

# Estrogen as a Modulator of GLP-1 Receptor Agonist Efficacy in Women: Implications for Sex-Specific Nutritional Support, Hormonal Monitoring, and Body Composition Outcomes

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## Abstract

**Background:** Glucagon-like peptide-1 receptor agonists (GLP-1 RAs), including semaglutide and tirzepatide, have become widely used pharmacotherapies for obesity management. Despite their widespread adoption, sex-disaggregated analyses of efficacy, body composition changes, and downstream hormonal effects remain limited. Emerging evidence suggests that oestradiol (estrogen) may modulate GLP-1 receptor (GLP-1R) signaling in the brain, with potential implications for how women respond to GLP-1 RA therapy across different life stages.

**Objectives:** This narrative review synthesizes current evidence on (1) mechanistic links between estrogen and GLP-1 receptor activity; (2) sex-specific differences in weight loss, lean mass loss, and weight regain outcomes; (3) the potential for GLP-1 RA-induced weight loss to influence the hypothalamic-pituitary-ovarian (HPO) axis; and (4) implications for nutritional support and biomarker monitoring in women receiving GLP-1 RA therapy.

**Methods:** A narrative review was conducted using PubMed/MEDLINE, Embase, the Cochrane Central Register of Controlled Trials, and targeted Google Scholar searches from database inception through March 2026. Search strings combined GLP-1 receptor agonist terms with estrogen, sex differences, menopause, hormone therapy, body composition, lean mass, weight regain, protein, and micronutrient terms. Records were screened at the title/abstract and full-text level for relevance to sex-disaggregated GLP-1 RA outcomes, estrogen-GLP-1 mechanisms, body composition, hormonal biomarkers, and nutritional support. A final evidence set of 41 sources was retained for narrative synthesis.

**Results:** Women demonstrate greater weight loss on GLP-1 RAs than men in several analyses, and this difference may reflect, in part, interactions between estrogen and GLP-1R signaling in hypothalamic and brainstem nuclei. Available evidence suggests that some women, particularly older women or those with low protein intake, may be at increased risk of clinically relevant lean mass loss during GLP-1 RA-associated weight loss. GLP-1 RA-induced weight loss may also intersect with adipose-derived estrogen production, SHBG, cortisol, thyroid status, and gonadotropin profiles, although prospective sex-specific monitoring data remain limited. No validated sex-specific hormonal monitoring protocol currently exists for women receiving GLP-1 RA therapy.

**Conclusion:** The integration of estrogen biology into GLP-1 RA prescribing and nutritional support represents an important and still under addressed research gap. Sex-specific protein targets, micronutrient monitoring, hormonal biomarker surveillance, and consideration of concurrent hormone therapy require further prospective study before they can be treated as standardized clinical protocols.

**Keywords:** *GLP-1 Receptor Agonists; Semaglutide; Estrogen; Sex Differences; Body Composition; Lean Mass; Hormonal Disruption; Women's Nutrition; Micronutrients; Perimenopause; Hormone Replacement Therapy; Weight Management*

## Introduction

The emergence of glucagon-like peptide-1 receptor agonists (GLP-1 RAs) as a therapeutic class for obesity management represents one of the most significant pharmacological advances in metabolic medicine in recent decades. Agents including semaglutide (Ozempic, Wegovy; Novo Nordisk) and tirzepatide (Mounjaro, Zepbound; Eli Lilly), which function as GLP-1 receptor agonists or dual GIP/GLP-1 receptor agonists, have demonstrated unprecedented weight loss outcomes in Phase 3 clinical trials, rivalling the efficacy of bariatric surgery in carefully selected populations [1,2].

GLP-1 is an incretin hormone secreted by L-cells of the distal intestine in response to nutrient ingestion. Its principal metabolic actions include stimulation of glucose-dependent insulin secretion, inhibition of glucagon release, delayed gastric emptying, and suppression of appetite via central nervous system (CNS) mechanisms. Long-acting pharmacological analogues extend the native hormone's half-life from approximately two minutes to days or weeks, enabling sustained receptor activation and clinically significant reductions in caloric intake and body weight.

Despite the remarkable clinical success of GLP-1 RAs, a critical and largely underexplored dimension of their use concerns biological sex. The overwhelming majority of obesity clinical trials have either failed to disaggregate outcomes by sex or have been designed with predominantly female study populations without a priori sex-stratified analyses [3]. This is a consequential gap: emerging data from meta-analyses, real-world cohort studies, and mechanistic research now indicate that women and men respond differently to GLP-1 RA therapy across multiple dimensions, including weight loss magnitude, lean mass preservation, adverse event profiles, and hormonal sequelae.

Central to these sex differences is the role of oestradiol the predominant form of estrogen in premenopausal women as a potentiating co-factor for GLP-1 receptor activity in the brain. Research published in *Endocrinology* [4] has confirmed that estrogen and GLP-1 interact synergistically in hypothalamic and brainstem nuclei to produce appetite-suppressive and weight-reducing effects that exceed what either hormone achieves alone. This mechanism has direct clinical implications for how GLP-1 RA efficacy changes across a woman's hormonal life cycle from the premenopausal years, through perimenopause and menopause, into the postmenopausal phase.

Beyond efficacy, GLP-1 RA-induced rapid weight loss in women may paradoxically reduce adipose-derived estrogen production, creating a feedback loop in which the drug undermines the very hormonal environment that optimizes its own action. This self-attenuating mechanism has received remarkably little attention in clinical nutrition literature, despite its potential implications for patient outcomes, treatment adherence, and downstream hormonal health.

This review synthesizes current mechanistic and clinical evidence on the estrogen-GLP-1 relationship, with the aim of informing sex-specific nutritional support strategies, hormonal monitoring protocols, and product development priorities for women receiving GLP-1 RA therapy. It is intended to bridge the gap between mechanistic endocrinology, clinical nutrition science, and applied nutritional supplementation practice.

## Methods

This narrative review was conducted as a structured evidence synthesis in nutritional science, not as a registered systematic review or meta-analysis. Electronic databases included PubMed/MEDLINE, Embase, the Cochrane Central Register of Controlled Trials, and targeted Google Scholar searches from database inception through March 2026. The main search strings were: ("GLP-1 receptor agonist" OR semaglutide OR tirzepatide OR liraglutide) AND (women OR female OR sex differences OR sex-disaggregated); ("GLP-1 receptor" OR GLP-1R) AND (estrogen OR oestradiol OR estradiol OR menopause OR hormone therapy); (semaglutide OR tirzepatide) AND ("body composition" OR "lean mass" OR sarcopenia OR DXA OR muscle); ("GLP-1 receptor agonist" OR semaglutide OR tirzepatide) AND ("weight

regain” OR discontinuation OR cessation); and (“GLP-1 receptor agonist” OR semaglutide OR tirzepatide) AND (protein OR micronutrients OR nutrition support). Google Scholar was used only to identify highly cited or recently published items not readily retrieved in database searches; non-scholarly sources were not used as primary evidence.

The search process identified 326 records before duplicate removal and relevance screening (PubMed/MEDLINE, n = 181; Embase, n = 82; Cochrane, n = 23; Google Scholar targeted records, n = 40). After removal of duplicates and clearly irrelevant records, 118 titles and abstracts were screened. Sixty-two full-text articles or conference abstracts were assessed for eligibility, and 41 sources were retained for narrative synthesis. Because this manuscript is a narrative review, no formal PRISMA flow diagram, protocol registration, risk-of-bias scoring, or quantitative evidence grading was performed.

Inclusion criteria comprised: (1) randomized controlled trials, meta-analyses, systematic reviews, or high-quality observational studies reporting sex-disaggregated GLP-1 RA outcomes; (2) mechanistic studies in human or validated animal models examining estrogen-GLP-1 interactions; (3) studies reporting body composition outcomes including lean mass and fat mass changes; (4) studies reporting hormonal biomarker changes or reproductive-axis considerations relevant to women receiving GLP-1 RAs; and (5) nutritional intervention, advisory, or consensus papers relevant to lean mass, bone, micronutrient status, or protein intake during pharmacological weight loss. Studies were excluded if they were unrelated to GLP-1 RA therapy, lacked relevance to sex-specific or nutrition-related outcomes, involved pediatric populations exclusively, were not available in English, or were non-scholarly sources such as commercial websites, blogs, or unsupported clinical commentary. Conference abstracts and preprints were included only when clearly labelled as preliminary evidence and were not used to support strong clinical recommendations.

### **The estrogen-GLP-1 receptor synergy: Mechanistic evidence**

#### **GLP-1 receptor distribution in the central nervous system**

GLP-1 receptors are expressed throughout the central nervous system, with particularly high density in regions governing appetite, energy balance, and reward processing: the nucleus of the solitary tract (NTS), the paraventricular nucleus (PVN) of the hypothalamus, the arcuate nucleus (ARC), the lateral hypothalamus (LH), the supramammillary nucleus (SUM), and the ventral tegmental area (VTA) [4]. Pharmacological GLP-1R activation in these regions suppresses food intake, reduces food-motivated behaviour, and modulates reward salience of palatable food.

Critically, the distribution and functional activity of GLP-1Rs in the CNS is not sex-neutral. Preclinical studies in rodent models have demonstrated that GLP-1R populations in specific hypothalamic sub-regions exhibit sexually dimorphic expression patterns that emerge in adulthood and are modulated by gonadal steroid hormones [4]. Female animals consistently demonstrate greater suppression of food-motivated behaviour following central GLP-1R activation, an effect that is partially but not entirely attributable to differences in body weight or pharmacokinetics.

#### **Estrogen as a CNS amplifier of GLP-1 receptor activity**

The interaction between oestradiol and GLP-1 signalling extends beyond simple co-expression of receptors. Experimental evidence now establishes that estrogen actively potentiates GLP-1R-mediated neuronal activation through several distinct mechanisms.

First, central administration of a GLP-1-estrogen conjugate a molecularly linked compound that selectively targets cells co-expressing both GLP-1R and oestrogen receptor (ER) activates brain regions that are not engaged by either molecule administered separately at equivalent doses [4]. This finding is mechanistically significant: it indicates that the co-presence of estrogen does not merely add to GLP-1 activity additively, but rather unlocks a distinct neural circuit architecture that constitutes a qualitatively different mode of appetite regulation. Regions identified as targets of this conjugate-specific activation include the SUM a hypothalamic area not previously implicated in feeding or food reward control as well as the LH and NTS [4,5].

Second, peripheral administration of the GLP-1-estrogen conjugate produced synergistic reductions in food reward behaviour, food intake, and body weight in both female and male rodents, with superior effects observed in females consistent with higher circulating estrogen levels [4]. This finding is noteworthy in that it suggests the potentiating effect of estrogen on GLP-1 activity is not exclusive to females but is amplified by the higher baseline estrogen concentrations characteristic of premenopausal women.

Third, surgical removal of gonadal steroid production via ovariectomy in female rats significantly diminished the ingestive behaviour response to GLP-1 and reduced activation of key appetite-regulatory brain regions including the PVN, while effects on the NTS were preserved [4]. This provides direct causal evidence that endogenous estrogen is required for full expression of CNS GLP-1R activity in females, and that estrogen withdrawal whether surgical or physiological, as in menopause - meaningfully attenuates GLP-1 RA efficacy.

These findings from preclinical models are biologically plausible and mechanistically coherent with the larger body of evidence on estrogen's role in hypothalamic energy balance regulation. Oestradiol regulates feeding behaviour through multiple overlapping pathways: direct modulation of appetite neuropeptides (NPY, AgRP, POMC) in the ARC, enhancement of satiety signalling from cholecystokinin (CCK) and leptin, and suppression of food reward via mesolimbic dopamine circuits [6,7]. The GLP-1 pathway intersects with each of these, creating multiple points of synergistic amplification.

### Clinical evidence for estrogen-GLP-1 synergy in women

The mechanistic evidence described above is consistent with clinical observations from human studies. A systematic review and meta-analysis by Alexander, *et al.* examined 64 randomized controlled trials encompassing 19,906 patients in sex-disaggregated analyses. The pooled analysis found that women lost an average of 10.88% of initial body weight on GLP-1 RAs, compared with 6.78% in men, a statistically significant difference of approximately 4 percentage points [8].

Corroborating data from the STEP trial programme (semaglutide 2.4 mg weekly) confirm consistent sex differences across multiple trial phases. In STEP 1, the estimated treatment difference versus placebo was 14.0% in women versus 8.0% in men; in STEP 2, 7.5% versus 4.6%; and in STEP 4, 16.2% versus 9.3% [9]. These differences persisted after adjustment for baseline body weight, suggesting that pharmacokinetic differences alone do not fully account for the observed sex gap, and that biological interactions including estrogen-mediated CNS sensitization are contributing factors.

A real-world retrospective study of 7,847 individuals with type 2 diabetes across 18 Italian diabetes centers also reported greater weight reduction among women than men on GLP-1 RA therapy over a median follow-up of four years. Because this evidence is observational and diabetes-focused, it should be interpreted as supportive rather than definitive evidence for sex-specific GLP-1 RA response in obesity treatment.

Clinical evidence directly testing the estrogen-GLP-1 synergy hypothesis remains limited but is emerging from studies combining GLP-1-based pharmacotherapy with hormone therapy (HT) in postmenopausal women. A 2024 peer-reviewed retrospective cohort study in Menopause examined semaglutide outcomes in postmenopausal women stratified by concurrent HT use and found greater weight loss among HT users at 12 months [10]. A separate peer-reviewed retrospective cohort study of tirzepatide in postmenopausal women similarly reported greater weight loss among HT users than non-users, but the authors emphasized the observational design and need for prospective trials [11].

### Sex differences in body composition outcomes

#### Lean mass loss: A disproportionate burden in women

Weight loss universally induces some reduction in lean body mass; this is a physiological reality that is not unique to GLP-1 RA therapy and is observed across dietary, behavioral, and pharmacological weight loss interventions [12]. However, the magnitude and composition

of lean mass loss associated with GLP-1 RA therapy has attracted significant clinical concern, and emerging data indicate that this burden is distributed unequally by sex.

The SEMALEAN study, a 12-month prospective cohort study of adults with obesity receiving semaglutide 2.4 mg, used dual-energy X-ray absorptiometry (DXA) to characterise body composition changes at baseline, seven months, and 12 months. The study reported significant reductions in weight and fat mass, an early decline in lean mass that stabilized over time, and improvement in muscle function. Subgroup analyses indicated greater weight and fat mass loss among women, but the study does not establish that women universally experience maladaptive lean mass loss [13].

Complementary preliminary evidence from a conference abstract presented by researchers at Massachusetts General Hospital and Harvard Medical School examined predictors of lean mass loss in 40 adults on semaglutide. After accounting for total weight loss, female sex, older age, and lower dietary protein intake were reported as factors associated with greater lean mass loss [14]. Because this evidence is conference-level and preliminary, it should be interpreted as hypothesis-generating rather than as a basis for definitive clinical recommendations.

The clinical significance of lean mass loss extends beyond aesthetics. Skeletal muscle is a major site of post-prandial glucose disposal and contributes to resting energy expenditure, mobility, and long-term functional status. Preliminary conference evidence has suggested a possible relationship between greater lean mass loss and less improvement in glycemic markers during semaglutide therapy, but this association requires confirmation in peer-reviewed prospective studies before firm conclusions can be drawn [14].

Long-term consequences of lean mass reduction are particularly relevant in ageing women, given the established association between sarcopenia, falls, functional decline, osteoporosis, and cardiometabolic risk. This concern supports the need for adequate protein intake, resistance exercise, and individualized body composition assessment during substantial weight loss, particularly in postmenopausal women and women with low baseline lean mass.

### **The adaptive vs maladaptive lean mass loss debate**

A Circulation review (American Heart Association, 2024) reviewed MRI and DXA data across multiple GLP-1 RA trials and concluded that changes in muscle volume z-scores were largely commensurate with expected physiological responses to weight loss - suggesting that lean mass loss in this context may be adaptive rather than maladaptive in many patients. This is an important nuance: the proportion of lean mass relative to total body mass typically improves on GLP-1 RA therapy even as absolute lean mass declines. However, this population-level framing obscures meaningful individual and sex-based heterogeneity that is of direct clinical relevance.

The key question is not whether some lean mass loss is inevitable; rather, it is whether the magnitude and distribution of that loss are clinically meaningful in higher-risk subgroups. Available evidence suggests that some women, particularly older women or those with low protein intake, may be at increased risk of clinically relevant lean mass loss. This is biologically plausible and potentially modifiable through nutrition, resistance training, and monitoring, but prospective sex-specific studies are needed.

### **The disruption loop: GLP-1-induced weight loss and hormonal sequelae in women**

#### **Adipose tissue as a source of estrogen**

Adipose tissue is not metabolically inert. It is the primary site of peripheral estrogen biosynthesis through aromatisation of androgen precursors a process catalysed by the cytochrome P450 enzyme aromatase (CYP19A1). This pathway accounts for the majority of estrogen production in postmenopausal women and contributes meaningfully to circulating estrogen levels in premenopausal women as well [6]. Consequently, significant reductions in adipose tissue mass of the magnitude achieved by GLP-1 RA therapy have predictable downstream effects on estrogen biosynthesis capacity.

This creates a physiologically meaningful feedback mechanism: GLP-1 RA-induced weight loss reduces body fat, which reduces adipose-derived estrogen production, which attenuates the neurobiological amplification of GLP-1R activity in the brain. In effect, the drug may progressively diminish the hormonal environment that optimizes its own central mechanism of action. The clinical manifestation of this self-attenuating loop has not been formally characterized in prospective studies, but the biological plausibility is supported by multiple converging lines of evidence.

### **Disruption of the hypothalamic-pituitary-ovarian axis**

Rapid weight loss irrespective of mechanism is a recognized disruptor of the hypothalamic-pituitary-ovarian (HPO) axis. The hypothalamus requires stable energy availability to maintain regular pulsatile gonadotropin-releasing hormone (GnRH) secretion, which drives the downstream cascade of luteinising hormone (LH) and follicle-stimulating hormone (FSH) release from the pituitary, and ultimately estradiol and progesterone production from the ovaries. Moderate caloric restriction can temporarily suppress GnRH pulsatility, and the magnitude of reproductive axis suppression correlates with the degree and rate of caloric restriction [15,16].

GLP-1 RA therapy can produce substantial caloric restriction and rapid weight loss, which may engage these energy-availability mechanisms with clinical relevance. Direct peer-reviewed evidence linking semaglutide or tirzepatide to menstrual irregularities in otherwise healthy reproductive-age women remains limited. Therefore, menstrual-cycle disruption during GLP-1 RA therapy should be framed cautiously as a biologically plausible concern related to rapid weight loss and energy deficit, not as a proven direct pharmacological effect of GLP-1R activation on reproductive tissues. Prospective studies that track menstrual status, energy intake, weight-loss rate, and gonadotropin profiles are needed.

### **Downstream hormonal biomarker disruption**

Beyond direct gonadotropin effects, GLP-1 RA-induced metabolic changes are expected to alter the circulating concentrations and functional dynamics of several hormonally relevant biomarkers in women.

Sex hormone-binding globulin (SHBG) is a hepatic glycoprotein that binds and inactivates circulating sex steroids, including estradiol and testosterone. SHBG levels are inversely regulated by insulin: hyperinsulinaemia suppresses hepatic SHBG production, while improvements in insulin sensitivity a direct effect of GLP-1 RA therapy increase SHBG synthesis. Rising SHBG concentrations reduce the bioavailability of free estradiol and free testosterone, with potentially complex consequences for reproductive and metabolic function [17].

Cortisol dynamics may also be altered during rapid weight loss and periods of low energy availability. The hypothalamic-pituitary-adrenal (HPA) axis is responsive to caloric restriction and metabolic stress, and sustained elevations in cortisol may interfere with GnRH pulsatility and muscle protein balance. However, GLP-1 RA-specific cortisol data in women are limited, and this pathway should be treated as a hypothesis requiring prospective biomarker evaluation rather than as an established clinical effect.

Thyroid function may also warrant attention in selected patients. Weight loss from pharmacological or non-pharmacological interventions can alter TSH concentrations and thyroid hormone requirements, particularly in individuals treated with levothyroxine, while broader evidence on direct GLP-1 RA effects on thyroid function remains inconclusive [18,19]. Routine thyroid cancer screening is not supported solely on the basis of GLP-1 RA use, but baseline thyroid history and symptom-guided thyroid function assessment remain clinically reasonable.

### **Weight regain after GLP-1 RA discontinuation: Need for sex-specific data**

The sustainability of GLP-1 RA-induced weight loss following drug discontinuation has emerged as a major clinical and public health concern. The STEP 1 trial extension demonstrated that participants who discontinued semaglutide after achieving maximum weight loss

regained, on average, two-thirds of lost weight within one year, with most of the regain occurring in the first 20 weeks post-discontinuation [20]. The SURMOUNT-4 trial for tirzepatide reported similar findings.

A systematic review and meta-analysis published in *The BMJ* evaluated weight regain after cessation of weight management medications across 37 studies involving 9,341 adults with overweight or obesity. The analysis found that weight and cardiometabolic benefits generally diminished after medication cessation, with modelling suggesting return to baseline weight in approximately 1.7 years on average [21]. This supports the concept that obesity is a chronic, relapsing condition and that discontinuation planning is clinically important.

Evidence for sex-divergent weight regain after GLP-1 RA discontinuation remains insufficient. Some preliminary self-reported and preprint data have suggested possible sex differences, but these sources should not be used as strong evidence for differential regain in women. Future discontinuation studies should report outcomes by sex, menopausal status, hormone therapy use, body composition, and nutritional intake to determine whether biologically meaningful sex-specific regain trajectories exist.

Real-world discontinuation is common. A large US cohort study of 125,474 adults with overweight or obesity reported substantial discontinuation within one year after initiation of dual-labelled GLP-1 RA therapy, with discontinuation patterns differing by diabetes status [22]. This amplifies the practical importance of longitudinal nutrition, physical activity, and weight-maintenance support, including but not limited to women receiving GLP-1 RA therapy.

### **Nutritional implications and recommendations for women on GLP-1 RA therapy**

#### **Protein: The non-negotiable foundation**

The evidence for protein's role in lean mass preservation during substantial weight loss is strong, although GLP-1 RA-specific prospective evidence remains developing. Preliminary semaglutide data presented in conference form identified lower dietary protein intake as a possible predictor of lean mass loss, consistent with the broader literature on protein requirements during caloric restriction and ageing [14,23].

Current consensus recommendations from the joint advisory of the American College of Lifestyle Medicine, the American Society for Nutrition, the Obesity Medicine Association, and The Obesity Society emphasize adequate protein intake, resistance exercise, and prevention of nutrient inadequacy during GLP-1 RA therapy [24]. Protein targets should be individualized using actual, adjusted, or ideal body weight depending on baseline BMI, adiposity, renal function, age, and clinical context. In many adults receiving GLP-1 RA therapy, a pragmatic target of approximately 1.2 - 1.6 g/kg/day based on adjusted or ideal body weight may be appropriate; older adults or those with low lean mass may require individualized higher targets under clinical supervision.

Protein distribution across meals is mechanistically as important as total daily intake. Post-prandial mTOR activation is a threshold-dependent phenomenon: approximately 2.5 - 3.0g of leucine per meal achievable with approximately 25 - 40g of high-quality protein is required to maximally stimulate muscle protein synthesis in adults, particularly older women [23]. Given that GLP-1 RA therapy dramatically reduces meal size and frequency, achieving protein distribution targets requires deliberate dietary planning and, in many cases, targeted supplementation.

#### **Micronutrients: The under addressed gap**

As caloric intake contracts under GLP-1 RA therapy, the micronutrient density of remaining calories becomes exponentially more important. Individuals consuming 1,000 - 1,400 kcal/day not uncommon among adherent GLP-1 RA users face near-certain micronutrient insufficiency without deliberate supplementation, regardless of food quality.

For women specifically, the following micronutrients warrant priority attention:

- **Iron:** Women of reproductive age with intact menstrual cycles are at baseline elevated risk of iron insufficiency. GLP-1 RA-induced reductions in food intake compound this risk, and GI motility changes may affect haem and non-haem iron absorption efficiency.
- **Folate and B12:** Critical for one-carbon metabolism, DNA synthesis, and neurological function. Reduced intake of animal proteins and fortified cereals during GLP-1 RA therapy increases deficiency risk.
- **Calcium and vitamin D:** Bone health is a particular concern in women approaching or in menopause, where estrogen-deficiency-related bone loss compounds any diet-induced micronutrient gaps. Adequate calcium (1000-1200 mg/day) and vitamin D (1500-2000 IU/day) are recommended.
- **Magnesium:** Involved in over 300 enzymatic processes including insulin signaling, muscle function, and cortisol regulation. Dietary magnesium is frequently insufficient in Western diets and further compromised by reduced caloric intake.
- **Zinc:** Critical for immune function, wound healing, and testosterone (and indirectly estrogen) synthesis. Lean meat and shellfish common zinc sources may be reduced in GLP-1 RA users due to appetite suppression and GI sensitivity.

Gender-specific micronutrient recommendations calibrated to life stage, menstrual status, and GLP-1 RA use represent an unmet formulation and education opportunity for the nutrition and supplement industry.

**The role of hormone therapy as a nutritional and metabolic complement**

The evidence that concurrent hormone therapy may be associated with greater GLP-1-based weight loss in postmenopausal women raises a question that sits at the intersection of endocrinology and nutritional medicine: should hormone therapy status be considered when evaluating response to GLP-1 RA therapy in postmenopausal women? The current evidence is observational and should not be interpreted as proof that HT causes enhanced GLP-1 RA efficacy, but the consistency between semaglutide and tirzepatide studies supports prospective investigation.

This is a clinical question that extends beyond the scope of nutritional science, and prescribing decisions regarding HT must be individualized based on cardiovascular risk, breast cancer history, thromboembolic risk, symptom profile, age, and time since menopause. The data are sufficiently interesting to merit formal investigation, but not sufficient to recommend HT solely as a metabolic adjunct to GLP-1 RA therapy outside appropriate clinical indications.

**Proposed biomarker monitoring framework for women on GLP-1 RA therapy**

No standardized sex-specific hormonal monitoring protocol currently exists for women receiving GLP-1 RA therapy. The following framework is a proposed research-informed framework based on the mechanistic and clinical evidence reviewed. It is not a validated standard of care and should not be interpreted as a clinical protocol. Formal validation through prospective study is required before broad clinical implementation can be recommended.

<b>Biomarker</b>	<b>Clinical Rationale</b>	<b>Monitoring Recommendation</b>
Oestradiol (E2)	Estrogen may modulate GLP-1R activity in appetite-regulatory pathways. Estradiol interpretation depends on menopausal status, menstrual-cycle phase, and hormone therapy use.	Baseline and follow-up only when clinically indicated or within a research protocol. Interpret by menopausal status and menstrual-cycle phase; no universal estradiol cut-off is proposed.
FSH / LH	HPO axis suppression indicator: Elevated FSH with low E2 confirms menopausal transition or axis disruption.	Baseline and 6 months. Repeat if menstrual irregularity reported.

SHBG	Rises with insulin sensitivity improvement; reduces free E2 bioavailability. May paradoxically attenuate estrogen effect.	Baseline and 6 months. Interpret in context of free vs total E2.
Cortisol (morning fasting)	Caloric restriction elevates cortisol; elevated cortisol suppresses GnRH and accelerates muscle catabolism.	Baseline and 3 months. 24-hour urinary cortisol if elevated single measure.
Thyroid panel (TSH, free T4, TPO antibodies)	Rapid metabolic change may unmask latent thyroid dysfunction. High prevalence of thyroid autoimmunity in women.	Baseline mandatory. Repeat at 6 months or if symptoms emerge.
Lean mass (DXA or BIA)	Quantifies muscle attrition. Critical in women >50 with pre-existing low lean mass.	Baseline and 6 months minimum. Every 3 months for high-risk groups.
Dietary protein (3-day food diary)	Protein intake is the most actionable modifiable predictor of lean mass loss on semaglutide.	Baseline and each clinical visit. Individualize target using actual, adjusted, or ideal body weight based on BMI, renal function, age, and clinical context.

**Table 1:** Proposed research-informed biomarker monitoring framework for women receiving GLP-1 receptor agonist therapy. This framework is not a validated standard of care and should be used only for research design, clinical hypothesis generation, or individualized clinician-directed assessment. HPO: Hypothalamic-Pituitary-Ovarian; SHBG: Sex Hormone-Binding Globulin; DXA: Dual-Energy X-ray Absorptiometry; BIA: Bioelectrical Impedance Analysis; TPO: Thyroid Peroxidase.

### Limitations of the Study

This narrative review is subject to several important limitations. First, the majority of mechanistic evidence for estrogen-GLP-1 synergy derives from preclinical rodent models. While the biological plausibility is high and consistent with human clinical observations, direct mechanistic studies in women using neuroimaging or invasive brain biomarker assessment are lacking. Translation from rodent to human neuroendocrinology is not always direct.

Second, sex-disaggregated analyses in existing GLP-1 RA clinical trials are largely post-hoc subgroup analyses rather than pre-specified primary endpoints. Many meta-analyses rely on published subgroup averages rather than individual participant-level data, introducing the possibility of ecological bias and residual confounding. Furthermore, obesity trials historically over-enroll women relative to population prevalence, which may influence subgroup comparisons.

Third, the proposed biomarker monitoring framework is derived from mechanistic reasoning and expert synthesis rather than validated prospective clinical data. It is presented as a research-informed framework, not as a standard of care. Formal evaluation of its clinical utility, cost-effectiveness, patient burden, and impact on outcomes requires prospective investigation.

Fourth, the PCOS population - in whom GLP-1 RA therapy may paradoxically improve hormonal balance by reducing insulin resistance-driven androgen excess - represents a distinct clinical context that is addressed only briefly in this review. The complexity of sex hormone dynamics in PCOS warrants dedicated investigation beyond the scope of the present paper.

Finally, this review focuses primarily on estrogenic sex differences and does not address the full complexity of sex hormone biology, including the roles of progesterone, androgens, and sex hormone-binding globulin in modulating GLP-1R activity and metabolic outcomes. These represent important areas for future investigation.

## **Conclusion**

The interaction between estrogen biology and GLP-1 receptor agonist pharmacology in women is mechanistically plausible, supported by preclinical data, and increasingly relevant to clinical nutrition and obesity medicine. Estrogen appears to modulate GLP-1R activity in appetite-regulatory pathways, which may partly explain why women in several analyses experience greater weight loss than men on GLP-1 RA therapy. Whether that advantage changes with age, menopause, hormone therapy use, or GLP-1 RA-induced fat loss remains an important research question.

The implications of this evidence are clinically relevant but should be framed with appropriate caution. Women on GLP-1 RA therapy may face lean mass loss, micronutrient inadequacy, reproductive-axis disruption related to rapid weight loss or low energy availability, and weight regain after discontinuation. However, the magnitude of these risks, and the extent to which they differ by sex, menopausal status, or hormone therapy use, require more rigorous prospective study.

This review supports a reorientation of GLP-1 RA research and nutritional support toward the biological reality of female sex hormone physiology. Specifically, future studies should evaluate (1) sex-specific hormonal biomarker monitoring in women initiating GLP-1 RA therapy; (2) individualized protein targets and micronutrient supplementation protocols, particularly for women over 50 or those with low lean mass; (3) the role of concurrent hormone therapy as a potential modifier of GLP-1 RA response in appropriately selected postmenopausal women; and (4) mandatory sex-disaggregated reporting in future GLP-1 RA clinical trials.

Current evidence supports further prospective studies to define sex-specific monitoring and nutritional strategies for women receiving GLP-1 receptor agonist therapy.

## **Conflict of Interest Statement**

The author declares no conflicts of interest in relation to the content of this manuscript. This review was conducted independently and reflects the author's scientific analysis of publicly available literature.

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## **Author Contributions**

Varun Chandra Koneru: Conceptualization, literature review, data synthesis, manuscript writing, and final approval.

## **Ethical Approval**

Not applicable. This manuscript is a narrative review of previously published literature and does not involve human participants or animal studies.

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