Original Article

Comparative Study of Efficacy and Safety of Lobeglitazone versus Pioglitazone as Add on Therapy to Metformin and Vildagliptin in Patients of Type 2 Diabetes Mellitus

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ABSTRACT

Introduction: The thiazolidinedione (TZDs) class of oral anti-hyperglycaemic drug represents one of the oral anti-hyperglycaemic drugs classes that predominantly control insulin resistance among those that have been created thus far. There is still an urgent clinical requirement generate and strengthen evidence on efficacy and safety of ne TZDs notwithstanding the ongoing discussion about the possible adverse effects of thiazolidinedione (TZD) and efforts to develop novel categories of insulin sensitizers.

Aims/objective: To compare the efficacy and safety of pioglitazone (15 mg/day) versus lobeglitazone (0.5 mg/day) in patients with T2DM and poor glucose control despite dual pharmacotherapy with metformin and vildagliptin.

Materials and Method: Patients in group L were given lobeglitazone 0.5 mg once daily as add on therapy to metformin 1000 mg plus vildagliptin 100 mg and patients in group P were given pioglitazone 15 mg once daily as add on therapy to metformin 1000 mg plus vildagliptin 100 mg. The primary endpoint was the reduction in mean HbA1c between baseline and end of study (12 months). The secondary outcome measures were fasting blood sugar (FBS), post-prandial blood sugar (PPBS), body weight, and incidence of adverse events.

Results: Addition of both the drugs to ongoing metformin + DPP-4 inhibitor therapy resulted in significant decrease in HbA1c, fasting blood sugar and post-prandial blood sugar. However, addition of lobeglitazone resulted in significantly better glycaemic control at 6 months and 12 months of follow-up. There was less incidence of adverse events like oedema, weight gain, headache and sinusitis in patients receiving lobeglitazone. There was no report of serious adverse events from either group.

Conclusion: The efficacy of lobeglitazone (0.5 mg/day) was better than pioglitazone (15 mg/day) as an add-on to ongoing metformin plus vildagliptin therapy in terms of the change in HbA1c concentration from baseline with no serious adverse events.

Keywords: Lobeglitazone, Pioglitazone, Thiazolidinediones, Diabetes Mellitus, Glycaemic Control, Safety.

INTRODUCTION

The prevalence of type 2 diabetes mellitus (T2DM) has risen to epidemic levels worldwide, in accordance to the International Diabetes Federation (IDF). [1] The selection of a glucose-lowering medicine for the treatment of T2DM can be difficult for certain people. Most recommendations advocate metformin as the first medication of choice. Combination therapy may be an option as the subsequent phase if metformin monotherapy is unable to sufficiently control the level of blood glucose. In many nations, metformin, and Dipeptidyl peptidase-4 (DPP4) inhibitors are frequently administered as a dual combination pharmacotherapy. [2-4] Regardless of the availability of these combination medications, a significant number of patients continue to have poorly managed levels of blood glucose. [5, 6]

Insulin resistance and beta-cell dysfunction are two features of type 2 diabetes mellitus (T2DM), a long-term, progressing metabolic illness. [7] Due to the complexity and multifaceted nature of T2DM's pathogenesis, a number of oral anti-hyperglycaemic drugs have been created on the basis of the underlying processes connected to T2DM. The thiazolidinedione (TZD) class of oral anti-hyperglycaemic drug represents one of the oral anti-hyperglycaemic drugs classes that predominantly control insulin resistance among those that have been created thus far. [8]

In addition to improving insulin resistance in fat cells, upregulating the uptake of glucose and utilisation by the muscles, and decreasing hepatic glucose synthesis, thiazolidinediones (TZDs) also activate peroxisome proliferator-activated receptor gamma. [9-12] The use of TZD is certainly going to rise given the pathophysiology of T2DM, which involves insulin resistance and beta-cell dysfunction. [13]

The usage of TZDs has significantly expanded since the United States Food and Drug Administration authorised pioglitazone and rosiglitazone in 1999. In contrast, fewer patients than anticipated use TZDs in clinical settings. [14] In fact, since Nissen and Wolski first described the cardiovascular risk of rosiglitazone in 2007, the use of TZDs has substantially decreased. [15] TZD use has decreased despite evidence that rosiglitazone had no discernible effects on cardiovascular outcomes. These issues include

cardiovascular disease, oedema, weight gain, and osteoporosis. [16-20]

There is still an urgent clinical requirement for a fresh TZD notwithstanding the ongoing discussion about the possible adverse effects of thiazolidinedione (TZD) and efforts to develop novel categories of insulin sensitizers. A new TZD moiety and substituted pyrimidines make up the PPAR (peroxisome proliferator-activated receptor) agonist known as lobeglitazone. [21] These altered pyrimidines were chosen based on their effectiveness in decreasing blood glucose level and lipid-modulating effects on diabetic mice as well as their experimental effects on accumulation of triglycerides in fat cells. [22, 23]

In contrast to pioglitazone, lobeglitazone has a minimal urine excretion rate in people, and 2-year carcinogenicity investigations in mice and rats have not revealed any tumours in the bladder. [24-26] In healthy persons' pharmacokinetic investigations, lobeglitazone was tolerated well and had no discernible impact on the pharmacokinetics of metformin or the other way around. [27]

In this study, we aimed to compare the efficacy and safety of pioglitazone (15 mg/day) versus lobeglitazone (0.5 mg/day) in patients with T2DM and poor glucose control despite dual pharmacotherapy with metformin and vildagliptin.

MATERIALS AND METHODS

This was an open label, randomized, single centred study with parallel 1:1 allocation conducted at a tertiary care centre of eastern India between October 2021 and November 2022. The trial had three phases: a 2-week screening phase, a 12-month therapy phase, and a 30-day follow-up phase. Following permission from the institutional ethics committee and in accordance with the Declaration of Helsinki and good clinical practise, the study was launched. Before enrollment, eligible patients provided written informed consent.

Inclusion Criteria

Patients with confirmed diagnosis of T2DM aged 19-80 years, patients previously on metformin plus vildagliptin for at least 3 months, patients with HbA1c level between 7.0% to 9.0%.

Exclusion Criteria

The main criteria for exclusion were a past history of serious cardiac disease (New York Heart Association Class III or IV), a major cardiovascular or cerebrovascular event within the preceding six months, the use of other blood glucose-lowering medications, kidney or liver dysfunction [eGFR less than 45 ml/min/1.73m^2 or a blood level of aspartate aminotransferase (AST) or alanine aminotransferase (ALT) 2.5 times greater than the upper normal limit, abnormal lipid profile [serum triglycerides greater than 500 mg/dl or low-density lipoprotein (LDL) greater than 160 mg/dl], pharmacotherapy with insulin or any TZDs in the past 8 weeks before screening, and history of bladder cancer.

With anticipated mean reduction of HbA1c at end of study in patients given lobeglitazone as 0.7 ± 0.1 and 0.8 in pioglitazone group with 0.05 alpha value and 95% power and 1:1 allocation, minimum sample size was found to be 52. So, 120 patients were randomised into two groups to compensate for possible 25% attrition and generate more powerful evidences.

Patients in group L were given lobeglitazone 0.5 mg once daily as add on therapy to metformin 1000 mg plus vildagliptin 100 mg and patients in group P were given pioglitazone 15 mg once daily as add on therapy to metformin 1000 mg plus vildagliptin 100 mg.

The primary endpoint was the reduction in mean HbA1c between baseline and end of study (12 months). The secondary outcome measures were fasting blood sugar (FBS), post-prandial blood sugar (PPBS), body weight, and incidence of adverse events.

Initial screening involved gathering information on anthropometric parameters, physical examination results, medical records, and laboratory test results. Complete blood count (CBC), fasting blood sugar, HbA1c, creatinine, lipid profiles, liver enzymes, and thyroid stimulating hormone were among the biochemical tests performed. At each 3 months of follow-up, the subjects had additional physical examinations and laboratory tests to compare to baseline levels (with the exception of CBC).

Statistical Analysis

Collected information on baseline demographic and clinical characteristics, and findings of laboratory reports were recorded in tabular form using Microsoft Excel 365. Unpaired t-test was used to test statistical significance of difference between group L and P with respect to continuous variables like age, body weight, duration of diabetes, HbA1c, PPBS and TSH were expressed as mean ± standard deviation (SD). Fisher's exact test or chi-square test was used to test statistical significance of difference between group L and P with respect to categorical variables like sex and incidence of adverse events. A p-value of less than 0.05 was taken as measure of statistical significance.

RESULTS

60 patients were recruited in each group. After recruitment 6 patients in pioglitazone group and 9 patients in lobeglitazone group were lost to follow up.

Table 1: Comparison of Baseline Demographic and Clinical Characteristics between Lobeglitazone Group and Pioglitazone Group.

Parameters	Pioglitazone Group (n = 54)	Lobeglitazone Group (n = 51)	P-Value
Age in years (Mean ± SD)	58.23 ± 6.58	56.47 ± 6.63	0.18*
Gender			>0.99**
Number of Males (%)	25 (46.30)	24 (47.06)	
Number of Females (%)	29 (53.70)	27 (52.94)	
Duration of T2DM in Years (Mean ± SD)	8.56 ± 4.24	8.05 ± 4.80	0.56*
Body Weight in kg (Mean±SD)	61.73 ± 9.62	62.58 ± 11.27	0.86*
BMI in kg/m^2 (Mean ± SD)	25.34 ± 3.29	25.59 ± 5.83	0.78*
TSH in µIU/ml (Mean ± SD)	2.41 ± 1.69	2.26 ± 1.63	0.64*
*Unpaired t-test **Fisher's exact test			

Both the groups were similar with respect to age, sex, duration of T2DM, body weight, BMI, and TSH at baseline with no statistically significant difference (p>0.05).

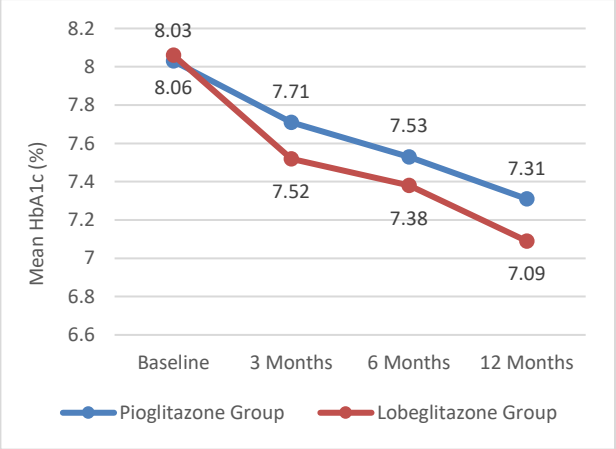

Figure 1: Comparison of Mean HbA1c between Lobeglitazone group and Pioglitazone Group

Table 2: Comparison of HbA1c Levels between Lobeglitazone Group and Pioglitazone Group

Time	Mean HbA1c (%) in Pioglitazone Group ± SD	Mean HbA1c (%) in Lobeglitazone Group ± SD	P-Value (Unpaired t-test)
Baseline	8.03 ± 1.13	8.06 ± 1.01	0.88
3 Months	7.71 ± 1.32	7.52 ± 1.34	0.46
6 Months	7.53 ± 1.18	7.38 ± 1.11	0.53
12 Months	7.31 ± 1.01	7.09 ± 1.05	0.13
P-Value (ANOVA)	<0.0001	<0.0001	

There was no statistically significant difference between lobeglitazone group and pioglitazone group with respect to HbA1c at baseline and till end of study (12 months). At 6 month and 12 months of follow up, HbA1c was lower in patients receiving lobeglitazone than patients receiving pioglitazone but the difference was not statistically significant (p>0.05). Lobeglitazone group and pioglitazone group showed significant decline in mean HbA1c from baseline and end of the study (p<0.05). [Table 2] [Figure 1]

Table 3: Comparison of Mean Fasting Blood Sugar at Different Follow-up between Lobeglitazone Group and Pioglitazone Group

Time	Mean FBS (mg/dl) in Pioglitazone Group ± SD	Mean FBS (mg/dl) in Lobeglitazone Group ± SD	P-Value (Unpaired t-test)
Baseline	174.47 ± 27.39	176.13 ± 28.48	0.76
3 Months	159.76 ± 27.33	151.27 ± 20.45	0.08
6 Months	149.62 ± 24.80	138.31 ± 18.92	**0.01**
12 Months	138.24 ± 22.77	129.31 ± 15.83	**0.02**
P-Value (ANOVA)	<0.0001	<0.0001	

There was no statistically significant difference between lobeglitazone group and pioglitazone group with respect to FBS at baseline and 3 months of follow-up. At 6 month and 12 months of follow up, FBS was lower in patients receiving lobeglitazone than patients receiving pioglitazone with statistically significant difference (p<0.05). Lobeglitazone group and pioglitazone group showed significant decline in mean FBS from baseline and end of the study (p<0.05). [Table 3]

Table 4: Comparison of Mean Post-prandial Blood Sugar at Different Follow-up between Lobeglitazone Group and Pioglitazone Group

Time	Mean PPBS (mg/dl) in Pioglitazone Group ± SD	Mean PPBS (mg/dl) in Lobeglitazone Group ± SD	P-Value (Unpaired t-test)
Baseline	231.58 ± 36.41	234.04 ± 34.37	0.72
3 Months	211.67 ± 33.24	201.51 ± 29.95	0.10
6 Months	197.73 ± 32.79	178.31 ± 27.63	**0.002**
12 Months	180.35 ± 30.69	159.45 ± 21.94	**0.0001**
P-Value (ANOVA)	<0.0001	<0.0001	

There was no statistically significant difference between lobeglitazone group and pioglitazone group with respect to PPBS at baseline and 3 months of follow-up. At 6 month and 12 months of follow up, PPBS was lower in patients receiving lobeglitazone than patients receiving pioglitazone with statistically significant difference (p<0.05). Lobeglitazone group and pioglitazone group showed significant decline in mean PPBS from baseline and end of the study (p<0.05). [Table 4]

Table 5: Comparison of Incidence of Adverse Events between Lobeglitazone Group and Pioglitazone Group

Parameters	Pioglitazone Group (n = 54)	Lobeglitazone Group (n = 51)	P-Value (Fisher's exact test)
Oedema	7	3	0.32
Weight Gain	9	6	0.58
Headache	4	1	0.36
Myalgia	2	0	0.49
Upper respiratory tract infection	3	1	0.62
Sinusitis	2	0	0.49

There was less incidence of adverse events like oedema, weight gain, headache and sinusitis in patients receiving lobeglitazone. However, the lobeglitazone group and pioglitazone group didn't differ significantly statistically as per result of fisher's exact test (p> 0.05). There was no report of serious adverse events from either group.

DISCUSSION

In this randomised controlled trial, efficacy, and safety of lobeglitazone as add on to ongoing metformin plus vildagliptin therapy for glycaemic control was compared with pioglitazone. Addition of both the drugs to ongoing metformin + DPP-4 inhibitor therapy resulted in significant decrease in HbA1c, fasting blood sugar and post-prandial blood sugar. However, addition of lobeglitazone resulted in significantly better glycaemic control at 6 months and 12 months of follow-up.

In 6 months, randomised, double-blinded non-inferiority study, the anti action of lobeglitazone when used together with metformin was assessed. [28] Patients with type 2 diabetes mellitus who received a constant dosage of metformin but had unsatisfactory glycaemic control were randomised to be given either lobeglitazone 0.5 mg daily or pioglitazone 15 mg daily as an add-on pharmacotherapy to metformin. The mean HbA1c decrease after 6 months of lobeglitazone add-on therapy was 0.74%, almost similar the reduction observed in the pioglitazone group, demonstrating that lobeglitazone was not less effective than pioglitazone as add-on therapy to metformin in terms of its anti-diabetic effect. [28]

Another randomised controlled study found that adding lobeglitazone with metformin for 6 months had glycaemic effectiveness that was comparable to sitagliptin plus metformin pharmacotherapy. [29] Other than metformin, there have not been any documented prospective randomised studies evaluating the efficacy of addition of lobeglitazone with other oral anti-diabetic drug on glycaemic control. Fortunately, retrospective research evaluated the effectiveness of lobeglitazone on glycaemic control both alone and in various combination therapies.[30]

The previous study done in an out-patient department, enrolled 423 patients who were given lobeglitazone for more than 6 months. After a median follow-up of nearly one year of lobeglitazone treatment, the mean reduction in HbA1c was 0.6% among all groups; for patients receiving lobeglitazone monotherapy it was 0.34%, for patients given dual therapy of lobeglitazone and metformin it was 0.52%, for patients given lobeglitazone with DPP-4 inhibitors it was 0.63%, and for patients receiving lobeglitazone plus sulfonylurea it was 0.33%. In the groups where triple therapy was given, the mean reduction in HbA1c was 0.84% in group receiving lobeglitazone plus metformin plus DPP-4 inhibitor, 0.88% in group receiving lobeglitazone plus DPP-4 inhibitor plus sulfonylurea, and 0.33% in group receiving lobeglitazone plus metformin plus sulfonylurea. These findings highlighted that when lobeglitazone is given in addition to DPP-4 inhibitor, it led to better glycaemic control than other regimens containing lobeglitazone. [30]

Earlier, an observational and prospective study explicitly assessed the efficacy of initial pharmacotherapy with triple regimen consisting of lobeglitazone for glycaemic control in patients with T2DM with an HbA1c level between 9.0% and 12.0%. 31 This research recruited used consecutive sampling and ensured that both groups were similar with respect to age and body mass index to compare triple therapy with lobeglitazone with conventional dual therapy consisting metformin. After one-year, mean HbA1c reduction was 4.05% in patients who were given triple regimen of metformin 1,000 mg/day with sitagliptin 100 mg/day with lobeglitazone 0.5 mg/day and mean HbA1c reduction was 3.28% in patients who were given metformin ≥1,000 mg/day with glimepiride ≥2 mg/day. In spite of the fact that the study investigated on the efficacy of the triple therapy with regimen consisting of lobeglitazone, it also has generated evidence for the effectiveness of lobeglitazone as add on therapy for patients on poor glycaemic control for patients of type 2 diabetes mellitus. 31

However, it is comforting to know that lobeglitazone, a purely PPAR-gamma agonist instead of a dual PPAR action, did not demonstrate any significant difference in its influence on lipid profile in comparison to pioglitazone. In the current study, oedema and a rise in body weight were two safety concerns that was associated with both lobeglitazone and pioglitazone. Furthermore, no serious drug-related adverse events (AEs) were noted during the research period, including heart failure necessitating admission.

The use of TZDs for various clinical cases may be improved by lowering the risks of side effects connected with their administration. Use of low doses when starting therapy may lower the chance of side effects. In previous studies, low-dose of pioglitazone (7.5 mg/day) demonstrated non-inferiority in glycaemic control and demonstrated less side effects than standard-dose of pioglitazone (15 mg/day).[32-24]

The total daily dose of pioglitazone in the current study was only 15 mg, which is a clinically significant limitation. Although pioglitazone has a maximum daily dose of 30 mg and is permitted for individuals who do not respond well to a dose of 15 mg, using a greater dose result in a higher cost for the patient. In a short-term trial with healthy participants, lobeglitazone was found to be well tolerated in doses as high as 4 mg for 7 days. 24 Further multi-centre trials evaluating the effectiveness and safety of larger doses of lobeglitazone and the maximal dose of pioglitazone should be encouraged by the findings of the current study.

CONCLUSION

Based on findings of our study, the efficacy of lobeglitazone (0.5 mg/day) was better than pioglitazone (15 mg/day) as an add-on to ongoing metformin plus vildagliptin therapy in terms of the change in HbA1c concentration from baseline with no serious adverse events. It is anticipated that lobeglitazone can be administered in individuals with renal failure without reducing the dose since it is primarily metabolised by the liver, with minor excretion through the kidneys, and because it might pose a lower risk of bladder carcinoma than other TZDs. More clinical and preclinical research is should be done to support the positive effects of lobeglitazone and its mode of action.

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REFERENCES

1. Aschner P, Karuranga S, James S, et al. The international diabetes Federation's guide for diabetes epidemiological studies. Diabetes Res Clin Pract. 2021; 172: 108630.
2. Committee of Clinical Practice Guidelines KDA. 2021 clinical practice guidelines for diabetes mellitus in Korea. Diabetes Metab J. 2021; 45(4): 461- 481.
3. Moon JS, Suh S, Kim SS, et al. Efficacy and safety of treatment with quadruple oral hypoglycemic agents in uncontrolled type 2 diabetes mellitus: a multi-center, retrospective, observational study. Diabetes Metab J. 2020; 45(5): 675-683.
4. Lee KA, Jin HY, Kim YJ, Im YJ, Kim EY, Park TS. Treatment patterns of type 2 diabetes assessed using a common data model based on electronic health records of 2000-2019. J Korean Med Sci. 2021; 36(36):e230.
5. Kim BY, Won JC, Lee JH, et al. Diabetes fact sheets in Korea, 2018: an appraisal of current status. Diabetes Metab J. 2019; 43(4): 487- 494.
6. Fang M, Wang D, Coresh J, Selvin E. Trends in diabetes treatment and control in U.S. adults, 1999-2018. N Engl J Med. 2021; 384(23): 2219- 2228.
7. Kahn SE. The relative contributions of insulin resistance and beta-cell dysfunction to the pathophysiology of type 2 diabetes. Diabetologia. 2003;46:3–19.
8. Lebovitz HE. Thiazolidinediones: the forgotten diabetes medications. Curr Diab Rep. 2019;19:151.
9. Kim H, Haluzik M, Gavrilova O, et al. Thiazolidinediones improve insulin sensitivity in adipose tissue and reduce the hyperlipidaemia without affecting the hyperglycaemia in a transgenic model of type 2 diabetes. Diabetologia. 2004; 47(12): 2215- 2225.
10. Kim WJ. Recent perspective on thiazolidinedione. J Korean Diabetes. 2021; 22(2): 97- 104.
11. Babar T, Skugor M. Diabetes mellitus treatment. In: C Cleveland, ed. Current Clinical Medicine. 2nd ed. Philadelphia: W.B. Saunders; 2010: 358- 363.e351.
12. Bae J, Park T, Kim H, Lee M, Cha B-S. Lobeglitazone: a novel thiazolidinedione for the management of type 2 diabetes mellitus. Diabetes Metab J. 2021; 45(3): 326- 336.
13. Davidson MA, Mattison DR, Azoulay L, Krewski D. Thiazolidinedione drugs in the treatment of type 2 diabetes mellitus: past, present and future. Crit Rev Toxicol. 2018; 48(1): 52- 108.
14. Suk JH, Lee CW, Son SP, et al. Current status of prescription in type 2 diabetic patients from general hospitals in busan. Diabetes Metab J. 2014; 38(3): 230- 239.
15. Nissen SE, Wolski K. Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. N Engl J Med. 2007; 356(24): 2457- 2471.
16. Nesto RW, Bell D, Bonow RO, et al. Thiazolidinedione use, fluid retention, and congestive heart failure: a consensus statement from the American Heart Association and American Diabetes Association. Circulation. 2003; 108(23): 2941- 2948.
17. Hernandez AV, Usmani A, Rajamanickam A, Moheet A. Thiazolidinediones and risk of heart failure in patients with or at high risk of type 2 diabetes mellitus. Am J Cardiovasc Drugs. 2011; 11(2): 115- 128.
18. Meier C, Kraenzlin ME, Bodmer M, Jick SS, Jick H, Meier CR. Use of thiazolidinediones and fracture risk. Arch Intern Med. 2008; 168(8): 820- 825.
19. Yanai H, Adachi H. The low-dose (7.5 mg/day) pioglitazone therapy. J Clin Med Res. 2017; 9(10): 821- 825.
20. Kim JH, Kim SS, Baek HS, et al. Comparison of vildagliptin and pioglitazone in Korean patients with type 2 diabetes inadequately controlled with metformin. Diabetes Metab J. 2016; 40(3): 230- 239.
21. Kim SG, Kim DM, Woo JT et al. Efficacy and safety of lobeglitazone monotherapy in patients with type 2 diabetes mellitus over 24-weeks: a multicenter, randomized, double-blind, parallel-group, placebo controlled trial. PLoS One 2014; 9: e92843. [PMC free article] [PubMed] [Google Scholar]
22. Kim BY, Ahn JB, Lee HW et al. Synthesis and biological activity of novel substituted pyridines and purines containing 2,4-thiazolidinedione. Eur J Med Chem 2004; 39: 433–447. [PubMed] [Google Scholar]
23. Lee HW, Kim BY, Ahn JB et al. Molecular design, synthesis, and hypoglycemic and hypolipidemic activities of novel pyrimidine derivatives having thiazolidinedione. Eur J Med Chem 2005; 40: 862–874. [PubMed] [Google Scholar]

24. Kim JW, Kim JR, Yi S et al. Tolerability and pharmacokinetics of lobeglitazone (CKD-501), a peroxisome proliferator-activated receptor-gamma agonist: a single- and multiple-dose, double-blind, randomized control study in healthy male Korean subjects. Clin Ther 2011; 33: 1819–1830. [PubMed] [Google Scholar]

25. Moon KS, Lee JE, Lee HS et al. CKD-501, a novel selective PPARgamma agonist, shows no carcinogenic potential in ICR mice following oral administration for 104 weeks. J Appl Toxicol 2014; 34: 1271–1284. [PubMed] [Google Scholar]

26. Lee HS, Chang M, Lee JE et al. Carcinogenicity study of CKD-501, a novel dual peroxisome proliferator-activated receptors alpha and gamma agonist, following oral administration to Sprague Dawley rats for 94–101weeks. Regul Toxicol Pharmacol 2014; 69: 207–216. [PubMed] [Google Scholar]

27. Shin D, Kim TE, Yoon SH et al. Assessment of the pharmacokinetics of co-administered metformin and lobeglitazone, a thiazolidinedione antihyperglycemic agent, in healthy subjects. Curr Med Res Opin 2012; 28: 1213–1220. [PubMed] [Google Scholar]

28. Jin SM, Park CY, Cho YM, Ku BJ, Ahn CW, Cha BS, et al. Lobeglitazone and pioglitazone as add-ons to metformin for patients with type 2 diabetes: a 24-week, multicentre, randomized, double-blind, parallel-group, active-controlled, phase III clinical trial with a 28-week extension. Diabetes Obes Metab. 2015;17:599–602. [PMC free article] [PubMed] [Google Scholar]

29. Kim SG, Kim KJ, Yoon KH, Chun SW, Park KS, Choi KM, et al. Efficacy and safety of lobeglitazone versus sitagliptin as an add-on to metformin in patients with type 2 diabetes with two or more components of metabolic syndrome over 24weeks. Diabetes Obes Metab. 2020;22:1869–73. [PubMed] [Google Scholar]

30. Lee JY, Cho Y, Lee M, Lee YH, Lee BW, Kang ES, et al. Clinical efficacy of the novel thiazolidinedione lobeglitazone in patients with type 2 diabetes. Diabetes Metab. 2018;44:452–5. [PubMed] [Google Scholar]

31. Lim S, Ku EJ, Lee SY, Lee JH, Lee JE, Kim KM, et al. Therapeutic efficacy and safety of initial triple combination of metformin, sitagliptin, and lobeglitazone in drug-naïve patients with type 2 diabetes: initial triple study. BMJ Open Diabetes Res Care. 2020;8:e000807 [PMC free article] [PubMed] [Google Scholar]

32. Majima T, Komatsu Y, Doi K, et al. Safety and efficacy of low-dose pioglitazone (7.5 mg/day) vs standard-dose pioglitazone (15 mg/day) in Japanese women with type 2 diabetes mellitus. Endocr J. 2006; 53(3): 325- 330.

33. Rajagopalan S, Dutta P, Hota D, Bhansali A, Srinivasan A, Chakrabarti A. Effect of low dose pioglitazone on glycemic control and insulin resistance in type 2 diabetes: a randomized, double blind, clinical trial. Diabetes Res Clin Pract. 2015; 109(3): e32- e35.

34. Kim J-D, Lee W-Y. Insulin secretory capacity and insulin resistance in Korean type 2 diabetes mellitus patients. Endocrinol Metab. 2016; 31(3): 354- 360.

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