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COMBINATION THERAPY IN DIABETES TYPE 2 MANAGEMENT

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INTRODUCTION

Diabetes Type 2 (D T2) is a disorder of metabolism that occurs when the body cannot use insulin effectively (insulin resistance), a condition that may progress to include inadequate insulin levels. Faulty glucagon function also plays a key role in causing the high blood sugar (hyperglycemia) seen in this disease" **(Barnard,K. *et al*., 2010).** In the same hyperinsulinemia is associated with type 2 diabetes mellitus also **(**Shahad, W. A. and Shatha, H. A.,2024). diabetes mellitus Type 2 characterized by hyperglycemia, because of the increased resistance of insulin in the hepatic/peripheral tissues and dysfunction of pancreatic B-cell **(Kader, S.,2009).** The global incidence of diabetes Type 2 (D T2) appear to rising in an alarming phase. This condition is a significant risk factor, multiplying the likelihood of cardiovascular disease by two to four times. Furthermore, T2D involves a spectrum of complications, from acute crises like hyperglycemia and ketoacidosis to chronic microvascular issues affecting the retina, kidneys, and nerves (retinopathy, nephropathy, and neuropathy) **(Barnard,K. *et al*., 2010).** Marked depletion in plasma and erythrocyte magnesium levels was evident in diabetic patients with advanced retinopathy with poor diabetic control The research results show that direct measurement of intracellular magnesium by using erythrocytes has suggested a sensitive indicator for the estimation of body magnesium store. **(**Kazaal, F.A. and Abdulaziz, L. S., 2011). Composition and duration of glucose-lowering drugs differ across multiple guidelines recommended in various countries. In most guidelines Metformin is considered drug of choice and recommended as the first-line therapy. However, it should not be regarded as the only recommendation in the initial treatment of newly diagnosed T2D. Many patients will have contraindication or show some intolerance with metformin therapy. Moreover, a large proportion of patients will remain pharmacologically naïve or on monotherapy during the entire treatment course in practice, even if a more aggressive approach is needed **(Barnard,K. *et al*., 2010).** Current therapeutic options are often limited by side effects and variable efficacy, highlighting the need for more effective and safer treatments **(Hameed**,R.M. and Mahmood, A.K. (2024). Therefore, there is a need to provide a practical combination therapy algorithm for patients with T2D who need treatment intensification.

The main anti-diabetic drugs can be grouped into different classes that act mainly by targeting the different underlying pathophysiological factors of T2D. As an initial step for the treatment of T2D, metformin, a biguanide, targeting mainly insulin resistance, is the drug of choice **(Levin, A.P.,2016).**

Rationale for T2D with Combination Therapy

Pharmacological intervention for Type 2 diabetes mellitus target is controlling hyperglycemia to prevent the complications of the disease. Patients with diabetes Type 2 present shows both insulin deficiency and insulin resistance. The former, in general, can manifest as postprandial hyperglycemia and the latter as fasting hyperglycemia, A definitive association has not been established. The emerging data that show high failure rate with long-term monotherapy and establish a prominence mealtime glycaemia and the role of postprandial glucose excursions of the emergence with progression of vascular complications. Conquer monotherapy failures and treat the different underlying defects of diabetes Type 2 pathology, oral antidiabetic combination therapy with complementary modes of action should be considered **(** Van Gaal, L.F. and De

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Leeuw, I.H., 2003). Although the management of the condition remains somewhat elusive, particularly in achieving and maintaining adequate glycemia, there has simultaneously been much advancement of knowledge regarding the pathophysiology of type 2 diabetes. Recognition of this multifactorial complexity has led to suggestions for treatment intensification that consider the individual affected by the condition. Along with newer agents that target different aspects of the disease process, the availability of combination therapies to target complementary aspects of pathophysiology may also improve management of diabetes treatment **(Levin,A.P., 2016).** A growing number of studies have elicited that, in comparison with monotherapy, combination therapy clinically provides significant benefits while controlling blood glucose, blood pressure, weight, as well as mitigating damage from certain complications and delaying progression in diabetes, including both type 1 diabetes (T1D), type 2 diabetes (T2D) and related complications. This proof tool up strong support for the recommendation of combination therapy for diabetes and the importance of treatment combinations. Generally, combined agents play an essential role in diabetes management. The validation of using multiple drugs enables more comprehensive and mora effective in controlling blood glucose without increasing the hypoglycemia risk or other serious adverse effects. So, specific treatment regimens may designed for patients individually which are implemented by supervision of healthcare professionals **(Xueqin, X. *et al*,2023).**

3. Common Combination in Medications Therapy:

Any one of the of pharmacotherapy classes may rationally combined with any other, With exceptions of combining glinides with sulfonylureas, that may be act by essentially identical methods, for these results the combination would not be rational. So, using two agents from the incretin class is not complementary. These exceptions, agents from any other classes may be combined successfully **(Kuritzky, L. and Samraj, P.G., 2011).**

3.1. Metformin

Lifestyle modification and metformin as monotherapy are recommended in treatment by first-line therapy of diabetes type 2. With the progression of diabetes type 2, failure of therapy is determined, making combination therapy necessary. Adding repaglinide to metformin addresses mealtime glucose variations while metformin works as stabilizer for basal glucose. These medications together provide sustained glycemic control in comparison with monotherapy. Data collecting from multiple studies elicits that combination therapy of repaglinide/metformin is more powerful and more tolerated compare with others technique , with less side effects and better glucose control. Diabetes complexity with elevated complexity of treatment choices, making the importance for need to an effective yet simpler therapy. Repaglinide/metformin combination therapy shows to be a valuable choice for type 2 diabetics considering improve glucose control if currently monotherapy currently is inadequately controlled **(Richard. and Raskin, P., 2011).**

Despite the wide array of oral medications for type 2 diabetes, achieving adequate glycemic control remains a challenge for nearly half of all patients. To help more individuals reach their treatment goals, effective and well-tolerated combination therapies have proven superior to maximizing the dose of a single agent. The combination of sitagliptin and metformin is a prime example, with clinical trials demonstrating HbA1c reductions between 0.5% and 2.1%. Significantly more patients achieve an HbA1c level below 7% with this pairing compared to metformin monotherapy, and the risk of hypoglycemia remains comparably low at 1-5%. This combination may also positively influence beta-cell function. Although injectable agents like exenatide or liraglutide offer greater glucose-lowering and weight loss effects, many patients prefer the convenience of an oral pill. Ultimately, sitagliptin and metformin provide a complementary, well-tolerated glucose-lowering effect, making them a valuable therapeutic choice **(Barnard,K. *et al*., 2010).**

3.2. Sulfonylureas

Sulfonylureas (SUs) have been a cornerstone in the control of diabetes Type 2 mellitus (DM T2) for the past 60 years. Other classes of drugs have been synthesized for the treatment of diabetes during this time. However, there is a need for logical analysis of refinements and combinations of old drugs which have stood the test of time. Sulfonylureas are also referred to as β-cell insulin

secretagogues, insulin secretagogues, and insulinotropic agents act primarily by stimulating the pancreatic β-cells to secrete insulin.

The sulfonylureas bind with the sulfonylurea receptors (SURs) in the pancreatic β-cell membrane causing the blockade of the adenosine triphosphate (ATP)-sensitive potassium channels (K+ SUR) 1.2 (KATP channels) leading to depolarization action of the β-cell membrane with consequent opening of voltage gated calcium channels, thus facilitating a massive influx of Ca2+ into the β-cells which causes exocytosis of preformed granules of insulin. Na+/Ca2+ and Ca++ pumps regulate the influx and efflux of calcium from the cell **(Kalra,S. *et al*., 2018).**

3.3. DPP-4 Inhibitors

Glucose-dependent insulin secretion impairment plays important role in the pathogenesis of diabetes mellitus type 2 (D T2). Incretins, hormones that are released by gut endocrine cells in response to a meal, exert valuable functions in glucose metabolism, including stimulation of insulin secretion from the pancreas, inhibition of glucagon release, and regulation of gastric motility. In humans, 90% of incretin hormone secretion is attributed to the glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP). Dipeptidyl peptidase-4 (DPP-4) inhibitors, the most researched class of incretin-based therapies, have shown effectiveness and safety in managing T2D **(Gomez-Peralta,F. *et al*., 2018).** The inhibitors' role of Dipeptidyl-peptidase IV (DPP-4 inhibit the incretins degradation, (GLP-1) and (GIP) **(Nancy,T. A. and Baptist, G., 2009).** Although benefits in reducing glycemic variability and lowering the risk of hypoglycemia and excessive weight gain have been postulated, limitations remain in terms of actual usage of these drugs in real-world settings **(Gomez-Peralta, F. *et al*., 2018).**

DPP-4 inhibitors were the pioneering class of incretin-based therapies approved for managing Type 2 Diabetes, demonstrating a good long-term safety record and efficacy in lowering HbA1c by 0.7% to 1.5%. A key therapeutic strategy involves combining these agents with metformin, a biguanide with its own established long-term safety and beneficial effects on weight and cardiovascular risk. Notably, a fixed-dose combination of both sitagliptin (a DPP-4 inhibitor) with metformin does not increase the rate of gastrointestinal side effects compared to using either drug alone. Dose adjustments for the combination product are similar to metformin monotherapy and are required less frequently than for sitagliptin monotherapy, making it a well-tolerated and effective option (**Barnard,K. *et al*., 2010).**

3.4. GLP-1 Receptor Agonists

With five agents to choose from in the United States and six in Europe, there are several factors to consider when selecting a specific GLP-1 receptor agonist. None of the agents are available generically, all have a relatively high cost **(Prasad-Reddy,L. and Isaacs, D.,2015).**

GLP-1 agonists (also known as GLP-1 receptor agonists, incretin mimetics, or GLP-1 analogs) represent a class of medications used to treat T2DM and, in some cases, obesity. Examples of drugs in this class include Exenatide, Liraglutide, Dulaglutide, and Semaglutide. According to the American Diabetes Association (ADA), metformin remains the preferred first-line therapy for treating T2DM. However, the addition of a GLP-1 analog should be considered in patients with a contraindication or intolerance to metformin, in patients with a hemoglobin A1c greater than 1.5% over target, or in patients who do not reach their target A1c in 3 months, particularly in patients with atherosclerosis, heart failure, or chronic kidney disease.(**Hunt, B. *et al* ,2019), (Burcelin, R. and Gourd,y P. ,2017), (Gourgari, E. *et al* ,2017),(American Diabetes Association, 2019).** Important differences between agents include dosing frequency and whether they have stronger effects on postprandial or fasting blood glucose. The longer-acting formulations, including exenatide weekly, dulaglutide, albiglutide, and liraglutide, have demonstrated greater effects on fasting blood glucose, while the shorter-acting agents, such as exenatide twice daily and lixisenatide, have a greater impact on postprandial glucose lowering. Other considerations are adverse effects. For example, albiglutide demonstrated less of an effect on hemoglobin A1C reduction compared to liraglutide but also had less incidence of adverse effects (**Prasad-Reddy, L. and Isaacs, D., 2015).**

3.5. SGLT-2 Inhibitors

Glucose homeostasis is maintained through multitiered physiological mechanisms. Hormones like insulin and glucagon play major roles at the center of metabolic control. In addition,

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distribution of glucose transporters on the cell surfaces adjusts the utilization of glucose in tissues, which is primarily influenced by insulin. SGLT-2 inhibitors act in the proximal renal tubule where they inhibit reabsorption of filtered glucose and lower plasma glucose concentration via glucosuria, thus reducing blood glucose independent of insulin (**Kalra,S. *et al.*, 2018).**

4. Benefits of Combination Therapy

The development and broad accessibility of many new drugs for type 2 diabetes (T2D) in recent decades have still left a large percentage of patients with their condition inadequately managed **(Barnard,K. *et al.*, 2010)**. Thus, treatment for T2D must remain on the agenda of healthcare professionals. Continued rise in T2D prevalence is not a situation that should be accepted as inevitable, but is one that, through appropriate innovation and application of existing knowledge, should be tackled. Current understanding of T2D pathogenesis, the marketing of new therapies and recognition of the benefits of combination therapy may lead to reinvigorated attempts to better manage this disease. The multiplicity of therapeutic options available for T2D provides clinicians with the means to reassess and readjust treatment as the disease progresses over time **(Levin, A.P., 2016).** Figure 1. Showing Suggestions for initial combination therapy.

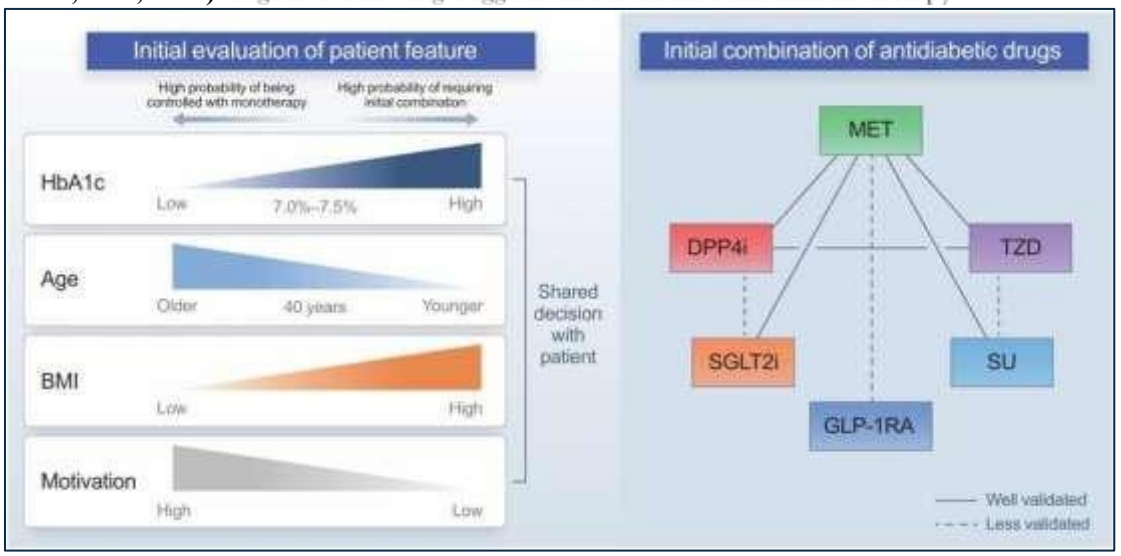

Figure 1. Initial combination therapy. HbA1c, glycated hemoglobin; BMI, body mass index; MET, metformin; DPP4i, dipepti dylpeptidase-4 inhibitor; TZD, thiazolidinedione; SGLT2i, sodium-glucose cotransporter 2 inhibitor; SU, sulfonylurea; GLP-1RA, glucagon like peptide 1 receptor agonist. (Ji Yoon, K. and Nam Hoon, K., 2024).

5. Improved Glycemic Control

All combination treatment strategies consistently lead to improved HbA1c control in both clinical trials and general patient populations. This finding is further supported by insurance claims databases, which confirm the benefits of combining drugs that target different mechanisms—an insight that can guide decision-making in everyday practice. A drawback of using insurance data is the limited information on patient adherence and dosing. Nevertheless, it is evident that a variety of distinctly effective combination therapies are available. Given that patients with type 2 diabetes face a remarkably high rate of cardiovascular events, the recent release of guidelines on using these combinations is particularly timely(Barnard,K. *et al.*, 2010). Under glycemic control is considered a factor that accelerates diabetic complications. The conclusion of study performed by(Mustafa, B.I.,1996),showed that hyperlipidemia accompanying in alloxan induced hyperglycemia, in part a possible factor in the pathogenesis of diabetic nephropathy ,also another study performed by (Ekklass H. A. and Kahtan, A. A.,2003) showed decreasing in serum glucose level and cholesterol in the same treated rabbits diabetic group after oral administration of aqueous extract of Nigella Sativa seeds for five weeks .Combination therapies utilizing pharmacotherapy with distinct mechanisms of action or vials offering dosing convenience present timely opportunities toward improved management of glucose-based cardiovascular risk. There are localized treatment and logistical concerns that need to be addressed to bring the additional potential of combination therapy to all patients. Although

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combinations of pharmacotherapy targeting different mechanisms of action offer the opportunity for significant adjunct benefits in HbA1c control and patient tolerability, advantages and limitations are each still determined by the characteristics of the individual biologic agents. Combination therapies are more complicated to dose versus monotherapies, especially with combination vials or insurance restrictions on single use prefilled pens **(Kuritzky,L. and Samraj,P.G., 2011).**

6.Weight Management

In individuals with T2D who have obesity or overweight, modest and sustained weight reduction results in improvement in glycemic control and decreased utilization of glucose-lowering medication. A total weight loss of 5% or higher reduces HbA1c levels and contributes to mitigating risk factors of cardiovascular disease, such as hyperlipidemia and hypertension, as well as other disease-related complications of obesity. Progressive improvements in glycemic control and cardiometabolic risk factors can occur when the total weight loss increases to 10% or more. In the approach to treating patients with T2D and obesity, prioritizing weight management and the use of therapeutics that offer glycemic control as well as the additional weight loss should be emphasized given their potential to attenuate the progression and severity of T2D **(Garvey, W.T. *et al*, 2022).** New research finds a combination of drugs improves weight loss, glucose control and insulin resistance better than either drug alone **(Larsen,A. T *et al*, 2024)**. The U.S. Food and Drug Administration (FDA) has approved several medications for weight management as adjuncts to reduced calorie diet and increased physical activity in individuals with a BMI ≥30 kg/m2 or ≥27 kg/m2 with one or more obesity-associated comorbid conditions (e.g., type 2 diabetes, hypertension, and/or dyslipidemia). Nearly all FDA-approved obesity medications have been shown to improve glycemia in people with type 2 diabetes and delay progression to type 2 diabetes in at-risk individuals **(Kahan, S. and Fujioka, K., 2017)**, and some of these agents (e.g., liraglutide and semaglutide) have an indication for glucose lowering as well as weight management **(Drugs.com,2023).**

7.Cardiovascular Benefits:

Type 2 diabetes mellitus is associated with a 2-4 times increased risk of cardiovascular (CV) disease. Glucagon-like polypeptide-1 receptor agonists (GLP1RA) and sodium-glucose cotransporter-2 inhibitors (SGLT2i) are two important classes of drugs with CV benefits independent of their antihyperglycemic efficacy. The CV outcome trials of both GLP1RA and SGLT2i have demonstrated CV superiority/neutrality concerning major adverse CV events (MACE). While GLP1RAs have exhibited a significant reduction in ischemic stroke and myocardial infarction (MI), SGLT2i have demonstrated a uniformly significant reduction in hospitalization for heart failure (HF) as a class effect. The unique clinical benefits and the distinct but complementary mechanisms of action make the combination of these drugs a mechanistically sound one. Recent meta-analyses suggest an independent and additive benefit of combination therapy of GLP1RA/SGLT2i vs monotherapy **(Vanishri, G. *et al* ,2025). (Zhu, J.J.,*et al*, 2024),** in a recent issue of the World Journal of Diabetes, demonstrates a numerically lower hazard ratio (HR) for CV outcomes with combination therapy vs monotherapy with either agent, with a reduction in MACE compared to GLP1RA alone [HR = 0.51, 95% confidence interval (CI): 0.16-1.65], or SGLT2i alone (HR = 0.48, 95%CI: 0.15-1.54). The CV death rate was also lower with combination therapy compared to GLP1RA alone (HR = 0.58, 95%CI: 0.08-3.39), or SGLT2i alone (HR = 0.55, 95%CI: 0.07-3.25). Fatal and non-fatal MI and fatal and non-fatal stroke were reduced with combination therapy compared to GLP1RA alone (HR = 0.45, 95%CI: 0.10-2.18 and HR = 0.86, 95%CI: 0.12-6.23, respectively), or SGLT2i alone (HR = 0.44, 95%CI: 0.09-2.10 and HR = 0.74, 95%CI: 0.10-5.47, respectively). Hospitalization for HF was prevented with combination therapy compared to GLP1RA alone (HR = 0.26, 95%CI: 0.03-1.88), or SGLT2i alone (HR = 0.33, 95%CI: 0.04-2.53). They also demonstrated that GLP1RA or SGLT2i monotherapy may not provide significant improvement in CV death and recurrent MI in patients with prior MI or HF, proposing a role for combination therapy in this subgroup. Appropriate patient selection is vital to optimize CV risk reduction as well as the cost-effectiveness of this combination therapy. Also, herbal extracts as add on therapy may show some cardiovascular benefits, according to study performed by **(Ghudhaib, K. K., 2014)** to estimate the effect of the

hydro-ethanolic catechin extract toward blood glucose, lipid profile and liver functions in alloxan diabetic mice. The study showed that hydro-ethanolic catechin extract may showed cardiovascular benefits in diabetics. Further studies focus on antidiabetic herbals extraction and add on therapy may be needed. Another study performed by **(Areej B. A. and Abbas, D.A., 2018)** showed that glimepiride and bromocriptine combination may provide improvement in some of lipid profile parameters in alloxan-induced diabetic rabbits.

CONCLUSION

Diabetes mellitus (DM) is one of the major chronic diseases affecting millions of people. Patients with type 2 diabetes (T2D) play an important role in diabetes control and significantly help to prevent the development of diabetes complications.

Over the past five decades, rapid advancements in understanding the essential metabolic and physiological pathways involved in diabetes etiology have led to the development of many diverse classes of anti-diabetic medications to target these mechanisms. These classes of drugs have very different mechanisms of action, and relative advantages or disadvantages for glycemic control, prevention of complications (In this review, the authors briefly summarize the types of oral combination therapies currently available for T2D, focusing on clinical indications, advantages, and disadvantages of those combinations; demonstrate clinical evidence supporting their effectiveness based on recently published head-to-head comparisons of combination regimens; and discuss practical approaches for effectively using newer combinations in the management of T2D.ncluding weight gain).

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