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Systematic Literature Review: Effectiveness of Insulin Combination Therapy with Glucagon-Like Peptide-1 (GLP-1) Incretin-Based Therapy in Patients with Type 2 Diabetes Mellitus

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A B S T R A C T

Diabetes mellitus remains an evolving metabolic and endocrine disease. Effective pharmacological management of type 2 DM is still a global concern. Insulin therapy often causes side effects of hypoglycemia, so other therapies are expected to be combined with insulin. The literature reviewed in this review used two databases, PubMed and Cochrane, based on objectives, clinical keywords, and choice of articles according to predetermined inclusion and exclusion criteria. The methodology was a systematic approach involving identification, analysis, synthesis, evaluation, and comparison of relevant literature. A total of two results were obtained showing that the composite of insulin-based therapy and GLP-1 therapy in patients with type 2 DM provides effective results to control the levels of blood sugar in type 2 DM patients.

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INTRODUCTION

Diabetes mellitus (DM) is a chronic and progressive disease that is caused by a disorder of insulin production such as an inadequate production of insulin or when the body is unable to utilize the insulin when it is produced, characterized by persistently high blood glucose levels. Diabetes remains the leading common cause of global death and morbidity affecting individuals of all characteristics such as ages, genders, and locations of geographic, thus. Nearly half of all adult patients with diabetes are ignorant of their condition, and an estimated 240 million people worldwide have undiagnosed diabetes. (Hossain MJ, 2024). RISKESDAS, Indonesia's basic health research data institution showed that the prevalence of diabetes patients rose to 8.5% from 6.9%. According to RISKESDAS data in 2018, 5% of DM patients have received insulin therapy (KEMENKES RI, 2018). The most common type of diabetes is type 2 diabetes, with along 90% of diabetes patients cases being T2DM (International Diabetes Federation, 2017).

Type 2 DM can occur due to abnormalities in insulin secretion, insulin activity, or both, and is either genetically or clinically characterized by poor carbohydrate tolerance, and is a heterogeneous metabolic disorder (PERKENI, 2021). DM is a complex chronic and progressive disease and its therapy needs to be gradually improved. DM will cause long-term complications if not treated properly. Several forms of blood glucose control for DM patients can be done by starting from lifestyle changes, oral anti-hyperglycemia drugs, to insulin. Insulin can be used if it fails to reach the target by using a combination of OHO with an optimal dose. If after the GDP examination the target is attained but the HbA1C level in the blood is still ≥ 7%, it is necessary to consider giving GLP-1 RA therapy. In the 2015 PERKENI consensus, GLP-1 based treatment is mentioned to be the new approach to the management of type 2 DM (PERKENI, 2015). The glucagon-like peptide-1 receptor agonist is a drug that acts like endogenous GLP-1 and increases the incretin effect in patients with type 2 DM s. GLP-1 RA can act on pancreatic beta cells to increase insulin secretion. Other benefits are the effect of inhibiting glucagon secretion by pancreatic alpha cells, losing weight, and inhibiting appetite (Pathini, 2018).

Current recommendations for DM control are based on achieving a glycated hemoglobin (HbA1c) target of 6.5-7.0% or lower in most patients, provided this target is achieved with medications associated with a very low risk of hypoglycemia. Insulin has the side effect of hypoglycemia which makes it necessary to develop effective drug combinations to reduce the incidence of hypoglycemia in type 2 dm patients receiving insulin therapy. Patients with a record of severe hypoglycemia, limited life expectancy, significant micro or macrovascular complications, comorbidities, or long-standing disease are advised to use looser targets (<8%) (Dedov et al, 2024).

GLP-1 RA can be given as a combination therapy with other oral hypoglycemic drugs or with insulin. The benefit of basal insulin is mainly to lower fasting blood glucose, while GLP-1 RA will lower blood glucose after meals, with the ultimate target of lowering HbA1c. Other benefits of combining

basal insulin with GLP-1 RA are the lower risk of hypoglycemia effect and reduced potential for weight gain (PERKENI, 2021).

This article centers on a specific topic with selected review papers that provide a thorough interpretation of the effectiveness of DM combination therapy critically and comprehensively as a form of narrative review. Thus, the purpose of this narrative review article is to conduct a literature search on the effectiveness of insulin combination therapy with GLP-1 treatment.

LITERATURE REVIEW

The literature review by Kurkin et al in 2024 concludes that the combination of an arginine GLP-1 antagonist and basal insulin in patients with long-term T2DM that is poorly controlled with various insulin therapy regimens may be an effective alternative to complicated regimens in achieving glycemic control targets, but with a better safety profile, improved adherence, and improved clinical treatment outcomes. It was also found that a reduction in the number of injections when combining two components in one dosage form can also have a positive effect on therapeutic outcomes, and the combined action of GLP-1 arginine antagonists and insulin in the pathogenetic therapy of T2DM leads to the implementation of various pleiotropic effects and slows down disease progression (Kurkin DV, *et al*., 2024).

METHODOLOGY

This research is a study using an approach that is Systematic Literature Review (SLR) with the PRISMA algorithm. The methodology in this study was designed to answer the researcher's questions using a systematic approach involving the identification, analysis, synthesis, evaluation, and comparison of relevant literature relating to the research problem or topic under consideration.

The literature search was conducted through two journal databases (PubMed and Cochrane). The keywords used were "insulin" AND "glucagon-like peptide-1" therapy AND "diabetes mellitus type 2" **(Table 1).** The literature search was conducted using predetermined inclusion criteria, namely journals published in the last 5 years, English language, and free full text. The types of research selected were cohort studies or RCTs in humans and middle-aged. The exclusion criteria chosen are articles that have abstracts that do not match the title, abstracts that do not match the keywords, and publications of more than the last 5 years.

Table 1. Search Strategy, Journal Databases used, and Search Results

Database	*Search Strategy*	*Hits*
PubMed	((("insulin" AND "glucagon-like peptide-1") therapy) AND "diabetes mellitus type 2")	3.135
Cochrane	((("insulin" AND "glucagon-like peptide-1") therapy) AND "diabetes mellitus type 2")	4

After that, duplicate journal results were filtered and articles that found the specified inclusion and exclusion criteria were then collected and examined. The data analysis method used in this study includes the application of descriptive statistical analysis. Descriptive statistics is an analysis of data that provides a thorough description of the facts without drawing broad conclusions or attempting to generalize. The researcher then conducted a thorough review and evaluation of the paper, focusing on the research findings presented in the discussion and conclusion sections. The researcher completed the study by comparing the results presented in the paper and concluding it.

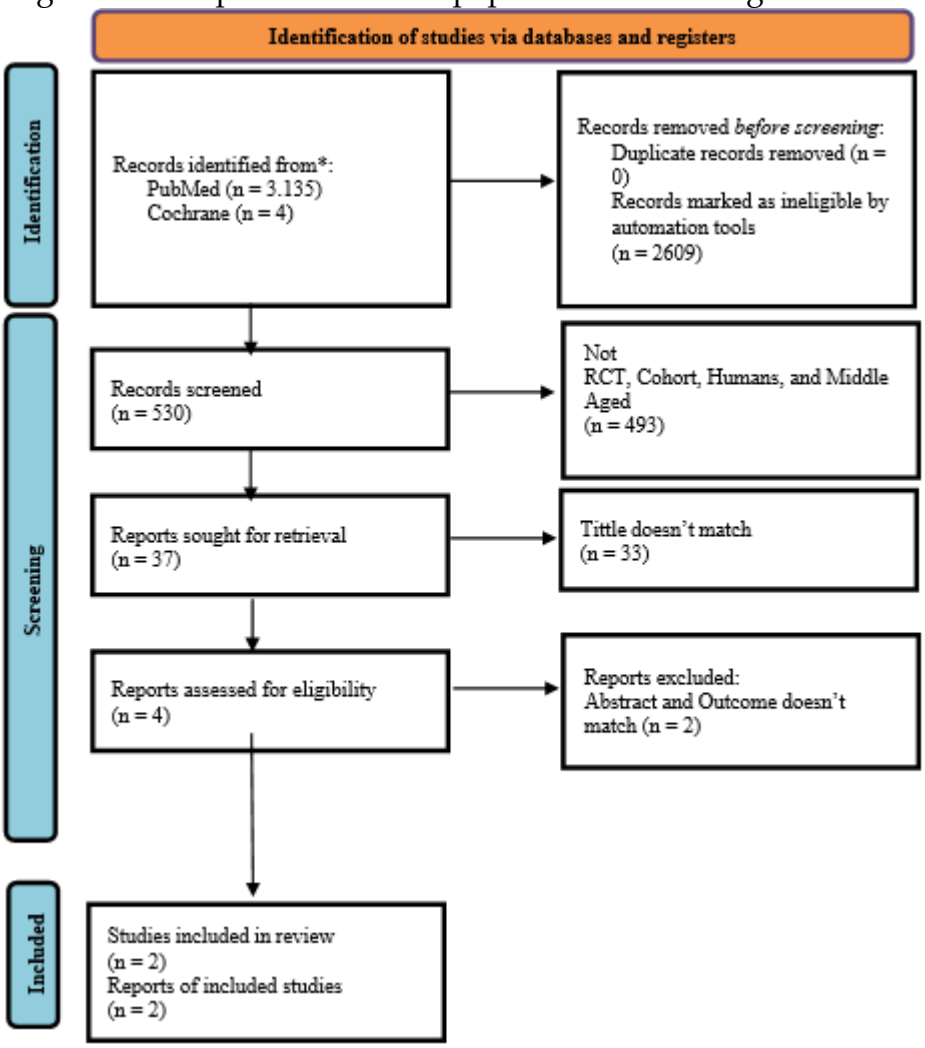

Figure 1. Flow Chart of Study Selection Method (PRISMA Flow Chart)

RESULT AND DISCUSSION

Based on the PRISMA-based Flow Chart analysis, 2 studies were taken that met the inclusion criteria. **Table 2** provides a summary of the characteristics of the publications that were disscused.

Table 2. Journal Characteristics

Authors	*Title*	*Sample*	*Aims*	*Results*
Tack *et al.*, 2019	*Long-term efficacy and*	Among 9,340 patients,	This research aimed to assess the long-	A total of 5171 (55%) patients received no

(*double-blind* RCT)	*safety of combined insulin and glucagon-like peptide-1 therapy: Evidence from the LEADER trial*	4,668 subjects received liraglutide therapy, and the other 4,672 were grouped with placebo in addition to the standard therapy.	term efficacy of the GLP-1RA liraglutide in subgroups based on insulin use in the LEADER trial.	insulin at baseline, 3159 (34%) received basal insulin alone and 1010 (11%) another insulin. Insulin users had slightly worse glycemic control (HbA1c) as well as a longer duration of diabetes than the subgroup without insulin. In all three subgroups it was found that Liraglutide reduced HbA1c and body weight compared to placebo (P<.001), and severe levels of hypoglycemia occurred in the subgroup using basal insulin only. Less insulin requirement with liraglutide. The risk reduction of CV events with liraglutide was found to be similar to the results of the main trial in the basal insulin only subgroup and the no-insulin group.
Liu *et al*., 2021 (*double-blind* RCT)	*Efficacy of once-daily glucagon-like peptide-1 receptor agonist lixisenatide as an add-on treatment to basal insulin in Asian and white adults with type*	Two individual studies got 944 participant data with 916 people included in the analysis.	To compare the efficacy of lixisenatide in Asian patients and white patients who were inadequately controlled with basal insulin	The result showed Similar baseline characteristics between Asian and white patients, except for higher weight, BI dose, and body mass index in patients who include into white

	2 diabetes mellitus: An individual-level pooled analysis of phase III studies	Among the 916 subjects, it was further divided into 468 individuals of Asian ethnicity with a placebo group of 220 and a lixisenatide therapy group of 248, while those of white ethnicity were divided into 448 (placebo n = 164; lixisenatide n = 284).		people. After 24 weeks lixisenatide decreased HbA1c levels in both ethnic groups, but there was no statistically significant difference between them, (least squares mean difference Asian patients -0.49, 95% confidence interval -0.68 to -0.30 and white patients least squares mean difference -0.45, 95% confidence interval -0.63 to -0.26; P=0.6287). However, there was no significant difference in the reduction of 2-hour PPG between the two groups (least squares mean difference for Asian vs. white patients: -3.37 vs -3.93; P = 0.3203). Once baseline HbA1c values were taken into account, lixisenatide therapy resulted in a -0.56% decrease in HbA1c for Asian patients and a -0.41% decrease for white people.

As a complex metabolic disorder, T2DM is characterized by a state of hyperglycemia due to a combination of insufficient insulin secretion and resistance to insulin action. DM management needs to be done comprehensively, in the early stages the recommended therapy generally includes healthy lifestyle

management combined with biguanid antidiabetic therapy such as metformin. A comprehensive lifestyle is very influential, one of which is diet. When ingesting food, the intestine secretes hormones that are released into the circulation system. Among these hormones, one of them is incretin hormone which stimulates the release of insulin from the pancreas which is important for the regulation of glucose concentration, especially postprandial. In patients with type 2 diabetes mellitus, the effect of incretin is reduced due to decreased sensitivity to pancreatic β-cells and α-cells resulting in elevated glucagon levels, both in fasting and postprandial conditions. (Drucker et al., 2010).

The epithelium of the gastrointestinal tract will secrete hormones such as incretin which has an important role in glucose tolerance. By stimulating glucose-dependent insulin secretion, incretins ensure postprandial glucose levels do not increase excessively despite the increased carbohydrate content consumed in the diet (Boer and Holst, 2020). There are 2 incretins types that are most important in studies such as glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1). Both GIP and GLP-1 are released in the post-prandial period in response to nutrient ingestion and function to increase glucose-stimulated insulin secretion. Until euglycemia conditions are reached, this effect on insulin secretion will be maintained, thus minimizing the risk of hypoglycemia occurring. The role of GLP-1 can also affect glucagon secretion by inhibiting it, decreasing gastric emptying, and stimulus through central nervous system pathways to reduce appetite. (Waldrop et al., 2018). The progressive understanding of incretin pathophysiology makes GLP-1 an attractive target for the development of novel anti-diabetic agents that support glucose and body weight reduction (Louisa et al., 2010).

The literature review by Kurkin et al in 2024 concludes that the combination of an arginine GLP-1 antagonist and basal insulin in patients with long-term T2DM that is poorly controlled with various insulin therapy regimens may be an effective alternative to complicated regimens in achieving glycemic control targets, but with a better safety profile, improved adherence, and improved clinical treatment outcomes. It was also found that a reduction in the number of injections when combining two components in one dosage form can also have a positive effect on therapeutic outcomes, and the combined action of GLP-1 arginine antagonists and insulin in the pathogenetic therapy of T2DM leads to the implementation of various pleiotropic effects and slows down disease progression (Kurkin DV, *et al*., 2024)

The Tack et al. study, (2019), discussed the efficacy and long-term safety of combined glucagon-like peptide-1 receptor agonist (GLP-1RA) and insulin therapy for the treatment of type 2 diabetes. The study focused on the use of liraglutide in combination with insulin and its benefits in improving glycemic control, reducing body weight, and reducing the need for insulin. The study compared patients on insulin with patients not on insulin, and found that liraglutide could effectively improve glycemic control, body weight, and reduce the need for insulin in both groups. The study also highlighted that combining GLP-1 RA and insulin has complementary benefits, such as limiting insulin-induced weight gain and reducing the risk of hypoglycemia. However, long-term

data regarding the safety and efficacy of GLP-1 RA and insulin combination therapy are still limited. This study provides important insights into the effectiveness of liraglutide in improving glycemic control and reducing body weight in patients taking basal insulin. The current GLP-1 RA drug preparations available for the treatment of type 2 diabetes and/or obesity are subcutaneous injection and oral administration. Subcutaneous injection GLP-1RA preparations include liraglutide, lixisenatide, dulaglutide, exenatide, and semaglutide. As for oral GLP-1 RA preparations, an example is semaglutide tablets. However, Indonesia currently still uses GLP-1RA subcutaneous injection, because semaglutide tablets are not yet available in Indonesia (National Drug Information Center (PIO Nas), 2023).

The results of the Tack et al. study (2019) also showed that most patients in the liraglutide treatment group achieved clinically relevant HbA1c reductions without weight gain at 36 months compared to the placebo group. Moreover, the addition of liraglutide to basal insulin effectively improved glycemic control and reduced body weight. Overall, this study suggests that the combination of liraglutide and insulin may be a viable treatment option for managing type 2 diabetes, as it can improve glycemic control, reduce body weight, and reduce the need for insulin without increasing the risk of severe hypoglycemia. The recommended dose of liraglutide for therapy of type 2 diabetes and/or obesity is 0.6 mg/day injection in the first week, while for the second week the dose is increased to 1.2-1.8 mg/day according to the patient's body response (Mehta, Marso and Neeland, 2017).

Liu et al. (2021) study discussed the rising prevalence of diabetes, especially in Asia and Europe. The number of people with diabetes in Europe is around 58 million people, while in Southeast Asia it is around 82 million people. The difficulty in maintaining glycemic control in type 2 diabetes is highlighted, despite the availability of various pharmacological interventions. This study introduces GLP-1 treatment as a newly established therapeutic option for type 2 diabetes. GLP-1 RA has shown positive effects by enhancing endogenous insulin response and inhibiting glucagon secretion. This study emphasizes the importance of evaluating the efficacy of this therapy in different ethnic populations to make informed decisions in disease management. Risk factors for the onset of type 2 diabetes may differ among ethnic groups due to pathophysiological differences. Specifically, this study focused on evaluating the addition of lixisenatide, a GLP-1 RA, to basal insulin (BI) therapy in Asian and white participants with type 2 diabetes mellitus. The study aimed to analyze changes in glycated hemoglobin (HbA1c) levels from randomization to the end of the treatment period (week 24) in both groups. The results showed a significant reduction in HbA1c levels in the lixisenatide group compared to the placebo group in Asian and white participants. The effect of lixisenatide treatment on 2-hour postprandial glucose (2h-PPG) was also significant in both populations. The study mentioned that baseline characteristics were comparable between treatment groups in both populations, as well as highlighting the importance of considering different ethnic groups when determining treatment response to lixisenatide as adjunctive therapy for BI. The study concluded that adding

lixisenatide to BI significantly reduced HbA1c and 2h-PPG levels in Asian and white participants with type 2 diabetes mellitus. The recommended dose of lixisenatide for type 2 diabetes therapy is 10 mcg/day for 14 days. On day 15, the dose can be increased to 20 mcg/day if necessary. Lixisenatide is used 1 hour before breakfast or dinner (Feng et al., 2021).

The most commonly reported side effects of GLP-1 RA treatment use are GI side effects including nausea, vomiting, and also diarrhea. These side effects are usually most distinguished when starting therapy with any type of GLP-1 RA or after expanding the dose of GLP-1 RA. Since these adverse effects can occur in patients who are fasting, it is likely that the symptoms are not related to the impact of GLP-1 RA therapy on gastrointestinal function such as slowing stomach emptying, but are caused by direct interaction with CNS GLP-1 receptors located in the brainstem. The side effect of nausea is usually reported in 25% of cases and GIT problems such as diarrhea and vomiting are reported in up to 10% of cases in patients treated with GLP-1 RA. For most patients, such side effects are self-limiting and cease spontaneously with continued treatment. The timing of these symptoms may be related to the time at which the drug reaches its maximum concentration or Tmax after a few hours to days after each injection. The standard recommendation often used to avoid these effects is to increase the dose slowly. This has been shown to reduce gastrointestinal side effects (Nauck et al., 2021).

Based on the comparison of the usage effect between the therapy of insulin (especially basal insulin combined with oral treatment) and one of the GLP-1 RA, there was a slight difference in the effectiveness of glycemic control. The difference was that GLP-1 RA gave a slightly better effect in reducing HbA1c. However, basal insulin and GLP-1 RA had similar effectiveness in patients with high baseline HbA1c. Therefore, the American Diabetes Association (ADA)/European Association for the Study of Diabetes (EASD) recommends using GLP-1 RA in patients with type 2 diabetes mellitus who fail oral treatment alone (Nauck et al., 2021).

Basal insulin-only therapy is capable of effectively managing plasma glucose levels however, it fails to adequately restrict the postprandial glycemic increase. One to three prandial insulin injections daily or the addition of GLP-1 RA as a supplement to insulin therapy can help with this. Furthermore, there is a chance that glycemic goals won't be met when GLP-1 RA treatment and oral medicine are combined. Therefore, combining insulin therapy (especially basal insulin) with GLP-1 RA is used as fasting, post-prandial, and overall glycemic control (HbA1c). This is because the combination of GLP-1 RA with basal insulin has the same effectiveness as intensive insulin (basal-bolus) in controlling HbA1c but with a low risk of hypoglycemia and weight gain in patients (Nauck et al., 2021). In addition, combining these two therapies optimizes the prandial insulin response to control post-prandial glucose and reduces insulin dose requirements (Kalra et al., 2019).

Basal insulin and GLP-1 RA combination is known as a highly effective treatment for advanced T2DM. A study comparing the use of basal insulin and GLP-1 RA separately and the combination of the two stated that the combination

of insulin with GLP-1 RA can achieve the lowest weight loss and HbA1c in patients when compared to the use of the two therapies separately. However, the combination of these two injection therapies is recommended only in patients who need it as a consideration related to the costs incurred to obtain these therapies (Nauck et al., 2021).

The initiation of GLP-1 RA treatment is generally affected by the clinical requirements of the patient. Patients with conception/pregnancy/lactation, diabetic ketoacidosis (DKA), pancreatitis, patients suffering from or with a family record for medullary thyroid carcinoma (MTC), multiple endocrine neoplasia (MEN2), and have hypersensitivity to certain drugs are contraindications to the use of GLP-1 RA therapy. The utilization of GLP-1 RA as monotherapy is given to patients with obesity, metformin intolerance, or patients suffering from or at high risk of atherosclerotic cardiovascular disease (ASCVD). Meanwhile, the use of GLP-1 RA as dual or triple therapy is given to patients with obesity criteria with increased appetite, metabolic syndrome, and cardiovascular disorders; patients with a risk of hypoglycemia; patients intolerant of metformin and/or (sodium-glucose transporter-2) SGLT2 inhibitors; or patients with (non-alcoholic steatohepatitis) NASH; and patients with polycystic ovary syndrome (PCOS). Combination therapy of GLP-1 RA with insulin may be prescribed in patients with uncontrolled hyperglycemia, concern for hypoglycemia or obesity in patients when the insulin dose is increased, or when the number of injections per day received by the patient is taken into account (Kalra et al., 2019).

Proactive monitoring helps to improve therapeutic outcomes and prevent potential adverse drug effects. The monitoring process of GLP-1 RA-based therapy includes HbA1c and (estimated glomerular filtration rate) (eGFR) monitoring at the start of therapy. Furthermore, regular glucose monitoring is required when GLP-1 RA therapy is added to insulin therapy (or vice versa) and if drugs that cause hypoglycemia such as sulfonylurea are also added to GLP-1 RA therapy (Kalra et al., 2019).

Overall, the results of the studies by Tack et al, 2019 and Liu et al, 2021 showed that combined insulin and GLP-1 therapy showed better glycemic control and a decrease in HbA1c and glucose levels for post-prandial in patients with type 2 diabetes mellitus. This is supported by a variety of additional research as explained above.

CONCLUSION AND RECOMMENDATIONS

Effective pharmacological management of diabetes has an important role in the success of controlled T2 DM therapy, the combination of insulin therapy with GLP-1 incretin-based therapy provides promising results in controlling blood sugar levels and reducing HbA1c levels in type 2 DM patients. Some recommendations that can help health workers are to consider the side effects of insulin-only therapy and drug compliance to select a combination of these two pharmacological therapies. so that the combination of these two drugs can be one of the therapeutic considerations.

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