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Basic Science

Effect of Diabetes Mellitus and Its Control on Myocardial Contractile Function in Rats

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Key words: Diabetes mellitus; Thyroid dysfunction; Diabetic cardiomyopathy; Insulin; Rosiglitazone.

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Abstract

AIM: This work was done to study the effect of both types of diabetes mellitus (DM) on myocardial contractility in rats. Also, we investigated the role of treatment of DM with insulin and rosiglitazone (used as treatment for type 1 and type 2 DM respectively) in improvement of myocardial dysfunction in diabetic rats.

METHODS: The study included 50 male Wistar albino rats, divided into 5 groups: control (group I), streptozotocin induced type 1 DM (group II), fructose induced type 2 DM (group III), insulin treated type 1 diabetic rats (group IV) and rosiglitazone treated type 2 diabetic rats (group V). At the end of the study, retro-orbital blood samples were withdrawn and blood glucose, plasma triglyceride (TG), total cholesterol (TC) and thyroid hormones levels were measured. Rats were then anesthetized and their hearts were excised and connected to Langendorff apparatus to perform mechanical cardiac performance tests including heart rate (HR), left ventricular developed pressure (LVDP) and maximum rate of pressure rise (+dp/dt).

RESULTS: Data of the study showed that relative to control group, there was significant increase in blood glucose, plasma TG and TC levels while, thyroid hormones and myocardial performance parameters showed significant decrease in both type 1 and type 2 diabetic rats. Treatment of type 1 diabetic rats with insulin and type 2 with rosiglitazone resulted in significant decrease in blood glucose, plasma TG and TC levels associated with significant improvement in thyroid hormones and myocardial performance parameters. The results also showed that insulin treatment of type 1 was more effective in ameliorating all parameters than treatment of type 2 by rosiglitazone.

CONCLUSION: We concluded that the induction of both types of diabetes resulted in decreased myocardial performance parameters. The treatment of type 1 and type 2 diabetes by insulin and oral rosiglitazone respectively improved to a great extent the altered metabolism and mechanical myocardial parameters, with more improving effect of insulin in type 1 than rosiglitazone in type 2 DM.

Introduction

Diabetes mellitus is a metabolic disorder characterized by the presence of hyperglycemia due to defective insulin secretion, defective insulin action or both. Patients with diabetes have a higher risk of cardiovascular events accounting for substantial premature morbidity and mortality [1]. Many studies in humans reported the existence of a diabetic cardiomyopathy (DCM). The underlying mechanisms of this cardiomyopathy are still incompletely understood because of experimental limitations in humans. Rodent models of type 1 and type 2 diabetes mellitus (DM) share several traits with human DCM and have greatly advanced the understanding of the underlying pathology of DCM [2]. Contractile dysfunction was observed in perfused hearts from diabetic mice. There was evident increase in left ventricular end diastolic pressure and decreased left ventricular developing pressure, cardiac output and cardiac power [3]. Also, diabetes affects the thyroid hormones level and is thought to be associated with decreased serum levels of thyroid hormones {3,3′,5-triiodo-L-thyronine (T3) and thyroxine (T4)}. Since insulin treatment improves both T3/T4 levels and β-adrenoceptor-mediated responses, it points out a possible relationship between insulin and thyroid hormones [4]. More importantly, left ventricular hypertrophy and diastolic dysfunction without hypertension in type 2 diabetics may be associated with elevated insulin resistance. The use of troglitazone (TRO) which is known to increase insulin sensitivity and decrease insulin resistance has resulted in an improvement in diastolic function [5]. Recently, the protective role of thyroid hormones was described in streptozotocin induced diabetes [6]. It

was reported that diabetes being associated with altered lipid metabolism, is commonly accompanied by thyroid dysfunction. This can produce significant metabolic disturbances that share in the mechanisms of DCM [7].

Accordingly in DM, hyperglycemia, disturbed thyroid functions and altered lipid metabolism may have a great role in the development of DCM and the correction of such disturbances will be very helpful in preventing its development. So, it is of extreme importance to evaluate the efficacy of management of DM in the correction of these changes and in prevention of DCM development and other cardiovascular complications.

The aim of the present work was to study the effect of induction of both types of DM on lipid profile and thyroid hormones plasma levels and the role of these metabolic disturbances in the development of DCM. Also, we investigated the role of treatment with insulin and rosiglitazone (used for treatment of type 1 and 2 DM respectively) in the control of these changes and in improvement of myocardial dysfunction in diabetic rats.

Material and Methods

Animals

Fifty adult male Wistar albino rats weighed between 200 – 250 g were housed in wire mesh cages at room temperature. Veterinary care was provided by local laboratory animal house unit in Faculty of Medicine, Cairo University. All animals were handled according to the guidelines established by institutional animal care and use committees. Rats were housed with normal light dark cycle, and were allowed to acclimatize to their environment for five days before start of experiment. All animals were kept under the same environmental conditions and had free access to water and food. The rats were divided into five groups (each group consisted of 10 rats) as follows; group I (control group), group II (Type 1 diabetic rats), group III (Type 2 diabetic rats), group IV (Insulin treated type 1 diabetic rats) and group V (rosiglitazone treated type 2 diabetic rats).

Induction of experimental type 1 diabetes: Thirty rats were injected intraperitoneally (i.p.) with a single dose of 60 mg/kg of streptozotocin (STZ) (Sigma, Chemical Co., St. Louis, MO, USA) dissolved in sodium citrate buffer (0.1 mol/liter, pH adjusted to 4.5) at a concentration of 20 mg/ml immediately before use [8]. After 3 days, fasting blood samples were collected through the retro-orbital route using capillary tubes to assess glucose level by using a glucometer (Aquo-Check, Roche). Animals showing blood glucose higher than 200 mg/dl were considered as diabetic and twenty of them were used for the study [9].

Induction of experimental type 2 diabetes: High–fructose diets (HFD) are usually used to induce type 2 diabetes animal model [10]. Thirty rats were fed with high fructose diet (60% fructose) and water for 4 weeks after which fasting blood samples were withdrawn through the retro-orbital route using capillary tubes to assess glucose level. Rats exhibiting plasma glucose more than 200 mg/dl were considered to have type 2 diabetes [9] and twenty of them were used for the study. The animals were kept on the HFD throughout the whole period of the study (for additional four weeks after development of diabetes).

Insulin treatment protocols

Four weeks after streptozotocin injection, diabetic animals were placed on an insulin regimen for four weeks. For these animals, insulin doses were individually adjusted to maintain the euglycemia state. Insulin was given in a dose of 10 IU/kg/day subcutaneously once per day between 9:00 and 11:00 a.m. Diabetic animals whose body weight fell below 90% of initial starting body weight during the in vivo protocol had to be eliminated from the study [11]. However, no animals were eliminated as there was no reduction in their body weight below 90% of the original weight.

Administration of rosiglitazone

Rosiglitazone maleate is an oral antidiabetic agent which acts primarily by increasing insulin sensitivity. After the development of type 2 DM by administration of HFD (the time at which hyperglycemia was confirmed), rosiglitazone was given to the diabetic animals for four weeks. It was given orally in a dose of 10 mg/kg/day dissolved in 10 ml distilled water via intra-gastric tube. This dose was chosen because it has been shown to be the effective therapeutic dose in diabetic rats [12].

Samples Used

Blood samples were withdrawn from all rats through the retro-orbital route using heparinized capillary tubes. The blood samples were delivered into centrifuge tubes then, centrifuged at 10,000 rpm for 20 minutes and plasma was separated and stored at -70˚C until used. The plasma was divided into 3 tubes for further determination of plasma levels of glucose, T3, T4, triglycerides (TG) and total cholesterol (TC).

Heart perfusion Conditions

After taking blood samples, all animals were heparinized with 100 U of heparin intraperitoneally (i.p.) for 15 min. Animals were then anesthetized with 10 mg/Kg sodium pentobarbitone (i.p.). The hearts were excised and placed in ice – cold Krebs – Henseleit Bicarbonate (KHB) buffer. Extraneous

tissues (Pericardium, lung, trachea, etc.) were removed. Aorta was cannulated with an 18 – gauge plastic cannula, in a non circulating Langendorff apparatus, with modified Krebs Henseleit solution at a constant flow rate of 12 ml/min. The perfusate solution consists of the following (in mmol/l): NaCl (116), $NaHCO_3$ (25), $CaCl_2$ (205), $MgSO_4$ (102), KCl (407), KH_2PO_4 (102) and glucose (5.5). The Langendorff apparatus was water jacketed to maintain a core temperature of the heart 38°C. The perfusate was oxygenated with 95% O_2 and 5% CO_2 gas mixture to maintain a PO_2 of > 40 mmHg. A water–filled latex ballon–tipped catheter was inserted into the left ventricle through the mitral annulus and inflated with distilled water (0.15 – 0.3 ml) to set an end diastolic pressure of 2 mmHg during the initial equilibration. The distal end of the catheter was connected to a polygraph (san–ei Japan) for recording the different haemodynamic parameters, via pressure transducer, according to the experimental design. Contractile function was assessed by measuring the following parameters: Heart rate (HR), left ventricular developed pressure (LVDP) which is defined as peak systolic minus end-diastolic pressure and the maximum rate of pressure rise (+dp/dt).

Pharmacological drugs used

Rosiglitazone was obtained from Smith Kline Beecham pharmaceuticals, Philadelphia, PA 19101, U.S.A. Long acting protamine zinc insulin (PZI) was purchased from Nile Company (Egypt). Fructose was obtained from Sigma-Aldrich Labrorchemik-alien GmbH. D-30976 Seelze.

Biochemical estimation

The blood glucose was assayed by the method adopted by Trinder [13] using kits supplied by Diamond Diagnostics. Fasting plasma TG was assayed by the method previously adopted by Wahlefeld [14] using TG quantification kit supplied by BioVision Research. Fasting plasma cholesterol was assayed by the method previously described by Sundvall et al. [15] using cholesterol assay kit supplied by BioAssay Systems. Plasma total T3 and T4 concentrations were determined by radioimmunoassay methods adopted by Burtis and Ashwood [16] using reagent kits purchased from Diagnostic Systems Laboratories (USA).

Statistical Methods

Data were processed using the Statistical Package for Social Sciences® (SPSS) program v. 20 (Chicago, IL, USA). Descriptive statistics were used, as means (M) and standard deviations (SD), frequency distribution, and comparisons. One way ANOVA test was used to compare between groups, followed by post hoc test (least significant difference) for inter-group comparisons. We considered differences to be statistically significant if P values were < 0.05.

Results

1. *Effect of induction of diabetes and its treatment with insulin and rosiglitazone on blood glucose, plasma triglycerides and total cholesterol levels in type 1 and type 2 diabetes respectively (Table 1).*

In group II, the induction of type 1 diabetes resulted in significant increase in blood glucose, plasma TG and TC as compared with group I. Similarly, the same changes are observed in group III (type 2 DM). However, blood glucose and plasma TC was significantly lower, and TG was significantly higher in group III than group II. Treatment of type I diabetic rats with insulin in group III caused significant reduction of blood glucose, plasma TG and TC levels. Also, treatment of type 2 diabetic rats with rosiglitazone in group V produced significant decrease in these parameters. Also, in rosiglitazone treated type 2 diabetic rats (group V) TG was significantly lower compared to insulin treated type1 diabetic rats (group IV). On the other hand, the reverse occurred for plasma TC level as it was significantly higher in group V compared to group IV.

Table 1: Effect of induction of diabetes mellitus and its treatment with insulin and rosiglitazone on blood glucose, plasma triglycerides and total cholesterol levels in type 1 and type 2 diabetes respectively.

	ControlGroup (G1)	Type 1 diabetic rats (G2)	Type 2 diabeticrat (G3)	Type 1 DM with insulin(G4)	Type 2 DM with rosiglitazone (G5)
Glucose (mg/dl)	95.8 ± 14.34	388.7 ± 36.90*	232.60 ± 37.85 #	117.60 ± 29.91†	101.20 ± 10.76 $^{\lozenge}$
Triglycerides (mg/dl)	66.1 ± 11.14	140.5 ± 9.58 *	192.3 ± 18.05 #	103.1 ± 2.28 †	75.6 ± 7.52 $^{\lozenge}$
Total cholesterol (mg/dl)	83.5 ± 7.81	223.3 ± 11.91*	144.3 ± 6.45 #	96.7 ± 6.4 †	114.6 ± 4.67 $^{\lozenge}$

Data are expressed as mean ± SD. * p < 0.05 group 2 compared with the group 1. # p < 0.05 group 3 compared with the group 1. † p < 0.05 group 4 compared with the group 2. $^{\lozenge}$ p < 0.05 group 5 compared with the group 3.

2. *Effect of induction of diabetes and its treatment with insulin and rosiglitazone on plasma tri-iodothyronine (T3) and tetra-iodothyronine (T4) levels in type 1 and type 2 diabetes respectively (Table 2)*

The induction of type 1 and type 2 diabetes in group II and III respectively produced significant decrease in both T3 and T4 plasma levels. However, this reduction is more evident in group II than group III. Treatment of type 1 diabetic rats with insulin (group IV) and type 2 diabetic rats with rosiglitazone (group V) resulted in significant increase in plasma levels of both hormones indicating improvement in thyroid

functions. Also, plasma T3 was significantly lower while, plasma T4 was significantly higher in rosiglitazone treated type 2 diabetic rats (group V), compared to insulin treated type 1 diabetic rats (group IV).

Table 2: Effect of induction of diabetes mellitus and its treatment with insulin and rosiglitazone on plasma tri-iodothyronine (T3) and tetra-iodothyronine (T4) levels in type 1 and type 2 diabetes respectively.

	Control Group (G1)	Type 1 diabetic rats (G2)	Type 2 diabetic rat (G3)	Type 1 DM with insulin (G4)	Type 2 DM with rosiglitazone (G5)
T3 (ng/dl)	285.90 ± 12.37	134.50 ± 11.33 *	189.70 ± 11.50 #	256.60 ± 17.75 †	222 ± 5.68 ◊
T4(ug/dl)	7.52 ± 0.80	2.19 ± 0.36 *	4.98 ± 0.21 #	5.09 ± 0.57 †	6.58 ± 0.47 ◊

Data are expressed as mean ± SD. *p < 0.05 group 2 compared with the group 1. #p < 0.05 group 3 compared with the group 1. † p < 0.05 group 4 compared with the group 2. ◊ p < 0.05 group 5 compared with the group 3.

3. *Effect of induction of diabetes and its treatment with insulin and rosiglitazone on heart rate, left ventricular developed pressure (LVDP) and maximum rate of pressure rise (+dp/dt) in type 1 and type 2 diabetes respectively (Table 3)*

In groups II and III, the induction of type 1 and type 2 diabetes by streptozotocin and HFD respectively resulted in significant reduction in heart rate, left ventricular developed pressure (LVDP) and +dp/dt. Also, LVDP increased significantly in group III compared to group II, while regarding HR and +dp/dt there is no significant differences between the 2 groups. The treatment of group IV with insulin and group V with rosiglitazone produced significant elevation in the same parameters. However, all these parameters were significantly lower in rosiglitazone treated group V diabetic rats compared to insulin treated group IV diabetic rats.

Table 3 : Effect of induction of diabetes mellitus and its treatment with insulin and rosiglitazone on heart rate, left ventricular developed pressure (LVDP) and maximum rate of pressure rise (+dp/dt) in type 1 and type 2 diabetes respectively.

	Control Group (G1)	Type 1 diabetic rats (G2)	Type 2 diabetic rat (G3)	Type 1 DM with insulin (G4)	Type 2 DM with rosiglitazone (G5)
Heart rate (beat/min)	178.60 ± 3.63	92.50 ± 6.88 *	99.40 ± 7.23 #	153.30 ± 10.13 †	104.70 ± 6.075 ◊
LVDP (mmHg)	100 ± 2.67	23.30 ± 2.98 *	50.90 ± 3.73 #	88.80 ± 2.86 †	69.10 ± 1.20 ◊
+dp/dt (mmHg/sec)	69.30 ± 2.66	38.70 ± 2.11 *	39.50 ± 2.46 #	61.40 ± 3.10 †	49.80 ± 2.10 ◊

Data are expressed as mean ± SD. *p < 0.05 group 2 compared with the group 1. #p < 0.05 group 3 compared with the group 1. † p < 0.05 group 4 compared with the group 2. ◊ p < 0.05 group 5 compared with the group 3.

Discussion

Diabetic cardiomyopathy (DCM) is a clinical condition diagnosed when ventricular dysfunction develops in patients with diabetes in the absence of coronary atherosclerosis and hypertension [17]. It was pointed out that diabetes associated with altered lipid metabolism is commonly accompanied by thyroid dysfunction. This can produce significant metabolic disturbances that share in the mechanisms of DCM [7].

In our study, the untreated diabetic rats (both type 1 & 2) exhibited an altered lipid metabolism manifested by significant increase in plasma level of TG and TC. These changes were in accordance with the work of Dansky et al. who found that both STZ-induced and fructose-induced diabetic rats developed elevations of TG and TC levels [18]. Several factors are likely to be responsible for this diabetic dyslipidemia. As insulin has a profound role in the regulation of key enzymes involved in the lipid and lipoprotein metabolism and due to its role on the synthesis and expression of apolipoproteins in hepatic and extra hepatic tissues, its deficiency or defect in its function affects overall lipid metabolism and lipid profile of various tissues [19]. In addition, a previous study showed that, cholesterol absorption is increased in insulin dependent diabetes and can be corrected by insulin treatment [20].

Interestingly, we observed in this work that DM especially type 2 showed more hypertriglyceridemia than type 1. This is because of peripheral insulin resistance and increased flux of fatty acids to the liver in type 2 DM. Also, there may be a reduction in total lipoprotein lipase activity or increased concentrations of the lipoprotein lipase inhibiting proteins [21].

Our results also demonstrated a highly significant reduction in plasma level of T3 and T4 in groups II, III respectively relative to control group. This effect of diabetes appears to involve changes in hypothalamic thyrotropin-releasing hormone (TRH) secretion and pituitary thyrotropin (TSH) release [22]. More importantly, this reduction is more evident in type 1 than type 2 as we noticed a higher T3 and T4 in type 2 diabetics (group III) relative to type 1 diabetics (group II). These results were in harmony with the results of another study which reported the same findings [23].

Data of the present work demonstrated that relative to control group I, cardiac mechanical performance was significantly reduced in type 1 and type 2 diabetic hearts (groups II & III respectively). A

highly significant decrease in HR, LVDP and +dp/dt was recorded in both groups signifying that isolated hearts from diabetic rats exhibited a certain degree of DCM. Our results are in agreement with the work of other researchers who reported similar findings in diabetic rats [24,25]. Indeed, alterations of diastolic and systolic function are widely reported in uncomplicated diabetic subjects and often predict the development of other chronic diabetic complications [26].

Although the etiology of myocardial injury and dysfunction in diabetes is not well understood, alteration of energy substrates in the form of excess plasma glucose and lipids can directly or indirectly induce mitochondrial reactive oxygen species (ROS) formation in the myocardium. DCM begins with a disturbance in the glucose metabolism that provokes hyperglycemia. A feature common to all cell types that are damaged by hyperglycemia is an increased production of advanced glycation end products (AGEs) and ROS [27,28]. High concentration of glucose triggers AGEs synthesis, in particular, glycated extra matrix proteins such as collagens. AGEs bind its specific receptors (RAGE) to activate NADPH oxidase (NOX) and to release ROS [29]. Protein kinase C (PKC) can also be stimulated by AGEs to phosphorylate proteins involved in Ca^{2+} handling and cardiomyocyte contraction [30, 31]. In addition, acute exposure to high glucose elevates inducible nitric oxide synthase (iNOS gene) expression and subsequent nitric oxide (NO), and peroxynitrite (ONOO−), which in turn stimulate poly-ADP ribose-polymerase-1 enzyme (PARP) as a compensatory antioxidant mechanism [32]. Increased accumulation of fatty acids (FAs) and their derivatives fatty acyl CoA, diacyglycerol (DAG), and ceramide dampens insulin signaling through activation of serine kinases such as protein kinase C [33]. Another target of free FAs in cardiomyocytes is the peroxisome proliferator-activated receptors-alpha (PPAR-α) pathway. An increase in PPAR-α expression was reported in almost all rodent models of DCM [34].

The dramatic accumulation of intramyocardial lipids in the diabetic heart led to the hypothesis of “toxic lipids” as mediators of cardiac dysfunction in DCM [35]. Accumulation of ceramide and diacylgycerol (DAG) has been demonstrated to alter intracellular signaling pathways and promote apoptotic cell death [36]. On sympathetic activation, augmented accumulation of norepinephrine, increased oxidative stress, and apoptosis may have contributed to abnormal vascular reactivity [37].

Moreover, the pathogenesis of myocardial dysfunction in diabetes can be explained by defects in calcium signaling. It was reported that the reduced L-type Ca^{2+} current density in myocytes from diabetic mice is partly due to reduced cell surface expression of the L-type Ca^{2+} channel [38]. The release of calcium ions from internal sarcoplasmic reticulum via type 2 ryanodine receptor calcium–release channel is an integral step in the cascade of events leading to cardiac muscle contraction [39]. Other potential mechanism is that the decrease in LVDP might be due to increased collagen deposition or increased glucose–mediated collagen cross–linking in diabetic mice independent of myocyte pathology [40].

The decreased myocardial performance observed in our study can be explained by significant decrease in the levels of T3 and T4 as observed in both type 1 and type 2 diabetic rats [41]. As diabetic animals had decreased values of circulating thyroid hormones and similar diminished thyroid hormone levels have been observed in humans with diabetes. The observed Hypothyroidism could induce cardiac remodeling in 3 ways; Firstly, by decreasing the activity of some enzymes included in intracellular calcium handling which further changes the expression of contractile protein [42]. Secondly, chronic inflammation [43] and tissue changes such as collagen alteration, dehydration or capillary distribution [44]. Thirdly, subclinical hypothyroidism is associated with hemodynamic changes that could also induce cardiac impairment [45]. In addition to the above-mentioned mechanisms that could induce LV dysfunction, increased systemic vascular resistance [46] and activation of the sympathetic nervous system and the renin-angiotensin-aldosterone system could also have a significant role in hemodynamic and structural changes of the LV [47].

In an attempt to assess the role of the different altered metabolic parameters on myocardial function, we compared the cardiac mechanical efficiency in both type 1 and type 2 diabetic rats. We found that LVDP in type 2 was significantly higher than in type 1 diabetic rats, while there was no significant difference in heart rate and +dp/dt. In support of our study, a previous research demonstrated that impaired LVDP and mechanical efficiency are maintained in type 2 more than type 1 diabetic mice [48].

Compared to non treated type 1 diabetic rats, treatment with insulin in group IV produced a highly significant decrease of blood glucose level and this improvement reached nearly normal level as no significant difference was observed relative to control group. Concerning the thyroid hormones, T3 and T4 levels were significantly increased in treated group IV as compared to non treated group II. While relative to control group, T3 and T4 levels were still significantly low. Improvement of thyroid hormones levels as observed in insulin treated type 1 diabetic rats was in agreement with Kosova et al**.** who noticed that there was a significant decrease in serum level of thyroid hormones in type 1 STZ induced diabetic rats and this decrease was greatly corrected after prompt subcutaneous insulin therapy [49]. One of the contributing factors involved in the hypothyroid state observed in diabetics are the changes that occur in hypothalamic TRH secretion as well as changes in pituitary thyrotropin hormone release. Insulin therapy

can normalize the hypothalamo-pituitary-thyroid axis, and increase the iodide trapping to thyroid gland in diabetic models [50].

Regarding mechanical cardiac performance, we found that insulin treatment of type 1 diabetic rats (group IV) resulted in a highly significant improvement of HR, LVDP, and +dp/dt compared to non treated type 1 diabetic rat (group II). However, relative to control group a significant difference still existed. These data suggest that type 1 diabetes results in progressive marked changes in the myocardium that can be prevented or improved by early insulin treatment. These results are consistent with the results of several authors who proved that insulin therapy for type 1 diabetic rats can improve the mechanical parameters of the heart and the metabolic dysfunction accompanying diabetes [3,51,52]. Several studies explained the protective effect of insulin on the heart as follows: the decrease in cardiac contractility induced by chronic diabetes results in part from decrease in expression and alteration in function of rayanodine type 2 calcium release channel in cardiac myocyte and these changes can be reversed by insulin treatment [53].

Although insulin increases transport of glucose into the cardiac myocytes, it has been demonstrated that insulin promotes a positive inotropic effect independent of glucose uptake [54]. Increasing evidence indicates that, in addition to its inimitable function in glucose metabolism, insulin plays critical roles in a variety of other physiological and pathological modulations, such as regulation of inflammatory response and nitric oxide production [55]. The improvement of cardiac power and metabolic parameters by insulin is due to overexpression of glucose transporter 4 (GLUT-4) [56]. In addition, in the mice insulin therapy has been found to increase T cell production of interleukin-4 (IL – 4), a cytokine associated with protection against diabetic ischemic heart [57]. Inukai reported that insulin affects the activity of genes that have insulin-responsive regions in their promoters in heart [58]. The discovered Insulin-Induced genes (Insig) may be responsible for other insulin mediated cardiac effects [59]. Furthermore, increased norepinephrine content in diabetic myocardium was completely prevented by insulin therapy started immediately after streptozotocin injection [60]. The altered pattern of substrate metabolism was restored to normal in perfused hearts from insulin treated rats, and contractile function was normalized even though signs of diabetes (hyperglycemia and hyperlipidemia) were still evident, indicating that altered cardiac metabolism is an important causative factor in the contractile dysfunction [61].

Concerning rosiglitazone treatment of type 2 diabetes (group V) for one month, we found that this drug produced highly significant decrease in blood glucose compared to non treated rats and with no significant difference relative to control rats. Rosiglitazone also produced highly significant decrease of plasma TG and TC levels as compared to non treated type 2 diabetic rats but still significantly lower than the normal rats. Rosiglitazone also affected the plasma levels of T3 and T4 as we noticed a significant increase in their levels, but this improvement was still significantly lower than the normal control levels.

Our results demonstrated that rosiglitazone improves the insulin sensitivity as it lowers the blood glucose level. Also, it improves the plasma level of TG more than TC level and elevates T3 and T4 levels as compared to untreated type 2 diabetic rats. Serum metabolic and lipoprotein subclass changes, which may be associated with this rosiglitazone-induced improvement may occur through the binding of rosiglitazone to peroxisome proliferator activated receptor gamma (PPARγ) resulting in improved insulin sensitivity and redistribution of adipose tissue.

Also, it was reported that rosiglitazone not only improved the insulin action, but also improved β – cells function [62]. Moreover, it decreased circulating TG, FFA and TC levels in rats without altering the total weight of white adipose tissue [63]. In addition, rosiglitazone might have an enhanced rate of TG removal by reducing insulin resistance in peripheral tissues and increasing the action of insulin on lipoprotein lipase (LPL) [64]. Our results also revealed a rising effect of rosiglitazone on thyroid hormones. This may be due to the direct effect of rosiglitazone on the thyroid gland through increasing its iodide trapping and binding and enhancing all the process of thyroid hormones synthesis [65].

Also, this explanation was confirmed by the Western blot studies with the sodium iodide symporter (NIS) which showed that rosiglitazone effect on iodide transport is expressed, at least in part, by an increased thyroid tissue content of the NIS transporter [66]. Our results are in agreement with other researchers work who demonstrated that rosiglitazone has an improving effect on cardiac performance [56,67]. Also, the protective effect of rosiglitazone against myocardial diabetic injury was evident by attenuation of decrease in +dp/dt and LVDP rats [68]. Moreover, rosiglitazone produced cardiac protection due to increase in angiotensin II (AT2) receptor mRNA and a marked reduction in angiotensin I (AT1) receptor mRNA. The mechanisms of AT2 receptor-mediated cardioprotection, involve stimulation of protein tyrosine or serine/threonine phosphatases in a Gi protein-dependent manner [69].

Conclusion: We concluded that the induction of both types of diabetes resulted in decreased myocardial performance parameters. The treatment of type 1 and type 2 DM by insulin and oral rosiglitazone respectively improved to a great extent the metabolic disturbances and myocardial contractile function with more improving effect of insulin in type 1 than rosiglitazone in type 2 DM. So, treatment of DM is

very important for improvement of myocardial dysfunction and management of DCM.

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