Indian J Med Res 163, April 2026, pp 427-435
DOI: 10.25259/IJMR_2041_2025

Review Article

Evolution of incretin-based therapies: From GLP-1 monotherapy to dual and triple agonists: A new era in metabolic therapy

Monika Gupta[1] & Jitendra Shukla[2]

Departments of [1]Pharmacology, and [2]Internal Medicine, Moti Lal Nehru Medical College, Prayagraj, Uttar Pradesh, India

Received August 2, 2025; Accepted December 21, 2025; Published April 27, 2026

Incretin-based therapies have revolutionised the management of metabolic disorders, transitioning from DPP-4 inhibitors to advanced GLP-1 receptor agonists (GLP-1RAs) and next-generation dual and triple agonists. This review explores the evolving role of incretin pharmacology in type 2 diabetes mellitus (T2DM), obesity, and metabolic dysfunction-associated steatotic liver disease (MASLD). Literature from PubMed, Scopus, and Google Scholar up to July 2025 was reviewed, emphasising pivotal trials and real-world evidence. While DPP-4 inhibitors offer modest glycaemic benefits, GLP1RAs such as liraglutide and semaglutide have demonstrated significant weight loss and cardiometabolic protection. Dual GIP/GLP-1 agonist tirzepatide and triple agonist retatrutide have shown unprecedented efficacy, with up to 24% body weight reduction and improvement in hepatic and inflammatory markers. Agents like cotadutide and efinopegdutide further expand indications to MASLD and metabolic dysfunction associated steatohepatitis (MASH). Despite promising outcomes, challenges persist in terms of cost, accessibility, and the underrepresentation of low- and middle-income countries in major trials. Pharmacogenomic variability may also influence therapeutic response. Incretin-based multi-agonists offer a transformative, multi-system approach to metabolic disease but require tailored implementation. This review provides an updated synthesis of therapeutic developments and outlines priorities for future research, regulatory policy, and equitable global integration as incretin-based therapies have evolved into a versatile class addressing glycaemic control, weight loss, and cardio-metabolic risk.

Keywords GLP-1 receptor agonists; Incretin therapy; MASH; Metabolic syndrome; Type 2 diabetes