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A SYSTEMATIC REVIEW ON PARALLEL EFFECT ON THIAZOLIDINEDIONES AND SODIUM-GLUCOSE CO-TRANSPORTER 2 (SGLT2) INHIBITORS

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ABSTRACT: Sodium-glucose cotransporter-2 (SGLT-2) inhibitors are medications mainly used for decreasing elevated blood glucose levels by offering unique mechanism of action by blocking glucose reabsorption into the bloodstream, leading to increased urinary excretion of glucose and effectively decreasing blood sugar levels. On other side thiazolidinediones are a class of oral anti-diabetic drugs improve insulin sensitivity by binding peroxisome proliferator-activated receptor-gamma receptor (PPAR-γ) in fat cells (adipocytes) and lowering circulating fat concentrations and thus enhance sensitivity to insulin and lowering the blood glucose level. So, combination of lobeglitazone and dapagliflozin are effective strategy for managing type 2 diabetes mellitus (T2DM). Lobeglitazone is a thiazolidinedione that improves insulin sensitivity, while dapagliflozin is an SGLT2 inhibitor that helps reduce blood glucose levels by promoting glucose excretion through urine. Clinical Studies have shown that this combination can lead to significant improvements in glycemic control, including reductions in HbA1c levels, body weight, and blood pressure. Additionally, the combination therapy has been found to decrease postprandial hyperglycemia more effectively than dapagliflozin alone.

KEYWORDS: Thiazolidinediones, sodium-glucose co-transporter 2 (SGLT2) inhibitors, Dapagliflozin, Lobeglitazone Sulphate, Hyperglycemia.

INTRODUCTION:

Sodium-glucose cotransporter-2 (SGLT-2) inhibitors:

Sodium-glucose cotransporter-2 (SGLT-2) inhibitors are a class of medications used to lower high blood glucose levels in people with type 2 diabetes. SGLT-2 inhibitors offer a unique mechanism of action compared to other diabetes medications. SGLT-2 inhibitors work in the kidneys by blocking glucose reabsorption. They prevent glucose from being reabsorbed back

into the bloodstream, leading to increased urinary excretion of glucose. By blocking this reabsorption, SGLT-2 inhibitors increase glucose excretion in the urine, effectively lowering blood sugar levels. They also have the added benefits of promoting weight loss and reducing blood pressure due to increased urinary glucose excretion and calorie loss..[1][2][3]

Other classes of diabetes medications, such as sulfonylureas (e.g., glipizide, gliclazide) and dipeptidyl peptidase-4 (DPP-4) inhibitors (e.g., sitagliptin, saxagliptin), primarily act on pancreatic beta cells or inhibit enzymes involved in glucose metabolism. SGLT-2 inhibitors lower blood sugar levels by reducing renal glucose reabsorption. They are effective in lowering both fasting and post-meal glucose level. Other medications, like metformin (a biguanide), also reduce blood glucose levels but through different mechanisms (e.g., decreasing liver glucose production).[5][6][7]

SGLT-2 inhibitors also have a modest blood pressure-lowering effect. SGLT-2 inhibitors have a low risk of hypoglycemia because they do not stimulate insulin release, whereas sulfonylureas can cause hypoglycemia. It also shows cardiovascular benefits, including reduced risk of heart failure and cardiovascular events. SGLT2 inhibitors improve cardiovascular and renal outcomes, including heart failure hospitalization, in large cardiovascular outcome trials involving patients with diabetes.[8] This effect also extends to people without diabetes who have heart failure with lower ejection fraction. Since the potential benefits are not anticipated to be associated with better glycaemic management, they are being further examined. Improved vascular function, a drop in blood pressure, early natriuresis with a decrease in plasma volume, an increase in haematocrit as a result, and modifications in tissue sodium handling are all likely to be involved.[9][10]

Although SGLT2 inhibition favors an improvement in HbA1c, the extent of this improvement is not enough to explain the significant clinical benefits observed in cardio-renal health. In those without diabetes, hyperglycemia would also not be a primary pathophysiological problem. The switch to lipid metabolism may have an energy benefit since it reduces lipotoxicity and increases ketone generation. SGLT2 inhibition's diuretic and natriuretic effects are essential to the cardiovascular benefit. It appears that the improvements in blood pressure, salt balance, and volume status that have been reported have an impact on both cardiovascular and renal health. Additionally linked have been oxidative stress, inflammation, and a decrease in albuminuria.[11][14]

SGLT2 inhibitors are administered in oral formulations. The indications determine the different doses. Dapagliflozin should not be administered until renal function has been evaluated. Before commencing therapy, patients who are experiencing volume depletion should have this rectified. SGLT2 inhibitors should be avoided prior to surgery, extended fasting, or serious medical conditions (when patients are at increased risk of developing ketoacidosis). Canagliflozin is available in 100 mg and 300 mg tablets. Canagliflozin is administered before the first meal of the day.[15] Dapagliflozin is available in 5 mg and 10 mg tablets.[16]

SGLT2 inhibitors are also available as FDC: canagliflozin and metformin, canagliflozin and metformin extended-release, dapagliflozin, and metformin extended-release, dapagliflozin and saxagliptin, empagliflozin and linagliptin, empagliflozin and metformin, empagliflozin and metformin ER, ertugliflozin and metformin, ertugliflozin and sitagliptin.[17][18]

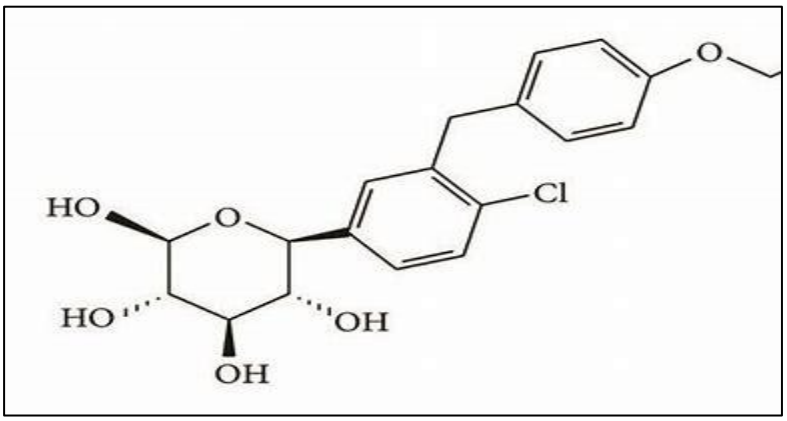

Fig 1: Structure Of Dapagliflozin(Sodium-glucose cotransporter-2 (SGLT-2) inhibitors)

Thiazolidinediones:

Thiazolidinediones, also known as glitazones, are a class of oral anti-diabetic drugs primarily used to treat type 2 diabetes. Thiazolidinediones improve insulin sensitivity by binding to a receptor called the peroxisome proliferator-activated receptor-gamma (PPAR-γ) in fat cells (adipocytes).This binding promotes the maturation of fat cells and deposition of fat into peripheral tissues. By reducing circulating fat concentrations, thiazolidinediones enhance a person's sensitivity to insulin. Thiazolidinediones are used either as monotherapy or in combination with other oral agents (such as metformin or sulfonylureas) for type 2 diabetes management. They help lower blood glucose levels by improving insulin action. [19-28]

Insulin availability is the primary target of therapeutic medications, including sulfonylureas, meglitinides, and insulin[29-32]. Insulin production is increased and hyperglucagonemia is

decreased by dipeptidyl dipeptidase 4 (DDP-4) inhibitors and glucagon-like peptide 1 (GLP-1) receptor agonists, which lower hyperglycemia [33, 34, 35]. GLP-1 receptor agonists have a slight effect on systolic blood pressure and body weight reduction.[33, 34] With the added benefit of reducing glucose toxicity, the sodium-glucose transport 2 (SGLT-2) inhibitors lower blood sugar via increasing renal excretion of glucose[36]. They increase the synthesis of glucose in the liver, the release of glucagon, ketogenesis, and lipid oxidation, it promotes mild weight loss, blood pressure reduction, and mild improvement in insulin resistance are important side effects of their treatment [36].

Therapeutic agents such as insulin, sulfonylureas, and meglitinides target primarily insulin availability [32]. Glucagon-like peptide 1 (GLP-1) receptor agonists and dipeptidyl dipeptidase 4 (DDP-4) inhibitors increase insulin secretion and decrease hyperglucagonemia, thereby lowering hyperglycemia [33,34,35]. GLP-1 receptor agonists have modest effects in decreasing body weight and lowering systolic blood pressure. The sodium-glucose transport 2 (SGLT-2) inhibitors lower blood glucose through an increase in renal excretion of glucose with a secondary benefit of decreasing glucose toxicity[36]. They increase hepatic glucose production, glucagon secretion, ketogenesis, and lipid oxidation[36]. A significant side effect of their treatment is a modest weight loss, a decrease in blood pressure, and a modest reduction in insulin resistance [36]. Weight loss itself decreases hepatic triglycerides, peripheral and visceral adipose tissue mass, and plasma triglycerides. GLP-1 receptor agonists and SGLT-2 inhibitors secondarily decrease insulin resistance in patients in proportion to their effect in promoting weight loss. Thiazolidinediones (TZDs) decrease insulin resistance directly through activation of PPARγ receptors which facilitate differentiation of mesenchymal stem cells into adipocytes, promote lipogenesis in peripheral adipocytes, decrease hepatic and peripheral triglycerides, decrease activity of visceral adipocytes, and increase adiponectin.[37][38]

These primary effects of TZDs markedly ameliorate insulin resistance and the metabolic syndrome and decrease insulin requirements. [36][37][38] GLP-1 receptor agonists and SGLT-2 inhibitors secondarily decrease insulin resistance in patients in proportion to their effect in promoting weight loss. Through the activation of PPARγ receptors, thiazolidinediones (TZDs) directly reduce insulin resistance by promoting lipogenesis in peripheral adipocytes, facilitating the differentiation of mesenchymal stem cells into adipocytes, lowering peripheral and hepatic triglycerides, decreasing visceral adipocyte activity, and raising adiponectin.[37][38] The metabolic syndrome, insulin resistance, and the need for insulin are all significantly

improved by these main actions of TZDs.[36][37][38] Metformin has little to no main effect on peripheral insulin resistance, however it does reduce hepatic insulin resistance.

Chong Kun Dang Pharmaceutical first developed lobeglitazone in Korea to treat diabetes. Lobeglitazone, the drug that Chong Kun Dang Pharmaceutical sells under the Duvie® brand, was approved by the Ministry of Food and Drug Safety (Korea) on July 4, 2013. Oral tablets containing 0.5 mg of free lobeglitazone are available as Duvie. One daily dose of 0.5 mg is the recommended dosage [8]. Since insulin resistance is common in Indians, Glenmark Pharmaceuticals Limited was the first to introduce lobeglitazone for the treatment of type 2 diabetes in the country. Lobeglitazone (0.5 mg) is the active ingredient in the medication, which is sold under the trade name LOBG. Patients are instructed to take the medication orally once day.

Lobeglitazone is a pharmacophore having 2,4-thiazolidin edione group with an ethoxy-benzyl N-methylamino group linked to it as a connecting link. Its structural formula is C24H24N4O5S and chemical name is 5-[4-(2-{[6-(4-methoxy-phenoxy)-pyrimidin-4-yl]-methyl-amino}-ethoxy)benzyl]-thiazolidine-2,4-dione hydrosulphuric acid.

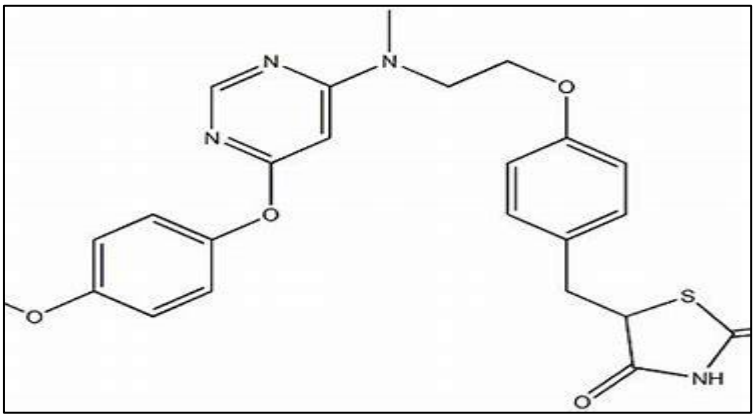

Fig 2: Structure Of Lobeglitazone

The development of lobeglitazone began with the addition of a p-methoxyphenoxy group to the pyrimidine moiety's 4-position in the rosiglitazone structure.[40] This enhances lobeglitazone's binding affinity for PPARγ; according to docking research, lobeglitazone's binding affinity is 12 times greater than rosiglitazone and pioglitazone.[41,42] Extended interaction with the hydrophobic pocket is made possible by the p-methoxyphenoxy group. This could also have an impact on the cyclin-dependent kinase 5-mediated phosphorylation of PPARγ at Ser245, which modifies the expression of genes linked to insulin sensitivity, such as adiponectin and adipsin, without affecting the general transcriptional activity of PPARγ.[43]

The class of oral antidiabetic drugs known as TZDs, which includes well-known members like pioglitazone, rosiglitazone, and lobeglitazone, has drawn interest due to its possible application in the treatment of ketoacidosis [44,45]. Current studies have explored the unique ways in which these medications can be effective in cases of ketoacidosis. For instance, pioglitazone's potential to improve insulin sensitivity and reduce insulin resistance has been studied [46]. This could lead to better glucose utilization. The activation of PPAR-γ, a crucial transcription factor in the metabolism of fats and carbohydrates, mediates this impact. Research indicates that pioglitazone may be used as an adjuvant therapy to treat diabetic ketoacidosis by targeting underlying insulin resistance [47,48]. According to studies, rosiglitazone may improve glucose utilization and insulin sensitivity, which could lessen insulin resistance—a major contributing factor to the development of DKA. Rosiglitazone's effects go beyond glycemic control by influencing the expression of genes involved in glucose and lipid metabolism.[47,48] To precisely define the role of rosiglitazone in the context of ketoacidosis, additional clinical research is necessary. [48]

PARALLEL EFFECT OF LOBEGLITAZONE AND DAPAGLIFLOZIN:

Combining lobeglitazone and dapagliflozin can be an effective strategy for managing type 2 diabetes mellitus (T2DM). Lobeglitazone is a thiazolidinedione that improves insulin sensitivity, while dapagliflozin is an SGLT2 inhibitor that helps reduce blood glucose levels by promoting glucose excretion through urine.

Although thiazolidinedione, an insulin sensitizer, improves glucose metabolism, weight gain and heart failure are possible side effects. SGLT2 inhibitors have the ability to lower body weight, promote diuresis, and mitigate the effects of heart failure. Synergistic effects of thiazolidinedione (lobeglitazone) and SGLT2 inhibitor (dapagliflozin) in obese mice fed a high-fat diet (HFD)was studied in clinical trial. For 12 weeks, they administered vehicle, dapagliflozin, lobeglitazone, and their combination to obese mice induced by high-fat diet. After a 12-week course of treatment, tests for insulin and glucose tolerance were conducted, and dual-energy X-ray absorptiometry was used to assess body composition both before and after the course of treatment. When compared to dapagliflozin alone, but not lobeglitazone monotherapy, treatment with a combination of dapagliflozin and lobeglitazone led to a significant decrease in postprandial hyperglycemia. In this trial, the weight gain associated with lobeglitazone monotherapy was not mitigated by adding dapagliflozin to the medication. Nevertheless, this combination stopped the growth of the liver and heart organ weight, and

OCR in 3T3-L1 cells increased following β-hydroxybutyrate and lobeglitazone combination treatment as opposed to lobeglitazone monotherapy. In HFD-induced obese mice, they found no favorable effect of dapagliflozin on body weight, but we did confirm the good effect of lobeglitazone on glucose metabolism. Nonetheless, the benefits of lobeglitazone and dapagliflozin combined therapy on the heart, liver, energy expenditure, and β-cell senescence are worth investigating in clinical trials.[57]

Studies have shown that this combination can lead to significant improvements in glycemic control, including reductions in HbA1c levels, body weight, and blood pressure. Additionally, the combination therapy has been found to decrease postprandial hyperglycemia more effectively than dapagliflozin alone.[49][50]

The combination of lobeglitazone and dapagliflozin offers some unique benefits compared to other diabetes medications. Here's a comparison with a few common classes of diabetes drugs:

1. **Metformin**: Often the first-line treatment for T2DM, metformin primarily reduces hepatic glucose production and improves insulin sensitivity. While effective, it doesn't provide the additional benefits of weight loss and blood pressure reduction seen with the lobeglitazone-dapagliflozin combination.
2. **Sulfonylureas (e.g., glipizide, glyburide)**: These stimulate insulin secretion from the pancreas. They can be effective in lowering blood glucose but often lead to weight gain and have a higher risk of hypoglycemia compared to the lobeglitazone-dapagliflozin combination.
3. **GLP-1 receptor agonists (e.g., liraglutide, exenatide)**: These enhance insulin secretion, suppress glucagon release, and slow gastric emptying. They are effective in reducing HbA1c and promoting weight loss, similar to the lobeglitazone-dapagliflozin combination. However, they are usually administered via injection, which might be less convenient than oral medications.
4. **DPP-4 inhibitors (e.g., sitagliptin, saxagliptin)**: These increase incretin levels, which help to regulate insulin and glucagon secretion. They are generally well-tolerated but may not be as effective in reducing HbA1c or promoting weight loss as the lobeglitazone-dapagliflozin combination.

5. **Insulin**: Essential for patients with advanced T2DM or those who cannot achieve glycemic control with oral medications. While highly effective in lowering blood glucose, insulin therapy can lead to weight gain and has a higher risk of hypoglycemia.

Overall, the lobeglitazone-dapagliflozin combination is particularly beneficial for patients looking to improve glycemic control while also achieving weight loss and blood pressure reduction. It also has a lower risk of hypoglycemia compared to some other medications.[51-54]

LONG TERM EFFECT OF LOBEGLITAZONE-DAPAGLIFLOZIN COMBINATION:

The long-term effects of the lobeglitazone-dapagliflozin combination in managing type 2 diabetes mellitus (T2DM) can be significant. The combination helps maintain better blood glucose levels over time. By improving insulin sensitivity (lobeglitazone) and promoting glucose excretion (dapagliflozin), it contributes to long-term glycemic control. Both lobeglitazone and dapagliflozin have weight-reducing effects. Over the long term, this can lead to sustained weight loss, which is beneficial for overall health and diabetes management. Dapagliflozin has been associated with blood pressure reduction. When combined with lobeglitazone, it can help manage hypertension, which is common in T2DM patients. Some studies suggest that SGLT2 inhibitors (like dapagliflozin) may reduce the risk of cardiovascular events, including heart attacks and strokes. This benefit extends to the combination therapy. SGLT2 inhibitors have shown renal protective effects. They can slow the progression of diabetic kidney disease, which is crucial for long-term health. Thiazolidinediones (like lobeglitazone) may affect bone density. Regular monitoring and appropriate supplementation are essential to mitigate any potential risks. While generally well-tolerated, any medication has potential side effects. Regular follow-ups with a healthcare provider are crucial to monitor for adverse effects.[55][56][57]

SIDE EFFECT OF LOBEGLITAZONE AND DAPAGLIFLOZIN:

Thiazolidinediones can lead to weight gain due to fluid retention and increased fat storage. It can lead to fluid buildup in the legs and ankles. Thiazolidinediones may increase the risk of heart failure, especially in patients with pre-existing heart conditions.[58]

SGLT2 Inhibitor can lead to genital yeast infections (in both men and women) and Urinary Tract Infections. Dapagliflozin promotes glucose excretion through urine, which can lead to dehydration. Hypotension (Low Blood Pressure): Especially when starting the medication.

Ketoacidosis is rare but serious; seek medical attention if you experience symptoms like nausea, vomiting, abdominal pain, or fruity breath odor.[59][60]

When considering the lobeglitazone-dapagliflozin combination, it's essential to be aware of potential interactions with other medications or supplements. Combining the combination with other oral hypoglycemic agents (e.g., sulfonylureas, meglitinides) may increase the risk of hypoglycemia. Regular blood glucose monitoring is crucial. Insulin therapy alongside this combination requires careful adjustment to prevent low blood sugar levels. Dapagliflozin is a diuretic, and combining it with other diuretics (e.g., furosemide, hydrochlorothiazide) may enhance diuresis and increase the risk of dehydration. Dapagliflozin can lower blood pressure. Combining it with other antihypertensive drugs (e.g., ACE inhibitors, beta-blockers) may lead to excessive blood pressure reduction. NSAIDs (e.g., ibuprofen, naproxen) can affect kidney function. Combining them with dapagliflozin may increase the risk of kidney problems. Lobeglitazone is metabolized by CYP2C8 enzymes. Drugs that inhibit or induce CYP2C8 may affect its levels like emfibrozil, clopidogrel. Inducers: Rifampin, phenytoin. Some herbal supplements (e.g., ginseng, cinnamon) may impact blood glucose levels. Discuss their use with your healthcare provider. Alcohol consumption can also affect blood sugar control.[60][61]

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