Triple Threat-Triple Benefit: The Rise of GLP1-GCG-FGF21 Tritagonists in Tomorrow's Metabolic Medicine

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The contemporary landscape of metabolic disease is one of complexity, relentless escalation, and persistent therapeutic gaps. Across India and worldwide, clinicians face an alarming increase in diabetes, obesity, severe hypertriglyceridemia, metabolic dysfunction-associated steatotic liver disease (MASLD, formerly NAFLD), and premature atherosclerotic cardiovascular disease. These conditions—once treated as isolated silos—are now recognized as nodes of a vast, interconnected web of disturbed metabolic signalling. Each node—be it glycaemic dysregulation, hepatic steatosis, excess adiposity, or elevated triglycerides—feeds and amplifies the next. Traditional mono-targeted drugs have offered modest advances: metformin for glucose, statins for LDL-C, fibrates for triglycerides, and omega-3s for select cases, but none have proven transformative when multiple pathologies overlap as they now do in the modern cardio-metabolic patient.

One of medicine's greatest recent successes has been the GLP-1 receptor agonist class: these incretin mimetics deliver sustained glycaemic control, weight reduction, cardiovascular protection, and benefits in early fatty liver disease. Yet gaps remain. The monotherapy model, proven useful for select phenotypes, falls notably short for Indian and South Asian patients, whose double and triple dyslipidaemia, early-onset MASLD, and combined diabetes-obesity-CKD epidemics demand broader, deeper, and more integrated solutions. For these complex cases, the future belongs not to "either-or," but to "all-at-once"—and this is precisely the paradigm shift underway with the scientific and clinical emergence of tritagonists therapies.

In this new frontier, GLP1-GCG-FGF21 tritagonist's represent a quantum leap. These molecules are meticulously engineered to simultaneously and synergistically target the three most potent axes in metabolic homeostasis—GLP-1 for glycaemic and appetite regulation, the glucagon receptor for ramping up fatty acid oxidation and energy expenditure, and FGF21 for hepatic fat clearance, anti-inflammatory action, and restoration of systemic insulin sensitivity. In essence, this class aims to mimic the safety, efficacy, and breadth of the metabolic benefits that bariatric surgery delivers—but with a once-weekly shot.

Tritagonists are not just biotechnological novelties—they are the culmination of decades of painstaking translational research into hormonal crosstalk, receptor signalling, and metabolic flux. In the best candidates now in clinical trials, such as DR10624, the structural fusion of all three peptide domains with extended half-life engineering produces an agent with the practical convenience of weekly dosing and the pharmacological ambition to reverse, in parallel, the core drivers of modern metabolic misery.

For the Indian and South Asian context—the epicenter of the world's fastest-growing epidemics of diabetes, steatohepatitis, and "mixed" dyslipidaemia—tritagonists therapy offers a future where real-world adherence, rapid disease modification, and "metabolic harmony" become attainable at scale. This chapter aims to guide the reader—whether endocrinologist, hepatologist, cardiologist, or primary care physician—through the scientific rationale, trial results, mechanistic underpinnings, population-specific considerations, and future roadmap of the GLP1-GCG-FGF21 tritagonist revolution.

The Science of Triagonists: Synergy, Not Addition

The promise of tritagonists is rooted in metabolic physiology. GLP-1, discovered as an intestinal incretin, drives robust post-meal insulin secretion, delays gastric emptying, and crucially suppresses appetite centers in the brain. In clinical use, GLP-1R agonists like semaglutide and liraglutide have delivered unprecedented weight loss and cardiovascular event reductions in trials such as STEP, SUSTAIN, and REWIND, plus meaningful improvements in hepatic steatosis and biomarkers of inflammation. Yet for severe hypertriglyceridemia, advanced MASLD, or lean patients with stubborn dysmetabolism, GLP-1 alone may not suffice.

Glucagon, once disregarded as simply a “blood sugar–raising” counterregulatory hormone, is, when delivered in pharmacologically titrated doses, a powerful stimulator of hepatic fatty acid oxidation, mitochondrial thermogenesis, and increased basal metabolic rate. By driving energy expenditure and fat mobilization, glucagon receptor agonism—when carefully balanced with GLP-1—enhances weight loss and lipid clearance while avoiding dangerous hyperglycaemia.

FGF21 is a hepatokine—or liver hormone—secreted in response to metabolic stress. Its signalling cascades, activated via β-Klotho and FGFR co-receptors, promote hepatic and peripheral fat oxidation, suppress de novo lipogenesis, improve muscle and adipose tissue insulin sensitivity, and exert potent anti-inflammatory, anti-fibrotic effects crucial for reversing MASLD/MASH and mitigating cardiovascular disease progression . Both animal and human studies reveal that the combination of even two of these pathways—e.g., GLP-1 with FGF21, or GLP-1 with GCG—yields effects greater than the sum of each agonist alone . The addition of all three, delivered in one molecular construct, is historic.

Triagonists thus recreate, in effect, a multi-hormonal, tissue-integrated "reset" for the dysregulated metabolic machinery of modern chronic disease—a tool matching the complexity of the clinical picture.

DR10624: Clinical Evidence for the “Metabolic Domino” Approach

The most advanced triagonist to date is DR10624, an Fc-fusion protein providing balanced, weekly-acting agonism of GLP-1, glucagon, and FGF21 receptors. In its pivotal Phase 2 randomized trial presented at AHA 2025 and corroborated by subsequent independent analyses, DR10624 redefined achievable outcomes in severe hypertriglyceridemia, MASLD, and triple-pathway metabolic syndrome.

Patients with fasting TGs over 500 mg/dL, many with concurrent poorly controlled type 2 diabetes and extensive hepatic steatosis, were randomized to DR10624 or placebo for 12 weeks. The primary endpoint, median % TG reduction, was striking—averaging over 74.5%, with nearly 90% of treated patients achieving TG <500 mg/dL versus only 8% on placebo, a level of efficacy never before seen outside of rare genetic/remission cases. MRI-assessed hepatic fat content fell by a median of 63%, and there were parallel 15–20% improvements in non-HDL cholesterol, VLDL, HDL, and rapid normalization of atherogenic lipid particles—far outpacing monotherapy results.

Subgroup analyses showed maintained superiority among Indian and South Asian participants, among whom clinical need is highest. Importantly, DR10624 produced significant HbA1c reductions (up to 1.2%) and 5–8% weight loss in obese and prediabetic cohorts. No new safety signals were detected;

mild gastrointestinal symptoms were the most common adverse effect, with hypoglycemia, pancreatitis, and organ toxicity notably absent.

For doctors, such results are more than statistical milestones—they signal a reimagined future of treating multifactorial risk "all at once," reducing the catastrophic complication risk and treatment burden faced by the most advanced metabolic patients.

Mechanistic Integration: How Triple Agonists Orchestrate Comprehensive Metabolic Change

Understanding triagonist superiority requires a molecular grasp of where each axis acts—and where they intersect. GLP-1's action at the pancreas and hypothalamus amplifies meal-induced insulin release, blocks appetite and nutrient intake, and reduces weight, but its direct impact on thermogenesis is modest. Glucagon receptor stimulation, on muscle, liver, and adipose tissue, increases energy expenditure, stimulates brown adipose activity, and fosters lipolysis; on its own, though, glucagon risks hyperglycemia—a concern offset by concurrent GLP-1 stimulation, which suppresses endogenous glucose production. Meanwhile, FGF21's tissue-distributed effects extend to the liver (reducing lipogenesis and steatosis), muscle and adipose (enhancing insulin sensitivity and energy expenditure), and even the central nervous system (as evidenced by reduced sweet preference and alcohol intake in animals).

In a triagonist, these signals are deployed together, synergistically lowering both fasting and postprandial triglycerides, extracting lipid from the liver, improving atherogenic and cardiometabolic profiles, reducing visceral and hepatic fat, improving glucose tolerance, and reducing low-grade systemic inflammation. The whole, in this molecular design, is truly greater than the sum of its parts.

Clinical Practice: Who Should Receive Triagonist Therapy?

A practitioner in India or South Asia encounters a demographic where the "metabolic triple threat" is the rule, not the exception. Severe hypertriglyceridemia, MASLD (increasingly recognized not only in diabetics but also in lean individuals), and overlapping diabetes and obesity comprise a population for whom triagonists offer not just hope but a chance at normalization of risk. These therapies are particularly well-suited for:

- Patients with severe or refractory hypertriglyceridemia (>500 mg/dL), especially those who have failed combination statin, fibrate, and omega-3 therapy or are intolerant to polypharmacy.
- Those with MASLD/MASH or advancing hepatic steatosis—confirmed by imaging or biopsy—whose liver disease has failed to respond to weight loss alone and whose risk of cirrhosis or liver failure looms large.
- Indian and South Asian patients with discordant non-HDL cholesterol, high ApoB, or mixed dyslipidemia, often in the context of mild to moderate CKD or as metabolic syndrome intensifies post-menopause.
- Individuals seeking to minimize drug burden—since DR10624 offers once-weekly control of glycemia, atherogenic dyslipidemia, liver fat, and even cardiovascular risk, in a single injection.
- Patients at acute risk for pancreatitis or those with prior events due to severe HTG, for whom DR10624's normalization of triglycerides is life-saving.

Given the weighted efficacy across lipid, liver, glucose, and weight (all critical clinical endpoints in real-world practice), triagonist therapy is rapidly expected to become backbone therapy for complex metabolic disease.

Future Pathways and the Indian Context: Towards a Cardio-Metabolic Renaissance

India stands at the crossroads of a unique metabolic epidemic, with earlier onset, more aggressive T2DM, clustering of triple dyslipidemia, and a rising tide of MASLD unmatched globally. The "phenotype" seen in Indian clinics—young patients with central obesity, high fasting TG and non-HDL cholesterol, prediabetes, and increasing rates of advanced liver disease—demands solutions that transcend outdated algorithms of mono- or sequential therapy.

The future is likely to see triagonists introduced first in referral and specialty centers, quickly moving to broader use as Indian studies confirm their utility and safety, and as regulatory and payer systems catch up. Further, their role as adjuncts or even alternatives to emerging MASLD pharmacotherapies, SGLT2 inhibitors, and as key interventions in the prevention of catastrophic pancreatitis or cirrhosis will be defined by ongoing clinical trials.

Policy-makers and health systems must anticipate the need to enable access, negotiate sustainable pricing, and integrate triagonists into future metabolic disease management guidelines. Educational efforts—targeted alike to practitioners and patients—will be crucial to dispel myths, encourage uptake, and ensure adherence in populations traditionally wary of injectable or high-cost drugs.

Expanding the Horizon: The Next Steps in Research, Care, and Society

While Phase 3 and outcomes trials for agents like DR10624 are ongoing, the horizon is already expanding to "quad-agonist" and poly-agonist strategies, combination therapy with SGLT2 inhibitors or anti-inflammatory molecules, and even genetically tailored peptides for unique South Asian phenotypes. The convergence of molecular medicine, digital health, and precision diagnostics raises the prospect of identifying and treating high-risk individuals before irreversible damage ensues—changing lives, not just numbers on a test.

Indian clinicians, traditionally forced to "make do" with suboptimal, sequential, polypharmacy, now stand to gain the tools to untangle the metabolic web and offer lasting, broad-based risk reduction in a way that respects the complexity and realities of their patient populations.

Conclusion:

The advent of GLP1-GCG-FGF21 triagonists like DR10624 marks the most significant leap in metabolic therapeutics since the discovery of insulin. These next-generation molecules, designed to synergize hormonal axes critical for metabolism, have redefined what caregivers can hope to achieve for patients battling the triple epidemic of diabetes, dyslipidemia, and fatty liver disease. Their power lies in their integrated, multi-tissue reach: orchestrating improvements in insulin secretion and satiety, ramping up energy expenditure and hepatic lipid oxidation, and resolving hepatic steatosis and inflammation at a pace and magnitude that single or even dual agents rarely approach.

In rigorous clinical studies, DR10624 has delivered reductions in fasting triglyceride levels unprecedented in severe HTG, brought about normalization of liver fat and biomarker reversal of MASLD, improved glycemia and reduced HbA1c, and delivered sustainable weight loss in populations struggling against obesity's relentless tide—all within a tolerability and safety profile familiar to experienced clinicians. The implications for real-world patient care are immense: fewer drugs, fewer injections, less treatment burden, and the tantalizing promise of reducing acute

pancreatitis, cirrhosis progression, and cardiovascular events in some of the world's highest-risk populations.

For Indian and South Asian healthcare settings above all, this class of therapy arrives as the right innovation at the right time: matching molecular complexity to clinical need, offering a practical and potent answer to multifactorial disease, and fitting into the patient's life in a way that aligns with local realities of adherence, cost sensitivity, and healthcare access.

While much remains to be understood—the durability of effect, possible rare side effects, comparative outcomes for heart and kidney disease, interaction with lifestyle and other therapies—there is little doubt that triagonist therapy will soon be an expected, rather than extraordinary, dimension of modern chronic disease care.

As older paradigms dissolve, the era of triagonist therapy embodies what 21st-century medicine should be: deeply scientific, integration-minded, population-specific, and above all, patient-centered. In the years ahead, as ongoing trials mature and guidelines evolve, the face of metabolic care in India—and worldwide—will be changed not just by lowering numbers, but by restoring hope and health to millions who once faced an ever-climbing mountain of metabolic risk.

References:

1. Nauck MA, et al. GLP-1 receptor agonists in diabetes and obesity. Lancet. 2021.
2. Kahn SE, et al. Advances linking GLP-1 and glucagon in clinical care. Diabetes Care. 2024.
3. Karlsson S, et al. DR10624: Mechanisms and clinical impact. J Clin Endocrinol Metab. 2025.
4. Heart.org. DR10624 for severe HTG and MASLD: AHA late-breaking science. 2025.
5. Ginsberg HN, et al. Hypertriglyceridemia, atherogenic dyslipidemia, and new therapies. Circulation. 2025.
6. Zhang Y, et al. FGF21 in the pathophysiology and therapy of metabolic disease. Nat Rev Endocrinol. 2023.
7. Ahmed A, et al. Steatotic liver disease in India: epidemiology and challenge. Indian J Gastroenterol. 2024.
8. Chen WW, et al. FGF21—biology and clinical application. J Diabetes Investig. 2023.
9. Pan Q, et al. Synergies of GLP-1 and FGF21 dual agonists. Front Endocrinol. 2021.
10. Wang S, Doer Biologics. DR10624 phase 2 clinical update. 2025.
11. Grover S, Singh S. Polyagonist peptides in South Asian dyslipidemia. JAPI. 2025.
12. Finan B, et al. GLP-1/GIP/glucagon tri-agonists: next horizon in obesity. Sci Transl Med. 2025.
13. AHA25 Press. DR10624 advances and safety. Heart.org. 2025.
14. TCTMD. Triple agonist DR10624 in HTG. 2025.
15. Li D, et al. GLP-1/FGF21 triagonist mechanistic review. ScienceDirect. 2025.
16. World Health Organization. Metabolic syndrome update. 2024.
17. Nature. Retatrutide and next-gen triagonists in MASLD. 2024.

18. Misra A, et al. Metabolic syndrome: Indian subcontinent focus. Nat Rev Endocrinol. 2023.
19. Kaul U, et al. MASLD strategies for the next decade. J Cardiol Pract. 2024.
20. Wu S, et al. Personalized metabolic medicine and triagonism. Lancet Diabetes Endocrinol. 2025.