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Research Article

Influence of Gemfibrozil (inhibitor of CYP 2C8) and Clarithromycin (inhibitor of CYP 3A4) and their Combination on the Hypoglycemic Effect of Pioglitazone in Rats

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ABSTRACT

Aim: Pioglitazone is metabolized by CYP 3A4 and CYP 2C8 and the risk of hypoglycemia may increase if combined with CYP inhibitors like clarithromycin (inhibitor of CYP 3A4) and Gemfibrozil (inhibitor of CYP 2C8). Therefore, this research aims to investigate the drug-drug interactions of gemfibrozil, clarithromycin and their combination with pioglitazone and their effects on blood glucose level.

Methods: The study was conducted in normal rats and streptozotocin-induced hyperglycemic rats.Albino malerats weighing 180 – 250 grams were used in this study. They were divided into groups among the control, pioglitazone, gemfibrozil, clarithromycin, and the combinations treatment groups. Blood samples were collected at intervals of 0, 1, 2, 4, 8 and 12 hours from the rats after drug administration and blood glucose level was measured.

Results: Administration of pioglitazone to normal rats pretreated with gemfibrozil produced a significant reduction ($P < 0.05$) in blood glucose level at time 2 hours, 8 hours and 12 hours compared to time zero. When pioglitazone administered to rats pretreated with clarithromycin, it showed no significant effect in blood glucose level. However; when pioglitazone administered after the combination of gemfibrozil and clarithromycin it produced significant reduction in blood glucose level after 1 hour, 2 hours, 4 hours, 8 hours and 12 hours. When pioglitazone was given with gemfibrozil to rats with streptozotocin-induced hyperglycemia, it showed significant reduction ($P < 0.05$) in blood glucose level after 12 hours compared to time zero. On the other hand, administration of pioglitazone and clarithromycin to hyperglycemic rats it produced no significant effect. However; administration of pioglitazone to hyperglycemic rats received a combination of gemfibrozil and clarithromycin produced significant decrease in blood glucose level after 4 hours, 8 hours and 12 hours compared to time zero.

Conclusion: In the current study, gemfibrozil has shown more impact on blood glucose with pioglitazone than clarithromycin with pioglitazone; while the combination of gemfibrozil and clarithromycin has produced more effect on the blood glucose lowering effect of pioglitazone which might be due inhibition of metabolism of pioglitazone.

Keywords: Drug-drug interactions, oral hypoglycemic agents, Pioglitazone, Gemfibrozil, Clarithromycin, CYP inhibitors.

INTRODUCTION

Diabetes mellitus is a chronic metabolic disordermanifested by impairment of insulin release and/or insulin receptor insensitivity(JM Okonta, 2006).

The prevalence of diabetes mellitus is globally increasing(Kaul, Bolger, Herrington, Giugliano, & Eckel, 2010). The incidence of type 2 diabetes is rising in the community and is expected to affect 380 million people by 2025(Schelleman, Bilker, Brensinger, Wan, & Hennessy, 2010; Xu et al., 2008).Complications of type 2 diabetes mellitus affect many organs of the body systems and producing long term complicationsincluding cardiovascular diseases, diabetic nephropathy, retinopathy and neuropathy(Gæde, Lund-Andersen, Parving, & Pedersen, 2008; JM Okonta, 2006; May & Schindler, 2016).

Diabetes mellitus is treated with dietary modification and hypoglycemic drugs(Xu et al., 2008). In most of the diabetic patients, several concomitant diseases may need additional pharmacological treatment(May & Schindler, 2016).Treatment of type 2 diabetes can be achieved by using oral hypoglycemic agents which include: sulfonylureas, meglitinides, biguanides, thiazolidinediones and alpha-glucosidase inhibitors(FEINGLOS, 2001).

Thiazolidinediones are oral hypoglycemic agents which act by improving insulin resistance, especially when used in combination with other hypoglycemic agents(FEINGLOS, 2001; Peter J. Cox, 2000). It improves hepatic and peripheral tissue utilization of glucose(Kaul et al., 2010).

Adverse drug reactions (ADRs) were responsible for many deaths and are associated with significant morbidity, mortality, and economic loss(K U Dinesh, 2007).

Thiazolidinediones (TZDs), an oral antidiabetic class of medications, have been shown to reduce bone mineral density and are also associated with bone fracturesTZDs also can cause weight gain, increase the risk for heart failure(Peron, Ogbonna, & Donohoe, 2015).

Many factors are affecting adverse drug reactions including drug-drug interactions (DDIs)(K U Dinesh, 2007).

Drug interactions happen when the effect of a specific drug is modified by another drug, plant or a dietary supplement(K U Dinesh, 2007; May & Schindler, 2016). Drug interactions can be classified into two categories including(JM Okonta, 2006) pharmacokinetic interactions: which may arise from alteration of absorption, distribution, metabolism or excretion of a drug; and(Kaul *et al.*, 2010) pharmacodynamic interactions, which alter pharmacologic efficacy of a drug(May & Schindler, 2016).

In the case of pharmacokinetic drug-drug interactions, at least one drug affects the metabolic pathway of the other concomitantdrug. The interaction results in either increased or reduced plasma levels of one or both interacting medications compared with plasma levels when the drugs are taken individualy. A frequent mechanism of pharmacokinetic interactions is inhibition or induction of degradingliver enzymes(May & Schindler, 2016).

Many clinically significant drug interactions with oral hypoglycemic drugs have been reported for example concomitant use of clarithromycin, or another potent inhibitor of CYP 3A4 will increase the plasma concentrations and effects of repaglinide; which belongs to meglitinides; and enhancing its blood glucose – lowering effect and increase the risk of hypoglycemia(Niemi, Neuvonen, & Kivistö, 2001).

Majority of the oral hypoglycemic agents are metabolized by the cytochrome p – 450 system. They are substrates for CYP 2C9, CYP 3A4 or CYP 2C8. Pioglitazone is metabolized by CYP 3A4 and CYP 2C8(Hansten, 2004).

It is reported thatco-administration of gemfibrozil; a potent inhibitor of CYP 2C8; can increase the area under the concentration curve (AUC) of pioglitazone more than 3-folds(Takagi, Sakamoto, Itoh, & Fujiwara, 2015; Tornio, Neuvonen, Niemi, & Backman, 2017).Many studies demonstrated that gemfibrozil is a potent CYP 2C8 inhibitor and may increase the risk of hypoglycemia when used concomitantly with pioglitazone(Aquilante et al., 2013; Backman, Filppula, Niemi, & Neuvonen, 2016; Neuvonen, Niemi, & Backman, 2006).

CYP2C8 and CYP3A4 are the main isoenzymes catalyzing biotransformation of pioglitazone (as

with troglitazone), whereas rosiglitazone is metabolized by CYP2C9 and CYP2C8(Scheen, 2007). Pioglitazone is metabolized mainly by CYP 2C8 and to a lesser extent by CYP 3A4 in vitro(Jaakkola, Backman, Neuvonen, & Neuvonen, 2005; Jaakkola, Laitila, Neuvonen, & Backman, 2006).

Gemfibrozil raises the plasma levels of pioglitazone, probably by inhibition of its CYP2C8-mediated metabolism. CYP2C8 appears to be of major importance and CYP3A4 of minor importance in pioglitazone metabolism in vivo in humans. Concomitant use of gemfibrozil with pioglitazone may increase the effects and risk of dose-related adverse effects of pioglitazone(Jaakkola *et al.*, 2005).

When an oral hypoglycemic drug is combined with a drug known to inhibit its metabolism, the drug interaction may occur. The plasma concentration of the hypoglycemic drug will increase resulting in an enhanced hypoglycemic effect(Hansten, 2004).

Since Pioglitazone is metabolized by CYP 3A4 and CYP 2C8, the risk of hypoglycemia may increase if combined with CYP inhibitors like clarithromycin which is a common inhibitor of CYP 3A4 and Gemfibrozil a common inhibitor of CYP 2C8(Hansten, 2004).

The rationale of the Study

Most diabetic patients may also suffer from other diseases besides diabetes and may take other medicines like gemfibrozil and clarithromycin concurrently with antidiabetic drugs which may lead to drug interactions and increase the risk of hypoglycemia. Therefore, this study aims to evaluate the pattern of drug-drug interactions between gemfibrozil (a common inhibitor of CYP 2C8), clarithromycin (a common inhibitor of CYP 3A4) and their combination with the oral hypoglycemic agent pioglitazone which is metabolized mainly by cytochrome P450 (CYP) 2C8 and CYP3A4 to assess the risk of hypoglycemia.

MATERIALS AND METHODS

Drugs

Pioglitazone tablets (ACTOS®, Takeda)was crushed and dissolved in gum acacia (5 %). Gemfibrozil (Lopid®, Pfizer) and clarithromycin (KLACID®, Abbott)were treated similarly.

Animals

Albino male rats weighing 180 – 250 gramswere obtained from the animal house, Faculty of Pharmacy, Northern Border University, KSA after ethical approval. They were divided into groups among the control, pioglitazone, gemfibrozil, clarithromycin,and the combinations treatment groups.

METHODS

Experimental design and treatment procedure

Effect of pioglitazone, gemfibrozil, clarithromycin and their combinations on the blood glucose level in normal rats:

The rats were divided into seven groups of five rats each and treated as follows:

1- Group -1: Normal control group;receivedgum acacia (5 %) in distilled water.

2- Group -2: Pioglitazone 10 mg/kg.

3- Group -3: Gemfibrozil 100 mg/kg.

4- Group -4: Clarithromycin 100 mg/kg.

5- Group -5: Gemfibrozil 100 mg/kg and Pioglitazone10 mg/kg.

6- Group -6: Clarithromycin 100 mg/kg and Pioglitazone10 mg/kg.

7-Group -7: Gemfibrozil 100 mg/kg plus Clarithromycin 100 mg/kg plus Pioglitazone10 mg/kg.

The rats were fasted for 12 hours;gemfibrozil and clarithromycin were administered orally, 30 minutes before the administration of pioglitazone and blood samples collected from retro-orbital plexus under anesthesia at intervals 0,1, 2, 4, 8 and 12hours after drug administration and blood glucose level was measured using a glucometer.

Effect of pioglitazone, gemfibrozil, clarithromycin and their combinations on the blood glucose level in streptozotocin (STZ) - inducedhyperglycemic rats:

Male albinorats of 180 – 250 g body weight wereused in this study. The rats were made hyperglycemic by injecting streptozotocin (50 mg/kg) intraperitoneally.

Induction of hyperglycemia in rats was achieved byadministration of streptozotocin (STZ) (50 mg/kg) freshly prepared in 0.1 M sodium citrate buffer by intraperitoneal injection. Blood glucose level was checked after 72 hours of STZ administration. Another 50 mg/kg of STZ was administered, and hyperglycemia confirmed after 72 hours. Rats with fasting blood glucose levels above 180 mg/dl were selected for the study and divided into seven groups of four rats per group and treated as follows:

1- Group -1: Diabetic control group; received gum acacia (5 %) in distilled water.

2- Group -2: Pioglitazone 10 mg/kg.

3- Group -3: Gemfibrozil 100 mg/kg.

4- Group -4: Clarithromycin 100 mg/kg.

5- Group -5: Gemfibrozil 100 mg/kg and Pioglitazone10 mg/kg.

6- Group -6: Clarithromycin 100 mg/kg and Pioglitazone10 mg/kg.

7-Group-7: Gemfibrozil 100mg/kg plus Clarithromycin 100 mg/kg plus Pioglitazone10 mg/kg.

The rats fasted for 12 hours; gemfibrozil and clarithromycin were administered orally, 30 minutes before the administration of pioglitazone and blood samples collected from retro-orbital plexus under anesthesia at intervals 0, 1, 2, 4, 8 and 12 hours after drug administration and blood glucose level was measured using a glucometer.

RESULTS

Effect of pioglitazone, gemfibrozil, clarithromycin and their combination on the blood glucose level in normal rats:

Table (1): Effect of pioglitazone, gemfibrozil, clarithromycin and their combination on the blood glucose level in normal rats (n = 5):

Group	Time zero	1 hour	2 hours	4 hours	8 hours	12 hours
Normal Control	122.40 (16.09)	113.25 (12.09)	78.75 (9.42)	107.00 (13.06)	94.00 (11.37)	73.25 (5.94)
Pioglitazone	102.40 (5.35)	106.40 (6.90)	*79.60 (5.89)	99.00 (4.11)	*79.25 (6.22)	*74.75 (5.98)
Gemfibrozil	104.60 (5.24)	105.20 (8.90)	*75.40 (2.20)	95.80 (3.71)	89.00 (7.48)	*80.60 (9.91)
Clarithromycin	109.00 (5.83)	92.20 (9.97)	*75.20 (6.61)	*86.80 (5.54)	*79.20 (3.71)	94.60 (1.78)
Gemfibrozil and Pioglitazone	120.80 (9.87)	120.60 (5.73)	*81.00 (8.85)	96.60 (9.84)	*89.40 (9.62)	*76.20 (10.07)
Clarithromycin and Pioglitazone	99.80 (6.74)	101.00 (5.21)	86.75 (15.85)	104.25 (5.23)	91.75 (4.37)	74.00 (3.81)
Gemfibrozil plus Clarithromycin plus Pioglitazone	119.40 (7.43)	*85.80 (5.15)	*79.60 (9.22)	*94.00 (5.80)	*75.80 (5.24)	*85.80 (3.46)

Values are expressed as mean ± SEM (ANOVA) (LSD)

* Significantly different as compared to the time zero$P < 0.05$

As shown in the table (1); Pioglitazone significantly ($P < 0.05$) decreased theblood glucose levelafter 2 hours, 8 hours and 12 hours when compared to blood glucose level at time zero. Gemfibrozil significantly ($P < 0.05$) decreased the blood glucose level after 2 hours, and 12 hours when compared to blood glucose level at time zero. Clarithromycin significantly ($P < 0.05$) reduced the blood glucose level after 2 hours, 4 hours and 8 hours when compared to blood glucose level at time zero.Gemfibrozil and Pioglitazone significantly ($P < 0.05$) decreased the blood glucose level after 2 hours, 8 hours and 12 hours when compared to blood glucose level at time zero. Gemfibrozil plus Clarithromycin plus Pioglitazone

significantly ($P < 0.05$) decreased the blood glucose level after 1 hour, 2 hours, 4 hours, 8 hours and 12 hours when compared to blood glucose level at time zero.

Effect of pioglitazone, gemfibrozil, clarithromycin and their combination on the blood glucose level in streptozotocin (STZ) - induced hyperglycemic rats

Table (2): Effect of pioglitazone, gemfibrozil, clarithromycin and their combinations on the blood glucose level in streptozotocin (STZ) - induced hyperglycemic rats (n = 4):

Group	Time zero	1 hour	2 hours	4 hours	8 hours	12 hours
Diabetic control	336.00 (45.16)	369.75 (31.93)	429.25 (36.08)	400.00 (40.43)	356.00 (47.98)	281.00 (40.21)
Pioglitazone	366.25 (60.24)	391.25 (65.70)	382.75 (72.79)	339.25 (66.56)	276.75 (57.61)	229.50 (50.95)
Gemfibrozil	436.25 (17.62)	408.00 (10.82)	429.25 (16.96)	417.00 (12.39)	*374.25 (17.57)	*347.25 (8.46)
Clarithromycin	337.75 (16.77)	388.25 (30.08)	*399.25 (24.57)	365.25 (10.97)	341.50 (2.90)	305.25 (22.22)
Gemfibrozil and Pioglitazone	369.50 (58.88)	402.25 (33.67)	430.25 (26.35)	365.25 (40.59)	303.50 (25.11)	*186.25 (32.51)
Clarithromycin and Pioglitazone	315.25 (67.15)	380.50 (79.06)	347.75 (71.46)	353.75 (38.98)	345.00 (42.58)	274.50 (31.17)
Gemfibrozil plus Clarithromycin plus Pioglitazone	482.00 (21.79)	474.50 (12.18)	445.75 (18.12)	*364.25 (24.25)	*326.50 (26.43)	*377.00 (17.75)

Values are expressed as mean ± SEM (ANOVA) (LSD)

* Significantly different as compared to the time zero $P < 0.05$

As shown in the table (2); Pioglitazone significantly ($P < 0.05$) decreased the blood glucose level after 2 hours, 8 hours and 12 hours when compared to blood glucose level at time zero.

Gemfibrozil significantly ($P < 0.05$) decreased the blood glucose level after 2 hours, and 12 hours when compared to blood glucose level at time zero. Clarithromycin significantly ($P < 0.05$) reduced the blood glucose level after 2 hours, 4 hours and 8 hours when compared to blood glucose level at time zero. Gemfibrozil and Pioglitazone significantly ($P < 0.05$) decreased the blood glucose level after 2 hours, 8 hours and 12 hours when compared to blood glucose level at time zero.

Gemfibrozil plus Clarithromycin plus Pioglitazone significantly ($P < 0.05$) decreased the blood glucose level after 1 hour, 2 hours, 4 hours, 8 hours and 12 hours when compared to blood glucose level at time zero.

DISCUSSION

Druginteractions are considered serious problems worldwide. It can occur between drugs or drugs and food which may lead to alterations in the pharmacokinetic and pharmacodynamic properties of a drug(Giri Mrudula, 2017).

Patients suffering from chronic diseases like diabetes mellitus can also have several comorbidities like hyperlipidemia, cardiovascular diseases, and infections which may lead to polypharmacy and increased risk of drug-drug interactions(Giri Mrudula, 2017; Tornio, Niemi, Neuvonen, & Backman, 2012).

Thiazolidinediones are oral hypoglycemic agents which act by improving insulin resistance, especially when used in combination with other hypoglycemic agents (FEINGLOS, 2001; Peter J. Cox, 2000). It improves hepatic and peripheral tissue utilization of glucose(Kaul et al., 2010).

Thiazolidinedione act by binding to peroxisome proliferator-activated receptor – g (PPAR-g) and results in a slow rise in insulin sensitivity in

hepatic, fat and skeletal muscle cell(Tornio *et al.*, 2012).

Thiazolidinediones are useful in the treatment of type 2 diabetes mellitus and are also reported to decrease pancreatic beta-cell destruction and hence may have benefits in the treatment and prevention of type 1 diabetes mellitus(Tafuri, Godil, Lane, & Wilson, 2013). Pioglitazone belongs to the thiazolidinediones andis metabolized by CYP2C8 mainly and to a lesser extent by CYP3A4(Tornio *et al.*, 2012), andit has a low risk of causing hypoglycemia(Charbonnel., 2011).

The purpose of the current study was to investigate the pattern of potential drug-drug interactions between gemfibrozil (inhibitor of CYP 2C8), clarithromycin (inhibitor of CYP 3A4) and their combination with the oral hypoglycemic agent pioglitazone to assess the risk of hypoglycemia. It wasconducted in two phases; phase one: the effects of gemfibrozil and clarithromycin on the blood glucose level in normal rats administered pioglitazone. Phase two: Effects of gemfibrozil and clarithromycin on the blood glucose level in streptozotocin-induced hyperglycemic rats administered pioglitazone.

Pioglitazone, when administered to normal rats, produced significant reduction ($P < 0.05$) in blood glucose level after 2 hours, 8 hours and 12 hours compared to time zero; while it produced no significant effect in streptozotocin-induced hyperglycemic rats.

This study found that administration of pioglitazone to normal rats pretreated with gemfibrozil produced a significant reduction in blood glucose level at time 2 hours, 8 hours and 12 hours compared to time zero. When pioglitazone administered to rats pretreated with clarithromycin, it showed no significant effect in blood glucose level. However; when pioglitazone administered after the combination of gemfibrozil and clarithromycin it produced significant reduction in blood glucose level after 1 hour, 2 hours, 4 hours, 8 hours and 12 hours.

In this study;pioglitazone has produced no significant effect when administered to rats with streptozotocin-induced hyperglycemia. When pioglitazone was given with gemfibrozil to rats with streptozotocin-induced hyperglycemia, it showed significant reduction in blood glucose level after 12 hours compared to time zero. On the other hand, administration of pioglitazone and clarithromycin to hyperglycemic rats it produced no significant effect. However; administration of pioglitazone to hyperglycemic rats received a combination of gemfibrozil and clarithromycin produced significant decrease in blood glucose level after 4 hours, 8 hours and 12 hours compared to time zero.

In a study conducted by Fullert*et al.* (2002) to assess the effects of pioglitazone in Non-diabetic patients with arterial hypertension; they found that pioglitazone significantly decreased both fasting glucose and fasting insulin concentrations(Haak *et al.*, 2002).In another study; David K. *et al.*(2006) studied the benefit of adding pioglitazone to statin therapy in non-diabetic patients with metabolic syndrome and they reported that glucose level decreased significantly while no hypoglycemia was observed(David K. Murdock, 2006). However; Takeshi Horio*et al.* (2005) noted that pioglitazone did not significantly decrease fasting plasma glucose or HbA1c in the non-diabetic subjects(Kawano *et al.*, 2005).

The metabolism of pioglitazone is mainly by cytochrome CYP2C8 and with a lesser extent by CYP3A4. It is reported that gemfibrozil increased the area under the curve (AUC) of pioglitazone by three folds in healthy subjects; while itraconazole which inhibitor of CYP3A4 produced no significant effect on pioglitazone metabolism(Tornio et al., 2012). In the current study; gemfibrozil has shown more effect with pioglitazone than clarithromycin with pioglitazone; while the combination of gemfibrozil and clarithromycin has produced more increase on the hypoglycemic effect of pioglitazone which might be due inhibition of metabolism of pioglitazone.

In this study; pioglitazone has produced no significant effect when administered to rats with streptozotocin-induced hyperglycemia. However; administration of pioglitazone to hyperglycemic rats received a combination of gemfibrozil and clarithromycin produced significant decrease in blood glucose level after 4 hours, 8 hours and 12 hours compared to time zero.

It is reported that pioglitazone administered to adults with slowly progressive type one diabetes mellitus it accelerated the progression of the disease(Tafuri *et al.*, 2013).

Kimberly Sue Tafuri *et al.* (2013) in their study concluded that pioglitazone given to children with type one diabetes mellitus had not preserved the function of the β cell(Tafuri *et al.*, 2013).However; many studies reported that thiazolidinediones could have a role in the treatment and prevention of type one diabetes mellitus by decreasing pancreatic β – cell destruction and also other studies in non – obese diabetic and streptozotocin-treated mouse models found that pretreatment with thiazolidinediones prevented the development of type one diabetes mellitus(Tafuri *et al.*, 2013). It is also reported that rosiglitazone, which belongs to thiazolidinediones, given alone or in combination with insulin was found to preserve β – cellfunction in adults with latent autoimmune diabetes(Tafuri *et al.*, 2013).

Yoshinori Miyazaki et al. (2002) found improvement in glycemic control by pioglitazone in a dose-dependent enhancement of beta- cell function(Miyazaki, Matsuda, & DeFronzo, 2002).

In the current study,administration of pioglitazone to Streptozotocin-induced hyperglycemic rats which administereda combination of gemfibrozil and clarithromycinproduced a significant decrease in blood glucose level. This reduction was observed after 4 hours, 8 hours and 12 hours after administration of pioglitazone compared to time zero; this might be due tothe increased blood concentration of pioglitazone due to inhibition of its metabolism by concomitant administration of gemfibrozil (inhibitor of CYP 2C8) and clarithromycin (inhibitor of CYP 3A4).

In this study; Clarithromycin (macrolide antibiotics) was given alone as a control to normal rats and also to the streptozotocin (STZ) induced hyperglycemic rats. In normal rats; clarithromycin produced a significant decrease in blood glucose level after 2 hours, 4 hours and 8 hours compared to time zero. However; when it was given to the STZ induced hyperglycemic rats, it caused a significant increase in blood glucose level after 2 hours compared to time zero.

Yoji Miyoshia (2013) reported that clarithromycin (a macrolide antibiotic) and cefcapenepivoxil (cephem antibiotic) when given to treat acute sinusitis to a patient with diabetes he developed severe hyperglycemia(Miyoshi., 2013). Meghani*et al.* (2012) found that clarithromycin significantly increased glucose level in diabetic rats, while rosiglitazone decreased glucose level in diabetic rats, however; Clarithromycin masked the glucose-lowering effect of rosiglitazone when given together(N. M. Meghani, 2012). In the current study, clarithromycin produced a significant increase in blood glucose level in STZ hyperglycemic rats after 2 hours compared to time zero. At the same time when clarithromycin was given in combination with pioglitazone, it did not prevent the increase in blood glucose level till 8 hours after administration to the hyperglycemic rats.

Interestingly; in this study when clarithromycin was administered alone to non-diabetic rats it showed a significant reduction in blood glucose level after 2 hours, 4 hours and 8 hours compared to time zero; but when administered in combination with pioglitazone no significant effect was produced.

In a study conducted by RohiniGambre*et al.* (2017) they reported that clarithromycin did not result ina significant reduction in blood glucose level in non –diabetic albino rabbits, but when combined with glibenclamide they produced significant decrease in blood glucose level(Rohini Gambre, 2017). However; other studies found that

some macrolide antibiotics; which is the same group of clarithromycin; can reduce blood glucose level in non-diabetic animals. Amr and his colleagues (2005), reported that erythromycin administered for seven days produced a significant decrease in blood glucose level in normal rats; but did not showa significant effect on blood glucose level when administered to alloxan diabetic rats(Rostom, Zaki, & H. El Bakry, 2005). Selenke*et al.* (1980) also reported that troleandomycin (macrolide antibiotics) reduced the glucose tolerance test of mice(Selenke WM, 1980).

Also in this study; Gemfibrozil was given alone as a control to normal rats, and the streptozotocin (STZ) induced hyperglycemic rats. In normal rats; Gemfibrozil produced a significant decrease in blood glucose level after 2 hours and 12 hours compared to time zero. When it was given to the STZ induced hyperglycemic rats, it produced significant reduction in blood glucose level after 8 hours and 12 hours compared to time zero.

Mussoni*et al.* (2000), studied the effects of gemfibrozil in patients with primary hypertriglyceridemia and reported that it caused marked reduction of plasma triglycerides and improvement of insulin sensitivity(Mussoni *et al.*, 2000). It is also mentioned that gemfibrozil has improved glucose metabolism and insulin action in diabetic and non-diabetic hypertriglyceridemic patients(DANJUN SONG, 2016). (DANJUN *et al.* (2016) documented that gemfibrozil in healthy wild-type (WT) mice caused down-regulation of blood glucose level and the liver glycogen content in the mice (DANJUN SONG, 2016).

However;other studies reported that gemfibrozil produced no changes in plasma glucose level in patients with type 2 diabetes mellitus. In a different study, it is also mentioned that gemfibrozil has not shown a modification in blood glucose level in STZ induced diabetic rats(DANJUN SONG, 2016).

Chandrashekhar *et al.* (2011) studied the interaction between gliclazide and gemfibrozil in animal models, and they found that gemfibrozil produced no hypoglycemic effect in rabbits when given alone but enhanced the hypoglycemic effect of gliclazide when given together(Chandrashekhar M Sultanpur, 2011).

CONCLUSION:

While most of the studies agree that gemfibrozil may affect the metabolism of pioglitazone; however, there is a controversial on the effect of gemfibrozil and clarithromycinon blood glucose level in normal and hyperglycemic rats. In the current study,gemfibrozil has shown more impact on blood glucose with pioglitazone than clarithromycin with pioglitazone; while the combination of gemfibrozil and clarithromycin has produced more increase on the hypoglycemic effect of pioglitazone which might be due inhibition of metabolism of pioglitazone.

The limitations in the comparison of this study with other studies may be the differences in species, doses, and duration of treatment.

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Conflict of interest: None to declare.

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