Therapeutic effect of glibenclamide and sertraline combination on serum level of lipids and glucose in type 2 diabetic rats

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Abstract

Background and Objective: Sertraline-lowering effects on blood sugar have been observed in many studies. Nowadays, glibenclamide is widely used in the treatment of diabetes. The aim of this study was to evaluate the therapeutic effect of the combination of sertraline and glibenclamide on serum glucose and lipids in type 2 diabetic rats.

Materials and Methods: In this study, 32 male rats were divided into four groups: diabetic, diabetic treated with glibenclamide, sertraline, combination of glibenclamide and sertraline. The drug dose of glibenclamide was 0.258 mg/kg and sertraline 30 mg/kg and the combined therapeutic dose was 50% of the previous doses. Diabetes was induced by a single dose of 60 mg/kg streptozotocin. Treatment was continued until day 16 after diabetes induction. Serum glucose levels were measured on days 4, 9 and 16.

Results: The present study showed that combination of glibenclamide and sertraline with 50% of treatment dose significantly decreased serum glucose on days 9 and 16. Sertraline alone significantly decreased serum glucose compared to the control group on day 16 (P <0.05). A significant increase in HDL and HDL to LDL ratio was observed in the two groups (P <0.05), but these changes were not observed in the glibenclamide group alone.

Conclusion: Combined treatment with glibenclamide and sertraline improved control of serum glucose and increased HDL and could lead to significant changes in serum glucose and lipid concentrations in diabetic rats.

Keywords: Type 2 diabetes, Sertraline, Glibenclamide, Glucose, Lipid

1. Introduction

Nowadays, Type 2 diabetes mellitus (T2DM) is the most prevalent and serious metabolic disease all over the world, globally as of 2015 it was estimated that there were 415 million people with type 2 diabetes making up about 90% of diabetes cases, that might progress to about 642 million by the year 2040 (1). Type 2 diabetes is a long-term metabolic disorder characterized by high blood sugar, insulin resistance, and relative lack of insulin with biochemical alterations of glucose and lipid metabolism (1). These lead to the generation of excess reactive oxygen species (ROS), which is hypothesized to be responsible for cell membranes damage. The Increase in ROS production and the simultaneous decline in antioxidative defense mechanisms under diabetic conditions are associated in the development of health problems, including heart disease, nerve damage, eye problems, limb amputation and kidney disease. To reduce these late complications, it is critical to keep both blood glucose and lipid level in the normal range (2).

Among the metabolic abnormalities that commonly accompany diabetes are disturbances in the production and clearance of plasma lipoproteins. Moreover,

development of dyslipidemia may be a harbinger of future diabetes. A characteristic pattern, termed diabetic dyslipidemia, consists of low high density lipoprotein (HDL), increased triglycerides, small dense low density lipoproteins (sdLDL) and postprandial lipemia. This pattern is most frequently seen in type 2 diabetes and may be a treatable risk factor for subsequent cardiovascular disease (3).

It has been reported that depression is highly prevalent in diabetics and is associated with poor glucose regulation and increased risk of diabetic complications.The relationship between type 2 diabetes and depression is bidirectional, meaning that each can put a person at risk for the other (4, 5).

Some people with type 2 diabetes can effectively control their blood glucose level by watching what they eat, exercising, and, if necessary, losing weight (6). However, that's not always possible, therefore, over the years, many medications have come out to treat type 2 diabetes. Sulfonylureas are oral antidiabetic drugs recommended as second line treatment in patients with type 2 diabetes. Despite the recent approval of several new drugs, sulfonylureas remain the most commonly prescribed antidiabetic drugs after treatment failure with the first line drug metformin. Whereas sulfonylureas, which are second-line drugs, are associated with excess cardiovascular and hypoglycemic risks, must be used carefully in an elderly diabetic patient population. Glyburide (also referred to as glibenclamide) and gliclazide, are two second-generation sulfonylurea drugs available in Canada. Glyburide has been associated with an increased risk for hypoglycemia and long-term cardiovascular mortality. This may be due to differences in tissue-specific binding of the respective sulfonylureas. Accordingly, glyburide is avoided in the elderly due to the potential risk (7).

Recently, there have been concerns that antidepressants may adversely affect glucose metabolism, not least because some antidepressants induce significant weight gain, which may contribute to insulin resistance. The noradrenergic nortriptyline and selective serotonin reuptake inhibitors (SSRIs) have been reported to worsen glycemic control in people with diabetes whereas tricyclic antidepressants hyperinsulinemia in mice. Because antidepressants may be used in people at higher risk of developing diabetes per se, and disentangling a drug effect from this complex relationship is challenging.

Studies with nortriptyline, a tricyclic antidepressant (TCA), paroxetine (SSRI) and fluoxetine (SSRI) showed no significant difference on glycemic control presumably because they were underpowered.

SSRIs and other antidepressant medications have a similar association with diabetes risk, it seems essential that epidemiological studies differentiate between antidepressants rather than considering them as a whole. In conclusion, from the evidence reviewed, there is a link between antidepressant use and diabetes, but causality is not established. Long-term prospective studies are required to assess this relationship further, but in the interim, caution is advised and a heightened alertness to the potential risk of diabetes is necessary, not least because of the large numbers of antidepressants that are prescribed (8)

However, studies showed that only sertraline which is an antidepressant of the selective serotonin reuptake inhibitor (SSRI) class had strong effect on glycaemic control (9).

Previous studies have suggested a possible relationship between dyslipidemia and depression, although; some researches show conflicting results in this regard. In addition, associations between depressive symptoms and low high-density lipoprotein (HDL) levels or elevated triglyceride levels were found in some studies. Significant associations were found among SSRI use and low HDL, increased total cholesterol level, high triglyceride level, and increased risk for diabetes. An increase was demonstrated in total cholesterol level after SSRI treatment (10).

In some studies, HDL levels were significantly lower in patients with major depressive disorder than in healthy controls, and serum total cholesterol levels were elevated in patients after treatment. However, no significant association was found between antidepressant therapy and HDL, total cholesterol, and triglyceride levels in other studies. The above discussion shows that there is a need for more studies on this subject (11).

2. Materials and Methods

To get the purpose of this study, 32 adult male Wistar rats, weighing 195-220 g, (Razi Institute, Iran), with blood glucose under 150 mg/dl (which was measured by glucometer from a blood drop of the cutting tail) as non-diabetic animals were randomly selected and housed eight per cage in a temperature controlled colony room under a 12 hour light/dark cycle. Animals were given free access to water and standard laboratory rat chow (Pars Company, Tehran, Iran). All the experiments were conducted between 11a.m. and 4p.m. under the normal room light and temperature 25°C.

Induction of diabetes was done by a single dose of streptozotocin (STZ) (Sigma, U.K.) in 60 mg/kg (dissolved in 0.9% saline immediately before injecting) which was intraperitoneally administrated. STZ is leading to destruction of pancreatic cells and decreasing of insulin levels in aforementioned induced diabetes rats. At the first 16 days of injection, due to

the incomplete disappearance of pancreatic beta cells, the induced diabetes was similar to type 2 diabetes (12, 13).

2.1. Experimental Design

The streptozotocin induced animals before that treated with drugs were randomly assigned into four groups of eight- rats, as follows:

It is worth mentioning that drugs were intraperitoneally injected to the above groups on days 3 to 16 after STZ injection:

Group 1: Diabetic animals with STZ

Group 2: Diabetic animals treated with glibenclamide (0.285 mg/kg) daily (13)

Group 3: Diabetic animals treated with sertraline (30 mg/kg) daily (14)

Group 4: Diabetic animals treated with a combination of glibenclamide (0.143 mg/kg) and sertraline (15 mg/kg) daily.

Glucose in the serum as the main parameter to achieve the efficiency of origin synthesized antidiabetic drugs was measured due to the STZ injection at 4, 9 and 16 days. Eventually, on the 16th day, the animals were anesthetized by ether which was provided from the Merck Corporation. The sample blood was collected from the apex of the heart through opening the chest of the rats. After 20 minutes, the samples were centrifuged at 30, 00 RPM for 10 min. Then, the

serum was separated and stored at -20°C to measure glucose, triglycerides, total cholesterol, low density lipoprotein (LDL), and high density lipoprotein (HDL).

2.2. Statistical Analysis

Data distribution was tested using statistical software SPSS19 (version 12). The data were expressed as the means ± S.E.M. After verification of parametric distribution of data, using Kolmogorov-Smirnov statistical test, one-way ANOVA and multiple comparison Tukey post-hoc tests were applied. In all computations, significance level was taken at $p < 0.05$.

3. Results

3.1. Effects of Glibenclamide and Sertraline Alone and In Combination on the Glucose Level

As shown in figure 1, a significant reduction ($p>0.05$) was found out in serum glucose level in diabetic group treated with glibenclamide and serteraline on day 9 (58.7%) and day 16 (68.4%) after STZ injection as compared to control group. In addition, a significant decrement in serum glucose level was found in group treated with serteraline alone on day 16 (56.6%).
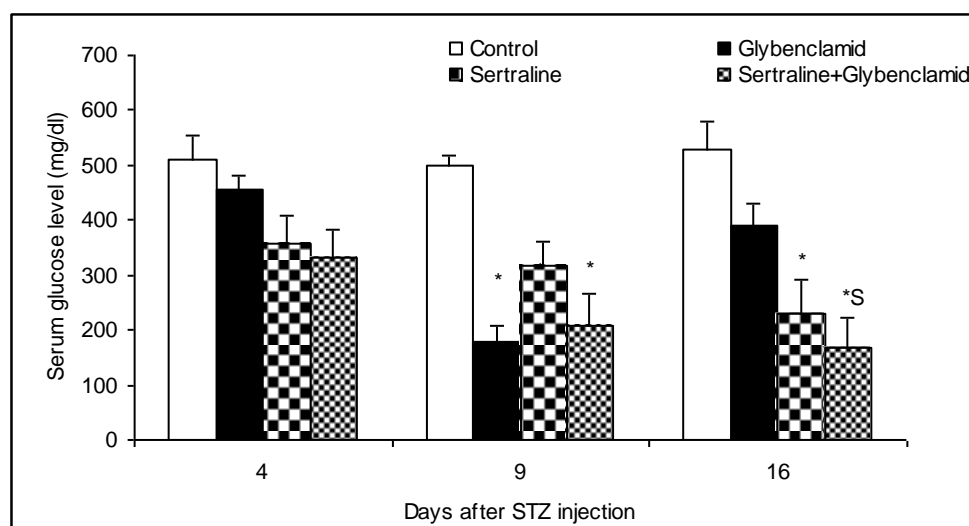

Figure. 1. Comparison of serum glucose concentration on days 4, 9 and 16 after STZ injection in study groups

3.2. Effects of Glibenclamide and Sertraline Alone and In Combination on Serum Lipid Profile

Table 1 shows that no significant difference was observed in taking glibenclamide and sertraline alone

and in combination on TG, LDL and cholesterol level. On the other hand, taking sertraline plus glibenclamide (41.37±6.36), especially sertraline) (65.12± 5.2) alone had a significant effect on HDL increase as compared to the control group (15.88±4.4). In addition, the HDL/LDL ratio increased

significantly in the sertraline and sertraline plus glibenclamide groups.

Table 1. Serum cholesterol, triglyceride LDL, HDL and HDL/LDL ratio in study groups on day 16

Group tests	Serum parameter (mg/dl)				
	Cholesterol	TG	LDL	HDL	HDL/LDL ratio
Control	78.22 ± 6.83	204.09 ± 19.52	62.33 ± 8.69	15.88 ± 4.44	0.25
Glibenclamide	81.00 ± 8.15	161.83 ± 28.85	70.12 ± 6.65	18.66 ± 4.27	0.26
Sertraline	78.85 ± 6.7	223.57 ± 30.07	69.25 ± 9.18	65.12 ± 5.22 *$	0.94 *
Sertraline+ Glibenclamide	68.28 ± 10.61	206.42 ± 16.62	43.62 ± 12.71	41.37 ± 6.36 *	0.96 *

4. Discussion

In this study, we destructed pancreatic beta cells with streptozotocin injections, which resulted in a pattern similar to type 2 diabetes in mice during the first 16 days (13). The present study showed that serum glucose decreased on days 9 and 16, which this reduction on the 16th day in the group treated with the combination of glibenclamide and sertraline compared to the groups treated with these drugs alone had a meaningful reduction. Takhr and his colleague's studies confirmed this finding (15). As has been shown, cytochrome P 450 is a large family of enzymes that is responsible for the metabolism of many drugs in the body and can be affected by several factors. When the two drugs bind to the enzyme at the same time, they inhibit the enzyme and decrease its function. Since hepatic metabolism of sertraline and glibenclamide is via cytochrome P 450, the inhibitory effects of co-administration of sertraline and glibenclamide on cytochrome P 450 result in decrease of metabolism, increase concentration and the half-life of glibenclamide in the serum, thereby further reducing blood glucose in the sample (15-17). The present study rejects the findings of Joan et al.'s study that glibenclamide had no stimulatory or inhibitory effect on the enzymatic system of drug metabolism in the liver (18).

Also, the study showed that sertraline was associated with a 56.6% decrease in blood glucose compared with the control group. This finding suggests that sertraline can induce hypoglycemic changes independently without association with other hypoglycemic factors, which previous studies support it (14, 19). However, fluoxetine in this group, with increases in serotonin and catecholamines, has opposite effects on blood glucose elevation (20). There is currently no precise mechanism to explain how this sertraline works, but it seems that increased serotonin in the blood is associated with increased endorphins (19), it can be concluded that administration of sertraline by stimulating opioid receptors can lead to glucose uptake in peripheral tissues and subsequently lowering blood glucose.

According to our results, on the 16th day of serum glucose in the group treated with glibenclamide alone, there was a slight decrease of only 26.2% as compared to the control group, while on the ninth day of the study a significant 64.5% decrease in glucose was observed in this group. Given that sulfonylurea drugs including glibenclamide lead to hypoglycemic via the mechanism of increasing endogenous insulin (21). It can be expected that the degeneration process in pancreatic beta cells following streptozotocin injection during the study period (13) decreased the endogenous insulin secreting cells in the pancreas and thereby reduced the therapeutic effects of glibenclamide and may be an appropriate justification for this finding.

In the survey of lipid profile in this study, triglyceride increased 9.5% in the sertraline alone group as compared to the control group, which was not significant, The effects of serotonin on the Htr2b receptor in adipose tissue cells may be the possible mechanism of this increase in triglycerides.

In some studies, elevated levels of free fatty acid and glycerol have been observed following elevated levels of serotonin (22), which is consistent with our study.

The results of serum total cholesterol, LDL, HDL and HDL to LDL ratios showed a slight decrease in total cholesterol in the group treated with combination of sertraline and glibenclamide which was not significant. As a whole, there were no significant changes in the three above groups, meanwhile, this finding is supported by the study of Garland and et al (23). Studies related to our finding are based more on the inverse effects of this association.

In addition, the effect of total cholesterol on serotonin concentration has been investigated and consequently the results of these studies showed that cholesterol deficiency in the blood was associated with a decrease in serum serotonin concentration (24). Moreover, depression was more prevalent in people with low cholesterol levels (25). Serotonin plays a key role in depression and many other psychiatric disorders. It is therefore possible to deduce that serotonin depletion is associated with cholesterol deficiency. Since cholesterol deficiency leads to a decrease in the concentration of tryptophan as the major amino acid involved in the production of serotonin, consequently, it can be expected that lowering cholesterol result in a decrease in serotonin production (26).

Based on the conclusions, treatment with sertraline alone resulted in an 11.1% increase in serum LDL level. Besides, in the study on paroxetine, the other drug in SSRIs group, 11% increase in serum LDL level was observed (27), which can be concluded a similar mechanism might be involved. Furthermore, the finding showed that the combination of sertraline and glibenclamide had a decreasing effect on serum LDL but this difference was not significant.

This research showed that serum HDL in the diabetic group treated with sertraline alone increased significantly 4-fold compared to the control group. On the other hand, in the group treated with glibenclamide and sertraline, this significant increase was observed to be 2.5-fold. But the group treated with glibenclamide alone did not show such changes However, Garland et al.'s study did not show a significant association between serum serotonin and HDL levels. In a study by Herrera et al, a significant relationship was found between a decrease in serotonergic function in the brain and a decrease in serum HDL, which is consistent with our study, although, the mechanism of cholesterol interaction with serotonin is not clear (28). But sertraline probably via increasing serotonin levels and inhibiting bile production (29) as well as decreasing the contractile and electrical activity of the lymphatic vessels (30) has such effects that of course needs further investigation. Given the increase in serum HDL levels in the sertraline-treated groups alone and the combination of sertraline and glibenclamide, an increase in the HDL-LDL ratio was predictable as compared to non-significant changes in serum LDL.

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