

Review Article

The GLP-1 Nutritional Paradox: A Global Meta-Analysis of Sarcopenic Risks and Micronutrient Gaps in the Post-Obesity Era

Safwan Hungund¹

1. Ramrao Adik Institute of Technology (RAIT), India

While the world celebrates the apparent end of the obesity epidemic through glucagon-like peptide-1 receptor agonist (GLP-1RA) pharmacotherapy, a largely uncharacterised crisis is quietly taking shape: the *malnutrition of the medicated*. GLP-1 receptor agonists, including semaglutide (Ozempic, Wegovy) and the dual GIP/GLP-1 agonist tirzepatide (Mounjaro, Zepbound), now constitute a pharmaceutical market valued at over USD 62 billion in 2025 and are consumed by tens of millions of individuals worldwide. Yet the clinical discourse remains almost entirely fixated on weight reduction endpoints, while the nutritional consequences of chronic caloric suppression, altered gastric emptying, and rapid lean-mass loss receive comparatively little systematic attention. This review addresses that gap through a structured synthesis of data drawn from landmark randomised controlled trials (STEP 1, SURMOUNT-1, SURMOUNT-5), large-scale observational databases encompassing more than 480,000 adults, expert consensus documents, and current clinical nutrition guidelines. We demonstrate that GLP-1RA therapy is associated with lean-mass loss constituting 26–40% of total weight lost, that newly diagnosed nutritional deficiencies affect up to 22% of users within twelve months, and that reported protein intake among GLP-1 users falls to approximately 54 grams per day – critically below muscle-preservation thresholds. Building on this evidence, we introduce two original analytical constructs: (1) the Nutrient Density Requirement Index (NDRI), a quantitative framework that calculates the proportional increase in protein and micronutrient intake per kilocalorie that a GLP-1 user must achieve relative to a non-medicated person to maintain lean-mass homeostasis; and (2) the Metabolic Quality Index (MQI), a novel composite metric that reframes weight-loss success in terms of the fat-to-lean-mass loss ratio rather than total kilograms lost. Together, these constructs provide clinicians, dietitians, and policy-makers with actionable tools for the first evidence-based *Nutritional*

Safety Protocol for GLP-1 Pharmacotherapy. The protocol is proposed as a replicable clinical standard applicable across primary care, endocrinology, and bariatric medicine worldwide.

Corresponding author: Safwan Yusuf Hungund, Safwanhungund@gmail.com

1. Introduction

The emergence of GLP-1 receptor agonists as first-line obesity pharmacotherapy represents one of the most significant paradigm shifts in modern metabolic medicine. Semaglutide 2.4 mg/week (Wegovy; Novo Nordisk) and tirzepatide 15 mg/week (Zepbound; Eli Lilly) respectively demonstrated mean weight reductions of 14.9% and 20.9% from baseline in their respective pivotal phase 3 trials, outcomes previously achievable only through bariatric surgery ^{[1][2]}. The global GLP-1 receptor agonist market was valued at approximately USD 62–66 billion in 2025 and is projected to reach USD 185–254 billion by the early 2030s ^{[3][4]}. Approximately 12% of US adults had used these agents for weight loss by 2024, reflecting an unprecedented rate of therapeutic adoption ^[5].

This adoption is clinically justified. Beyond weight reduction, GLP-1RAs confer statistically significant reductions in cardiovascular events, hepatic steatosis, and glycaemic burden, making them genuinely transformative agents ^{[1][2]}. The central argument of this paper is not that GLP-1RAs are harmful. It is that the pharmacological triumph over obesity has created an unintended secondary condition: a population losing body mass at unprecedented speed while receiving almost no structured nutritional guidance to ensure the quality of that loss.

Three interconnected problems define this condition. First, GLP-1RAs suppress appetite so effectively that total caloric intake drops by 16–39%, generating a nutrient vacuum in which the body's requirements for protein, vitamins, and minerals cannot be met from reduced dietary volume unless the density of remaining intake is dramatically elevated ^[6]. Second, lean body mass (LBM) – encompassing skeletal muscle, bone mineral content, and connective tissue – constitutes 26–40% of total mass lost in major GLP-1 trials ^[5] ^[7] ^[8], creating measurable risk for sarcopenic obesity, a condition characterised by simultaneous excess adiposity and deficient skeletal muscle mass. Third, newly diagnosed nutritional deficiencies affect up to 22% of GLP-1 users within twelve months, with vitamin D, iron, thiamine, and vitamin B12 emerging as the most consistently implicated nutrients ^{[7][8]}.

Despite these signals, no validated universal nutritional safety framework exists for GLP-1 pharmacotherapy. Guidelines from the American Diabetes Association, the European Association for the Study of Obesity, and the Obesity Medicine Association each address nutrition in passing, but none proposes a quantitative standard for nutrient-density requirements under conditions of pharmacologically suppressed intake [9][10]. This paper advances toward filling that gap by: (a) conducting a structured narrative synthesis of the available clinical, trial, and epidemiological data; (b) introducing the Nutrient Density Requirement Index (NDRI) and Metabolic Quality Index (MQI) as novel, computable clinical metrics; and (c) proposing a tiered Nutritional Safety Protocol that integrates these tools into practical clinical workflows.

2. Background and Pharmacological Context

2.1. Mechanism of Action and Weight-Loss Physiology

GLP-1 is an endogenous incretin hormone secreted by L-cells in the distal small intestine in response to nutrient ingestion. It stimulates glucose-dependent insulin secretion, suppresses glucagon release, delays gastric emptying, and acts centrally on the hypothalamic arcuate nucleus to reduce appetite and food intake [1]. Pharmacological GLP-1RAs replicate and extend these effects through prolonged receptor activation. Semaglutide achieves approximately 94% amino-acid sequence homology with native GLP-1, while tirzepatide, as a dual GIP/GLP-1 receptor agonist, adds agonism at the glucose-dependent insulinotropic polypeptide receptor, resulting in additive insulinotropic and anorectic effects [2].

The physiological consequence of sustained GLP-1RA administration is a state of pharmacologically imposed hypophagia. Clinical trial data indicate that total caloric intake in GLP-1RA users is reduced by 16–39% relative to pre-treatment baselines [6]. This reduction drives weight loss through the creation of a sustained negative energy balance. However, weight loss under conditions of caloric restriction follows a predictable compositional pattern: both fat mass (FM) and lean body mass (LBM) are mobilised. The ratio of FM to LBM loss is a critical determinant of metabolic health outcomes and constitutes the central clinical concern of this paper.

2.2. The Global Epidemiology of GLP-1 Use

The scale of GLP-1RA adoption warrants emphasis because the nutritional implications are not merely a clinical curiosity confined to academic medicine; they represent a population-level public health

challenge. By 2025, the combined weight-management and diabetes management indications of semaglutide and tirzepatide had generated a market exceeding USD 62 billion annually ^{[3][4]}. Forecasts project continued expansion driven by oral GLP-1 formulations, expanded indications (including cardiovascular risk reduction, kidney disease, and non-alcoholic fatty liver disease), and biosimilar entry following the March 2026 US patent expiry of semaglutide. If even a fraction of the estimated 890 million adults worldwide living with obesity ultimately receive GLP-1 therapy, the nutritional consequences of under-supervised pharmacologically suppressed intake will constitute a health burden of substantial magnitude.

2.3. Sarcopenic Obesity: Definition and Clinical Stakes

Sarcopenic obesity (SO) is defined as the co-existence of excess adiposity and pathologically reduced skeletal muscle mass and/or function. Consensus frameworks for diagnosis include the ESPEN-EASO criteria, the Asian Working Group for Sarcopenia 2019 (AWGS-2019) guidelines, and the European Working Group on Sarcopenia in Older People second revision (EWGSOP2) ^{[11][12]}. Diagnostic thresholds vary across criteria; however, all frameworks agree that the simultaneous presence of reduced muscle mass and obesity compounds cardiovascular, metabolic, and functional risk beyond either condition alone ^[11].

Skeletal muscle serves functions that extend well beyond locomotion. It is the primary site of postprandial glucose disposal, accounting for approximately 80% of insulin-stimulated glucose uptake. It generates myokines (including irisin, interleukin-6, and myonectin) that regulate adipose tissue metabolism, hepatic glucose production, and systemic inflammation. It constitutes the dominant amino-acid reservoir mobilised during physiological and pharmacological stress. Loss of skeletal muscle mass therefore carries consequences for glycaemic control, immune function, thermoregulation, and physical independence that are mechanistically distinct from, and additive to, the risks imposed by residual adiposity. GLP-1RA therapy, by imposing rapid and large-magnitude weight loss, creates the precise conditions under which iatrogenic SO can develop, particularly in older adults, those with pre-existing low muscle mass, and those who receive no nutritional or exercise intervention alongside pharmacotherapy.

3. Methods

3.1. Study Design

This study employs a structured narrative synthesis with quantitative network meta-analysis elements, following guidance adapted from the Scale for the Assessment of Narrative Review Articles (SANRA) and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) framework for scoping reviews [7]. Because the primary aim is to synthesise heterogeneous data types (RCT body composition substudies, large observational databases, dietary intake surveys, and mechanistic studies) toward a novel clinical framework, this hybrid design is more appropriate than a strict quantitative meta-analysis, which would require homogeneous comparator structures that do not exist across the identified literature.

3.2. Data Sources and Search Strategy

Data were identified from the following sources:

1. **PubMed/MEDLINE:** Searches conducted from inception through March 2026 using the MeSH terms and free-text combinations: “GLP-1 receptor agonist”, “semaglutide”, “tirzepatide”, “liraglutide”, “lean body mass”, “sarcopenia”, “sarcopenic obesity”, “micronutrient deficiency”, “protein intake”, “body composition”, and “dietary intake”.
2. **ClinicalTrials.gov:** Registered trial protocols and published substudies from STEP 1 [1], STEP 3, STEP 4, SURMOUNT-1 [2], SURMOUNT-3, SURMOUNT-5 [13], and SCALE-Obesity [14].
3. **Large observational databases:** A US administrative claims database study encompassing 461,382 adults on GLP-1RAs [7][8], providing twelve-month deficiency incidence data.
4. **Expert consensus documents:** Joint advisory from the American College of Lifestyle Medicine (ACLM), American Society for Nutrition (ASN), Obesity Medicine Association (OMA), and the Obesity Society [9]; EASO/ESPEN expert statement [15]; and expert consensus from Delphi-modified processes [16].

3.3. Inclusion and Exclusion Criteria

Studies were included if they: (a) involved adult human participants (age ≥ 18 years) receiving a GLP-1RA or GLP-1/GIP dual agonist; (b) reported at least one body composition endpoint (LBM, fat mass, or lean-

to-fat ratio) or at least one nutritional/micronutrient outcome; (c) were published in English in a peer-reviewed outlet or registered in an official trial database; and (d) provided sufficient data for quantitative extraction or structured qualitative synthesis.

Studies were excluded if they: (a) were paediatric; (b) lacked nutrition-relevant endpoints; (c) were case reports with fewer than three patients (except for mechanistically important thiamine/B12 case series); or (d) were grey literature without primary data.

3.4. Data Extraction and Synthesis

Quantitative data on lean mass loss proportions, body weight changes, micronutrient deficiency incidence rates, and protein intake were extracted into standardised tables. Where multiple doses of the same agent were reported, the highest approved weight-management dose was prioritised for cross-trial comparisons (semaglutide 2.4 mg/week; tirzepatide 15 mg/week). Network meta-analysis principles were applied qualitatively to compare agents not directly compared in head-to-head trials, drawing on the SURMOUNT-5 head-to-head data ^[13] as the primary direct comparator. Mathematical derivation of the NDRI and MQI (presented in Section 5) used reported trial-level means, standard deviations, and published dietary reference intakes as inputs.

4. Results

4.1. Body Composition Changes Across Key Trials

Table 1 summarises body composition data from the major GLP-1RA randomised controlled trials with dual-energy X-ray absorptiometry (DXA) substudies.

Trial	Agent	Total BW ^a change (%)	Fat mass change (%)	LBM change (%)	LBM as % of total loss
STEP 1 ^{[1][17]}	Sema 2.4 mg	−15.0	−19.3	−9.7	≈40%
SURMOUNT-1 ^[18]	Tirz 15 mg	−21.3	−33.9	−10.9	≈26%
SCALE-Obesity ^[14]	Lira 3.0 mg	−8.0	−12.5	−5.7	≈29%
Karakasis et al. 2024 ^b ^[19]	GLP-1RAs (pooled)	−3.55 kg	−2.95 kg	−0.86 kg	≈25%
Jiao et al. 2025 ^c ^[20]	GLP-1RAs (pooled)	—	—	Greater vs. ctrl	LBM% unchanged

Table 1. Body composition changes in landmark GLP-1RA randomised controlled trials (DXA substudies)

^a BW = body weight; Sema = semaglutide; Tirz = tirzepatide; Lira = liraglutide; LBM = lean body mass.

^b Network meta-analysis of 22 RCTs (n = 2,258). Values in absolute kg. MD = mean difference vs. placebo (95% CI for LBM: −1.30 to −0.42 kg).

^c Meta-analysis of GLP-1RA users vs. controls; absolute LBM reduction greater in users but proportional LBM percentage of total body mass unchanged.

The data reveal a consistent pattern: while the absolute magnitude of lean mass loss is greater with higher-potency agents (reflecting larger total weight loss), the proportion of total weight lost as lean mass ranges from approximately 25% with tirzepatide to approximately 40% with semaglutide when expressed relative to total weight reduction. The clinical relevance of this range is substantial: for a 100 kg individual losing 15 kg on semaglutide, lean mass loss of 40% corresponds to 6 kg of LBM – a deficit that, if concentrated in skeletal muscle, exceeds the threshold associated with functional impairment in older adults ^{[15][21]}.

4.2. Rates of Newly Diagnosed Nutritional Deficiencies

Table 2 presents deficiency incidence data from the largest available observational study, encompassing 461,382 GLP-1RA users in a US administrative database, alongside the Urbina et al. (2026) six-study

narrative review of 480,825 adults [7][8].

Deficiency / Nutrient	Incidence at 6 months	Incidence at 12 months	Primary mechanism
Any nutritional deficiency	12.7%	22.0%	Combined (see below)
Vitamin D	7.5%	13.6%	Reduced dietary fat absorption; lower sun exposure in obese population
Iron	Elevated	Elevated	Reduced gastric acid (delayed emptying); lower haem intake with reduced red meat consumption
Vitamin B12	Progressive	Progressive	Intrinsic factor reduction; delayed gastric emptying; reduced animal protein intake
Thiamine (B1)	Case-series level	Case-series level	Severe vomiting-associated depletion; documented Wernicke encephalopathy cases [22][23]
Calcium	> 60% below RDI ^a	> 60% below RDI	Reduced dairy intake; low-calorie diet inadequacy
Zinc	Elevated	Elevated	Reduced dietary variety; altered mucosal zinc transport

Table 2. Incidence of newly diagnosed nutritional deficiencies in GLP-1RA users at 6 and 12 months

^a RDI = Recommended Dietary Intake. Calcium and iron data sourced from dietary intake analyses; more than 60% of participants consumed below RDI levels for both nutrients. Thiamine deficiency data from case series [22][23][24]. All incidence figures from Urbina et al. 2026 [7] and Butsch et al. 2025 [8].

Vitamin D deficiency at 13.6% by twelve months is the most commonly identified abnormality. However, the thiamine deficiency signal warrants specific clinical attention. Documented cases of Wernicke encephalopathy – a potentially fatal thiamine deficiency syndrome – have been reported in individuals using semaglutide, attributed to severe nausea-associated food restriction [22][23][24]. This outcome, while

rare in absolute terms, represents a qualitatively serious harm that would have been entirely preventable with structured nutritional monitoring.

4.3. Protein Intake Among GLP-1 Users

A prospective dietary tracking study of 332 adults (116 GLP-1RA users, including semaglutide and tirzepatide; 216 controls) conducted between July 2025 and February 2026 analysed 5,741 days of real-world dietary data using a validated food tracking application [25]. GLP-1RA users consumed approximately 54 g of protein per day, compared with 62 g per day in non-users. After adjustment for body weight, protein intake per kilogram of body mass was significantly lower in the GLP-1 group.

Current evidence-based recommendations for lean mass preservation during GLP-1RA-assisted weight loss specify a protein intake of 1.2–1.5 g/kg/day of actual body weight [9][16]. For a typical trial participant with a mean body weight of approximately 100 kg (as in SURMOUNT-1), this corresponds to a daily protein requirement of 120–150 g. The observed intake of 54 g represents a shortfall of 66–96 g/day – a deficit of approximately 55–64% relative to the preservation threshold. Table 3 frames this shortfall across three body weight scenarios.

Body weight (kg)	Observed intake ^a (g/day)	Minimum target @ 1.2 g/kg (g/day)	Optimal target @ 1.5 g/kg (g/day)	Deficit vs. minimum (%)
75	54	90	113	40.0%
100	54	120	150	55.0%
125	54	150	188	64.0%

Table 3. Observed vs. recommended protein intake in GLP-1RA users across body weight strata

^a Mean observed intake from Williams-Nguyen et al. 2026 [25]. Recommendations from the ACLM-ASN-OMA joint advisory [9] and the Delphi-consensus nutrition statement [16].

The implication is stark: at observed dietary patterns, the majority of GLP-1RA users are consuming

protein at levels that guarantee progressive lean mass loss regardless of the drug’s direct pharmacological effects on body composition.

4.4. Network Meta-Analysis: Comparative Lean Mass Loss Across Agents

Drawing on the Karakasis et al. (2024/2025) network meta-analysis of 22 RCTs ^[19] and the SURMOUNT-5 head-to-head trial ^[13], Table 4 presents a comparative synthesis of agents ranked by the proportion of total weight loss attributable to lean mass.

Agent	Dose	Mean total BW loss (%)	LBM as % of loss	Network rank ^a (LBM preservation)
Tirzepatide	15 mg/wk	20.9–21.3%	≈25–26%	1 (best)
Tirzepatide	10 mg/wk	19.5%	≈26%	2
Semaglutide	2.4 mg/wk	14.9–15.0%	≈38–40%	3
Liraglutide	3.0 mg/day	8.0%	≈29%	4 ^b
Semaglutide + Resistance Training ^c	2.4 mg/wk	≈13.0%	≈18%	1 (modified)

Table 4. Network meta-analysis summary: lean mass loss as proportion of total weight loss by agent and dose

^a Rank 1 = greatest lean mass preservation relative to total weight lost. Rankings are qualitative, informed by Karakasis et al. 2024 ^[19], Look et al. 2025 ^[18], and Martin et al. 2021 ^[17].

^b Liraglutide’s lower lean loss proportion vs. semaglutide may partly reflect smaller total weight loss magnitude.

^c Data from Peralta-Rey et al. 2025 prospective study ^[26]: 200 adults, structured resistance training + protein counselling at semaglutide/tirzepatide initiation; 13% BW lost, 3% muscle mass lost at 6 months. This row represents an intervention arm, not drug monotherapy.

The network analysis reveals that tirzepatide is superior to semaglutide in lean mass preservation when expressed as a percentage of total weight loss, and that the combination of structured resistance training with adequate protein intake reduces lean mass loss to approximately 18% of total weight lost – a result substantially better than either drug achieves in monotherapy trials [26][5].

5. Novel Analytical Constructs: NDRI and MQI

5.1. The Nutrient Density Requirement Index (NDRI)

The fundamental nutritional challenge facing GLP-1RA users is not absolute caloric restriction per se but the collapse of nutrient delivery per unit of caloric intake. When total energy consumption falls by 16–39%, all nutrients that are consumed in proportion to food volume – including protein, most B vitamins, iron, zinc, and calcium – decline in parallel unless dietary quality is actively and substantially elevated. We term the quantitative magnitude of this required elevation the **Nutrient Density Requirement Index**.

5.1.1. Formal Definition

Let E_0 denote the habitual daily energy intake (kcal/day) of an individual prior to GLP-1RA initiation, and let $E_1 = E_0(1 - \delta)$ denote the post-treatment intake, where $\delta \in (0, 1)$ is the fractional reduction in caloric intake (empirically, $\delta = 0.16$ to 0.39 from trial data [6]).

Let N_{req} denote the daily requirement for a given nutrient (in appropriate units, e.g., grams for protein, micrograms for B12), assumed unchanged by pharmacotherapy since GLP-1RAs do not alter basal metabolic nutrient requirements. Let $\rho_0 = N_{\text{req}}/E_0$ denote the pre-treatment nutrient density required per kilocalorie.

Post-treatment, to maintain the same absolute nutrient delivery N_{req} from a reduced caloric intake E_1 , the required nutrient density ρ_1 per kilocalorie satisfies:

$$\rho_1 = \frac{N_{\text{req}}}{E_1} = \frac{N_{\text{req}}}{E_0(1 - \delta)} = \frac{\rho_0}{1 - \delta} \quad (1)$$

where ρ_1 is the post-treatment required nutrient density per kilocalorie, ρ_0 is the pre-treatment baseline nutrient density, and δ is the fractional caloric reduction imposed by GLP-1RA therapy.

The Nutrient Density Requirement Index is then defined as:

$$\text{NDRI} = \frac{\rho_1}{\rho_0} = \frac{1}{1 - \delta} \quad (2)$$

where NDRI represents the multiplicative factor by which per-calorie nutrient density must increase to maintain nutrient adequacy under GLP-1RA-induced caloric suppression. An NDRI of 1.0 indicates no additional density requirement (i.e., no caloric suppression). An NDRI > 1.0 quantifies the proportional increase in nutrient density per kilocalorie that is required.

5.1.2. Numerical Instantiation

Table 5 applies Equation (2) across the empirically observed range of caloric suppression and calculates absolute protein and vitamin D targets for a reference 80-kg individual with a habitual intake of 2,000 kcal/day.

δ (caloric reduction)	E_1 (kcal/day)	NDRI	Required protein density ^a (g/100 kcal)	Absolute protein target ^b (g/day)	Observed intake (g/day)
0.00 (baseline)	2,000	1.00	4.80	96.0	62
0.16 (low)	1,680	1.19	5.71	96.0	54
0.25 (moderate)	1,500	1.33	6.40	96.0	54
0.39 (high)	1,220	1.64	7.87	96.0	54

Table 5. NDRI values and derived nutrient targets across observed caloric suppression ranges

^a Protein density required to deliver $N_{\text{req}} = 1.2 \text{ g/kg} \times 80 \text{ kg} = 96 \text{ g/day}$ from reduced caloric budget E_1 .

^b Absolute protein requirement held constant at 96 g/day (1.2 g/kg for 80-kg individual) per ACLM-ASN-OMA advisory [9]. At $\delta = 0.39$, 100 g of protein must be delivered in 1,220 kcal, requiring approximately every 100-kcal food portion to deliver $\approx 79 \text{ g}$ of protein – a density achievable only in lean animal proteins, legumes, and protein-enriched products.

The NDRI framework makes explicit a constraint that is clinically intuitive but has not previously been formalised: the greater the appetite suppression, the more protein-dense and micronutrient-dense every meal must be. At the upper range of observed caloric suppression ($\delta = 0.39$), achieving protein adequacy requires that the average food consumed deliver 7.87 g of protein per 100 kcal – a standard that

essentially excludes refined carbohydrates, sweetened beverages, and ultra-processed foods from a meaningful share of the diet. This has immediate implications for food choice counselling.

5.1.3. Extension to Micronutrients

The NDRI is not restricted to protein. Applying Equations (1) and (2) to key micronutrients at $\delta = 0.25$ (moderate suppression):

$$\text{NDRI}_{\text{B12}} = \frac{1}{1 - 0.25} = 1.33 \Rightarrow \rho_{\text{B12},1} = 1.33 \times \rho_{\text{B12},0} \quad (3)$$

$$\text{NDRI}_{\text{Fe}} = \frac{1}{1 - 0.25} = 1.33 \Rightarrow \rho_{\text{Fe},1} = 1.33 \times \rho_{\text{Fe},0} \quad (4)$$

where $\rho_{\text{B12},0}$ and $\rho_{\text{Fe},0}$ are the pre-treatment per-kilocalorie densities of vitamin B12 and iron respectively required to meet recommended daily intakes. These equations confirm that a 25% caloric reduction mandates a 33% increase in the per-calorie density of every nutrient consumed – an increase that is unlikely to occur spontaneously in the absence of structured dietary counselling.

5.2. The Metabolic Quality Index (MQI)

5.2.1. Rationale

Current clinical standards for evaluating the success of obesity pharmacotherapy rely almost exclusively on total body weight reduction. A patient who loses 15% of body weight is designated a responder; a patient who loses 5% is designated a non-responder or partial responder. This binary framing is inadequate because it treats 15 kg of loss composed of 14 kg fat and 1 kg muscle as equivalent to 15 kg of loss composed of 8 kg fat and 7 kg muscle, despite the latter representing a substantially more harmful outcome. We propose the **Metabolic Quality Index** to operationalise the compositional quality of weight loss.

5.2.2. Formal Definition

Let ΔFM denote the absolute reduction in fat mass (kg) over a defined treatment period, and let ΔLBM denote the absolute reduction in lean body mass (kg) over the same period. Both quantities are assumed positive when mass is lost. The Metabolic Quality Index is defined as:

$$\text{MQI} = \frac{\Delta\text{FM}}{\Delta\text{FM} + \Delta\text{LBM}} \times 100 \quad (5)$$

where MQI is expressed as a percentage representing the proportion of total mass lost that consists of fat mass. An MQI of 100 would indicate that all weight lost is fat (ideal, not physiologically achievable under caloric restriction). An MQI of 75 indicates that 75% of weight lost is fat and 25% is lean mass, corresponding to the benchmark observed in tirzepatide SURMOUNT-1 data. An MQI below 70 may be considered clinically suboptimal, warranting nutritional and exercise intervention.

5.2.3. MQI Clinical Benchmarks

$$\text{MQI}_{\text{ideal}} > 85\% \quad (\text{resistance training} + \text{protein optimised}) \quad (6)$$

$$\text{MQI}_{\text{acceptable}} = 70\% - 85\% \quad (\text{standard GLP-1RA therapy with basic dietary guidance}) \quad (7)$$

$$\text{MQI}_{\text{concerning}} < 70\% \quad (\text{elevated sarcopenic risk; nutritional intervention indicated}) \quad (8)$$

Equation (5) defines MQI as the fat fraction of total mass lost, expressed as a percentage. Equations (6) through (8) define three clinically actionable zones. The threshold values are derived from trial data: semaglutide monotherapy in STEP 1 achieves an MQI of approximately 60% (40% LBM of total loss), placing it in the “concerning” zone for the average patient; structured resistance training combined with protein intake shifts MQI to approximately 82% [26]; and tirzepatide with bimagrumab combination achieves an MQI of approximately 93% in early phase data [27].

5.2.4. MQI as a Regulatory and Prescribing Tool

The MQI provides a mechanism for (a) benchmarking the body-compositional efficacy of novel pharmacological agents beyond weight loss alone; (b) stratifying individual patients for nutritional and exercise intervention intensity; and (c) generating a common comparator metric across heterogeneous trial designs, since DXA-measured fat and lean mass data are now routinely collected in GLP-1RA trials. We recommend that future regulatory submissions and clinical guidelines for obesity pharmacotherapy incorporate MQI alongside total weight loss as a co-primary endpoint.

6. A Tiered Nutritional Safety Protocol for GLP-1 Pharmacotherapy

6.1. Protocol Rationale

The clinical evidence reviewed above, the NDRI framework, and the MQI benchmarks together justify the establishment of a structured, tiered nutritional safety protocol to accompany GLP-1RA prescribing. The model is deliberately analogous to the post-bariatric surgery nutritional monitoring framework, which

has demonstrated efficacy in preventing nutritional sequelae in a comparably high-risk context ^[28]. The protocol is organised into three tiers corresponding to risk level.

6.2. Tier 1: Universal Baseline Assessment (All Patients)

At the point of GLP-1RA initiation, every patient should receive:

1. **Nutritional biochemistry panel:** Serum 25-hydroxyvitamin D, complete blood count with indices (for iron-deficiency anaemia), ferritin, serum B12, folate, albumin, pre-albumin, and thiamine (where clinically indicated).
2. **Body composition assessment:** DEXA or bioelectrical impedance analysis (BIA) to establish baseline LBM and FM, enabling subsequent MQI calculation.
3. **Dietary intake quantification:** Minimum three-day food diary or validated diet history, assessed by a registered dietitian or clinical nutritionist.
4. **NDRI-guided counselling:** Calculation of the patient's NDRI based on anticipated caloric reduction (δ estimated from agent and dose), with personalised per-kilocalorie density targets for protein and key micronutrients.

6.3. Tier 2: Monitoring and Adjustment (All Patients, Months 1–12)

1. **Monthly body weight and composition checks** for the first six months; three-monthly thereafter. MQI calculation at each timepoint with intervention triggered if MQI falls below 70%.
2. **Biochemistry re-screening at months 3, 6, and 12** for the nutrients identified in Table 2.
3. **Protein intake reassessment** at every clinical encounter, with reinforcement of the target of 1.2–1.5 g/kg/day. Protein-containing meal prioritisation (protein eaten first at each sitting) should be recommended as a practical compliance strategy ^[16].
4. **Physical activity prescription:** Minimum two to three sessions of progressive resistance training per week targeting major muscle groups, documented in the clinical record. Evidence from multiple sources indicates that structured resistance training reduces lean mass loss by 40–50% relative to no exercise intervention during GLP-1RA-assisted weight loss ^{[26][29]}.

6.4. Tier 3: High-Risk Intensification (Selected Patients)

Patients with one or more of the following risk factors warrant intensified monitoring and intervention: age ≥ 65 years; BMI ≥ 40 kg/m²; pre-existing sarcopenia (by EWGSOP2 or AWGS-2019 criteria); type 2

diabetes with peripheral neuropathy; inflammatory bowel disease; prior bariatric surgery; or confirmed pre-treatment micronutrient deficiency.

For Tier 3 patients, the protocol adds:

1. Routine prophylactic supplementation with: multivitamin-mineral complex; additional vitamin D3 (2,000–4,000 IU/day); elemental iron if ferritin is below 30 ng/mL; and oral B12 (1,000 µg/day or intramuscular injection if absorption is uncertain).
2. Mandatory referral to a registered dietitian for structured medical nutrition therapy, incorporating NDRI-tailored meal planning.
3. Consideration of combination pharmacotherapy to preserve lean mass (e.g., bimagrumab or myostatin inhibition, currently in clinical trials) [27].
4. MQI target elevation to $\geq 80\%$ as a treatment goal, with pharmacological dose adjustment considered if MQI persistently falls below 70% despite nutritional and exercise optimisation.

6.5. Protocol Summary Table

Tier	Population	Key Actions	Key Targets
Tier 1	All patients (initiation)	Biochemistry panel; BIA/DEXA; diet history; NDRI calculation	Baseline MQI; baseline nutrient status
Tier 2	All patients (months 1–12)	Monthly/quarterly BW + BIA; 3-monthly biochemistry; protein counselling; exercise prescription	MQI $\geq 70\%$; protein ≥ 1.2 g/kg/day; ≥ 2 –3 RT sessions/week
Tier 3	High-risk patients	Prophylactic supplementation; registered dietitian referral; combination pharmacotherapy consideration	MQI $\geq 80\%$; normalise all deficient biomarkers

Table 6. Tiered Nutritional Safety Protocol for GLP-1RA Pharmacotherapy: Overview

7. Discussion

7.1. The Paradox at the Heart of Pharmacological Weight Loss

GLP-1RA pharmacotherapy achieves, for the first time in the history of non-surgical medicine, the magnitude of weight loss previously associated only with bariatric procedures. This is a genuine therapeutic breakthrough. The paradox identified in this paper is that the very mechanism driving this success – sustained pharmacological appetite suppression – simultaneously creates the conditions for nutritional harm if the caloric reduction is not managed with the same rigour applied after bariatric surgery.

Bariatric medicine learned this lesson the hard way. Post-operative nutritional deficiencies were widespread in the early decades of bariatric surgery, and the field responded with structured post-operative nutritional protocols, mandatory supplementation, and lifelong monitoring [28]. GLP-1RA prescribing is today conducted at a scale that dwarfs bariatric surgery, with a fraction of the nutritional infrastructure. The NDRI and MQI frameworks proposed here are designed to begin filling that gap by providing clinicians with computable, actionable tools that do not require specialist expertise to apply.

7.2. Lean Mass Loss: Proportion Matters More Than Absolute Amount

A common misreading of the body composition data from STEP 1 and SURMOUNT-1 holds that lean mass loss is “acceptable” because the absolute kilogram deficit is modest (6–7 kg) relative to total weight lost. This interpretation misunderstands the physiology. Absolute lean mass loss must be interpreted in the context of pre-treatment lean mass reserve, patient age, functional status, and rate of loss. A 70-year-old patient with borderline sarcopenia at baseline who loses 6 kg of lean mass over 68 weeks may cross the functional impairment threshold during that period. A 35-year-old patient with abundant muscle reserve may tolerate the same loss with no detectable consequence. The MQI reframes this by expressing lean loss as a proportion of total loss, which is directly interpretable regardless of individual baseline characteristics and which facilitates cross-trial comparison.

The finding that resistance training plus protein optimisation shifts MQI from approximately 60% (semaglutide monotherapy) to approximately 82% [26] is perhaps the most actionable finding in this entire body of literature. It demonstrates that the composition of weight loss is substantially modifiable

through non-pharmacological means, and that the 40% lean mass loss seen in STEP 1 is not an inevitable pharmacological consequence but a product of the absence of structured nutritional and exercise support.

7.3. The NDRI as a Universal Clinical Tool

The Nutrient Density Requirement Index is mathematically straightforward (Equation (2)), requires only two inputs (pre-treatment caloric intake and anticipated or observed caloric reduction), and is directly translatable into dietary counselling messages. A patient who reduces intake from 2,000 kcal to 1,400 kcal ($\delta = 0.30$, NDRI = 1.43) needs to be told not merely to “eat more protein” but that every 100 calories consumed must now deliver 43% more protein than their pre-treatment diet. This framing creates a specific, measurable dietary behaviour change target rather than a vague exhortation.

The NDRI also has regulatory implications. It provides a basis for establishing minimum nutrient density standards for medical nutritional products marketed to GLP-1RA users – a category that has grown rapidly but without regulatory standards for compositional adequacy.

7.4. Limitations

Several limitations of this synthesis warrant explicit acknowledgement. First, the majority of available body composition data derive from DXA substudies involving small participant numbers ($n = 95\text{--}160$) nested within larger trials; the substudies may not perfectly represent the full trial population. Second, the observational deficiency incidence data are subject to detection bias, as patients receiving GLP-1RA therapy may be more likely to have nutritional screening ordered by attentive physicians, inflating apparent incidence relative to the background population. Third, the NDRI and MQI are derived constructs that require prospective validation in dedicated clinical studies before they can be adopted as formal clinical standards. Fourth, the reviewed literature is dominated by data from high-income countries (United States, Western Europe), and the nutritional consequences of GLP-1RA use in populations with pre-existing food insecurity or different dietary patterns require specific investigation.

7.5. Future Research Directions

Priority research gaps include: (a) prospective RCTs with nutritional intervention arms powered to detect differences in sarcopenia incidence and functional outcomes at one, three, and five years; (b) validation studies of the NDRI across diverse populations and caloric suppression patterns; (c) investigation of MQI as a regulatory endpoint in obesity pharmacotherapy trials; (d) mechanistic studies examining the

interaction between delayed gastric emptying and micronutrient absorption kinetics under chronic GLP-1RA exposure; and (e) pharmacoeconomic analyses of the cost of nutritional monitoring protocols relative to the healthcare costs of treating sarcopenic obesity, Wernicke encephalopathy, and fragility fractures in unmonitored GLP-1RA users.

8. Conclusion

The promise of GLP-1 receptor agonist pharmacotherapy is real. These drugs have demonstrably changed what is achievable in obesity medicine, and the benefits they confer – for weight, cardiometabolic risk, and quality of life – are well-established in the clinical literature. This paper makes no argument against their use.

It does argue, however, that a therapeutic revolution affecting tens of millions of people worldwide demands an equally rigorous revolution in accompanying nutritional care. The data presented here establish that GLP-1RA users lose 26–40% of total weight as lean mass, that 22% develop a newly diagnosed nutritional deficiency within twelve months, that observed protein intake falls to 54 g/day against a target of 120–150 g/day for a typical user, and that the entire spectrum of lean mass loss is substantially modifiable through resistance training and adequate protein intake. These findings are not peripheral considerations; they are central to the long-term health outcome of every patient on these medications.

The NDRI and MQI provide the field with two tools: one to calculate and communicate how much more nutrient-dense diet must become under conditions of pharmacologically suppressed appetite, and one to evaluate whether the weight being lost is compositionally acceptable. The tiered Nutritional Safety Protocol proposed here translates these tools into clinical practice in a format designed to be adoptable across primary care, endocrinology, and bariatric medicine without specialist nutritional infrastructure at every prescribing site.

The post-obesity era has arrived. It is time for its nutritional framework to arrive as well.

Abbreviations

ACLM	American College of Lifestyle Medicine
ASN	American Society for Nutrition
AWGS	Asian Working Group for Sarcopenia
BIA	Bioelectrical Impedance Analysis
BW	Body Weight
DXA	Dual-Energy X-Ray Absorptiometry
ESPEN	European Society for Clinical Nutrition and Metabolism
EWGSOP2	European Working Group on Sarcopenia in Older People (2nd revision)
FM	Fat Mass
GIP	Glucose-Dependent Insulinotropic Polypeptide
GLP-1	Glucagon-Like Peptide-1
GLP-1RA	GLP-1 Receptor Agonist
LBM	Lean Body Mass
MQI	Metabolic Quality Index
NDRI	Nutrient Density Requirement Index
OMA	Obesity Medicine Association
RCT	Randomised Controlled Trial
SO	Sarcopenic Obesity

Statements and Declarations

Funding

This research received no external funding.

Potential Competing Interests

The author declares no conflict of interest.

Ethics

This study is a secondary analysis of aggregated, previously published data. No primary human subjects data were collected; ethics board approval was not required.

Data Availability

All data supporting the analyses in this paper are available in the referenced published sources. No primary data were generated. The mathematical derivations (NDRI and MQI) are fully reproduced in the body of the manuscript.

Author Contributions

Safwan Yusuf Hungund: Conceptualisation, data synthesis, mathematical framework development (NDRI and MQI), writing – original draft, writing – review and editing.

Acknowledgements

The author acknowledges the foundational contributions of the STEP and SURMOUNT trial investigators, the ACLM-ASN-OMA-TOS advisory committee, and the research teams whose body composition substudies provided the quantitative basis for the frameworks developed in this paper.

References

1. ^{a, b, c, d, e}Wilding JP, Batterham RL, Calanna S, Davies M, Van Gaal LF, Lingvay I, McGowan BM, Rosenstock J, Tran MTD, Wadden TA, et al. (2021). "Once-Weekly Semaglutide in Adults with Overweight or Obesity." *N Engl J Med.* **384**:989–1002. doi:[10.1056/NEJMoa2032183](https://doi.org/10.1056/NEJMoa2032183).
2. ^{a, b, c, d}Jastreboff AM, Aronne LJ, Ahmad NN, Wharton S, Connery L, Alves B, Kiyosue A, Zhang S, Liu B, Bunc k MC, et al. (2022). "Tirzepatide Once Weekly for the Treatment of Obesity." *N Engl J Med.* **387**:205–216. doi: [10.1056/NEJMoa2206038](https://doi.org/10.1056/NEJMoa2206038).
3. ^{a, b}Grand View Research (2026). *GLP-1 Receptor Agonist Market Size, Share & Trends Analysis Report, 2026–2033*.

4. ^a ^bGrand View Research (2025). "Grand View Research: San Francisco, CA, USA, 2025." Grand View Research. <https://www.grandviewresearch.com/industry-analysis/glp-1-receptor-agonist-market>.
5. ^a ^b ^cTinsley GM, Navarro S (2025). "Preservation of Lean Soft Tissue During Weight Loss Induced by GLP-1 and GLP-1/GIP Receptor Agonists: A Case Series." *SAGE Open Med Case Rep*. doi:[10.1177/2050313X25138872](https://doi.org/10.1177/2050313X25138872)
- 4.
6. ^a ^b ^cWilliams D, Sulo S, Butsch WS (2024). "Dietary Intake by Patients Taking GLP-1 and Dual GIP/GLP-1 Receptor Agonists: A Narrative Review and Discussion of Research Needs." *Obes Pillars*. **11**:100121. doi:[10.1016/j.obpill.2024.100121](https://doi.org/10.1016/j.obpill.2024.100121).
7. ^a ^b ^c ^d ^eUrbina K, Garza E, Saju A, Nazir N, Agarwal A (2026). "Micronutrient and Nutritional Deficiencies Associated with GLP-1 Receptor Agonist Therapy: A Narrative Review." *Clin Obes*. doi:[10.1111/cob.70070](https://doi.org/10.1111/cob.70070).
8. ^a ^b ^c ^dButsch WS, Sulo S, Chang AT, Huang S, Barenbaum LL, Gower B, Weaver M, Wasilewski-Masker K (2025). "Nutritional Deficiencies and Muscle Loss in Adults with Type 2 Diabetes Using GLP-1 Receptor Agonists: A Retrospective Observational Study." *Obes Pillars*. doi:[10.1016/j.obpill.2025.100300](https://doi.org/10.1016/j.obpill.2025.100300).
9. ^a ^b ^c ^d ^eMechanick JJ, Zeevi D, Matarese LE, Sherif B, Kushner RF, et al. (2025). "Nutritional Priorities to Support GLP-1 Therapy for Obesity: A Joint Advisory from the American College of Lifestyle Medicine, the American Society for Nutrition, the Obesity Medicine Association, and the Obesity Society." *Am J Clin Nutr*. doi:[10.1016/j.ajcnut.2025.04.001](https://doi.org/10.1016/j.ajcnut.2025.04.001).
10. ^aBrown A, Mellor D, Makaronidis J, Shuttlewood E, Miras AD, Pournaras DJ (2025). "Bridging the Nutrition Guidance Gap for GLP-1 Receptor Agonist Therapy Assisted Weight Loss: Lessons from Bariatric Surgery." *Int J Obes*. doi:[10.1038/s41366-025-01952-w](https://doi.org/10.1038/s41366-025-01952-w).
11. ^a ^bCederholm T, Jensen GL, Correia MITD, Gonzalez MC, et al. (2019). "GLIM Criteria for the Diagnosis of Malnutrition." *Clin Nutr*. **38**:1–9. Sarcopenic Obesity consensus: Baumgartner, R.N. Body Composition in Healthy Aging. *Ann. N. Y. Acad. Sci.* 2000, 904, 437–448.
12. ^aAsia-Oceania Association for the Study of Obesity, International Association of Gerontology and Geriatrics Asia/Oceania Region (2025). "The Asia-Oceania Consensus: Definitions and Diagnostic Criteria for Sarcopenic Obesity." *Obes Res Clin Pract*. doi:[10.1016/j.orcp.2025.04.001](https://doi.org/10.1016/j.orcp.2025.04.001).
13. ^a ^b ^cJoshi SR, et al. (2026). "Tirzepatide vs. Semaglutide in the SURMOUNT-5 Head-to-Head Trial: 72-Week Outcomes." *Appl Clin Trials Online*. <https://www.appliedclinicaltrialsonline.com/view/tirzepatide-weight-loss-semaglutide-surmount-trial>.
14. ^a ^bPi-Sunyer X, Astrup A, Fujioka K, Greenway F, Halpern A, Krempf M, Lau DCW, le Roux CW, Violante Ortiz R, Jensen CB, et al. (2015). "A Randomized, Controlled Trial of 3.0 mg of Liraglutide in Weight Management

- t." *N Engl J Med.* **373**:11–22. doi:[10.1056/NEJMoa1411892](https://doi.org/10.1056/NEJMoa1411892).
15. ^{a, b}Neeland IJ, Linge J, Birkenfeld AL (2024). "Changes in Lean Body Mass with Glucagon-Like Peptide-1-Based Therapies and Mitigation Strategies." *Diabetes Obes Metab.* **26**(Suppl. 4):16–27. doi:[10.1111/dom.15728](https://doi.org/10.1111/dom.15728).
 16. ^{a, b, c, d}Barber TM, Kabisch S, Pfeiffer AFH, Weickert MO, et al. (2025). "Nutritional and Lifestyle Supportive Care Recommendations for Management of Obesity with GLP-1-Based Therapies: An Expert Consensus Statement Using a Modified Delphi Approach." *Obes Pillars.* doi:[10.1016/j.obpill.2025.100725](https://doi.org/10.1016/j.obpill.2025.100725).
 17. ^{a, b}Martin A, Rehfeld JF, Knop FK, Fabricius-Bjerre A, Thomsen BJ, Christou S, Davies M, Wilding JPH (2021). "Impact of Semaglutide on Body Composition in Adults with Overweight or Obesity: Exploratory Analysis of the STEP 1 Study." *BMC Med.* <https://pmc.ncbi.nlm.nih.gov/articles/PMC8089287/>.
 18. ^{a, b}Look M, Dunn JP, Kushner RF, Ahmad NN, Anderson JW, Aronne LJ, Jastreboff AM (2025). "Body Composition Changes During Weight Reduction with Tirzepatide in the SURMOUNT-1 Study of Adults with Obesity or Overweight." *Diabetes Obes Metab.* doi:[10.1111/dom.16275](https://doi.org/10.1111/dom.16275).
 19. ^{a, b, c}Karakasis P, Patoulas D, Fragakis N, Mantzoros CS (2025). "Effect of Glucagon-Like Peptide-1 Receptor Agonists and Co-Agonists on Body Composition: Systematic Review and Network Meta-Analysis." *Metabolism.* **164**:156113. doi:[10.1016/j.metabol.2024.156113](https://doi.org/10.1016/j.metabol.2024.156113).
 20. ^aJiao R, Lin C, Cai X, Wang J, Wang Y, Lv F, Yang W, Ji L (2025). "Characterizing Body Composition Modifying Effects of a Glucagon-Like Peptide 1 Receptor-Based Agonist: A Meta-Analysis." *Diabetes Obes Metab.* **27**:259–267. doi:[10.1111/dom.16012](https://doi.org/10.1111/dom.16012).
 21. ^aMastroleo Z, Gerber S, Malloy A, Peralta-Rey D (2025). "Impact of GLP-1 Receptor Agonist Therapy in Patients at High Risk for Sarcopenia." *Curr Nutr Rep.* **14**:63. doi:[10.1007/s13668-025-00649-w](https://doi.org/10.1007/s13668-025-00649-w).
 22. ^{a, b, c}Sheth K, Garza E, Saju A, Nazir N, Agarwal A (2024). "Wernicke Encephalopathy Associated with Semaglutide Use." *Cureus.* **16**:e61783. doi:[10.7759/cureus.61783](https://doi.org/10.7759/cureus.61783).
 23. ^{a, b, c}Sharma N, Vura NVRK, Shweikh F, et al. (2024). "Semaglutide-Linked Dry Beriberi: A Rare Adverse Reaction." *Am J Gastroenterol.* **119**:S4690.
 24. ^{a, b}Gras C, De Wit V, Oussedik N, et al. (2025). "Semaglutide-Induced Wernicke Encephalopathy: A Comprehensive Analysis." *Eur J Clin Nutr.* **79**:1160–1163. doi:[10.1038/s41430-025-01653-7](https://doi.org/10.1038/s41430-025-01653-7).
 25. ^{a, b}Williams-Nguyen J, et al. (2026). "Critically Low Protein Intake in GLP-1 Receptor Agonist Users: Prospective Dietary Tracking in 332 Adults." Presented at the American Society for Nutrition Annual Meeting, 2026. Reported in: *Today.com Health Desk*, April 2026.
 26. ^{a, b, c, d, e}Peralta-Rey D, et al. (2025). "Resistance Training and Protein Counselling at GLP-1RA Initiation: Outcomes in 200 Adults with Overweight/Obesity." Presented at Endocrine Society Annual Meeting, 2025.

27. ^{a, b} American Diabetes Association Scientific Sessions (2025). "Bimagrumb and Semaglutide Combination Therapy: Body Composition Outcomes." Press release and late-breaking abstract. <https://diabetes.org/newsroom/press-releases/new-glp-1-therapies-enhance-quality-weight-loss-improving-muscle-0>.
28. ^{a, b} Sherf Dagan S, Goldenshluger A, Globus I, Schweiger C, Kessler Y, Sandbank GK, et al. (2017). "Nutritional Recommendations for Adult Bariatric Surgery Patients: Clinical Practice." *Adv Nutr.* 8:382–394. doi:[10.3945/an.116.014258](https://doi.org/10.3945/an.116.014258).
29. ^Δ Bellicha A, van Baak MA, Battista F, Beaulieu K, Blundell JE, Busetto L, et al. (2021). "Effect of Exercise Training on Weight Loss, Body Composition Changes, and Weight Maintenance in Adults with Overweight or Obesity: An Overview of 12 Systematic Reviews and 149 Studies." *Obes Rev.* 22(Suppl. 4):e13256.

Declarations

Funding: No specific funding was received for this work.

Potential competing interests: No potential competing interests to declare.