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Original Article

Comparison of Three Different Glucose-lowering Drugs on Serum Levels of Glucose and Pancreas Histopathology in Streptozotocin-Induced Diabetic Rats

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ABSTRACT

Introduction: Diabetes mellitus is a metabolic disorder resulting from a defect in insulin secretion, insulin action, or both. The aim of the present study was to compare the effect of three different blood glucose-lowering drugs in streptozotocin-induced diabetic rats.

Materials and methods: A total of 60 male Wistar rats (220–250 g and 2-3 months of age) were selected for the current study, and they then were divided into five equal groups. Group 1 included healthy control rats receiving standard diet, group 2 involved diabetic rats receiving standard diet plus acarbose (25mg/kg/day) via gastric feeding tube daily for 8 weeks, group 3 embraced diabetic rats receiving standard diet plus pioglitazone (1 mg/kg/day) via gastric feeding tube daily for 4 weeks, and group 4 received of diabetic rats receiving standard diet plus repaglinide (10 mg/kg/day) via gastric feeding tube daily for 4 weeks. Diabetes was induced by intraperitoneal injection of streptozotocin at a dosage of 65 mg/kg body weight. At the end of the study, the samples were taken for histopathological investigation of pancreas and serum glucose levels. The mean diameter of pancreatic islets and the percentage of beta and alpha cells were calculated in all groups.

Results: The fasting blood glucose in three treated and normal control rats was significantly less than the diabetic control group. One hour after treatment the blood glucose level reduced significantly in three treated and normal control rats compared to the diabetic control group. On day 7, the percentage of alpha cells in the pioglitazone and acarbose groups increased significantly, compared to the diabetic control group. On day 28, the percentage of beta cells in the treated groups increased significantly, compared to normal and diabetic control groups. Moreover, the mean of islet diameter in the treated groups increased significantly, compared to the normal and diabetic control groups. The percentage of alpha cells in the repaglinide group significantly reduced on day 28, compared to the diabetic control group.

Conclusion: Among the administrated drugs, pioglitazone had the most positive effects on controlling blood glucose, increasing beta cells as well as improving the diameter of pancreatic islets.

1. Introduction

Diabetes mellitus is one of the most common endocrine disorders affecting almost 6% of the world's population. According to the report of the International Diabetes Federation in 2001, the number of diabetic patients will reach 300 million in 2025. More than 97% of these patients will have type II diabetes[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 alpha-glycosidase inhibitor and antidiabetics are used for the treatment of diabetes. Acarbose

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shows its effect by inhibiting intestinal enzymes (alpha-glycosidases), thereby interfering with the catabolism of disaccharides, oligosaccharides, and polysaccharides in the intestines. Thus, digestion of carbohydrates is delayed depending on the dose, and more importantly, glucose release and its presence in the blood slow down. Moreover, both fluctuations in daily blood sugar and average blood sugar level decrease as a result of this delayed glucose intake through the intestines with acarbose. Acarbose also reduces abnormal high concentrations of glycosylated hemoglobin[3-5]. A possible explanation for the discrepancies is an observation that acarbose is significantly more effective in patients eating a relatively high carbohydrate Eastern diet[6,7]. Acarbose inhibits enzymes (glycoside hydrolases) required for 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-glucosidase hydrolyzes oligosaccharides, trisaccharides, and disaccharides to glucose and other monosaccharides in the small intestine. Inhibition of these enzyme systems reduces the digestion rate of complex carbohydrates. Therefore, less glucose is absorbed because the carbohydrates are not broken down into glucose molecules. In diabetic patients, the short-term effect of these drugs is a decrease in current blood glucose levels and the long-term effect is a reduction in Hemoglobin A1c (HbA1c) level[8]. Acarbose reduces postprandial plasma glucose and may improve metabolic control in non-insulin-dependent diabetes mellitus when combined with the diet[9]. This reduction averages an absolute decrease of 0.7%, which is a decrease of about 10% in typical HbA1c values in diabetes studies[6].

Pioglitazone, a thiazolidinedione (TZD) insulin sensitizer, is a peroxisome proliferator-activated receptor gamma (PPAR-γ) agonist. It increases insulin sensitivity by regulating the expression of a variety of genes involved in carbohydrate and lipid metabolism, increases Glucose transporter-4 (GLUT-4) and glucokinase activity, decreases phosphoenolpyruvate carboxykinase (PEPCK) expression, and decreases production by a fat cell of several mediators that may cause insulin resistance, such as tumor necrosis factor α (TNF α) and resistin[10,11]. 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, and reduces the quantity of glucose, insulin, and glycated hemoglobin in the bloodstream. Regardless of being clinically insignificant, 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 choice of drug for this issue. More recently, pioglitazone and other active TZDs have been shown to bind to the outer mitochondrial membrane protein mitoNEET with an affinity comparable to that of pioglitazone for PPARγ[12,13]. Pioglitazone increases hepatic and peripheral insulin sensitivity, thereby inhibiting gluconeogenesis and increasing peripheral and splanchnic glucose uptake[14].

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 by closing ATP-dependent potassium channels in the membrane of the beta cells. This depolarizes the beta cells, opens the calcium channels of cells, and the resulting calcium influx induces insulin secretion[15]. Repaglinide is metabolized by cytochrome CYP3A4 in the liver[16]. The aim of the present study was to compare the serum level of glucose and histopathological effects of three different blood glucose-lowering drugs in streptozotocin-induced diabetic rats.

2. Materials and Methods

2.1. Ethical approval

All procedures were approved by the Animal Care Committee of Veterinary Medicine, Islamic Azad University, Tabriz Branch, Iran. The principles of laboratory animal care were followed, and specific international laws were observed.

2.2. *Animals*

A total of 60 male Wistar rats weighing approximately 220–250 g with 2-3 months of age were acclimated to laboratory conditions for 4 weeks, followed by maintenance under controlled temperature (25-28°C) and light conditions (12/12-hours light/dark cycle). Animals received standard extruded pellet and water *ad libitum* until treatment. Rats selected for the study were purchased from Animal House, Islamic Azad University, Iran, and randomly divided into five equal groups. Group 1 included healthy control rats who received a standard diet, group 2 diabetic rats received standard diet plus acarbose (25mg/kg/day) via gastric feeding tube daily for 4 weeks, group 3 involved diabetic rats received standard diet plus pioglitazone (1mg/kg/day) via gastric feeding tube daily for 4 weeks, and group 4 entailed diabetic rats who received standard diet plus repaglinide (10 mg/kg/day) via gastric feeding tube daily for 4 weeks.

2.3. Diabetes infusion

Diabetes was induced by intraperitoneal injection of streptozotocin (single dose, Sigma, St. Louis, Mo, USA) at a dosage of 65 mg/kg body weight. The STZ was extemporaneously dissolved in 0.1 M cold sodium citrate buffer, pH 4.5. After 48 hours, animals with fasting blood glucose higher than 250 mg/dl were considered diabetic and were used in the present study[17].

2.4. Micrometric perusal methods

The pancreases fixed in a 10% neutral-buffered formalin solution were embedded in paraffin and used for histopathological examination. Therefore, 5 micrometer thick sections were cut, deparaffinized, hydrated, and

stained with hematoxylin-eosin. A minimum of 10 fields for each slide was examined and assigned for the severity of changes using scores on a scale of mild (1+), moderate (2+), and severe (3+) damage[18-21].

2.5. Blood sample

Fasting blood glucose was estimated by using the Bio check Glucose Test Strip (Accu-chek sensor) of Roche Diagnostics, Germany, at the end of the study (6 six rats in each group). The animals of different groups were sacrificed under light anesthesia (diethyl ether) at the end of the treatment (6 six rats in each group).

2.6. Statistical analysis

The Statistical Package for Social Sciences (SPSS Inc., Chicago, IL, USA), version 13, 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 using the Kolmogorov-Smirnoff and Levene tests, respectively. The data obtained were tested by ANOVA followed by Tukey's posthoc multiple comparison test. P value less than 0.05 was considered statistically significant.

3. Results

3.1. Fasting blood glucose levels

Mortality was not seen in this study. Three treated and diabetic control groups showed significant differences from the normal control group ($p < 0.05$). The three treated and normal control rats indicated significant differences with the diabetic control group ($p < 0.05$).

3.2. Blood glucose levels one hour after the last treatment

The three treated and normal control groups showed a significant difference from the diabetic control group ($p < 0.05$, Table 1). It should be noted that the best effect on one-hour glucose was in the pioglitazone group, which was significantly different from the diabetic control group ($p < 0.05$) however it did not have a significant difference compared to other treatment groups ($p > 0.05$, Table 1).

3.2. Histopathological findings

On day 7, the percentage of alpha cells in the pioglitazone and acarbose groups increased significantly compared to the diabetic control group ($p < 0.05$, Table 2). On day 28, the percentage of beta cells in the treated groups increased significantly compared to normal and diabetic control groups ($p < 0.05$, Table 2). On day 28, the mean of islet diameter in the treated groups increased significantly compared to the normal and diabetic control groups ($p < 0.05$, Table 2). On day 28, the percentage of alpha cells in the repaglinide group was significantly reduced compared to the diabetic control group ($p < 0.05$, Table 2). The obtained results indicated that anti-diabetic drugs have beneficial effects on the regeneration of pancreatic islets and cells which were so obvious in beta cells (Table 2).

Table 1. Serum levels of fasting and one-hour blood glucose in diabetic rats after treatment with glucose-lowering drugs

Group	Normal control	Diabetic	Repaglinide	Pioglitazone	Acarbose
Fasting blood glucose level (mg/dl)	132^{a}	558^{e}	264^{b}	251^{b}	257^{b}
One-hour blood glucose (mg/dl)	111^{a}	462^{e}	141^{ab}	99^{a}	138^{ab}

^{a,b,c,e} Different superscripts letters in the same group mean significant differences ($p < 0.05$)

Table 2. Pancreas parameters of diabetic rats after treatment with glucose-lowering drugs

Parameter	Group									
	Repaglinide		Pioglitazone		Acarbose		Diabetic group		Normal control	
	Day 7	Day 28	Day 7	Day 28	Day 7	Day 28	Day 7	Day 28	Day 7	Day 28
Islets diameter (μ)	82	58	82	64	83	66	77	40	79	46
α-cells (%)	17	36	24	42	23	40	14	50	15	62
β-cells (%)	82	63	75	57	75	59	80	29	81	36

*Data compared to the diabetic group

4. Discussion

Diabetes mellitus is a group of metabolic disorders characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both. The chronic hyperglycemia of diabetes is associated with long-term damage, dysfunction, and failure of various organs, especially the eyes, kidneys, nerves, heart, and blood vessels[22]. As the disease progresses, tissue or vascular damage ensues leading to severe diabetic complications, such as retinopathy[23], neuropathy[24], nephropathy[25], cardiovascular complications[26], and ulceration[27]. 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[28]. Based on etiology, the term type 1 and type 2 were widely used to describe Insulin-dependent diabetes mellitus (IDDM) and Non-insulin-dependent diabetes mellitus NIDDM, respectively. The term juvenile-onset diabetes has sometimes been used for IDDM and maturity-onset for NIDDM. Based on etiology, type 1 is present in patients who have little or no endogenous insulin secretory capacity and 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 results from immunological destruction of pancreatic ß cells leading to 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 decarboxylates (anti-GAD), IA-2, or insulin antibodies that identify the autoimmune process with ß-cell destruction[28].

Type 2 diabetes is the most common form of diabetes and is characterized by disorders of insulin secretion and insulin resistance[29]. In Western countries, the disease affects up to 7% of the population[30]. Globally, it affects 5-7% of the world's population[30,31]. This prevalence is underestimated because many cases, perhaps 50% in some populations, remain undiagnosed. The prevalence of type 2 diabetes varies considerably throughout the world, ranging from more than 1 percent in a certain population of developing countries. The findings of the current study showed that anti-diabetic drugs have good hypoglycemic effects by the improvement of pancreatic cells and islets. Wu et al observed that acarbose chewable tablets had a definite curative effect on treating type 2 diabetic patients as HbA1c and blood glucose levels decreased significantly after the 12-week treatment[32]. Mughal et al reported that acarbose treatment was associated with a significant reduction in fasting blood glucose[33]. They concluded that the benefits of acarbose on cardiovascular risk may be related to its stimulation of GLP-1 secretion. Therefore, the hypoglycemic effect of acarbose is similar to that of sulfonylureas, metformin, and glinide drugs and is superior in patients with T2DM consuming an Eastern diet than in those eating a Western diet[34].

Defronzo et al found that improved beta-cell function was closely associated with final glucose tolerance status obtained by pioglitazone[35]. Gad et al reported that diabetic rats treated with pioglitazone decreased serum glucose by almost 30%[36]. Pioglitazone had comparable effects on estimates of carbohydrate metabolism and insulin sensitivity in high-fat-fed rats, but different effects in diabetic rats. In another study, Low-dose pioglitazone (15 mg/day) improves glycemic control, beta-cell function, and inflammatory state in obese patients with type 2 diabetes[37]. A study by Matsumoto et al demonstrated that pioglitazone decreased serum asymmetric dimethylarginine (ADMA) levels in a glucose-lowering independent manner[38]. Elevation of fibronectin by pioglitazone may contribute to the reduction of serum levels of ADMA in impaired glucose tolerance or type 2 diabetic subjects, thus playing a protective role against cardiovascular disease.

A study by Hezarkhani et al showed the usefulness of a continuous glucose monitoring system (CGMS) not only as a diagnostic but also as an educational and therapeutic tool that is in combination with Repaglinide (with the lowest effective dose and duration), could be effective in monitoring the reduction of fasting blood glucose and glycemic excursions in Diabet type 2 patients[39]. Manzella et al observed that Repaglinide and glibenclamide administration were both associated with a significant decline in fasting plasma glucose, HbA1c, triglycerides, and FFAs and with a significant increase in fasting plasma insulin, 2-hour plasma insulin, and HDL cholesterol levels. In addition, repaglinide administration had a stronger reduction in 2-hour plasma glucose levels, compared to glibenclamide administration[40]. Stein et al 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 as well as older agents to best maximize oral drug therapy for diabetes[41]. Of the recently introduced oral hypoglycemic/antihyperglycemic agents, the dipeptidyl peptidase 4 (DPP-4) inhibitors are moderately efficacious, compared to mainstay treatment with metformin with a low side-effect profile and have good efficacy in combination with other oral agents and insulin which are recommended as alternatives when metformin use is limited by gastrointestinal (GI) side effects or when sulfonylurea treatment results in significant hypoglycemia or weight gain. Meglitinide analogs are limited by their frequent dosing, expense, and hypoglycemia (repaglinide > nateglinide), while Alpha-glucosidase inhibitors are also limited by their dosing schedule and GI side-effect profile. Bile-acid sequestrants and bromocriptine have the lowest efficacy with regard to HbA1c reduction, also are plagued by GI adverse reactions, but have a low risk of hypoglycemia. The results of the current study are compatible with the above-mentioned studies, so it can be concluded that tested drugs have positive hypoglycemic effects by improvement of pancreatic beta cells and islets.

Declarations

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Competing interests

The authors declare that they have no competing interests.

Authors' contribution

Alireza Sadeghi designed the study and performed the sampling and practical procedures. Daryoush Babazadeh revise the draft of the manuscript, and check the final version of the article, Ali Shabestari Asl performed the statistical analysis and revise the draft of the manuscript and remove the language errors, Pouria Ahmadi Simab wrote the draft of the manuscript. All authors check the final proof of the article and the statistical results.

Availability of data and materials

All data and related findings of the thesis are prepared for publishing in the present journal.

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