Study of the effect of treatment with the renin-angiotensin system inhibitors enalapril & losartan and the lipid lowering drug atorvastatin and their interactions in diabetic rats

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Abstract: Diabetes is a serious metabolic disorder with micro and macrovascular complications that results in significant morbidity and mortality. The incidence of cardiovascular diseases in diabetic patients has increased up to 3 folds and is a leading cause of death worldwide. Diabetic nephropathy is a significant cause of chronic kidney disease and end-stage renal failure globally hyperglycemia induces endothelial dysfunction through the generation of oxidative stress which has been suggested to be the key player in the generation of renal and cardiovascular complications. In this study we invetigated the effects of losartan, enalapril and atorvastatin on the vascular and the biochemical changes induced by diabetes mellitus in rats. Adultmale albino rats were used in this study and divided into eleven groups (10 rats each). **Group 1**: Normal untreated non diabetic rats received saline, **Group 2**: Diabetic rats treated with distelled water, **Group 3**: Diabetic rats treated with glimepride, **Group 4**: Diabetic rats treated with losartan, **Group 5**: Diabetic rats treated with enalapril, **Group 6:** Diabetic rats treated with atorvastatin. After 8 weeks of treatment, blood samples are withdrawn for measurement of (fasting blood glucose level, serum insulin level, lipid profile, blood urea, serum creatinine and antioxidant parameters) and the vascular reactivity of rats aortae to the vasoconstrictive drugs (such as norepinehrine) and the vasodilator drugs (such as acetylcholine) was measured. The benificial effects of RAS inhibitors and atorvastatin can be explained by its antihypertensive, antioxidant and anti-inflammatory activities. While the hypoglycaemic effect of losartan is due to an increase in non-oxidative glucose metabolism and blood flow in insulin-resistant hypertensive patients**,** improves β-cell function and glucose tolerance in young type 2 diabetic and improve insulin sensitivity to reduce elevations in fasting and fed glucose concentrations**.**

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Keywords: Study; effect; treatment; renin-angiotensin; system; inhibitor; enalapril; losartan; lipid; lowering drug atorvastatin; interaction; diabetic; rat

1. Introduction

Diabete mellitus (DM) is a metabolic disorder of multiple etiology characterized by chronic hyperglycemia with disturbances of carbohydrate, fat and protein metabolism resulting from defects in insulin secretion and/or insulin action **(ADA, 2011).** In spite of the availability of different classes of oral hypoglycemic drugs, the incidence of microvascular complications (nephropathy, retinopathy and neuropathy) and macrovascular complications (atherosclerosis, coronary artery disease, peripheral arterial disease and stroke) continues to rise unabated in diabetic patients, even with treatment **(Roglic and Unwin 2010).**

Evidence implicates the role of oxidative stressin the different stages of the development of diabetes mellitus, starting from the pre-diabetes state, impaired glucose tolerance, postprandial hyperglycemia, mild diabetes and finally to overt DM **(Ceriello et al., 1998).**

In view of evidence which implicates a role of oxidative stressin β-cell dysfunction and insulin resistance, antioxidants could play a role in preventing diabetes mellitus and/or its progression. Antioxidants such as vitamin C, vitamin E, β-carotene, α-lipoic acids and honey have been shown to ameliorate hyperglycemia through increased β-cell mass and insulin secretion **(Erejuwa, 2012).**

There is strong evidence implicating a role of oxidative stressin diabetic nephropathy, retinopathy and neuropathy which constitute the microvascular complications **(Giacco and Brownlee 2010).** Similarly, a role of oxidative stressis implicated in the macrovascular complications (coronary artery disease, peripheral arterial disease and cerebrovascular disease) **(Giacco and Brownlee 2010).**

A great deal of attention has been focused on the role of the renin- angiotensin system (RAS) in the endocrine pancreas. Activation of this system has a pivotal role in the pathogenesis of diabetic complications **(Maharsy et al.,2007)**. However, previous report suggests that it may also contribute to the development of diabetes itself as confirmed by a cross talk between angiotensin II (Ang II) receptor

signaling and insulin signaling pathways that involved in the development of IR **(Andreozzi et al., 2004).**

Clinical trials have demonstrated the ability of the RAS blockade to prevent new onset diabetes and the development of diabetic complications **(Vigayaraghavan k and deedwania pc, 2005).** Losartan (Los), an angiotensin subtype 1 receptor (AT1) antagonist, is potent and orally active angiotensin receptor blocker (ARB). There are controversial reports on the effects of LOS on insulin sensitivity **(Shiuchi et al.,2004)** and **(Kamper et al.,2010). W**hereas other suggests that ARBs have neutral effect on insulin sensitivity **(Nakagawa et al.,1999).** Enalapril has significant anti-hyperglycemic activities which enhance the effect of oral antidiabetic drugs in diabetic animal **(Neeraj et al.,2013).**

Atorvastatin is among the most clinically used lipid- lowering drugs. Accumulating evidences have shown that some beneficial pleiotropic effects of these agents may be independent of serum cholesterol levels **(Heeba et al.,2009)** and **(Takemoto and liao2001).**

Atorvastatin has been demonstrated to inhibit superoxide production in isolated rat vascular smooth muscle cells via inhibition of Ang II- induced NADPH oxidase activation **(Wassmann et al., 2002)** and induce the expression of the antioxidant, anti inflammatory, and anti-apoptotic enzyme, heme oxygenase-1 **(Heeba et al.,2009).** On the other hand, atorvastatin therapy dose dependently causes insulin resistance and increases the risk of type-2 diabetes in hypercholesterolemic patients **(Kok KK et al.,2010).**

Combined therapy with statins and RAS inhibitors may be important in developing optimal management stratigies in patients with hypertension, hypercholesterolemia, diabetes, metabolic syndrome or obesity to prevent CVD **(Hae-young lee et al., 2014).**

Aim of the work

The aim of this study is to evaluate the role Renin-angiotensin-aldosterone system blockers and their combinations with hypolipidemic drug (Atorvastatin) in protection against diabetes mellitus-induced compilations by investigating the following:

1-The vascular reactivity changes induced by diabetes in rats & the effect of renin angiotensin system blockers (The ACE inhibitor enalapril and the angiotensin receptor blocker losartan) and the lipid lowering drug atorvastatin on the vascular reactivity of diabetic rats aortae.

2-The biochemical changes induced by diabetes in rats & the possible effect of (losartan, enalapril and atorvastatin) on fasting blood glucose level, serum insulin level, lipid profile, serum urea and creatinine.

3-The oxidative stress status in diabetic rats as a possible cause of the pathogenesis of diabetes and its complications and the antioxidant effect of (losartan, enalapril and atorvastatin).

4-The effect of combination of (losartan, enalapril or atorvastatin) with glimepride on the vascular reactivity & biochemical changes induced by diabetes in rats.

2. Materials and Methods

Experimental animals:

Adult male albino rats were chosen as an animal model for this study. Rats were brought from animal house, Faculty of Medicine, Assiut University, Assiut, Egypt, and were maintained on a balanced diet with water supply freely in clean containers. They were kept for two weeks to adapt to the laboratory conditions before the start of the experiment. one hundred and ten age-matched male albino rats with initial body weights ranging from 150 to 200g were used.

The rats were divided into eleven groups (10 rats each).

Group 1: Normal untreated non diabetic rats received saline, **Group 2**: Diabetic rats treated with distelled water, **Group 3**: Diabetic rats treated with glimepride, **Group 4**: Diabetic rats treated with losartan, **Group 5**: Diabetic rats treated with enalapril, **Group 6** Diabetic rats treated with atorvastatin,.

Procedures:

1-Induction of diabetes

The animals were injected by a single intrapertonial injection of streptozotocin 50 mg /kg body weight **(Mifsud et al., 2002)**.

- The animals were allowed to drink 5 % glucose solution overnight to overcome the drug induced hypoglycaemia **(Kaleem et al., 2006)**.

- Diabetes was confirmed through detecting blood glucose concentration by glucose oxidase method using glucometer with glucose test strip (One Touch Basic) **(Olanlokun 2008).** The animals were considered diabetic if their blood glucose values were above 250 mg/dl on the 3rd day after STZ injection **(Kaleem et al., 2006)**.

-The treatment was started on the 4th day after STZ injection and this was considered as the 1st day of treatment. The treatment was continued for 8 weeks.

2- Collection of blood samples

A-The animal was anaesthetized with ether by placing the rat in an anesthetic box filled with ether vapor which was maintained by periodically applying liquid ether to a cotton wool on the base of the box. When surgical stage of anesthesia was reached (judged by loss of withdrawal reflexes), the animal was removed and placed on a table and blood was collected from the retro-orbital plexus using capillary

tube (0.75-1.0 mm internal diameter) inserted in the medial canthus medial to the eye globe.

B-After eight weeks, rats were fasted overnight and blood was collected from carotid artery after sacrificing of animals. The blood was collected into a dry clean graduated glass centrifuge tube. It was rapidly set to centrifuge at 5000 r.p.m for 10 minutes about half of the supernatant serum was sucked out into a clean dry glass serology tube using Pasteur pipette.

3-Isolated aortic rings:

On the day of experiment, animals were killed by a blow on the head and cutting the throat. Abdominal and thoracic walls were opened. The thoracic aorta was dissected and cut, placed in dish containing Kreb's-Henseleit solution of the following composition (mM/L): (NaCl 118.4, KCl 4.69, kH2PO4:1.17, MgSO4 1.18, CaCl 2.52, glucose 11.10 and NaHCO3 25) aerated with carbogen (95% oxygen and 5% carbogen dioxide), cleaned from the surrounding attached tissues and cut into small rings (about 4mm length).

Biochemical measurements:

Blood glucose measurements:

The blood glucose level was determined by enzymatic colorimetric method **(Trinder and Ann 1969).** Using diamond diagnostic kits.

Serum insulin level

Serum insulin was determined by an enzyme-linked immunosorbent assay (ELISA) kit **(Csont, 2007).**

Lipid Profile

Serum cholesterol level was done by enzymatic–colometric method (**Ellefson and caraway 1976**). Egyptian company for biotechnology-Egypt.

Serum triglycerides measurements:

Serum triglycerides were estimated by an enzymatic colorimetric method **(bucolo and david 1973).** Egyptian company for biotechnology-Egypt.

Determination of Serum High Density Lipoproteins:-

Serum high density lipoprotein (HDL) was estimated by precipitation method **(Friedewaled1972). Egyptian Company** for biotechnology-Egypt.

Determination of Serum Low Density Lipoproteins:-

The serum LDL-cholesterol was estimated according to (**Friedewald formula 1972)** using the following equation;-

LDL in mg/dl= Total cholesterol – Triglyceride/5-HDL

Renal function tests:

Serum urea level was done by urease – Colorimetric method **(Batton and Crouch 1977).** Using Egyptian company for biotechnology kits.

Serum creatinine measurements

Serum creatinine level was measured by kinetic method **(Young 1995).** Biolabo reagents kits –France.

Statistical analysis

Statistical analysis of the difference between groups was performed by using *student t test*. The data were presented in the form of mean ± standard error A value of P< 0.05 were used as the limit for statistical significance.

3. Results

Effect of treatment with glimepride on the contractile response of the diabetic rats aortae to norepinephrine.

Cumulative concentration-response curves elicited by NE on aortic ring preparations obtained from the normal rats, the diabetic untreated rats and the diabetic rats treated with glimepride (0.5 mg/kg) for 8 weeks. The results show that the contractile response of the aortae was increased significantly (P<0.001) in the diabetic untreated rats in comparison with the normal rats, and decreased significantly (P< 0.05) in the diabetic rats treated with glimepride in comparison with the diabetic untreated rats, but still there is a significant (P<0.05) increase in the response of the aortae of the diabetic rats treated with glimepride as compared to the normal rats aortae as shown in figure (1).

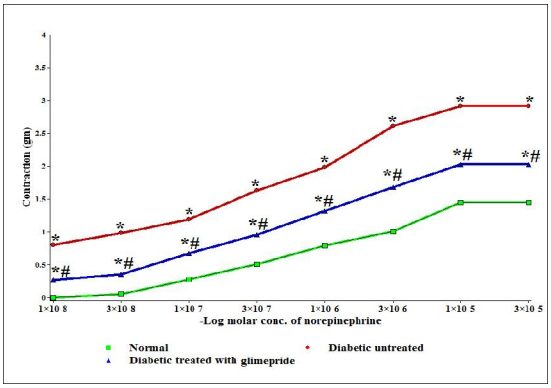

Figure (1): Effect of chronic treatment with glimepride on the contractile response of the diabetic rats aortae to norepinephrine.

Each value represents the mean ± SE (standard error) of 7 – 9 animals.

* Significant difference from the normal rats (P< 0.01).

#Significant difference from the diabetic untreated rats (P< 0.01).

Effect of treatment with losartan on the contractile response of the diabetic rats aortae to norepinephrine.

Cumulative concentration-response curves elicited by NE on aortic ring preparations obtained from the normal rats, the diabetic untreated rats, the diabetic rats treated with losartan (2 mg/kg) and the diabetic rats treated with losartan (2mg/kg) + glimepride (0.5mg/kg) for 8 weeks. The results show that the contractile response of the aorta of the diabetic rats treated with losartan was decreased significantly (P< 0.05) in comparison with the diabetic untreated rats, but still there was a significant (P< 0.05) increase in comparison with the normal rats. While treatment with losartan & glimepride significantly decreased (P< 0.001) the contractile response of the aortae of the diabetic rats with no significant difference (P> 0.05) as compared to normal rats as shown in figure (2).

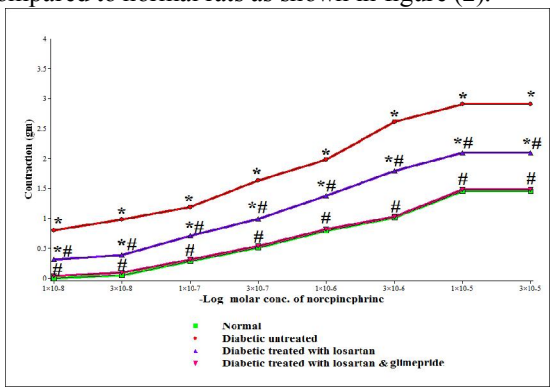

Figure (2): Effect of treatment with losartan on the contractile response of the diabetic rats isolated aortae to norepinephrine.

Each value represents the mean ± SE (standard error) of 7 – 9 animals.

*Significant difference from the normal rats (P< 0.01).

#Significant difference from the diabetic untreated rats (P< 0.01).

Effect of treatment with enalapril on the contractile response of the diabetic rats aortae to norepinephrine.

Cumulative concentration-response curves elicited by NE on aortic ring preparations obtained from the normal rats, the diabetic untreated rats, the diabetic rats treated with enalapril (3.2 mg/kg) and the diabetic rats treated with enalapril (3.2 mg/kg) + glimepride (0.5mg/kg) for 8 weeks. The results show that the contractile response of the aorta of the diabetic rats treated with enalapril was decreased significantly (P< 0.05) in comparison with the diabetic untreated rats, but still there was a significant (P< 0.05) increase in comparison with the normal rats. While treatment with enalapril & glimepride significantly decreased (P< 0.01) the contractile response of the aortae of the diabetic rats with no significant difference (P> 0.05) as compared to normal rats as shown figure (3).

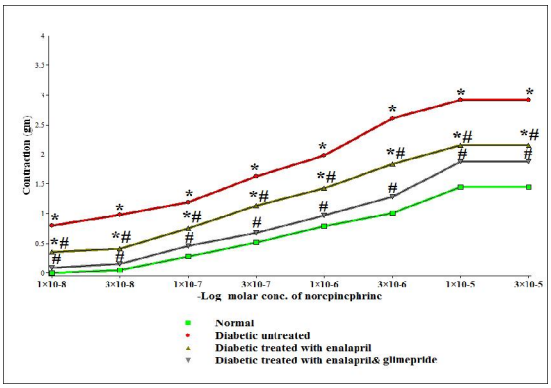

Figure (3): Effect of treatment with enalapril on the contractile response of the diabetic rat's isolated aortae to norepinephrine.

Each value represents the mean ± SE (standard error) of 7 – 9 animals.

* Significant difference from the normal rats (P< 0.01).

Significant difference from the diabetic untreated rats (P< 0.01).

Effect of treatment with atorvastatin on the contractile response of the diabetic rats aortae to norepinephrine.

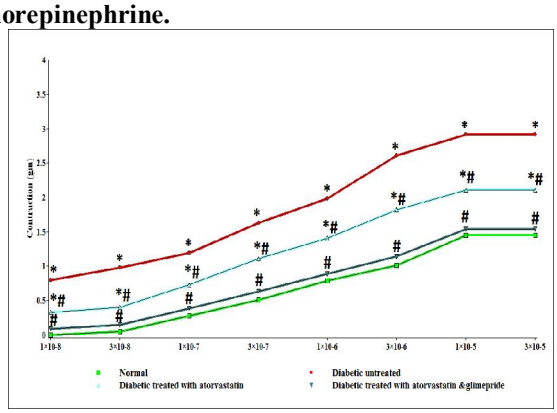

Figure (4): Effect of treatment with atorvastatin on the contractile response of the diabetic rat's isolated aortae to norepinephrine.

Each value represents the mean ± SE (standard error) of 7 – 9 animals.

* Significant difference from the normal rats (P< 0.01).

Significant difference from the diabetic untreated rats (P< 0.01).

Cumulative concentration-response curves elicited by NE on aortic ring preparations obtained from the normal rats, the diabetic untreated rats, the diabetic rats treated with atorvastatin (10 mg/kg) and the diabetic rats treated with atorvastatin (10 mg/kg) + glimepride (0.5mg/kg) for 8 weeks. The results show that the contractile response of the aorta of the diabetic rats treated with atorvastatin was decreased

significantly (P< 0.05) in comparison with the diabetic untreated rats, but still there was a significant (P< 0.05) increase in comparison with the normal rats. While treatment with atorvastatin & glimepride significantly decreased (P< 0.01) the contractile response of the aortae of the diabetic rats with no significant difference (P> 0.05) as compared to normal rats as shown in figure (4).

Effect of treatment with glimepride on the relaxant response of the diabetic rats isolated aortae to acetylcholine.

Cumulative concentration-response curves elicited by Ach on NE precontracted aortic ring preparations obtained from the normal rats, the diabetic untreated rats and the diabetic rats treated with glimepride (0.5 mg/kg) for 8 weeks. The results show that the relaxant response of the aortae was decreased significantly (P<0.001) in the diabetic untreated rats in comparison with the normal rats, and increased significantly (P< 0.01) in the diabetic rats treated with glimepride in comparison with the diabetic untreated rats, but still there was a significant (P>0.05) decrease in the response of the aortae of the diabetic rats treated with glimepride as compared to the normal rats aortae as shown in figure (5).

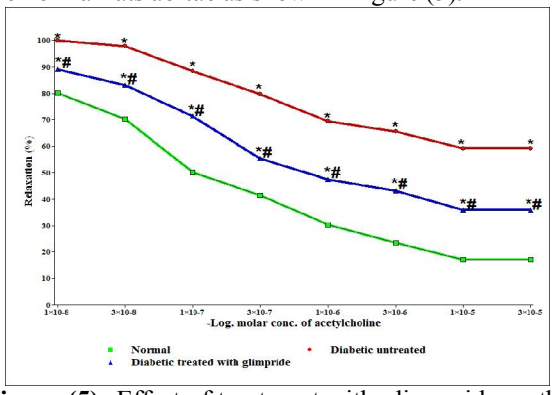

Figure (5): Effect of treatment with glimepride on the relaxant response of the diabetic rats isolated aortae to acetylcholine.

Each value represents the mean ± SE (standard error) of 7 – 9 animals.

* Significant difference from the normal rats (P< 0.01).

Significant difference from the diabetic untreated rats (P< 0.01).

Effect of treatment with losartan on relaxant response of the diabetic rats isolated aortae to acetylcholine.

The results show that the relaxant response of the aortae of the diabetic rats treated with losartan was increased significantly (P< 0.01) in comparison with the diabetic untreated rats, but still there was a significant (P< 0.05) decrease in comparison with the normal rats. While treatment with losartan & glimepride significantly increased (P< 0.01) the relaxant response of the aortae of the diabetic rats with no significant difference (P> 0.05) as compared to normal rats as shown in figure (6).

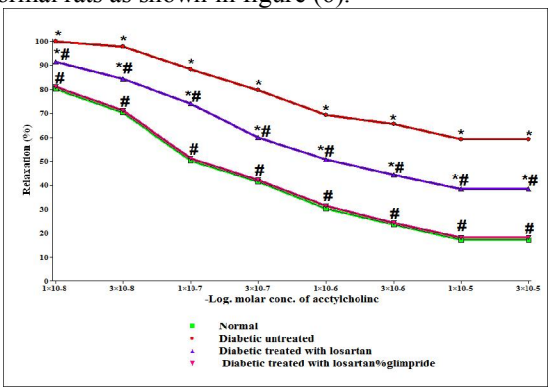

Figure (6): Effect of treatment with losartan on the relaxant response of the diabetic rats isolated aortae to norepinephrine.

Each value represents the mean ± SE (standard error) of 7 – 9 animals.

* Significant difference from the normal rats (P< 0.01).

Significant difference from the diabetic untreated rats (P< 0.01).

Effect of treatment with enalapril on the relaxant response of the diabetic rats aortae to acetylcholine.

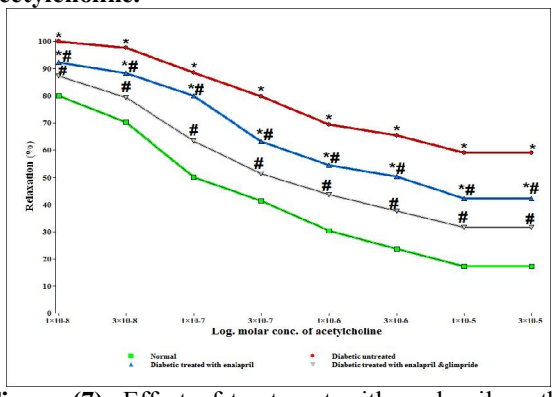

Figure (7): Effect of treatment with enalapril on the relaxant response of the diabetic rats isolated aortae to acetylcholine.

Each value represents the mean ± SE (standard error) of 7 – 9 animals.

* Significant difference from the normal rats (P< 0.01).

Significant difference from the diabetic untreated rats (P< 0.01).

Cumulative concentration-response curves elicited by Ach on NE precontracted aortic ring

preparations obtained from the normal rats, the diabetic untreated rats, the diabetic rats treated with enalapril (3.2 mg/kg) and the diabetic rats treated with enalapril (3.2 mg/kg) + glimepride (0.5 mg/kg) for 8 weeks. The results show that the relaxant response of the aortae of the diabetic rats treated with enalapril was increased significantly (P< 0.05) in comparison with the diabetic untreated rats, but still there was a significant (P < 0.05) decrease in comparison with the normal rats. While treatment with enalapril & glimepride significantly increased (P< 0.01) the relaxant response of the aortae of the diabetic rats with no significant difference (P> 0.05) as compared to normal rats as shown in figure (7).

Effect of treatment with atorvastatin on the relaxant response of the diabetic rats aortae to acetylcholine.

Cumulative concentration-response curves elicited by Ach on NE precontracted aortic ring preparations obtained from the normal rats, the diabetic untreated rats, the diabetic rats treated with atorvastatin (10mg/kg) and the diabetic rats treated with atorvastatin (10mg/kg) + glimepride (0.5 mg/kg) for 8 weeks. The results show that the relaxant response of the aortae of the diabetic rats treated with atorvastatin was increased significantly (P< 0.05) in comparison with the diabetic untreated rats, but still there was a significant (P < 0.05) decrease in comparison with the normal rats. While treatment with atorvastatin & glimepride significantly increased (P< 0.01) the relaxant response of the aortae of the diabetic rats with no significant difference (P> 0.05) as compared to normal rats as shown in figure (8).

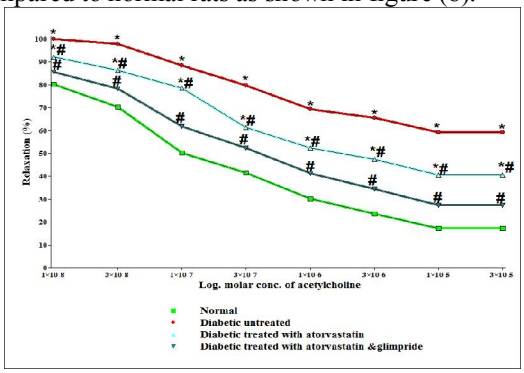

Figure (8): Effect of treatment with atorvastatin on the relaxant response of the diabetic rats isolated aortae to acetylcholine.

Each value represents the mean ± SE (standard error) of 7 – 9 animals.

* Significant difference from the normal rats (P< 0.01).

Significant difference from the diabetic untreated rats (P< 0.01).

Effect of treatment with glimepride on fasting blood glucose of the diabetic rats.

The results show that fasting blood glucose was increased significantly (P< 0.001) in the diabetic untreated rats in comparison with the normal rats. in the diabetic rats treated with glimepride, fasting blood glucose was decreased significantly (P< 0.01) in comparison with the diabetic untreated rats, but still there was a significant (P<0.05) increase as compared to the normal rats as shown in figure (9).

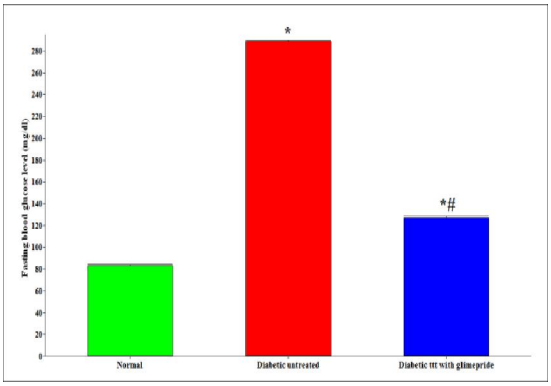

Figure (9): Effect of treatment with glimepride on fasting blood glucose of the diabetic rats.

Each value represents the mean ± SE (standard error) of 7 – 9 animals.

* Significant difference from the normal rats (P<0.01).

#Significant difference from the diabetic untreated rats (P<0.01)

Effect of treatment with losartan on fasting blood glucose of the diabetic rats.

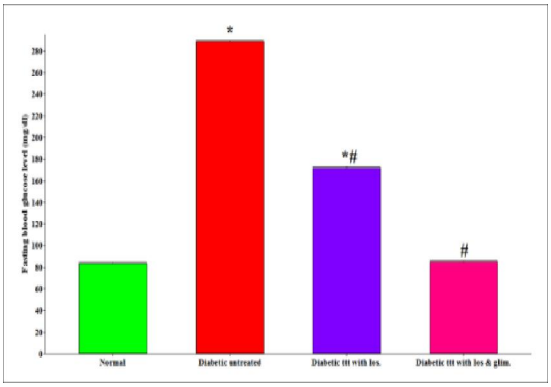

Figure (10): Effect of treatment with losartan on fasting blood glucose of the diabetic rats.

Each value represents the mean ± SE (standard error) of 7 – 9 animals.

* Significant difference from the normal rats (P<0.01).

Significant difference from the diabetic untreated rats (P<0.01).

The results show that fasting blood glucose of the diabetic rats treated with losartan was decreased significantly (P< 0.01) in comparison with the diabetic untreated rats, but still there was a significant (P< 0.05) increase in comparison with the normal rats. While treatment with losartan & glimepride significantly decreased (P< 0.01) the fasting blood glucose of the diabetic rats with no significant difference (P> 0.05) as compared to normal rats as shown in figure (10).

Effect of treatment with enalapril on the fasting blood glucose of the diabetic rats.

The results show that the fasting blood glucose of the diabetic rats treated with enalapril was slightly decreased in comparison with the diabetic untreated rats, but this decrease is not significant (P> 0.05). While treatment with enalapril & glimepride significantly decreased (P< 0.01) the fasting blood glucose of the diabetic rats but still there was a significant (P< 0.05) increase in comparison with the normal rats as shown in figure (11).

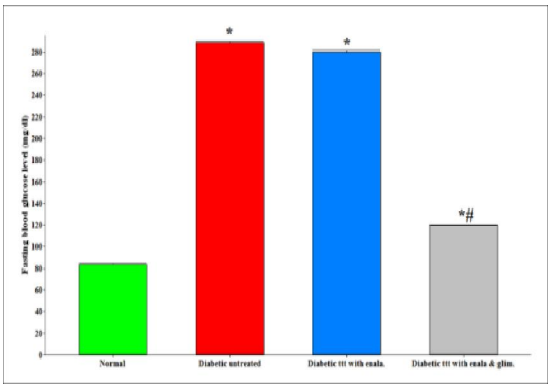

Figure (11): Effect of treatment with enalapril on the fasting blood glucose of the diabetic rats.
Each value represents the mean ± SE (standard error) of 7 – 9 animals.
* Significant difference from the normal rats (P<0.01).
# Significant difference from the diabetic untreated rats (P<0.01).

Effect of treatment with atorvastatin on the fasting blood glucose of the diabetic rats.

The results show that the fasting blood glucose of the diabetic rats treated with atorvastatin was slightly decreased in comparison with the diabetic untreated rats, but this decrease is not significant (P> 0.05). while treatment with atorvastatin & glimepride significantly decreased (P< 0.01) the fasting blood glucose of the diabetic rats but still there was a significant (P< 0.05) increase in comparison with the normal rats as shown in figure (12).

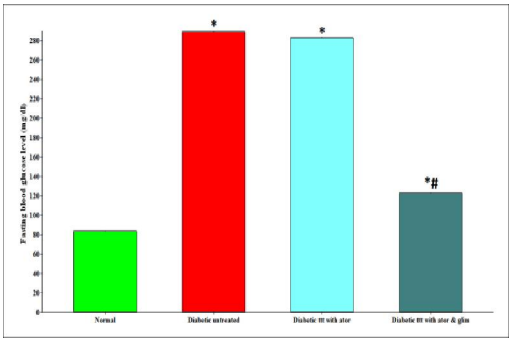

Figure (12): Effect of treatment with atorvastatin on the fasting blood glucose of the diabetic rats.
Each value represents the mean ± SE (standard error) of 7 – 9 animals.
* Significant difference from the normal rats (P<0.01).
# Significant difference from the diabetic untreated rats (P<0.01).

Effect of treatment with glimepride on serum insulin level of the diabetic rats.

The results show that serum insulin level was decreased significantly (P< 0.001) in the diabetic untreated rats in comparison with the normal rats. in the diabetic rats treated with glimepride, serum insulin level was increased significantly (P< 0.01) in comparison with the diabetic untreated rats, but still there is a significant (P<0.05) decrease as compared to the normal rats as shown in figure (13).

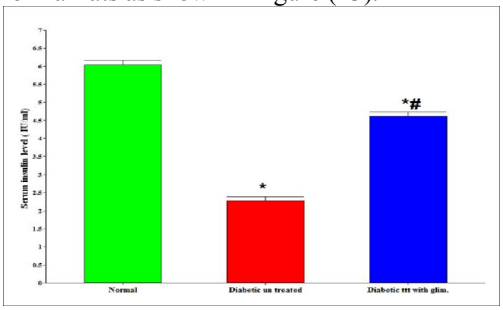

Figure (13): Effect of treatment with glimepride on serum insulin level of the diabetic rats.
Each value represents the mean ± SE (standard error) of 7 – 9 animals.
* Significant difference from the normal rats (P<0.01).
# Significant difference from the diabetic untreated rats (P<0.01).

Effect of chronic treatment with losartan on serum insulin level of the diabetic rats.

The results show that serum insulin of the diabetic rats treated with losartan was increased significantly (P< 0.01) in comparison with the diabetic untreated rats, but still there was a significant (P< 0.05) decrease in comparison with the normal rats. While treatment with losartan & glimepride significantly increased (P< 0.01) serum insulin of the

diabetic rats with no significant difference (P> 0.05) as compared to normal rats as shown in figure (14).

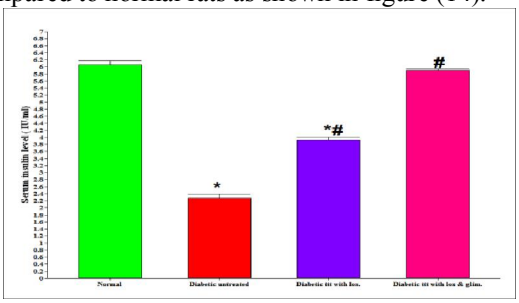

Figure (14): Effect of chronic treatment with losartan on serum insulin level of the diabetic rats.

Each value represents the mean ± SE (standard error) of 7 – 9 animals.

* Significant difference from the normal rats (P<0.01).

Significant difference from the diabetic untreated rats (P<0.01).

Effect of treatment with enalapril on serum insulin level of the diabetic rats.

The results show that serum insulin level of the diabetic rats treated with enalapril was slightly increased in comparison with the diabetic untreated rats, but this increase is not significant (P> 0.05). while treatment with enalapril & glimepride significantly decreased (P< 0.01) the serum insulin level of the diabetic rats but still there was a significant (P< 0.05) increase in comparison with the normal rats as shown in figure (15).

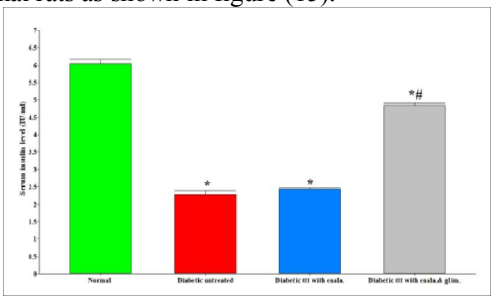

Figure (15): Effect of treatment with enalapril on serum insulin level of the diabetic rats.

Each value represents the mean ± SE (standard error) of 7 – 9 animals.

* Significant difference from the normal rats (P<0.01).

Significant difference from the diabetic untreated rats (P<0.01).

Effect of treatment with atorvastatin on serum insulin level of the diabetic rats.

The results show that the serum insulin level of the diabetic rats treated with atorvastatin was slightly increased in comparison with the diabetic untreated rats, but this increase is not significant (P> 0.05). while treatment with atorvastatin & glimepride significantly increased (P< 0.01) the serum insulin level of the diabetic rats but still there was a significant (P< 0.05) decrease in comparison with the normal rats as shown figure (16).

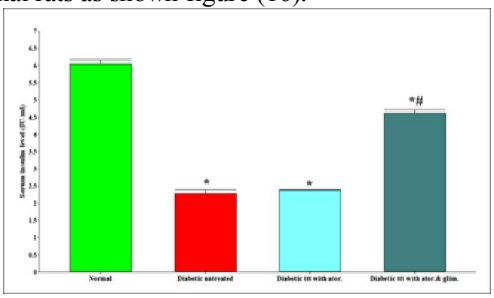

Figure (16): Effect of treatment with atorvastatin on serum insulin level of the diabetic rats.

Each value represents the mean ± SE (standard error) of 7 – 9 animals.

* Significant difference from the normal rats (P<0.01).

Significant difference from the diabetic untreated rats (P<0.01).

Effect of treatment with enalapril on serum cholesterol of the diabetic rats.

The results show that serum cholesterol of the diabetic rats treated with enalapril alone and combination of enalapril and glimepride was significantly decreased (P< 0.01) in comparison with the diabetic untreated rats but still there was a significant (P< 0.05) increase in comparison with the normal rats. Combination of enalapril and glimepride significantly decreased (P< 0.01) serum cholesterol of the diabetic rats as compared to enalapril alone as shown in figure (17).

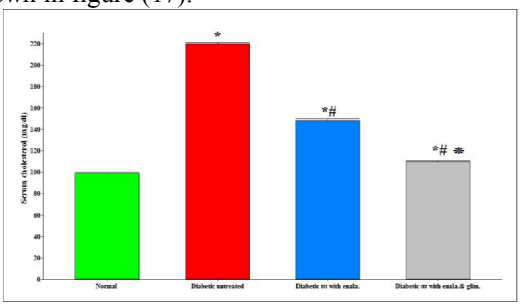

Figure (17): Effect of treatment with enalapril on serum cholesterol of the diabetic rats.

Each value represents the mean ± SE (standard error) of 7 – 9 animals.

* Significant difference from the normal rats (P<0.01).

Significant difference from the diabetic untreated rats (P<0.01).

*Significant difference from the diabetic rats treated with enalapril (P<0.01).

Effect of treatment with atorvastatin on serum cholesterol of the diabetic rats.

The results show that serum cholesterol of the diabetic rats treated with atorvastatin was decreased

significantly (P< 0.01) in comparison with the diabetic untreated rats, but still there was a significant (P< 0.05) increase in comparison with the normal rats. While treatment with atorvastatin & glimepride significantly decreased (P< 0.01) serum cholesterol of the diabetic rats with no significant difference (P> 0.05) as compared to normal rats as shown in figure (18).

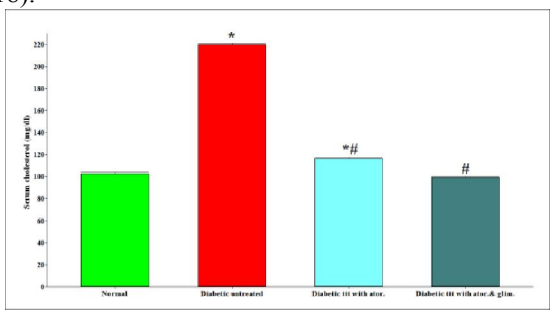

Figure (18): Effect of treatment with atorvastatin on serum cholesterol of the diabetic rats.

Each value represents the mean ± SE (standard error) of 7 – 9 animals.

*Significant difference from the normal rats (P<0.01).

Significant difference from the diabetic untreated rats (P<0.01).

Effect of treatment with glimepride on serum triglycerides of the diabetic rats.

The results show that serum triglycerides was increased significantly (P< 0.01) in the diabetic untreated rats in comparison with the normal rats. In the diabetic rats treated with glimepride, serum triglycerides was decreased significantly (P< 0.01) in comparison with the diabetic untreated rats, but still there is a significant (P<0.05) increase as compared to the normal rats as shown in figure (19).

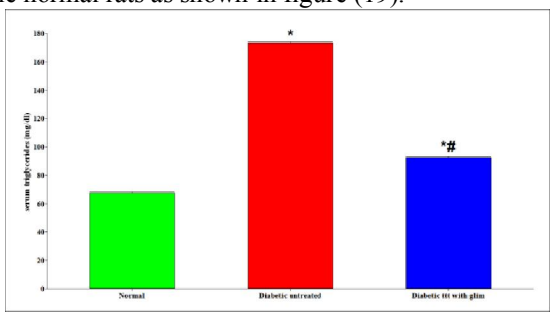

Figure (19): Effect of treatment with glimepride on serum triglycerides of the diabetic rats.

Each value represents the mean ± SE (standard error) of 7 – 9 animals.

* Significant difference from the normal rats (P<0.01).

Significant difference from the diabetic untreated rats (P<0.01).

Effect of treatment with losartan on serum triglycerides of the diabetic rats.

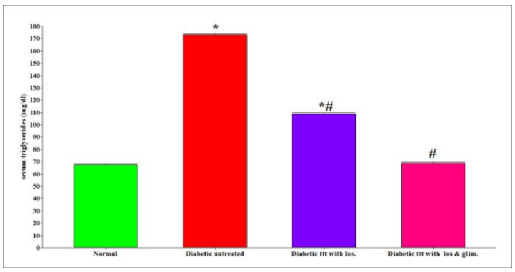

Figure (20): Effect of treatment with losartan on serum triglycerides of the diabetic rats.

Each value represents the mean ± SE (standard error) of 7 – 9 animals.

*Significant difference from the normal rats (P<0.01).

Significant difference from the diabetic untreated rats (P<0.01).

The results show that serum triglycerides of the diabetic rats treated with losartan was decreased significantly (P< 0.01) in comparison with the diabetic untreated rats, but still there was a significant (P< 0.05) increase in comparison with the normal rats. while treatment with losartan & glimepride significantly decreased (P< 0.01) the serum triglycerides of the diabetic rats with no significant difference (P> 0.05) as compared to normal rats as shown in figure (20).

Effect of treatment with enalapril on serum triglycerides of the diabetic rats.

The results show that serum triglycerides of the diabetic rats treated with enalapril alone and combination of enalapril & glimepride was significantly decreased (P< 0.01) in comparison with the diabetic untreated rats but still there was a significant (P< 0.05) increase in comparison with the normal rats. Combination of enalapril & glimepride significantly decreased (P< 0.01) serum triglycerides of the diabetic rats as compared to enalapril alone as shown in figure (21).

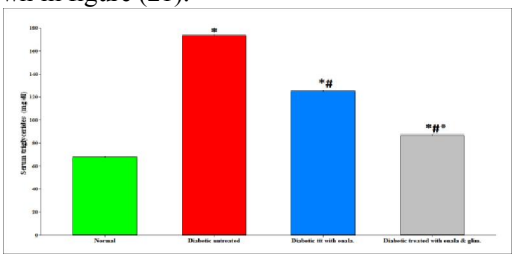

Figure (21): Effect of treatment with enalapril on serum triglycerides of the diabetic rats.

Each value represents the mean ± SE (standard error) of 7 – 9 animals.

* Significant difference from the normal rats (P<0.01).

Significant difference from the diabetic untreated rats (P<0.01).

*Significant difference from the diabetic rats treated with enalapril (P<0.01).

Effect of treatment with atorvastatin on serum triglycerides of the diabetic rats.

The results show that serum triglycerides of the diabetic rats treated with atorvastatin alone and combination of atorvastatin & glimepride was significantly decreased (P<0.01) in comparison with the diabetic untreated rats but still there was a significant (P< 0.05) increase in comparison with the normal rats. Combination of atorvastatin & glimepride significantly decreased (P< 0.01) the serum triglycerides of the diabetic rats with no significant difference (P> 0.05) as compared to normal rats as shown in figure (22).

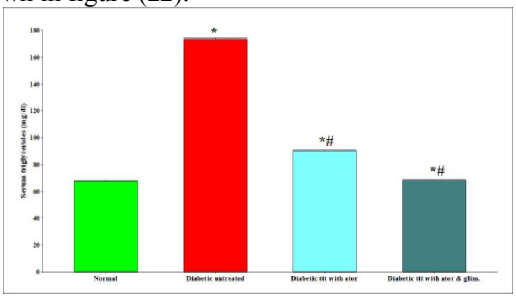

Figure (22): Effect of treatment with atorvastatin on serum triglycerides of the diabetic rats.

Each value represents the mean ± SE (standard error) of 7 – 9 animals.

*Significant difference from the normal rats (P<0.01).

Significant difference from the diabetic untreated rats (P<0.01).

Effect of treatment with glimepride on serum HDL of the diabetic rats.

The results show that serum HDL was decreased significantly (P< 0.01) in the diabetic untreated rats in comparison with the normal rats. In the diabetic rats treated with glimepride, serum HDL was increased significantly (P< 0.01) in comparison with the diabetic untreated rats, but still there was a significant (P<0.05) decrease as compared to the normal rats as shown in figure (22).

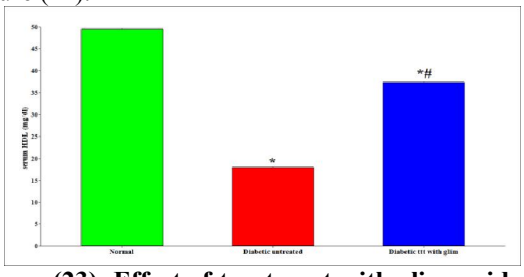

Figure (23): Effect of treatment with glimepride on serum HDL of the diabetic rats.

Each value represents the mean ± SE (standard error) of 7 – 9 animals.

* Significant difference from the normal rats (P<0.01).

Significant difference from the diabetic untreated rats (P<0.01).

Effect of treatment with losartan on serum HDL of the diabetic rats.

The results show that serum HDL of the diabetic rats treated with losartan was increased significantly (P< 0.01) in comparison with the diabetic untreated rats, but still there was a significant (P< 0.05) decrease in comparison with the normal rats. While treatment with losartan & glimepride significantly increased (P< 0.01) these rum HDL of the diabetic rats with no significant difference (P> 0.05) as compared to normal rats as shown in figure (24).

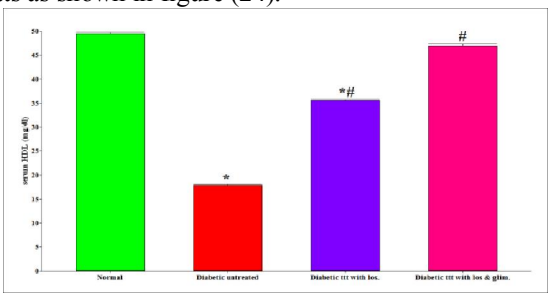

Figure (24): Effect of treatment with losartan on serum HDL of the diabetic rats.

Each value represents the mean ± SE (standard error) of 7 – 9 animals.

* Significant difference from the normal rats (P<0.01).

Significant difference from the diabetic untreated rats (P<0.01).

Effect of treatment with enalapril on serum HDL of the diabetic rats.

The results show that serum HDL of the diabetic rats treated with enalapril was significantly increased (P< 0.01) in comparison with the diabetic untreated rats but still there was a significant (P< 0.05) decrease in comparison with the normal rats. Combination of enalapril & glimepride significantly increased (P< 0.01) serum HDL of the diabetic rats with no significant difference (P> 0.05) as compared to normal rats as shown in table (47) and figure (47).

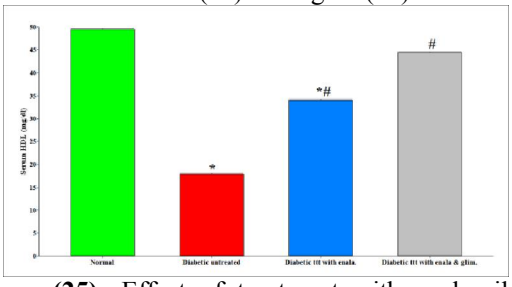

Figure (25): Effect of treatment with enalapril on serum HDL of the diabetic rats.

Each value represents the mean ± SE (standard error) of 7 – 9 animals.

* Significant difference from the normal rats (P<0.01).

Significant difference from the diabetic untreated rats (P<0.01).

Effect of treatment with atorvastatin on serum HDL of the diabetic rats.

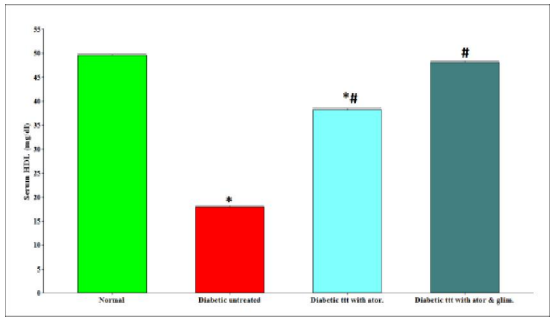

Figure (26): Effect of treatment with atorvastatin on serum HDL of the diabetic rats.

Each value represents the mean ± SE (standard error) of 7 – 9 animals.

* Significant difference from the normal rats (P<0.01).

Significant difference from the diabetic untreated rats (P<0.01).

The results show that serum HDL of the diabetic rats treated with atorvastatin was significantly increased (P< 0.01) in comparison with the diabetic untreated rats but still there was a significant (P< 0.05) decrease in comparison with the normal rats. Combination of atorvastatin & glimepride significantly increased (P< 0.01) serum HDL of the diabetic rats with no significant difference (P> 0.05) as compared to normal rats as shown in figure (26).

Effect of treatment with glimepride on serum LDL of the diabetic rats.

The results show that serum LDL was increased significantly (P< 0.01) in the diabetic untreated rats in comparison with the normal rats. In the diabetic rats treated with glimepride, serum LDL was decreased significantly (P< 0.01) in comparison with the diabetic untreated rats, but still there is a significant (P<0.05) increase as compared to the normal rats as shown in figure (27).

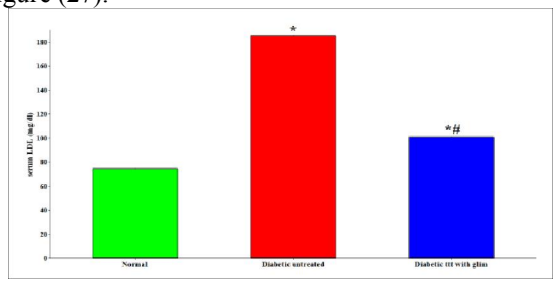

Figure (27): Effect of treatment with glimepride on serum LDL of the diabetic rats.

Each value represents the mean ± SE (standard error) of 7 – 9 animals.

*Significant difference from the normal rats (P<0.01).

Significant difference from the diabetic untreated rats (P<0.01).

Effect of treatment with losartan on serum LDL of the diabetic rats.

The results show that serum LDL of the diabetic rats treated with losartan was decreased significantly (P< 0.01) in comparison with the diabetic untreated rats, but still there was a significant (P< 0.05) increase in comparison with the normal rats. while treatment with losartan+ glimepride significantly decreased (P< 0.01) the serum LDL of the diabetic rats with no significant difference (P> 0.05) as compared to normal rats as shown in figure (28).

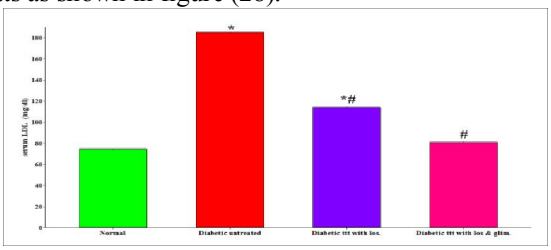

Figure (28): Effect of treatment with glimepride on serum LDL of the diabetic rats.

Each value represents the mean ± SE (standard error) of 7 – 9 animals.

* Significant difference from the normal rats (P<0.01).

Significant difference from the diabetic untreated rats (P<0.01).

Effect of treatment with enalapril on serum LDL of the diabetic rats.

The results show that serum LDL of the diabetic rats treated with enalapril alone and combination of enalapril & glimepride was significantly decreased (P< 0.01) incomparis on with the diabetic untreated rats but still there was a significant (P< 0.05) increase in comparison with the normal rats. Combination of enalapril & glimepride significantly decreased (P< 0.01) serum LDL of the diabetic rats as compared to enalapril alone as shown figure (29).

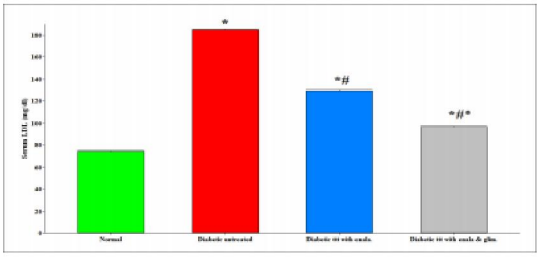

Figure (29): Effect of treatment with enalapril on serum LDL of the diabetic rats.

Each value represents the mean ± SE (standard error) of 7 – 9 animals.

* Significant difference from the normal rats (P<0.01).

Significant difference from the diabetic untreated rats (P<0.01).

* Significant difference from the diabetic rats treated with enalapril (P<0.01).

Effect of treatment with atorvastatin on serum LDL of the diabetic rats.

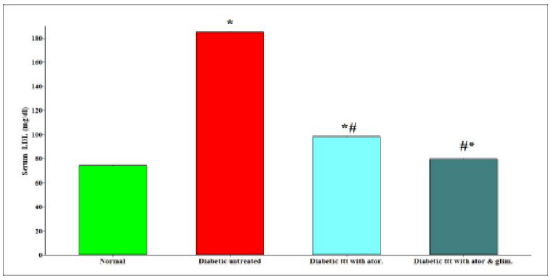

Figure (30): Effect of treatment with atorvastatin on serum LDL of the diabetic rats.

Each value represents the mean ± SE (standard error) of 7 – 9 animals.

* Significant difference from the normal rats (P<0.01).

Significant difference from the diabetic untreated rats (P<0.01).

* Significant difference from the diabetic rats treated with atorvastatin (P<0.01).

The results show that serum LDL of the diabetic rats treated with atorvastatin alone and Combination of atorvastatin & glimepride was significantly decreased (P< 0.01) in comparison with the diabetic untreated rats but still there was a significant (P< 0.05) increase in comparison with the normal rats. Combination of atorvastatin & glimepride significantly decreased (P< 0.01) serum LDL of the diabetic rats as compared to atorvastatin alone as shown in figure (30).

Effect of treatment with glimepride on blood urea of the diabetic rats.

The results show that blood urea was increased significantly (P< 0.01) in the diabetic untreated rats in comparison with the normal rats. In the diabetic rats treated with glimepride, blood urea was decreased significantly (P< 0.01) in comparison with the diabetic untreated rats, but still there was a significant (P<0.05) increase as compared to the normal rats as shown in table (59) and figure (59).

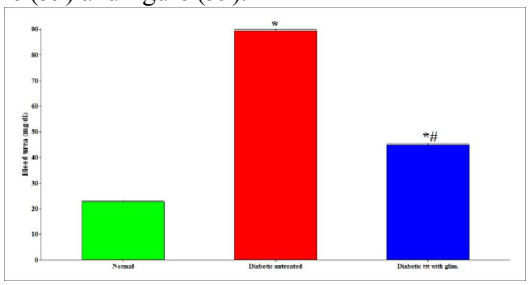

Figure (31): Effect of treatment with glimepride on blood urea of the diabetic rats.

Each value represents the mean ± SE (standard error) of 7 – 9 animals.

*Significant difference from the normal rats (P<0.01).

Significant difference from the diabetic untreated rats (P<0.01).

Effect of treatment with losartan on blood urea of the diabetic rats.

The results show that blood urea of the diabetic rats treated with losartan was decreased significantly (P< 0.01) in comparison with the diabetic untreated rats, but still there was a significant (P< 0.05) increase in comparison with the normal rats. While treatment with losartan & glimepride significantly decreased (P< 0.01) blood urea of the diabetic rats with no significant difference (P> 0.05) as compared to normal rats as shown in figure (32).

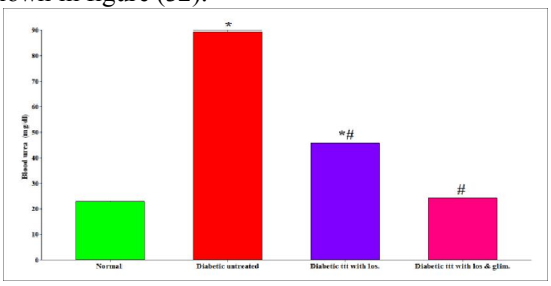

Figure (32): Effect of treatment with losartan on blood urea of the diabetic rats.

Each value represents the mean ± SE (standard error) of 7 – 9 animals.

* Significant difference from the normal rats (P<0.01).

Significant difference from the diabetic untreated rats (P<0.01).

Effect of treatment with enalapril on blood urea of the diabetic rats.

The results show that blood urea of the diabetic rats treated with enalapril was significantly decreased (P< 0.01) in comparison with the diabetic untreated rats but still there was a significant (P< 0.05) increase in comparison with the normal rats. while treatment with enalapril & glimepride significantly decreased (P< 0.01) blood urea of the diabetic rats with no significant difference (P> 0.05) as compared to normal rats as shown in Figure (33):

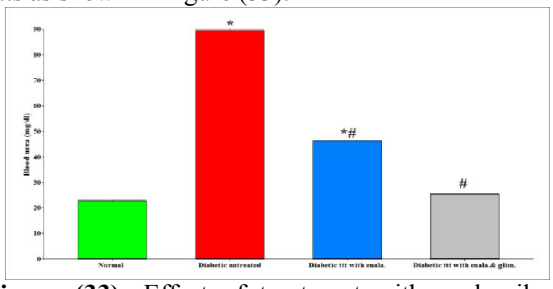

Figure (33): Effect of treatment with enalapril on blood urea of the diabetic rats.

Each value represents the mean ± SE (standard error) of 7 – 9 animals.

*Significant difference from the normal rats (P<0.01).

Significant difference from the diabetic untreated rats (P<0.01).

Effect of treatment with atorvastatin on blood urea of the diabetic rats.

The results show that blood urea of the diabetic rats treated with atorvastatin was significantly decreased (P< 0.01) in comparison with the diabetic untreated rats but still there was a significant (P< 0.05) increase in comparison with the normal rats. While treatment with atorvastatin & glimepride significantly decreased (P< 0.01) blood urea of the diabetic rats with no significant difference (P> 0.05) as compared to normal rats as shown in figure (34).

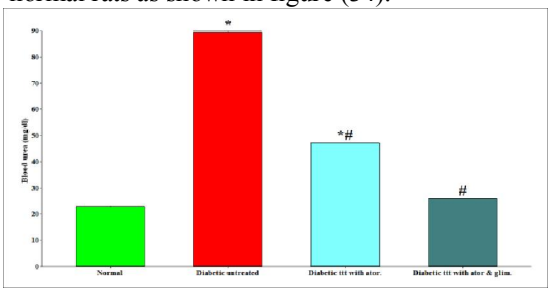

Figure (34): Effect of treatment with atorvastatin on blood urea of the diabetic rats.

Each value represents the mean ± SE (standard error) of 7 – 9 animals.

*Significant difference from the normal rats (P<0.01).

Significant difference from the diabetic untreated rats (P<0.01).

Effect of treatment with glimepride on serum creatinine of the diabetic rats (table 66 & figure66).

The results show that serum creatinine was increased significantly (P< 0.01) in the diabetic untreated rats in comparison with the normal rats. in the diabetic rats treated with glimepride, serum creatinine was decreased significantly (P< 0.01) in comparison with the diabetic untreated rats, but still there was a significant (P<0.05) increase as compared to the normal rats as shown in Figure (35).

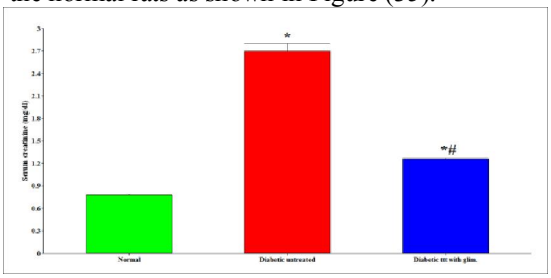

Figure (35): Effect of treatment serum creatinine of the diabetic rats (table 66 & figure66).

Each value represents the mean ± SE (standard error) of 7 – 9 animals.

with glimepride on * Significant difference from the normal rats (P<0.01).

Significant difference from the diabetic untreated rats (P<0.01).

Effect of treatment with losartan on Serum creatinine of the diabetic rats.

The results show that serum creatinine of the diabetic rats treated with losartan was decreased significantly (P<0.01) in comparison with the diabetic untreated rats, but still there was a significant (P<0.05) increase in comparison with the normal rats. While treatment with losartan & glimepride significantly decreased (P<0.01) serum creatinine of the diabetic rats with no significant difference (P>0.05) as compared to normal rats as shown in figure (36).

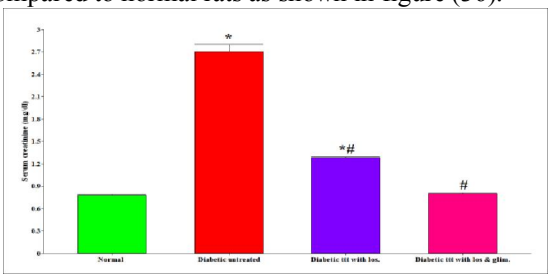

Figure (36): Effect of treatment with losartan on Serum creatinine of the diabetic rats.

Each value represents the mean ± SE (standard error) of 7 – 9 animals.

* Significant difference from the normal rats (P<0.01).

Significant difference from the diabetic untreated rats (P<0.01).

Effect of treatment with enalapril on serum creatinine of the diabetic rats.

The results show that serum creatinine of the diabetic rats treated with enalapril was significantly decreased (P< 0.01) in comparison with the diabetic untreated rats but still there was a significant (P< 0.05) increase in comparison with the normal rats. while treatment with enalapril & glimepride significantly decreased (P< 0.01) serum creatinine of the diabetic rats with no significant difference (P> 0.05) as compared to normal rats as shown in figure (37).

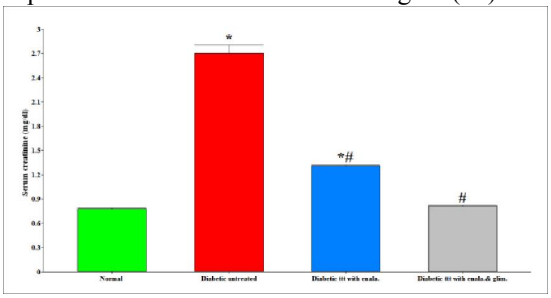

Figure (37): Effect of treatment with enalapril on serum creatinine of the diabetic rats.

Each value represents the mean ± SE (standard error) of 7 – 9 animals.

* Significant difference from the normal rats (P<0.01).

Significant difference from the diabetic untreated rats (P<0.01).

Effect of treatment with atorvastatin on serum creatinine of the diabetic rats.

The results show that serum creatinine of the diabetic rats treated with atorvastatin was significantly decreased (P< 0.01) in comparison with the diabetic untreated rats but still there was a significant (P< 0.05) increase in comparison with the normal rats. while treatment with atorvastatin & glimepride significantly decreased (P< 0.01) serum creatinine of the diabetic rats with no significant difference (P> 0.05) as compared to normal rats as shown in figure (38).

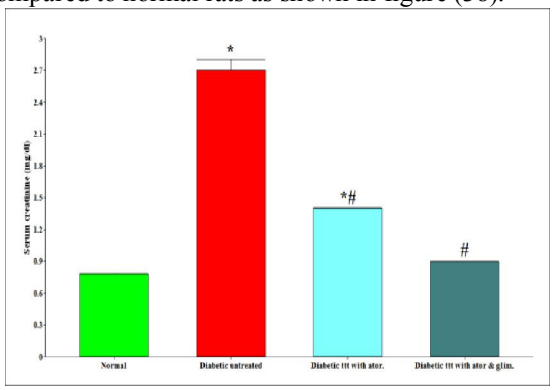

Figure (38): Effect of treatment with atorvastatin on serum creatinine of the diabetic rats.

Each value represents the mean ± SE (standard error) of 7 – 9 animals.

* Significant difference from the normal rats (P<0.01).

Significant difference from the diabetic untreated rats (P<0.01).

Effect of treatment with glimepride on blood level of glutathione of the diabetic rats.

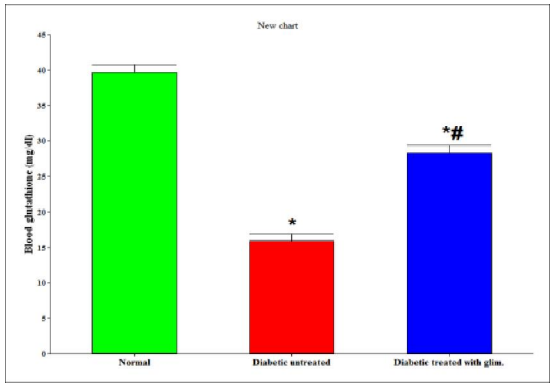

Figure (39): Effect of treatment with glimepride on blood level of glutathione of the diabetic rats.

Each value represents the mean ± SE (standard error) of 7 – 9 animals.

* Significant difference from the normal rats (P<0.01).

Significant difference from the diabetic untreated rats (P<0.01).

The results show that blood glutathione was decreased significantly (P< 0.001) in the diabetic untreated rats in comparison with the normal rats. |in the diabetic rats treated with glimepride, blood glutathione was increased significantly (P< 0.001) in comparison with the diabetic untreated rats, but still there was a significant (P<0. 01) decrease as compared to the normal rats as shown in figure (39).

Effect of treatment with losartan on blood level of glutathione of the diabetic rats.

The results show that blood glutathione of the diabetic rats treated with losartan was increased significantly (P< 0.01) in comparison with the diabetic untreated rats, but still there was a significant (P< 0.05) decrease in comparison with the normal rats. While treatment with losartan & glimepride significantly increased (P< 0.01) blood glutathione of the diabetic rats with no significant difference (P> 0.05) as compared to normal rats as shown in figure (40).

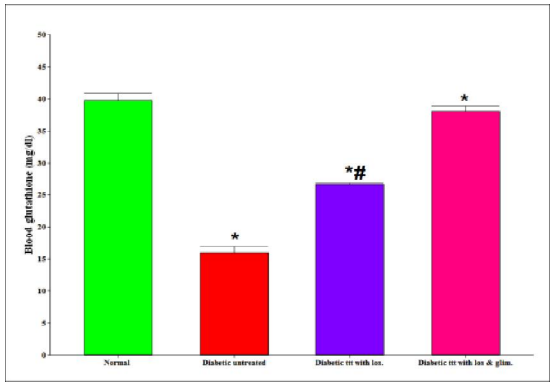

Figure (40). Effect of treatment with losartan on blood level of glutathione of the diabetic rats.

Each value represents the mean ± SE (standard error) of 7 – 9 animals.

* Significant difference from the normal rats (P<0.01).

Significant difference from the diabetic untreated rats (P<0.01).

Effect of treatment with enalapril on blood level of glutathione of the diabetic rats.

The results show that blood glutathione of the diabetic rats treated with enalapril was significantly increased (P< 0.01) in comparison with the diabetic untreated rats but still there was a significant (P< 0.05) decrease in comparison with the normal rats. While treatment with enalapril & glimepride significantly increased (P< 0.001) blood glutathione of the diabetic rats but still there was a significant (P< 0.05) decrease in comparison with the normal rats as shown in figure (41).

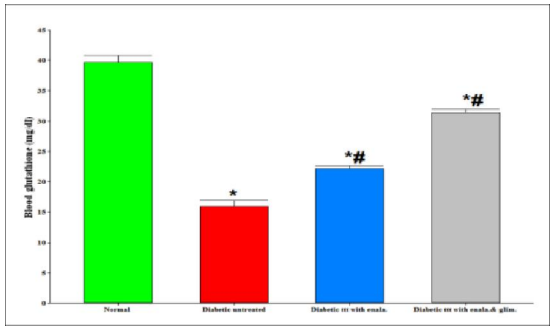

Figure (41): Effect of treatment with enalapril on blood level of glutathione of the diabetic rats.
Each value represents the mean ± SE (standard error) of 7 – 9 animals.
* Significant difference from the normal rats (P<0.01).
# Significant difference from the diabetic untreated rats (P<0.01).

Effect of treatment with atorvastatin on blood level of glutathione of the diabetic rats.

The results show that blood glutathione of the diabetic rats treated with atorvastatin was significantly increased (P< 0.01) in comparison with the diabetic untreated rats but still there was a significant (P< 0.05) decrease in comparison with the normal rats. While treatment with atorvastatin & glimepride significantly increased (P< 0.001) blood glutathione of the diabetic rats but still there was a significant (P< 0.05) decrease in comparison with the normal rats as shown in figure (42).

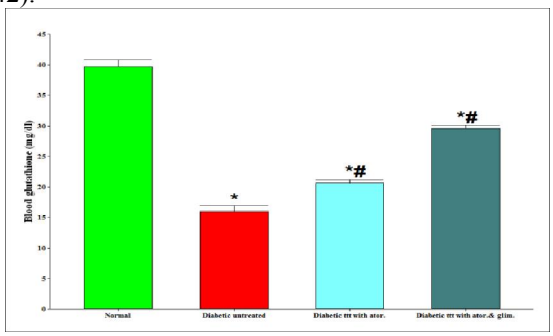

Figure (42): Effect of treatment with atorvastatin on blood level of glutathione of the diabetic rats.
Each value represents the mean ± SE (standard error) of 7 – 9 animals.
* Significant difference from the normal rats (P<0.01).
# Significant difference from the diabetic untreated rats (P<0.01).

Effect of treatment with glimepride on blood level of superoxide dismutase of the diabetic rats.

The results show that blood superoxide dismutase was decreased significantly (P< 0.01) in the diabetic untreated rats in comparison with the normal rats. in the diabetic rats treated with glimepride, blood superoxide dismutase was increased significantly (P< 0.01) in comparison with the diabetic untreated rats, but still there was a significant (P<0.05) decrease as compared to the normal rats as shown in figure (43).

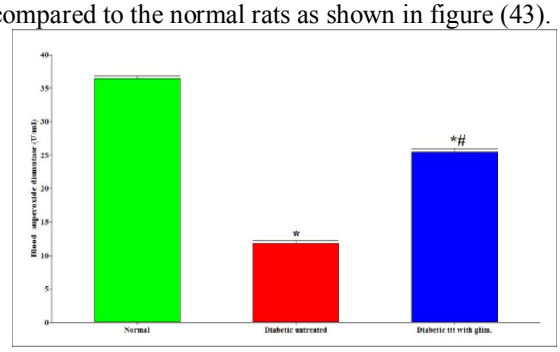

Figure (43): Effect of treatment with glimepride on blood level of superoxide dismutase of the diabetic rats.
Each value represents the mean ± SE (standard error) of 7 – 9 animals.
* Significant difference from the normal rats (P<0.01).
# Significant difference from the diabetic untreated rats (P<0.01).

Effect of treatment with losartan on blood level of superoxide dismutase of the diabetic rats.

The results show that blood superoxide dismutase of the diabetic rats treated with losartan was increased significantly (P< 0.01) in comparison with the diabetic untreated rats, but still there was a significant (P< 0.05) decrease in comparison with the normal rats. While treatment with losartan & glimepride significantly increased (P< 0.01) blood superoxide dismutase of the diabetic rats with no significant difference (P> 0.05) as compared to normal rats as shown in figure (44).

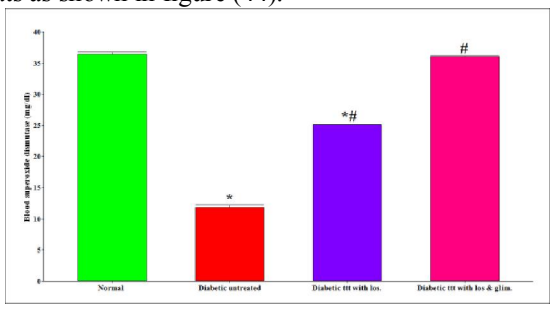

Figure (44): Effect of treatment with losartan on blood level of superoxide dismutase of the diabetic rats.
Each value represents the mean ± SE (standard error) of 7 – 9 animals.
* Significant difference from the normal rats (P<0.01).
# Significant difference from the diabetic untreated rats (P<0.01).

Effect of treatment with enalapril on blood level of superoxide dismutase of the diabetic rats.

The results show that blood superoxide dismutase of the diabetic rats treated with enalapril

was significantly increased (P< 0.01) in comparison with the diabetic untreated rats but still there was a significant (P< 0.05) decrease in comparison with the normal rats. while treatment with enalapril & glimepride significantly increased (P< 0.01) blood superoxide dismutase of the diabetic rats with no significant difference (P> 0.05) as compared to normal rats as shown in figure (45).

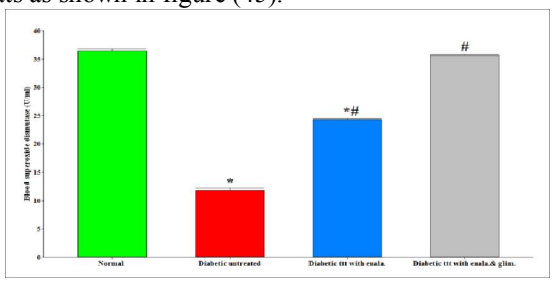

Figure (45): Effect of treatment with enalapril on blood level of superoxide dismutase of the diabetic rats.

Each value represents the mean ± SE (standard error) of 7 – 9 animals.

* Significant difference from the normal rats (P<0.01).

Significant difference from the diabetic untreated rats (P<0.01).

Effect of treatment with atorvastatin on blood level of superoxide dismutase of the diabetic rats.

The results show that blood superoxide dismutase of the diabetic rats treated with atorvastatin was significantly increased (P< 0.01) in comparison with the diabetic untreated rats but still there was a significant (P< 0.05) decrease in comparison with the normal rats. while treatment with atorvastatin & glimepride significantly decreased (P< 0.01) blood superoxide dismutase of the diabetic rats with no significant difference (P> 0.05) as compared to normal rats as shown in figure (46).

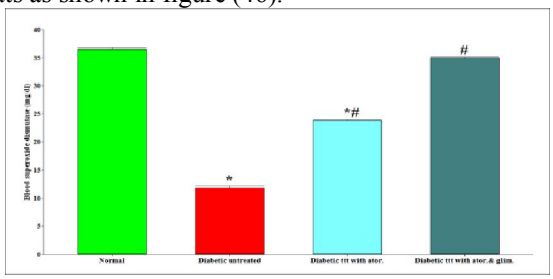

Figure (46): Effect of treatment with atorvastatin on blood level of superoxide dismutase of the diabetic rats.

Each value represents the mean ± SE (standard error) of 7 – 9 animals.

* Significant difference from the normal rats (P<0.01).

Significant difference from the diabetic untreated rats (P<0.01)

Effect of treatment with glimepride on serum malondialdehyde of the diabetic rats.

The results show that serum malondialdehyde was increased significantly (P< 0.01) in the diabetic untreated rats in comparison with the normal rats. in the diabetic rats treated with glimepride, serum malondialdehyde was decreased significantly (P< 0.01) in comparison with the diabetic untreated rats, but still there was a significant (P<0.05) increase as compared to the normal rats as shown in figure (47).

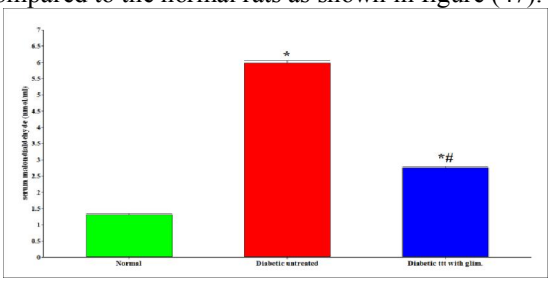

Figure (47): Effect of treatment with glimepride on serum malondialdehyde of the diabetic rats.

Each value represents the mean ± SE (standard error) of 7 – 9 animals.

* Significant difference from the normal rats (P<0.01).

Significant difference from the diabetic untreated rats (P<0.01).

Effect of treatment with losartan on serum malondialdehyde of the diabetic rats.

The results show that serum malondialdehyde of the diabetic rats treated with losartan was decreased significantly (P< 0.01) in comparison with the diabetic untreated rats, but still there was a significant (P< 0.05) increase in comparison with the normal rats. while treatment with losartan & glimepride significantly decreased (P< 0.01) serum malondialdehyde of the diabetic rats with no significant difference (P> 0.05) as compared to normal rats as shown in figure (48).

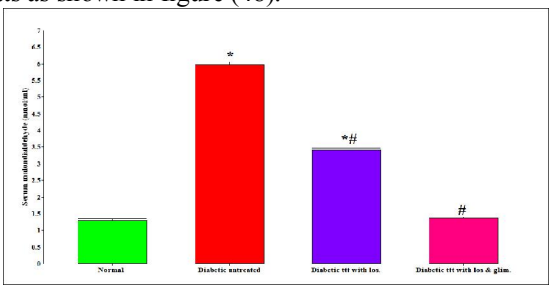

Figure (48): Effect of treatment with losartan on serum malondialdehyde of the diabetic rats.

Each value represents the mean ± SE (standard error) of 7 – 9 animals.

* Significant difference from the normal rats (P<0.01).

Significant difference from the diabetic untreated rats (P<0.01).

Effect of treatment with enalapril on serum malondialdehyde level of the diabetic rats.

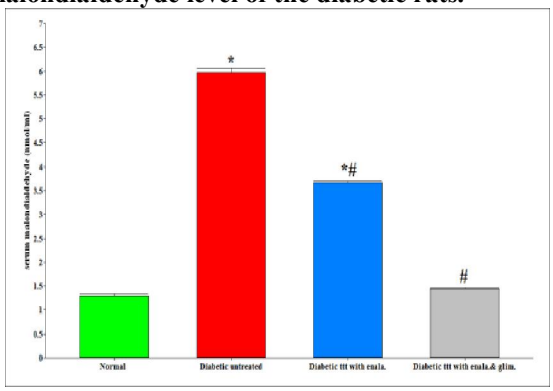

Figure (49): Effect of treatment with enalapril on serum malondialdehyde level of the diabetic rats.
Each value represents the mean ± SE (standard error) of 7 – 9 animals.
*Significant difference from the normal rats (P<0.01).
Significant difference from the diabetic untreated rats (P<0.01).

The results show that serum malondialdehyde of the diabetic rats treated with enalapril was significantly decreased (P< 0.01) in comparison with the diabetic untreated rats but still there was a significant (P< 0.05) increase in comparison with the normal rats. while treatment with enalapril & glimepride significantly decreased (P< 0.01) serum malondialdehyde of the diabetic rats with no significant difference (P> 0.05) as compared to normal rats as shown in figure (49).

Effect of treatment with atorvastatin on serum malondialdehyde level of the diabetic rats.

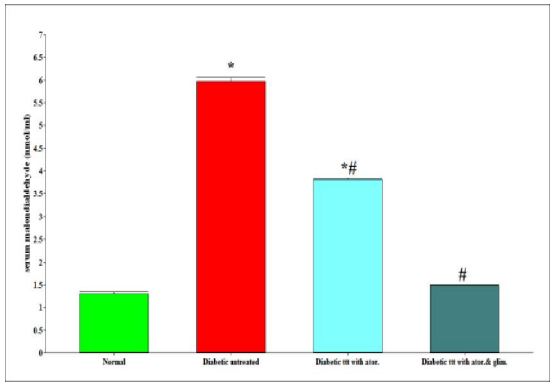

Figure (50): Effect of treatment with atorvastatin on serum malondialdehyde level of the diabetic rats.
Each value represents the mean ± SE (standard error) of 7 – 9 animals.
* Significant difference from the normal rats (P<0.01).
# Significant difference from the diabetic untreated rats (P<0.01).

The results show that serum malondialdehyde of the diabetic rats treated with atorvastatin was significantly decreased (P< 0.01) in comparison with the diabetic untreated rats but still there was a significant (P< 0.05) increase in comparison with the normal rats. while treatment with atorvastatin & glimepride significantly decreased (P< 0.01) serum malondialdehyde of the diabetic rats with no significant difference (P> 0.05) as compared to normal rats as shown in figure (50).

Effect of treatment with glimepride on fasting blood glucose of the diabetic rats.

The results show that fasting blood glucose was increased significantly (P< 0.001) in the diabetic untreated rats in comparison with the normal rats. in the diabetic rats treated with glimepride, fasting blood glucose was decreased significantly (P< 0.01) in comparison with the diabetic untreated rats, but still there was a significant (P<0.05) increase as compared to the normal rats as shown in figure (51).

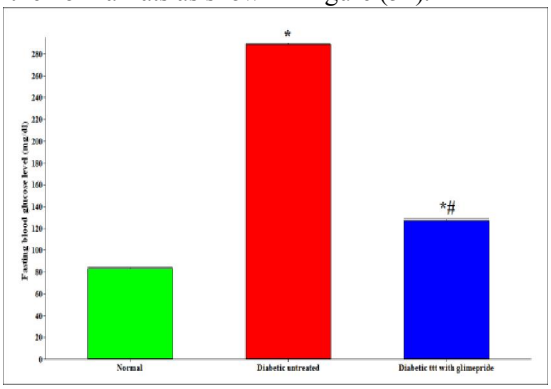

Figure (51): Effect of treatment with glimepride on fasting blood glucose of the diabetic rats.
Each value represents the mean ± SE (standard error) of 7 – 9 animals.
* Significant difference from the normal rats (P<0.01).
#Significant difference from the diabetic untreated rats (P<0.01).

Discussion

Diabetes mellitus is a metabolic disorder characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both. DM affects approximately 170 million individuals worldwide and is expected to alter lives of at least 366 million individuals within a future span of 25 years **(Maiese et al., 2008).**

Diabetes is a serious disorder with micro and macrovascular complications that result in significant morbidity and mortality. The incidence of CVD in diabetic patients has increased up to 3 folds and is a leading cause of death worldwide **(Grundy et al,. 1999).**

Several studies have shown that hyperglycaemia induces endothelial dysfunction through the generation of oxidative stress which has been suggested to be the key player in the generation of cardiovascular complications **(Brownlee, 2001).**

The renin-angiotensin system plays a crucial role in circulatory homeostasis and the regulation of vascular tone. There is growing body of evidence that enhanced activation of RAAS and the subsequent increase of AII & aldosterone levels contribute to changes of the insulin signaling pathway and promote the formation of ROS that induces endothelial dysfunction & CVD **(Cooper et al., 2007).** Therefore, both hyperglycemia and AII mediated action lead to oxidative stress and play a central role in the progression of diabetes and development of diabetic complication **(Cooper et al., 2007).**

Hypertension is common in diabetes affecting up to60% of patients and increases the risk of complications **(National high blood pressure educational program 1994).**

Renin angiotensin system inhibitors are safe and effective drugs for the treatment of hypertension. Exogenous administration of RAAS blockers may be beneficial in counteracting functional changes of atherosclerosis because the RAAS has been reported to be an important contributory factor in the pathophysiology of CVD **(Cooper et al., 2007).**

Because hypertension frequently occurs together with insulin resistance and dyslipidemia **(Reaven et al., 1996)**, The availability of multifunctional molecules that treat more than just increased blood pressure or the associated metabolic disturbances could be of considerable clinical value **(Reaven et al., 1996)**.

Statins are widely used in hyperlipidemia **(Liao.,2004)**. Hovewer, statins have not only lipid-lowering properties but also have significant effects on inflammation and oxidative stress (**Sugiyama et al., 2005).** These are called pleiotropic effects and they are independent the effects on the lipid profile (**Shaw et al., 2009) and (Lahera et al., 2007)**. Moreover, statins have been shown to modulate endothelial nitric oxide synthase (eNOS) (**Endres et al., 1998)**.

Atorvastatin (AT) was the most effective statin commonly used in lowering cholesterol compared to other statins. AT has also improving on the markers of oxidative stress and inflammation in diabetic rats (**Mauser et al., 2007) and (Gonzalez et al., 2000)**.

In the present study we evaluate and compare the effects of glimepride, ACE inhibitor (enalapril), ARB (losartan) and (atorvastatin) on the blood glucose level, insulin level, lipid profile, kidney function, oxidative stress parameters and the vascular reactivity in streptozotocin induced diabetic rats.

Diabetes mellitus in rodents is a reliable and useful model for rapid observation of the protective effects of investigated agents on diabetes- induced damage **(Yilmaz et al., 2004).** STZ injected intraperitoneally at a dose of 50mg/kg effectively induced diabetes after 72 hrs as reflected by high blood glucose levels in normal fasted rats. The hyperglycemia and diabetes were imputed to the selective destruction of pancreatic β cells that secrete insulin **(Zheng et al., 2007).**

The results of the present study show that the contractile response of the rat's isolated aortae induced by norepinephrine (NE) is increased significantly in the diabetic untreated rats in comparison with the normal rats. While results eliceted by acetylcholine (ACh) on NE precontracted aortic ring preparations show that the relaxant response of the aorta was decreased significantly in the diabetic untreated rats in comparison with the normal rats.

The results obtained by the present study are in agreement with the results obtained by **Desoky et, al., 2014**, They reported that diabetes was associated with deterioration in vascular reactivity. We have found significant increases in aorta responsiveness to phenylephrine (PE) and to KCl and a large decrease in aorta responsiveness to ACh.

Roghani et. al., 2013, They showed that contraction of aortas to KCl and PE from diabetic rats significantly increased as Compared to the aortic rings from control animals. Impaired endothelial function, enhanced sensitivity of calcium channels, an increase in vasoconstrictor prostanoids due to increased O2.−and increased sensitivity to adrenergic agonists might all be responsible for increased contractile responses in diabetic rats.

In endothelial cells of most of the vascular beds, ACh can stimulate production and release of endothelial-derived relaxing factors including NO, prostacyclin and endothelium-derived hyperpolarizing factor and in this way leads to relaxation of vascular smooth muscle in an endothelium-dependent manner. The ACh-induced relaxation response is endothelium-dependent and NO-mediated (**Zhang et, al., 2011).**

Roghani et. Al., 2013 also showed that the endothelium-dependent relaxant response was reduced in aortas from STZ-induced diabetic rats.

On the other hand our results were in disagreement with the results obtained by **Ramanadham et, al., 1984,** They reported that responses in aortae obtained from diabetic animals to the alpha-agonists, NE, and methoxamine, were found to be depressed relative to control tissue.

Results presented by **Xavier et. al., 2003,** They demonstrated that STZ induced diabetes produced an enhanced responsiveness to PE in aortas, although

evidencing an increased production of endothelium-derived NO.

Mohd & Macha 2006, They reported that The vasoconstriction of PE was significantly augmented in diabetic rats aortic rings, compared with aortic rings taken from normal rats. They added that The relaxant effect of ACh was significantly reduced in aortic rings from diabetic rats compared with aortic rings from normal rats.

Wang et. al., 2015, They reported that co-administration of nifedipine and metformin, irbesartan and glibenclamide/glimepiride/metformin reversed the endothelial cell dysfunction induced by high glucose.

The obtained results from the present study are in agreement with the results obtained by **mostafa et. al., 2014**, They reported that combination of Losartan and L-carnitine exhibited additive beneficial responses towards the inflammatory and oxidative stress markers as well as endothelial dysfunction in STZ- induced diabetic rats.

Mostafa et. al., 2014, They reported that aorta of diabetic rats exhibited enhanced O2 generation and this was associated with decreased eNOS expression. While treatment with either losartan or L -carnitine markedly enhanced NO availability via increasing eNOS expression levels.

Xiang et. al., 2014, They reported that endothelial dysfunction occurred in metabolic syndrome (MS) rats was characterized by depressed endothelium-dependent vasorelaxation. Combination therapy of losartan and pioglitazone improved endothelial dysfunction of MS rats to a greater extent than either monotherapy. Among the various endothelium-derived molecules, NO has been demonstrated to play a key role in the regulation of vascular tone and BP. Reduction in production and/or oxidative NADPH oxidase has been shown to be a major source of superoxide anion (O2 −, the main >species of reactive oxygen species) in cardiovascular tissues **(Taniyama and Griendlin 2003)**.

The obtained results from the present study are in agreement with the results obtained by **Tourandokht et al.2004**, They reported that The endothelial functions (ACh-dependent relaxation) was impaired in the aorta from diabetic rats, enalapril treatment improved endothelial function in diabetic rats. Enalapril also significantly reduced the PE-dependent constriction in diabetic rats.

Baluchnejadmojarad et al., 2004, They reported that administration of enalapril could decrease vascular responsiveness to vasoconstrictors, such as phenylephrine and produce increased relaxation response to acetylcholine in diabetic rats.

Several possible mechanisms could explain the protective effect of enalapril on the functional abnormalities observed in the diabetic rat aorta. The results of previous studies have shown that acute in vitro administration of ACE inhibitors could decrease vascular responsiveness to a-adrenergic agonists and produce increased relaxation responses, possibly as a result of decreased degradation of the bradykinin **(Kikta and Fregly, 1982).**

The obtained results from the present study are in agreement with the results obtained by **sena. et al., 2014** and **Lefer et al. 2001** they reported that atorvastatin ameliorate the abnormal vascular relaxation and partially restore NO production in the aorta of diabetic mice.

Murrow *et al.* 2012, They reported that atorvastatin has been shown to normalize endothelial function and reduces oxidative stress by inhibiting vascular NADPH oxidases and preventing eNOS uncoupling by an up-regulation of GTP cyclohydrolase1 **(Wenzel *et al.* 2008).**

The obtained results from the present study are in agreement with the results obtained by Manpreet **et al., 2015**, They reported that STZ treated rats shows significant increase in blood glucose levels by increase the formation ROS by breaking the single strand of DNA which leads to the activation **of PARP and** result in apoptotic and necrotic death of Islets of Langerhans **(Balakumar et al., 2008 and Hrabak et al., 2006).**

Thesis work show that fasting blood glucose was increased significantly and serum insulin level was decreased significantly in the diabetic untreated rats in comparison with the normal rats. In the diabetic rats treated with glimepride, fasting blood glucose was decreased significantly and serum insulin level was increased significantly in comparison with the diabetic untreated rats, and this finding was in agreement with the results obtained by **Mohamed et al., 2014,** Showed that STZ induced a significant elevation in serum glucose concomitant with significant reduction of serum insulin as compared to the control counterpart. Treatment with glimepride resulted in significant reduction of serum glucose with significant rise of serum insulin.

Marwa *et al., 2012*, They reported that single injection of streptozotocin (50 mg/kg, i.p.) increase blood glucose level and decrease insulin sensitivity index, that are the main characteristics of type II diabetes mellitus and revealed that glimepiride (0.5 mg/kg) significantly reduced the serum glucose level of STZ-induced diabetic rats after two weeks of daily dose administration.

Saleh and Maged., 2011, They reported that treatment of **diabetic rats** with glimepiride increased insulin levels and lowered markedly glucose levels.

Mir *et al.*, 2008; Hsu *et al.*, 2009 and Mowla *et al.*, 2009, They reported that glimepiride (0.5 mg/kg) significantly reduced the serum glucose level of STZ-

induced diabetic rats after two weeks of daily dose administration.

Korytkowski *et al.*, 2002 and Rosenstock *et al.*, 1996, They reported that glimepiride significantly elevated serum insulin level in STZ-diabetic rats.

Depending on the findings of the present study, it could be suggested that the hypoglycemic effect of glimepiride was attributed to its stimulation of insulin secretion. This explanation is in accordance with that given by **(Philipson and Steiner, 1995; Fuhlendorff *et al.*, 1998 and Muller, 2005)** they found that glimepiride binds to sulfonylurea receptors on β-cells leading to blocking of K^{+}_{ATP} channels, opening of voltage-gated calcium channels and increase in Ca^{2+} influx leading to insulin release from pancreatic β-cells.

Magda et al., 2009, They reported that glimepiride treatment of diabetic rats resulted in improving glycemic control without significantly increasing the weight compared to control, but a significant increase in comparison to nontreated diabetic rats was estimated. This was in accordance with results of **Gottschalk et al. (2007)** but contradicted with **Radermecker and scheen., 2006,** Who detected a further reduction in body weight in glimepiride treated diabetic rats.

In contrast to our results, **Duckworth *et al.*, 1972; Olefsky and Reaven, 1976; Beck-Nielsen *et al.*, 1979 and See *et al.*, 2003,** They observed that glimepiride has hypoglycemic action without significant effect on plasma insulin level, indicating that glimepiride has, in addition, an extrapancreatic activity which includes both insulin-mimetic and insulin-sensitizing activity **(Muller, 2005).**

The present work shows that fasting blood glucose is decreased significantly and serum insulin level is increased significantly in the diabetic rats treated with losartan in comparison with the diabetic untreated rats, Our results also show that treatment of the diabetic rats with a combination of glimpride and losartan normalized blood glucose and serum insulin levels.

Thesis findings are in agreement with the result obtained by Murali and Goyal, 2001, They reported that administration of losartan orally to diabetic rats was observed to improve insulin sensitivity to reduce elevations in fasting and fed glucose concentrations**.**

Hanan et al., 2016, They reported that Chronic treatment of diabetic rats with losartan showed a mild improvement of diabetic glycemia, which is similar to the findings of (**Murali and Goyal 2001).**

Other studies reveal that losartan increases sensitivity and enhances β-cell responsiveness to glucose and enhances glucose homeostasis Fang and Huang, 1998**,** In subjects with type 2 diabetes and nephropathy **(**Henriksen ***et al***. 2001 **&** Jin and Pan, 2007**).**

Thesis findings are in agreement with the result obtained by **murthy et al., 2013,** Who found that the co-administration of losartan with glimepiride results in alteration of the hypoglycemic activity of glimepiride and was more pronounced in the multiple-dose interaction study in diabetic rats.

Schupp, ***et al***., 2004, Who reported that Losartan-mediated improvement in insulin sensitivity is mainly due to an increase in non-oxidative glucose metabolism and blood flow in insulin-resistant hypertensive patients**.**

Chu ***et al***. 2006, Who reported that AT1 receptor antagonism improves β-cell function and glucose tolerance in young type 2 diabetic mice.

Nesren et, al. 2010, Who showed that adjunct use of losartan, AgII receptor blocker, with the oral hypoglycemic agent in type 2 DM patients significantly decreased fasting blood glucose levels, and this observation was compatible with that reported by **Jin and Pan., 2007**, Who indicate that administration of losartan, in relatively high therapeutic doses, in DM patients with nephropathy significantly reduces fasting blood glucose levels, mostly due to an increase in insulin sensitivity and improving glucose homeostasis. Additionally, it has been suggested that the plasma glucose-lowering activity of ARBs was associated with an increase in glucose utilization by peripheral tissues and/or reduction in hepatic gluconeogenesis in the absence of insulin **(Chan et, al. 2003)**.

Srikanth et al. 2013, Who reported that Atorvastatin co-administration with Pioglitazone resulted in enhanced Pioglitazone concentrations and enhanced glucose reductions.

Thesis findings is consistent with previous studies that showed that statin therapy can improve the parameters of glucose metabolism in diabetic and nondiabetic patients **(Paniagua et al. 2002, Costa et al. 2003, Sonmez et al. 2003, Watts et al. 2003, Güclü et al. 2004)**. High-dose statin therapy, however, deteriorates glycemic control in patients with diabetes **(Simsek et al. 2012).** Additionally, monotherapy with atorvastatin was able to decrement FFAs, HOMA and augment HDL-cholesterol and improved endothelial function. An improvement in HOMA index indicates that insulin resistance is ameliorated due to a decrement in fasting glucose.

Goyal et al., 2011, Who reported that in STZ-diabetic rats, insulin deficiency is associated with hypercholesterolemia and hypertriglyceridemia. A low level of plasma HDL is one component of a cluster of coronary disease risk factors that also includes abdominal obesity, hypertension, hyperinsulinemia, and insulin resistance**.**

The results of the present study show that The increase in serum concentrations of total cholesterol, triglycerides, LDL and consequent decrease in HDL levels were noted in diabetic rats as compared to normal rats. Treatment with glimpride significantly attenuated diabetes-induced alteration in lipid levels.

The obtained results from the present study are in agreement with the results obtained by other workers; **Hadi et. al., 2012,** Who reported that Oral administration of glimepiride causes significant decrease in the serum levels of triglycerides, total cholesterol and LDL-cholesterol in contrast to significant elevation in HDI.-cholesterol and body weight.

Mohamed et. al., 2014, Who reported that Oral administration of glimepiride (0.1 mg/kg) showed near-normal plasma lipid profile in STZ-induced diabetic rats.

Yassin and Mwafy 2007, They revealed that glimepiride improved HDL-c level via improvement of plasma adiponectin level as adiponectin could increase HDL-c levels directly via increased lipoprotein lipase and decreased hepatic lipase activity. On other hand, the antilipidemic action of glimepiridemay reside in their ability to stimulate insulin secretion and action.

The present work shows that total cholesterol, serum triglycerides and LDL were decreased significantly, while HDL was increased significantly in the diabetic rats treated with losartan.

These results are in agreement with the results obtained by **Salum et. al., 2014 and Kyvelou et. al., 2006,** They reported that administration of losartan potassium in diabetic rats resulted in decrease in triglycerides and total cholesterol, the lipid-lowering property of ARBs, as they suggested that some ARBs activate peroxisome proliferator-activated receptor-g, which is involved in the regulation of carbohydrate and lipid metabolism.

murali and goyal., 2001, They reported that losartan treatment significantly reduced cholesterol levels in diabetic animals without altering insulin levels. The decrease in cholesterol levels in diabetic rats may be due to improvement in insulin sensitivity by losartan.

Nesren et, al. 2010, Who reported that significantly greater improvement in the lipid profile of diabetic patients treated with captopril or losartan compared to those treated with the oral hypoglycemic agent alone; this might be attributed to the interference with the local rennin-angiotensin system in the skeletal muscles, which affect exercise performance and carbohydrate metabolism in this site **(Strazzullo, and Galletti., 2004).**

The results of the present study show that treatment with enalapril improves lipidprofile in STZ-induced diabetic rats. These results are in agreement with the results obtained by **Hassanin and Malek 2014,** They reported that enalapril at a dose of 5 mg/kg/day for duration of 12 weeks showed fall in total cholesterol and triglyceride levels, as compared to the untreated diabetic rats. However, a fall in the serum LDL was also observed.

The results of the present study are also supported the clinical study by **Xu et al., 2007,** Which included hypertensive patients with dyslipidemia received either telmisartan or enalapril for 6 months. They show that The level of TG in the telmisartan group decreased obviously after 3-month treatment compared with that of pretherapy and the enalapril, and the level of TG decreased more significantly after 6-month treatment. The level of HDL cholesterol was significantly higher after 6-month treatment in the telmisartan group than that of pretherapy and the enalapril group.

Mansour et al., 2002, Who reported that administration of enalapril at dose (20 mg/kg/day) prevented the rise in total cholesterol and triglycerides.

The mechanism could be linked to reduction of sympathetic activity by the Renin Angiotensin Aldosterone System (RAAS) inhibitors, or due to their direct effect on the lipid cascade **(Hassanin and Malek 2014**).

Previous studies have shown that enalapril and other ACEIs reduce the levels of ApoB in the serum. ApoB is the chief apoprotein of LDL and VLDL cholesterol. Further, normalization of insulin control may also play a role in managing hyperlipidaemia (**Chan et al., 1994**).

Diabetic nephropathy is a major long-term complication of diabetes mellitus. Clinically there is development of microalbuminuria with progression to overt proteinuria, increased in blood pressure and reduced renal function **(Sally et al., 2008).** Excessive deposition of extracellular matrix protein in the glomeruli and subsequent mesangial expansion are the main structural alterations in diabetic nephropathy **(Sung and Dong, 2000).** Accumulating evidences suggest that in patients with diabetes mellitus there is increased rates of lipoprotein oxidation. Hyperlipidemia may be involved in the pathogenesis of renal injury and is also considered a risk factor for diabetic nephropathy **(Noriko et al., 2002).**

Diabetic nephropathy is the most common cause of ESRD. Since diabetic ESRD patients are more prone to cardiovascular mortality than other ESRD patients, early identification of diabetic nephropathy and prompt renoprotective treatment are critical for the prevention of end organ damage from diabetic nephropathy **(Remuzzi et al., 2002).**

Nagy., 2015, Who reported that the improvement in blood urea, serum creatinine and subsequent

amelioration of histomorphological changes in kidneys of glimepiride treated rats can be attributed to the recovery of renal function which is explained by the regenerative capability of the renal tubules as good metabolic control is beneficial in slowing the progression of renal dysfunction in diabetes**.**

McCall., 2001, Who reported that glimepiride could ameliorate the glomerular and tubular lesions that characterize diabetic renal dysfunction and subsequently recover renal morphology and function. Reno-protective effect glimepiride of was further evidenced by histological observations made on the renal tissue of glimepiride treated rats that revealed normal structure of renal parenchyma.

Ravi **et al., 2011,** Who reported that Diabetic rats treated with pioglitazone and glimepiride showed reduction in albumin excretion rate, total protein excretion rate, plasma fibronectin, TGF-β1, TNF-α, transferrin concentration and renal structural changes. Interventions that have ameliorated the progression of diabetic nephropathy have been associated with a reduction in urinary protein excretion and thus renoprotective therapy should aim to achieve the maximal antialbuminuric effect (**Wang and Hirschberg., 2000)** and **(Parving., 1998)**.

Sajad et al., 2008, Who reported that the improvement in blood urea, serum creatinine and subsequent amelioration of histomorphological changes in kidneys of glimepiride treated rabbits can be attributed to the recovery of renal function **(Tedong et al., 2006)**, which is explained by the regenerative capability of the renal tubules **(Kissane, 1985).**

Tedong et al. 2006, Who have reported that the normoglycemia in diabetic rats with treatment therapies could ameliorate the glomerular and tubular lesions that characterize diabetic nephropathy and subsequently recover renal morphology and function.

There are many possible mechanisms for renal protection observed with glimepiride. Firstly, **Krauss et al. 2003,** Who demonstrated that glimepiride administration caused a decrease of peroxides and malondialdehyde levels and an increase in the activity of superoxide dismutase and glutathione peroxidase following streptozotocin administration. Ultimately, they suggested that its renoprotective action could be attributed to its protective effect against the development of oxidative stress in diabetics as it acts as free radical scavenger.

A second mechanism was introduced by **Asano et al. (1999)** via the restoration of normal mesangial contractility. Diminished mesangial contractility is responsible for the glomerular hyperfunction which is considered as a significant contributor to the development of glomerulsclerosis. However, functional activation of sulphonyle urea receptor 2 (SUR2) on mesangial cells by sulfonylurea induces elevation of intracellular Ca2+ resulting in limitation of the glomerular filtering surface area and hence hyperfiltration in already hypertrophied glomeruli. A third suggested mechanism for the renoprotective effect of glimepiride could be by acting as an exogenous competitive inhibitor of α- endosulfine, the endogenous ligand of a unique (SUR) that displaces it from its receptors.

Heron et al. 1998, Who proved that both α-endosulfine and glimepiride compete for the same receptors and found that α- endosulfine inhibits glibenclamide-invoked currents in patch clamping experiments on insulinoma cells. More recently, **Yee et al. (2004)** found that α-endosulfine could act as a regulator of mesangial cell signal transduction, glucose uptake and glomerular filtration.

The RAAS is an important pathway of progression in cardiovascular disease, diabetic nephropathy, and chronic renal disease through a mechanism of inflammation, fibrosis, and necrosis **(Brown et al., 2008).** For this reason, ACE inhibitors and ARBs are effective in the treatment of chronic heart failure and diabetic nephropathy **(Brenner et al., 2001).**

Major guidelines for treatment of hypertension in Japan, the United States and Europe recommend the use of (ACEIs) and (ARBs), which suppress the renin–angiotensin system, as the antihypertensive drugs of first choice in patients with coexisting diabetes **(Shimamoto et al., 2014).**

The results of the present study showed that treatment of the diabetic rats with either losartan, enalapril or atorvastatin significantly decrease blood urea and serum creatinine levels as compared to diabetic untreated rats.

The obtained results from the present study are in agreement with the results obtained by Manpreet **et al., 2015,** They reported that STZ treated rats shows significant increase in serum creatinine and urea level in serum level selevation of these levels causes severe damage to nephron, which indicates the abnormal kidney functioning, which was considered as significant markers of renal dysfunction, After the 3-week treatment with NaHS and losartan alone or in combination produce significantly decrease in serum creatinine and BUN levels in STZ-diabetic rats.

Jiantong et al., 2018, Who reported that serum creatinine, blood urea, urinary protein levels were noted to be markedly increased in Contrast-Induced Nephropathy in Diabetic Rats. Treatment with enalapril significantly attenuated the increased serum creatinine, blood urea, urinary protein levels Therefore, we hypothesized that enalapril may improve renal function by promoting vasodilation.

The results of the present study are also supported by Many large-scale of clinical studies

which have shown that, in patients with DM nephropathy, ACEIs and ARBs decrease albuminuria and prevent nephropathy progression **(Parving et al., 2001).**

Thesis findings are in agreement with the result obtained by **Liao et al., 2016,** Who found that diabetic rats showed obvious renal histological abnormalities and increasing CREA, BUN and UCAR levels, which reflected seriously impaired renal function, atorvastatin treatment effectively reduced renal histological injury and improved renal function in the diabetic rats.

Deedwania., 2014 and Zhou et al., 2014, They reported that diabetic rats showed obvious renal histological abnormalities and increasing CREA, BUN and UCAR levels, which reflected seriously impaired renal function, atorvastatin treatment effectively reduced renal histological injury and improved renal function in the diabetic rats.

Inflammatory factors have been proved to play an important role in the onset and progression of DKD **(Arora and Singh.,2013, Navarroand Mora, 2008).** Cytokines such as, TNF-α can induce renal cells apoptosis and necrotic death, and even disturb cell-cell junction, leading to endothelial dysfunction **(Navarroand Mora, 2008).**

Nastaran et al., 2016, Who reported that the rats were made diabetic by an intravenous injection of streptozotocin (40mg/kg) and the treated rats received atorvastatin for 8 weeks (at dose of 40mg/kg/day). At the end of the experiment, blood samples were collected to measure glucose and creatinine levels. The concentration of malondialdehyde (MDA) and the activity of renal catalase were assessed. Results: Chronic uncontrolled hyperglycemia significantly increased the blood creatinine in diabetic group compared to normal animals. Also, hyperglycemia caused a decrease in the activity of catalase enzyme along with an increase in the MDA concentration compared to normal group Atorvastatin significantly decreased the blood creatinine of diabetic animals compared to normal group. Finally, in the treated diabetic animals, renal activity of catalase enzyme increased and MDA concentration decreased. Conclusion: The findings of this study indicated that atorvastatin is able to strengthen the renal antioxidant system during diabetic nephropathy. Therefore, it appears that atorvastatin prevents hyperglycemia-induced nephropathy through the inhibition of free radical production.

Mohammad et al., 2016, Who reported that atorvastatin is able to prevent hyperglycemia induced renal damages and diabetic nephropathy possibly through attenuation of NF-κB expression in renal tissue. It is suggested that reduction of NF-κB expression by atorvastatin decreases the kidney inflammation and inhibits the progression of diabetic nephropathy independent of plasma cholesterol or glucose alterations.

Free radicals are generated as by-products of normal cellular metabolism; however, several conditions are known to disturb the balance between ROS production and cellular defense mechanisms. This imbalance can result in cell dysfunction and destruction resulting in tissue injury. The increase in the level of ROS in diabetes could be due to their increased production and/ or decreased destruction by nonenzymic and enzymic CAT, GSH-Px, and SOD antioxidants. The level of these antioxidant enzymes critically influences the susceptibility of various tissues to oxidative stress and is associated with the development of complications in diabetes. Also this is particularly relevant and dangerous for the beta islet, which is among those tissues that have the lowest levels of intrinsic antioxidant defenses **(Robertson, 2004).**

Diabetes produces disturbances of lipid profiles, especially an increased susceptibility to lipid peroxidation, which is responsible for increased incidence of atherosclerosis, a major complication of DM. An enhanced oxidative stress has been observed in these patients as indicated by increased free radical production, lipid peroxidation and diminished antioxidant status **(Moussa, 2015).**

The results of the present study show that blood level of glutathione and superoxide dismutase was decreased significantly, while serum malondialdehyde was increased significantly in the diabetic untreated rats as compared with the normal rats. Treatment with glimepride significantly increased the reduced levels of glutathione and superoxide dismutase and decreased the elevated levels of serum malondialdehyde in comparison with the diabetic untreated rats.

These results are in agreement with the results obtained by **Marwa et al., 2012,** Who showed that STZ (50 mg/kg) significantly decreased blood GSH, serum NO and blood SOD levels and significantly increased serum MDA level as compared to normal control value. Treatment with glimepride significantly reduced serum MDA level and increased blood GSH level, blood SOD activity and serum NO level of diabetic rats. glimpride possibly exerts such antioxidant effects due to the characteristics of its molecular structure.

Similar results have been reported by **(Krauss *et al.*, 2003; Kakadiya *et al.*, 2010; Kakadiya and Shah, 2011)** for TBARS; **(Kakadiya *et al.*, 2010; Kakadiya and Shah, 2011)** for GSH and **(Krauss *et al.*, 2003; Rabbani *et al.*, 2009; Kakadiya *et al.*, 2010; Kakadiya and Shah, 2011)** for SOD.

The present observations suggest that glimepiride possesses antioxidant activity against the STZ-induced oxidative stress. This suggestion is in accordance with that of **(Rabbani *et al.*, 2009).**

These results are in agreement with the results obtained Kamper **et al., 2010,** Who reported that STZ (50 mg/kg) significantly decreased blood GSH, serum NO and blood SOD levels and significantly increased serum MDA level as compared to normal control value. Treatment with glimepride significantly reduced serum MDA level and increased blood GSH level, blood SOD activity and serum NO level of diabetic rats and improve the islets environment and accelerating beta-cell regeneration.

This antioxidant effect of glimepiride may be attributed to its activation of the redox sensitive transcription factor NF (Kappa) B, activation of antioxidant enzymes such as SOD which is responsible for dismutation of superoxide ion into oxygen and hydrogen peroxide, thus protecting the cell from damage caused by superoxide activity **(Kono, 1978 and Valko *et al.*, 2007)** and to its free radical quenching properties, which leads to an increase in the number of β-cells in the islets of Langerhans in glimepiride-treated diabetic animals **(Schiekofer *et al.*, 2003).**

The antioxidant capacity of glimepride might be through inhibition of cellular cyclo-oxygenase pathways or up regulate antioxidant enzyme genes like paroxonase, superoxide dismutase, catalase gene through reducing the activation of the rodex sensitive nuclear factor Kappa-B (NF-be) or through that glimpride possessed agonistic activities for PPARγ **(fan *et al.*, 2008).**

The results of the present study show that treatment of the diabetic rats with either losartan, enalapril or atorvastatin significantly increased the reduced levels of glutathione and superoxide dismutase and decreased the elevated levels of serum malondialdehyde in comparison with the diabetic untreated rats. loasartan is more effective in improving antioxidant status than other enalapril or atorvastatin.

These results are in agreement with the results obtained by **Snigdha et al. 2014**, Who reported that there was a significant increase in tissue MDA level in liver and kidney in diabetic group compared to control group. Administration of Losartan and valsartan significantly decreased MDA level in diabetic rats.

Experimental studies in both animals and humans have demonstrated that the ACE inhibitors and ARBs possess antioxidant effects through their action on the AT1R and AT2R **(Watanabe et al. 2005).**

These results are in agreement with the results obtained by other workers; **Elena et al. 2001,** they reported that rats under chronic STZ-induced hyperglycemia, prolonged administration of enalapril protects against heart, kidney, and liver damage and concurrently attenuates oxidative stress in these tissues.

El-Mahalaway et al. 2013, Who reported that the level of MDA was significantly increased, whereas the level of SOD, CAT, and GSH were significantly decreased in the kidneys of the diabetic untreated rats; however, the level of MDA was decreased, whereas the level of SOD, CAT, and GSH were increased in the diabetic rats treated with enalapril.

These results are in agreement with the results obtained **Mohammadi etal.,2013,** Who reported that show that STZ (50 mg/kg) significantly decreased blood GSH, serum NO and blood SOD levels and significantly increased serum MDA level as compared to normal control value. Treatment with atorvastatin significantly reduced serum MDA level and increased blood GSH level, blood SOD activity and serum NO level of diabetic rats via prevention hyperglycemia-induced oxidative stress in the pancreas tissue of these animals.

Atorvastatin significantly reduced lipid peroxidation and increased the activities of glutathione peroxidase and catalase in hyperlipidemic hamsters. These effects could be correlated to the protective antioxidant effect, and/or the significant lipid lowering effect of atorvastatin. Furthermore, the reduction in lipid peroxides could be a direct consequence of the significant decrease in LDL-C which is more prone to oxidation **(Bolayirli et al.,2007)**. Statins have been shown in animal models to act as antioxidants by decreasing LDL oxidation (Rosenson and Tangney, 1998) and to modulate oxidation of lipoproteins **(Hussein et al.,1997*)*,** superoxide generation **(Giroux et al.,1993)**, and scavenger receptor expression **(Umetani et al.,1996)**. Moreover, the metabolites of atorvastatin were found to be potent antioxidant **(Mason, 2006).** Additionally, atorvastatin may provide protection from oxidative damage, induced by hyperlipidemia, indirectly *via* upregulating expression of the free radical scavenging enzyme catalase **(Kishor et al., 2007)** which is concordant with the present results.

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