Research Article

A Comparative Study for the Effect of Rosiglitazone and Sitagliptin on the Myocardium of Diabetic Experimental Animals

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ABSTRACT

Diabetes mellitus (DM) is a metabolic disorder that can cause microvascular and macrovascular complications which increase the possibility of morbidity and mortality. Diabetic cardiomyopathy (DCM) characterized by functional and structural dysregulation of the heart in DM in which hyperglycemia is the main factor involved in DCM pathogenesis. Diabetes was induced in rats by intraperitoneal injection of alloxan (70 mg/kg) and fasting blood glucose ≥ 200mg/dL considered to be diabetic. This work involved the use of 40 experimental animals. Rats were divided into 6 group: control group, non-diabetic rats with rosiglitazone (3 mg/kg/day), non-diabetic rats with sitagliptin (20 mg/kg/day), diabetic rats (alloxan 70 mg/kg IP injection), diabetic rats (alloxan 70 mg/kg IP injection) treated with rosiglitazone (3 mg/kg/day), diabetic rats (alloxan 70 mg/kg IP injection) treated with sitagliptin (20 mg/kg/day). Each diabetic rat was left for 1 month and then was given the specified doses of drugs for 1 month, the mortality rate was 50%. The results in this work showed that sitagliptin in DM group significantly decreased serum glucose level, serum cholesterol level, serum LDL level, serum creatinine kinase-MB level compared to DM group and increased serum adiponectin level compared to DM group but no significant difference in serum interleukin -1 beta, triglyceride, HDL, VLDL level. On the other hand, rosiglitazone did not show significant changes on these parameters although reduction in serum glucose level was observed. According to the results and the conditions of this work, treatment with sitagliptin showed more valuable effect than treatment with rosiglitazone in the prevention of cardiovascular complication by reducing serum levels of cholesterol, LDL, increasing serum level of adiponectin and decreasing damage of cardiomyocyte which can be correlated to the decrease in serum creatinine kinase-MB level.

Keywords: diabetes mellitus, diabetic cardiomyopathy, rosiglitazone, sitagliptin, creatinine kinase-MB, interleukin-1 beta.

INTRODUCTION

Diabetes mellitus (DM) is a metabolic disorder of proteins, carbohydrates as well as fats, which affect many people.[1] DM is associated with hyperglycemia, occurs due to either defects in insulin action, insulin secretion, or both of them.[2]

The main factors involved in the progression of DM are augmentation of lipid peroxidation, alteration in the antioxidant enzyme activities, impaired glutathione metabolism.[3] Advanced glycation end products (AGEs) play an important role in the complications of diabetes, like retinopathy, nephropathy and neuropathy via sequence of pathological alterations.[4]

Diabetic cardiomyopathy (DCM) is the damage of cardiovascular system in diabetic patients which is described as hypertrophy and dilatation of the myocardium, reduction in both systolic and diastolic function of the left ventricle. It occurs in dependently to the presence of hypertension or ischemic heart disease, hyperglycemia is the main causing factor affecting structural features and functional properties.[5]

The most important pathogenic factor relating DM with cardiomyopathy is the AGEs formation. AGEs form a cross-link to proteins in vessel wall, consequently caused thickened and leaked of the vasculature and formed irreversible deposits in artery layer.[6] AGEs produce reactive oxygen species (ROSs) that weaken cellular contacts and disturb function of the cardiac vessels resulting in dysfunction of endothelial vasomotor.[7]

In insulin resistance, there is an irregularity in the action of insulin which is directly correlated with the cardiovascular risk factors like central obesity, hyperglycemia, increase formation of AGEs, increase triglyceride level, decrease high-density lipoprotein (HDL) level and hypertension.[8]

Insulin resistance may possibly elevate blood pressure through losing the normal vasodilator activity of insulin[9], or through the effect of hyperinsulinemia which include water and Na^+ retention, increased concentrations of the intracellular sodium[10], an effect which might result in enhanced contractility and proliferation of vascular smooth muscle.[11]

Reactive oxygen species (ROSs) induce oxidative stress when their production exceeds their degradation by antioxidant. ROSs might lead to injury of cells through oxidation, disturbance in homoeostasis of vessels via interfering with nitric oxide (NO) and via modulating of intracellular signaling pathways, also, elevated level of ROSs can lead to cardiac dysfunction by destruction of DNA and proteins in addition to apoptosis.[12]

Hyperglycemia lead to increase of AGEs formation, this causes changes in the structural proteins and increased myocardial stiffness. Hyperglycemia also generates oxidative stress which stimulate factors of profibrogene

that give rise to interstitial fibrosis, important feature in DCM.[13]

Thiazolidinediones (TZDs) are one class of insulin sensitizers which targets peroxisome proliferator-activated (PPAR) receptors, and in particular PPAR-gamma (PPARγ) agonists. TZDs exert their antidiabetic activity through regulation of glucose metabolism which results in increased insulin sensitivity; in addition, TZDs regulate fatty acid secretion and adipocyte production. TZDs act on PPARγ which are expressed in various tissues including the heart.[14]

TZDs regulate insulin sensitivity by modulates glucose and lipid metabolismin adipose tissue. TZDs also regulate adipokines levels such as adiponectin, TNF-α, MCP-1, and resistin. Insulin sensitivity is improved, due to reduced levels of free fatty acid in circulation and improved adipokine profiles, which is also mediated by decrease production of glucose in the liver; stimulating uptake of glucose in skeletal muscle and promoting insulin secretion from the pancreas.[15]

Administration of rosiglitazone *in vivo*, a PPARγ agonist, inhibited MPO over expression and reduced activity of MPO in ischemic reperfused hearts. Liu reported that PPARγ agonists inhibit expression of iNOS which can be induced by lipopolysaccharide and prevent production of NO.[16] Accordingly, MPO-induction, H_2O_2/NO-dependent protein nitration are important processes responsible for tissue injury, this suggests that PPARγ may have a role as cardioprotective due to their inhibitory properties.[17]

The "incretin effect" was approved to be responsible for approximately 60% of postprandial insulin response, and results from peptide hormones released by the intestine in response to oral intake of nutrients.[18] Two incretin hormones are primarily associated with this effect, the glucagon-like peptide-1 (GLP-1) which is produced by intestinal L-cells, and, in addition to stimulating insulin secretion from pancreatic β-cells, suppresses glucose-dependent glucagon secretion, induces satiety, and slows gastric emptying.[19] The second hormone is gastric inhibitory polypeptide (GIP), produced by duodenal cells, which also stimulates insulin secretion but does not suppress glucagon release.[20]

The usual and clinically applicable action of DPP-4 is the degradation of endogenous glucagon-like peptide 1 (GLP-1), by interfering with this effect, DPP-4 inhibitors improve insulin secretion.[21]

Sitagliptin reduces hyperglycemia and glucose intolerance; in addition, it has a lipid-lowering effect. Most important effect of sitagliptin is decreased apoptosis and necrosis of the heart, hypertrophy and fibrosis in experimental T2DM, these effects can be associated with increased insulin responsiveness through stabilization of plasma GLP-1.[22]

GLP-1 controls blood glucose mostly by improving secretion of insulin and confers cardioprotective effect after congestive heart failure and myocardial infarction.[23] DPP-IV and GLP-1R has been expressed in various tissues such as vessel, liver and heart, proposing extra-pancreatic activities.[24] GLP-1R induce activation of transcription factor via RISK (cAMPPKAPI3KAkt) pathway.[25] Peroxisome proliferator-activated receptors (PPAR) are free fatty acid-binding nuclear receptors that serve as transcription factors to control inflammatory and cardiac metabolic genes.[26] PPARδ might regulate pro-fibrotic genes to avoid heart failure and cardiac fibrosis.[27]

Alloxan (2, 4, 5, 6-tetraoxypyrimidine; 5, 6-dioxyuracil) was synthesized by oxidation of uric acid and it has been shown that alloxan induces an abrupt elevation in secretion of insulin in the existence or lack of glucose.[28] These changes happened only after treatment with alloxan and was not detected after continuous exposure of β cells to alloxan.[29] The rapid elevated concentration of insulin was also detected *in vivo* after injection of rats with alloxan.[30] At first alloxan stimulate insulin release and this last for short period and is followed by complete suppression for the response of β cells to glucose, even when used sugar in high concentration.[31] The alloxan is quickly uptake by the β cells in the pancreas.[32]

Dialuric acid is the reduced product of alloxan. Dialuric acid later re-oxidized to alloxan generating a redox cycle for the formation of superoxide radicals.[33] The reaction between dialuric acid with alloxan lead to formation of intermediate alloxan radicals (HA•) and an unidentified "compound 305", the latter emerges when alloxan is reduced by glutathion.[34]

Superoxide radicals stimulate ferritin to release ferric ions and reduce them to ferrous ions and alloxan radicals could reduceFe3+, Then, superoxide radicals subject to dismutation to hydrogen peroxide: $O_2•- + O_2•- + 2 H+ \rightarrow H_2O_2 + O_2$, highly reactive hydroxyl radicals are formed in the presence of Fe^{2+} and hydrogen peroxide according to the Fenton reaction:

$Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + OH^- + OH^{•-}$, the DNA of pancreatic islets is one of the targets for reactive oxygen species DNA damage triggers poly ADP-ribosylation, a route that play important role in DNA repair.[35]

The aim of this study was comparison between the cardioprotective activity of sitagliptin and rosiglitazone on diabetic experimental animals (rats). The study used selected parameters (serum level of glucose, cholesterol, triglyceride, HDL, LDL and VLDL) in addition to selected biomarkers (adiponectin, interleukin -1 beta and creatinine kinase-MB) as well as histopathological examination of the heart to achieve the goal.

MATERIALS AND METHODS

Forty rats, weighing 180–220g were placed up in a 12 hours light-dark cycle with regulated temperature 25°C. Rats were adapted for 7 days and then divided into 6 group: control group, non-diabetic group with rosiglitazone (3 mg/kg/day), non-diabetic group with

sitagliptin (20 mg/kg/day), diabetic rat group (alloxan 70 mg/kg, IP injection), diabetic rat group (alloxan 70 mg/kg, IP injection) treated with rosiglitazone (3 mg/kg/day), diabetic rat group (alloxan 70 mg/kg, IP injection) treated with sitagliptin (20 mg/kg/day). Rats were treated with drugs (sitagliptin and rosiglitazone) via gavage feeding for 1 month.

Diabetes was induced by intraperitoneal injection of alloxan (70 mg/kg), which was dissolved in distilled water and always prepared freshly for immediate use within 5 min. Rats were starved overnight. Blood glucose level was checked for each rat after 2 days, 1, 2, and 3 weeks after alloxan injection via glucometer (Aqua check). Rats with hyperglycemia (fasting blood glucose ≥ 200 mg/dl) considered to be diabetic. The mortality rate was 50% (40 of 80 rats subjected to alloxan treatment died), each diabetic rat was left for 1 month and then was given the decided doses of drug for 1 month. At the end of the experiment, the rats were subjected to ethyl ether inhalation and blood samples were collected by puncture from the heart. Samples were collected into tube and left for clot formation, then centrifuged at 3,000x g for 10 minutes and serum was removed.

Serum glucose was measured by colorimetric kit (spinreact; spain). Serum interleukin-1β level was measured by ELIZA kit (abcam; UK). Serum level of creatinine kinase-MB was measured by i-CHROMA method (Boditech Med Int; Korea). For histological examination of heart tissue, 10% of formalin used for fixation and serial of alcohol applied on the specimens of the heart which are sectioned at (5mm) thickness and stained with Haemotoxyline and Eosin staining.

RESULTS

Effect of sitagliptin and rosiglitazone on serum glucose level

DM+sitagliptin group (148.33±13.85mg/dL) and DM+rosiglitazone group (126.40± 8.80mg/dL) showed significantly reduced serum glucose level (P < 0.01) compared to blood glucose level of DM group which was (403.83 ± 42.00 mg/dL) as shown in figure 1.
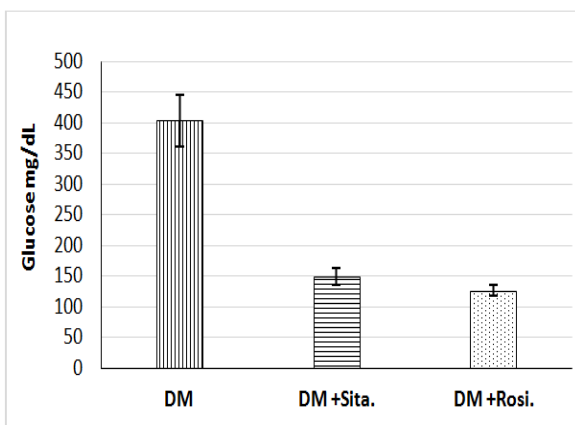
Figure 1: Effect of sitagliptin (20 mg/kg/day) and rosiglitazone (3 mg/kg′day) on serum glucose level.

Effect of sitagliptin and rosiglitazone on serum interleukin-1 beta level

Statistical analysis showed no significant difference in serum IL-1β level between DM group (265.20 ± 12.76 pg/ml), DM+ sitagliptin group (274.40 ± 24.37 pg/ml) and DM+ rosiglitazone group (339.20 ± 30.41 pg/ml) as shown in figure 2.
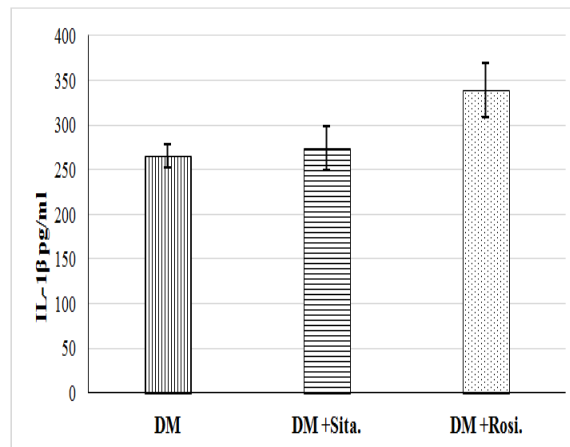
Figure 2: Effect of sitagliptin (20mg/kg/day) and rosiglitazone (3 mg/kg′day) on serum interleukin -1beta level.

Effect of sitagliptin and rosiglitazone on serum creatinine kinase-MB level

Diabetic rats treated with Sitagliptin (5.23 ± 0.52 ng/ml) showed significantly decreased in serum creatinine kinase level (P<0.05) compared to diabetic group (6.93 ± 0.23 ng/ml) and DM+rosiglitazone group (6.86 ± 0.57 ng/ml) as shown in figure 3.
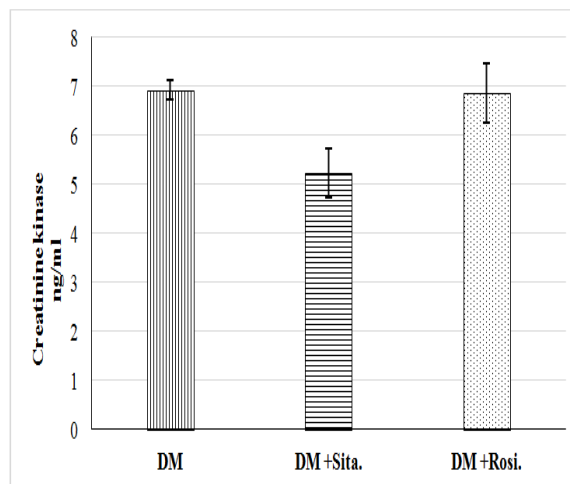
Figure 3: Effect of sitagliptin (20 mg/kg/day) and rosiglitazone (3 mg/kg′day) on serum creatinine kinase-MB level.

Histological examination

Cross section of diabetic rat's myocardium

Section of diabetic cardiac muscle fibers showed congestion, necrosis, infiltered cells, uniformity of cells

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appear disrupted and the nucleus were inconsistent (H&E×40) as shown in figure 4.
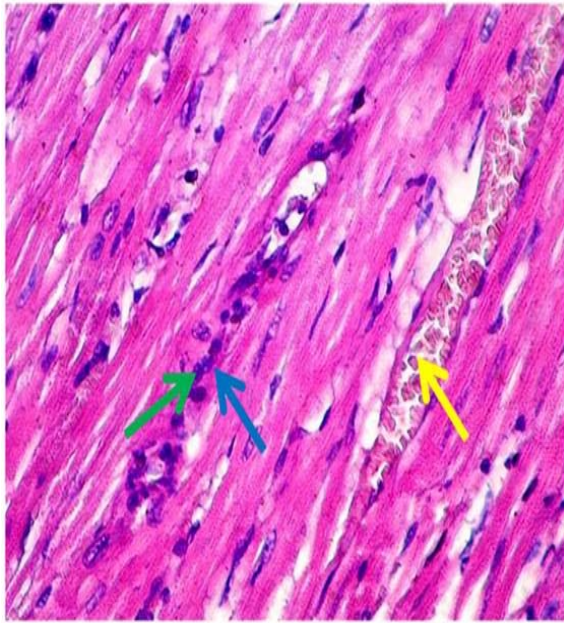

Figure 4: Cross section of diabetic rat's myocardium, yellow arrow= congestion, green arrow= Infiltered cells, blue arrow=necrosis (H&E×40).

Cross section of diabetic rat's myocardium treated with sitagliptin.

Section of cardiac muscle fibers of diabetic rat treated with sitagliptin showed congestion, necrosis and odema (H&E×40) as shown in figure 5.
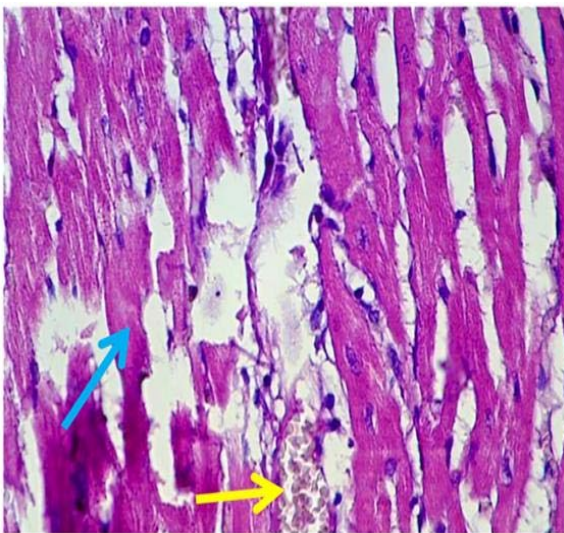

Figure 5: Cross section of diabetic rat's myocardium treated with sitagliptin, yellow arrow = congestion, blue arrow=necrosis (H&E×40).

Cross section of diabetic rat's myocardium treated with rosiglitazone.

Section of cardiac muscle fibers of diabetic rat treated with rosiglitazone showed congestion, necrosis, odema and severe inflammation with infiltered cells (H&E×40) as shown in figure 6.
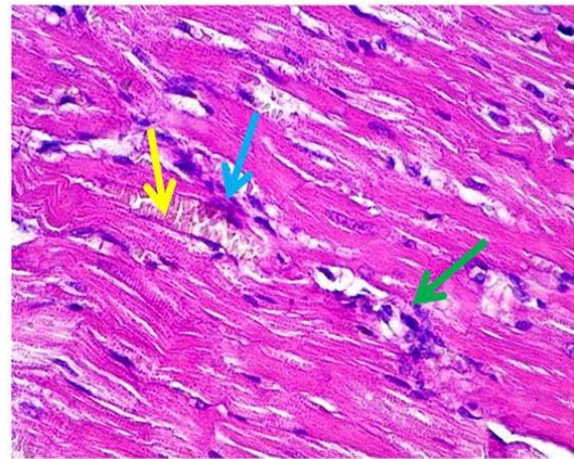

Figure 6: Cross section of diabetic rat's myocardium treated with rosiglitazone, yellow arrow = congestion, green arrow= Infiltered cells, blue arrow=necrosis (H&E×40).

DISCUSSION

The dysregulation of metabolic pathway in DM adversely affect the cardiovascular system (CVS), it might be affect the cardiac myocytes and the cellular components of the vascular walls. There are other mechanisms which might be involved such as disturbance in the Ca^{+2} homeostasis, renin- angiotensin- aldosterone system, induction of the oxidative stress and generation of reactive oxygen species. The continued scientific work of researchers in this field has provided newer insights to the understanding of the molecular and pathophysiological mechanism which make the heart susceptible for such problems.

The selection of antidiabetic treatment may affect the CVS outcome and the precise control to the metabolic dysregulation in DM reduce the incidence of DCM and associated cardiovascular death.

This study compared the effects of sitagliptin (DDP-4 inhibitor) and rosiglitazone (Thiazolidinedione) on metabolic parameters, in addition to adiponectin, IL-1β and creatinine kinase. The effectiveness of sitagliptin and rosiglitazone were compared according to serum glucose and lipid levels during the 4 weeks course of treatment.

The results in this work showed that sitagliptin significantly reduced serum glucose level in diabetic rats at the given dose (20 mg/kg/day) compared to untreated diabetic rats which is expected from it's DDP-4 inhibitory activity that involves increased GIP and GLP-1 concentration which will stimulate insulin secretion and suppress secretion of glucagon thereby improving circulatory glucose level.

The results in this work showed that rosiglitazone reduced serum glucose level in diabetic rats at the given dose (3 mg/kg/day) compared to untreated diabetic rats, this effect is expected to be mainly due to the ability of rosiglitazone (which targets PPARγ) to reduce production

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of hepatic glucose and improve insulin sensitivity in various tissue thereby regulate glucose metabolism.

Hyperglycaemia and hyperlipidemia result in the development of oxidative stress, systemic and local inflammation, which are an essential factors for degradation of βcell, insulin resistance and T2DM in several persons. Adipocytes are the main secretors of both pro-inflammatory and anti-inflammatory mediators, frequently mentioned as adipokines e.g. IL-6, IL-1β and TNF-α secreted by the adipose tissue considered as independent prognosis for diabetes.[36]

Regarding the markers of inflammation, the results in this work found that diabetic group treated with sitagliptin (20 mg/kg/day) for 4 weeks showed no significant difference in IL-1β serum level compared with untreated diabetic group and this disagree with the results explored by Ferreira (2010) which are shown that sitagliptin (10 mg/kg/day) for 6 weeks significantly reduce the level of serum IL-1β in T2DM rats and this could be due to an improvement of tissue redox cycle, with a notable positive effect on lipid peroxidation in the myocardium and pancreas. These effects, together with a decrease in TGs level, might lead to reduce destruction of pancreatic β cells.[36]

The results in this work showed that diabetic group treated with rosiglitazone (3 mg/kg/day) over 4 weeks showed no significant difference in serum IL-1β level compared with untreated diabetic group and this disagree with the results displayed by Lee (2010) which showed that rosiglitazone (3 mg/kg/day) over 12 weeks significantly reduced the level of serum IL-1β in T2DM rats. This could be due to decrease in the expression of inflammatory cytokine mRNA (TNF-α, IL-1β and IL-6) at skeletal muscle in rats treated with rosiglitazone.[37]

The presence of GLP-1 receptors in heart cells and vascular endothelial cells, suggest the beneficial effect of DPP-IV inhibitors, which act on GLP-1 receptors, in attenuation of cardiovascular complication that associated with T2DM.[38]

The results in this work found that diabetic group treated with sitagliptin (20 mg/kg/day) over 4 weeks showed significant decrease in serum creatinine kinase-MB level compared with untreated diabetic group and with diabetic group treated by rosiglitazone (3 mg/kg/day). Additionally, the group treated with sitagliptin (20 mg/kg/day) over 4 weeks showed significant decrease in serum creatinine kinase-MB level compared with control group and this showed the cardioprotective effect of sitagliptin in T2DM-induce cardiovascular insults.

Gao (2013) approved that pretreatment with rosiglitazone significantly increased the level of intracellular antioxidant enzymes and decreased the level of serum CK-MB by interfering with the formation and stimulation of inflammatory cells and cytokines, inhibit the expression of monocyte chemoattractant protein-1, intercellular adhesion molecule and inducible oxide

synthase thereby rosiglitazone could be considered as cardioprotective drug in myocardial–ischemia reperfusion model.[39]

The results in this work showed that non-diabetic group treated with rosiglitazone showed no significant difference in creatinine-kinase MB level from control group as well as diabetic group treated with rosiglitazone, this disagree with the Gao (2013) study which might be due to the use of rosiglitazone as prophylactic agent.[39]

The results of the myocardium tissue stained by H&E and examined through light microscope under magnification 40X in diabetic rats treated with sitagliptin showed congestion, necrosis and odema as shown in figure 5 and some of these changes are hallmarks of diabetes as shown in figure 4 which suggest that sitagliptin did not exert complete cardioprotective effect inspite of their beneficial effect in lowering creatinine kinase-MB level.

The results of the myocardium tissue stained by H&E and examined under light microscope under magnification 40X in diabetic rats treated with rosiglitazone showed congestion, necrosis, odema and severe inflammation as shown in figure 6 which suggest a synergistic effect of diabetic disease with rosiglitazone therapy at the experimental conditions used in this study.

CONCLUSION

According to the results displayed previously, we can conclude that alloxan successfully induced diabetes in rats at dose 70mg/kg. Both drugs (sitagliptin and rosiglitazone) exerted antidiabetic activity and reduced serum glucose level in diabetic rats around normal, control value within the doses used. DM group treated with sitagliptin decreased the damage of the cardiomyocyte which mostly related to decreasing serum creatinine kinase-MB level. DM group treated with rosiglitazone showed only improvement in control glucose level without any significant effect on inflammatory markers or in preventing cardiomyocyte damage. Treatment with sitagliptin gave more beneficial effect than treatment with rosiglitazone in DM models, taking in consideration the doses and the duration in this study, by decreasing serum level of creatinine kinase-MB level.

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