Advances in Bioresearch
Adv. Biores., Vol4 (4) December 2013: 26-32
©2013 Society of Education, India
Print ISSN 0976-4585; Online ISSN 2277-1573
Journal's URL:http://www.soeagra.com/abr/abr.htm
CODEN: ABRDC3

ORIGINAL ARTICLE

Comparison Evaluation of Effect of three Different Blood Glucose Lowering Drugs in Streptozotocin Induced Diabetic Rats

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ABSTRACT
Diabetes mellitus (DM) is a metabolic disorder resulting from a defect in insulin secretion, insulin action, or both. The objective of present study was to compare the effect of three different blood glucose lowering drugs in streptozotocin induced diabetic rats. In this study, 20 male Wistar rats (220–250 g and 2-3 month age) were selected then were divided into four equal groups: group1; healthy control rats received standard diet; Group 2 diabetic rats received standard diet plus acarbose at a dose of 25mg/kg daily through gastric gavage for 8 weeks; Group 3, diabetic rats received standard diet plus pioglitazone at a dose of 1mg/kg daily through gastric gavage for 8 weeks; Group 4, diabetic rats received standard diet plus repaglinide at a dose of 10mg/kg daily through gastric gavage for 8 weeks. Diabetes was induced by intraperitoneal injection of streptozotocin at a dose of 60 mg/kg body weight. After 48 h, animals with fasting blood glucose levels greater than 250 mg/dl were considered diabetic and then included in this study. Our data showed that anti-diabetic drugs have good hypoglycemic effects by improvement of pancreatic cells and islets.
Keywords: *Diabetes Mellitus, Acarbose, Pioglitazone, Repaglinide, STZ, Rat.*

Received 25/09/2013 Accepted 02/12/2013

INTRODUCTION

Diabetes mellitus is a serious metabolic disorder which is a major source of ill health all over the world and its incidence is expected to increase by 5.4% in 2025 [1]. Diabetes mellitus is characterized by hyperglycemia and is associated with disturbances in carbohydrate, protein and fat metabolism which occurs secondary to an absolute (type I) or relative (type II) lack of insulin [2].

Acarbose is an anti-diabetic drug used to treat type 2 diabetes mellitus and, in some countries, prediabetes. However, a recent large study concludes "acarbose is effective, safe and well tolerated in a large cohort of Asian patients with type 2 diabetes" [3]. A possible explanation for the differing opinions is an observation that acarbose is significantly more effective in patients eating a relatively high carbohydrate Eastern diet [3,4]. Acarbose inhibits enzymes (glycoside hydrolases) needed to digest carbohydrates, specifically, alpha-glucosidase enzymes in the brush border of the small intestines and pancreatic alpha-amylase. Pancreatic alpha-amylase hydrolyzes complex starches to oligosaccharides in the lumen of the small intestine, whereas the membrane-bound intestinal alpha-glucosidases hydrolyze oligosaccharides, trisaccharides, and disaccharides to glucose and other monosaccharides in the small intestine. Inhibition of these enzyme systems reduces the rate of digestion of complex carbohydrates. Less glucose is absorbed because the carbohydrates are not broken down into glucose molecules. In diabetic patients, the short-term effect of these drugs therapies is to decrease current blood glucose levels; the long-term effect is a reduction in HbA1c level [4].This reduction averages an absolute decrease of 0.7%, which is a decrease of about 10% in typical HbA1c values in diabetes studies [3].

Pioglitazone is a prescription drug of the class thiazolidinedione (TZD) with hypoglycemic (antihyperglycemic, antidiabetic) action to treat diabetes. It is used to improve glucose control in adults over the age of 18 with type 2 diabetes. Pioglitazone selectively stimulates the nuclear receptor peroxisome proliferator-activated receptor gamma (PPAR-γ) and to a lesser extent PPAR-α [5,6]. It modulates the transcription of the insulin-sensitive genes involved in the control of glucose and lipid

metabolism in the muscle, adipose tissue, and the liver. As a result, pioglitazone reduces insulin resistance in the liver and peripheral tissues; increases the expense of insulin-dependent glucose; decreases withdrawal of glucose from the liver; reduces quantity of glucose, insulin and glycated hemoglobin in the bloodstream. Although not clinically significant, pioglitazone decreases the level of triglycerides and increases that of high-density lipoproteins (HDL) without changing low-density lipoproteins (LDL) and total cholesterol in patients with disorders of lipid metabolism, although statins are the drug of choice for this. More recently, pioglitazone and other active TZDs have been shown to bind to the outer mitochondrial membrane protein mitoNEET with affinity comparable to that of pioglitazone for PPARγ [7,8].

Repaglinide is an anti-diabetic drug in the class of medications known as meglitinides, and was invented in 1983. Repaglinide lowers blood glucose by stimulating the release of insulin from the pancreas. It achieves this by closing ATP-dependent potassium channels in the membrane of the beta cells. This depolarizes the beta cells, opening the cells' calcium channels, and the resulting calcium influx induces insulin secretion [9].The objective of present study was to compare the effect of three different blood glucose lowering drugs in streptozotocin induced diabetic rats.

MATERIALS AND METHODS

In this study, 20 male Wistar rats (220–250 g and 2-3 month age) were selected for the study and were purchased from Animal House, Islamic Azad University and randomly divided into four equal groups: group1; healthy control rats received standard diet; Group 2 diabetic rats received standard diet plus acarbose at a dose of 25mg/kg daily through gastric gavage for 8 weeks; Group 3, diabetic rats received standard diet plus pioglitazone at a dose of 1mg/kg daily through gastric gavage for 8 weeks; Group 4, diabetic rats received standard diet plus repaglinide at a dose of 10mg/kg daily through gastric gavage for 8 weeks. Animal care and experiments confirmed with the Guide for the Care and Use of Laboratory Animals of China and approval of the ethics committee of Islamic Azad University was obtained before the commencement of the study. The animals were housed under standard environmental conditions (23±1°C, with 55±5% humidity and a 12 h light/12 h dark cycle) and maintained with free access to water and a standard laboratory diet *ad libitum*. Diabetes was induced by intraperitoneal injection of streptozotocin (Sigma, St. Louis, Mo, USA) at a dose of 60 mg/kg body weight. STZ was extemporaneously dissolved in 0.1 M cold sodium citrate buffer, pH 4.5. After 48 h, animals with fasting blood glucose levels greater than 250 mg/dl were considered diabetic and then included in this study [10]. Fasting blood glucose was estimated by using one touch glucometer (Accu-chek sensor) of Roche Diagnostics, Germany.The animals of different groups were sacrificed under light anesthesia (diethyl ether) 1 day after the end of the treatment.

The pancreases fixed in a 10% neutral-buffered formalin solution were embedded in paraffin and were used for histopathological examination. Five micrometer-thick sections were cut, deparaffinized, hydrated, and stained with hematoxylin-eosin. A minimum of 10 fields for each slide were examined and assigned for severity of changes using scores on a scale of mild (1+), moderate (2+), and severe (3+) damage [11-14].

The Statistical Package for Social Sciences (SPSS Inc., Chicago, IL, USA), version 13.0, was used for statistical analysis. All data are presented as mean ± SEM. Before statistical analysis, all variables were checked for normality and homogeneity of variance by using the Kolmogorov-Smirnoff and Levene tests, respectively. The data obtained were tested by ANOVA followed by Tukey's post-hoc multiple comparison test. $P<0.05$ was considered statistically significant.

RESULTS

Data obtained from the analysis of groups on days 7, 14 and 28 showed that use of anti-diabetic drugs improve the pathologic changes and Langerhans cells health parameters.

Data showed that measured parameters on day 7 were not significant in compared with diabetic control group. However, the improvement of pancreatic cells was a little better on day 14 in compared with diabetic control group. There was significant difference among obtained data on day 28 ($P<0.05$). Thus, our data showed that anti diabetic drugs have good efficacy on improvement of pancreatic cells and islets (table 1). Also, we observed that there is no significant difference among treatment groups ($P>0.05$).

Histopathologically, the structure of pancreatic cells is going to be improved by using anti-diabetic drugs which was obvious by appearing the normal islets and cells especially beta cells (figures 1-5).

Table 1: data obtained from measurement of pancreas health parameters

Group	Day	Parameter	Mean		p-value*
			Statistic	Std. Error	
Repaglinide	7	Mean of islets diameter	81.6667	1.66667	0.064
		Percent of α-cells in a islet	16.6667	2.02759	
		Percent of β-cells in a islet	81.6667	2.02759	
	14	Mean of islets diameter	69.6667	2.60342	0.053
		Percent of α-cells in a islet	27.6667	1.85592	
		Percent of β-cells in a islet	70.3333	1.45297	
	28	Mean of islets diameter	58.0000	2.00000	0.010
		Percent of α-cells in a islet	35.6667	0.88192	
		Percent of β-cells in a islet	62.3333	1.45297	
Pioglitazone	7	Mean of islets diameter	81.3333	1.76383	0.063
		Percent of α-cells in a islet	23.6667	2.40370	
		Percent of β-cells in a islet	74.3333	2.96273	
	14	Mean of islets diameter	74.0000	2.30940	0.053
		Percent of α-cells in a islet	30.0000	3.78594	
		Percent of β-cells in a islet	68.3333	3.75648	
	28	Mean of islets diameter	63.6667	2.33333	0.010
		Percent of α-cells in a islet	41.3333	2.02759	
		Percent of β-cells in a islet	56.6667	2.40370	
Acarbose	7	Mean of islets diameter	82.6667	1.76383	0.060
		Percent of α-cells in a islet	22.6667	2.90593	
		Percent of β-cells in a islet	75.0000	2.88675	
	14	Mean of islets diameter	74.3333	2.33333	0.051
		Percent of α-cells in a islet	29.0000	3.46410	
		Percent of β-cells in a islet	69.0000	3.78594	
	28	Mean of islets diameter	66.0000	1.00000	0.011
		Percent of α-cells in a islet	39.3333	2.33333	
		Percent of β-cells in a islet	59.0000	2.08167	
Diabetic group	7	Mean of islets diameter	77.0500	1.0010	-
		Percent of α-cells in a islet	14.0000	2.33333	
		Percent of β-cells in a islet	80.0000	2.40370	
	14	Mean of islets diameter	64.0040	2.80581	-
		Percent of α-cells in a islet	22.0114	2.33333	
		Percent of β-cells in a islet	55.0040	2.90593	
	28	Mean of islets diameter	40.0462	2.40370	-
		Percent of α-cells in a islet	50.0331	2.32371	
		Percent of β-cells in a islet	29.0140	2.32510	
Normal control	7	Mean of islets diameter	78.6667	2.40370	-
		Percent of α-cells in a islet	15.0000	1.15470	
		Percent of β-cells in a islet	81.0000	1.00000	
	14	Mean of islets diameter	70.0000	1.15470	-
		Percent of α-cells in a islet	30.3333	0.88192	
		Percent of β-cells in a islet	67.6667	1.45297	
	28	Mean of islets diameter	45.6667	2.33333	-
		Percent of α-cells in a islet	62.0000	2.08167	
		Percent of β-cells in a islet	35.6667	2.33333	

*Data compared with diabetic group.

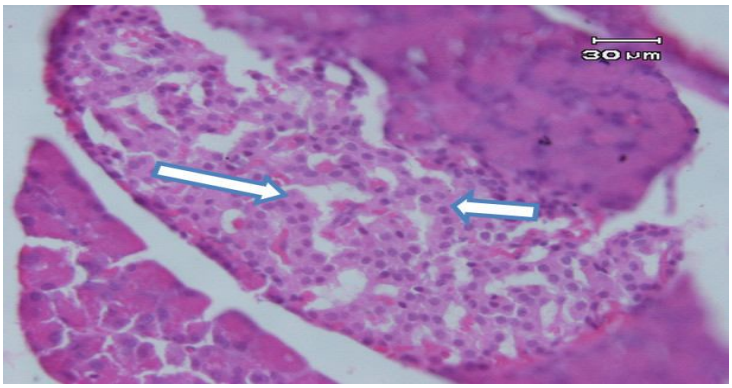

Figure 1: Histopathologic view of pancreas tissue in normal rats. Langerhans islets are big and beta cells with euchromatic nucleus and eosinophilic cytoplasm are frequent. There is no inflammation or pathologic changes (H&E, 400x).

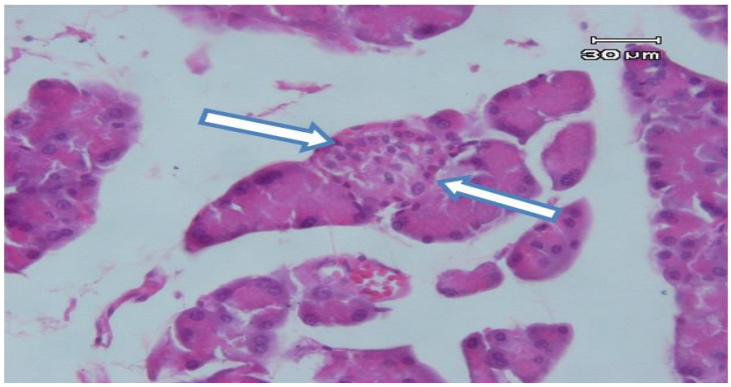

Figure 2: Histopathologic view of pancreas tissue in diabetic rats. Reduction in number and size of islets especially beta cells is obvious (H&E, 400x).

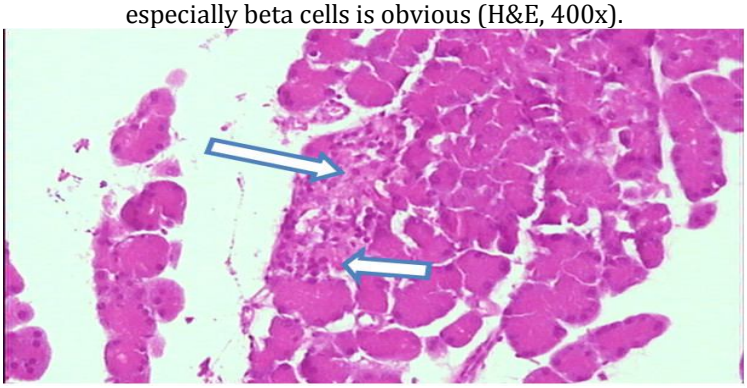

Figure 3: Histopathologic view of pancreas tissue in diabetic rats treated with acarbose. One of the Langerhans islets is obvious which has normal size and regeneration of beta cells is seen (arrows). It must be noted that regeneration is not complete so that fibrosis and mono nucleus inflammatory cells are seen (H&E, 100x).

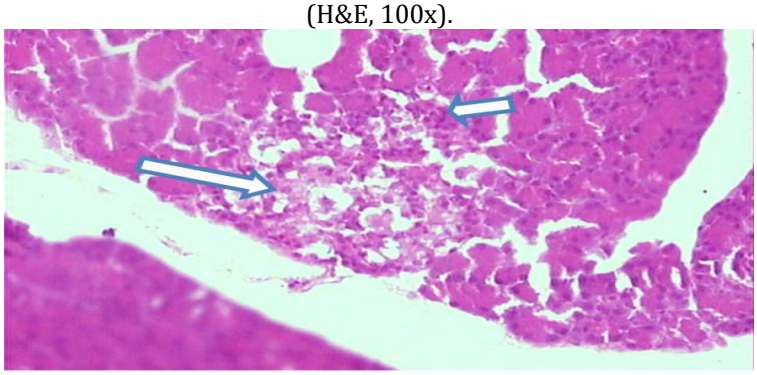

Figure 4: Histopathologic view of pancreas tissue in diabetic rats treated with pioglitazone. One of the Langerhans islets is obvious which has normal size and regeneration of beta cells is seen (long arrow). It must be noted that regeneration is not complete so that mono nucleus inflammatory cells (short arrow) and frequent vacuels are seen (H&E, 100x).

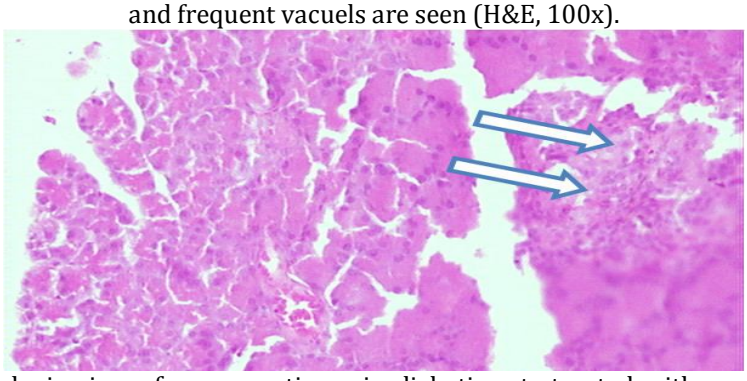

Figure 5: Histopathologic view of pancreas tissue in diabetic rats treated with repaglinide. One of the Langerhans islets is obvious which has normal size and regeneration of beta cells is seen (arrows). It must be noted that regeneration is not complete so that mono nucleus inflammatory cells and fibrosis are seen (H&E, 100x).

DISCUSSION

Diabetes mellitus (DM) is a metabolic disorder resulting from a defect in insulin secretion, insulin action, or both [15]. Insulin deficiency in turn leads to chronic hyperglycaemia with disturbances of carbohydrate, fat and protein metabolism [16]. As the disease progresses tissue or vascular damage ensues leading to severe diabetic complications such as retinopathy [17], neuropathy [18], nephropathy [19], cardiovascular complications [20] and ulceration [21]. Thus, diabetes covers a wide range of heterogeneous diseases.Diabetes mellitus may be categorized into several types but the two major types are type 1 and type 2 [22]. On the basis of aetiology, the term type 1 and type 2 were widely used to describe IDDM and NIDDM, respectively. The term juvenile-onset diabetes has sometimes been used for IDDM and maturity-onset for NIDDM. On the basis of etiology, type 1 is present in patients who have little or no endogenous insulin secretory capacity and who therefore require insulin therapy for survival. The two main forms of clinical type 1 diabetes are type 1a (about 90% of type 1 cases in Europe) which is thought to be due to immunological destruction of pancreatic ß cells resulting in insulin deficiency; and type 1b (idiopathic, about 10% of type 1 diabetes), in which there is no evidence of autoimmunity. Type 1a is characterized by the presence of islet cell antibody (ICA), anti-glutamic acid decarboxylat (anti-GAD), IA-2 or insulin antibodies that identify the autoimmune process with ß-cell destruction [22].

Type 2 diabetes is the commonest form of diabetes and is characterized by disorders of insulin secretion and insulin resistance [23]. In Western countries the disease affects up to7% of the population [24]. Globally, it affects 5-7% of the world's population [24,25]. This prevalence is underestimated because many cases, perhaps 50% in some population, remain undiagnosed. The prevalence of type 2 diabetes varies considerably throughout the world, ranging from >1%in certain population of the developing countries. Our data showed that anti-diabetic drugs have good hypoglycemic effects by improvement of pancreatic cells and islets. Wu et al., (2012) observed that acarbose chewable tablets have a definite curative effect in treating type 2 diabetic patients as HbA1c and blood glucose levels decreased significantly after the 12-week treatment [26]. Zheng et al., (2013) showed that twenty-four weeks of acarbose monotherapy in newly diagnosed patients with T2D is associated with significantly increased levels of both fasting and postprandial GLP-1 as well as significantly increased NO levels and NOS activity for those patients in whom postprandial GLP-1 levels were increased [27]. They concluded that the benefits of acarbose on cardiovascular risk may be related to its stimulation of GLP-1 secretion. So, the hypoglycemic effect of acarbose is superior in patients with T2DM consuming an Eastern diet than in those consuming a Western diet and is similar to that of sulfonylureas, metformin, and glinide drugs [28].

Defronzo et al., (2013) showed that improved beta cell function was most closely associated with final glucose tolerance status which has been achieved by pioglitazone [29].

In another study, Low-dose PIO (15 mg/day) improves glycaemic control, beta cell function and inflammatory state in obese patients with type 2 diabetes [30]. Study of Tahara et al., (2013) demonstrated that pioglitazone decreased serum ADMA levels in a glucose-lowering independent manner. Elevation of fibronectin by pioglitazone may contribute to the reduction of serum levels of ADMA in IGT or type 2 diabetic subjects, thus playing a protective role against cardiovascular disease [31].

Study of Hezarkhani et al., [32] showed the usefulness of Continuous glucose monitoring system (CGMS) not only as a diagnostic but also as an educational and therapeutic tool that in combination with Repaglinide (with the lowest effective dose and duration) can significantly reduce FBG and glycemic excursions in DM2 patients and hypoglycemic events are low . Stein et al., [33] concluded that several new oral agents have been approved for type 2 diabetes management in recent years. It is important to understand the efficacy and safety of these medications in addition to the older agents to best maximize oral drug therapy for diabetes. Of the recently introduced oral hypoglycemic/antihyperglycemic agents, the DPP-4 inhibitors are moderately efficacious compared with mainstay treatment with metformin with a low side-effect profile and have good efficacy in combination with other oral agents and insulin. They are a recommended alternative when metformin use is limited by gastrointestinal (GI) side effects or when SU treatment results in significant hypoglycemia or weight gain. Meglitinide analogs are limited by their frequent dosing, expense and hypoglycemia (repaglinide >nateglinide), while AGIs are also limited by their dosing schedule and GI side-effect profile. BAS and bromocriptine have the lowest efficacy with regard to HbA(1c) reduction, also are plagued by GI adverse reactions, but have a low risk of hypoglycemia. The results of our study is compatible with the above mentioned studies, so it can be concluded that tested drugs have good hypoglycemic effects by improvement of pancreatic cells and islets with low side effects.

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Citation of This Article

Alireza Sadeghi, Seyed Ali Shabestari Asl, JavadAshrafi Helan. Comparison Evaluation of Effect of three Different Blood Glucose Lowering Drugs in Streptozotocin Induced Diabetic Rats. Adv. Biores. Vol 4[4] December 2013: 26-32