Diabetes Mellitus affects an estimated 194 million adults worldwide and approximately 90–95% of them have type–II diabetes. Diabetes is the fifth leading cause of death in the developed world (1).

Successfully managing diabetes is a daily struggle since current treatments do not provide adequate blood sugar control leaving patients and caregivers frustrated (2). According to Center for Disease Control and Prevention’s National Health and Nutrition Examination Survey, approximately 60% of diabetics with the standard treatment guidelines as per American Diabetic Association do not achieve glycated haemoglobin (Hb A1C) level less than 7 percent (3).

Over the past few years, many new therapeutic entities have become available for the treatment of diabetes. Among those under research and development, the drugs that mimic incretins are of great significance.

Incretins are the hormones secreted by intestine in response to absorption of glucose. They stimulate glucose dependent insulin secretion and decrease the secretion of glucagon. In humans, there are two main incretin hormones, GIP (Glucose-dependent Insulintropic Peptide) and GLP-I (Glucagon Like Peptide-1) (4). The incretin concept has developed in the background of observation that there is more release of insulin in response to oral glucose vis-à-vis intravenous route. It was conceived that glucose in digestive tract activated a feed-forward mechanism for insulin secretion in anticipation to rise of blood glucose. Following the carbohydrate intake, both the hormones, GIP and GLP-1 are secreted by endocrine cells located in the epithelium of small intestine. The endocrine cell senses an increase in the concentration of glucose in the gut and triggers the release of both GIP and GLP-1. Both these hormones on reaching their target tissue, the beta cells of pancreas, lead to the stimulation and release of insulin in addition to release caused by increased glucose level in the blood and decreased release of glucagon.

**Fig-1: Feed forward mechanism for insulin secretion in anticipation to rise of blood glucose levels**

<table>
<thead>
<tr>
<th>Glucose</th>
<th>Orally</th>
<th>Intravenously</th>
</tr>
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<tbody>
<tr>
<td>Increased conc. of glucose is sensed by endocrine cells of epithelium of intestine</td>
<td>Circulation</td>
<td>Beta cells</td>
</tr>
<tr>
<td>Triggers release of incretin hormones GIP &amp; GLP–1 present in the gut.</td>
<td>Insulin</td>
<td>Pancreas</td>
</tr>
<tr>
<td>Carried by circulation to</td>
<td></td>
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<tr>
<td>a) Stimulates release of insulin</td>
<td></td>
<td></td>
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<tr>
<td>b) Inhibits release of Glucagon</td>
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Of the two natural incretins, GIP has been found to loose most of its insulinitropic activity, while GLP-1 retains its activity longer in type-II diabetic patients. The insulinitropic effect of GLP-1 has been found to correspond with blood glucose level without the risk of hypoglycaemia.

In addition, GLP-1 has been found to (a) promote satiety leading to reduced food intake and weight reduction (b) delay stomach emptying which increase glucose absorption time and thus limits hyperglycaemia and (c) increases the beta cell mass and function by neogenesis from precursor cell and inhibition of apoptosis of beta cell. These features of GLP–1 make it a suitable therapeutic agent for the treatment of type-II DM.

**Development of Exenatide**

Exenatide, is a first long acting analogue of GLP-1 (“incretinomimetic”) that has been approved for treatment of NIDDM. GLP–1, the native gut hormone, after subcutaneous or intravenous administration was proteolytically degraded by the enzyme dipeptidyl peptidase–IV (DPP–IV) and eliminated from the circulation too fast, to be therapeutically useful. This led to development of analogues of GLP–1, having prolonged pharmacokinetics. During the course of these studies, venom isolated from salivary glands of lizard (Gila monster) was found to contain a peptide with amino acid sequence closely resembling GLP–1 and was named as exendin–4. Exenatide was developed as a synthetic analogue of exendin–4. It was found that (a) was not degraded by DPP-IV (b) acted as GLP-1 receptor agonist with higher affinity (c) possessed glucoregulatory effects similar to that of natural GLP-1 and (d) was more stable (5).

**Clinical Studies with Exenatide**

Twice daily subcutaneous administration of exenatide in type–II DM patients resulted in a significant improvement in glycaemic control without causing hypoglycaemia. Treatment with insulin or sulfonylureas requires substantial dose adjustments whereas with exenatide, there is likely to be a standard therapeutic dose for most patients since the probability of hypoglycaemia is low (6). The only disadvantage is that being a peptide it has to be administered subcutaneously. Thus the synthetic analogue of GLP–1, exenatide offers us a new and attractive option with a number of favorable features as an ideal therapeutic agent for the treatment of type-II DM. Exenatide also provides hope for the patients who have failed on oral therapy and in whom insulin therapy is not an alternative due to obesity or possible recurrent hypoglycaemia. This is also likely to halt the progression of the disease through neogenesis and increase in functional activity of beta cells.

**Other Incretin Mimetics**

Liraglutide and CJC–1131 with long half-life are other synthetic analogues of GLP-1, resistant to DPP-IV with biological profile similar to that of GLP-1 that are being evaluated for clinical use (7).

**References**


