# A Review: Comparison of Efficacy of Liraglutide Versus Sitagliptin add-on-to Metformin in Type 2 Diabetes Mellitus patients

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**ABSTRACT:**
**Background:** The aim of this review is to compare the efficacy of liraglutide versus sitagliptin add-on-to metformin in patients with Type 2 Diabetes Mellitus and inadequate glycemic control for rational use of drugs. **Methods:** We searched for randomized controlled trials (RCT) in MEDLINE, Web of science, PubMed, Cochrane library, CNKI, and Wanfang database and extracted data from all randomized controlled trials (RCTs) up to July 11, 2019 of liraglutide versus sitagliptin given in combination with metformin. RCTs were selected only if they were RCTs comparing DPP-4 inhibitor (sitagliptin) monotherapy to metformin monotherapy with the GLP-1 Receptor Agonists (liraglutide), duration of treatment was ≥26 weeks and reported data on hemoglobin A1c (HbA1c) change, fasting plasma glucose (FPG) change, Odds ratio (OR), mean difference (MD), 95% confidence interval are used to analyze the outcomes. **Results:** A total of 2,257 patients from 6 RCTs were included in the study. When compared with sitagliptin (100mg) in combination with metformin group, the group of patients treated with liraglutide1.2mg and 1.8mg and metformin, produced greater reduction in HbA1c, FBG. (95% CI). The group of patients with 1.8mg liraglutide had significant weight loss. The incidence of nausea, hypoglycemic episodes, gastrointestinal problems was higher than the sitagliptin with metformin groups. **Conclusions:** The results of this study indicated that the liraglutide – metformin combination therapy could significantly lower the HbA1c level and increased reduction of body weight. ADRs such as gastrointestinal problems, hypoglycemic episodes were common in liraglutide treatment group.

**KEYWORDS:** Type 2 Diabetes Mellitus, Glucogon like peptide-1 receptor agonist, Dipeptidyl peptidase 4 inhibitors, Randomized Clinical Trails, Liraglutide, Metformin, Sitagliptin.

## INTRODUCTION:

Type 2 Diabetes Mellitus is a chronic disease characterized by increased levels of blood sugar. It is also called type 2 diabetes mellitus and adult-onset diabetes. It is because it starts almost always in middle- and late-adulthood. children and teens are also can develop this condition. Type 2 diabetes is much more prevalent than type 1 diabetes mellitus.

A good glycaemic control can decrease the risk of microvascular, macrovascular complications. Newer treatments with improved efficacy and fewer side-effects are needed.

The reason for failure in achieving adequate glycaemic control is because of both the limitations in current therapies, progressive nature of T2DM including poor tolerability and adherence Metformin is considered as the first-line oral hypoglycemic drug which is a synthetic biguanide.[1] It can be used for monotherapy and combination therapy for T2DM, because of its glucose-lowering effects, minimal side effects, and cost it is mostly recommended. Initially, metformin alone is often effective, the effect of glucose control is limited, so a second drug is often required in most of the patients. Currently, metformin can be combined with insulin secretagogue, sulfonylureas, DPP-4 inhibitors, and GLP-1 receptor agonist to reduce HbA1c levels and achieve better glucose control. Metformin is available as single formulation and as a combination which eases its use in management of T2DM and patient's adherence to the drugs[2]. It has a strong control in blood glucose levels of obese patients with T2DM as well as proved to be effective

in normal-weight patients.[6] It has been recently found that metformin can decrease levels of inflammatory markers in cardiotoxicity caused by administraton of doxorubicin[3]. It also found to be used in regulation of menstrual cycle and reduce hyperandrogenic effects in young adolescents.[4]

Liraglutide is an GLP-1 analogue used to treat diabetes mellitus type 2 which improves control of blood glucose. It is used in those in who metformin an another diabetic mediation such as a sulfonylurea are not sufficient.[10] Recent studies showed that it had better reduction in HbA1c levels without major damages in renal function and increase in hypoglycemia risk and reduction in body weight.[11] It has effect on meal-related hyperglycemia (for 24 hours after administration) decreases it by increasing insulin's secretion when required by increasing glucose levels, delaying gastric emptying time, and inhibiting post prandial glucagon secretion. Liraglutide is also found to be effective in reducing inflammatory markers and enhancing GDNF release in mouse models of parkinson's disease.[12]. Zang et all assessed that Chinese patients with type 2 diabetes; the results showed that liraglutide with metformin combination therapy has more effect in reducing the level of HbA1c, and no differences in weight gain and incidence of hypoglycemia were exhibited in the therapies.[13]

In 2006, DPP4 inhibitors were introduced as a medicine in treatment for diabetes mellitus. First of all, sitagliptin followed by vildagliptin, saxagliptin, linagliptin and alogliptin. Sitagliptin is a well known oral hypoglycemic agent of DPP4 inhibitor class.[14] These enhance, prevent the proteolytic break down of endogenous glucagon like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), which are hormones released in response to food intake (incretins). It is the first and only prescribed medication in the class of oral hypoglycemic agent, which enhances the body's own ability to lower blood glucose and it is elevated.[15,18]. GLP-1 receptor agonists are also called as incretin mimetics. These has a short duration of action, so to overcome this limitation several modifications either in the drug or the formulations are being developed. Sitagliptin and liraglutide have different modes of action and are, therefore, has the different efficacy and safety profiles. Enzyme DPP4 selective inhibition, results in enhance glucose dependent insulin secretion from the pancreas and decreased hepatic glucose production by metabolism of endogenic incretin hormones like GLP-1, GIP 1,2[16]

To provide an up-to-date of the clinical efficacy of DPP-4 inhibitors compared with GLP 1 receptor agonists we have conducted a review.[17]

## METHODS:

We conducted a systematic literature review to identify relevant trials published up to July 11, 2019 to examine the comparative efficacy of liraglutide and DPP-4 inhibitors (sitagliptin) both In combination with metformin for the treatment of uncontrolled T2DM (aged ≥18 years).

### 1. Data Sources and Searches:

We searched the electronic databases, including MEDLINE, EMBASE, Cochrane Collaborative database, PubMed, CNKI, Web of science, and Wanfang database without language restriction.[5]: "Glucagon like polypeptide-1 or GLP-1 receptor agonists, liraglutide" and "dipeptidyl peptidase-4 inhibitors,'DPP-4 inhibitors' or sitagliptin" and "metformin" and "diabetes or diabetes mellitus or type 2 diabetes mellitus" these subject terms are used in this search. July 11, 2019 is the publication deadline, before conducting the literature search. Briefly, we searched for T2DM patients within RCTs.

### 2. Eligibility Criteria:

The study enrolled 2,257 participants from Europe, China, Japan, and the United States. Inclusion criteria, all participants were aged 18 to 80 years old, and they were diagnosed with T2DM based on the standards criteria of American Diabetes Association (ADA). We included randomized-controlled (RCTs) evaluating outcomes, were taken to compare the efficacy and safety of liraglutide versus sitagliptin both in combination with metformin in patients with T2DM.[8] The patients had HbA1c above 6.5% at baseline and had been treated with metformin monotherapy (≥1000mg daily) for 3 months or longer prior to enrollment.[8] All patients had minimum treatment duration of 12 weeks and the outcomes should contain the changes of HbA1c, fasting blood sugar (FBS), post prandial blood sugar(PPBS). Articles excluded which include significant shortcomings in study protocol or data analysis .

### 3. Data Application in Practice:

Liraglutide, a GLP-1 receptor agonist, and sitagliptin, a DPP-4 inhibitor, are currently approved by the US Food and Drug Administration (FDA), these improves glycemic control in patients with type 2 diabetes mellitus.[8] After 12 weeks of the trail, liraglutide significantly reduced HbA1c and expedite weight loss more effectively than sitagliptin. GLP-1 receptor agonist works by stimulating insulin release, reducing glucagon secretion (thereby hepatic glucose production).

**4. Data extraction and Quality Assessment:**

Two investigators independently extracted data by scanning all abstracts and proceedings in duplicate to identify papers relevant for full-text review using a standardized tool. On the basis of the inclusion criteria, the reviewers carefully scrutinized the baseline characteristics of participants, study design, daily dose of liraglutide and sitagliptin, and subsequent outcomes.[9] The following baseline patient characteristics were extracted: age (years); gender (% female); HbA1c (%); duration of diabetes (years), fasting blood sugar (mg/dl), post prandial blood sugar(mg/dl). Information on efficacy outcomes was extracted: change from baseline (CfB) in HbA1c, and the proportion of patients meeting HbA1c target levels. For the continuous outcomes, the CfB was extracted whenever available, along with corresponding sample size, and measures of dispersion (e.g., standard deviation [SD], 95% confidence intervals [CI], etc.) for all relevant intervention groups., The baseline measurement and at the end of treatment was used to calculate CfB, if it was not provided in the full text publications.

The Study quality was evaluated by using the Cochrane risk of bias tool. Any disagreements during the data extraction process and quality assessment were resolved by consultation. Ethical approval and informed consent are not required for this kind of study.[24]

**5. Statistical analysis:**

We employed meta-analysis to analyze the outcomes using Rev Man software. (The software was released by the cochrane Collaboration, the Nordic Cochrane Centre, Copenhagen, Denmark) . The outcomes were expressed as the odds ratio (OR) and 95% confidence intervals (95% CIs). we used mean difference (MD) with 95% CI for continuous outcomes, from the posterior distribution of relative treatment effect. Each outcome was analysed separately for each 12 weeks. To assess the heterogeneity, the Chi-square test based Q-statistic and $I^2$ statistic were used. Substantial heterogeneity were considered as $I^2$ values of 50% or more, and the heterogeneity difference showed when P<.05. when I2 values were <50% the fixed-effects model was used, otherwise the random-effects model should be applied instead. All studies that are included were evaluated in terms of the risk of bias using the Cochrane risk of bias tool, and sensitivity analysis was conducted by excluding the mixed studies that lead to potential bias.

## RESULTS:

**1. Description of the studies :**

After primary search from the databases, 440 references in English and 6 references in Chinese were arranged systematically. Finally, 6 studies met the inclusion criteria and were selected for our study.[18-23] A total of 2,257 participants were included in 6 studies and 1,120 participants were randomized and injected with liraglutide subcutaneously and 1,136 with sitagliptin orally. The daily dosages of liraglutide were 1.2 or 1.8mg subcutaneously, 100mg sitagliptin was taken orally once daily, and 1000mg metformin both the groups were taken on a daily basis. All RCTs that included in the studywere carried out more than 26 weeks period. All studies that are included were evaluated in terms of the risk of bias using the Cochrane risk of bias tool. Only 3-5 studies provided details for allocation concealment, blinding of participants, and personnel and blinding of outcome assessment. The selection bias was the largest risk of bias. Almost all studies had a Jadad score, and only 1 of the 5 studies scored more than 4; the other 4 got scores of less than or equal to 3.

**2. Change in Glycosylated Hemoglobin (HbA1c):**

In this analysis, we examined the HbA1c changes of all the 2,257 individuals involved. Because of the moderate heterogeneity between the 2 groups (P=.05, I 2=56%) random effect models were used to analyze this outcome. Subgroup analyses were performed based on the dosages of 1.2mg and 1.8mg liraglutide combination with metformin and 100mg sitagliptin combination with metformin displayed the former has the better efficacy to control the of HbA1c level (p <0.00001, MD= -0.35,95% CI -0.51 to -0.20). The difference in the GLP-1 levels achieved by the respective incretin-based agents may account for the better HbA1C reduction, increased satiety and reduced gastric emptying exhibited by GLP-1 receptor agonists. In choosing between the convenience of an oral sitagliptin and a once-daily subcutaneous liraglutide, both with combination with metformin the latter may be preferred

because it reduces both HbA1c. This combination of effects also may account for the difference in loss of weight observed between these agents.

**3. Body weight:**
Most trials reported data on patient weight changes among them Five studies involving 1098 patients noted the changes of body weight. The fixed effect models were used to analyse the data, as heterogeneity between the 3 groups was low (P=.18, I2=38%). The 1.8mg liraglutide with metformin could significantly control weight gain (P<.00001, MD=_1.12, 95% CI _1.54 to _0.70) when compared with sitagliptin combination with metformin therapy.

**4. Fasting plasma glucose (FBG):**
When administered with metformin, liraglutide (1.2 mg/day) significantly lowered the FPG concentration when compared with metformin, sitagliptin 100mg (WMD=−0.72mmol/L, 95%CI: −1.27, −0.17; P= 0.010). on the basis of the following criteria, some patients were to be discontinued because of hypoglycaemia:(1) they had fingerstick glucose values or repeated fasting plasma glucose (FPG) values of <2.8 mmol/l (50 mg/dl) with or without symptoms;(2) fingerstick glucose or FBG ≤3.9 mmol/l (70 mg/dl) without a reasonable explanation and with symptoms.

**5. Sensitivity analysis:**
We used the method of combined data (both random or fixed effect models) for implementing a sensitivity analysis. The overall effect was similar and the values of MD or OR was close in random or fixed effect models. We also performed a sensitivity analysis by eliminating the mixed and potential biased studies, and the results revealed no significant difference.[13]

## DISCUSSION:

Diabetes Mellitus(DM) is a chronic disease which is associated with abnormally high levels of the sugar glucose in the blood.[25] It is mainly due to one of two mechanisms may be 1. Inadequate production of insulin (which is produced by the pancreas and lowers blood glucose) or 2. Inadequate sensitivity of cells to the insulin and patients with DM often suffer from hyperglycaemia.[26] Some of the complications related to DM include neuropathy, nephropathy, retinopathy, cerebrovascular, and cardiovascular diseases. According to the ADA and the European Association for the Study of Diabetes (EASD) suggested that the management of patients with T2DM should be focused on better control of blood sugar level to ensure HbA1c ≤7%, lifestyle changes include smoking cessation, controlling blood pressure, and lipid levels in a suitable range.

Metformin is the first-line drug of choice for the treatment of T2DM, particularly in people who are overweight as it reduces appetite and intestinal absorption of carbohydrate. It also inhibits hepatic gluconeogenesis and increases glucose uptake, and thereby decrease in the blood glucose and body weight thus plays an important role in treating endothelial dysfunction and cardiovascular problems.[27] increased glucose utilization and decreased hepatic glucose production account for glucose lowering effect of metformin. The beneficiary effect of metformin on serum lipids as been related to reduction in fattyliver.[28] Many clinical trials proved that in T2DM patients, metformin when given in combination with other anti-hyperglycaemic agents keep HbA1c within normal range and controls body weight in a safe and efficacious manner.[29]

GLP-1RAs (liraglutide) are a class of anti hyperglycaemic agents available for the management in people with T2DM. As per ADA/EASD treatment algorithm, the use of GLP-1RAs as a second line therapy when glucose control on metformin alone is inadequate. The GLP-1RAs have been shown to improve glycaemic control with body weight reduction compared to other conventional glucose lowering agents in the individual RCTs.[30] Previous studies have shown that liraglutide significantly improved both HbA1c and FBG, dose dependent weight loss, and enhanced βcell function. The supraphysiologic levels provide critical differences in effectiveness with liraglutide compared with DPP4 inhibitors (sitagliptin). This suggests a preference for use of liraglutide over sitagliptin in most of diabetes patients who are above ideal body weight or who are at risk of cardiovascular diseases and may especially benefit from weight loss and cut down mortality.[31]

In this study, the results showed that liraglutide in combination with metformin was more effective in reducing HbA1c levels than sitagliptin with metformin (P<0.00001). This supports the GLP-1 receptor agonists plus metformin as an early therapy. This combination is better at achieving the composite endpoint of HbA1c <7%, with

less hypoglycemic events and provides additional benefit. This study of 6 RCTs includes 2257 patients receiving liraglutide showed that liraglutide in all doses added on to metformin significantly lowered body weight, while the effect of exercising control is less desirable. Other studies showed that DPP4 inhibitor sitagliptin had a negligible effect. In treatment of T2DM weight reduction is linked to cardiovascular benefits and may be at least as important than HbA1c reduction . As liraglutide lower both HbA1c and body weight, they may provide additional benefit. As for the side effects, some studies have found that frequency of nausea, gastrointestinal problems was higher with liraglutide than sitagliptin.[32]

6 RCTs were included in the analysis with the larger sample sizes for estimated result to assess the efficacy of the therapies in future. The data came from the published literature, some negative data were difficult to extract, resulting in the publication bias.[33]

## CONCLUSION:

Liraglutide added on to metformin has a better control on HbA1c levels and reduction in body weight than the sitagliptin-metformin combination. This analysis suggests that liraglutide offers a more efficacious treatment for T2DM than the DPP4 inhibitor sitagliptin, while gastrointestinal problems were a common side effect worth mentioning in the sitagliptin-metformin therapy. Considering the poor methodological quality of the studies included, future studies with higher quality RCTs and larger sample are needed to confirm the conclusions.

## ABBREVIATIONS:

CNKI=China National Knowledge Infrastructure; RCTs=Randomized Controlled Trails; HbA1C= glycated hemoglobin; CI=confidence interval; DPP-4 = dipeptidyl peptidase-4; ADRs= Adverse Drug Reactions; GLP-1= glucagon-like peptide-1; ADA=American Diabetes Association; FDA=US Food and Drug Administration; CfB=Change from Baseline; GIP=glucose-dependent insulinotropic polypeptide; EASD=European Association for the Study of Diabetes.

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