# Incretin Mimetics in the Indian Context: Revisiting Exenatide

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## Abstract

Management of type 2 diabetes mellitus (T2DM) needs to address hyperglucagonemic states, too, along with the insulin centric approach. Incretin physiology needs utmost attention as in type 2 diabetes incretins level declines like beta-cell function. Professor Robert Unger and his team had re-emphasized the importance of glucagon as the central pathogenic hormone in diabetes, which is responsible for accelerated catabolic destructions in the absence of insulin. Glucagon-like peptide 1 (GLP-1) analogs and dipeptidyl peptidase 4 (DPP4) inhibitors have the greatest potential to reduce the ill-effects of glucagon and metformin, and α-glucosidase inhibitors produce some effect to increase endogenous GLP-1 level and can address hyperglucagonemia. Using GLP-1 analog could be helpful to address misbalanced incretins axis in diabetics. Different professional societies of diabetes are now recommending GLP-1 receptor agonist (GLP-1 RA) like liraglutide, semaglutide, and dulaglutide in a variety of subgroups like people with atherosclerotic cardiovascular disease, heart failure, chronic kidney disease, patient needing weight loss, or having high risk of hypoglycemia. Though exenatide had not shown beneficial role in cardiovascular outcome trial, it was proved to be safe in high risk cardiovascular patients. As Indian patients are more prone to develop incretin deficiency compare to the Caucasians, if we have more generic exenatide (in the 2017 patent expired), it may address this issue holistically. Past history of pancreatitis and family history of medullary thyroid carcinoma are two important serious concerns while using any GLP-1 RA. Informed prescribing on gastrointestinal side effects, such as nausea, anorexia, vomiting, and loose motion, needs to be addressed, and patients should be educated regarding mitigation strategies for these adverse effects.

**Keywords:** Exenatide, Glucagon, GLP-1 RA, Incretin, Type 2 diabetes.

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Diabetes mellitus has traditionally been looked upon as a state of metabolic dysfunction wherein there is a constant tug-of-war between insulin, the hypoglycemic hormone, and the hyperglycemic factors (e.g., glucose, interleukins, TNF-alpha, norepinephrine, and cortisol). If we recollect the beloved cartoon show of our childhood, "The Tom and Jerry Show," we can draw a corollary with diabetes by considering Tom, the cat, as insulin and Jerry as the metabolic mice (glucose, interleukins, TNF-alpha, norepinephrine, and cortisol). "When the cat is away, the mice will have a free hand"—to avoid this, we have to ensure that insulin is always adequately available to avoid metabolic mice-related damages. But if we think back to the aforementioned cartoon show, we shall also recall the presence of a third character called Spike, the dog, who helped Jerry evade Tom and create mischief. Similarly, in the "Tom and Jerry" game of diabetes, there is also a third factor that works in the same manner as Spike, the dog. Let us look into who the dog Spike is and how to control it, so that the metabolic mice do not receive any assistance in causing impairment in diabetes.

Science, on its path of progress, has been plagued by the "Dogma Displacement Inertia" whereby there has always been some level of resistance to the acceptance of new knowledge and doctrines. It is common knowledge that for centuries, people believed in the doctrine of geocentrism which was proposed by Aristotle way back in 370 BC. But even after the great Galileo proved the doctrine of heliocentrism and paid for it with his life, the geocentric theory continued to find favor in the field of astronomy for more than 200 years. Thus, displacement of dogma has always been a herculean task. Diabetes, which is glucocentric is nowadays being acknowledged as lipocentric. It is high time that diabetes is addressed as having a binary solar system with two suns—insulin and glucagon, around which its whole pathophysiology revolves. To manage diabetes rationally, we have to address insulinopenia and hyperglucagonemia holistically. The pathophysiological understanding of this disease has long revolved around insulin, either insulin deficiency or insulin resistance. In the whole process, the vital role of glucagon, as the hyperglycemic hormone, in the etiopathogenesis of diabetes mellitus has been relegated to the background.

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## Interplay of Insulin and Glucagon in Glucose Homeostasis

Insulin and glucagon have opposing actions on the liver which indicates that both these hormones work in tandem to strike the perfect balance to regulate hepatic glucose metabolism, thus maintaining euglycemia. During starvation, rigorous exercise, hypoglycemia, or any such situation, when there is an increased demand for glucose in the body, insulin secretion decreases and glucagon secretion increases. This serves to remove the inhibitory

effect of insulin on hepatic glucose production while facilitating the stimulatory effect of glucagon on the same. This results in increased glucose turnover from the liver by the processes of hepatic gluconeogenesis and glycogenolysis. On the other hand, when there is abundant glucose in the body, e.g., following a meal, glucagon secretion decreases and the anabolic effects of insulin take an upper hand, resulting in increased peripheral utilization of the excess glucose and its storage in the form of glycogen to meet future needs. Therefore, it is obvious that the actions of both insulin and glucagon are equally important to maintain glucose homeostasis by virtue of their tight control on both hepatic glucose production and glucose utilization/storage according to the changing needs of the body.

## The Glucagonocentric Approach to Diabetes

Subsequent to the discovery of insulin in 1921, the entire concept of diabetes has been insulin-centric with the principal idea being that lack of insulin directly causes all abnormalities associated with diabetes. Since 1975, with increased understanding about glucagon and its effects, the "bi-hormonal" concept took over which advocates that the manifestations of diabetes are caused either by the deficiency of insulin or by the excess of glucagon.

In recent times, it has been the pioneering work by Professor Robert Unger which re-emphasized the importance of glucagon as the central pathogenic hormone in diabetes.[1,2] It is already known that in the presence of insulin deficiency, glucagon increases hepatic glucose and ketone production, thus causing catabolic manifestations. The pivotal role of glucagon is proven by the fact that hyperglucagonemia is present in every form of poorly controlled diabetes. It has also been observed that leptin and somatostatin, which are suppressors of glucagon, also suppress all catabolic manifestations of diabetes during total insulin deficiency.

In type 1 diabetes mellitus (T1DM), the β-cells are destroyed, and thus, when there is hyperglycemia, the paracrine release of bursts of insulin in response to increased glucagon secretion from the α-cells does not occur.[3] Since there in no rise in insulin secretion, glucagon secretion continues and is not suppressed as it normally would. This paradoxical increase in glucagon levels may be the cause of the exaggerated postprandial hyperglycemia of T1DM because an endogenous source of glucose is superimposed on the exogenous meal-derived glucose.

In T2DM where insulin resistance is a hallmark, the β-cells initially respond by compensatory increase in insulin secretion. But, when this increased workload of the β-cells persists for a considerable period of time, they fail to adequately respond, leading to a state of insulin deficiency. Both insulin resistance and insulin deficiency are instrumental in the development of hyperglycemia. Apart from insulin resistance, other factors which increase the β-cell workload are obesity, increased food intake, increased gastric emptying, and increased glucagon secretion, leading to enhanced hepatic glucose output. Decreased β-cell response will result in diminished insulin secretion in response to elevated glucose in addition to decreased first-phase insulin response. Therefore, an imbalance between β-cell workload and β-cell response contributes to the hyperglycemia of T2DM.

With our increasing knowledge about the pathophysiology of diabetes, it has become more evident that dysregulation of incretin hormones is another fundamental defect in the pathogenesis of Type 2 diabetes. Incretins are peptide hormones released by the intestine following a meal, which enhance insulin secretion. This additional insulin response (incretin effect) is observed only when glucose is administered orally in the form of a rise in C-peptide levels following glucose meal, but is absent when glucose is administered intravenously. The incretin effect is reduced in subjects with type 2 diabetes compared to healthy subjects.[4]

The physiological levels of insulin in the pancreatic islet cell, liver, and peripheral tissues are around 2000, 60, and 20 μIU/mL, respectively. If the intra-islet insulin level decreases, alpha cells in the pancreatic islets will be stimulated to secrete glucagon, leading to hyperglucagonemia. Exogenously administered insulin is unable to achieve the normal physiological levels of insulin within islet cells. The normal relationship of insulin concentration between pancreatic islet cells: liver: peripheral tissue is 100:2:1. But in case of exogenous insulin administration, this ration is always 1:1:1. So, if we attempt to achieve intra-islet insulin concentration similar to the normal nondiabetic physiological levels, it would result in severe hypoglycemia. Therefore, during insulin therapy, as the intra-islet insulin levels are very low compared to the normal values, hyperglucagonemia occurs which is responsible for the development of different manifestations of metabolic decompensation. Thus, to counter this phenomenon, in addition to insulin therapy, we also need antidiabetic agents which can counter the increased levels of glucagon.

Among the available antidiabetic drugs, GLP-1 analogs and DPP4 inhibitors have the greatest potential to reduce the ill-effects of glucagon. Metformin and α-glucosidase inhibitors having some effect to increase endogenous GLP-1 level and can address hyperglucagonemia. In the management of type 2 diabetes, insulin initiation has already been emphasized upon. But timely initiation of incretin mimetics is also equally important as they can be good "glucagon dog" catchers, thus allowing the "insulin cat" to control the "metabolic mice."

## Role of Incretins in Diabetes

The evidence from antagonist and knockout models suggests that glucose-dependent insulinotropic peptide [or gastric inhibitory peptide (GIP)] and GLP-1 are the dominant peptides responsible for the majority of nutrient-stimulated insulin secretion. In T2DM, GIP secretion has been found to be normal, but there is a defective beta-cell response to exogenously administered GIP. On the other hand, although GLP-1 secretion is diminished, the glucoregulatory responses to exogenously administered GLP-1 are preserved. Additionally, GLP-1 inhibits postprandial glucagon secretion, reduces appetite, and slows gastric emptying, whereas GIP has opposite effects on these parameters. Both GLP-1 and GIP can stimulate β-cell mass/growth.[4–8]

## Incretin Mimetics—The Answer to Glucagon Imbalance

Incretin mimetics are drugs which are analogs of the physiologically produced incretins mainly of GLP-1. The currently available GLP-1 analogs include dulaglutide, semaglutide, liraglutide, lixisenatide, and exenatide. Studies have shown that continuously infused GLP-1 improves many metabolic defects of T2DM by increasing insulin secretion, increasing first-phase insulin response, decreasing glucagon and glucose output, suppressing appetite, and slowing gastric emptying.[9,10] Incretin-based therapy has now established itself as one of the most lucrative approaches to manage T2DM because of the fact that they have comparable efficacy to other commonly used agents (e.g., metformin, sulfonylureas) with

the added advantages of weight neutrality or weight reduction propensity and greatly reduced risk of hypoglycemia.[11]

Recent studies have suggested that type 2 diabetics in our country have a unique "Asian Indian Phenotype" which refers to certain clinical and biochemical abnormalities in Indians which are not seen in type 2 diabetics from other racial groups. These include increased insulin resistance and greater abdominal adiposity, i.e., higher waist circumference, despite lower body mass index and lower adiponectin levels.[12] Meta-analysis of studies which looked into the ethnicity-based differences in glycemic response to incretin-based therapies suggested that Asians may respond better to such therapies.[11] These ethnic differences may also be attributed to significant difference in fasting and glucose-stimulated GLP-1 levels among different races.[13] Therefore, to manage Indian diabetics better, it is important to use incretin mimetics rationally.

## The Growing Relevance of Exenatide in the Indian Context

Exenatide is the synthetic version of exendin-41. Exendin-4 and GLP-1 both have equivalent binding affinities for the GLP-1 receptor in *in vitro* assays, and both peptides stimulate the receptor equipotently. The added advantage of exenatide lies in the fact that it is not inactivated by DPP4 enzyme which cleaves endogenous GLP and therefore has a much longer plasma half-life than GLP-1.[10,14] In a retrospective epidemiological study by Best et al., exenatide-treated patients were found to be 19% less likely to have a CVD event than patients treated with other glucose-lowering agents. Also, exenatide-treated patients were also less likely to experience CVD-related and all-cause hospitalization.[15] In the exenatide study of cardiovascular event lowering (EXSCEL) where 14,752 patients were followed up for a median period of 3.2 years, exenatide was found favorable for cardiovascular outcomes, fatal and nonfatal as well as hospitalization.[16]

Impairment of cognition is another concern in long-standing T2DM. In fact, Alzheimer's disease (AD) is also termed as type 3 diabetes by some authorities. In animal studies, GLP-1 receptor agonists have shown favorable effects on cerebral ischemia such as decrease in cerebral infarct size and improvement of neurological deficit primarily by inhibiting inflammation, apoptosis, and oxidative stress-related derangements. Their beneficial effect on diabetes and/or obesity-associated cognitive impairment might also stem from their ability to modulate synaptic plasticity, thus improving learning and memory. Apart from reducing hippocampal neurodegeneration, there is a growing body of evidence generated from preclinical studies which suggests that GLP-1 RAs have neuroprotective effects in other neurodegenerative diseases as well. In animal models of Parkinson's disease, GLP-1 RAs improved motor activity and prevented degeneration of dopaminergic neurons, whereas in AD models, they demonstrated promising effects in improving nearly all neuropathological features and cognitive functions. Although clinical trials need to be further conducted extrapolate these results in man, GLP-1 RAs do seem to be a promising therapy for diabetes-associated cognitive decline. Exenatide, therefore, can also be beneficial for diabetes patients who are more likely to develop cognitive dysfunction. This could be a good example of drug repurposing.

The American Diabetes Association/European Association for the Study of Diabetes consensus report "Management of Hyperglycemia in Type 2 Diabetes, 2018" recommends that pharmacological therapy of hyperglycemia should be individualized for each patient based on considerations of efficacy and key patient factors namely, presence of comorbidities such as atherosclerotic cardiovascular disease (ASCVD), chronic kidney disease (CKD), and heart failure (HF), risk of hypoglycemia risk, effects on body weight, side effects, cost and patient preferences. As per the ADA guidelines, 2019, if target HbA1c levels are not achieved by lifestyle modifications and metformin alone, GLP-1 agonists are one of the recommended therapies apart from SGLT2 inhibitors, both in the presence and absence of established ASCVD or CKD. GLP-1 RA can be used when patients need weight reduction or where hypoglycemia is a concern. According to the AACE/ACE guidelines, 2020 also, GLP-1 agonists figure prominently as alternative agents in monotherapy, dual therapy, and triple therapy for T2DM across a wide spectrum of HbA1c values.[17] The ESC/EASD guidelines on diabetes, prediabetes, and cardiovascular disease 2019 also recommend using GLP-1 agonists with proven CV benefit in drug naïve T2DM patients or those on metformin with ASCVD or high/very high CV risk (target organ damage or multiple risk factors).[18] As per the RSSDI guidelines, GLP-1 analogs.[19]

- Can be considered in overweight/obese patients as first-line therapy in patients with metformin intolerance
- Can be considered in overweight/obese patients as second-line therapy in patients with metformin inadequacy
- Are viable second-line or third-line options for the management of patients with uncontrolled hyperglycemia
- Can be considered to reduce the risk of CV events
- Can be added to insulin therapy if glycemic goals are not achieved with reasonably high doses of insulin or if unacceptable weight gain or hypoglycemia occurs. Dose reduction of insulin may be needed in such cases.

In a country like India which has a large number of diabetics across all socioeconomic sections with primarily out-of-pocket health expenditure, cheap GLP-1 agonists can revolutionize the management of diabetes management. At current estimates, the monthly expenditure with the various available GLP-1 analogs are as follows: dulaglutide—Rs. 9,996/-, liraglutide (1.2 mg per day)—Rs. 10648/-, lixisenatide—Rs. 8228/-, and exenatide—Rs 2900/-. Cheap GLP-1 RA can revolutionize treatment of T2DM in India. As there was expiry of patent[20] for exenatide in 2017, it is expected that more Indian pharmaceutical industry would come up for manufacturing generic exenatide which will further decrease cost of exenatide and make it affordable to our patients.

The only concerns with the use of exenatide are pancreatitis, personal, or family history of MTC and in patients with multiple endocrine neoplasia syndrome type 2 (MEN 2). It is important to take history of pancreatitis or personal and family history of medullary thyroid carcinoma before prescribing any GLP-1 receptor agonist. We should be with pharmacovigilant eyes where we are prescribing this agent. But if we go through major trials with incretin mimetics-based therapies, there were no increased risk of this two concerns. GLP-1 RA increases somatostatin level by stimulating delta cell of islets. We know somatostatin analogs are used to treat pancreatitis. Mice exposed to 36-fold, rats to eightfold, and monkeys to 60-fold of human dose of liraglutide with no microscopic changes of pancreatitis. Rat and mice have large number of C cells which are very sensitive to GLP-1 analog. MTC is seen in rat and mice studies. In monkeys, GLP-1 analogs are not producing any C cell growth. Human have 0–105 receptors of GLP-1 per C cell, while rodents have 1,600–13,000 receptors of GLP-1 per C cell.[21] So though we should be watchful and follow the philosophy of "primum non nocere—above all, do no harm"—but no need to panic over

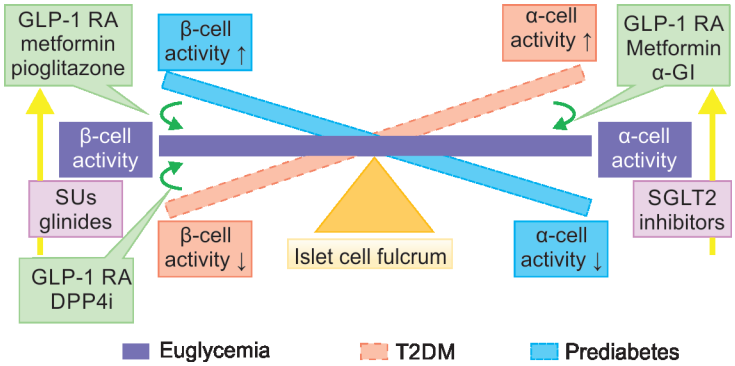


**Fig. 1:** In euglycemic individuals, pancreatic α-cell and β-cell activities remain in equilibrium to maintain normal plasma glucose levels. In prediabetes, the β-cell activity increases with a consequent fall in the α-cell activity. Drugs such as GLP-1 RA, metformin, and pioglitazone can reverse the prediabetic state to normoglycemic state. Similarly, in T2DM, the β-cell activity decreases with an attendant rise in α-cell activity. GLP-1 RA and DPP4i can improve β-cell response and thus prove useful in T2DM. At the same time, GLP-1 RA, metformin, and α-GI can inhibit the augmented α-cell activity to restore the individual to a normoglycemic state[19] (GLP-1 RA, glucagon-like peptide-1 receptor agonists; DPP4i, dipeptidyl peptidase 4 inhibitors; α-GI, α-glucosidase inhibitors; SUs, sulfonylureas; SGLT2, sodium glucose co-transporter 2)

medullary thyroid carcinoma, which is very rare with GLP-1 receptor agonist in human. Gastrointestinal adverse effects like nausea, vomiting, diarrhea, and constipation are common with GLP-1 RA. It is important to aware patients regarding that. Otherwise, these can frighten patients and leads to premature termination of therapy. Small amount interval feeding is important to combat these side effects. There will be development of tolerance to common GI side effects after initial few days. So it is also recommended to start with low dose and to go slow.

Thus, exenatide is a very promising GLP-1 analog which holds immense potential in bringing about a sea change in the management of diabetes in India (Fig. 1).

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