Original Article

Efficacy and Safety of Lobeglitazone versus Pioglitazone as Add on Therapy to Metformin and Vildagliptin in Patients of Type 2 Diabetes Mellitus: A Randomised Controlled Trial

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ABSTRACT

Introduction: Among the classes of oral anti-hyperglycemic medications that have been developed to date, the thiazolidinedione family is one that primarily regulates insulin resistance. Despite the ongoing discussion concerning the potential adverse effects of thiazolidinedione (TZD) and initiatives to develop new categories of insulin sensitizers, there is still an urgent clinical demand to generate and reinforce evidence on the efficacy and safety of the TZDs.

Materials and Method: Lobeglitazone 0.5 mg was administered once daily to patients in group L + M + V as an add-on medication to metformin 1000 mg + vildagliptin 100 mg, whereas pioglitazone 15 mg was administered once daily to patients in group P + M + V and metformin 1000 mg + vildagliptin 100 mg. The decrease in mean HbA1c between baseline and 12 months was the primary outcome. Body weight, incidence of adverse effects, post prandial blood glucose, and fasting blood glucose were the secondary outcome measures.

Results: At 6 month and 12 months of follow up, decrease in HbA1c (0.18) was greater in patients receiving lobeglitazone than patients receiving pioglitazone (0.14). At 6 month and 12 months of follow up, there was greater fall in FBG & PPBG in lobeglitazone group than pioglitazone group and the difference was statistically significant ($p<0.05$). Patients on lobeglitazone experienced a lower frequency of adverse effects.

Conclusion: Lobeglitazone was more effective in achieving glycaemic control than pioglitazone in terms of changing the baseline HbA1c concentration without causing any significant side effects.

Keywords: Lobeglitazone, Pioglitazone, Thiazolidinediones, Type 2 Diabetes Mellitus, Glycaemic Control, Adverse Events.

INTRODUCTION

The International Diabetes Federation (IDF) reports that type 2 diabetes mellitus (T2DM) is becoming epidemically common over the globe. [1] For some patients, choosing a glucose-lowering medication to treat type 2 diabetes might be challenging. The majority of recommendations support metformin as the first-choice drug. If metformin monotherapy is unable to adequately manage the blood glucose level, combination therapy may be a possibility as the next step. Metformin and Dipeptidyl peptidase-4 (DPP4) inhibitors are commonly used in conjunction as medication in several countries. [2-4] Even with the accessibility of these combination drugs, a sizable portion of patients still have poorly controlled blood glucose levels. [5, 6]

The long-term, progressive metabolic disease known as type 2 diabetes mellitus (T2DM) is characterized by insulin resistance and beta-cell dysfunction. [7] Owing to the intricate and diverse pathophysiology of type 2 diabetes, several oral anti-hyperglycaemic medications have been developed based on the fundamental mechanisms associated with the disease. Among the classes of oral anti-hyperglycaemic medications that have been developed to date, the thiazolidinedione (TZD) family is one that primarily regulates insulin resistance. [8]

Thiazolidinediones (TZDs) not only decrease insulin resistance in adipose tissue, but they also stimulate peroxisome proliferator-activated receptor gamma, upregulate muscle glucose uptake and utilisation, and reduce hepatic glucose production. [9–12] Given that the pathogenesis of type 2 diabetes involves both insulin resistance and beta-cell dysfunction, the use of TZD is expected to increase. [13]

Since pioglitazone and rosiglitazone were approved by the US Food and Drug Administration in 1999, the use of TZDs has increased dramatically. On the other hand, TZD use in clinical settings is lower than expected among patients. [14] In actuality, the use of TZDs has significantly declined since Nissen and Wolski initially reported the cardiovascular risk associated with rosiglitazone in 2007. [15] Despite data showing rosiglitazone had no appreciable impact on cardiovascular outcomes, the use of TZD has declined. Osteoporosis, weight gain, oedema, and cardiovascular disease are among these issues. [16–20]

Despite the continuous debate regarding the potential side effects of thiazolidinedione (TZD) and attempts to create

new classes of insulin sensitizers, there is an urgent clinical need for a new TZD. Lobeglitazone is a PPAR (peroxisome proliferator-activated receptor) activator that consists of a novel TZD moiety and substituted pyrimidines. [21] These modified pyrimidines were selected because to their ability to lower blood glucose levels, their ability to modulate lipid levels in diabetic mice, and their experimental impact on triglyceride production in adipose tissue. [22, 23]

Lobeglitazone has a lower renal elimination rate in humans than pioglitazone, and studies on its carcinogenicity in mice and rats over a two-year period have not shown any bladder tumours. [24-26] In pharmacokinetic studies conducted on healthy individuals, lobeglitazone was well tolerated and did not appear to affect the pharmacokinetics of metformin in any manner. [27]

In this study, we compared the safety and effectiveness of lobeglitazone (0.5 mg/day) and pioglitazone (15 mg/day) in patients with type 2 diabetes who had poor glycaemic control even after receiving metformin plus vildagliptin dual pharmacotherapy.

MATERIALS AND METHODS

In a tertiary care facility in eastern India, this open-label, randomized, single-centred study had parallel 1:1 allocation and was carried out between October 2022 and November 2023. The two-week screening phase, the 12-month therapy phase, and the 30-day follow-up phase comprised the trial's three phases. The study was started after receiving approval from the institutional ethics committee and in compliance with the Declaration of Helsinki and best clinical practices. Eligible patients gave written informed permission before to enrolment.

Inclusion Criteria

Participants between the ages of 19 and 80 who have been diagnosed with type 2 diabetes, who have taken vildagliptin and metformin for at least three months, and whose HbA1c level was between 7.0% and 9.0%.

Exclusion Criteria

A past history of serious cardiovascular disease (New York Heart Association Class III or IV) or a major cardiovascular or cerebrovascular adverse event within six months of enrolment or the concomitant use of other anti-diabetic drugs or renal dysfunction diagnosed by eGFR < 45 ml/min/1.73m^2 or elevated liver enzymes (2.5 x Upper limit of normal) or dyslipidaemia or history of taking any other TZDs within 2 months of screening or history of bladder carcinoma.

With anticipated mean reduction of HbA1c at end of study in patients given lobeglitazone as 0.7 ± 0.15 and 0.8 in pioglitazone group with 0.05 alpha value and 85% power and 1:1 allocation, minimum sample size was found to be 80. So, 100 patients were randomised into two groups to compensate for possible 20% attrition.

Patients in group L + M +V recieved lobeglitazone 0.5 mg once daily as add on therapy to metformin 1000 mg plus vildagliptin 100 mg and patients in group P + M +V received pioglitazone 15 mg once daily as add on therapy to metformin 1000 mg + vildagliptin 100 mg.

The decrease in mean HbA1c between baseline and trial completion (12 months) was the main outcome. Body weight, the frequency of adverse events, post-prandial blood glucose (PPBG), and fasting blood glucose (FBG) were the secondary outcome measures.

Anthropometric measurements, physical examination findings, medical records, and results of laboratory tests were collected as part of the first screening process. Among the biochemical tests carried out were the complete blood count (CBC), fasting blood glucose, HbA1c, serum creatinine, lipid profile, liver function test, and thyroid profile. The subjects underwent further physical examinations and laboratory investigations at each three-month follow-up to compare to baseline values.

Statistical Analysis

Microsoft Excel 365 was used to capture the data in tabular form for the baseline demographic and clinical features as well as the results of laboratory reports. The statistical significance of the difference between groups L + M + V and P + M + V was tested using the unpaired t-test for continuous variables such as age, body weight, PPBS, TSH, HbA1c, and duration of diabetes. The results were expressed as mean ± standard deviation (SD). The statistical significance of the difference between groups L + M + V and P + M + V with regard to categorical factors like sex and the frequency of adverse events was tested using Fisher's exact test or chi-square test. A statistically significant p-value was defined as less than 0.05.

RESULTS

Most of the patients were of age greater than 50 years and there was slight female preponderance. Duration of diabetes of most of the patients was greater than 5 years. Most of the patients were euthyroid as per TSH levels. Age, sex, body weight, BMI, TSH, and the length of time the patient had type 2 diabetes were similar in both groups at baseline, and there was no statistically significant difference ($p>0.05$).

Both the groups were comparable with respect to HbA1c at baseline and till end of study (12 months) with no statistically significant difference ($p>0.05$). However, at 6 month and 12 months of follow up, decrease in HbA1c (0.18) was greater in patients receiving lobeglitazone than patients receiving pioglitazone (0.14). Patients in both the group had significant decrease in HbA1c from baseline and end of the study ($p<0.05$). [Table 2] [Figure 1]

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

Parameters	Pioglitazone Group (n = 50)	Lobeglitazone Group (n = 50)	P-Value
Age in years (Mean ± SD)	59.34 ± 6.69	57.58 ± 6.74	0.98*
Gender			
Number of Males (%)	23	24	>0.99**
Number of Females (%)	27	26	
Duration of T2DM in Years (Mean ± SD)	7.67 ± 2.35	7.16 ± 2.91	0.34*
Body Weight in kg (Mean ± SD)	62.84 ± 9.73	63.69 ± 12.38	0.70*
BMI in kg/m^2 (Mean ± SD)	25.45 ± 3.40	25.70 ± 5.94	0.80*
TSH in µIU/ml (Mean ± SD)	2.52 ± 1.80	2.37 ± 1.74	0.67*
*Unpaired t-test **Fisher's exact test			

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	8.14 ± 1.24	8.17 ± 1.12	0.90
3 Months	7.82 ± 1.43	7.63 ± 1.45	0.51
6 Months	7.64 ± 1.29	7.49 ± 1.22	0.55
12 Months	7.42 ± 1.12	7.20 ± 1.16	0.34
P-Value (ANOVA)	<0.0001	<0.0001	

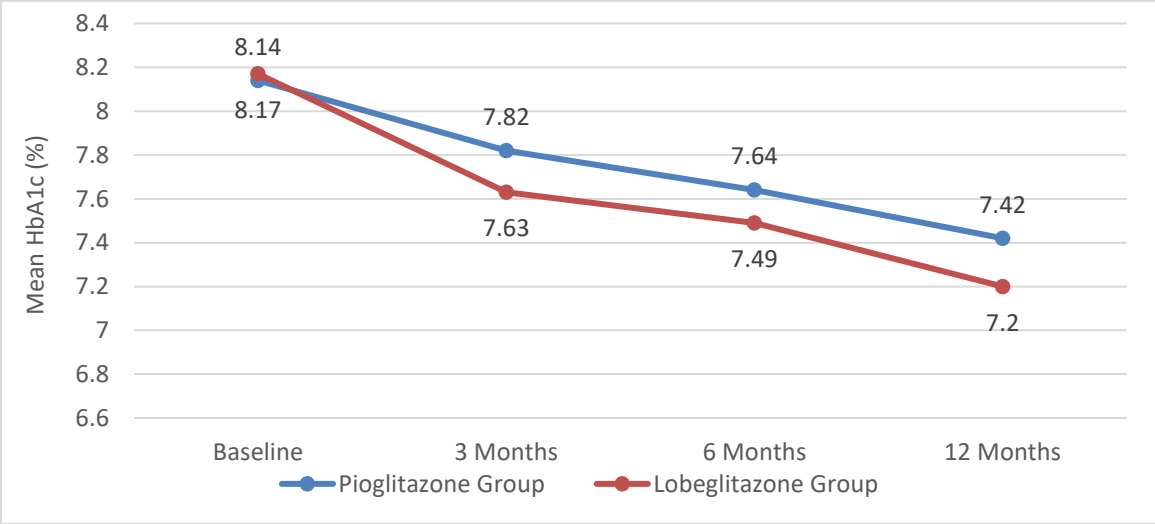

Figure 1: Comparison of Mean HbA1c between Lobeglitazone group and Pioglitazone Group

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

Time	Mean FBG (mg/dl) in Pioglitazone Group ± SD	Mean FBG (mg/dl) in Lobeglitazone Group ± SD	P-Value (Unpaired t-test)
Baseline	175.36 ± 28.28	177.02 ± 28.37	0.77
3 Months	160.87 ± 27.44	152.16 ± 20.34	0.08
6 Months	150.51 ± 24.69	140.20 ± 18.81	**0.02**
12 Months	139.13 ± 22.66	130.20 ± 15.72	**0.02**
P-Value (ANOVA)	<0.0001	<0.0001	

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

Time	Mean PPBG (mg/dl) in Pioglitazone Group ± SD	Mean PPBG (mg/dl) in Lobeglitazone Group ± SD	P-Value (Unpaired t-test)
Baseline	232.47 ± 36.41	235.03 ± 34.26	0.72
3 Months	212.56 ± 33.24	202.40 ± 29.84	0.11
6 Months	198.62 ± 32.79	179.20 ± 27.52	**0.002**
12 Months	181.24 ± 30.69	160.34 ± 21.83	**0.0002**
P-Value (ANOVA)	<0.0001	<0.0001	

Both the groups were comparable with respect to FBG at baseline and 3 months of follow-up with no statistically significant difference (p>0.05). At 6 month and 12 months of follow up, there was greater fall in FBG in lobeglitazone group than pioglitazone group and the difference was statistically significant (p<0.05). Patients in both the group had significant decrease in FBG from baseline and end of the study (p<0.05). [Table 3]

Both the groups were comparable with respect to PPBG at baseline and 3 months of follow-up with no statistically significant difference (p>0.05). At 6 month and 12 months of follow up, there was greater fall in PPBG in lobeglitazone group than pioglitazone group and the difference was statistically significant (p<0.05). Patients in both the group had significant decrease in PPBG from baseline and end of the study (p<0.05). [Table 4]

Patients on lobeglitazone experienced a lower frequency of side effects such as oedema, weight gain, headaches, and sinusitis. However, the Fisher's exact test result showed no statistically significant difference between the lobeglitazone and pioglitazone groups (p>0.05). Neither group reported any significant adverse events. [Table 5]

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

Parameters	Pioglitazone Group (n = 50)	Lobeglitazone Group (n = 50)
Oedema	6	3
Weight Gain	8	5
Headache	3	1
Myalgia	2	0
Upper respiratory tract infection	2	1
Sinusitis	2	0

DISCUSSION

The effectiveness and safety of lobeglitazone as an adjuvant to current metformin + vildagliptin pharmacotherapy for glycaemic management were compared with pioglitazone in this randomised controlled trial. When both medications were added to the ongoing metformin + DPP-4 inhibitor therapy, the HbA1c, fasting blood sugar, and post-prandial blood sugar all significantly decreased. At 6 and 12 months of follow-up, however, the inclusion of lobeglitazone led to noticeably better glycaemic management.

In a similar 6-month randomised, double-blind, non-inferiority trial conducted to evaluate the anti-action of lobeglitazone in combination with metformin, patients with type 2 diabetes mellitus who were receiving a constant dosage of the medication but did not achieve sufficient glycaemic control were randomly assigned to receive either pioglitazone (15 mg daily) or lobeglitazone 0.5 mg daily. After six months of lobeglitazone add-on therapy, the mean HbA1c decreased by 0.74%, which was practically identical to the drop seen in the pioglitazone group. This indicates that lobeglitazone was equally as successful as pioglitazone as metformin add-on therapy in terms of its anti-diabetic effect. [28]

Another randomised controlled trial indicated that the glycaemic effectiveness of 6 months of lobeglitazone plus metformin was equivalent to that of sitagliptin plus metformin medication. [29] There were no published prospective randomized trials assessing the impact of lobeglitazone in addition to other oral anti-diabetic drugs on glycaemic management, except from metformin. Thankfully, studies conducted in the past have assessed the impact of lobeglitazone on glycaemic management whether used alone or in different combinations. [30]

In an earlier study conducted in an outpatient department, 423 patients who received lobeglitazone for longer than six months were included. The mean reduction in HbA1c after a median follow-up of almost a year following lobeglitazone therapy was 0.6% across all groups; it was 0.34% for patients getting lobeglitazone monotherapy, 0.52% for patients getting lobeglitazone + metformin dual therapy, 0.63% for patients getting lobeglitazone along with DPP-4 inhibitors, and 0.33% for patients getting lobeglitazone plus sulfonylurea. Three groups received triple therapy: 0.84%, 0.88%, and 0.33% of the groups received lobeglitazone + metformin plus DPP-4 inhibitor, sulfonylurea, and lobeglitazone plus metformin plus sulfonylurea, respectively, with a mean reduction in HbA1c. These results demonstrated that compared to other lobeglitazone regimens, glycaemic control was improved when

lobeglitazone was administered in conjunction to a DPP-4 inhibitor. [30]

An earlier observational and prospective trial evaluated the effectiveness of a triple regimen, which included lobeglitazone, as the first line of treatment for glycaemic control in patients with type 2 diabetes who had a HbA1c level between 9.0% and 12.0%. [31] In order to evaluate combination therapy with lobeglitazone with traditional dual therapy consisting of metformin, this study used successive sampling to guarantee that all groups were identical in terms of age and body mass index. After a year, patients on the triple regimen of metformin 1,000 mg/day, sitagliptin 100 mg/day, and lobeglitazone 0.5 mg/day experienced a mean HbA1c decrease of 4.05%, while those on the metformin ≥1,000 mg/day and glimepiride ≥2 mg/day regimen experienced a mean HbA1c decrease of 3.28%. Despite the fact that the trial examined the efficiency of a triple therapy regimen that included lobeglitazone, it also produced evidence about the usefulness of lobeglitazone as an adjuvant treatment for patients with type 2 diabetes who had poor glycaemic control. [31]

In contrast to pioglitazone, lobeglitazone, a PPAR-gamma agonist only, did not show any appreciable variation in its impact on lipid profile, which is reassuring. Oedema and an increase in body weight were two safety issues linked to both lobeglitazone and pioglitazone in the current investigation. Moreover, no significant adverse events (AEs) related to the medication were reported during the study period, including cardiac failure requiring hospitalization.

Reducing the potential for adverse effects associated with TZD treatment may enhance its usage for a variety of clinical conditions. When beginning therapy, using modest doses may reduce the likelihood of side effects. Low-dose pioglitazone (7.5 mg/day) showed less adverse effects and non-inferiority in glycaemic control compared to standard-dose pioglitazone (15 mg/day) in earlier studies. [32–24]

A clinically major limitation of the current trial was the overall daily dose of pioglitazone, which was only 15 mg. Pioglitazone can be used in patients who fail to respond adequately to a dose of 15 mg, however utilizing a higher dose will cost the patient more money. The maximum recommended daily dose of pioglitazone is 30 mg. Lobeglitazone proved to be well tolerated in a short-term trial with healthy individuals, even at doses up to 4 mg for seven days. [24] The results of this investigation should motivate other multi-centred trials to assess the safety and efficacy of higher lobeglitazone dosages as well as the maximum pioglitazone dose.

CONCLUSION

Based on the results of our investigation, lobeglitazone (0.5 mg/day) was more effective as an add-on to continuous metformin plus vildagliptin therapy than pioglitazone (15 mg/day) with regards to the reduction in HbA1c level from baseline with no significant adverse effects. Since lobeglitazone is mostly metabolized by the liver and excreted in small amounts by the kidneys, it is expected that it can be supplied to patients with renal failure without lowering the dose. Additionally, compared to other TZDs, lobeglitazone may also carry a lower risk of bladder cancer. To validate the beneficial effects of lobeglitazone and its specific mechanism of action, more preclinical and clinical research has to be conducted.

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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]

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.

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.

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.

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.

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.

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.

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.

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.

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.

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

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.