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Comparative Study on Monotherapy (Metformin) and Combination Therapy (Metformin + Dpp-4 Inhibitors) In Type 2 Diabetic Patients

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ABSTRACT

Diabetes is one of the most common and chronic endocrine disorder occurring in clinical practice around the world. Regulation of insulin secretion is important to maintain normal blood sugar levels in the body. In patients with type-2 Diabetes mellitus, the development of insulin secretion and peripheral insulin resistance lead to formation of hyperglycaemia. Metformin is the main drug prescribed for people with type 2 diabetes. It helps maintain glucose levels by blocking gluconeogenesis in the liver. Dipeptidyl peptidase-4 (DPP-4) inhibitors is also known as gliptins, act as enhancers of incretin. Dpp-4 inhibitors have become an increasingly established class of oral antidiabetic agents have been introduced in the treatment of type 2 diabetes. They inhibit glucagon secretion and induce postprandial insulin secretion. Sitagliptin was the first drug introduced in 2006. The other most commonly used substance is linagliptin, vildagliptin, saxagliptin and allogliptin. These compounds can improve glycaemic control both as monotherapy and in combination with other oral hyperglycaemic drugs. Compared with monotherapy, combination therapy of Metformin and DPP-4 inhibitors are more effective. In addition to this lifestyle intervention, which includes adjusting diet and increasing physical activity, they are also the cornerstones of treatment.

KEY WORD: DPP-4 inhibitors, Metformin, Insulin Resistance, Hyperglycemia, Gluconeogenesis.

I. INTRODUCTION:

Type 2 diabetes (T2DM) is one of the most common non-communicable chronic diseases that seriously endanger human health. Insulin resistance and islet dysfunction are two important defects in the pathophysiological basis of T2DM. Several anti-diabetic drugs play an important role in the modern treatment of T2DM. Metformin is recommended as a first-line oral anti-diabetic drug to improve blood sugar control by lowering liver insulin levels. Dipptidylpeptidase-4 (DPP-4) inhibitors can protect the increasing hormone from degradation, thereby improving islet dysfunction. Increasing evidence shows that in patients with D2DM, combined treatment with DPP-4 inhibitors and metformin can provide better blood sugar control compared with monotherapy. Studies have shown that there is a certain interconnection between the two types of antidiabetic drugs Can increase its effect on metabolic control.This reviewdiscusses the importance of combination therapy (Metformin + DPP-4 inhibitors) when compared with Metformin Monotherapy.

METFORMIN

Metformin is mainly used first line drugs to treat type 2 diabetes, especially in obese patients. Compared with insulin, glibenclamide and chlorpropamide, metformin has been shown to reduce diabetes mortality and complications by 30%. Metformin lowers serum glucose through a variety of mechanisms, especially non-pancreatic mechanisms, without increasing insulin secretion. Enhance the effect of insulin; therefore, it is called "insulin sensitizer". Metformin also inhibits the production of endogenous glucose in the liver, which is mainly related to the reduction of gluconeogenesis and little effect on glycogen decomposition. In addition, metformin can activate adenosine monophosphate kinase (AMPK), thereby inhibiting the key enzymes involved in gluconeogenesis and glycogen synthesis in the liver, while stimulating insulin signalling and glucose transport in muscles. AMPK regulates the metabolism of cells and organs. Any reduction in

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liver energy will result in the activation of AMPK. To some extent, this study is believed to explain the mechanism of metformin on liver gluconeogenesis. In addition, metformin increases peripheral glucose clearance, mainly due to the increase in non-oxidative glucose clearance in skeletal muscle. It usually does not cause hypoglycaemia, so it should be considered an anti-diabetic drug. Compared with insulin and sulfonylurea, metformin treatment of diabetes has less weight gain. Weight gain will help you better control your blood sugar levels. The results showed that in 10 years, patients who received metformin gained about 1 kilogram, those who received glibenclamide gained about 3 kilograms, and those who received insulin gained 6 kilograms.[1]

SAFETY AND EFFICACY OF METFORMIN: Although the risk of hypoglycaemia is small, the risk of gastrointestinal reactions is higher, and patients with impaired renal function are contraindicated. Kidney function declines with age, so elderly people taking metformin need to be closely monitored. The United Kingdom, Canada, and Australia) reported that the use of metformin is contraindicated, or lower doses of metformin should be used depending on the situation. Kidney function. The use of metformin is also associated with an increased risk of lactic acidosis, but this has not been widely reported. Currently, there are few empirical data on the safety and effectiveness of oral antidiabetics (including metformin) in the elderly. Evidence-based clinical guidelines for the treatment of T2DM confirm that the elderly lack direct evidence. STOP/START Standard Version 2 considers metformin as a potentially unsuitable drug for the elderly with severe renal insufficiency. Improper prescription may mean wrong dosage, no clear instructions or no basis.[2]

DPP-4 INHIBITORS:
DPP-4 inhibitors are important oral anti-diabetic drugs. They are prescribed as second-line treatment after metformin fails as an insulinotropic drug, without the inherent risks of hypoglycaemia and weight neutrality. DPP-4 inhibitors inhibit DPP-4. 1 The plasma concentration of glucose-dependent stimulation of insulin secretion and inhibition of glucagon secretion increases 2-3.5 times. Endocrine effect, local inhibitory effect of DPP-4 inhibitors can inhibit the decomposition of GLP-1 in the intestinal mucosa, and promote favourable metabolic regulation by stimulating the autonomic afferent nervous system. The bioavailability of DPP-4 inhibitors is very good, and the pharmacodynamics and pharmacokinetic properties are also very good. They also inhibit the secretion of glucagon. They should be used primarily as a second-line treatment to supplement the patient's metformin. People with type 2 diabetes have no previous cardiovascular disease, and their treatment goal is to avoid hypoglycaemia. Fixed-dose combinations with metformin are widely used. The side effects of DPP-4 inhibitors are beneficial, and the treatment andDPP-4 inhibitors have some limited side effects and proven to be safe for the cardiovascular system. Inhibitor-4 has been shown to be safe for the cardiovascular system. Another beneficial property of DPP-4 inhibitors is their effectiveness and safety. Overview of patients with impaired renal function.[3]

SAFETY AND EFFICACY OF DPP-4 INHIBITORS: An important advantage of Gliptin is compared with other hypoglycaemic agents, including other new hypoglycaemic agents, such as sodium/glucose cotransporter inhibitors. 2. Compared with sulfonylureas, they have excellent tolerance /safety. The difference between the two groups was 08% (95% confidence interval [CI]: 0.03-0.14, p = 0.001) This 12-week randomized, open-label, parallel study evaluated the efficacy and safety of vildagliptin, sitagliptin, and linagliptin in patients with T2DM. These patients received conventional oral hyperglycaemic drugs and the dual combination of insulin is not well controlled. At the 6th and 12th weeks, the blood glucose control of these groups was better than baseline. The fasting blood glucose of tagagliptin and linagliptin decreased, but the magnitude was slightly different. After 12 weeks, the fasting blood glucose drop caused by vildagliptin was significantly greater than that of sitagliptin. Compared with sitagliptin, Lina-gliptin and vildagliptin also caused a significant decrease in postprandial blood sugar. At the 12th week, the postprandial blood glucose levels of patients treated with linagliptin decreased most significantly, followed by vildagliptin. Three DPP-4 inhibitors have shown excellent blood sugar control effects as additional agents for the treatment of T2DM. [4]

II. LITERATURE REVIEW:

The fixed dose combination (FDC) of DPP-4 inhibitors (Alogliptin) Plus metformin shows better glycaemic control from which greater decrease in mean Glycated Haemoglobin A1c

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(HbA1c) and Fasting Plasma Sugar (FPS) as compared with alogliptin or metformin alone in type 2 diabetic patients who were inadequately controlled with diet and exercise. In which alogliptin was added to stable dose of metformin. By administration of both class of drugs shows greater efficacy and Safety. Higher proportion of patients receiving fixed dose combination therapy showed HbA1c clinical response when compared with the metformin monotherapy. Addition a meta-analysis of various dpp4 inhibitors plus metformin discovered no increase in the risk of hypoglycaemia or prolonged gastrointestinal complaints compared to metformin monotherapy.[5]In fixed dose combination (FDC) of oral antihyperglyceamic agents (AHA) might improve the medication adherence, metabolic target achievement and reduce the bill burden. Dpp-4 inhibitors are selected as second choice medication combined with metformin which is well tolerated, associated with reduced frequency of hypoglycaemia when compared to other class of AHA. The glycaemic improvement was observed in FDC of Dpp-4 inhibitors + metformin, but these did not result in a reduction in glycosylated haemoglobin (A1C) and no significant weight or blood pressure changes noted in this study.[6]

Clinical studies have shown that this combination therapy has the best efficacy and safety, indicating that the combined use of Dpp-4 inhibitors and metformin in the treatment of type 2 diabetes. Adding DPP 4 inhibitors to metformin is no worse than adding sulfonylurea drugs to reduce HbA1c in patients with type 2 diabetes. Bioequivalence studies have shown that the simultaneous administration of DPP-4 inhibitors and metformin can be extended to FDC and FDC sustained-release tablets. While considering the safety issues in terms of oral side effects, there are similarities between metformin monotherapy and DPP-4 inhibitor plus metformin combination therapy. Metformin mainly improves insulin resistance and may inhibit plasma Dpp-4 activity by increasing the biological activity of GLP-1 in the blood and increasing the expression of GLP-1 receptors in pancreatic β cells, and DPP-4 inhibitors improves pancreatic islet function. When these two classes of antidiabetic drugs are used in combination, they have a synergistic effect. [7]

This novel strategy of combination of metformin and the Dpp-4 inhibitors is clear rationale and expected to be of increasing value in the future treatment of type 2 Diabetes mellitus which is highly tolerable efficient and safe. Indicated strategies for the prolonged action of the endogenous incretin hormone. Stated that total cholesterol, triglycerides, body weight are reduced and HDL cholesterol was slightly increased just in case of sitagliptin Plus metformin when compared to vildagliptin combination.[8]

Randomised trial suggests fewer sufferersstated gastrointestinal negativeactivitieswithinside theorganizationwith vildagliptin introduced to metformin than withinside theorganization with monotherapy.[12] Additionallystomachache and diarrhoea happenednotablymuch less with sitagliptin or metformin FDC Versus an equal dose of metformin monotherapy. Aprevalence of nausea, vomiting becomecomparable in eachgroup.[7]

The metabolites produced by dipeptidyl peptidase IV (DPP-IV) can act as GLP-1 receptor antagonists, so the effect of GLP-1 injection alone is short-lived and fully demonstrates their anti-diabetic properties. Requires continuous intravenous infusion. In order to develop the therapeutic potential of GLP-1, it is recommended that specific DPP-IV inhibitors be used clinically. We have shown that administration of such inhibitors can completely protect exogenous GLP-1. DPP-IV-mediated degradation greatly enhances its insulinotropic effect and provides evidence that endogenous GLP-1 can be equally protected, and the side effects of inhibitory therapy may be mild. Shows that inhibiting DPP-IV significantly improved the condition.[9]

Compared with placebo, saxagliptin (2.5, 5, and 10 mg) plus metformin showed a statistically significant adjusted mean decrease compared with placebo in 24 weeks (-0.59, -0.69 and -0.58 vs. +0, 13%; all P <0.0001), FPG (-14.31, -22.03 and -20.50 and +1.24 mg/dl; all P <0.0001) and PPG AUC (-8.891, -9.586, and -8.137 vs. -3.291 mg min/dl; all P <0.0001). The number of patients achieving A1C values more than tripled17%; all P <0.0001) β-cell function and postprandial C-peptide, insulin, and glucagon AUC improved in all saxagliptin treatment groups at week 24. The incidence of hypoglycaemia side effects and weight loss was similar to that of placebo.[10]

Compared with metformin and sulfonylureas, the combination therapy of metformin and DPP-4 inhibitors significantly reduced the relative risks of non-fatal cardiovascular events, cardiovascular mortality, and all-cause mortality; There were no significant differences in fatal cardiovascular events. Based on these results, it is easy to understand the uncertain

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results of many large clinical studies that compared DPP-4 inhibitors and sulfonylureas studies on non-fatal cardiovascular events and cardiovascular mortality. All-cause mortality in patients with T2DM and T2DM, and fatal cardiovascular events are still unexplainable.[11]

The impact of initial therapy with the fixed dose combination of sitagliptin and Metformin compared with Metformin monotherapy in type2 DM patients and drugnaivepatients with moderate to severe hyperglycaemia. After 18 weeks FDC has resulted in controlled Hba1c levels and FPG relative to baseline. The study has proved that sitagliptin with Metformin dual therapy has shown active levels of GLP - 1 than Metformin monotherapy or sitagliptin monotherapy. Sitagliptin and Metformin Fixed dose combination resulted high glycaemic improvement with the lower incidence of unwanted effects i.e., abdominal pain, Nausea, diarrhoea and Vomiting with similar effects of weight loss from baseline.[13]

The article provides data of DPP4 Inhibitors as add on Therapy to Metformin. The study proved that DPP4 Inhibitors improve the Beta cells function in type2 DM patients. DPP4 is inhibited by more than 80% by sitagliptin and vildagliptin resulted reduced Fasting blood Sugar, postprandial blood sugar and Hba1c levels. The potency of DPP4 inhibitors with Metformin monotherapy improve beta cell Function and inhibition of alpha cell secretion there by improves Insulin sensitivity. The study proved 4 inhibition is primary treatment in type 2 Diabetic patients as it is safe, tolerable, effective Orally active. Long term studies have proved the addition of DPP4 Inhibitors to the monotherapy regimen have proved the lower incidence of adverse effects, combination Therapy have decreased the incidence of Hypoglycaemia.[14]

The effectiveness of Dpp4 inhibitors Impact in polygenic disorder patients, studies conducted in diabetes Patients who also suffer from coronary heart disease. DPP4 inhibitors coronary artery perfusion, additionally contribute to reduction In Blood pressure. GLP 1 analogues with Dpp4 inhibitors resulted lowering PPBS and Hba1c levels and increase in insulin levels.DPP4 inhibitors as an addition to Type 2 DM patients have shown similar incidence of weight loss over 52 weeks of therapy .The study over trails proved that DPP4 inhibitors controls postprandial blood glucose Hba1C levels decreasing glucagon levels, increase insulin levels and also improves the coronary artery function.[15]

The effectiveness of Dpp4 inhibitors With Metformin combination resulted higher efficacy than Metformin alone in controlling blood sugar levels and also improved pancreatic islet beta cell function. Meta-analysis showed that efficacy of Combined drug use of Dpp4 inhibitors with Metformin was better than Metformin monotherapy in controlling Hba1c levels in type2 DM Patients. Several, Meta-analysis studies proved that single drug often Metformin monotherapy is difficult to control blood glucose levels due to complex pathogenesis of TYPE 2 Diabetes mellitus.Thecombination therapy of DPP4 inhibitors with Metformin inhibit the activity of DPP4 there by controlling FPG,elevating the levels of Glucagon like peptide and Glucose dependent insulin tropic polypeptide, improved better pancreatic beta cell Function than monotherapy.[16]

The study to evaluate the effectiveness of combination therapy compared with monotherapy in drug Naive type 2 diabetes mellitus patients. A systemic review of 36 studies were included in the Meta-analysis and proved that Compared with Metforminmonotherapy, dual therapy of Metformin with other anti- diabetic drugs DPP4 inhibitors has resulted in reduced glycated haemoglobin hba1c levels. The initial combination therapy has resulted significant control in fasting blood glucose,post prandial bloodglucose and glycated haemoglobin levels in naive type 2 Diabetes mellitus patients.[17]

To study the results of saxagliptin as an add to therapy in type 2 Diabetes mellitus combination therapy of saxagliptin to Metformin monotherapy has improved the glycaemic control, lower Incidence of hypoglycaemia and weight gain. Saxagliptin with Metformin Combination therapy for 24 weeks study has proved that patients have Improved glycaemic control, reduced fasting blood glucose levels and Postprandial blood glucose levels and also significantly increased post Prandial insulin AUC levels compared with Metformin monotherapy. Dual therapy with saxagliptin has also improved Beta cell function and also observed mean changes in bodyweight control from the baseline.[18]

The study of effectiveness Of non insulin diabetic drugs added to metformin monotherapy on theglycaemic control, weight gain and hypoglycaemia in type 2 diabetes mellitus patients. Because of progressive nature of diabetes two patients required combination therapy to obtain individualized glycaemic control. Combination

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therapy with complementary and different mechanism of action controls glycaemic levels better than monotherapy and permits the use of lower dose of mixed antihyperglycemic medication. A randomised controlled trial was conducted combination of Metformin with all the antidiabetic drugs improve hba1c control. But with Metformin and DPP4 Inhibitors observed glycaemic control with weight loss or no weight change and controlled hypoglycaemic risk.[19]

The initiation and conducting the study to compare the safety ,efficacy and tolerability of vildagliptin with metformin combination therapy that provides superior glycaemic control to individual monotherapy in naive patients with Type2 DM. Study conducted on the patients who Fail to optimise controlled sugar level from randomised controlled trial was Conducted to the 4 groups of drug naive patients i.e., vildagliptin with high Dose Metformin, Vildagliptin with low dose Metformin monotherapy of Metformin,vildagliptin respectively. Superior glycaemic control means hba1c -1.8%, was observed in vildagliptin with high dose Metformin combination therapy with Lower or no incidence of weight gain and hypoglycaemia.[20]

The effectiveness of initial combination therapy with linagliptin plus metformin versus linagliptin or metformin monotherapy in patients with type 2 diabetes. Patients are selected who are not under controlled blood sugar level or no improve in hba1c from level. Superior results in controlling hba1c from baseline -1.7% was observed in linagliptin and high dose Metformin combination with Safety, tolerability of no weight gain and Lower risk of hypoglycaemia. Initial combination with Linagliptin and Metformin was superior to monotherapy.[21]

The study provides the efficacy and safety of the dipeptidyl peptidase-4 inhibitor alogliptin plus metformin (A + M) initial therapy versus either as monotherapy in drug-naïve T2DM. Type 2 Diabetes drug naive patients given with Alogliptin low dose, high dose Metformin combination therapy, Monotherapies DPP4 inhibitorAlogiptin, Metformin respectively. Results are observed among drug naive group.Alogliptin plus metformin initial combination therapy are well tolerated and efficacious in controlling glycaemia in drug naive T2DM patients than either as monotherapy.[22]

To assess the efficacy and safety profile of saxagliptin plus metformin pharmacotherapy-naive Chinese patients with type 2 diabetes mellitus. patients who are not under control to maintain glycaemic levels in monotherapy are taken into the study and divided into three groups saxagliptin with Metformin combination therapy, saxagliptin with placebo, metformin with placebo. Mean reduction in HbA1c was greater with saxagliptin plus metformin -3.0% than with saxagliptin plus placebo or metformin plus placebo. Recused fasting plasma glucose, postprandialglucose levels are observed in patients who achieved therapeutic glycaemic response, with saxagliptin plus metformin than with either of the monotherapy.[23]

The treatment with the initial combination of DPP4 and metformin was provided the substantial and additive glycemic improvement. Diet and exercise were generally well tolerated in patients with type 2 diabetes. Patients received counselling on diet and exercise consistent with American diabetes association recommendations throughout the study. Sitagliptin and metformin have different mechanisms that can predict possible additional hypoglycemic effects. In addition, a recently completed study showed that sitagliptin and metformin increased active GLP-1 levels in healthy subjects after fasting and after meals. Subjects and combinations additionally increase the level of active GLP-1. [24]

A 54-week study of patients with type 2 diabetes and also inadequatelyglycemic control on diet and exercise, the combination therapy of dpp4 and metformin provided the substantial and durable glycemic control, improved markers of beta cell function and was generally well tolerated. It is also concluded or showed that the complementary mechanism of action of sitagliptin and Metformin, which together target 3 core pathophysiologic defects of type 2 diabetes; declining beta cell function, increased insulin resistance and excess Hepatic glucose output. Data on clinical and laboratory side effects, physical examinations, vital signs, and electrocardiogram (ECG) were collected throughout the study. Researchers rate clinical side effects based on the intensity of the side effects and their association with the study drug. Laboratory tests include whole blood biochemical tests, hematology and urinalysis. The clinical side effects of interest are hypoglycemia and Certain adverse events in the gastrointestinal tract (abdominal pain, nausea, vomiting and diarrhea). [25]

Teneligliptin add on to metformin during early course of treatment would be a multi model approach in treatment of diabetic patients. The efficacy of the combination therapy of teneligliptin and metformin was assessed by paired t test which was performed after completion of 12 weeks of

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therapy. It was observed that when compared to metformin monotherapy there was significant decrease in fast blood glucose levels after addition of teneligliptin. In this study, Inclusion criteria: patients receiving metformin monotherapy of 7.0% to 9.0% of glycated hemoglobin (HbA1c), and the age group was men and women between 20 and 60 years old. Exclusion criteria: type 1 diabetes, kidney disease, previous heart disease or liver and patients. Targets various OHAs, such as α-glucosidase inhibitors, sulfonylureas, SGLT-2 inhibitors and insulin.[26]

The systematic review and mixed treatment comparison of dpp4 inhibitors, either as monotherapy or as twin medical aid, showed that dpp4 inhibitors have similar effectualness in terms of mean reduction in hemoprotein A1c from baseline, exaggerated proportion of patients achieving HbA1c <7%, mean amendment in weight from baseline and range of patients experiencing symptom event. In this the design shows A systematic review of randomized controlled trials (RCT), health economic evaluation studies, systematic reviews, and meta-analysis, followed by a mixed Bayesian meta-analysis of primary care comparison and the use of randomized methods. The results of the effects model are expressed as a weighted average deviation from the baseline or odds ratio (OR) with a 95% confidence interval.[27]

Recent advances in pharmacotherapy permit physicians to target aldohexose excursions and variability. Daily assessment of glycaemic standing, together with measures of FPG and postprandial glucose, is also a a lot of reliable indicator of blood sugar control and also the long-run risk of complications than measuresof HbA1c levels alone.1 management of FPG levels was shown to benecessary however meagre for reaching HbA1c levels of lessthan 7%; decreases in postprandial aldohexose levels allowednearly double the share of patients to succeed in the HbA1cof drugswith complementary mechanisms of action that target FPG and postprandial aldohexose to scale back to scale back earlier intervention could limit cardiovascular risk. This informationsupports the necessity for earlier andmore aggressive treatment regimens. supported action of incretin hormones, DPP-4 inhibitorsdemonstrate a coffee propensity for symptom and act in an exceedinglyweight-neutral manner, creating them engaging candidatesfor combination medical aid. Prolonged incretin actions throughthe use of DPP-4 inhibitors play a clinically vital role inthe treatment of type two polygenic disorder by up postprandial, FPG, and, ultimately, HbA1c levels. The complementarymechanism of action of DPP-4 inhibitors with alternative oral antidiabetic medicine affords clinicians an efficient and tolerable drugchoice once victimisation combination regimens for management ofhyperglycaemia in patients with sort two polygenic disorder. [28]

Numerous clinical trials have incontestable that DPP-4 inhibitors give effective and consistent glycemic management with a good tolerability profile, together with no severe symptom and weigh. though totally different DPP-4 inhibitors area unit distinctive in their metabolic properties, excretion, recommended indefinite quantity, and daily indefinite quantity, and head-to-head clinical trials scrutiny the varied DPP-4 inhibitors are scarce, the obtainable knowledge relating to indirect comparisons suggest that every one obtainable DPP-4 inhibitors have nearly the same effectiveness and safety profile. Thus, we have a tendency to might expect a similar effectiveness and safety with the novel DPP-4 matter, teneligliptin, though this drug needs careful long-run post marketing police investigation and extra clinical trials to evaluate its effectiveness and safety yet on gain further indications for its clinical use.[29]

This meta-analysis incontestable that saxagliptin and antidiabetic combination medical care improves aldohexose management in patients with sort a pair of polygenic disease compared with antidiabetic monotherapy. Combination medical care has larger reduction in HbA1c and FPG than antidiabetic monotherapy, and doesn't increase the incidence of assorted adverse reactions. Saxagliptin, a selective DPP-4 inhibitor, is suggested as associate adjuvant therapy to attain ideal aldohexose targets in patients with sort a pair of polygenic disease. It's incontestable that saxagliptin is weight neutrality and low risk forhypoglycemia once used as monotherapy. Saxagliptin and antidiabetic drug combination therapy provides a complementary mechanism of action. this mix medical aid provides further decrease in HbA1c from baseline, and permit a lot of patients to attain HbA1c goal than the individual part. In addition, saxagliptin most likely be appropriate for subjects with sort a pair of polygenic disease UN agency cannot take antidiabetic drug, and scale back scale back risk, particularly for patients with heart

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disease.Saxagliptin combined with antidiabetic drug are often effective in rising glycemic management in patients with kind a pair of polygenic disorder and remittent incidence of symptom. a lot of high-quality RCTs square measure demanded to guage and effectiveness of saxagliptin combination with antidiabetic drug in future.[30]

Sitagliptin a hundred mg was well tolerated in this test. No clinically meaningful variations within the overall incidence of clinical adverse experiences, clinical adverse experiences resulting in discontinuation, serious clinical adverse experiences, or laboratory adverse experiences were ascertained within the sitagliptin cluster compared with the placebo cluster. The addition of sitagliptin to current medical aid didn't cause a rise in the incidence of epithelial duct aspect effects, that square measure generally associated with Glucophage treatment alone. Sitagliptin treatment was related to a awfully low incidence of hypoglycemia adverse experiences, with a rate kind of like that seen within the placebo cluster. moreover, none of the hypoglycemia episodes exhibited marked severity. Treatment with sitagliptin LED to a little, however statistically significant, mean decrease from baseline in weight, with no important in weight amendment compared with placebo. Sitagliptin treatment additionally LED to slight, statistically important in lipid parameters. No clinically meaningful variations were ascertained in the sitagliptin cluster compared with placebo with relevance mean changes in serum chemistry and hematology analytes,and there have been no clinically significant changes in very important signs or ECGs with sitagliptin treatment in patients with sort a pair of diabetes WHO had inadequate glycemic control with antidiabetic alone, the addition of sitagliptin a hundred mg once-daily was well tolerated and provided effective and sustained improvement in A1C, FPG, and 2-h post meal aldohexose, yet as significant enhancements in indexes of hormone secretion and -cell operate, including HOMA- and therefore the and therefore the magnitude relation. Treatment with sitagliptin was related to an occasional rate of hypoglycemia that was just like that seen with placebo, yet as a neutral result on body weight.[31]

Teneligliptin in management of type 2 diabetes mellitus short term studies (12 week's) and long term studies (52 week's) reported that reduction of both blood glucose levels and HbA1c was observed by giving teneligliptin therapy. Reduction of HbA1c was around 0.8%- 0.9% in 12 weeks. Teneligliptin has few tolerable adverse effects and weight neutral and dose adjustment is not required to both renal and hepatic impairment patients. It is useful in monotherapy and in combination with other antidiabetic drugs. This drug is recently approved, and therefore, long-term safety studies including cardiovascular safety studies are still awaited and required. However, current data of teneligliptin do not point any signal for serious adverse effect.[32]

Combination treatment in the management of type 2 diabetes: focus on vildagliptin and metformin as a single tablet concluded that the combination of vildagliptin and metformin shows some favorable effects on pancreatic alpha and beta cells. This combination therapy reaches their glycemic targets when compared to metformin monotherapy without weight gain. The availability of vildagliptin and metformin in a single table further enhance convenience and likely adherence to treatment. Metformin is therefore recommended by all guidelines as fi rst-line therapy for T2DM. The International Diabetes Federation (IDF) suggests to use metformin in all cases inadequately controlled by non-pharmacological treatments (IDF, on line) while a recent consensus document of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) recommends to prescribe metformin at diagnosis, together with lifestyle interventions (Nathan et al 2006, 2008).Upon progression of the disease, progressive loss of β-cell function and mass makes it difficult for patients to maintain glycemic control with monotherapy. As a result, combination therapy involving agents with complementary mechanism of action is the next logical step in the management of T2DM. Established treatment options for metformin monotherapy failure include the addition of sulfonylureas (or glinides), thiazolidinediones, acarbose, or insulin.[33]

Double-blind, randomized clinical trial assessing the efficacy and safety of early initiation of sitagliptin during metformin up titration in the treatment of patients with type 2 diabetes: The study suggest that early initiation of sitagliptin with metformin in patients with type 2 DM can decrease the glycemic levels and there were no changes in BP, heart rate and body weight. Early initiation of sitagliptin may be safe and effective in type 2 DM.Speed HbA1c goal attainment for many patients who are unlikely to achieve target glycemic control through metformin does up titrationalone. Dipeptidyl peptidase-4 (DPP-4)

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inhibitors block DPP-4-mediated degradation of the incretin hormones glucagon-like peptide-1 and glucose-dependent insulinotropic peptide, thereby promoting glucose-dependent insulin secretion and improved glucose control. Sitagliptin is among the DPP-4 inhibitors approved for the treatment of T2DM as monotherapy and in combination with other AHAs.4 When used in combination with metformin, sitagliptin provides clinically meaningful improvement in glycemic control and is generally well tolerated, without body weight gain or increased incidence of hypoglycemia however, these studies have evaluated sitagliptin as add-on therapy to patients on stable doses of metformin, or as initial co-administration with metformin.[34]

Sitagliptin with metformin is associated with lower likelihood of disease progression in newly treated people with type 2 diabetes: a cohort study concluded that In conclusion, that initiating metformin therapy with a DPP-4 inhibitor provides better glycemic control and delays the need for exogenous insulin in people with metformin may therefore lower the likelihood of disease progression compared with adding sitagliptin later in therapy.Dpp-4 inhibitors protect incretin hormones from degradation and improve pancreatic islet disfunction. Metformin users, we found that treatment with sitagliptin was associated with fewer insulin starts and a greater degree of HbA1c reduction compared to later sitagliptin use. These observations suggest that sitagliptin with metformin delays the progression of type 2 diabetes. Much like early initiation of insulin therapy, sitagliptin with metformin may change the natural history of the disease, which could ultimately lead to fewer medications and a lower risk of complications.[35]

Effect of Initial Combination Therapy with Sitagliptin, a Dipeptidyl Peptidase-4 Inhibitor, and Metformin on Glycemic Control in Patients with Type 2 Diabetes. Initial combination therapy with sitagliptin and metformin provided substantial and additive glycemic improvement in these patients with type 2 diabetes, suggesting that the marked benefit of this combination is the product of the complementary actions of these two agents. This combination was also generally well tolerated, with a tolerability pro-file similar to metformin alone.[36]

Saxagliptin given in combination with metformin as initial therapy improves glycemic control in patients with type 2 diabetes compared with either monotherapy in a randomized controlled trial. Initial combination therapy with saxagliptin and metformin provided added efficacy without additional tolerability issues. Combination therapy is often associated with an increased risk for hypoglycemia, particularly combinations that use sulphonylureas or insulin. Hypoglycemic events with saxagliptin þ metformin combination therapy was similar to monotherapy, even with significantly greater glycaemic efficacy achieved with combination therapy. Although weight gain has been observed with intensive glycaemic control, similar degrees of weight loss were observed in both combination treatment and monotherapy groups. Failure to achieve and maintain adequate glycaemic control is due to the progressive nature of T2DM and limitations of current therapies. Achieving specific glycaemic goals can substantially reduce morbidity, making effective treatment of hyperglycaemia a top priority, particularly for individuals with a high HbA1c. By using agents that differ in their MOA and side-effect profiles, combination regimens can begin to address the numerous pathophysiological abnormalities that characterize T2DM.Initial combination therapy with saxagliptin and metformin represents such an option for the management of patients with T2DM. [37]

III. CONCLUSION:

Metformin primarily improves insulin resistance and DPP-4 inhibitors improve pancreatic islet function by maintaining endogenous GLP-1 bioactivity. In addition, metformin increases the plasma levels of GLP-1 and upregulates the expression of the GLP-1 receptor in pancreatic β-cells and DPP-4 inhibitors could improve insulin resistance. Therefore, taking these two types of hypoglycemic drugs at the same time can produce additional or even synergistic effects on the treatment of T2DM. In fact, clinical studies have shown the best efficacy and safety of this concomitant treatment, indicating that the combination therapy of DPP-4 inhibitors and metformin is a promising strategy for the treatment of T2DM. Hence Combination of Metformin and DPP-4 inhibitors produce better results in controlling of T2DM when compared with the Metformin monotherapy.

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