear cells	85±8 a, b	80±5a, b

(a) P < 0.05 significantly different from Normal group.
(b) P < 0.05 significantly different from Diabetic group.
(c) P < 0.05 significantly different from Diabetic +Mononuclear cells group.
*Each value represents the mean± SD (standard deviation)

Table 7: Comparison between level of HDL in study groups

Studied groups	HDL after 4 weeks (mg/L)	HDL after 8 weeks (mg/dL)
Normal	54±4	55±3
Diabetic	34±2a	34.67±0.96 a
Diabetic + fenofibrate	45± 5a, b	45±3a, b
Diabetic + atorvastatin	45±7 a, b	46±6 a, b
Diabetic + mononuclear cella	50±3b	51±4 b

(a) P < 0.05 significantly different from Normal group.
(b) P < 0.05 significantly different from Diabetic group.
(c) P < 0.05 significantly different from Diabetic +Mononuclear cells group.

The level of glutathione in liver of study groups was significantly lower in diabetic group and significantly higher in all treated groups than the control diabetic group and non significant difference between treated and normal group.

Table 8: GSH level in liver of study groups

Studied groups	GSH (mu mol/l)
Normal	3.25±0.5
Diabetic	1.51±0.1 a
Diabetic + fenofibrate	3.11±0.4 b
Diabetic + atorvastatin	3.32±0.2 b
Diabetic + mononuclear cellsb	3.34±0.2b

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(a) P < 0.05 significantly different from Normal group.
(b) P < 0.05 significantly different from Diabetic group.
(c) P < 0.05 significantly different from Diabetic +Mononuclear cells group
*Each value represents the mean± SD (standard deviation)

Histopathology study of the liver showed preserved architecture with regular hepatocytes showing eosinophilic cytoplasm and normal central vein with patent sinusoids in normal control group whereas the diabetic control group showed liver tissue partially disrupted architecture with hepatocytes showing degenerative changes and steatosis and dense cytoplasm and congested dilated central vein . In fenofibrate treated group there is marked improvement with mostly preserved architecture with hepatocytes showing minimal degenerative changes and mildly congested dilated central vein with patent sinusoids architecture whereas in atorvastatin treated group hepatocytes showed degenerative changes and dense cytoplasm and congested dilated central vein with lymphocytic inflammatory cell infiltrate.

In mononuclear cells treated groups there is marked improvement with mostly preserved architecture with hepatocytes showing minimal degenerative changes and mildly congested dilated central vein with patent sinusoids (fig 1:5).

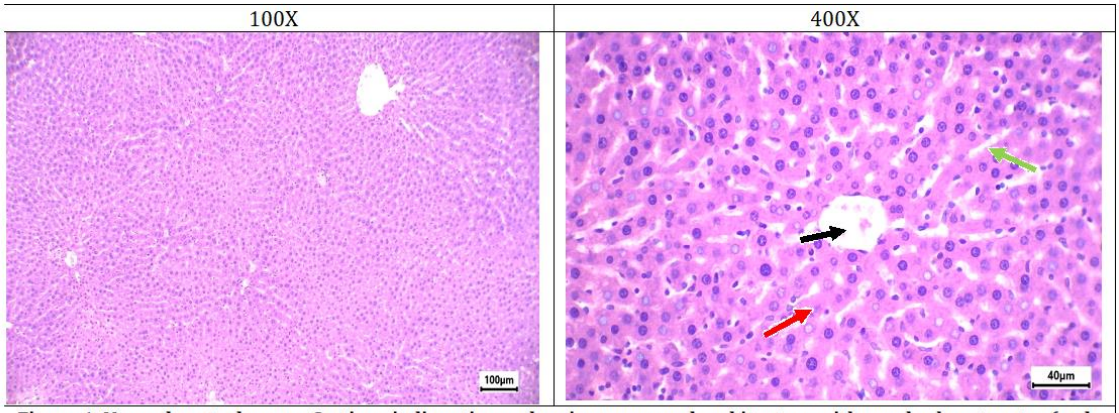

Figure 1: Normal control group: Sections in liver tissue showing preserved architecture with regular hepatocytes (red arrow) showing eosinophilic cytoplasm and normal central vein (black arrow) with patent sinusoids (green arrow)

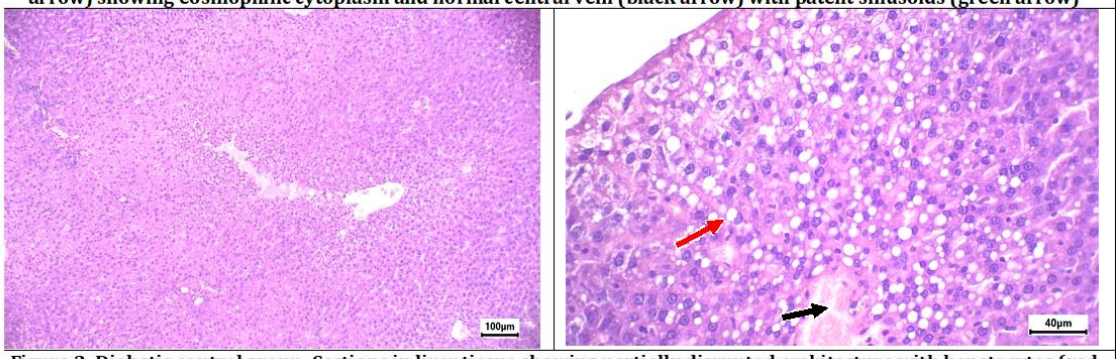

Figure 2: Diabetic control group: Sections in liver tissue showing partially disrupted architecture with hepatocytes (red arrow) showing degenerative changes and steatosis and dense cytoplasm and congested dilated central vein (black arrow)

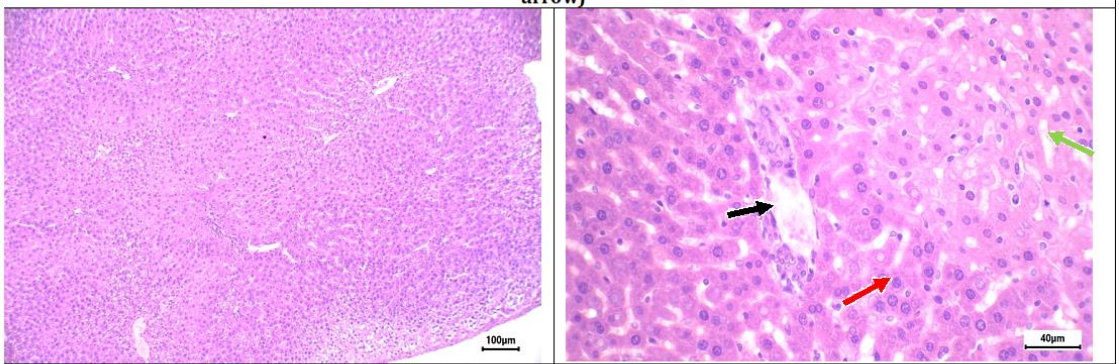

Figure 3: Fenofibrate treated group: Sections in liver tissue showing marked improvement with mostly preserved architecture with hepatocytes (red arrow) showing minimal degenerative changes and mildly congested dilated central vein (black arrow) with patent sinusoids (green arrow)

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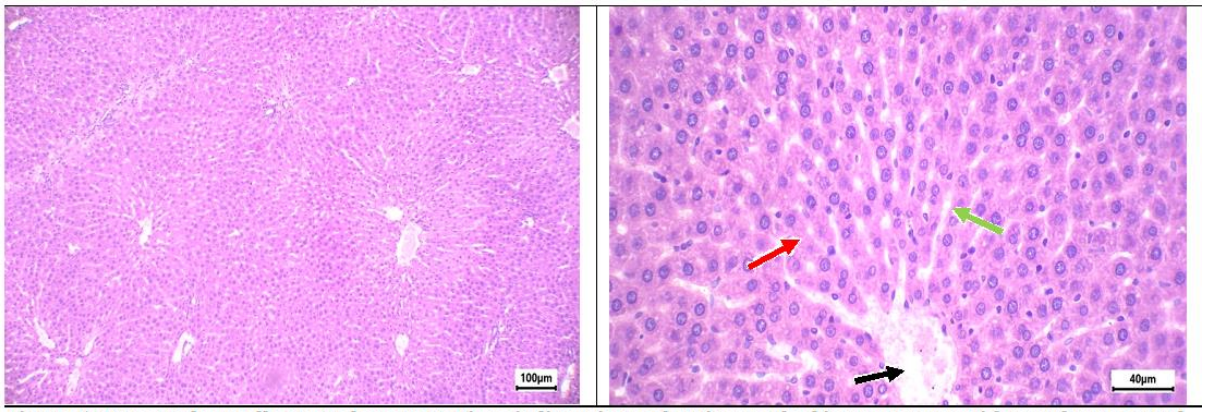

Figure 5: Mononuclear cells treated group:Sections in liver tissue showing marked improvement with mostly preserved architecture with hepatocytes (red arrow) showing minimal degenerative changes and mildly congested dilated central vein (black arrow) with patent sinusoids (green arrow)

All Images captured using:

- Calibrated standard digital microscope camera (Tucsen® ISH100, Fuzhou, China) using Olympus® CX23 (Japan) microscope, with resolution of 10 MP (megapixels) 3656 x 2740 pixel.
- "IS Capture" software for capture and image enhancements.

All H&E-stained slides captured at original magnification 100x and 400x, (Objectives 10x and 40x respectively), UIS optical system (Universal Infinity System, Olympus®, Japan).

DISCUSSION

In this study we found decreased body weight in diabetic group and body weight tend to increase in fenofibrate and atorvastatin group and was higher in mononuclear cell treated group. In a study by Mohamadin and coworkers [12], they studied the effect of statin on oxidative stress in STZ-induced diabetic rats. They found decreased body weight in diabetic rats compared to normal control rats. In the group treated with statin there was increase in body weight compared to diabetic control group.

The present study agrees with Olukman et al [13] who found that finofibrate group did not cause decrease decrease blood glucose levels in diabetic rats and also supported by the study of Kadian et al(14), who studied the the effect of fenofibrate in diabetes. They found a marked increased blood level of glucose in diabetic group compared to normal group.

In this study we found increased systolic blood pressure (SPB) (mmHg) diabetic group and treated groups was lower but mononuclear cells was significantly lower than diabetic groups.

The increase in systolic blood pressure in diabetic group can be explained by the fact that cardiovascular system is deteriorated in diabetic rats [15]. Another study investigated [16] the effect of statins on cardiovascular system of diabetic rats. They found that SBP was higher in diabetic group, and there was a significant reduction in SBP in all statin groups. They assumed that decease of systolic blood pressure may be caused by decrease peripheral resistance due to improvement in endothelial function.

The lipid profile in diabetic control group was significantly increase in TC, TG and LDL and significant decreased in HDL-C when compared to other study groups, the lipid profile was improved in all treated groups and completely improved in mononuclear cell treated group.

In a study by Carmona et al. [17] they found that fenofibrate decreased serum triglyceride, and decreased total cholesterol levels. In a study by Kadian et al [18] stated that there was a significant increase in serum cholesterol and decrease in HDL observed in diabetic rats when compared to normal.

In the present study we found a significant decrease in GSH level in diabetic rats when compared to normal or treated groups

The present study agrees with Mohamadin et al [12] who found decrease level phospholipid hydroperoxide glutathione (GSH-Px) during diabetes. Treating diabetic rats with statin caused marked improvement of antioxidant enzyme activities.

In our study we found that treating diabetic rat with monunclear cells caused significant improvement of antioxidant enzymes compared to other study groups and non significant difference compared to normal group indicating marked improvement.

It is reported that treatment with cell therapies lead to tremendous opportunities for serious diseases and tissue injuries [19]. This lead to emerging science of regenerative medicine, which give the opportunity and the potential to treat several previously uncurable diseases [20].

In our study, we found that treatment with mononuclear cells proved to have a protective role on the liver by increasing antioxidant activity of the liver. Cell therapy as an emerging therapeutic strategy can be used for several intractable liver injuries, such as acute liver injury, acute-on-chronic liver failure [21].

It is stated that these cells can successfully reach the liver after intravenous injection in the mice [22].

In this study, we have no evidence that these cells could migrate to the liver , and we will perform this in a further study with cell labeling and tracking techniques. Therefore, human umblical cord blood mononuclear cells treatment can provide an alternative therapy in future clinical practice. The underlying mechanism for improving diabetic complications needs to be further explored.

CONCLUSION

This study proved that mononuclear cells treatment of diabetic rat caused reversal of diabetic complication on the liver and there was nonsignificant difference compared to normal in all parameters measured whereas treatment with fenofibrate or atorvastatin did not cause significant increase in body weight or decreased blood glucose of diabetic group compared to normal, but there was a significant decrease in blood pressure, lipid profile, and level of antioxidant (GSH) in the liver . The histopathological changes of the liver showed marked improvement of liver with mostly preserved architecture and hepatocytes in mononuclear cells treated group and only partial improvement in fenofibrate or atorvastatin group. These finding suggest that treatment with mononuclear cells is a promising and more effective alternative to other antihyperlipedimic drugs in treating liver complications in diabetes mellitus.

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