Twincretins: Emerging therapies for diabetes and obesity

Sanjay Kalra,[1] Fatema Jawad[2]

The human race is facing a new challenge: the growing pandemic of diabetes and obesity. Current estimates suggest that there are 537 million adults living with diabetes worldwide, including 33 million in Pakistan. The age adjusted prevalence of diabetes is 10% across the globe, and 30.8% in Pakistan.[1] Obesity is even more common: it is expected that 17.5% of all adults, i.e., 1025 million men and women, will be living with obesity by the year 2030. In Pakistan, it is expected that the prevalence will rise to 9% in men (7million) and 17% in women (13 million) by the end of this decade.[2]

Keywords: CagriSema, GLP1RA, GIP, Glucagon receptor, Metabolic syndrome, Tirzepatide.

DOI: 10.47391/JPMA.01-23

The Syndemic

Diabetes and obesity go hand in hand, and "diabesity" is now considered a syndemic: a combination of two epidemics.[3] The impact of diabetes and obesity on individual, societal and national health is well-known. Both disorders lead to significant costs of care, directly and indirectly. It is the complications of these diseases, however, which create the heaviest burden on the health care system. Most of these complications are easily avoidable, provided they are identified, managed or prevented in time.

The KgA1C Paradox

It becomes difficult, at times, to manage multiple co-morbidities simultaneously. Conventional glucose lowering therapy has struggled with the KgA1c paradox.[4] The paradox highlights the fact that many glucose lowering drugs, such as conventional sulfonylureas, glitazones and insulins, lead to weight gain (Kg increase) along with HbA1c reduction. This weight gain negates the beneficial cardiovascular outcomes achieved with glucose control.

Incretin-Based Therapy

Advances in our understanding of the pathophysiology of diabetes, and in its pharmaco-therapeutics, have helped us to overcome the KgA1c paradox. The incretin pathway is listed as a major contributor to glucose homoeostasis, and drugs meant to increase the level of glucagon-like peptide 1 (GLP1)-GLP1 receptor agonists (GLP1RA) and dipeptidyl peptidase 4 inhibitors (DPP4i) are now used to successfully manage diabetes.[5] GLP1RA such as liraglutide, semaglutide and dulaglutide offer the added advantage of beneficial cardiovascular outcomes, while DPP4i such as sitagliptin, linagliptin and vildagliptin have an unparalleled safety record with minimal hypoglycaemia or weight gain. Obesity, too. Is a multifactorial syndrome, with a wide range of therapeutic techniques and targets. The GLP1RAs semaglutide and liraglutide are used for obesity management as well, albeit in higher doses than those used in diabetes praxis.

Newer Co-Formulations

These GLP1RA alone, or in combination with existing drugs, are unable to achieve desired glycaemic and barometric goals in all persons living with diabetes and obesity. Apart from the existing GLP1RA, newer co-formulations like dual and triple agonists for various incretin peptide receptors are being researched.[6] Examples include dual agonists for GLP-1 and glucose-dependent insulinotropic polypeptide (GIP) receptor, dual agonists for GLP-1 and amylin receptor, as well as triple agonists aimed at GLP-1, GLP and glucagon receptors. These drugs act simultaneously at multiple targets, reducing appetite and improving glucose homoeostasis, thus achieving comprehensive gluco-bariatric control.

Tirzepatide

Tirzepatide is a novel twincretin which targets the GLP1 and well as GIP receptors. This once weekly injection is approved by the (United States Federal Drug Administration (FDA) for the management of type 2 diabetes. A metanalysis of seven trials (6609 participants) has reported a dose-dependent lowering of HbA1c, ranging from 1.62% to 2.06%, along with a reduction in body weight of 6.31 to 9.36 kg.[7] The drug is safe and well tolerated, with the most common side effects being mild and transient gastrointestinal symptoms.[7] In a 72 week-long trial, 5mg, 10mg or 15mg once weekly tirzepatide has shown to lead to 15%, 19.5% and 20.9% reduction in body weight in euglycaemic persons with obesity. A

[1]Department of Endocrinology, Bharti Hospital, Karnal, India, [2]Department of Endocrinology and Diabetology, Sindh Institute of Urology and Transplantation, Karachi, Pakistan.

Correspondence: Fatema Jawad. Email: fatemajawad@gmail.com

ORCID ID: 0000-0003-4129-5072

significant weight loss (≥5%) was seen in 85%, 89% and 91% of participants randomized to the 5 mg, 10mg and 15mg dose, respectively.[8]

Cagrisema

CagriSema, a once-weekly subcutaneous combination of semaglutide and a novel amylin analogue, cagrilintide. is another dual agonist, which is undergoing development.[9] A 32-week long phase 2 clinical trial has demonstrated the efficacy and safety of a fixed dose combination of 2.4 mg semaglutide and 2.4 mg cagrilintide, compared to the individual components, in 92 people with type 2 diabetes and overweight. CagriSema achieved a numerically higher HbA1c reduction of 2.18% compared to a semaglutide (1.79%) and cagrilintide (0.93%) alone. A numerically higher weight loss of 15.6% was achieved, compared to semaglutide (5.1%) and cagrilintide (8.1%) alone. A phase 3 development programme for CagriSema in people with type 2 diabetes, and in those with overweight/obesity, is underway.[10]

Pragmatic Approach

The introduction of new drugs in the armamentarium of treatment is always very exciting but one must be mindful of the fact that such drugs should not be used without medical supervision. Dietary restriction, physical activity/ exercise and behavioural modification will continue to remain the cornerstone of diabetes and obesity management. Contra- indications must be ruled out prior to starting twincretin therapy, and close monitoring done to mitigate possible adverse effects which are usually mild and transient. Appropriate patient counseling is necessary in order to explain anticipated benefits as well as side effects. The cost is an important factor to be considered.

References

1. IDF Diabetes Atlas .2021 Available at: https://diabetesatlas.org/atlas/tenth-edition/ Last accessed on 26 August 2022.
2. World Obesity Atlas 2022. Available at: https://www.worldobesity.org/resources/resource-library/world-obesity-atlas-2022 Last accessed on 26 August 2022.
3. Kalra S. Diabesity. J Pak Med Assoc. 2013;63:532-4.
4. Davidson J, Kalra S, Singh V, Fegade M, Singh G, Mane A. Resolving the KgA1c paradox in the management of type 2 diabetes mellitus. Diabetes & Metabolic Syndrome: Clin. Res. Rev.. 2017;11: S159-68.
5. Holst JJ. Incretin therapy for diabetes mellitus type 2. Curr Opin Endocrinol Diabetes Obes. 2020;27:2-10.
6. Kalra S, Bhattacharya S, Kapoor N. Contemporary classification of glucagon-like peptide 1 receptor agonists (GLP1RAs). Diabetes Ther. 2021;12:2133-47.
7. Karagiannis T, Avgerinos I, Liakos A, Del Prato S, Matthews DR, Tsapas A, Bekiari E. Management of type 2 diabetes with the dual GIP/GLP-1 receptor agonist tirzepatide: a systematic review and meta-analysis. Diabetologia. 2022; 17:1-1.
8. Jastreboff AM, Aronne LJ, Ahmad NN, Wharton S, Connery L, Alves B, et al. Tirzepatide Once Weekly for the Treatment of Obesity. New Eng J Med. 2022;387:205-216
9. Kalra S, Arora S, Kapoor N. Person-centered choice of anti-obesity pharmacotherapy. J Pak Med Assoc. 2022;72:1449-50.
10. Novo Nordisk successfully completes phase 2 trial with CagriSema in people with type 2 diabetes. Available at: https://www.globenewswire.com/news-release/2022/08/22/2502111/0/en/Novo-Nordisk-successfully-completes-phase-2-trial-with-CagriSema-in-people-with-type-2-diabetes.html Last accessed on 26 August 2022.