

Incretin mimetics: where will they make a difference?

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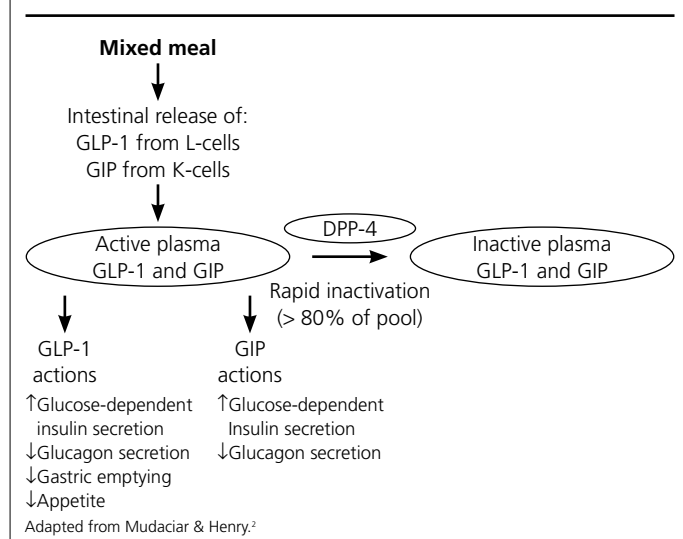
The incretin mimetics have recently been added to our available choice of anti-hyperglycaemic agents in South Africa. As our targets for diabetes control tighten, our available choices of treatment, by necessity, will need to be expanded. The benefits that the incretin mimetics afford include weight loss that is sustained, possible beta-cell sparing and of course significant lowering of the blood glucose level.

These agents address both fasting and post-prandial glucose levels, reduce the risk of hypoglycaemia and avoid the weight gain seen with sulphonylurea drugs and insulin. They exert their effect through a glucose-dependant stimulation of insulin secretion, inhibition of glucagon secretion, slowing of gastric emptying, and by a reduction in appetite.¹

The first in this class of incretin mimetics is the glucagon-like peptide-1 (GLP-1) receptor agonists, of which exenatide (Byetta) has been the first to be introduced to our market. The second, liraglutide (Victoza), is in the process of registration.² The dipeptidyl peptidase 4 (DPP-4) inhibitors act as incretin enhancers, that is by slowing the inactivation of the incretin hormone (GLP-1) and glucose-dependant insulinotropic peptide.

The incretins are released by the gastrointestinal tract in response to food. They are involved with the process of glucose-dependant insulin secretion and if their inactivation is inhibited, will prolong their effect and so slow glucose absorption. Several of these agents are in the process of registration at the Medicines Control Council (MCC) and are not yet available in South Africa (Fig. 1).³

Figure 1. The incretin concept.



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Although the GLP-1 agonists were initially introduced for use at the time of oral agent failure (metformin, sulphonylureas, repaglinide, TZDs) before the use of insulin, more and more studies have been done using these agents in type 2 diabetic patients (T2DM) on various regimens of insulin therapy. At present, exenatide is approved as adjunctive therapy in T2DM for those patients on metformin, sulphonylurea, or a combination of these. It can also be used with a thiazolidinedione. Monotherapy with exenatide is presently under review by the FDA. It would be logical to use this agent earlier in the progressive decline of beta-cell function in T2DM but the cost prevents us from doing so. With the much cheaper generic alternatives of metformin and the various sulphonylureas on the South African market, the cost of GLP-1 agonists is prohibitive.

However, the use of the GLP-1 agonists in patients already on combined oral therapy (metformin) and various insulin regimens is a great possibility. In one study by Bunck *et al.*,⁴ they assessed β -cell function, comparing exenatide subcutaneously twice a day with insulin glargine once daily, titrated to a pre-specified regimen to control blood sugars to between 4.5 and 5.5 mmol/l. Beta-cell function was assessed using an arginine-stimulated hyperglycaemic clamp at weeks zero and 52 and after a four-week off-drug period. All the patients were on metformin treatment.

The authors found a significant improvement of β -cell function in the exenatide group at 52 weeks compared to insulin glargine. It also became clear that ongoing treatment is necessary to maintain this benefit, as both β -cell function and glycaemic control returned to pre-treatment values when these agents were stopped.⁴

It is not possible to review here all the studies where exenatide was compared to various insulin therapies, but all of these concluded that exenatide was not inferior to or better than the insulin regimen. At the same time, exenatide-treated patients did not suffer hypoglycaemia or weight loss, and improved their post-prandial glucose levels while achieving the same or better HbA_{1c} levels (Figs 2, 3).⁴