



Injectable Therapies for Diabetes and Obesity: From Evolution to Revolution

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Over the last two decades, there has been remarkable progress in the management of diabetes and obesity brought about by a better understanding of pathophysiology and improved pharmacological therapies and surgical techniques. In the current issue of this journal, two review articles addressed different aspects of injectable therapy in diabetes and obesity, spanning over a century of scientific achievements from insulin discovery to the latest game-changing twincretins.^{1,2} The first review by Eledrisi and Danjuma compared insulin analogs and human insulins.¹ The second review by Wardeh et al considered the dual glucagon-like peptide-1/glucose-dependent insulinotropic polypeptide (GIP) receptor agonist (RA), tirzepatide, for diabetes and obesity.² The two articles looked at conventional and advanced pharmacological management of two groups of agents addressing the same topics. This commentary underscores some of the key insights of those two articles in a clinical context.

It has been over a century since insulin was first identified and introduced to clinical practice with progressively rising interest and research (►Fig. 1). Since then, insulin has gone through a dramatic evolution ending with insulin analogs that are thought to provide better glucose control and lower rates of hypoglycemia compared to human insulins. Eledrisi and Danjuma have nicely demonstrated in their review that the use of insulin analogs could not be cost-effective if used across the board in all patients with diabetes. The only advantage of the use of insulin analogs seems to be with

type 1 diabetes thus offering less risk of nocturnal hypoglycemia. This benefit seems to be neutral in type 2 diabetes and less obvious especially if it is taken in the context of the hospitalized patient setting where regular insulin seems to provide an excellent and a cheaper solution to keeping blood glucose levels within the recommended target. The authors have nicely tabulated the summaries of different systematic reviews giving the busy practitioner readily handle into very useful information related to different modes of insulin therapy, their mode of action, and their relative costs.¹ The review should help rationalize the use of insulin in a cost-efficient manner. This is particularly relevant to parts of the world with limited access to resources due to long-standing economic hardships, and civil or armed conflicts including many of the Middle East and North African countries.³

For many decades, insulin was the only available injectable therapy for diabetes. Similarly, several effective hypoglycemic agents capable of improving diabetic control were for the most part associated with weight gain. This remained the case till the production of newer innovative oral and injectable hormones such as Amylin and incretin-based therapies. The oral dipeptidyl peptidase 4 (DDP4) inhibitors were introduced first. Later several GLP-1 RAs were introduced. A fundamental difference between GLP-1 RA and DDP4 inhibitors was the effect on weight. Whereas DDP4 inhibitors were weight-neutral, the GLP-1 RA had an advantageous effect on weight. This is particularly relevant to managing diabetes, a condition inherently linked to

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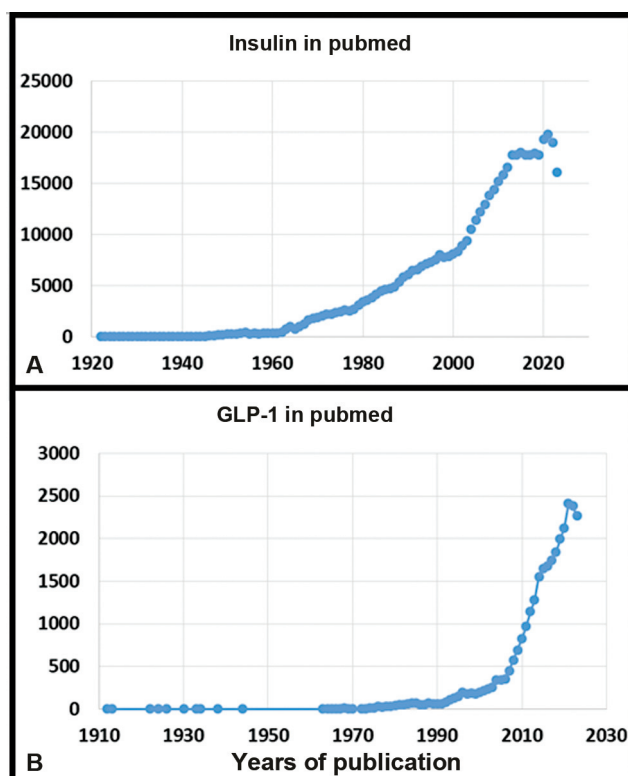


Fig. 1 The number of records over the years retrieved from (A) PubMed (NIH, United States) database on insulin (B) and on GLP-1 and GIP. The progressive rise in productivity and time relationships is illustrated.

overweight and obesity. An increasing body of knowledge has accumulated over a very short period (**Fig. 1**).

GLP-1 RA's come as short-acting like exenatide and lixisenatide, once daily like liraglutide, and longer-acting once-weekly preparations like exenatide, dulaglutide, and semaglutide. The short-acting ones mainly affect postprandial glucose. Long-acting GLP-1 RA is more effective in lowering hemoglobin A1c (HbA1c). Overall, GLP-1 RA does not cause significant hypoglycemia unless combined with drugs known to cause hypoglycemia (i.e., insulin or insulin-secretagogues). They could also be combined for convenience with basal insulin; this combination results in better glycemic control, with a lower rate of hypoglycemia, lower insulin dose, and less weight gain. There are at least two preparations available in clinical use that contain basal insulin combined with GLP-1 RA in one pen: degludec insulin with liraglutide and glargine insulin with lixisenatide. However, GLP-1A should not be combined with DPP 4 inhibitors due to no perceived additional benefit. The benefits of GLP-1 RAs are in improving glycemic control and maintaining a low risk of hypoglycemia while causing significant weight loss. Furthermore, liraglutide, semaglutide, and dulaglutide provide an added benefit of improving cardiovascular outcomes, as shown in several cardiovascular outcome trials.⁴⁻⁶ The main side effects of GLP-1 RA are nausea, vomiting, and diarrhea, all of which are largely dose-dependent. For this reason, they are initiated at low doses and titrated up slowly to minimize side effects.^{7,8} Perhaps, the most important barrier to using these agents more widely is cost, sometimes the best agent is

not available for use simply because of payors' restrictions or total denial of coverage.

In the second review, Wardeh et al have extensively reviewed the evidence on tirzepatide. It is the first member of a new class of dual GLP-1 RA and GIP RA (twincretin). The article elegantly demonstrated the adversary or opposing function of this twincretin where the glucagonostatic effect of the GIP regulates hyperglycemia, where the glucagonotropic function is exerted during normal/hypoglycemic status paving the road for the nonhypoglycemic benefit, like weight modulation, to be accomplished with no further risk of hypoglycemia, a fascinating outcome of a synergistic combination of the two agents together.⁹ Tirzepatide has been extensively studied in terms of diabetes management, as well as in the modulation of cardiovascular risk factors, including weight, fatty liver, hypertension, and dyslipidemia with an overall favorable impact on all the formerly mentioned outcomes.¹⁰ It is worth noting that tirzepatide has shown superiority in both glycemic control (with a relatively low HbA1c of 7.9-8.5%) and weight reduction when it was compared to dulaglutide, semaglutide, insulin glargine, and insulin degludec, with the maximal effect attained at a higher dose of 15 mg weekly.^{11,12} Similarly, the higher amounts of semaglutide showed a comparable effect on weight. However, there are no head-to-head trials so far. From the GLP-1 RA, liraglutide, dulaglutide, injectable semaglutide proven cardioprotective.^{4,13} Tirzepatide was made available in the United Arab Emirates (UAE) in October 2022. Since then, real-world data on its use in over 6,500 patients with diabetes at the Imperial College London Diabetes Center Group in Abu Dhabi are available in an abstract form.¹⁴ Anecdotal, there has been extensive off-label use of tirzepatide for obesity in the UAE. This experience should be subjected to scrutiny to generate real-world data from our region to guide practice with a culturally sensitive approach.

The two review articles in this issue have highlighted the salient technical and conceptual developments of injectable therapies for diabetes and obesity.^{1,2} The evolution of insulin therapy has paved the way for the future use of closed-loop systems for diabetes control. Although the weight-reducing effect of the incretins was discovered by serendipity, it has proven to be a game changer in managing obesity. The twincretins may soon reduce the use of bariatric surgery and limit it to extreme degrees of morbid obesity. Their use may be adopted for chronic use for obesity similar to chronic management of diabetes.

Compliance with Ethical Principles

Ethical approval is not required.

Authors' Contribution

All the authors have contributed equally.

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Conflict of Interest

None declared.

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