

## Research Paper

# Efficacy and Safety Comparison between Pioglitazone and Linagliptin in Combination with Metformin among Patients with Type 2 Diabetes Mellitus: A Meta-Analysis of Randomized Controlled Trials

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## Abstract

**Objective:** To compare the safety and efficacy of linagliptin with pioglitazone in combination therapy of metformin for the management of type 2 diabetes mellitus (T2DM). **Materials and Methods:** A meta-analysis research design is applied to evaluate the primary and secondary outcomes. Literature search was carried out using databases such as PubMed, Cochrane Library, MEDLINE Complete, Scopus, Clinical Trial Registry, and Web of Science. Studies were considered eligible if the eligibility criteria were met. Cochrane Collaboration Tool was used to assess the risk of bias in randomized clinical trials. **Results:** A total of 170 citations were identified during the database search. Further evaluation of articles confirmed 16 clinical trials suitable for the research which were randomized, double-blinded, and published as full articles. The articles were evaluated with low risk of bias and high-quality evidence. The mean baseline hemoglobin A1c (HbA1c) ranged from 6.93% to 9.99% and 7.1% to 8.89% for linagliptin with metformin and pioglitazone with metformin groups, respectively. Two among the 12 groups show a slight increase in the mean HbA1c levels which is nonsignificant due to their sample size. Overall, the combination therapy of linagliptin with metformin led to a reduction of 1.35% which is significantly higher than pioglitazone combined with metformin which led to a 1.27% reduction. The mean baseline values of fasting plasma glucose levels varied from 158.2 mg/dl to 198.0 mg/dl in linagliptin plus metformin group, whereas in pioglitazone plus metformin group, the values varied from 137.0 mg/dL to 212.4 mg/dL. The high heterogeneity could refer to the inconsistencies between the studies. The combination of linagliptin with metformin showed a significant reduction of 0.56% in body mass index, whereas pioglitazone with metformin led to a 0.37% reduction. **Conclusion:** The findings showed better efficacy profiling of linagliptin–metformin combination compared with pioglitazone combination therapy.

**Keywords:** Diabetes mellitus, dipeptidyl peptidase-4Is, linagliptin, management, meta-analysis, SGLT2s

## INTRODUCTION

The occurrence of diabetes mellitus has increased over the years and it became the most prevalent disease worldwide among the chronic diseases, rising up to 9.9% by the year 2045.<sup>[1,2]</sup> The statistics in International Diabetes Federation estimates a death every 7 s due to diabetes, with 50% commonly taking place in the population below the age of 60 years.<sup>[1]</sup> Long-term diabetes therapy includes both pharmacological approaches including combinations of drugs along with a nonpharmacological approach which focuses on modifying lifestyle to reach the ultimate glycemic targets.<sup>[3]</sup>

Thiazolidinediones (TZDs) are a class of drugs used to treat type 2 diabetes which differ in activity from other antidiabetic medications due to their ability to bind to the nuclear peroxisome proliferator-activated receptors- $\gamma$  (PPAR $\gamma$ ) and

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modify the transcriptional activity.<sup>[4,5]</sup> These PPAR $\gamma$  play a role in regulating the metabolism of carbohydrates and lipid.<sup>[2]</sup> TZDs increase the insulin secretion in the peripheral areas leading to adipogenesis and decreasing the glucose production.<sup>[6,7]</sup> This mechanism enhances insulin sensitivity, hence lowering fasting and postprandial glucose levels.<sup>[6]</sup> Prolonged use of TZDs can lead to adverse effects in terms of bone loss and higher possibilities of fractures in women with type 2 diabetes mellitus (T2DM).<sup>[2,8]</sup>

Dipeptidyl peptidase 4 (DPP 4), also called CD 26, is a cell marker that is found in plenty of tissues including lymphocytes, T-cells, B-cells, and natural killer cells.<sup>[9]</sup> The DPP 4 inhibitors preferably known as gliptins are generally prescribed in combination.<sup>[1]</sup> They contribute to lowering the glycemic status by blocking the activity of DPP-4 and act as incretin enhancers.<sup>[10]</sup> Incretins are an enzyme which puts down the action of gastrointestinal (GI) hormones.<sup>[10]</sup> Insulin is produced by incretins when they are stimulated and inhibit the glucagon secretion by the liver depending on when the body needs it or not.<sup>[8]</sup> Gliptins show relatively lower adverse effects when compared to other oral antidiabetic medications. The incidence of cardiovascular mortality, GI disturbances, and other general infections is reduced with the use of gliptins when compared to sulfonylureas.<sup>[10,11]</sup>

Linagliptin was observed to show a modest decrease in hemoglobin A1c (HbA1c) levels without causing hypoglycemia, hence is considered in patients with established kidney disease.<sup>[12]</sup> Linagliptin when taken as an add-on therapy for long term along with insulin or other antihyperglycemic drugs, a significant higher change in mean HbA1c levels from baseline was observed.<sup>[1]</sup>

No long-term data were published on risk factors associated with complications of the disease and comorbidities of patients. Patient-oriented outcomes such as side effects of the medication, quality of life, and metabolic control are briefly defined yet require more elucidated data.

The objective of the study is to evaluate the safety and efficacy of linagliptin with pioglitazone with metformin combination in patients with T2DM.

## MATERIALS AND METHODS

### Search strategy

A thorough literature search was carried out using databases such as PubMed, Cochrane Library, MEDLINE Complete, Scopus, Clinical Trial Registry, and Web of Science.

While carrying out the search, different keywords were used which were combined using Boolean operators (AND and OR) such as Pioglitazone AND Metformin, type 2 Diabetes mellitus AND Clinical Trials AND Linagliptin, Adverse effects OR Side effects, Safety AND Efficacy, and Compliance OR Adherence. Various other keywords included to conduct the search were fasting plasma glucose (FPG), HbA1c, body mass index (BMI), and complications with different combinations.

### Eligibility criteria

Studies were considered eligible if the following criteria were met: (1) randomized control trials were conducted on T2DM patients receiving a combination of pioglitazone with metformin, (2) trials conducted on T2DM patients receiving a combination of linagliptin with metformin, (3) showed the efficacy of the treatment on FPG and HbA1C levels, (4) patient's adherence to the given treatment, (5) reports adverse events, (6) studies conducted on patients  $\geq 18$  years old including male and female participants, and (7) randomized controlled trials published from 2004 onward, limited to publication in the English language. Everything other than what is mentioned is an exclusion.

### Quality assessment

Cochrane collaboration tool<sup>[13]</sup> was used to assess the risk of bias in randomized clinical trials. The criteria for assessing the quality of articles were random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, and selective reporting. For each study, the risk of bias was graded.

### Study process

This study is a systematic review and a meta-analysis article. The studies were selected based on eligibility criteria from various databases. The critical appraisal was performed based on the Cochrane review tool. Data were extracted from Excel sheets for evidence synthesis and evaluation of effectiveness. Further, the publication bias and risk of bias were determined using statistical software.

### Outcomes

In relation to drug therapy, fasting blood sugar and HbA1c levels are considered as the primary outcome. The mean changes and mean standard deviation values of fasting blood sugar are compared between pioglitazone with metformin and linagliptin with metformin groups using odds ratio. A comparison of the mean change in HbA1c levels from baseline to the end of the trial is performed between both the groups. The secondary clinical outcomes studied are body weight, adverse effects, and patient compliance. The number of adverse events in the study groups is also reported which results from the combination medications. Patient compliance along with adverse effects and body weight is analyzed in numbers (one in hundred of the trial group).

### Statistical analysis

After collecting data, the data are written on a spreadsheet that contains the author's name, then a description which includes what year the study was conducted, type of a study, sample size, and then the forest plot is designed to check point estimates and confidence intervals (CI).

Effect size measures the magnitude of observed effect between two variables. This can be done by three most common methods such as Pearson's R and Cohen's D (for continuous variables) and odds ratio (for categorical variables). Sometimes, meta-analysis depends on fixed-effects or random-effects statistical models. For

complex data, multivariate methods for meta-analysis have been used. To assess heterogeneity,  $I^2$  test is used. Publication bias is an important aspect to consider when negative findings have less probability of it getting published which will be performed using a funnel plot. Cochrane Review Manager (RevMan) version 5.3 software for analysis and data synthesis is used.

## RESULTS

A total of 170 citations were identified during the database search. Further evaluation of articles confirmed 16 clinical trials suitable for the research, which were randomized, double-blinded, and published as full articles. PRISMA flow diagram is illustrated in Figure 1.

Eight study groups each were selected for linagliptin and pioglitazone in combination with metformin. All the studies had patients above 18 years old along with HbA1c, FPG, BMI, adverse event, and compliance as either primary or secondary outcome. The duration of studies varied from 12 weeks to 54 weeks. The characteristics for each trial included are shown in Table 1.

## Assessment of risk of bias

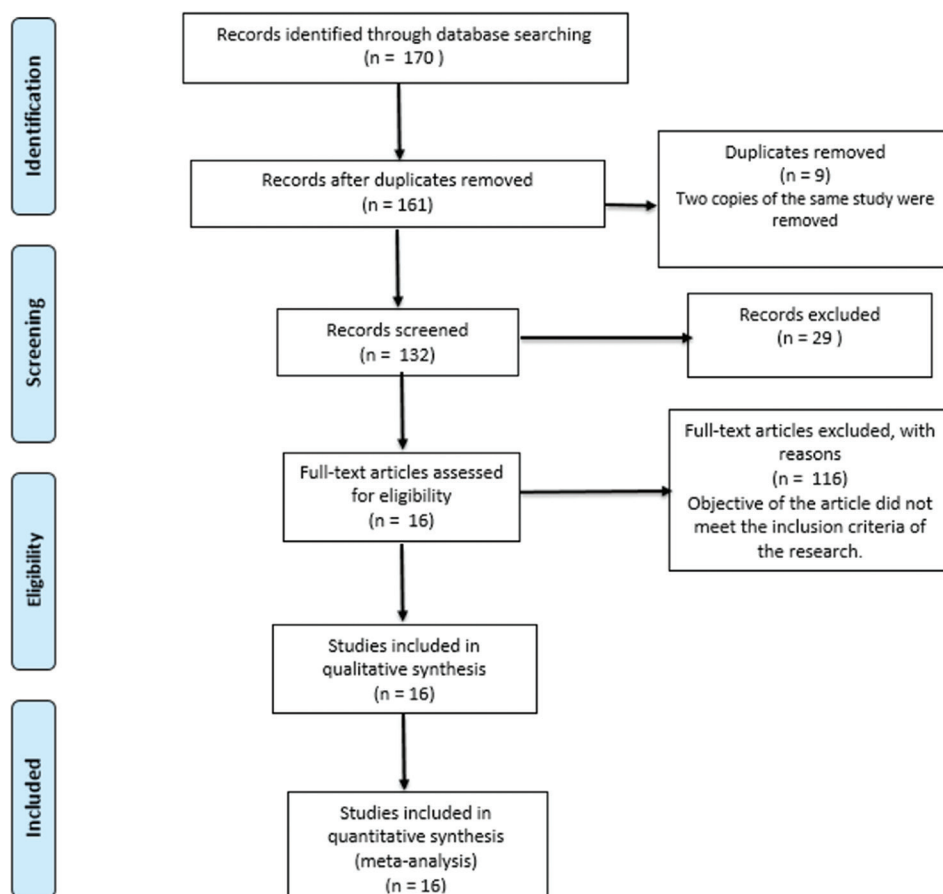
Cochrane tool was used to independently assess the risk of bias for all the trials. The following domains were considered selection bias, performance bias, detection bias, attrition bias,

and reporting bias. Overall, the articles were evaluated with low risk of bias and high-quality evidence. Detailed quality assessment for each article is mentioned in Table 2.

## DISCUSSION

### Glycemic outcomes

Any changes observed in HbA1c and FPG levels were considered to be the primary outcomes. The mean baseline HbA1c ranged from 6.93% to 9.99% and 7.1% to 8.89% for linagliptin with metformin and pioglitazone with metformin groups, respectively. As seen with linagliptin along with metformin group, patients with a higher HbA1c baseline ( $>9.0\%$ ) had reduced HbA1c levels below 7.5%.<sup>[15,18,21]</sup> Patients with a HbA1c baseline  $>8.0\%$  showed reductions up to 7.1% and below.<sup>[14,16,19]</sup> One among them showed no reduction, whereas one showed increased HbA1c values.<sup>[20]</sup> Only one group showed the minimum HbA1c level of 7.34% which showed a reduction of 0.08% after the treatment.<sup>[17]</sup> Observing from the forest plot, 12 groups with patients receiving linagliptin in combination with metformin reported HbA1c levels. Two results showed a decrease in HbA1c levels but are nonsignificant. Two among the 12 groups show a slight increase in the mean HbA1c levels which is nonsignificant due to their sample size [Figure 2].



**Figure 1:** PRISMA flow diagram showing screening of articles

**Table 1: Characteristics of randomized controlled trials included in the meta-analysis**

| Author/year [Reference]                   | Patient population                 | Duration of study (weeks) | Treatment regimen                                                                   | Number of patients (n)                                                                              | Primary outcome        | Secondary outcome       | Conclusion                                                                                                                                                                                                                                                                     |
|-------------------------------------------|------------------------------------|---------------------------|-------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------|------------------------|-------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Ji <i>et al.</i> , 2015 <sup>[14]</sup>   | Aged 18-80 years                   | 14                        | Linagliptin+metformin                                                               | 344                                                                                                 | HbA1c                  | GI adverse events, FPG  | A 12% and 15% reduction in HbA1c and FPG levels from baseline was observed respectively                                                                                                                                                                                        |
| Ross <i>et al.</i> , 2016 <sup>[15]</sup> | Aged ≥18 years                     | 24                        | Linagliptin+metformin                                                               | 132                                                                                                 | HbA1c                  | Efficacy response       | 28.7% reduction in HbA1c levels from baseline                                                                                                                                                                                                                                  |
| Haak <i>et al.</i> , 2012 <sup>[16]</sup> | Aged 18-80 years                   | 24                        | Linagliptin 2.5 mg+metformin 500 mg bid<br>Linagliptin 2.5 mg+metformin 1000 mg bid | Linagliptin 2.5 mg+metformin 500 mg bid (n=143)<br>Linagliptin 2.5 mg+metformin 1000 mg bid (n=143) | HbA1c                  | FPG                     | Linagliptin 2.5mg+metformin 500 mg showed 13.8% and 16.4% reduction in HbA1c and FPG levels respectively<br>Linagliptin 2.5mg+metformin 1000 mg showed 18.3% and 24.7% reduction in HbA1c and FPG levels respectively                                                          |
| Haak <i>et al.</i> , 2013 <sup>[17]</sup> | Aged 18-80 years                   | 54                        | Linagliptin 2.5 mg+metformin 500 mg bid, linagliptin 2.5 mg+metformin 1000 mg bid   | Linagliptin 2.5 mg+metformin 500 mg bid (n=225)<br>Linagliptin 2.5 mg+metformin 1000 mg bid (n=171) | safety, adverse events | HbA1c, FPG, body weight | Linagliptin 2.5 mg+metformin 500 mg bid showed 7.9% and 7.87% decline in HbA1c and FPG levels respectively<br>Linagliptin 2.5 mg+metformin 1000 mg bid showed 11.8% and 19.7% decline in HbA1c and FPG levels respectively<br>No clinically significant changes in body weight |
| Ross <i>et al.</i> , 2015 <sup>[18]</sup> | Aged ≥18 years                     | 24                        | Linagliptin+metformin                                                               | 159                                                                                                 | HbA1c                  | FPG, body weight        | 28.7% and 24% reduction in HbA1c and FPG values from baseline was observed                                                                                                                                                                                                     |
| Mu <i>et al.</i> , 2017 <sup>[19]</sup>   | Aged 18-80 years<br>Asian patients | 24                        | Linagliptin 2.5 mg+Metformin 500 mg, bid linagliptin 2.5 mg+metformin 1000 mg bid   | Linagliptin 2.5 mg+Metformin 500 mg, (n=148) linagliptin 2.5 mg+metformin 1000 mg (n=147)           | HbA1c                  | FPG, body weight        | Linagliptin 2.5 mg+metformin 500 mg reduced HbA1c and body weight by 24.7% and 0.4% from baseline respectively<br>Linagliptin 2.5 mg+metformin 1000 mg reduced HbA1c and body weight by 26.3% and 1% from baseline respectively                                                |

Contd...

**Table 1: Contd...**

| Author/year<br>[Reference]                       | Patient<br>population                      | Duration<br>of study<br>(weeks) | Treatment regimen                                                                              | Number of patients<br>(n)                                                                                          | Primary<br>outcome                                                                    | Secondary<br>outcome                                                            | Conclusion                                                                                                                                                                                  |
|--------------------------------------------------|--------------------------------------------|---------------------------------|------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------|---------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Deshmukh<br><i>et al.</i> , 2015 <sup>[20]</sup> | Aged 18-<br>80 years<br>Indian<br>patients | 24                              | Linagliptin 2.5<br>mg+metformin 500<br>mg bid , linagliptin 2.5<br>mg+metformin 1000<br>mg bid | Linagliptin 2.5<br>mg+metformin 500 mg<br>bid (n=36) linagliptin<br>2.5 mg+metformin 1000<br>mg bid (n=44)<br>n=80 | HbA1c                                                                                 | FBG, relative<br>efficacy                                                       | At week 24,<br>17% reduction in<br>HbA1c levels from<br>the baseline was<br>observed. 18% and<br>14% decline in<br>FPG for high dose<br>metformin and low<br>dose metformin<br>respectively |
| Ma <i>et al.</i> ,<br>2017 <sup>[21]</sup>       | Aged≥18<br>years<br>Asian<br>patients      | 24                              | Linagliptin+metformin                                                                          | 62                                                                                                                 | Hb1Ac                                                                                 | FPG, body<br>weight.                                                            | 30% and 31%<br>decline in HbA1c<br>and FPG levels<br>from baseline,<br>respectively                                                                                                         |
| Derosa <i>et al.</i> ,<br>2006 <sup>[22]</sup>   | Aged≥18<br>years                           | 12                              | Pioglitazone+metformin                                                                         | 48                                                                                                                 | BMI,<br>HbA1c,<br>lipid<br>profile, Lp<br>(a), HCT                                    | FPG, PPG,<br>and the<br>HOMA<br>index                                           | By the end of 12<br>months, 17%, 13%<br>and 1.1% decline<br>in HbA1c, FPG<br>and BMI levels<br>from baseline<br>was observed<br>respectively                                                |
| Kaku 2009 <sup>[23]</sup>                        | Aged 20-<br>65 years                       | 40                              | Pioglitazone+metformin                                                                         | 83                                                                                                                 | HbA1c                                                                                 | FPG                                                                             | 8.5% and 13%<br>decline in HbA1c<br>and FPG levels<br>from baseline<br>was observed<br>respectively                                                                                         |
| Lavalle<br><i>et al.</i> , 2011 <sup>[24]</sup>  |                                            | 3                               | Pioglitazone+metformin                                                                         | 17                                                                                                                 | HbA1c,<br>FPG,<br>serum<br>insulin,<br>BMI,<br>blood<br>pressure,<br>lipid<br>profile |                                                                                 | 22% and 21.8%<br>decline in HbA1c<br>and FPG levels<br>from baseline<br>was observed,<br>respectively                                                                                       |
| Perez <i>et al.</i> ,<br>2009 <sup>[25]</sup>    | Aged≥18<br>years                           | 24                              | Pioglitazone 15 mg/<br>metformin 850 mg BID                                                    | Pioglitazone+metformin<br>(n=201)                                                                                  | HbA1c                                                                                 | FPG, fasting<br>insulin and<br>insulin<br>resistance                            | 20.5% and 22.4%<br>decline in HbA1c<br>and FPG levels<br>from baseline<br>was observed,<br>respectively                                                                                     |
| Perez <i>et al.</i> ,<br>2010 <sup>[26]</sup>    | Aged≥18<br>years                           | 24                              | Pioglitazone 15 mg/<br>metformin 850 mg BID                                                    | Pioglitazone+metformin<br>(n=201)                                                                                  | HbA1c                                                                                 | Mortality,<br>nonfatal<br>myocardial<br>infarction,<br>stroke                   | HbA1c and body<br>weight reduced by<br>20.5% and 0.69<br>kg from baseline,<br>respectively                                                                                                  |
| Pfützner<br><i>et al.</i> , 2011 <sup>[27]</sup> | Aged 18-<br>75 years                       | 24                              | Pioglitazone 15<br>mg+metformin 850 mg<br>BID                                                  | Pioglitazone+metformin<br>(n=146)                                                                                  | Mean<br>increase<br>of HDL<br>cholesterol                                             | Lipid profile,<br>HbA1c,<br>FPG, C<br>reactive<br>peptide,<br>blood<br>pressure | 11% and 13%<br>reduction in HbA1c<br>and FPG levels<br>was observed,<br>respectively                                                                                                        |

Contd...

Table 1: Contd...

| Author/year [Reference]                       | Patient population | Duration of study (weeks) | Treatment regimen      | Number of patients (n) | Primary outcome | Secondary outcome                                                              | Conclusion                                                                              |
|-----------------------------------------------|--------------------|---------------------------|------------------------|------------------------|-----------------|--------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------|
| Matthews <i>et al.</i> , 2005 <sup>[4]</sup>  | Aged 35-75 years   | 52                        | Metformin+pioglitazone | 317                    | HbA1c           | FPG, insulin, lipids, C-peptide, proinsulin and urinary albumin and creatinine | 0.99% and 17% decline in HbA1c and FPG levels from baseline was observed, respectively  |
| Ceriello <i>et al.</i> , 2005 <sup>[28]</sup> | Aged 35-75 years   | 52                        | Metformin+pioglitazone | 54                     | HbA1c           | FPG, insulin, and weight changes                                               | 12% and 13.5% decrease in HbA1c and FPG levels from baseline was observed, respectively |

PPG=Postprandial plasma glucose, HOMA=Homeostasis model assessment, BMI=Body mass index, FPG=Fasting plasma glucose, HDL=High-density lipoproteins, HCT=Hematocrit

Table 2: Quality assessment of included articles based on Cochrane collaboration tool

| Reference | Selection bias (random sequence generation) | Selection bias (allocation concealment) | Performance bias (blinding participants and personnel) | Detection bias (blinding outcome assessment) | Attrition bias (incomplete outcome data) | Reporting bias (selective reporting) | Overall quality score | Overall quality |
|-----------|---------------------------------------------|-----------------------------------------|--------------------------------------------------------|----------------------------------------------|------------------------------------------|--------------------------------------|-----------------------|-----------------|
| [14]      | Low risk                                    | Low risk                                | Low risk                                               | Low risk                                     | Low risk                                 | Low risk                             | 6/6                   | High quality    |
| [15]      | Low risk                                    | Low risk                                | Low risk                                               | Low risk                                     | Low risk                                 | Low risk                             | 6/6                   | High quality    |
| [16]      | High risk                                   | High risk                               | Low risk                                               | Low risk                                     | Low risk                                 | Low risk                             | 4/6                   | High quality    |
| [17]      | High risk                                   | High risk                               | Low risk                                               | Low risk                                     | Low risk                                 | Low risk                             | 4/6                   | High quality    |
| [18]      | Low risk                                    | Low risk                                | Low risk                                               | Low risk                                     | Low risk                                 | Low risk                             | 6/6                   | High quality    |
| [19]      | Low risk                                    | High risk                               | Low risk                                               | Low risk                                     | Low risk                                 | Low risk                             | 5/6                   | High quality    |
| [20]      | High risk                                   | High risk                               | Low risk                                               | Low risk                                     | Low risk                                 | Low risk                             | 4/6                   | High quality    |
| [21]      | Low risk                                    | Low risk                                | Low risk                                               | Low risk                                     | Low risk                                 | Low risk                             | 6/6                   | High quality    |
| [22]      | Low risk                                    | Low risk                                | Low risk                                               | Low risk                                     | High risk                                | Low risk                             | 5/6                   | High quality    |
| [23]      | Low risk                                    | High risk                               | Low risk                                               | Low risk                                     | Low risk                                 | Low risk                             | 5/6                   | High quality    |
| [24]      | Low risk                                    | High risk                               | High risk                                              | Low risk                                     | Low risk                                 | Low risk                             | 4/6                   | High quality    |
| [25]      | High risk                                   | High risk                               | Low risk                                               | Low risk                                     | Low risk                                 | Low risk                             | 4/6                   | High quality    |
| [26]      | High risk                                   | High risk                               | Low risk                                               | Low risk                                     | Low risk                                 | Low risk                             | 4/6                   | High quality    |
| [27]      | High risk                                   | High risk                               | Low risk                                               | Low risk                                     | Low risk                                 | Low risk                             | 4/6                   | High quality    |
| [4]       | High risk                                   | High risk                               | Low risk                                               | Low risk                                     | Low risk                                 | Low risk                             | 4/6                   | High quality    |
| [28]      | Low risk                                    | Low risk                                | Low risk                                               | Low risk                                     | Low risk                                 | Low risk                             | 6/6                   | High quality    |

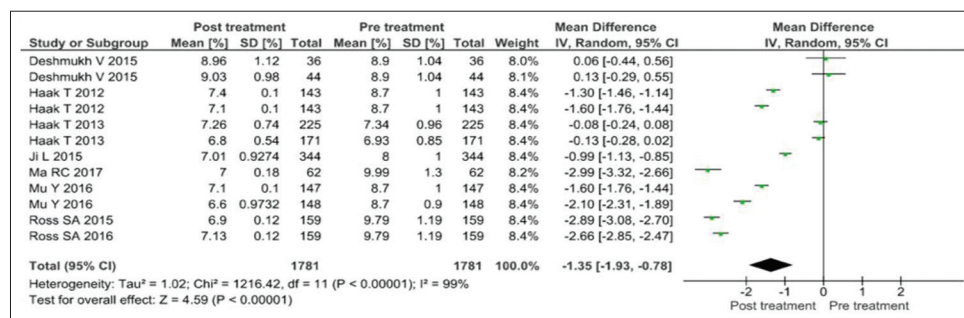


Figure 2: Forest plot of hemoglobin A1c in linagliptin plus metformin group

Eight study groups reported HbA1c levels with patients receiving pioglitazone in combination with metformin [Figure 3]. As seen with pioglitazone along with metformin group,

patients with a higher HbA1c baseline (>8.0%) had reduced HbA1c levels below 7.5%.<sup>[4,22,25,26,28]</sup> Patients with a HbA1c baseline >7.0% showed reductions up to 6.5%.<sup>[23,24,27]</sup> Data

analysis revealed considerably higher heterogeneity  $I^2 = 99\%$  and  $97\%$  in linagliptin plus metformin and pioglitazone plus metformin groups; respectively, showcasing intragroup variability. Differences among the studies due to various factors led to a diverse result, hence showing high heterogeneity. Overall, the combination therapy of linagliptin with metformin led to a reduction of  $1.35\%$  which is significantly higher than pioglitazone combined with metformin which led to a  $1.27\%$  reduction.

Combination of metformin with linagliptin and pioglitazone has shown a significant reduction in the FPG levels by  $35.64\%$  and  $34.63\%$ , respectively, that was collected from 16 clinical trials [Figures 4 and 5]. As seen with linagliptin along with metformin group, patients with higher FPG baseline ( $>190$  mg/dL) had reduced FPG levels below  $150$  mg/dL except for one group which showed a reduction up to  $162$  mg/dL.<sup>[15,16,18]</sup> As seen with pioglitazone with metformin group, patients with higher FPG baseline ( $>200$  mg/dL) reduced below  $180$  mg/dL.<sup>[4,28]</sup> The mean baseline values of FPG levels varied from  $158.2$  mg/dl to  $198.0$  mg/dl in linagliptin plus metformin group, whereas in pioglitazone plus metformin group, the values varied from  $137.0$  mg/dL to  $212.4$  mg/dL. After performing data analysis, relatively high heterogeneity was observed with linagliptin plus metformin having  $I^2 = 91\%$

and in case of pioglitazone plus metformin  $I^2 = 100\%$ . The high heterogeneity could refer to the inconsistencies between the studies.

### Nonglycemic outcomes

After analyzing all the data, four groups of linagliptin with metformin and two groups of pioglitazone with metformin included BMI status in their study. As seen with linagliptin along with metformin group, patients with higher BMI baseline ( $>29$ ) had reduced levels up to  $28.56$  and  $28.8$ .<sup>[14,18]</sup> As seen with pioglitazone with metformin group, patients with higher BMI baseline ( $>30$ ) reduced by  $0.7$ .<sup>[24]</sup> The mean baseline values of combined therapy of linagliptin with metformin were between  $26$  kg/m<sup>2</sup> and  $29.8$  kg/m<sup>2</sup> and for pioglitazone with metformin were  $26.9$  kg/m<sup>2</sup> and  $33.9$  kg/m<sup>2</sup> [Figures 6 and 7]. Several study lines crossed the line of null effect illustrating no statistically significant difference in the BMI between the pre- and posttreatment groups. Network meta-analysis reveals  $I^2$  of  $0\%$  for both the groups indicating no heterogeneity of results between each study data. Overall, the combination of linagliptin with metformin showed a significant reduction of  $0.56\%$  in BMI, whereas pioglitazone with metformin led to a  $0.37\%$  reduction.

All the studies reported adverse events and the most common among them was hypoglycemia. From the 16 trials, a total

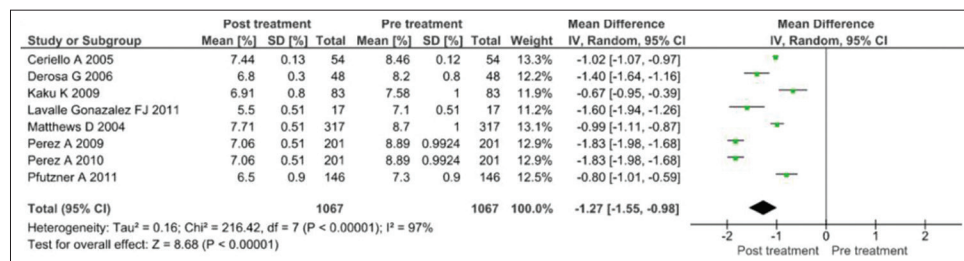


Figure 3: Forest plot of hemoglobin A1c in pioglitazone plus metformin group

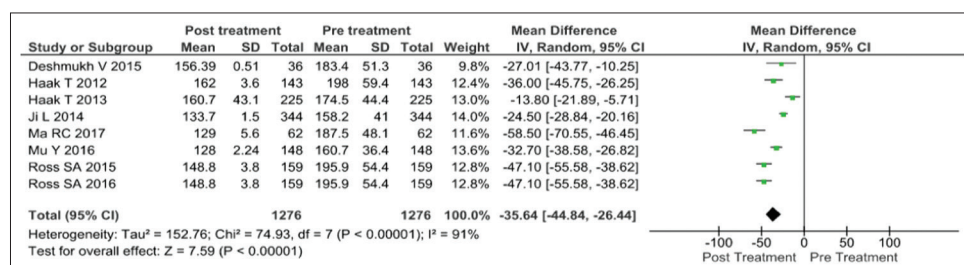


Figure 4: Forest plot of fasting plasma glucose in linagliptin plus metformin group

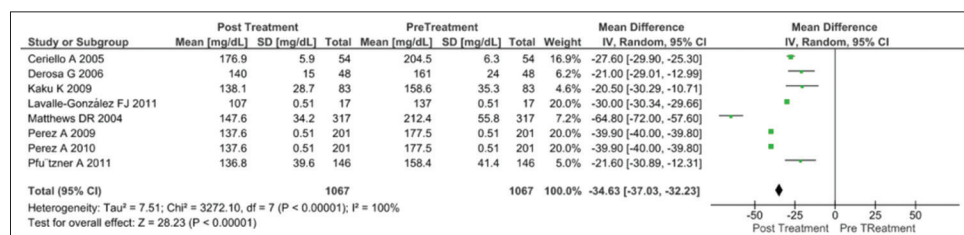


Figure 5: Forest plot of fasting plasma glucose in pioglitazone plus metformin group

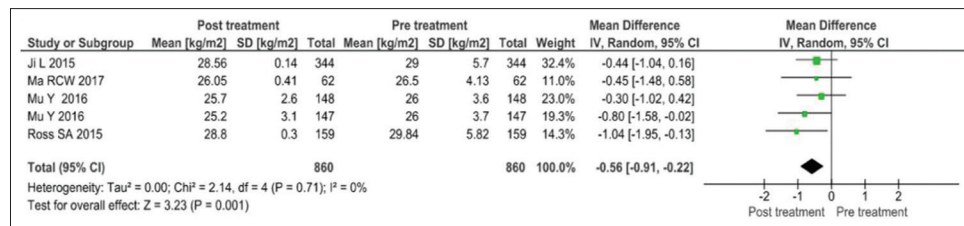


Figure 6: Forest plot of body mass index in linagliptin plus metformin group

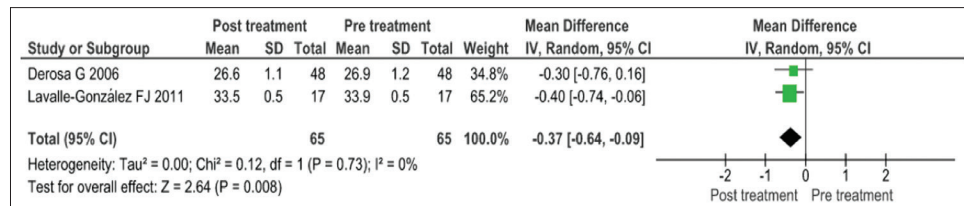


Figure 7: Forest plot of body mass index in pioglitazone plus metformin group

Table 3: Odds ratio for adverse events (hypoglycemia)

| Study group            | Hypoglycemia | Nonhypoglycemia | Total | OR    |
|------------------------|--------------|-----------------|-------|-------|
| Pioglitazone+metformin | 2            | 144             | 146   | 0.67  |
| Linagliptin+metformin  | 3            | 144             | 147   |       |
| Pioglitazone+metformin | 4            | 313             | 317   | 0.668 |
| Linagliptin+metformin  | 3            | 157             | 159   |       |

OR=Odds ratio

Table 4: Odds ratio for patient compliance

| Study group            | Compliant | Noncompliant | Total | OR    |
|------------------------|-----------|--------------|-------|-------|
| Linagliptin+metformin  | 76        | 83           | 159   | 21.57 |
| Pioglitazone+metformin | 79        | 4            | 83    |       |

OR: Odds ratio

of 6 studies (4 from linagliptin with metformin and 2 from pioglitazone with metformin) outlined hypoglycemia. The odds ratio for hypoglycemia between both the groups was 0.67 (95% CI: 0.1098–4.0496). Data extraction revealed six studies outlined GI events, two studies reported hypertension, and two reported other drug-related adverse effects in linagliptin combined with metformin group. In the pioglitazone + metformin group, three studies reported peripheral edema and only one study reported six patients attaining insomnia. No death events in any of the groups were reported [Table 3].

Patient adherence to the medication is considered a secondary outcome. A total of 6 studies (which comprise 5 for linagliptin with metformin and 1 for pioglitazone with metformin) defined patient compliance. The odds ratio for patient compliance between the groups of linagliptin and pioglitazone is 21.57 (7.5358–61.7355 at 95% CI) [Table 4].

## CONCLUSION

Network meta-analysis results provide evidence to prove linagliptin in combination with metformin showed better safety

in patients along with efficacy in terms of reducing HbA1c, FPG levels, and BMI in comparison with pioglitazone in combination with metformin.

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## Conflicts of interest

There are no conflicts of interest.

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