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EVOLVING TREATMENTS IN TYPE 2 DIABETES: A FOCUS ON METFORMIN, TIRZEPATIDE, AND SEMAGLUTIDE

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ABSTRACT

Type 2 diabetes (T2D) remains a major global health challenge, driven by insulin resistance, β-cell dysfunction, and associated comorbidities such as cardiovascular disease and chronic kidney disease. Metformin remains the cornerstone treatment because of its cardiovascular advantages, safety, and effectiveness, despite its limits in advanced disease and renal impairment. Recent developments in medicine have brought incretin-based medications, such as semaglutide, a long-acting GLP-1 receptor agonist, and tirzepatide, a dual GIP/GLP-1 receptor agonist. In comparison to selective GLP-1 agonists, tirzepatide exhibits better glycemic control, weight loss, and β-cell preservation; nonetheless, there are issues with gastrointestinal tolerability. Semaglutide, which comes in injectable and oral forms, has demonstrated improvements in heart failure with retained ejection fraction and obesity, as well as a notable decrease in cardiovascular risk. The backbone and incretin-based drugs as supplements, providing complementary enhancements in weight control, glycemic control, and long-term results. In order to maximize patient-centered care, this study emphasizes the

integration of metformin, tirzepatide, and semaglutide into clinical practice, highlighting changing treatment paradigms in type 2 diabetes.

KEYWORDS: Type 2 diabetes (T2D), Insulin resistance, Metformin, Incretin-based medications, Semaglutide, Tirzepatide, cardiovascular risk,

INTRODUCTION

Insulin resistance, a relative lack of insulin, and elevated blood sugar are the hallmarks of type 2 diabetes (T2D), formerly known as adult-onset diabetes.[1] Increased thirst, frequent urination, exhaustion, and inexplicable weight loss are typical symptoms.[2] Increased appetite, a pins-and-needles feeling, and slowly healing sores are other symptoms.[3] Type 2 diabetes (T2D) is a chronic metabolic disorder characterised by insulin resistance and impaired insulin secretion, leading to elevated blood glucose levels. The WHO estimates that over 422 million persons worldwide had diabetes in 2014, indicating that the prevalence of type 2 diabetes has increased to concerning levels. According to the International Diabetes Federation (IDF), 537 million persons worldwide had diabetes in 2021, a considerable increase over a six-year span.[4] In order to maximize patient outcomes and improve quality of life, this review highlights the significance of a multimodal strategy that incorporates pharmacotherapy, nanotechnologies, regenerative therapies, and lifestyle modifications. It focuses on recent developments in the treatment of type 2 diabetes. The authors' review ends with a discussion of the difficulties we currently face in treating and managing type 2 diabetes, possible future paths, and the necessity of enhancing long-term management techniques for those who have the disease.[5]

Metformin's Foundational Role

Metformin is the most widely prescribed drug for the treatment of type 2 diabetes (T2D) and is considered an “essential medicine” by the World Health Organization.[6] Several studies have shown that metformin effectively improves glycemic control in patients with T2D, yet it rarely causes hypoglycemia due to its remarkable safety profile Hepatic gluconeogenesis suppression is the main cause of metformin's antidiabetic impact, while its exact mode of action is still up for discussion. In this review, we will go over the suggested mechanisms of action of metformin in light of the most recent research to date as well as early studies conducted in individuals with type 2 diabetes that stretch back several decades.

We start with a succinct section titled "Historical Overview" that provides an overview of the events leading up to the initial discovery of metformin and its extensive therapeutic use. Next, we go into early research on T2D patients ("Insights From Metformin's Effects on Glucose Metabolism in Patients With Type 2 Diabetes"), which shed important light on how metformin works in people.[7]

2.1 Mechanisms of Action and Glycemic Control

Type 2 diabetes (T2D) and hyperglycaemia are related to the presence of oxidative stress, caused by increased production of reactive oxygen species (ROS), among other factors.[8][9] High glucose levels increase the generation of ROS in the mitochondria, which causes oxidative stress, lipid peroxidation, and tissue damage. Furthermore, insulin resistance (IR) and decreased tissue sensitivity to glucose and its absorption are linked to mitochondrial dysfunction.[10] A final potential gut-mediated mechanism of action of metformin involves alteration of the intestinal microbiome.

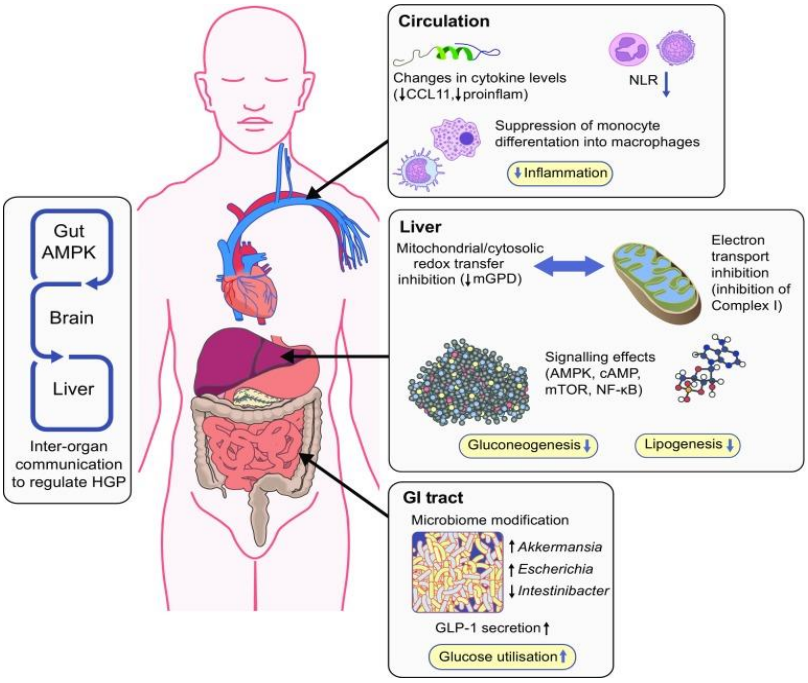

Fig. 1: Actions of metformin on metabolism and inflammation.[11]

2.2 Cardiovascular and Renal Protective Effects

Since 1990, the incidence of cardiovascular disease (CVD), one of the world's major causes of death, has been rising annually. In 2019, cardiovascular disease (CVD) accounted for 18.6 million fatalities, or around 30% of all deaths worldwide, and affected 523 million individuals, or 6% of the entire population.[12][13] Both clinical trials and preclinical evidence

showed that metformin significantly improved cardiovascular health. Depending on the patients' initial features, metformin was able to enhance clinical cardiovascular outcomes in DM patients with varying favorable effects. In animal models of cardiovascular disease, it primarily provides cardiovascular protection by lowering ECs and cardiomyocyte apoptosis, lowering oxidative stress, reducing inflammatory responses, enhancing mitochondrial function, and controlling lipid homeostasis. The metabolic transduction route, which involves AMPK activation and control of its downstream effectors, including eNOS, mTOR, and PGC-1α, is the primary molecular mechanism at play.

The earliest and most prevalent CV consequence of diabetes in this population was chronic kidney disease (CKD), which was responsible for 36% of these occurrences. Furthermore, a 1.8-fold increase in the probability of all-cause or CV death was linked to the onset of CKD. A diagnosis of chronic kidney disease (CKD) has a significant negative influence on clinical outcomes for individuals with diabetes, according to further data from the nationally representative US National Health and Nutrition Examination Survey (NHANES).[14]

For many years, however, metformin was not recommended for individuals with chronic kidney disease (CKD) (estimated GFR [eGFR] <60 mL/min/1.73 m2) due to a suspected link between metformin use and a higher risk of lactic acidosis. Serum lactate levels are somewhat raised by metformin, but they often stay well within the normal range.[15]

2.3 Limitations in Advanced Disease and Obesity

Because of its proven effectiveness and good tolerance, metformin has been recommended as the first line of treatment for patients with type 2 diabetes in all guidelines within the last ten years.[16]

However, because metformin is eliminated by the kidney, there has always been a concern that it should not be used in patients whose serum creatinine is higher than 1.5 mg/dL for men and 1.4 mg/dL for women due to the possibility of metformin-associated lactic acidosis (MALA), as indicated by the FDA warning label. The risk of lactic acidosis with a previous biguanide, phenformin, which is no longer used, was the reason for this worry.

However, at the time of the FDA label, there was little to no data to substantiate this risk for metformin. Furthermore, a completely different picture is painted by mechanistic and dosage findings about the effects and application of metformin in kidney disease.[17]

2.4 Positioning in Current Guidelines

Metformin's place in clinical guidelines is relatively steady, even with the influx of new therapeutic choices. Metformin is recommended as a foundation therapy by the majority of national, regional, and worldwide recommendations, which emphasize the avoidance of therapeutic inertia and the early achievement of several treatment goals. Decades of evidence-based recommendations are reinforced by the 2024 American Diabetes Association Standards of Care, which maintain Metformin's first-line status. Following the rules, however, paints a more nuanced picture. 38.5% of the 40,150 patients who had incident type 2 diabetes started taking glucose-lowering drugs within a year, with metformin continuing to be the most popular drug between 2014 and 2022. According to these statistics, there is a considerable therapeutic inertia in the therapy of diabetes, even if metformin continues to hold its leading position.[18]

Tirzepatide: Dual GIP/GLP-1 Innovations

Glucagon-like peptide (GLP-1) and nutrient-stimulated gastric inhibitory polypeptide (GIP), also referred to as glucose-dependent insulinotropic polypeptide or gastric inhibitory polypeptide, are secreted by K and L cells, respectively, in the upper segment of the small intestine and throughout the ileum. Incretin-mimetic GLP-1 receptor agonists have been utilized to treat type 2 diabetes mellitus (T2D) for the past ten years. Because GIP does not show promise in treating diabetes, it has not been developed as a medication[19] .GIP was shown to stimulate insulin secretion in a glucose-dependent manner following the identification of its amino acid sequence in 1971. The structure of prepro-GIP was effectively discovered using the cloning of the GIP cDNA [20].It was shown that the gene for GIP was located in the chromosome and that GIP mRNA was expressed in the upper portion of the small intestine.[21][22] Obesity brought on by a high-fat diet has been linked to GIP. GIP (secreted by K-cells in the upper segment of the small intestine) and GLP-1 (secreted by L-cells throughout the intestine) in response to nutrient ingestion act on GIPRs and GLP-1Rs expressed in various organs.[23]

GI = gastrointestinal; GIP = gastric inhibitory polypeptide; GIPR = GIP receptor; GLP-1 = glucagon-like peptide; GLP-1R = GLP-1 receptor.

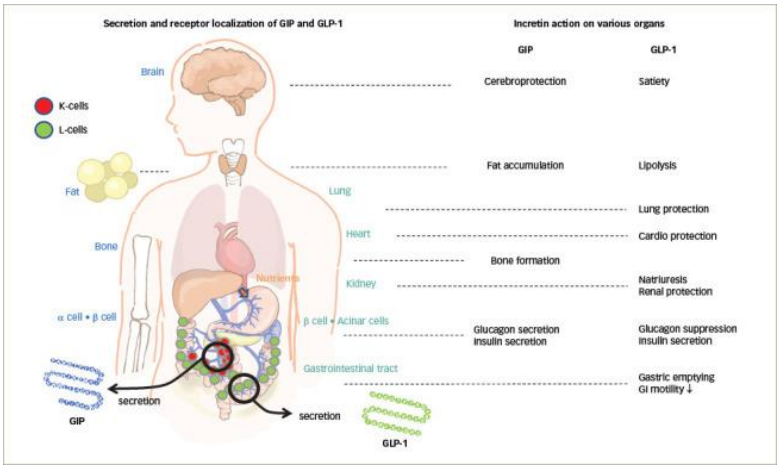

Figure 2: GIP and GLP-1 secretion acting on receptors in various organs.[24]

3.1 Tirzepatide: Dual GIP/GLP-1 Innovations

Tirzepatide exhibits skewed signaling at the GLP-1R and is an unbalanced agonist of the GIPR and GLP-1R. Predicting the qualities of medications needed for clinical success requires a deep comprehension of the pharmacological characteristics of multireceptor agonists. The majority of these drugs currently being researched to treat metabolic disorders are agonists for the GIPR, the glucagon receptor, or both, but they also exhibit activity at the GLP-1R as the anchor pharmacophore.[25] The best combination of characteristics, such as unique receptor potencies and the capacity to activate specific intracellular signaling pathways, as well as a pharmacokinetic profile that permits desired receptor occupancy, should ultimately enhance efficacy above and beyond that of selective GLP-1R agonists. Examining tirzepatide's pharmacological characteristics in light of the phase 2 trials' efficacy results creates a standard by which to compare subsequent compounds in the class, as it is the first multireceptor agonist to be admitted into a phase 3 program.

To comprehend tirzepatide's pharmacology, it is essential to describe how it activates GIPR and GLP-1R and relate these processes to biological activity. The multifaceted nature of receptor activation and the varying sensitivities of assay techniques frequently complicate the study of GPCRs.[26]

3.2 Weight Loss and β-Cell Preservation Mechanisms

We measured HOMA2-B indices as an initial assessment of pancreatic beta-cell function, as blood samples were collected under fasting conditions. Percent change from baseline in HOMA2-B indices (computed either with fasting insulin or with fasting C-peptide) were significantly increased in all treatment groups except placebo at 26 weeks. Tirzepatide doses

of 5 mg, 10 mg, and 15 mg produced HOMA2-B percent increases from baseline (calculated using fasting C-peptide) ranging from 93% to 163% ($P < .001$), compared to 72% for dulaglutide ($P < .001$), 29% for tirzepatide 1 mg ($P = .049$), and 1% for placebo ($P = .932$), indicating marked β-cell function gains. Similar trends held for HOMA2-B derived from fasting insulin. At 26 weeks, absolute HOMA2-B changes for all tirzepatide doses and dulaglutide significantly exceeded placebo ($P < .001$), with tirzepatide 10-mg and 15-mg groups outperforming dulaglutide ($P \leq .004$). Dose-dependent HOMA2-B rises over time appear in Supplemental (Can be Seen Figures 3A and 3B).[27]

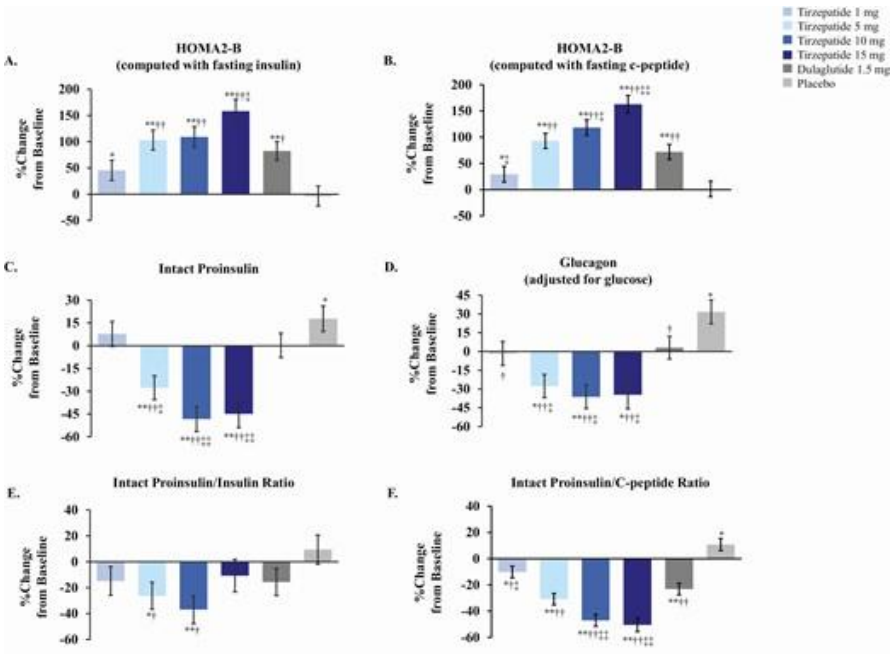

Figure 3: Percent change from baseline in markers of beta-cell function with tirzepatide treatment at 26 weeks.

3.3 Safety Profile and Gastrointestinal Tolerability

Obesity remains a global concern with prevalence rate exceeding 40% worldwide.[28] Clinicians must exercise caution while prescribing tirzepatide due to the elevated risk of gastrointestinal side effects. Frequent adverse effects, such as nausea and diarrhea, may have a major impact on patients' everyday activities and willingness to stick with treatment. The patient's past history of gastrointestinal sensitivity and their capacity to tolerate comparable treatments should be carefully taken into account during the strategic patient selection process for tirzepatide therapy. This classification may reduce the likelihood of side effects and enhance the drug's overall tolerability profile.

Starting therapy at the lowest tirzepatide dose and increasing it gradually as necessary to achieve desired efficacy at the lowest effective dose could be a crucial strategy to reduce the likelihood of side effects. Additionally, the observed rise in injection site reactions raises questions regarding tirzepatide's formulation and administration method. This emphasizes the necessity of better injectable equipment and instruction for patients on how to administer it. Additionally, we saw a higher likelihood of baldness in the tirzepatide group, which may have been brought on by hormonal shifts and nutritional deficits brought on by abrupt and severe weight loss.[29]

Regarding the administration schedule, liraglutide is given once daily, whereas tirzepatide and semaglutide are given once weekly. Compared to once-daily treatments, injectable pharmaceutical solutions given once a week may offer the advantages of better adherence and easier use.[30]

Semaglutide: GLP-1 Receptor Agonist Evolution

Bayliss and Starling first described the connection between the pancreas, the gut and incretin hormones in the early part of the twentieth century.[31][32] Since then, a number of strategies have been employed to increase the half-life of native GLP-1, some of which have produced pharmacological medicines that effectively treat type 2 diabetes. We outline one such strategy, albumin binding, and explain how it was used to create the once-daily liraglutide and later the once-weekly semaglutide, which are human GLP-1 analogs. Along with some new biology, the pharmacology of these two long-acting GLP-1 analogs is reviewed in terms of enhancing glycemic control, lowering body weight, and lowering cardiovascular (CV) risk. We also discuss the significance of precise tissue expression measurement of the target (GLP-1 receptor).

4.1 Cardiovascular Outcome Trials (CVOTs)

A glucagon-like peptide-1 (GLP-1) analog called semaglutide (Novo Nordisk, Denmark) is used to treat type 2 diabetes (T2D).[33] Semaglutide is available in two formulations: once-daily oral and once-weekly subcutaneous (s.c.).[34] The two semaglutide formulations have different routes of administration, but once absorbed into the bloodstream, their pharmacokinetic profiles and therapeutic effects are comparable.[35]

Understanding the CV effects of semaglutide in terms of relative and absolute risk reduction in the wider spectrum of T2D patient profiles that are encountered in ordinary clinical

practice was the goal of this investigation. With participants spread across the range of baseline CV risk, we performed a post hoc meta-analysis of data from the SUSTAIN and PIONEER phase 3a trials in order to evaluate the impact of CV treatment. A CV risk prediction model that was created using a separate dataset from the LEADER CVOT, which assessed CV outcomes with liraglutide versus placebo, was used to disperse the subjects. The LEADER clinical trial program shared the same explanatory variables and endpoint definitions as the SUSTAIN and PIONEER projects.[36]

4.2 Role in Heart Failure and CKD Comorbidities

In the United States, heart failure with preserved ejection fraction (HFpEF) accounts for over half of all heart failure cases and is a common and growing kind of heart failure.[37] Once-weekly semaglutide at a dose of 2.4 mg reduced HF-related symptoms and physical limits (measured in 6-MWT) and resulted in a higher degree of weight loss than placebo after 52 weeks in this retrospective analysis, which involved patients with HFpEF and obesity. Additionally, the analysis demonstrated that semaglutide performed better than the placebo in terms of obtaining more favorable results in the evaluation of the hierarchical composite endpoint. Furthermore, compared to the placebo, semaglutide treatment caused a more notable decrease in CRP levels. It is noteworthy that those on semaglutide had fewer severe side effects than those on the placebo. Furthermore, the semaglutide and placebo groups saw comparable rates of discontinuation due to significant side events.[38]

5. Combination and Sequential Therapies

5.1 Metformin as Backbone for GLP-1/GIP Add-Ons

The rising prevalence of type 2 diabetes mellitus (T2DM), a chronic metabolic disease marked by insulin resistance and β-cell dysfunction, offers significant challenges to public health systems around the world[39].[40] Even though GLP-1 receptor agonists are effective treatments, their clinical use is usually linked to gastrointestinal issues like nausea, vomiting, and diarrhea. Rare but dangerous side effects like pancreatitis and cholelithiasis have also been reported in clinical reports.[41]

Medication nonadherence is one of the main reasons for patients not attaining their A1C goal. We introduced premixed insulin, metformin, and a GLP-1 receptor agonist in our clinic to help our obese patients with poorly controlled type 2 diabetes on high-dose basal or basal-bolus insulin therapy with their medication regimen and to reduce the number of daily injections they needed. Here, we present the findings.

Safety Profile[42]

Nausea and diarrhea are typical but mild side effects that go away with titration; for certain side effects, including as nausea, the combination is more tolerable than GLP-1RA monotherapy. Lactic acidosis (metformin, renal caution) and pancreatitis (agonists) are uncommon concerns; no significant interactions have been observed. Long-term monitoring of B12 levels and renal function is recommended.[42]

5.2 Tirzepatide + Semaglutide Synergies (Triple Therapy Potential)

A weekly injectable drug called tirzepatide (LY3298176) activates both GIP and GLP-1Rs. Its ability to bind to albumin is enhanced by a fatty acid modification, which also prevents the DPP4 enzyme from breaking it down. The GIP receptor is the primary target of tirzepatide, which has a stronger effect than the GLP-1R. Even though it is less potent and activates the GLP-1 receptor as much as natural GLP-1, it still effectively controls blood sugar and weight by fully engaging the GIP receptor. Tirzepatide has demonstrated greater effectiveness than GLP-1RAs alone since it increases insulin secretion, inhibits glucagon release, and lowers lipotoxicity all at once.[42][43] For the treatment of type 2 diabetes, sernaglutide, an analogue of glucagon-like peptide-1 (GLP-1), is approved (at subcutaneous injection doses up to 1 mg, once weekly) and is advised as a second-line treatment following metformin.[44] Additionally, semaglutide has been proven to improve weight reduction and glycemic management in patients with type 2 diabetes in meta-analyses of randomized controlled trials (RCTs).

CONCLUSION

Type 2 diabetes demands a multimodal approach integrating foundational therapies like metformin with innovative incretin-based agents such as tirzepatide and semaglutide. These advancements enhance glycemic control, promote substantial weight loss, preserve β-cell function, and offer cardiovascular and renal protection, surpassing traditional options. Despite challenges like gastrointestinal tolerability and therapeutic inertia, combination strategies—metformin as backbone with GLP-1/GIP agonists—optimize outcomes. Future directions emphasize personalized regimens, nanotechnology, regenerative therapies, and sustained lifestyle interventions to curb the global epidemic and improve long-term quality of life for patients.

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