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Research Article

TO STUDY THE EFFECT OF ZOFENOPRIL (ANGIOTENSIN CONVERTING ENZYME INHIBITOR) IN TYPE 2 DIABETES INDUCED NEPHROPATHY IN RATS

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ABSTRACT

The aim of present study was to evaluate the effect of Zofenopril (ACE inhibitor) in type 2 diabetes induced nephropathy in rats. Type 2 diabetes was induced by administering high-fat-diet (HFD) and streptozotocin (35mg/kg; i.p.) single dose. The rats with blood glucose levels more than 250mg/dl were selected as diabetic and taken for further studies. Diabetic rats were treated with two different doses of Zofenopril (1mg/kg and 10 mg/kg/day) p.o. for 21 days while continuing on HFD. Various parameters such as blood glucose, total cholesterol, serum creatinine, urine albumin excretion and markers of oxidative stress such as thiobarbituric acid reactive substance (TBARS) and glutathione (GSH) levels were measured. Treatment of Zofenopril (1mg/kg and 10mg/kg) in diabetic rats orally for 21 days significantly decreased total cholesterol, serum creatinine, and urine albumin levels when compared with diabetic control rats. Treatment of diabetic rats with Zofenopril 1mg/kg and 10mg/kg) orally for 21 days, showed less significant decrease in blood glucose levels when compared to diabetic control rats. Zofenopril treatment also significantly decreased the kidney TBARS levels, while increasing the GSH levels in diabetic rats. These findings suggest that Zofenopril has beneficial effects in preventing the progression of diabetes induced nephropathy in rats. In conclusion, the present study demonstrates that Zofenopril can be used to prevent progression of diabetes induced nephropathy. Administration of Zofenopril improves renal function and ameliorates renal histopathological changes in HFD fed, low dose STZ-induced type 2 diabetic rats; possibly by improvement in lipid metabolism and inhibition of lipid peroxidation process.

KEYWORDS: Type 2 diabetes, Nephropathy, Oxidative stress, Streptozotocin.

INTRODUCTION

Diabetes is a global burden on healthcare resources and its morbidity and mortality is continuously increasing. It has been estimated that worldwide prevalence of diabetes is 366 million and increased upto 552 million people by 2030[1]. Diabetes mellitus (DM) is a group of metabolic disorders characterized by elevated blood glucose levels (hyperglycemia) resulting from defects in insulin secretion, insulin action, or both and leads to long term multiorgan complications. Insulin deficiency in turn leads to chronic hyperglycaemia with disturbances of carbohydrate, fat and protein metabolism[2]. The severe type of hyperglycemia in diabetes mellitus causes abnormality in kidney function, long-term damage, and various major organ failure such as diabetic nephropathy, diabetic neuropathy and diabetic retinopathy[3]. With global epidemic of diabetes, diabetic nephropathy has become an important clinical and public health challenge. The overall prevalence of microalbuminuria is 38.8 % in the study population[4]. India has a high incidence and prevalence of diabetes and >30% have nephropathy. In India 62.4 million people are suffering from diabetic nephropathy[5].

Diabetic nephropathy (DN) is characterized by decreased Glomerular Filteration Rate (GFR), excessive deposition of extracellular matrix proteins thickening of the peripheral glomerular basement membrane, glomerular hypertrophy, tubulointerstitial fibrosis, decreased excretion of albumin and decreased creatinine clearance[6]. Diabetic nephropathy is a significant health and economic burden across the world[7]. Type 2 diabetic nephropathy is one of the major long-term microvascular complications occurring in nearly 40% of diabetic patients[8].

The pathophysiology of diabetic nephropathy is multifactorial in nature[9]. The various mechanisms which are activated by hyperglycemia lead to changes such as mesangial cell proliferation, hypertrophy, modulation in the glomerular filtration rate, tissue damage of the renal endothelium, alterations in its membrane permeability, thickening of the basement membrane, activation of inflammatory responses, accumulation of extracellular matrix and increased cell matrix production. Hyperglycaemia may act through formation and accumulation of advanced glycation end products, activation of protein kinase C[10], acceleration of the polyol pathway[11], activation of hexosamine pathway[12], and production of reactive oxygen species and over-expression of transforming growth factor-β[13]. Oxidative stress has been considered to be a common pathogenetic factor of the diabetic complications including nephropathy[14]. Oxidative stress occurs due to an imbalance between Reactive Oxygen Species (ROS) and intracellular antioxidants that results in cellular damage in diabetic nephropathy[15].

Currently used antidiabetic agents for the treatment of diabetes have little or no impact on diabetic nephropathy. Angiotensin-converting enzyme (ACE) inhibitors are effective and widely accepted therapy for the treatment of nephropathy in T2DM[16].

Zofenopril belongs to (ACE) inhibitor group characterized by high lipophilicity, sustained angiotensin converting enzyme (ACE) inhibition, antioxidant and tissue protective activities[17]. In animal

models, orally administered zofenopril is unique in producing a long-lasting inhibition. Zofenopril is capable of scavenging oxygen free radicals and also have protective effects in endothelial cells[18]. The major difference of Zofenopril as compared with other drugs is that it is converted into an active form zofenoprilat both in serum and other different tissues. However, no comprehensive evidence has yet been documented for the nephroprotective activity of Zofenopril (ACE) inhibitor experimentally or clinically. Keeping this in view, the present study was designed to evaluate the protective effect of Zofenopril in type 2 diabetes induced nephropathy in rats.

MATERIALS AND METHODS

Experimental animals

The experimental protocol used in present study was approved by the Institutional Animal Ethics Committee (IAEC). Age matched young male Sprague-Dawley rats weighing about 200-250 grams were employed in the present study. All the experimental animals were procured from Panacea Biotech Limited, Lalru, Punjab, India. The experimental animals were housed in the animal house of Rayat and Bahra Institute of Pharmacy (RBIP), Sahauran and were maintained under standard laboratory conditions with controlled temperature (22 ± 2°C), humidity (40-60%), 12 hours light-dark cycle, adequate ventilation. The animals were maintained on standard laboratory diet (Ashirwaad Feeds Ltd., Kharar, India) and having free access to water ad libitum. The care of the animals was carried out as per the guidelines of the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA), Government of India (Reg. no-1380/a/10/CPCSEA).

Drugs and Chemicals

All the drug solutions were freshly prepared before use. Streptozotocin was purchased from Sigma-Aldrich Corporation, India. Zofenopril was obtained as a gift sample from Kanha Biogenetics, Pvt. Ltd. (Baddi) India. Zofenopril in two different doses (1mg/kg and 10mg/kg) orally was freshly prepared in DMSO solution and administered to animals by using oral cannula.

Induction and assessment of nephropathy in type 2 diabetes mellitus (T2DM) in rats

Induction of T2DM was as per the method of Srinivasan et al., 2005[19]. Rats were allocated into two different dietary regimens feeding with NPD and HFD (58% fat, 25% protein and 17% carbohydrate, as a percentage of total kcal) for the initial period of 2 weeks. After the dietary manipulations, rats were injected with low dose of STZ injection (35 mg/kg; i.p.), while the respective control rats were given saline solution in a dose volume of 1ml kg−1, i.p, respectively. The rats were allowed to continue to feed on their respective diets until the end of study. The rats with blood glucose levels more than 250 mg/dl were selected as diabetic and were taken for the further pharmacological studies.

Experimental Design

The experimental protocol used was as follows:

Group I (Normal control group): Animals of this group were not subjected to any treatment. They were kept for 42 days. Biochemical estimations such as blood glucose, total cholesterol, serum creatinine and UAE were validated on different time intervals, i.e., 0, 14, 21 and 42 days. TBARS and GSH levels were measured at the end of experiment.

Group II (Diabetic control group): Animals in this group were served as diabetic control followed by High fat diet and single dose of Streptozotocin (35mg/kg, i.p.).

Group III (Diabetic Nephropathy +Zofenopril 1mg/kg): Animals of this group were treated with administration of Zofenopril (1mg/kg) orally for 21days. All biochemical parameters were validated as mentioned in group I.

Group IV (Diabetic Nephropathy +Zofenopril 10mg/kg): Animals of this group were treated with administration of Zofenopril (10 mg/kg) orally for 21days. All biochemical parameters were validated as mentioned in group I.

Collection of Blood and Tissue Samples

Blood from the experimental rats was withdrawn by retro orbital plexus technique using heparinized capillary tubes. The collected blood was placed in Eppendorff tubes (1.5 ml). In this study, blood was collected on day 0, 14, 21, 42 and used for blood glucose, cholesterol and serum creatinine estimations. After the experimental regimen, animals were sacrificed by cervical dislocation. The kidneys were excised, cleaned and washed with ice-cold phosphate-buffer saline to remove residual blood and processed for measurements of thiobarbituric acid reactive substances (TBARS) and reduced glutathione (GSH).

Estimations of oxidative stress parameters in kidney tissue homogenates

The tissue lipid peroxidation reaction was assessed by estimating thiobarbituric acid reactive substances (TBARS) by the method of Wills et al. 1966[20]. The reduced glutathione (GSH) level was assessed by the method of Ellman, 1959[21].

Histopathological Analysis

The haematoxylin-eosin staining of kidney tissue was carried out as described by Shibata et al., 2000)[22]. The kidney was dehydrated in graded concentrations of alcohol, immersed in xylene and then embedded in paraffin. From the paraffin blocks, sections of 5-µm in thickness was made and stained with haematoxylin and eosin to assess the pathological changes occurs in glomeruli using light microscopy (400x).

Statistical Analysis

The observations were statistically analyzed with the help of InStat3. The results were expressed as mean ± standard error of the mean (S.E.M). The data of body weight and the biochemical parameters were statistically analyzed with the help of two-way ANOVA followed by Bonferroni's multiple comparison tests. One-way ANOVA followed by Tukey's multiple comparison tests was used to compare the results of oxidative stress parameters. The $p<0.05$ was considered to be statistically significant.

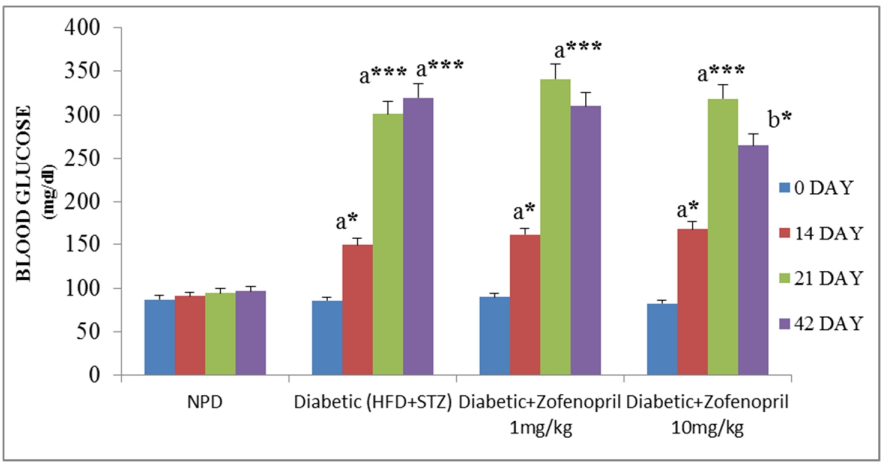

Figure 1: Effect of different doses of Zofenopril on blood glucose levels of diabetic rats.
Values are expressed as mean ± SEM, n=8. *p < 0.05, **p < 0.01& ***p<0.001. a as compared with normal rats, b as compared with diabetic rats

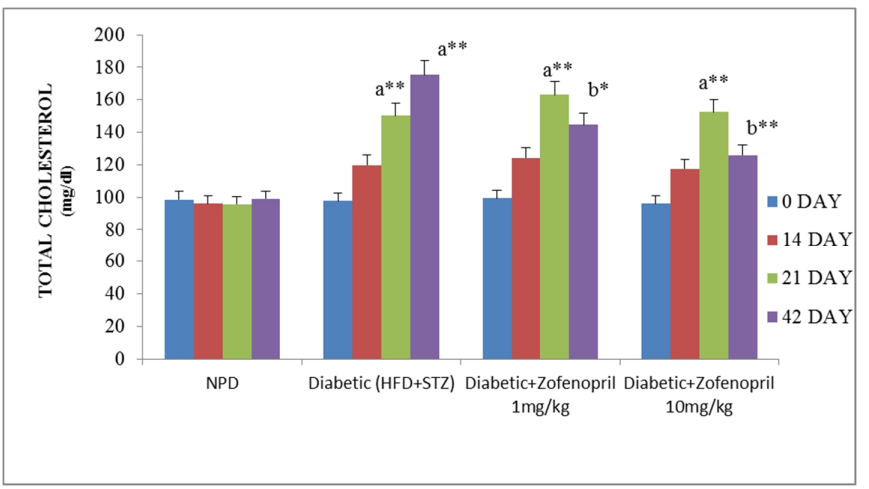

Figure 2: Effect of different doses of Zofenopril on Total Cholesterol levels of diabetic rats
Values are expressed as mean ± SEM, n=8. *p < 0.05 & **p < 0.01. a as compared with normal rats, b as compared with diabetic rats

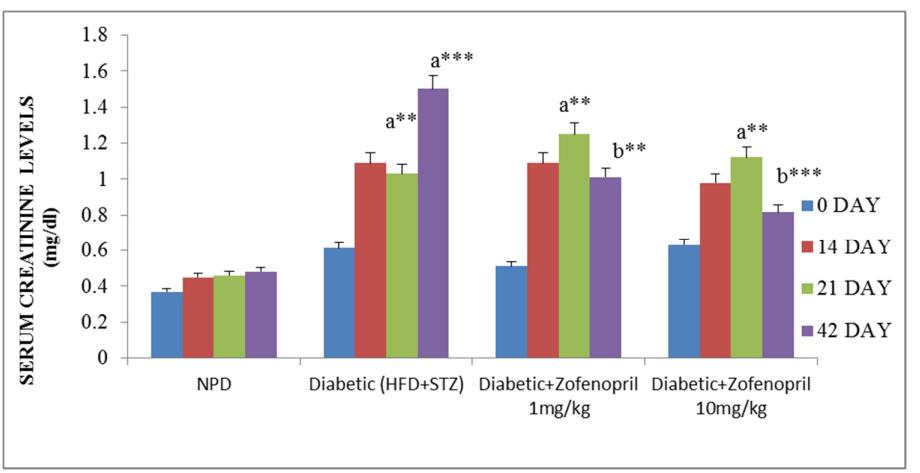

Figure 3: Effect of different doses of Zofenopril on serum creatinine levels of diabetic rats
Values are expressed as mean ± SEM, n=8. *p < 0.05, **p < 0.01& ***p<0.001. a as compared with normal rats, b as compared with diabetic rats

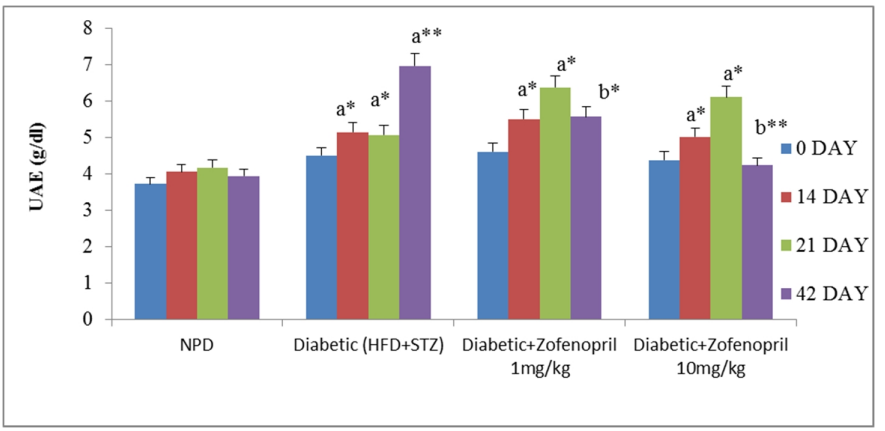

Figure 4: Effect of different doses of Zofenopril on UAE level of diabetic rats
Values are expressed as mean ± SEM, n=8. *p < 0.05 & **p < 0.01. a as compared with normal rats, b as compared with diabetic rats.

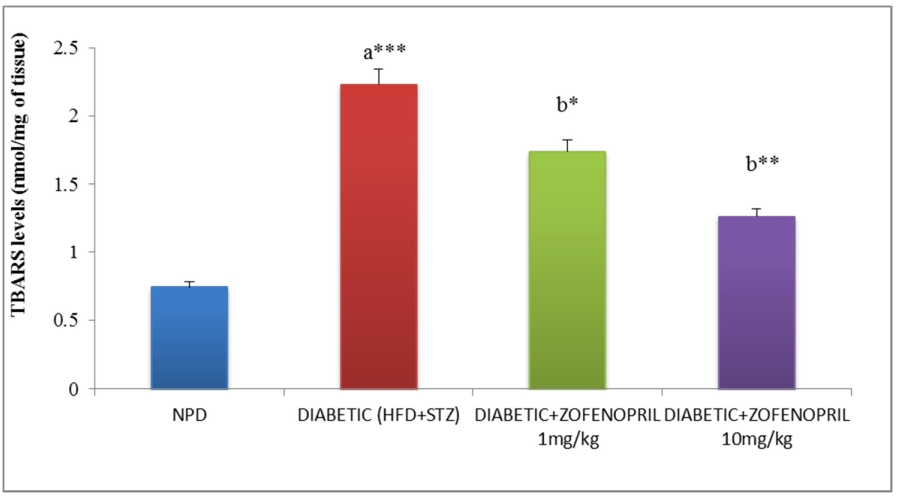

Figure 5.1: Effect of different doses of Zofenopril on lipid peroxidation (TBARS) levels on kidney tissue homogenates of rats
Values are expressed as mean ± SEM, n=8. *p < 0.05, **p < 0.01& ***p<0.001. a as compared with normal rats, b as compared with diabetic rats.

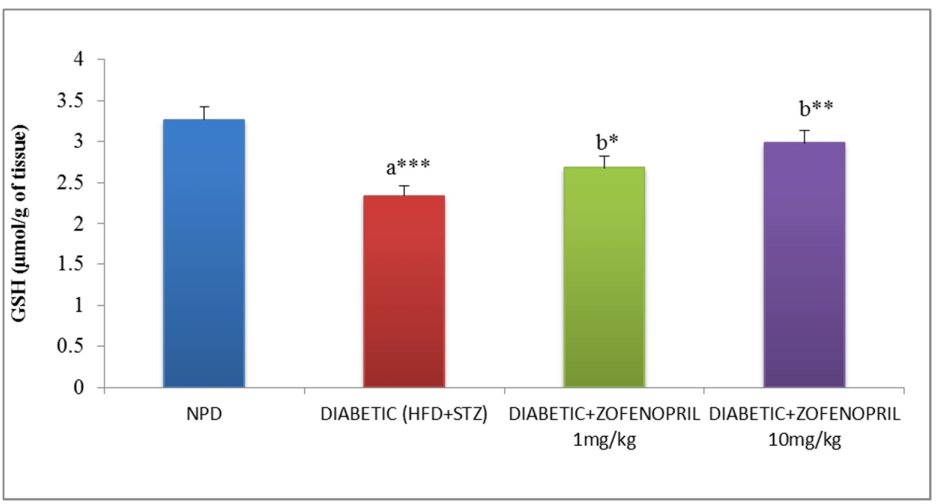

Figure 5.2: Effect of different doses of Zofenopril on glutathione (GSH) levels on kidney tissue homogenates of diabetic rats
Values are expressed as mean ± SEM, n=8. *p < 0.05, **p< 0.01& ***p<0.001. a as compared with normal rats, b as compared with diabetic rats

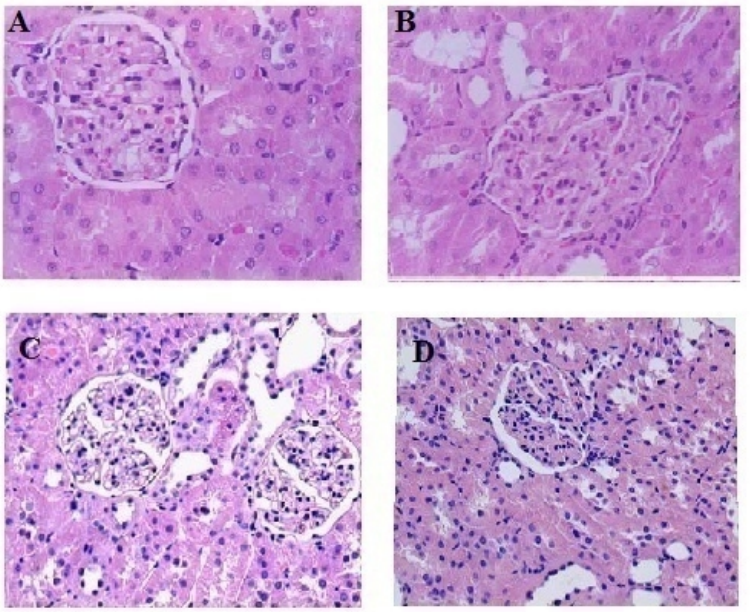

Figure 6: Histological changes in kidney of experimental rats. (A) NPD-fed group (NC), kidney showed normal sized glomerulus, normal cortical tubule and normal proximal convoluted tubules; (B) Diabetic control group (DC), kidney showed glomerular hypercellularity that lead to obliteration of the renal space, (C) Diabetic rat treated with Zofenopril (1mg/kg/day; p.o) showed an improvement of glomerular cellularity and tubular degeneration (D) Diabetic rat treated with Zofenopril (10 mg/kg/day; p.o), showed apparently healthy renal cortex.

RESULTS

Effect of different doses of Zofenopril on blood glucose levels of diabetic rats: Feeding with HFD and injection of STZ (35mg/kg; i.p.) significantly ($p<0.01$) increased blood glucose levels in diabetic rats, which was persistently elevated throughout the observation period, when compared with NPD-fed rats. Blood glucose levels of diabetic rats and NPD-fed rats were shown in the (Figure 1). Treatment of diabetic rats with Zofenopril 1mg/kg and 10mg/kg) orally for 21 days, showed less significant decrease in blood glucose levels when compared to diabetic control rats.

Effect of different doses of Zofenopril on total Cholesterol levels of diabetic rats: Feeding with HFD and injection of STZ (35mg/kg; i.p.) significantly ($p<0.001$) increased cholesterol levels in diabetic rats, which was persistently elevated throughout the observation period, when compared with NPD-fed rats. Cholesterol levels of diabetic rats and NPD-fed rats were shown in (Figure 2). Treatment of diabetic rats with Zofenopril 1mg/kg orally for 21 days, significantly ($p<0.05$) decreased cholesterol levels. However, treatment with Zofenopril 10mg/kg orally for 21 days showed more significant ($p<0.01$) decrease in cholesterol levels when compared with diabetic control rats.

Effect of different doses of Zofenopril on serum creatinine levels of diabetic rats: Feeding with HFD and injection of STZ (35mg/kg; i.p.) significantly ($p<0.001$) increased serum creatinine levels in diabetic rats, which was persistently elevated throughout the observation period, as compared to NPD-fed rats. Serum creatinine levels of diabetic rats and NPD-fed rats were shown in the (Figure 3). Treatment of diabetic rats with Zofenopril 1mg/kg orally for 21 days, significantly ($p<0.01$) decreased serum creatinine levels. However, treatment with Zofenopril 10mg/kg orally for 21 days showed more significant ($p<0.001$) decrease in serum creatinine levels when compared with diabetic control rats.

Effect of different doses of Zofenopril on urine albumin excretion levels of diabetic rats: Feeding with HFD and injection of STZ (35mg/kg; i.p.) significantly ($p<0.05$) increased urine albumin excretion levels in diabetic rats, which was persistently elevated throughout the observation period, as compared to NPD-fed rats. Urine albumin excretion levels of diabetic rats and NPD-fed rats were shown in the (Figure 4). Treatment of diabetic rats with Zofenopril 1mg/kg orally for 21 days, significantly ($p<0.05$) decreased urine albumin excretion levels. However, treatment with Zofenopril 10mg/kg orally for 21 days showed more significant ($p<0.01$) decrease in urine albumin excretion levels when compared with diabetic control rats.

ESTIMATION OF OXIDATIVE STRESS PARAMETERS

Effect of different doses of Zofenopril on lipid peroxidation (TBARS) levels on kidney tissue homogenates of diabetic rats: Feeding with HFD and injection of STZ (35mg/kg; i.p.) significantly ($p<0.001$) increased lipid peroxidation (TBARS) levels in diabetic rats, which was persistently elevated throughout the observation period, as compared to NPD-fed rats. Lipid peroxidation (TBARS) levels of diabetic rats and NPD-fed rats were shown in the (Figure 5.1). Treatment of diabetic rats with Zofenopril 1mg/kg orally for 21 days, significantly ($p<0.05$) decreased lipid peroxidation (TBARS) levels. However, treatment with Zofenopril 10mg/kg orally for 21 days showed more significant ($p<0.01$) decrease in lipid peroxidation (TBARS) levels when compared with diabetic control rats.

Effect of different doses of Zofenopril on glutathione (GSH) levels on kidney tissue homogenates of diabetic rats: Feeding with HFD and injection of STZ (35mg/kg; i.p.) significantly ($p<0.001$) decreased glutathione (GSH) levels in diabetic rats, which was persistently decreased throughout the observation period, as compared to NPD-fed rats. Glutathione (GSH) levels of diabetic rats and NPD-fed rats were shown in the (Figure 5.2). Treatment of diabetic rats with Zofenopril 1mg/kg orally for 21 days, significantly ($p<0.05$) increased glutathione (GSH) levels. However, treatment with Zofenopril 10mg/kg orally for 21 days showed more significant ($p<0.01$) increase in glutathione (GSH) levels when compared with diabetic control rats.

Histopathological Analysis

Histopathological sections of kidneys in NPD-fed rats showed adequate preservation of tubular structures with the presence of glomerular capsule. There were no sign in kidney of NPD-fed rats. Histopathology study in diabetic rat showed cloudy swelling of tubules and glomeruli and damage to cells. The kidney sections of diabetic rat also showed congestion, proteinuria, haemorrhage, and tubular degeneration. Whereas, kidney specimen of the diabetic control group showed markedly severe destruction in glomerular and tubulointerstitial lesions such as glomerular sclerosis, atrophy, interstitial expansion, and interstitial cellular infiltration. Sections were examined under light microscope.

DISCUSSION

In the present study, the HFD+STZ rats exhibited significant increase in blood glucose and total cholesterol levels as compared with NPD-fed rats. Treatment with Zofenopril (1mg/kg) showed no change in blood glucose level. However Treatment with Zofenopril (10mg/kg) orally for 21 days showed less significant change in blood glucose level as compared to diabetic control rats. However, treatment with Zofenopril (1mg/kg and 10mg/kg) orally for 21 days significantly decreased total cholesterol level as compared to diabetic control rats and results were comparable with the previous studies[23, 24].

Diabetic rats showed increase the levels of serum creatinine and urine albumin excretion (UAE) as compared to NPD-fed rats. Treatment with Zofenopril (1mg/kg and 10mg/kg) orally for 21 days significantly decreased serum creatinine and urine albumin excretion (UAE) levels when compared with diabetic control rats. The results were comparable to the previous study in which Zofenopril produced significant antidiabetic effect and has been widely approved for the treatment of diabetic nephropathy[24, 25].

There was significant increase in TBARS level in the kidneys of diabetic rats which shows increased oxidative stress when compared with NPD-fed rats. Treatment with Zofenopril (1mg/kg and 10mg/kg) orally for 21 days significantly decreased TBARS levels in diabetic rats as compared to diabetic control rats.

There was significant decrease in the GSH levels of diabetic rats when compared with NPD-fed rats. Treatment with Zofenopril (1mg/kg and10mg/kg) orally for 21 days in diabetic rats significantly increased in GSH level as compared to diabetic control rats. The results of Zofenopril were comparable to the previous studies[24, 26].

Morphological and physiological studies have identified the renal tubule systems during nephropathy in T2DM. Therefore any direct protective effect of Zofenopril would be apparent on the tubule system. The histological results reveal widespread acute tubular necrosis, focal segmental glomerular degeneration in diabetic rats.

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