**GLUCOREGULATORY ACTIONS OF INCRETINS/ANTI-INCRETINS**

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**INTRODUCTION**

One of the biggest lifestyle-related diseases of the twenty-first century is diabetes mellitus (DM), which is also one of the most difficult public health issues of the day. Its current prevalence in the world is 387 million (8.3%), and by 2035, it is expected to rise to 592 million. Remembered as the 'diabetes capital of the world,' India was home to 61.3 million people with Type 2 Diabetes Mellitus (T2DM) in 2011, and estimates suggest that number will rise to 101.2 million by 2030 [1].

The majority of diabetes cases can be categorized into four main etio-pathogenetic groups. Type 1 diabetes is the first type of the disease, which is defined by a complete lack of insulin secretion. Using genetic markers and serological evidence of an autoimmune process occurring in the pancreatic islets, those who are more likely to acquire this kind of diabetes can be identified. Because of a combination of insulin action resistance and insufficient compensatory insulin secretory response, the second category, known as type 2 diabetes, is far more common. Other particular kinds of diabetes and gestational diabetes are included in the third and fourth groups, respectively [2].

**TYPE 2 DM AND INCRETIN- ANTI-INCRETIN THEORY**

At least a century has passed since the invention of ***incretins*** (Table 1).

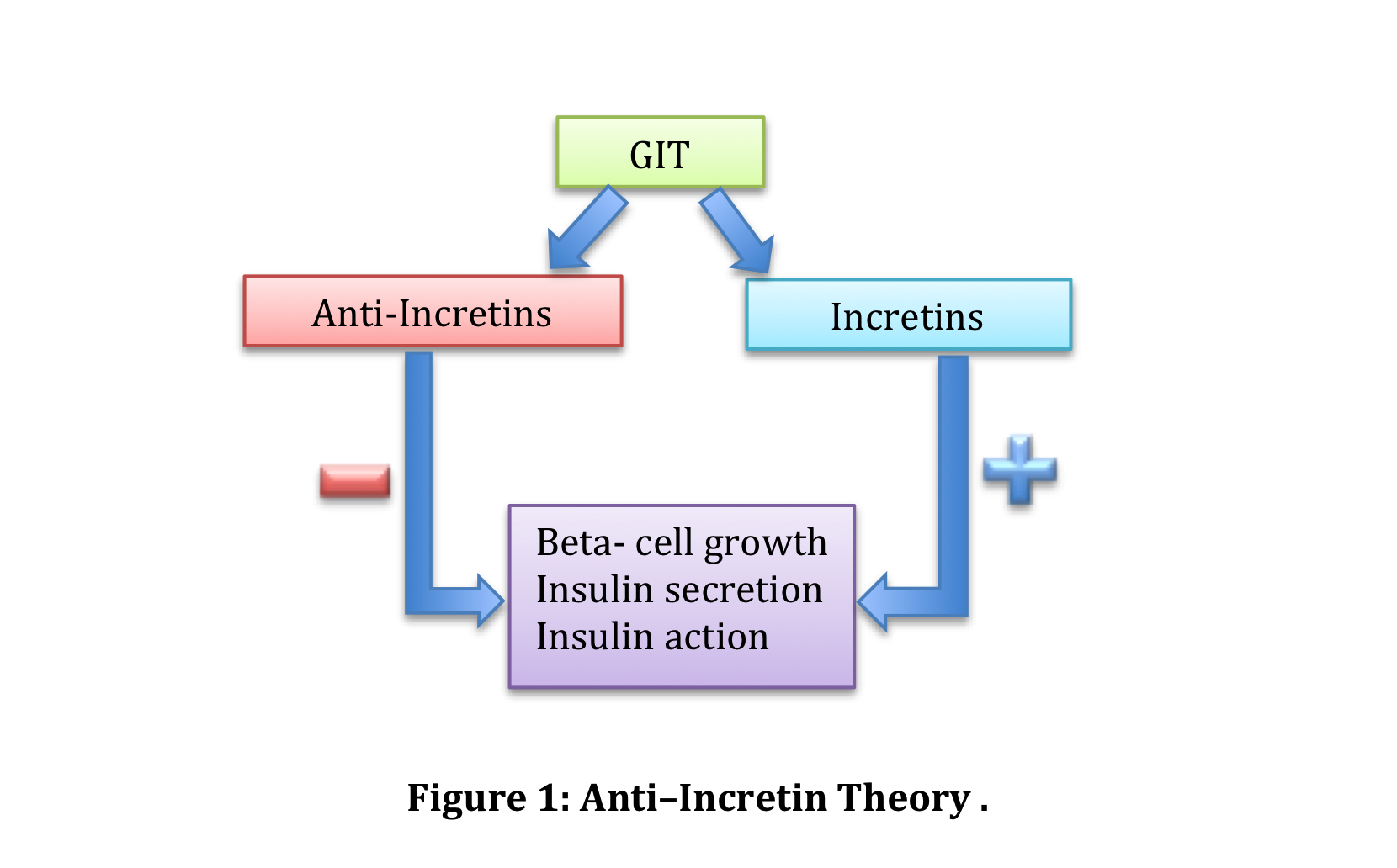
**TABLE 1: Milestones in Diabetology with special reference to Incretin/Anti-incretin Theory.**

|  |  |
| --- | --- |
| Year | The Development of Incretin-Based Therapies |
| 1906 | The use of a hormone generated from the stomach to treat diabetes was initially suggested. |
| 1921–1922 | It was demonstrated that insulin extracted from the pancreatic has the ability to treat type 1 diabetes. |
| 1932 | The word "incretin" was initially used to describe a chemical that originated in the gut and is most likely a hormone that controls the release of insulin after meals. |
| 1964–1967 | Clinical evidence for the positive modulation of insulin secretion by a gut-derived factor. |
| 1971 | Gastro Intestinal Peptide (GIP), the first incretin, was extracted and sequenced. |
| 1985 | Glucagon-Like Peptide-1 (GLP-1), the second incretin, was explained. |
| 2002 | Exendin-4, a GLP-1 receptor agonist extracted from the saliva of Gila monster lizards, has been demonstrated to potently enhance insulin secretion in both T2DM and non-T2DM patients in a glucose-dependent manner. |

Glucagon-Like Peptide-1 (GLP-1) is the second and last incretin to be identified, after Gastrointestinal Peptide (GIP) was the first [3]. Gut hormones known as incretins stimulate the release of insulin after a meal in a glucose-dependent way [4]. They are released into the bloodstream from the gut upon food consumption, thereafter they modify the insulin secretory response to the nutrients in the meal. As a result, by definition, incretin hormones increase insulin secretion at the typical physiological quantities seen in the plasma following meals [3]. The two incretins that have been investigated the most are GIP and GLP-1. They also have indirect metabolic effects [4]. They carry out their insulinotropic actions via unique G-protein-coupled receptors, which are widely distributed on both islet β cells and non-islet cells.

C-peptide values show that β-cells secrete more insulin in response to oral glucose delivery than to intravenous glucose administration. The "incretin effect" is the name used to describe this variation in insulin secretion [5,6,7]. It is thought to be responsible for between 50% and 70% of the total insulin produced in response to oral glucose ingestion.

The anti-incretin theory proposes that as nutrients pass through the gastrointestinal tract, they also trigger another set of hormones known as anti-incretins. To counteract the effects of other postprandial glucose-lowering mechanisms as well as the effects of incretins, such as the reduction of hepatic glucose synthesis via food sensing, glucagon, and ghrelin stimulation, these anti-incretins function through negative feedback mechanisms [Figure: 1] [8].



Healthy individuals maintain a state of balance between incretins and anti-incretins [9, 10]. The "anti-incretin" theory posits the existence of neuroendocrine signals in the gastrointestinal system that are stimulated by nutrition and counteract the effects of incretins. In normal physiology, there is a harmonious equilibrium between incretins and anti-incretins, which ensures appropriate blood glucose levels and the proper functioning of β-cells. According to this notion, the release of anti-incretin signals either excessively or prematurely could upset the incretin-anti-incretin homeostatic process, which would then impact the activities of several organs involved in regulating metabolism, such as the brain, adipose tissue, and β-cells. Moreover, according to this notion, gastric bypass surgery may be able to reduce the overproduction of anti-incretins in people with Type 2 Diabetes (T2DM), thereby reestablishing the proper balance between incretins and anti-incretins and eventually improving T2DM [11]. The favorable results of some bariatric surgical procedures, which quickly resulted in better glucose tolerance, indicate that dopamine operates as a "anti-incretin" signal to offset the stimulatory action of GLP-1 [12].

**BIOCHEMICAL ASPECTS OF INCRETINS**

***Gene structure and synthesis***

GIP was the first incretin hormone to be discovered. The single 42-amino acid peptide that makes up human GIP is generated by PC1/3 of proGIP during post-translational processing. The precursor, known as ProGIP, is a 153-amino acid molecule that is encoded by a 459-bp open reading frame. The gip gene, which codes for ProGIP, is located on chromosome 17q. Secretin, glucagon, and vasoactive intestinal peptide are among the hormones in the structurally related family that includes GIP [3].

GLP-1 and glucagon-like peptide-2 (GLP-2) are two glucagon-like peptides that are encoded by the proglucagon gene in addition to glucagon. These peptides and glucagon have approximately 50% amino acid homology. It's crucial to remember that whereas GLP-1 is insulinotropic and has the ability to reduce blood sugar, GLP-2 lacks these qualities and is not considered an incretin [3].

***Stimulants and Secretion***

Insulin production is stimulated by glucose in a glucose-dependent manner by GIP, which expedites the absorption of glucose into tissues by insulin. This hormone is produced and secreted by enteroendocrine cells, also known as K cells, which are mostly found in the proximal small intestine, which includes the duodenum and jejunum, in response to nutrients [3].

Conversely, glucose-dependent insulin secretion is markedly stimulated by GLP-1, another peptide having incretin action. Throughout the small and large intestine, enteroendocrine L cells produce and secrete it. Prohormone convertase 1/3 (PC1/3) posttranslationally processes proglucagon to produce GLP-1. Notably, unlike GIP-secreting K cells, there are more L cells in the distal ileum and colon than in the duodenum and jejunum. The terminal ileum seems to have the highest concentration of K/L cells. In humans, plasma levels of GLP-1 rise quickly in a matter of minutes after oral glucose ingestion. Similar to the secretion profile of GIP, the release of GLP-1 after a meal exhibits a biphasic pattern with an extended late phase (1-2 hours) and an early phase (15-30 minutes) [3, 6].

***Mechanism of action***

Both GIP and GLP-1 are widely distributed hormones that exert their effects by binding to specific G-protein–coupled receptors [5,6]. These receptors are present in various organs, including the brain, duodenum, kidneys, liver, lungs, pancreas, and stomach [5]. In particular, the GLP-1 receptor (GLP-1R) is expressed in islet α- and β-cells, the central nervous system, the gastrointestinal tract, the heart, kidney, and the lungs, whereas the GIP receptor is found in pancreatic β-cells, the central nervous system, and adipose tissue [6].

***Degradation***

Both GLP-1 and GIP are protein hormones subject to rapid degradation by dipeptidyl peptidase 4 (DPP-4) [7].

**BIOCHEMICAL ASPECTS OF ANTI-INCRETINS**

Dopamine (DA), which is produced and released from non-neuronal tissues outside of the nervous system, has other regulatory responsibilities in addition to its well-established neuronal activities [12]. The dynamics of GLP-1 and DA release point to the possibility of a second layer of regulation of glucose homeostasis in the gut [12]. Insulin production is regulated by human islet β-cells via the autocrine DA-mediated inhibitory mechanism. Not only do these β-cells express the DA active transporter and the big neutral amino acid transporter (in a heterodimer form), but they can also absorb circulating DA or L-3,4-dihydroxyphenylalanine (L-DOPA), which is the precursor of DA's production. The ability of DA or L-DOPA to be imported from the extracellular environment raises the possibility that DA possesses endocrine signaling capabilities as well. DA may genuinely have an anti-incretin activity, according to the foregut theory, which also explains the early effects of bariatric surgery on Type 2 Diabetes Mellitus (T2DM). Concurrent rises in DA, L-DOPA, and incretin blood levels after a mixed meal stimulus in humans provide evidence for this. Recent findings indicate that during glucose-stimulated insulin secretion (GSIS) in human β-cells, DA mediates an inhibitory circuit. Based on their results and previous research, the scientists have suggested that there may be an extra layer of glucose homeostasis involving endocrine signaling that starts in the stomach following mixed meal stimulation. In GSIS, the dopamine receptor (D2R) is translocated to the cell surface, where it binds to dopamine (DA). During this process, DA and insulin are also generated. The DA signaling through D2R is a significant inhibitor of glucose-dependent insulin production [13].

A negative feedback loop is produced when dopaminergic transmission suppresses the pancreatic islets' production of insulin in response to glucose stimulation. During this cycle, DA is produced by β-cells from L-DOPA in the blood and acts as an autocrine signal that is released alongside insulin. Insulin secretion increased by glucose is tonicly inhibited by it. The gastrointestinal (GI) tract's cells create L-DOPA, which is more concentrated in the plasma after a mixed meal [12]. Interestingly, β-cells have every element required for the production and secretion of DA.

The concept of a secondary layer of glucose homeostasis regulation stems from the foregut and hindgut hypotheses, which were created to explain the effect of bariatric surgery on Type 2 Diabetes Mellitus (T2DM). According to the hindgut hypothesis, rapid nutrition delivery to the distal intestine triggers the synthesis of "incretins," which enhance the release and/or functionality of insulin and, eventually, lower blood glucose levels [12]. An alternate theory regarding the foregut states that avoiding the upper small intestine leads to the elimination or decrease of a signal that promotes hyperglycemia (also known as "anti-incretin"). It is now understood that the main cause of this incretin action is GLP-1, which is produced from L-cells found in the colon and ileum. According to the foregut hypothesis [12], dopamine and/or L-DOPA satisfy a number of requirements for being classified as an anti-incretin.

**HOW THIS THEORY CHANGES THE WAY WE THINK ABOUT T2DM**

Traditionally, three elements have been linked to the pathogenesis of Type 2 Diabetes Mellitus (T2DM): 1) an increase in hepatic glucose synthesis, 2) an increase in insulin resistance, and 3) a progressive decline in insulin secretion by pancreatic β-cells. But it's now evident that other factors play a significant role in the pathophysiology of type 2 diabetes. These include: 1) Reduced function of the GI incretin hormones, GLP-1 and GIP; and 2) Overabundance of anti-incretin signals [7].

According to the anti-incretin theory, an excess of anti-incretin signals may lead to insulin resistance, decreased insulin secretion, and depleted β-cells, ultimately resulting in Type 2 Diabetes Mellitus (T2DM). This excess may be caused by the composition of macronutrients or chemical additives in modern diets. Conversely, if anti-incretin signals fall below the thresholds that control incretin-driven reactions, postprandial hypoglycemia and uncontrolled β-cell proliferation may happen. Both the advantages and disadvantages of gastric bypass surgery may be explained by changes in the ratio of anti-incretin to incretin factors [8]. Additional hypotheses to account for the compromised incretin effect include: 1) the progressive loss of mass and function of all β-cells that happens naturally as the disease progresses, and 2) the compromised ability of β-cells to secrete in response to incretin stimuli [14].

The precise mechanisms responsible for the diminished β-cell response to GIP are not yet fully understood. However, recent investigations indicate that hyperglycemia may disrupt the physiological response by causing a down-regulation of GIPR expression and activity [3], as well as a reduction in receptor signaling. Both rodent and human islets have exhibited a loss of GIPR expression and reduced responsiveness to GIP, particularly under conditions of hyperglycemia. This phenomenon has been linked to the ubiquitination and subsequent degradation of GIP receptors [4].

While the concentration of GIP remains within the normal range or shows a moderate increase in patients with Type 2 Diabetes Mellitus (T2DM), the insulinotropic effects of GIP are markedly reduced or absent [3,7]. This impaired responsiveness to GIP likely contributes to a deterioration in insulin secretion. However, it appears unlikely that T2DM arises from deficient incretin secretion. One commonly cited reason for utilizing Exenatide or DPP-4 inhibitors is their ability to normalize incretin levels, which are purportedly reduced compared to non-diabetic individuals [3Unlike GIP, decreased GLP-1 secretion causes this incretin hormone to be present at lower levels in T2DM patients [15]. Nonetheless, GLP-1's insulinotropic actions are mainly preserved [14]. Therefore, it is clear that, in comparison to GIP, the incretin action of GLP-1 is more retained in T2DM [3].

**PROOF OF CONCEPT**

***Bariatric/metabolic surgery*** Until a few years ago, it was thought that the pancreas and liver were the key regulatory organs for glucose metabolism. This highlights the important function that the small intestine plays in preserving glucose homeostasis. Research has demonstrated that several gastrointestinal (GI) procedures, including bariatric surgery [9], lead to sustained weight loss and rapid glycemic control. These procedures have also been shown to induce remission of Type 2 Diabetes Mellitus (T2DM) and improvements in hypertension, dyslipidemia, as well as reductions in cardiovascular disease risk and diabetes-related mortality [8]. As a result, this has led to the emergence of metabolic surgery as an innovative medical discipline. Metabolic surgery involves surgical manipulation of the GI tract, such as through procedures like Roux-en-Y gastric bypass (RYGB) or Bilio-Pancreatic-Diversion (BPD), which leads to sustained remission of T2DM and prevents postprandial hyperinsulinemic hypoglycemia. BPD surgery, which bypasses the duodenum, entire jejunum, and the initial part of the ileum, results in the normalization of peripheral insulin sensitivity. On the other hand, RYGB, which bypasses a shorter segment of the intestine, primarily enhances hepatic insulin sensitivity and significantly increases insulin secretion. The underlying pathophysiology of this metabolic effect is rooted in the anti-incretin theory [9].

As a result, bariatric/metabolic surgery is now recognized as a successful treatment for Type 2 Diabetes Mellitus (T2DM), a comorbidity linked to obesity. An 83% reversal of hyperglycemia was seen in patients more than ten years ago, according to Pories et al.'s 10-year follow-up study on the impact of bariatric surgery on type 2 diabetes [13]. Several human studies have shown that treatments such as Roux-en-Y gastric bypass (RYGB) and other surgeries can improve type 2 diabetes through a variety of gastrointestinal processes, including:

Modifications to gut hormones: RYGB generates a three- to four-fold increase in postprandial levels of GLP-1, an incretin hormone that stimulates the production of insulin by the pancreas and has anti-apoptotic effects on β-cells. Increased expression of islet GLP-1 receptors may be the cause of the rise in β-cell mass following RYGB.

Bile acids metabolism.

Modifications in intestinal micro-biota and nutrient sensing.

Intestinal glucose metabolism reprogramming, emphasizing the vital yet previously underappreciated role of the gut in glucose homeostasis. This emphasizes the necessity of more investigation into the mechanisms guiding GI surgery.

Particularly noteworthy is the restoration of the first-phase insulin response by RYGB, resulting in hypersecretion of C-peptide and insulin after nutrient intake. This suggests an enhancement of β-cell function. Research has validated the theory that RYGB can promote the proliferation of β-cells. Additionally, immune-reactive cells for GLP-1 receptors were discovered to be 3.8 times greater following RYGB, suggesting that the enhanced glucose tolerance seen after RYGB could be explained by an increase in β-cell mass [8].

According to the hindgut theory, "incretins" are secreted when foods reach the distal intestine, and these substances then improve insulin release and/or its effects. By reducing insulin secretion and/or increasing insulin resistance, gastrointestinal bypass counteracts the effects of incretins and, on the other hand, lowers the production of upper gastrointestinal components that generally protect against hypoglycemia, according to the foregut hypothesis [13].

In conclusion, if organs known to produce and store large amounts of insulin secretion inhibitors (such DA) from food sources were skipped or only partially removed, it is plausible that the body would become more glucose-tolerant [12].

**PHARMACOLOGICAL AND CLINICAL ASPECTS**

The recognition and enhanced understanding of the role of incretins and the enzymes responsible for their degradation have led to the clinical development of various agents for treating DM [7,15]. However, the clinical use of natural incretins is limited due to their short half-life, resulting from rapid inactivation by DPP-4, making continuous infusion impractical [6]. There are two main incretin-based treatment strategies for type 2 diabetes:

GLP-1 receptor agonists are synthetic or chemically modified peptides that bind to GLP-1 receptors and imitate the functions of natural GLP-1. They are resistant to degradation. They are called incretin mimetics because they share many of the glucoregulatory properties of incretin peptides [6, 7].

DPP-4 inhibitors: These drugs work by inhibiting the enzyme responsible for degrading endogenous incretin hormones (both GIP and GLP-1). By reducing the degradation of these hormones, DPP-4 inhibitors prolong their activity, acting as incretin enhancers [6, 14].

Some of the incretin-based therapeutic agents include Exenatide, Liraglutide, and Exenatide long-acting release (LAR), which are GLP-1 agonists. Additionally, there are Albiglutide and Taspoglutide among GLP-1 agonists, as well as Sitagliptin, Saxagliptin, Vildagliptin, and Alogliptin, which are DPP-4 inhibitors [6].

Research indicates that long-acting glucagon-like peptide-1 receptor agonists (LA-GLP-1RAs) may offer additional therapeutic advantages when compared to other existing incretin-based treatments. In contrast to alternative incretin-based therapies, LA-GLP-1RAs demonstrate more substantial enhancements in parameters like hemoglobin A1C (HbA1C) and fasting plasma glucose levels. Their impact on postprandial glucose levels is relatively lower, suggesting a potentially favorable profile regarding adverse events. Additionally, they exhibit a similar reduction in body weight when compared to the twice-daily administration of Exenatide [16].

Incretin-based therapies have brought about a significant transformation in the medical treatment of Type 2 Diabetes Mellitus (T2DM). These therapies offer distinct therapeutic advantages, including: 1) A notable reduction in hemoglobin A1C (HbA1C) levels when employed as monotherapy or in combination treatments, 2) A low risk of hypoglycemia, 3) Beneficial effects on body weight, and 4) Enhanced effectiveness when used alongside other anti-diabetic medications in combined treatment regimens for glycemic control. Importantly, their safety and tolerability profiles are comparable to those of other anti-diabetic drugs [17].

**INCRETIN-BASED THERAPY IN THE PRE-DIABETIC AND FRANK DIABETIC STAGE**

Evidence points to a very long latency period between the first problems in glucose metabolism and the development of diabetes, and many people with prediabetes run the risk of developing the disease or continuing to have abnormal blood sugar levels. As a result, numerous tactics have been investigated to stop the development of diabetes. Even if there isn't much data supporting the use of incretin-based therapy for prediabetes, it seems like a longer course of treatment is necessary. To attain glycemic control objectives following a diabetes diagnosis, current recommendations from organizations like the ADA, EASD, and others call for early usage of Metformin and first lifestyle adjustments, such as weight loss and increased physical activity. Unless there is a contraindication, metformin is usually the first-choice medication for the majority of patients. Additionally, recent research has demonstrated that metformin affects the incretin system by upregulating preproglucagon expression and increasing GLP-1 receptor expression, which in turn raises GLP-1 levels. However, in specific scenarios (such as when dealing with issues like hypoglycemia or weight gain, and when Metformin is contraindicated or not well-tolerated), incretin-based therapies should be considered as a viable treatment option When a single medication is not enough to reach glycemic objectives in the second phase of treatment, supplementing therapy with incretin mimetics and DPP-4 inhibitors becomes relevant. Adding incretin mimetics to i) Metformin, ii) pioglitazone (the only medication of the TZD class currently on the market), iii) a sulfonylurea, or iv) Insulin are essentially the four alternatives available.

When combined with Metformin or pioglitazone, the primary advantages of incretin-based therapies lie in their pathophysiological effects. While Metformin and pioglitazone act as insulin sensitizers (affecting muscle, adipose tissues, and the liver, as seen with TZDs), incretins target different pathological mechanisms (as previously discussed), thereby enhancing their glucose-lowering efficacy. When used alongside Metformin, the key benefits of incretin-based therapies include a reduced risk of hypoglycemia and improved weight control. ..It is particularly beneficial for individuals who need to boost their endogenous insulin secretion yet are at high risk of hypoglycemia when using sulfonylureas to combine metformin with incretin mimetics or DPP-4 inhibitors. It is thought that both incretins and TZDs benefit β-cells by maintaining and improving their function, which may lead to an increase in β-cell mass. The justification for combining insulin and incretin-based treatments in the management of type 2 diabetes stems from their complementing effects on fasting and postprandial glucose control. ..When insulin therapy is not the favored course of action and patients do not achieve sufficient glycemic control with dual therapy, a three-drug combination may be taken into consideration during the third phase of treatment intensification. When treating insulin resistance is the main goal, combining incretin-based drugs with metformin and a TZD may be a promising strategy in these situations. Metformin, a sulfonylurea or TZD, and exenatide, liraglutide, and sitagliptin may be used in a triple combination therapy.

**CLINICAL OUTCOMES**

Both GLP-1 receptor agonists and DPP-4 inhibitors have demonstrated their safety and effectiveness in managing hyperglycemia in individuals with T2DM. These two drug classes exhibit distinct characteristics beyond their differing mechanisms of action, which can assist healthcare providers in identifying patients who are likely to benefit from one or the other.

First, think about the mode of administration: DPP-4 inhibitors are taken orally as tablets, while GLP-1R agonists need to be injected subcutaneously. It is possible that this differentiation will have a big impact on treatment adherence and ease of usage.

Consider the effect on body weight as well. GLP-1R agonists are known to cause large and long-lasting weight loss, while DPP-4 inhibitors have little to no effect on body weight. As a result, GLP-1R agonist medication may be more beneficial for obese patients.

Third, assess the likelihood of adverse effects: The use of GLP-1R agonist medication has been linked to an increased incidence of gastrointestinal side effects, chiefly nausea. On the other hand, DPP-4 inhibitors seem to be associated with an increased risk of infections.

**CONCLUSIONS AND FUTURE PERSPECTIVES**

A deeper understanding of the roles GIP and GLP-1 play in the pathogenesis of type 2 diabetes (T2DM) could offer physicians significant new perspectives on the therapeutic use of incretin-based therapies, such as DPP-4 inhibitors and the GLP-1 receptor agonist exenatide. These antidiabetic medications, which were created based on the many pharmacological effects of incretin hormones, provide a way to address the complex nature of type 2 diabetes and get around some of the drawbacks of traditional treatment, especially with regard to weight control. Considering the robust association among type 2 diabetes, obesity, and elevated cardiovascular risk, this becomes more and more convincing. Nowadays, when metformin treatment fails, incretin-based treatments are most frequently used as adjuncts to achieve acceptable glycemic control. However, they are also advised for use as part of triple combination therapy later on in the disease's course and for monotherapy early on. Furthermore, these compounds have potential as a therapeutic intervention for those with prediabetes. The surgical modulation of the total body dopamine content in concert with the activation of GLP-1 synthesis may account for the swift improvement in glucose tolerance and improved insulin secretion observed prior to weight reduction after RYGB. On the other hand, since blocking the dopaminergic feedback increases the amount of insulin secreted, it is possible that the dopamine receptor or a downstream mechanism in its activation pathway could be targeted for new drugs intended to treat type 2 diabetes. In [12]

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