



ORIGINAL ARTICLES

Evaluation of Therapeutic Potential of Atorvastatin against Diabetic Retinopathy: A Biochemical Histopathological Study

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ABSTRACT

The aim of the present work is to investigate the potential retinal neuroprotective effects of atorvastatin in a diabetic hypercholesterolemic animal model in rats and the possible development of hepatotoxicity as a drug adverse effect. Twenty four albino Wistar rats of both sexes were used and divided into four groups; two groups (I and II) served as controls. In group III, diabetes was induced by a single intraperitoneal injection of alloxan 120 mg/kg. Hypercholesterolemia was also induced by addition of cholesterol to the animal diet (10 grams cholesterol/ 1kg diet). In group IV, diabetes and hypercholesterolemia were induced and rats received atorvastatin in a dose of 5 mg/kg daily orally for two months. Serum levels of glucose, cholesterol, triglycerides, total antioxidants, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were measured after 1 and 2 months. Then, animals were sacrificed and subjected to light microscopic examination of the retina and liver. Untreated diabetic hypercholesterolemic animals exhibited significant deterioration of the measured biochemical parameters; elevation of serum levels of glucose, cholesterol, triglycerides, ALT and AST and significant decrease in serum total antioxidants in addition to marked histopathological changes of the retina and liver. Treatment with atorvastatin in group IV improved significantly the diabetes-induced deterioration of serum cholesterol, triglyceride and total antioxidants together with significant improvement of retinal histopathological picture as compared to untreated model of group III suggesting its protective role against diabetic retinopathy. However, there was insignificant effect on the AST serum level and the histopathological picture of the liver in addition to significant deterioration of serum level of ALT when comparing group IV with group III. In conclusion, atorvastatin can partially protect the retina against the development of diabetic retinopathy but care should be taken as regards the hepatotoxic effect of the drug.

Key words: Atorvastatin, HMG-CoA reductase inhibitors, experimental diabetes and hypercholesterolemia, diabetic retinopathy, biochemical analysis, histopathological examination.

Introduction

Statins are a group of drugs approved for their cholesterol reduction properties and are commonly used to treat atherosclerosis and coronary artery disease (Kohno, 2007). These drugs inhibit 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, the rate limiting enzyme in cholesterol biosynthesis, which converts HMG-CoA to mevalonate. Apart from cholesterol, mevalonate is also the substrate for the synthesis of nonsteroid isoprenoids such as coenzyme Q. Depletion of these isoprenoids results in the so called pleiotropic effects of statins which are independent of cholesterol lowering effect (Beltowski, 2009). These pleiotropic actions include anti-inflammatory, anti-apoptotic and anti-proliferative effects. In addition, data from experimental and observational studies indicated that statins have neuroprotective effects and can be a treatment option for neurodegenerative diseases of the central nervous system and the ocular structures particularly the retina (Schmeer, 2007).

Diabetic retinopathy is a common and potentially devastating microvascular complication in diabetes and is a leading cause of acquired blindness among people of occupational age. However, therapeutic options for the treatment of proliferative diabetic retinopathy, photocoagulation and vitrectomy, are limited by considerable side effects. Therefore, development of novel therapeutic strategies that specially target diabetic retinopathy is desired in patients with diabetes (Yamagishi, 2006). Development of diabetic retinopathy involve a group of complex interrelated mechanisms such as oxidative stress, angiogenesis and the formation of advanced glycation end products (AGEs) (Brownlee, 2001). Statins were reported to possess antioxidant effects. Simvastatin treatment caused reduction of oxidative stress and improvement of renal endothelial function in a model of obesity and hypertension in rats (Knight, 2010). In addition, atorvastatin could improve endothelial dysfunction and reduce markers of oxidative stress in patients with diabetes mellitus (Usharani, 2008). Statins

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were also reported to inhibit angiogenesis in both in vivo and in vitro studies (Park, 2002). Interaction of AGEs with their receptors is involved in the development and progression of diabetic retinopathy. Statins interfere with AGE receptor signaling and therefore prevent the damaging effects of AGEs in various tissues (Yamagishi, 2006).

Statins are a generally safe class of drugs that are widely used throughout the world and are rarely associated with severe adverse effects. Hepatotoxicity is one of the major complaints that occur during lipid-lowering therapy with statins. Transient elevation of serum transaminases occurs in up to 3% of patients using statins but is usually self-limiting and without serious consequences (Clarke, 2006). Drug-induced liver injury from statins typically presents with an acute hepatocellular liver injury pattern, although mixed or cholestatic injury pattern have also been reported. Nonspecific autoantibodies as well as features of autoimmune-like hepatitis may be present in some patients. In addition, acute liver failure and death rarely occur in patients with statin hepatotoxicity (Russo, 2009).

The aim of the present work is to investigate the potential retinal neuroprotective effects of atorvastatin in a diabetic hypercholesterolemic animal model in rats and the possible development of hepatotoxicity as a drug adverse effect. Determination of serum levels of glucose, cholesterol, triglycerides, total antioxidants, alanine aminotransferase (ALT) and aspartate aminotransferase, (AST) was performed together with light microscopic examination of the retina and liver.

Materials and Methods

Induction of Animal Model of Diabetes and Hypercholesterolemia:

Wister rats were injected intraperitoneally with a single dose of 120 mg/kg alloxan (Sigma, Germany). The blood glucose level was measured after 48 hours to insure the development of hyperglycemia. Hypercholesterolemia was induced by addition of cholesterol (Oxford Laboratories, Mumbai) to the animal diet (10g cholesterol/1kg diet) which started 48 hours after injection of alloxan and continued throughout the duration of the experiment (two months) (Mathe, 1995).

Animal Groups:

Twenty four Albino Wistar rats of both sexes weighing 140-150 grams were used. They were housed individually in separate cages under veterinary supervision. They were used in accordance with institutional guidelines and with the statement for use of animals in ophthalmic and vision research. They were fed with the standard diet (with the added cholesterol) and water for two months and kept in 12 hours dark/light cycles under controlled temperature and humidity. Animals were divided into four groups each consisting of six rats.

A- Control Groups:

Group I. The animals received an equivalent volume of distilled water once daily by means of a stomach tube (negative control).

Group II. The animals received atorvastatin (Ator from EIPICO, Egypt) in a dose of 5 mg/kg daily orally by means of a stomach tube for two months (positive control).

B- Diabetic hypercholesterolemic Model Groups:

Group III. Diabetic hypercholesterolemic model was induced and the animals were left untreated.

Group IV. Diabetic hypercholesterolemic model was induced and the animals received atorvastatin in a dose of 5 mg/kg daily orally by means of a stomach tube starting 48 hours after induction of diabetes and continued for two months.

Biochemical Analysis:

Serum glucose (Siest, 1981), cholesterol (Allain, 1974), triglycerides (Buccolo, 1973), total antioxidants (Koracevic, 2001), ALT (Murray, 1984) and AST (Murray, 1984) levels were measured enzymatically by colorimetric methods (at the 1st and 2nd months of the experiment) using kits obtained from Biodiagnostic (Egypt) for glucose and total antioxidants, Linear Chemicals (Spain) for serum lipids and Diamond Diagnostics (Germany) for ALT and AST.

Histopathological Examination:

Histopathological examination was carried out according to Drury and Wallington (Drury, 1980). After two months, the eyes were enucleated, dissected and immediately double fixed in 4% glutaraldehyde buffer, then 1.3% osmium tetroxide in phosphate buffer (pH 7.3). Retinal specimens were processed and embedded in araldite Cy 212. Semi-thin sections were stained with toluidine blue (TB). Specimens of liver tissue were also collected, processed for paraffin sections and stained by haematoxyline and eosin (Hx&E). Slides were examined by Olympus light microscope and photographed by Olympus camera.

Statistical Analysis:

Values of serum levels of glucose, cholesterol, triglycerides, total antioxidants, ALT and AST were expressed as mean \pm SD. Analysis of variance (ANOVA) and student t test were performed to compare the values between groups. A post-hoc test was used to isolate significant differences if ($P < 0.05$).

Results:

Biochemical Analysis:

The mean glucose, cholesterol, triglycerides, total antioxidants, ALT and AST serum levels (at the 1st and 2nd months) are showed in Tables (1, 2, 3, 4, 5 and 6 respectively). Control rats (groups I and II) showed normal values of the estimated parameters which were not significantly changed all through the duration of the experiment.

Regarding induction of diabetic hypercholesterolemic model in group III, rats exhibited deterioration in the tested parameters. The mean blood glucose level increased significantly to 166.50 ± 13.74 and 157.83 ± 19.82 mg/dl at the 1st and 2nd months respectively (Table 1). In addition, cholesterol serum level increased to 101.67 ± 12.55 and 105.33 ± 14.58 mg/dl (Table 2) while triglyceride level reached 171.67 ± 14.72 and 185.00 ± 18.71 mg/dl (Table 3) at the 1st and 2nd months respectively. As for serum total antioxidant level, it was also decreased to 0.66 ± 0.16 and 0.67 ± 0.15 mg/dl 1st and 2nd months respectively (Table 4). Hepatic enzymes also increased significantly to 26.33 ± 2.88 and 32.67 ± 7.99 for ALT and 36.50 ± 8.53 and 34.17 ± 9.91 for AST at the 1st and 2nd months respectively (Tables 5 and 6). All these values were significantly higher than the control values.

After treatment of diabetic hypercholesterolemic rats with atorvastatin (group IV), it was observed that the serum glucose levels were still markedly elevated to 154.17 ± 12.95 and 150.33 ± 18.04 mg/dl at the 1st and 2nd months respectively. They were still significantly higher than control group values with insignificant difference from untreated model after 1 and 2 months (Table 1). On the other hand, serum cholesterol and triglyceride levels were significantly improved in animals treated with atorvastatin as compared to the untreated model. Cholesterol levels reached 60.00 ± 9.08 and 66.67 ± 10.25 mg/dl at the 1st and 2nd months respectively with insignificant difference from control levels (table 2). As for serum triglyceride level, it reached 78.33 ± 26.39 and 69.50 ± 19.31 ; it was still significantly higher than control values after 1 month and insignificantly different from control level after 2 months (Table 3). Moreover, group IV showed markedly improved serum total antioxidant levels reaching values that were significantly higher than the untreated model values and insignificantly different from control group values. These values were 1.14 ± 0.34 and 1.23 ± 0.18 mg/dl at the 1st and 2nd months respectively (Table 4). Regarding hepatic enzymes in group IV, ALT serum levels were 30.83 ± 3.87 and 39.17 ± 3.97 (Table 5) while AST serum levels were 35.00 ± 9.98 and 35.50 ± 8.24 (Table 6) at the 1st and 2nd months respectively. Serum enzyme levels were significantly higher than control values after 1 and 2 months in rats treated with atorvastatin. Moreover, compared to untreated diabetic hypercholesterolemic model, atorvastatin caused more significant deterioration of ALT but not AST serum levels (Tables 5 and 6).

Histopathological Examination:

Examination of the retina:

The histological examination of the retinas of rats of negative controls (group I) showed the normal layers of the retina (Fig. 1). In addition, the retinas of rats of group II treated with atorvastatin (positive control) appeared fairly normal. Light microscopic examination of the retinas of diabetic hypercholesterolemic rats (group III) revealed significant histopathological changes. There were increased phagosomes and vacuoles in the retinal pigment epithelium. Both the outer and inner nuclear layers showed significant edema. Dilated blood capillaries were seen in the ganglion cell layer. Lucent cytoplasm and coalescence of adjacent cell membranes of ganglion cells was also apparent (Fig. 2). Diabetic hypercholesterolemic animals treated with atorvastatin (group IV) exhibited protection of the retina against the histopathological changes observed in group III.

Table 1: Mean levels (\pm SD) of serum glucose at the 1st and 2nd months of the experiment in group I (negative controls), group II (positive controls receiving 5mg/kg/day atorvastatin orally for 2 months), group III (untreated diabetic hypercholesterolemic model) and group IV (diabetic hypercholesterolemic model treated with 5mg/kg/day atorvastatin orally for 2 months).

Groups	Group I	Group II	Group III	Group IV
Mean \pm SD after 1 months	73.50 \pm 12.01	75.17 \pm 10.30	166.50 \pm 13.74	154.17 \pm 12.95
P1		0.817	0.000*	0.000*
P2				0.098
Mean \pm SD after 2 months	74.67 \pm 10.76	75.67 \pm 10.46	157.83 \pm 19.82	150.33 \pm 18.04
P1		0.911	0.000*	0.000*
P2				0.408

Data are expressed as mean \pm SD; n = 6; * Significant difference at p < 0.05; P1 compared to group I; P2 compared to group III.

Table 2: Mean levels (\pm SD) of serum cholesterol at the 1st and 2nd months of the experiment in group I (negative controls), group II (positive controls receiving 5mg/kg/day atorvastatin orally for 2 months), group III (untreated diabetic hypercholesterolemic model) and group IV (diabetic hypercholesterolemic model treated with 5mg/kg/day atorvastatin orally for 2 months).

Groups	Group I	Group II	Group III	Group IV
Mean \pm SD after 1 months	62.50 \pm 12.10	55.67 \pm 5.99	101.67 \pm 12.55	60.00 \pm 9.08
P1		0.263	0.000*	0.678
P2				0.000*
Mean \pm SD after 2 months	59.67 \pm 9.11	56.00 \pm 15.33	105.33 \pm 14.58	66.67 \pm 10.25
P1		0.620	0.000*	0.348
P2				0.000*

Data are expressed as mean \pm SD; n = 6; * Significant difference at p < 0.05; P1 compared to group I; P2 compared to group III.

Table 3: Mean levels (\pm SD) of serum triglycerides at the 1st and 2nd months of the experiment in group I (negative controls), group II (positive controls receiving 5mg/kg/day atorvastatin orally for 2 months), group III (untreated diabetic hypercholesterolemic model) and group IV (diabetic hypercholesterolemic model treated with 5mg/kg/day atorvastatin orally for 2 months).

Groups	Group I	Group II	Group III	Group IV
Mean \pm SD after 1 months	52.50 \pm 13.32	50.00 \pm 16.73	171.67 \pm 14.72	78.33 \pm 26.39
P1		0.817	0.000*	0.025*
P2				0.000*
Mean \pm SD after 2 months	51.00 \pm 16.26	59.50 \pm 13.30	185.00 \pm 18.71	69.50 \pm 19.31
P1		0.398	0.000*	0.075
P2				0.000*

Data are expressed as mean \pm SD; n = 6; * Significant difference at p < 0.05; P1 compared to group I; P2 compared to group III.

Table 4: Mean levels (\pm SD) of serum total antioxidants at the 1st and 2nd months of the experiment in group I (negative controls), group II (positive controls receiving 5mg/kg/day atorvastatin orally for 2 months), group III (untreated diabetic hypercholesterolemic model) and group IV (diabetic hypercholesterolemic model treated with 5mg/kg/day atorvastatin orally for 2 months).

Groups	Group I	Group II	Group III	Group IV
Mean \pm SD after 1 months	1.38 \pm 0.31	1.37 \pm 0.29	0.66 \pm 0.16	1.14 \pm 0.34
P1		0.926	0.000*	0.142
P2				0.007*
Mean \pm SD after 2 months	1.36 \pm 0.24	1.22 \pm 0.13	0.67 \pm 0.15	1.23 \pm 0.18
P1		0.211	0.000*	0.228
P2				0.000*

Data are expressed as mean \pm SD; n = 6; * Significant difference at p < 0.05; P1 compared to group I; P2 compared to group III.

Table 5: Mean levels (\pm SD) of serum alanine aminotransferase at the 1st and 2nd months of the experiment in group I (negative controls), group II (positive controls receiving 5mg/kg/day atorvastatin orally for 2 months), group III (untreated diabetic hypercholesterolemic model) and group IV (diabetic hypercholesterolemic model treated with 5mg/kg/day atorvastatin orally for 2 months).

Groups	Group I	Group II	Group III	Group IV
Mean \pm SD after 1 months	18.33 \pm 3.01	18.33 \pm 2.42	26.33 \pm 2.88	30.83 \pm 3.87
P1		1.00	0.000*	0.000*
P2				0.020*
Mean \pm SD after 2 months	17.33 \pm 2.07	19.17 \pm 1.83	32.67 \pm 7.99	39.17 \pm 3.97
P1		0.504	0.000*	0.000*
P2				0.026*

Data are expressed as mean \pm SD; n = 6; * Significant difference at p < 0.05; P1 compared to group I; P2 compared to group III.

Table 6: Mean levels (\pm SD) of serum aspartate aminotransferase at the 1st and 2nd months of the experiment in group I (negative controls), group II (positive controls receiving 5mg/kg/day atorvastatin orally for 2 months), group III (untreated diabetic hypercholesterolemic model) and group IV (diabetic hypercholesterolemic model treated with 5mg/kg/day atorvastatin orally for 2 months).

Groups	Group I	Group II	Group III	Group IV
Mean \pm SD after 1 months	17.33 \pm 2.42	17.67 \pm 1.75	36.50 \pm 8.53	35.00 \pm 9.98
P1		0.932	0.000*	0.000*
P2				0.704
Mean \pm SD after 2 months	17.50 \pm 1.87	18.67 \pm 2.16	34.17 \pm 9.91	35.50 \pm 8.24
P1		0.763	0.000*	0.000*
P2				0.730

Data are expressed as mean \pm SD; n = 6; * Significant difference at p < 0.05; P1 compared to group I; P2 compared to group III.

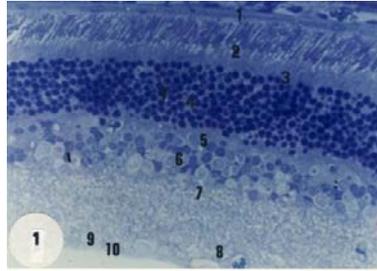


Fig. 1: Light micrograph of a semi-thin section of control rat retina (group I) showing layers of the retina arranged from outside inwards: 1- pigment epithelium, 2- photoreceptors, 3- outer limiting membrane, 4- outer nuclear layer, 5- outer plexiform layer, 6- inner nuclear layer, 7- inner plexiform layer, 8- ganglion cell layer, 9- nerve fiber layer and 10- inner limiting membrane (TB X500).

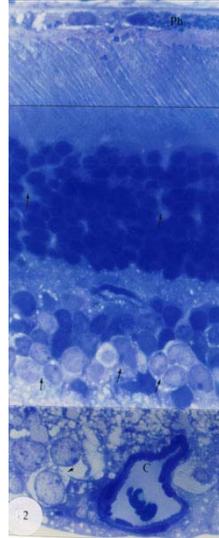


Fig. 2: Light micrograph of a semi-thin section of diabetic hypercholesterolemic rat retina (group III) showing increased phagosomes (ph) and vacuoles in the retinal pigment epithelium. Edema is evident in both outer and inner nuclear layers (arrows). A dilated tortuous blood capillary (C) is seen in the ganglion cell layer. Lucent cytoplasm and coalescence of adjacent cell membranes of ganglion cells is clear (arrow head) (TB X500).

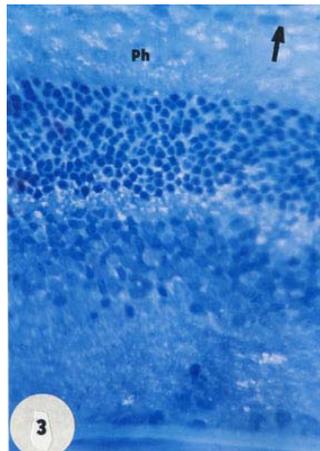


Fig. 3: Light micrograph of a semi-thin section of diabetic hypercholesterolemic rat retina treated with atorvastatin for two months (group IV) showing ill-defined retinal pigment epithelium (arrow) with disorganized fragmented outer and inner layers of photoreceptors (ph). Edema is evident in both the outer and inner plexiform layers (TB X500).

However, there were some light microscopic changes in the retina. The retinal pigment epithelium appeared ill-defined with fragmentation of outer and inner layers of photoreceptors. The outer and inner plexiform layers appeared edematous (Fig. 3).

Examination of the liver:

Light microscopic examination of the liver of rats of negative control group (group I) showed the normal appearance of liver architecture (Fig. 4). Animals of group II (positive controls treated by atorvastatin for two months) also exhibited normal appearance of the hepatic structure apart from mild congestion of central vein (Fig. 5). Histopathological examination of the liver of diabetic hypercholesterolemic rats (group III) revealed significant Light microscopic changes. There was loss of hepatic architecture. Cytoplasm of hepatocytes showed marked vacuolations. The central vein was dilated with infiltration by perivascular inflammatory cells (Fig. 6). Treatment of diabetic hypercholesterolemic rats with atorvastatin (group IV) showed almost the same histopathological changes of the liver tissue as that observed in group III. Although there was more significant deterioration of serum level of ALT in group IV compared to group III, the two groups exhibited the same hepatic light microscopic picture.

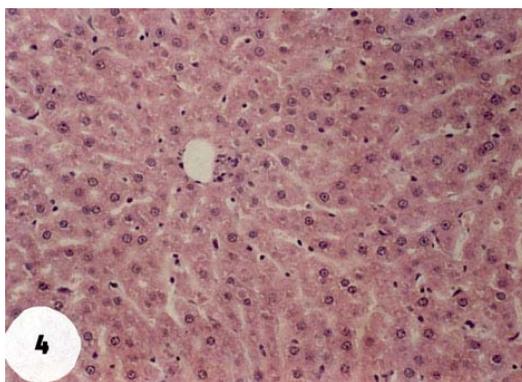


Fig. 4: Light micrograph of control rat liver (group I) showing the normal liver with the central vein and radiating fashion of liver cords which consist of two cell thickness separated by blood sinusoids (Hx & E X500).

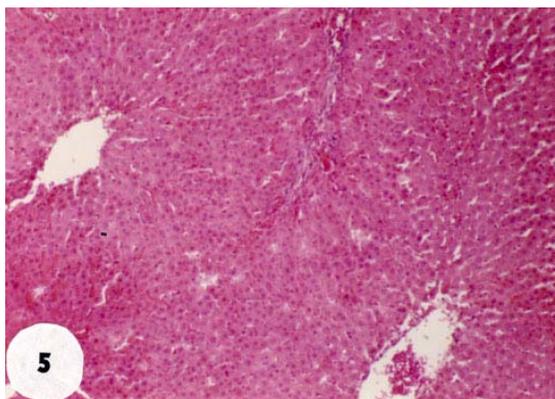


Fig. 5: Light micrograph of positive control rat liver of group II (treated with atorvastatin alone for two months) showing preserved structure of hepatic configuration with mild congestion of the central vein (Hx & E X500).

Discussion:

Statins, HMG-CoA reductase inhibitors are used as cholesterol lowering drugs worldwide. They were suggested to have a potential therapeutic role as neuroprotective agents in a variety of diseases of the central nervous system including ischemic stroke, Alzheimer disease, multiple sclerosis and some eye and retinal diseases such as diabetic retinopathy (Schmeer, 2006). In the present study, atorvastatin was evaluated for the prevention of development of diabetic retinopathy in a diabetic hypercholesterolemic model in albino rats.

Induction of the model produced significant increase in the serum levels of glucose, cholesterol, triglycerides, ALT and AST in addition to significant decrease in serum total antioxidants. These results are in agreement with several reports which documented these changes in serum glucose, lipids and hepatic enzymes in various animal models of diabetes alone or associated with hypercholesterolemia (Fernandes, 2010; Gupta, 2005; Mutalik, 2005). In addition, diabetes can also produce significant deterioration of serum antioxidants in patients and in animal models (Kaimal, 2010; Sivajothi, 2007) which is also in line with the result of the present work. The present study demonstrated histopathological changes in the retina and liver of untreated diabetic hypercholesterolemic rats. Similar results were previously reported in the retina of rats with diabetes (Amemiya, 2001). Moreover, similar degenerative histopathological changes were reported in livers of animals with experimental diabetes (Koyuturk, 2005) which is in accordance with the results of the present work.

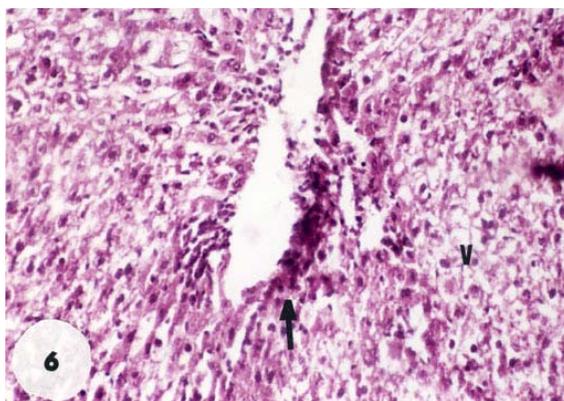


Fig. 6: Light micrograph of diabetic hypercholesterolemic rat liver (group III) showing loss of hepatic architecture. Vacuolar changes (V) of cytoplasm of hepatocytes are clearly obvious. The central vein is dilated and perivascular inflammatory cells are evident (arrow) (Hx & E X500).

Treatment of diabetic hypercholesterolemic rats with atorvastatin produced significant decrease in serum cholesterol and triglycerides with significant increase in total antioxidants accompanied by improvement of the retinal histopathological picture when compared with untreated model. Atorvastatin is used worldwide for the treatment of hyperlipidemia and its effect on serum lipids is well documented. Regarding its antioxidant effect, previous reports demonstrated the antioxidant effects of atorvastatin in diabetic patients, in hypercholesterolemic patients (Cangemi, 2008) and in spontaneous hypertensive rats (Kishi, 2008). Other statins were also reported to possess antioxidant effects such as pravastatin (Kassan, 2009) and rosuvastatin (Sicard, 2008) in spontaneous hypertensive rats and simvastatin in a rat model of obesity and hypertension. All these reports are in agreement with the results of the present investigation.

As regards protection of the retina, several statins were previously reported to protect the retina against diabetic retinopathy which is in line with the results of the present work. Simvastatin could retard the progression of retinopathy in diabetic patients with hypercholesterolemia (Sen, 2002) and exhibited retinal protective effect in rats with experimental diabetes (Al-Shabrawey, 2008; Miyahara, 2004). Lovastatin was reported to protect the blood-retinal barrier and ameliorates retinal inflammation in diabetic mice (Li, 2009). Disturbance of the blood-retinal barrier is demonstrated in the present investigation as disorganization of the outer segment of photoreceptors in untreated model rats. The present work also showed that atorvastatin produced partial protection of the blood-retinal barrier demonstrated by partial improvement of the disorganized outer segment of photoreceptors.

Several mechanisms have been suggested for the retinoprotective effects of statins. Oxidative stress which is linked to accelerated apoptosis of retinal capillary cells is an important mechanism in the pathogenesis of diabetic retinopathy (Kowluru, 2006). Statins were reported to protect the retina against oxidative stress and the accelerated apoptosis of retinal capillary cells (Kowluru, 2009) in diabetic rats. In addition, neovascularization or angiogenesis is a common and potentially visually threatening complication of diabetic retinopathy. Vascular endothelial growth factor (VEGF) plays a critical role in the pathogenesis of retinal neovascularization (Eichler, 2006). Simvastatin was reported to decrease the levels of VEGF in the retina which were increased due to diabetes together with inhibition of leukocyte-induced endothelial cell damage and subsequent regression of blood-retinal barrier breakdown. Moreover, inflammatory processes contribute to the development of diabetic retinopathy (Kern, 2007). Statins were reported to have significant anti-inflammatory effects. Lovastatin was also effective in protecting the blood-retinal barrier of diabetic rats via its anti-inflammatory effects. Another mechanism is related to AGEs. Interaction of AGEs with their receptors is involved in the endothelial cell

dysfunction that is important for the development and progression of diabetic retinopathy. Statins interfere with AGE receptor signaling and therefore prevent the damaging effects of AGEs in various tissues.

Concerning the liver, the present work demonstrated that administration of atorvastatin to normal rats (group II) produced insignificant change in serum levels of both liver enzymes; ALT and AST together with normal light microscopic picture of the liver. Atorvastatin produces transient rise of serum transaminases in only up to 3% of patients. It was recommended that therapy with these drugs require monitoring of ALT serum levels because animal studies and premarketing clinical trials showed primarily minor elevations of ALT (Gershovich, 2004). Induction of the model of diabetes and hypercholesterolemia produced significant elevation of serum enzymes with histopathological changes in liver tissue. Treatment of the model with atorvastatin produced more significant deterioration of ALT serum levels with persistence of the deteriorated serum level of AST and the histopathological changes in liver tissue. Therefore, the present work demonstrates that the damaged liver can further be deteriorated by atorvastatin and care should be taken while administering statins in the presence of any risk factor of liver damage.

In conclusion, atorvastatin can partially protect the retina against the development of diabetic retinopathy and this effect may be related to its antioxidant activity. However, care should be taken as regards the hepatotoxic effect of the drug. Further studies are recommended to investigate other potential protective mechanisms of statins against diabetic retinopathy and other retinal neurodegenerative diseases.

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