Semaglutide Hype or Hope: Evidence-based Review in Diabesity

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Abstract

India is struggling with the twin epidemics of diabetes and weight issues, holding the second position globally in the former and third in the latter. Despite multiple advancements with therapies that offer glycemic control and weight benefits, there has remained a gap for a comprehensive drug for the management of "diabesity." Semaglutide, since its global approval in 2017, has become a blockbuster, owing to the popularity of "Ozempic." While Ozempic has been traditionally approved for glycemic control in type 2 diabetes mellitus (T2DM), it does offer significant other benefits powerful weight loss, cardiovascular benefits, renal protection benefits, and functional improvement in peripheral arterial disease. The drug is approved in India for first-line use in adults with T2DM as an adjunct to diet and exercise. The long use of semaglutide globally and in India has ensured adequate data on efficacy and safety, ensuring confidence and trust. Gastrointestinal side effects are the most common adverse events seen with the molecule, as with other GLP-1 drugs. This review highlights the global clinical data and practicalities of the use of Ozempic in diabesity in the Indian context.

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Diabesity and Diabetes–Problem Statement in India

Type 2 diabetes (T2D) and obesity are two interconnected pandemics and are together called "Diabesity." In India, obesity and overweight issues are responsible for approximately 70% of T2D cases, and even more in many other countries.[1] India now has an estimated 101 million adults with diabetes and 136 million with prediabetes, corresponding to an adult dysglycemia prevalence of roughly 25%.[2] National Family Health Survey-5 (2019–2021) data indicate that about 24% of women and 22.9% of men aged 15–49 years are overweight or have obesity (BMI ≥25 kg/m^2), with a two- to three-fold increase in prevalence since NFHS-3.[3] In two large prospective cohorts, higher BMI was a dominant predictor of T2D: in women (*n* = 114,281; 14-year follow-up), obesity was associated with ~30–90× higher diabetes risk vs normal weight; even small BMI increases were linked to large risk jumps (e.g., BMI 33.0–34.9 kg/m^2 had 13.7× higher risk than BMI 31.0–32.9 kg/m^2); a similar graded pattern was seen in men, with obesity associated with ~8–50× higher risk.[4,5] These findings confirm a substantial overlap between diabetes and excess adiposity, contributing to a large pool of individuals with "diabesity" along with multiple metabolic risk factors.

The illustration of diagnostic criteria for diabetes/prediabetes and for overweight/obesity is given in Figure 1. Overlaps define diabesity (diabetes + obesity) and prediabesity (prediabetes + overweight), which represent cardiometabolically high-risk phenotypes.

Contemporary guidelines for T2D management (e.g., ADA Standards of Care 2026; RSSDI clinical practice recommendations 2022) therefore emphasize early use of glucose-lowering agents that provide sustained glycemic control, meaningful weight loss, and cardiorenal risk reduction.[6,7] In this context, the choice of first-line pharmacotherapy for type 2 diabetes in India should be driven by good evidence for both efficacy on hyperglycemia and weight issues and for prevention of cardiovascular and renal complications.

Characteristics of an Ideal First-line Agent for Diabesity

The ideal first-line therapy for T2D (especially in patients with weight issues) should fulfill several key criteria (Table 1).[8,9]

Unmet Needs with Current First-line Therapies in India

In practice, the most common first-line pharmacotherapy for T2D in India has traditionally been metformin, with sulfonylureas often added as second-line (due to low cost), with newer classes like DPP-4 inhibitors or SGLT-2 inhibitors being increasingly used (Fig. 2). However, each of these options has limitations when tackling diabesity.[8,9]

- *Metformin*: Weight-neutral, but many patients experience gastrointestinal side effects. Monotherapy may not achieve sufficient HbA1c reduction in moderate-to-severe hyperglycemia, and it provides no cardiovascular or other end-organ risk reduction proven in trials. Further, metformin is contraindicated in advanced renal impairment and has been associated with vitamin B_{12} deficiency.
- *Sulfonylureas (SUs)*: These insulin secretagogues (e.g., glimepiride, gliclazide) are effective at lowering glucose initially, but they often cause weight gain and carry a significant risk of hypoglycemia. Moreover, they have not shown CV benefits; some studies raise concerns about their long-term CV safety. Long-term use of SUs has been associated with exhaustion of pancreatic beta cells, leading to potential ineffectiveness.
- *DPP-4 inhibitors*: These drugs (e.g., sitagliptin, vildagliptin) are weight-neutral and well-tolerated, but their glycemic efficacy is modest (average reduction ~0.6–0.8%). They have not demonstrated a major reduction in adverse cardiovascular events in large trials (they are considered CV-neutral), and their effect on weight or other organ outcomes is minimal. DPP-4 inhibitors may be insufficient as first-line monotherapy.
- *SGLT-2 inhibitors*: These drugs (e.g., empagliflozin, dapagliflozin) do offer multiple benefits, including moderate glucose lowering and modest weight loss (~2–3 kg), along with proven reductions in heart failure and CKD progression. However, as an initial therapy, they have

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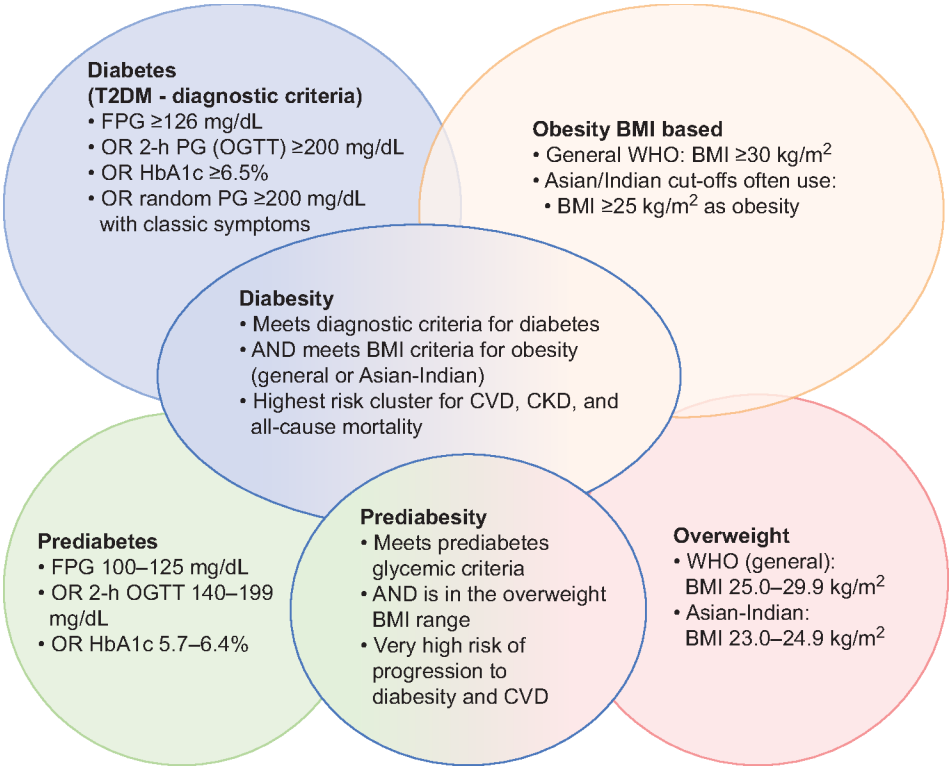

Fig. 1: Diagnostic overlap of diabetes, obesity, prediabetes, and overweight: Defining "diabesity" and "prediabesity." While these are defined overlaps, there are also other overlaps that exist in the real-world clinical setting

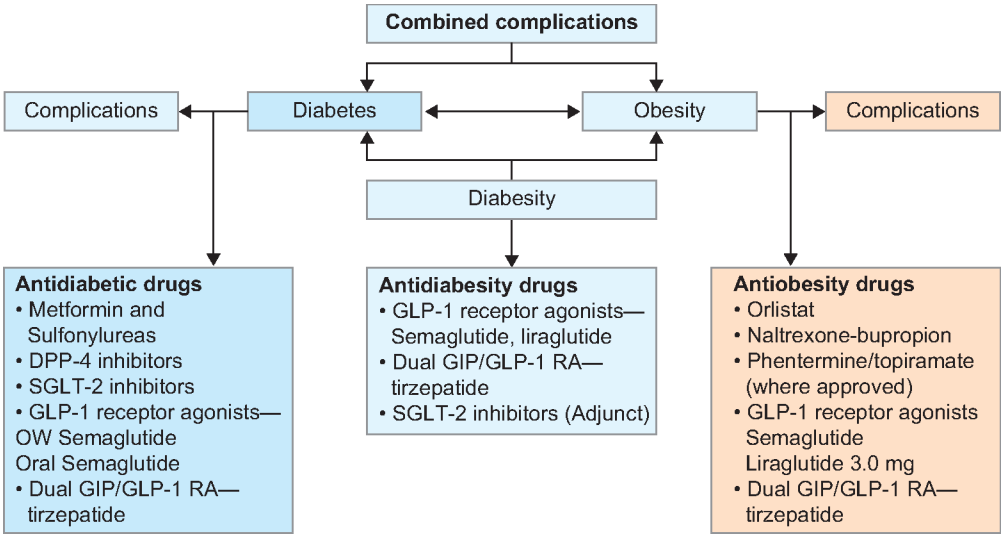

Fig. 2: Relationship between diabetes, obesity, and "diabesity" and corresponding treatment classes

some drawbacks: HbA1c reduction is mild to moderate (~0.5–1.0%), and can cause genitourinary infections.

Collectively, these limitations mean that Indian patients on these first-line agents fail to achieve optimal outcomes in diabesity management. There remains an unmet need for a first-line medication that can simultaneously deliver potent glucose-lowering, promote weight loss, and improve long-term cardiovascular and renal outcomes.

Semaglutide as an Ideal First-line Solution vs Current Options

This review focuses on weekly injectable semaglutide 1.0 mg (titrated upwards from 0.25 mg and 0.5 mg)–known popularly with the brand name of Ozempic® from Novo Nordisk. Across the SUSTAIN phase 3 program, once-weekly injectable semaglutide 1.0 mg produced mean HbA1c reductions of ~1.5–1.8% with substantial weight loss over ~30–56 weeks, clearly exceeding the glycemic and weight effects of DPP-4 inhibitors (~0.6–0.8% HbA1c, weight-neutral) and SGLT2 inhibitors (~0.5–1.0% HbA1c, ~2–3 kg weight loss), and avoiding the weight gain and hypoglycemia seen with sulfonylureas. In SUSTAIN 2, 3, and 4, semaglutide was consistently superior to sitagliptin, once-weekly exenatide, and insulin glargine, respectively, for HbA1c and weight outcomes when added to metformin, with or without other oral agents.[10–12] These data position semaglutide as a single agent

Table 1: Key characteristics of an ideal first-line pharmacologic agent for diabesity (diabetes with weight issues)

Criterion	*Requirement/definition*	*Rationale in diabesity context*
Potent glycemic control	Produces substantial HbA1c reduction and durable glycemic control	Reduces risk of microvascular complications (retinopathy, nephropathy, neuropathy) in high-risk patients
Weight reduction	Induces clinically meaningful weight loss	Addresses obesity as a core driver of insulin resistance and cardiometabolic risk
Convenient dosing and adherence	Simple regimen (e.g., once-daily or once-weekly) with low treatment burden	Enhances long-term adherence in a chronic, lifelong disease
Risk of hypoglycemic events	Low inherent risk of hypoglycemia	Addresses the key barrier of hypoglycemia in the management of diabetes and diabesity, potentially improving adherence in the long term
Long-term organ protection	Demonstrates improvement in cardiovascular and renal outcomes, plus reduction in major adverse events and mortality	Aligns with guideline shift from "glucose-centric" to "cardiorenal risk-centric" diabetes management
Proven safety profile	Acceptable GI/other AEs, no major organ-specific toxicity; supported by RCTs and real-world data	Suitable for early, long-term use in broad populations, including older adults and those with comorbidities

Table 2: How current first-line classes and semaglutide meet key "diabesity" criteria

Drug class	*Strong HbA1c lowering*	*Significant weight loss*	*Proven CV benefit (MACE reduction)*	*Proven renal protection*	*Low hypoglycemia risk*	*Simple dosing*
Metformin	✓	Δ (neutral)	Δ (legacy only)	Δ (does not provide benefit)	✓	✓ (daily)
Sulfonylureas	✓	× (gain)	×/Δ (uncertain)	×	×	✓ (daily)
DPP-4 inhibitors	Δ (modest)	× (neutral)	× (CV-neutral)	×	✓	✓ (daily)
SGLT-2 inhibitors	Δ (moderate)	✓	✓ (mainly HF/ at-risk)	✓	✓	✓ (daily)
Semaglutide 1.0 mg	✓✓ (very high)	✓✓ (marked)	✓ (↓ MACE in SUSTAIN-6)	✓ (FLOW, albuminuria ↓)	✓ (intrinsic low hypoglycemia)	✓ (weekly)

✓✓, clearly superior/strong effect; ✓, clearly meets criterion; Δ, partial/limited; ×, does not meet criterion or opposite effect

capable of equitably achieving targets for both glycemia and body weight, in contrast to current first-line drugs, which typically optimize one domain at the expense of the other (Table 2).

Further, data from the SUSTAIN 6 cardiovascular outcomes trial shows a 26% reduction of 3-point major adverse cardiovascular events in people with established ASCVD or at high risk of ASCVD. The FLOW trial, a dedicated renal outcomes trial with semaglutide, showed a significant 24% risk reduction of renal end-points. Also, the STRIDE trial has shown a 13% functional improvement in peripheral arterial disease (PAD) outcomes with semaglutide.

Contemporary guidelines position semaglutide ahead of other molecules: ADA/EASD and AACE recommend GLP-1 RAs with proven CV benefit (including semaglutide) as preferred early therapy in people with type 2 diabetes and established ASCVD, high CV risk or obesity, independent of metformin use; ADA standards 2026 also position GLP-1 RAs as the 4th pillar of CKD management (based on FLOW results); RSSDI guidance similarly highlights GLP-1 RAs in Indians living with obesity/overweight and type 2 diabetes mellitus (T2DM) with added cardiorenal risk. Thus, semaglutide aligns closely with the "ideal" first-line diabesity agent with high glycemic control efficacy, significant weight loss, low hypoglycemia risk, and outcome benefits.

The ADA 2026 and RSSDI 2022 recommendations endorse early use of GLP-1 RAs and SGLT-2 inhibitors with proven CV and renal benefit, particularly in people with obesity, ASCVD, or CKD, rather than focusing only on metformin-based HbA1c control.[6,7] Reflecting this evidence, the 2025 update of the WHO Model List of Essential Medicines added semaglutide, dulaglutide, liraglutide, and tirzepatide for adults with T2DM, established cardiovascular or chronic kidney disease, and obesity (BMI ≥ 30 kg/m^2), based on data showing improved glycemic control, weight loss, and reduced premature mortality with GLP-1-based therapy.[13]

Clinical Evidence: Efficacy and Outcomes with Semaglutide

Glycemic Control

In SUSTAIN 1 (drug-naïve T2DM), semaglutide reduced HbA1c by 1.55% at 30 weeks; 80% of patients achieved HbA1c < 7%.[14] In SUSTAIN 2, semaglutide added to metformin ± TZD reduced HbA1c by 1.6% vs 0.5% with sitagliptin.[10] Similar advantages were seen versus once-weekly and insulin glargine.[11,12,15,16] Subgroup analyses of SUSTAIN results reveal up to 2.8% mean reduction of HbA1c in people with high baseline HbA1c of more than 9%. Real-world SURE studies report HbA1c reductions of ~ 1.5% in routine practice.[17]

Weight Loss

Across SUSTAIN 1 to 4, semaglutide produced a mean weight loss of ~4–6 kg, versus ~1–2 kg with sitagliptin or canagliflozin, and weight gain with basal insulin and sulfonylureas.[10,14,18] In SUSTAIN 2, weight change was–6.1 kg with semaglutide vs–1.9 kg with sitagliptin.[10] Approximately two-thirds of patients achieved ≥5% (clinically meaningful) weight loss with semaglutide. Subanalysis data of SUSTAIN show that the mean weight loss reached up to ~8 kg in people with high baseline BMI. It is important to note that achieving weight loss in T2D is always challenging (as evident from studies in nondiabetic people with obesity, where the weight loss magnitude is much higher): roughly half of body-weight variability is attributed to genetic factors and half to environmental influences (e.g., energy-dense diets and lower physical activity), and body weight is tightly defended by interacting hormonal, metabolic, and neural mechanisms. After diet-induced weight loss, adaptive biological responses

tend to increase appetite and favor weight regain, contributing to plateaus and making sustained weight reduction more difficult in people with diabetes.[19]

Cardiovascular Outcomes

In SUSTAIN-6, semaglutide (0.5 or 1.0 mg weekly) in T2D (with established ASCVD or high risk of ASCVD) reduced 3-point MACE by 26% vs placebo over a median 2.1 years (HR 0.74; 95% CI 0.58–0.95), with a marked reduction in nonfatal stroke.[11]

Renal Outcomes

In SUSTAIN-6, semaglutide reduced the composite kidney outcome (new or worsening nephropathy) by 36% (HR 0.64; 95% CI 0.46–0.88), mainly via lower incidence of new macroalbuminuria.[11] The dedicated FLOW trial in T2DM with CKD (eGFR 25–75 mL/min/1.73 m^2 and albuminuria) reported that semaglutide reduced the primary composite kidney outcome (sustained ≥50% eGFR decline, kidney failure, or renal/CV death) by 24%.[20,21] Additionally, UACR improvement was seen by around 32% vs placebo. These results translated roughly to 5 additional years of high-quality life before ESRD development.

Peripheral Artery Disease and Limb Outcomes

The STRIDE study focused on people with T2D and early peripheral artery disease (PAD). Semaglutide led to a significant improvement in functional capacity. Over 12 months, semaglutide improved maximal treadmill walking distance by ~40 meters on average (~13% improvement from baseline). Patients also reported better leg pain symptoms and quality of life. These signals position semaglutide as a therapy that may reduce limb-related complications (possibly even amputations, as suggested by some observational data) in addition to protecting the heart and kidneys.[22,23]

Weekly Convenience, Safety, and Legacy

Semaglutide's convenient once-weekly regimen (0.25 mg initially for 4 weeks, 0.5 mg for the next 4 weeks, and then 1.0 mg) reduces dosing burden. Patient-reported outcomes demonstrate greater treatment satisfaction and preference for once-weekly semaglutide vs once-daily injections in SUSTAIN and SURE studies.[24]

Safety profile is typical of GLP-1 RAs: gastrointestinal AEs (nausea, vomiting, diarrhea) are the most frequent, generally mild to moderate, transient, and mitigated by stepwise titration; hypoglycemia is rare unless combined with insulin or sulfonylureas. In SUSTAIN-6, an increased risk of diabetic retinopathy complications was observed in patients with preexisting advanced retinopathy who achieved large, rapid HbA1c reductions in a short duration.[11] This is also in line with large-scale studies such as DCCT and UKPDS, wherein a sudden lowering of sugars led to a temporary worsening of retinopathy in high-risk patients. However, improvement in microvascular complications (including retinopathy) in the long run has been shown in these studies with continued intensive control. There have been isolated reports of the association of GLP-1 RAs with NAION (non-arteritic anterior ischemic optic neuropathy/neuritis). These reports are predominantly from centers that are ophthalmic centers, where there is a potential identification bias–NAION has risk factors including obesity, overweight, hypertension, T2D, and concomitant PDE-5 inhibitor use. Pooled analysis of data (presented at EASD 2025) from semaglutide RCTs shows a comparable incidence of NAION versus placebo, indicating no clear causal association with semaglutide. EMA has recommended a label update in the EU to include NAION as a "very rare" adverse drug reaction (incidence of up to 1 in 10,000). As a cautionary measure, high-risk people can undergo an ophthalmic examination to rule out potential risk factors, including a crowded optic cup–disk ratio.[11]

No consistent signal has been seen for pancreatitis or medullary thyroid carcinoma in human data. The broader GLP-1 RA class (liraglutide, dulaglutide) has independently demonstrated CV and renal benefits, and semaglutide extends this class legacy with greater potency for HbA1c/weight and now dedicated kidney and obesity/CV evidence.[11,20,25–28]

Summary and Conclusion—Semaglutide as an Ideal First-line Agent in India

For Indian patients, where diabesity is common and cardiorenal complications drive morbidity and cost, a first-line therapy that simultaneously and robustly addresses glycemia, weight, and cardiorenal risk is desirable. Semaglutide delivers large HbA1c reductions, clinically meaningful weight loss, risk reductions in MACE, and slower kidney disease progression, additional PAD functional improvement, with inherently low hypoglycemic risk and an acceptable, predictable safety profile. With generic versions lined up for launch in India, the use of semaglutide is bound to increase, although the safety, quality, and consistency of generic semaglutide have yet to be time-tested. The innovator molecule, Ozempic® has stood the test of time since its US-FDA approval in 2017. Compared with traditional first-line drugs, Ozempic® offers the most comprehensive "diabesity" management profile in a single agent. The "Ozempic hype" is not merely just hype but rather gives substantial hope to Indian clinicians and patients alike as a worthy tool to correct the grim cardiometabolic picture in India and globally.

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Conflict of Interest

Nil

Authors' Contributions

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NA

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