

Weight loss from GLP-1 receptor agonists and facial ptosis: Specific mechanism or epiphenomenon of weight loss? A critical review

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Abstract

The expanding use of glucagon-like peptide-1 receptor agonists (GLP-1RA) for the treatment of type 2 diabetes mellitus and obesity has made a set of facial aesthetic changes popularly known as “Ozempic face” clinically common, characterized by volume loss, deepening of folds, and soft-tissue ptosis. A central controversy persists regarding causality, however: do these changes result from a specific pharmacological effect of the GLP-1 pathway on dermal cells, or are they merely an epiphenomenon of the magnitude and speed of weight loss, independent of the drug class? This narrative critical review synthesizes the available evidence on epidemiology, clinical presentation, molecular and tissue mechanisms, and aesthetic management options, with emphasis on the methodological gaps that prevent a definitive causal attribution. We conclude that the association between GLP-1RA and accelerated facial ptosis is robust and reproducible, but the existence of a receptor-specific mechanism remains a biologically plausible, still-unproven hypothesis, given the absence of studies that control for the rate of weight loss as a confounding variable.

Keywords: GLP-1 receptor agonists, semaglutide, facial aging, ptosis, Ozempic face.

Perda de peso decorrente de agonistas do receptor de GLP-1 e ptose facial:
mecanismo específico ou epifenômeno da perda de peso? Uma revisão crítica

Resumo

O uso crescente dos agonistas do receptor do peptídeo semelhante ao glucagon-1 (GLP-1RA) para o tratamento do diabetes mellitus tipo 2 e da obesidade tornou clinicamente comum um conjunto de alterações estéticas faciais popularmente conhecidas como “rosto de Ozempic”, caracterizadas por perda de volume, aprofundamento das pregas e ptose dos tecidos moles. Entretanto, persiste uma controvérsia central quanto à causalidade: essas alterações resultam de um efeito farmacológico específico da via do GLP-1 sobre as células dérmicas ou são meramente um epifenômeno da magnitude e da velocidade da perda de peso, independentemente da classe do medicamento? Esta revisão crítica narrativa sintetiza as evidências disponíveis sobre epidemiologia, apresentação clínica, mecanismos moleculares e teciduais e opções de manejo estético, com ênfase nas lacunas metodológicas que impedem uma atribuição causal definitiva. Concluímos que a associação entre os GLP-1RA e a aceleração da ptose facial é robusta e reproduzível, mas a existência de um mecanismo específico mediado pelo receptor permanece uma hipótese biologicamente plausível, ainda não comprovada, dada a ausência de estudos que controlem a velocidade da perda de peso como variável de confusão.

Palavras-chave: agonistas do receptor de GLP-1, semaglutida, envelhecimento facial, ptose, rosto de Ozempic.

1. Introduction

Glucagon-like peptide-1 receptor agonists (GLP-1RAs) are incretin-mimetic drugs that reproduce the action of endogenous GLP-1, stimulating glucose-dependent insulin secretion, suppressing glucagon release, delaying gastric emptying, and reducing appetite through central mechanisms (Drucker, 2018). Originally approved for the management of type 2 diabetes mellitus (T2DM), agents such as semaglutide and tirzepatide subsequently obtained regulatory approval for chronic weight management in obesity, after randomized clinical trials demonstrated mean body-weight reductions of approximately 15% and 21%, respectively (Wilding et al., 2021; Jastreboff et al., 2022). This regulatory expansion has been paralleled by a distinct and unapproved pattern of use: prescription for cosmetic weight reduction in individuals who do not meet the BMI or comorbidity thresholds of the approved indication.

Prescription volumes have grown sharply, with estimates of an increase of nearly 300% between early 2020 and late 2022 (Jodat et al., 2026). This growth has been accompanied by a recurring aesthetic complaint. In 2023, dermatologist Paul Jarrod Frank coined the term "Ozempic face" to describe the facial changes observed in patients undergoing semaglutide therapy, particularly those using the drug for cosmetic weight reduction outside the approved indication (Daneshgaran et al., 2025; Humphrey; Lawrence, 2023; Sciscent et al., 2024).

The term originated in media and social media discourse, preceding any scientific characterization of the phenomenon, and quickly became dissociated from a specific molecule, coming to designate the pattern of facial aging associated with rapid and pronounced weight loss of any cause (Catalfamo et al., 2025). This clinical recognition also appears in the otolaryngology literature, which already describes the phenomenon in the context of GLP-1RA use for aesthetic purposes outside the approved indication (Seidel; Bode, 2025).

The rapid popularization of the term created a mismatch between public perception and the evidence base. Facial plastic surgeons have reported a marked increase in demand for volumetric restoration procedures, and online searches for "Ozempic face" have come to correlate with searches for facial fillers and aesthetic practitioners (Mansour et al., 2024; O'Neill et al., 2024). This mismatch makes a critical review timely, one that distinguishes the solid observational association from the still-uncertain causal attribution to the pharmacological mechanism. This article has three objectives: (i) to map the epidemiology and clinical presentation of GLP-1RA-associated facial volume loss and laxity; (ii) to critically confront the two competing causal hypotheses, receptor-specific effect versus epiphenomenon of weight loss; and (iii) to review aesthetic management options and discuss how the therapeutic response indirectly informs the causal debate.

2. Materials and Methods

This is a narrative critical review. The search was conducted in PubMed/MEDLINE, Europe PMC, and OpenAlex, complemented by manual screening of the reference lists of retrieved articles. Scopus and Embase were initially defined as target databases, following the strategy of the reference systematic review on this topic (Daneshgaran et al., 2025), but were not searched because institutional access was unavailable; Europe PMC and OpenAlex were used as open-access alternatives. This substitution is acknowledged as a limitation, as Embase indexes conference abstracts and European pharmacological literature not fully covered by the databases searched here.

Combinations of the descriptors "GLP-1 receptor agonist," "semaglutide," "tirzepatide," "Ozempic face," "facial aging," "facial volume loss," "ptosis," and "skin laxity" were used with Boolean operators. The search was executed programmatically via the respective APIs on 31 July 2026. The prioritized period was January 2023 to January 2026, reflecting the recent nature of the phenomenon, without excluding earlier foundational references on GLP-1 pharmacology and skin-aging biology (Drucker, 2018).

Original articles, reviews, case series and case reports, radiographic facial volumetry studies, and in vitro studies addressing the relationship between GLP-1RA, weight loss, and changes in the soft tissues of the face were included. Records with no direct relation to the face, non-scientific outreach material, and publications with full data duplication were excluded. Identification counts, duplicate removal, title/abstract screening, and eligibility assessment are summarized in Figure 1. All included references were verified for authorship and publication venue in indexed databases before incorporation into the synthesis.

Twenty-five studies were included. The evidence base consists predominantly of case reports, case series, observational studies, narrative and systematic reviews, and mechanistic in vitro studies; comparative studies with control groups are few, and no randomized trial has facial soft-tissue change as a primary outcome. This composition is detailed in Table 2 and constrains the strength of any causal inference drawn in this review. Given

the narrative and critical nature of the synthesis, no quantitative meta-analysis or formal aggregate risk-of-bias assessment was applied; methodological quality was weighed qualitatively during interpretation, prioritizing studies with objective volumetric measurement over those relying on subjective clinical description.

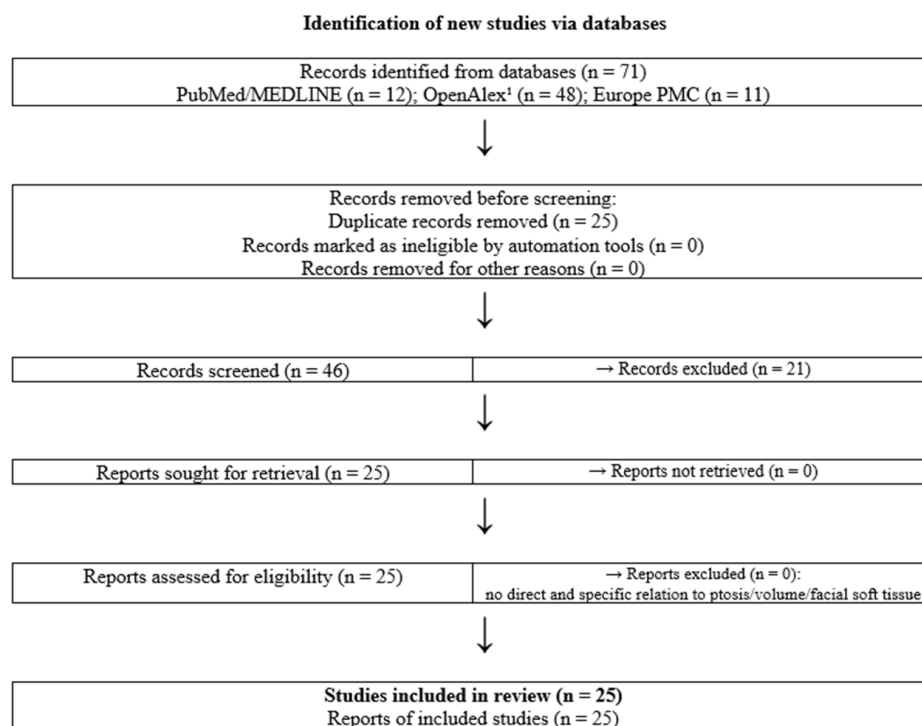


Figure 1. PRISMA flow diagram of the actual search process (API execution on 07/31/2026). Source: Authors, 2026.

3. Evidence Synthesis

3.1 Overview of included studies

Table 1 summarizes, in alphabetical order, the 25 eligible studies identified by the actual search described in Section 2 (Figure 1) and effectively incorporated into this synthesis, along with the publication journal and the main contribution of each to the review.

Table 1. Eligible studies incorporated into the synthesis (n = 25), in alphabetical order.

Nº	Author(s), Year	Journal	Main Contribution
1	Avelar et al., 2026	Clin Cosmet Investig Dermatol	Clinical series of PLLA+HA in GLP-1RA users
2	Baggett et al., 2025	Cosmetics	Commentary; parallel with post-bariatric changes
3	Catalfamo et al., 2025	J Clin Med	Case series; endotissue bipolar radiofrequency
4	Cedirian et al., 2025	Dermatol Ther (Heidelb)	Benefit-risk review for dermatologists
5	Chen et al., 2026	Ophthalmic Plast Reconstr Surg	Case-control study; orolabial changes
6	Daneshgaran et al., 2025	Aesthet Surg J Open Forum	Reference systematic review on the topic
7	Durairaj et al., 2025	Aesthet Surg J Open Forum	Clinical series; calcium hydroxylapatite

8	Haykal et al., 2025	J Cosmet Dermatol	Clinical commentary on multimodal management
9	Humphrey; Lawrence, 2023	Facial Plast Surg	Implications for facial plastic surgeons
10	Kapantais; Tsoutsanis, 2025	J Clin Med	Review of periorbital/ocular changes
11	Kılıç, 2025	J Diabetes Metab Disord	Review of the clinical presentation of the phenomenon
12	Kirsanova et al., 2025	Russ J Skin Vener Dis	Preventive cosmetology protocol
13	Lorenc et al., 2026	Aesthet Surg J	Multicenter open-label study; PLLA+HA
14	Mnajjed; Mims, 2025	Plast Reconstr Surg Glob Open	Trend analysis (Google Trends)
15	Montecinos et al., 2024	Dermatol Rev	Characterization of elastin/collagen/volume loss
16	Moradi et al., 2026	Aesthet Surg J Open Forum	Guideline based on expert interviews
17	Morzhanaeva et al., 2025	Meditinskiy Sovet	Biostimulatory mechanism of PLLA
18	Nguyen et al., 2026	J Cosmet Dermatol	Trial of topical volumizing cream
19	Parkinson, 2026	J Aesthet Nurs	Case series; distinct topical formulation
20	Paschou et al., 2025	Endocrine	Receptor-specific mechanistic hypothesis (ADSC/GLP-1R)
21	Ridha et al., 2024	Aesthet Surg J	ADSC mechanism
22	Saffari et al., 2026	Ophthalmic Plast Reconstr Surg	Retrospective cohort
23	Sataray-Rodriguez et al., 2025	J Biomed Sci Eng	Collagen and skin elasticity
24	Seidel; Bode, 2025	HNO	Review of the phenomenon as a lifestyle issue
25	Sharma et al., 2025	Otolaryngol Head Neck Surg	Real radiographic volumetry

Source: Authors, 2026.

3.2 Epidemiology and clinical presentation

GLP-1RA-associated facial ptosis does not affect patients uniformly. The literature converges on a higher-risk profile composed of individuals over 40 years of age, a pre-treatment body mass index in the 40 to 49.9 kg/m² range, and those who lose a high proportion of excess weight, especially above 75% (Sharma et al., 2025). Men in this age group and patients with more pronounced weight loss showed, in perceptual assessments, a greater degree of apparent facial aging (Sharma et al., 2025). The common denominator of these factors is the magnitude of adipose tissue loss in a face that already shows a physiological decline in elastin turnover and skin recoil capacity.

3.2.1 Affected facial fat compartments

The human face is supported by superficial and deep fat compartments, whose differential depletion alters contour and projection. Imaging volumetry studies have quantified this loss. In a radiographic analysis of midface volume, a median loss of 11.0% in the superficial compartment and 7.0% in the deep compartment was reported after GLP-1RA therapy (Sharma et al., 2025). The periorbital region and temples are among the areas most vulnerable to disproportionate volume loss in patients undergoing massive weight loss under GLP-1RA. Consistently, clinical data suggest an average loss of approximately 7% of midface volume for every 10 kg of body weight lost, predominantly at the expense of the superficial fat pads (American Academy of Ophthalmology, 2025). Periorbital vulnerability is also supported by independent findings: volume loss,

hypotonia, and ocular surface changes have already been described in this region (Kapantais; Tsoutsanis, 2025), and a retrospective cohort built from the TriNetX database found a significantly higher incidence of brow ptosis, dermatochalasis, and the need for surgical correction (blepharoplasty, blepharoptosis repair, rhytidectomy) among GLP-1RA users compared with diagnosis-matched controls (Saffari et al., 2026).

The perioral region appears to be affected in a similar manner: in a case-control study matched for age, sex, and ethnicity, drug users showed a significant increase in philtrum width, upper vermilion height, lower lip height, and mouth width (Chen et al., 2026). This latter sample, however, was considerably older (68 years, on average) and involved modest weight loss (3.4 kg, on average), which contrasts with the higher-weight-loss profile described at the beginning of this section and suggests that measurable changes can arise even outside the classic pattern of massive weight loss in younger patients.

Taken together, the periorbital and perioral findings broaden the phenotype of GLP-1RA-associated facial ptosis beyond the midface and lower-face fat compartments described initially. The persistence of the association even in subgroups with more modest weight loss, including the type 2 diabetes cohort discussed further ahead, makes it even more relevant to directly investigate the contribution of the pharmacological mechanism, and not merely the magnitude of weight loss.

In the lower third of the face, volumetric loss and ligamentous laxity are associated with the formation of platysmal bands, increased submental flaccidity and jowling, and chin ptosis (Kılıç, 2025). The integrated result is a generalized downward displacement of the soft tissues, with accentuated wrinkles, deepening of the nasolabial fold and melomental folds, flattening of the malar eminence, and lip thinning, configuring the phenotypic pattern that drives the search for rejuvenation (Sharma et al., 2025; Kılıç, 2025).

The public-health dimension of the phenomenon is reflected in demand data. Surveys by facial plastic surgery societies documented an increase in facial fat grafting attributed to the trend, and a substantial share of surgeons anticipate growing demand for non-surgical procedures, such as injectable fillers and skin-tightening technologies (Jodat et al., 2026; American Academy of Facial Plastic and Reconstructive Surgery, 2024). Online search-trend analysis corroborates this shift from public perception to care-seeking demand (Mansour et al., 2024). Google Trends data confirm this pattern: searches for terms related to “Ozempic face” grew significantly between 2022 and 2025, with a positive correlation specific to fillers, but not to surgical procedures (Mnajjed; Mims, 2025).

3.3 Molecular and tissue mechanisms

Regardless of the predominant causal pathway, the tissue substrate of facial ptosis involves an interaction between adipose depletion, extracellular matrix remodeling, and changes in dermal quality. Skin aging is characterized by reduced mitotic activity, barrier dysfunction, decreased collagen and elastin production, and increased oxidative stress with DNA and cell membrane damage (Paschou et al., 2025). Rapid fat loss removes the structural support on which the skin rests, while aged dermis shows a reduced recoil capacity, a combination that translates volume subtraction into visible flaccidity (Carboni et al., 2024).

Histological studies of patients after pronounced weight loss reveal altered organization and density of dermal collagen and elastic fibers, suggesting that weight loss, and not merely gravitational displacement, contributes to the deterioration of skin quality (Paschou et al., 2025). On the molecular side, the receptor-specific hypothesis postulates that GLP-1R signaling in ADSCs would reduce the production of trophic factors, such as IGF, compromising the antioxidant protection of fibroblasts and the stimulation of collagen synthesis (Paschou et al., 2025). Interaction with the AGE/RAGE axis, in turn, connects the phenomenon to classic skin-aging pathways in dysglycemic contexts (Paschou et al., 2025). In cosmetic dermatology, this picture has been characterized by the combined loss of elastin, collagen, adipose volume, and muscle, associated with excessive skin flaccidity (Montecinos et al., 2024).

3.4 Aesthetic solutions: Management options

Once facial ptosis has developed, a therapeutic arsenal is available that can be organized according to the predominant target of each modality: replacement of lost volume, tissue tightening and biostimulation, relaxation of muscular hyperactivity, and surgical correction of tissue excess and repositioning. There is emerging consensus that no single modality fully resolves the condition, and that the most effective strategy is multimodal and staged, combining approaches with complementary mechanisms and respecting the anatomy and timing of each intervention (Daneshgaran et al., 2025; Haq, 2025). GLP-1RA-associated changes place surgeons in a

clinical gray zone, in which established rejuvenation protocols must be adapted to the unusual pace and extent of this volume loss (American Academy of Ophthalmology, 2025).

The need for a proactive response from aesthetic practitioners is highlighted in a clinical commentary on the topic, which recommends combining fillers, energy-based devices, and, when indicated, surgery, with attention to empirical gaps and the ideal timing of intervention (Haykal et al., 2025). More practical recommendations come from a guideline based on a questionnaire and interviews with four highly experienced specialists: a multimodal non-surgical approach (volumization with hyaluronic acid fillers, skin tightening with collagen-biostimulating devices, and treatment of wrinkles and bands), regular follow-up, and nutritional, psychological, and lifestyle support (Moradi et al., 2026).

3.4.1 Volumetric replacement: Fillers and fat grafting

Volume replacement constitutes the central pillar of treatment, as it directly targets the primary mechanism of the condition, depletion of the fat pads. Hyaluronic acid fillers constitute the first line, offering immediate, adjustable, and reversible correction of deflated compartments, with results that typically persist for 12 to 24 months (Daneshgaran et al., 2025; Haq, 2025). The use of hyperdiluted calcium hydroxylapatite (hyperdiluted Radiesse) has been described specifically for GLP-1RA users undergoing rapid weight loss, combining volume replacement and collagen biostimulation to restore subcutaneous support and attenuate the gaunt appearance (Durairaj et al., 2025).

Poly-L-lactic acid (PLLA), a biostimulator that induces progressive neocollagenesis, has been investigated for improving facial laxity subsequent to GLP-1 analog therapy, with a gradual result dependent on multiple sessions (Signori et al., 2024). The biostimulatory rationale of PLLA involves macrophage differentiation toward the M2 subtype, with increased TGF- β expression in fibroblasts and recruitment of myofibroblasts and ADSCs to the application site, a mechanism particularly relevant in patients with drug-induced subcutaneous fat loss (Morzhanaeva et al., 2025).

Recent clinical studies provide more robust evidence for this indication: a multicenter case series of 15 women treated with PLLA and hyaluronic acid filler documented a statistically significant reduction in facial laxity and wrinkle severity at 90 days, with aesthetic improvement reported by 100% of participants (Avelar et al., 2026). A multicenter open-label study of 41 patients treated with PLLA combined with two hyaluronic acid fillers specific to the malar region demonstrated objective improvement in skin quality, facial contour, and hydration, with results maintained for up to nine months and no treatment-related adverse events (Lorenc et al., 2026).

Autologous fat grafting represents the more structural and durable volumetric alternative. Being autologous, abundant, biocompatible, and naturally integrated, it is considered by many authors the filler of choice for correcting facial atrophy, with the additional advantage that its fractions, macrofat, microfat, and nanofat, allow volume restoration while simultaneously improving skin texture and pigmentation (Strong et al., 2024). Its main limitation is partial and unpredictable graft resorption, with reported losses between 20% and 90% of the injected volume and retention stabilizing around twelve months, which motivates planned overcorrection and, occasionally, additional sessions (Lv et al., 2021). In the context of GLP-1RA-induced weight loss, fat transfer is frequently combined with facelifting to restore natural contours and avoid a skeletonized appearance (American Academy of Facial Plastic and Reconstructive Surgery, 2024).

3.4.2 Botulinum toxin and the role of neuromodulators

Botulinum toxin type A occupies a conceptually distinct position among these modalities. Unlike fillers and biostimulators, it does not act on the volume deficit that lies at the core of GLP-1RA-associated ptosis, but rather on the dynamic-wrinkle component and the muscular hyperactivity that accentuates the aged appearance. Its role in management is therefore adjuvant, not a substitute for volume replacement, which makes it inadequate as a stand-alone intervention for the condition. In a staged multimodal protocol described in the literature, the initial treatment step specifically prioritized skin quality and dynamic wrinkles, with botulinum toxin type A applied to the lateral canthal lines (9 units per side), the frontal region (12 units), and the glabella (20 units), preceding volume replacement with hyaluronic acid, polydioxanone threads, and polynucleotides (Haq, 2025). The rationale for this sequence is to first treat the dynamic component and texture, and only then restore structural volume, maximizing the synergy between modalities.

In the lower third of the face and the cervicofacial transition, botulinum toxin has a more specific application in relaxing the platysmal bands. By releasing the platysma's downward muscular pull, this procedure attenuates the

appearance of neck cords and contributes to jawline definition, being particularly relevant for cervical laxity, sometimes informally called “Ozempic neck,” which accompanies accelerated weight loss, given that cervical skin, thinner and with lower collagen density than facial skin, retracts less efficiently after volume loss (Catalfamo et al., 2025; Kılıç, 2025). Even so, the specific evidence for this indication in the GLP-1RA context is limited to reports and case series, without standardized comparative studies quantifying the isolated gain attributable to the neuromodulator.

3.4.3 Tightening and biostimulation technologies

When the predominant component is skin laxity, and not merely volume loss, energy-based technologies offer tightening through induction of neocollagenesis. Endotissue bipolar radiofrequency has been reported as an approach for the non-surgical treatment of GLP-1RA-associated laxity, promoting lifting through controlled thermal stimulation and dermal remodeling (Catalfamo et al., 2025). Microfocused ultrasound (MFU/HIFU) acts on deeper planes, including the superficial musculoaponeurotic system, creating zones of thermal injury that trigger immediate collagen contraction and subsequent neocollagenesis.

A systematic review documented improvement in skin tightening and wrinkle reduction in about 92% of patients at 90 days, with the effect sustained for up to one year, although of modest magnitude and without longer follow-up data (Contini et al., 2023). Polydioxanone (PDO) threads combine immediate mechanical lifting with stimulation of collagen production along the thread's path and have been incorporated into multimodal post-weight-loss rejuvenation protocols. A systematic review of PDO implants supports their safety and performance profile, although the effect is transient and evidence specific to the GLP-1RA context is limited (Haq, 2025; Martins et al., 2019).

Complementary topical approaches have also been investigated: a 12-week trial of a multi-ingredient volumizing cream in patients with rapid weight loss (including GLP-1/GIP users) demonstrated reduced wrinkle severity and increased skin and subcutaneous thickness on ultrasonography, in addition to improved hydration and skin firmness, although without direct comparison to injectable or surgical interventions (Nguyen et al., 2026). In an independent case series, four patients using GLP-1/GIP treated for four weeks with a distinct multi-ingredient topical formulation reported subjective improvement in firmness, elasticity, volume, hydration, and skin smoothness, which in turn reinforces the adjuvant role of topical approaches in this context (Parkinson, 2026).

3.4.4 Surgical approach

In cases of more pronounced ptosis and tissue excess, especially in patients with massive weight loss and low skin elasticity, non-surgical technologies achieve only partial correction and surgery becomes necessary. Midface lifting, using deep-plane techniques that reposition the superficial musculoaponeurotic system and the fat pads as a unit, is identified as an essential component of aesthetic rehabilitation, almost always combined with fat transfer to restore contours and avoid the skeletonized appearance that an isolated lift can produce (American Academy of Facial Plastic and Reconstructive Surgery, 2024). Rhytidectomy and neck lifting, alone or combined, definitively address the excess skin and platysmal bands that volume loss reveals (Daneshgaran et al., 2025). The decision between non-surgical and surgical approaches depends on the degree of laxity, skin quality, and patient expectations.

3.4.5 Preventive and adjuvant strategies

Beyond correction, literature signals the relevance of strategies that reduce the intensity of the condition before it develops. These include modulating the rate of weight loss, preserving lean mass through adequate protein intake and resistance training, and early optimization of dermal quality through supportive dermatological care. Coordination between the team conducting weight-loss therapy and the team providing aesthetic management enables proactive intervention, started during the weight-loss phase, rather than a purely reactive approach (Daneshgaran et al., 2025).

Preventive cosmetology protocols describe indicating collagen-stimulation therapies, biorevitalization, phototherapy, and radiofrequency already during preparation for starting GLP-1RA therapy, to preserve skin quality, facial musculature, and fat compartments before the condition develops (Kirsanova et al., 2025). A summary of the main modalities, their mechanisms, supporting evidence, and limitations is presented in Table 2.

Table 2. Overview of the main aesthetic solutions for GLP-1RA-associated facial ptosis, organized by therapeutic target.

Modality	Mechanism / Target	Supporting Evidence	Main Limitation
Hyaluronic acid fillers	Immediate compartmental volume replacement	Case series, multimodal protocols	Temporary (12–24 months); vascular risk
Hyperdiluted calcium hydroxylapatite	Volume replacement and collagen biostimulation	Specific case series in GLP-1RA users	Intermediate durability; technique-dependent
Poly-L-lactic acid (PLLA)	Gradual collagen biostimulation	Specific clinical series in GLP-1RA users (n = 15; n = 41); systematic review	Gradual result; multiple sessions
Autologous fat grafting	Autologous volumetric replacement and texture improvement	Reviews and meta-analysis of retention	Variable resorption (20–90%); surgical procedure
Botulinum toxin type A	Dynamic wrinkles; platysmal band relaxation	Multimodal case report; clinical extrapolation	Does not replace volume; adjuvant role only
Radiofrequency/microfocused ultrasound	Tightening via thermal neocollagenesis	Systematic reviews in facial laxity	Modest gain; does not correct volume
Polydioxanone (PDO) threads	Mechanical lifting and collagen stimulation	Systematic review of safety/performance	Transient effect; no GLP-1RA-specific data
Multi-ingredient topical volumizing creams	Hydration, firmness, and perceived volume	12-week trial (n = 33); case series (n = 4)	Modest effect; no direct comparison to injectable interventions
Midface lift/rhytidectomy	Repositioning of SMAS and fat pads	Expert recommendation; surgical series	Invasive; requires combination with volume restoration

Note: SMAS: superficial musculoaponeurotic system; GLP-1RA: GLP-1 receptor agonists. The evidence grading reflects a predominance of case series and reviews, not of randomized trials specific to this indication. Source: Authors, 2026.

4. Discussion

4.1 The causal debate: Specific pharmacological mechanism versus epiphenomenon of weight loss

The point of greatest tension in the literature is not the existence of facial ptosis, which is well documented, but its causal attribution. Two positions, held by distinct groups of authors, organize the debate.

4.1.1 The receptor-specific mechanism thesis

A group of authors argues that GLP-1RA would exert a direct deleterious effect on dermal homeostasis, beyond simple fat subtraction. Paschou et al. (2025) propose that adipose-derived stem cells (ADSCs) and fibroblasts express the GLP-1 receptor (GLP-1R) on their surface, such that pharmacological receptor stimulation would inhibit ADSC proliferation and differentiation and reduce their capacity to produce protective cytokines.

According to the same authors, the shortage of these cytokines would favor the production of reactive oxygen species (ROS) and oxidative damage to fibroblasts, in addition to reducing their migration and synthetic activity, with additional complementary mechanisms: decreased glucose uptake by ADSCs, with reduced ATP production and apoptosis; indirect reduction of estrogen production by dermal white adipose tissue, with less stimulation of collagen synthesis by fibroblasts; and interaction with advanced glycation end products (AGEs) and activation of

their receptors (RAGE). From this perspective, “Ozempic face” would be, at least in part, a cellular consequence of GLP-1R signaling, and not only of fat loss.

This proposal finds partial convergence in a second, independent review (Ridha et al., 2024), which attributes accelerated facial aging to the loss of dermal and subcutaneous white adipose tissue and to changes in ADSC proliferation and differentiation, with repercussions on hormonal and metabolic factors that compromise the skin's structural integrity and barrier function. Even so, it should be noted that the most specific links in this mechanistic chain (GLP-1R expression in ADSCs/fibroblasts, ROS production, ATP depletion, estrogen reduction, the AGE/RAGE axis) remain concentrated in these two secondary sources, still lacking direct validation by biomarkers in human tissue comparing users and non-users.

The clinical recognition of the phenomenon itself, documented by reviews that systematically describe the pattern of facial presentation (Kılıç, 2025) and its implications for the practice of facial plastic surgeons (Humphrey; Lawrence, 2023), precedes and motivates the search for a specific causal mechanism, even though these clinical descriptions, on their own, do not distinguish between the two competing hypotheses.

4.1.2 The weight-loss epiphenomenon thesis

The competing position, which holds majority support, argues that facial changes are non-specific and result from the magnitude and speed of weight loss, regardless of the agent that induces it. The argument rests on three observations. First, equivalent phenotypic and histological findings occur after massive weight loss from bariatric surgery, with structural changes in the dermis and reduced density of collagen and elastic fibers, in the absence of any GLP-1RA exposure (Paschou et al., 2025).

Second, a dedicated dermatological review argues that the relationship between the GLP-1 mechanism of action and facial fat loss is not characterized and may be unrelated, attributing the condition to the physics of rapid subcutaneous depletion combined with the natural decline in elastin turnover, an effect that would only become perceptible with accelerated weight loss (Carboni et al., 2024). Third, the authors note that natural weight loss, through diet and exercise, also affects facial appearance, but more gradually and less markedly, which suggests that the determining variable is speed, not the molecule (Catalfamo et al., 2025). This parallel is echoed in a recent synthesis, according to which post-weight-loss aesthetic changes are not exclusive to GLP-1RA and were already well described after bariatric interventions, pointing to a shared mechanism tied to weight loss itself (Baggett et al., 2025).

Adding to this debate is a more recent conceptual critique, which questions whether “Ozempic face” constitutes a distinct clinical entity or merely a construct amplified by the media and by nomenclature. It is argued that framing the phenomenon as a specific entity may exceed the currently available evidence base (Sharp, 2026). This position does not deny the observed changes but warns against reifying a label before causal specificity has been demonstrated.

4.1.3 The Central methodological gap

Resolving the debate runs into a design gap that neither side has yet overcome. No controlled study directly compares individuals who lost equivalent magnitude and speed of weight through GLP-1RA versus another method, such as an isocaloric or hypocaloric diet or bariatric surgery, while holding age, sex, degree of photoaging, and rate of weight loss constant. Without this control, the speed of weight loss remains a confounding variable inseparable from the putative pharmacological effect.

The evidence supporting the receptor-specific thesis is, for the most part, in vitro or mechanistic in nature, extrapolated to the clinical outcome, whereas the clinical evidence is predominantly observational, composed of case series and case reports without an adequate comparison group. The most comprehensive systematic review on the topic, in surveying the plastic surgery literature, explicitly acknowledged the limitations imposed by the biases of the included studies, most of which lacked a control group (Daneshgaran et al., 2025). Until this comparative design is carried out, causal attribution to the drug mechanism remains a biologically plausible, but unproven, inference.

A partial approximation of this design already exists in the literature: a retrospective cohort study (TriNetX database) compared GLP-1RA users and non-users within the type 2 diabetes subgroup, in which weight loss tends to be more modest than that observed in users treated for obesity, and even so found a higher incidence of brow ptosis and need for botulinum toxin among drug users (Saffari et al., 2026). This finding does not formally

control for the rate of weight loss between groups, but it weakens the interpretation that the magnitude of weight loss alone explains the phenomenon, and points to a replicable path (comparison by clinical subgroup with naturally distinct weight loss) while the ideal design is not carried out.

The extension of the phenotype to periorbital (Kapantais; Tsoutsanis, 2025) and perioral (Chen et al., 2026) regions, broadens the scope of what a definitive causal explanation would need to cover: a purely physical mechanism of adipose support loss would need to explain why compartments with different proportions of superficial fat respond differently, while a receptor-specific mechanism would need to demonstrate differential GLP-1R density or sensitivity in these regions, neither hypothesis has been directly tested at this level of anatomical granularity.

4.2 The dermatological paradox of GLP-1

An aspect frequently omitted from the aesthetic debate is that GLP-1 signaling also exhibits beneficial cutaneous effects, which complicates the narrative of a drug that is simply deleterious to the skin. GLP-1RAs have documented anti-inflammatory and antioxidant properties, with therapeutic benefit in inflammatory dermatoses such as psoriasis and hidradenitis suppurativa (Krajewski et al., 2024; Vilarrasa et al., 2024). *In vitro*, semaglutide reduced oxidative stress and promoted healing in human dermal fibroblasts, exerting a cytoprotective effect (Anastasiou et al., 2025).

Reviews on the role of GLP-1 in dermatology describe a reduced inflammatory response, increased angiogenesis, and favorable modulation of tissue regeneration mediated by TGF- β and metalloproteinases (Patino et al., 2025; Persson et al., 2025). There is also a proposal that GLP-1R signaling itself could, under certain conditions, favor collagen production and matrix turnover, partially mitigating the adverse effects of fat loss (Sataray-Rodriguez et al., 2025). This duality becomes sharper in a benefit-risk review aimed at dermatologists and plastic surgeons, which describes pleiotropic anti-inflammatory and immunomodulatory effects in dermatoses such as psoriasis, hidradenitis suppurativa, and acanthosis nigricans, alongside emerging adverse skin reactions and relevant perioperative considerations (delayed gastric emptying, risk of pulmonary aspiration) in candidates for aesthetic procedures (Cedirian et al., 2025).

This duality, the same signaling axis associated with both protective and potentially deleterious skin effects, reinforces that the observed clinical outcome results from a complex balance between mechanical volume subtraction, prior dermal status, and molecular effects that may operate in opposite directions. Simplifying the phenomenon to a single cause, whether fat loss or the receptor, is incompatible with the heterogeneity of the evidence.

4.3 Mechanistic interpretation of therapeutic responses

The mechanistic interpretation of these therapeutic responses is instructive. If structural volume replacement alone fully restores the prior appearance, the finding favors the interpretation that the phenomenon is predominantly structural, that is, a matter of fat and support subtraction. If, conversely, a deficit in dermal quality, elasticity, or texture persists even after adequate volume replacement, the finding would support the hypothesis of a cellular or receptor-specific contribution not correctable by volume alone.

The current literature, centered on reports of technical efficacy rather than standardized comparative outcomes, still does not allow conclusive discrimination between these scenarios, which brings the problem back to the same design gap discussed earlier. The available clinical studies illustrate this interpretive limit. Series using poly-L-lactic acid and hyaluronic acid fillers report consistent aesthetic and skin-quality improvement after isolated volume replacement (Avelar et al., 2026; Lorenc et al., 2026), which would at first favor the structural interpretation; however, none of these studies included a no-intervention comparison arm or measured objective dermal markers that would allow a concomitant cellular contribution to be excluded.

The same biostimulatory rationale attributed to PLLA (Morzhanaeva et al., 2025) also extends to hyperdiluted calcium hydroxylapatite (Durairaj et al., 2025); collagen induction via M2 macrophages and TGF- β is mechanistically compatible with both causal hypotheses, since it stimulates the dermal matrix regardless of which process caused its initial deterioration. Topical approaches (Nguyen et al., 2026; Parkinson, 2026) and preventive cosmetology protocols (Kirsanova et al., 2025) report benefits that are mostly subjective and related to skin quality, without directly addressing the volumetric component, which makes them informative but not decisive adjuvants for the central debate. Multimodal guidelines based on clinical experience (Haykal et al., 2025; Moradi et al., 2026) acknowledge this uncertainty by recommending a combination of modalities and

individualized follow-up rather than a single protocol grounded in a specific causal mechanism, a clinically prudent stance that also reflects the absence of an outcome capable of definitively arbitrating between the two theses.

4.4 Gaps and research agenda

The synthesis of evidence exposes an interconnected set of gaps that define a research agenda. First, and as a priority, controlled studies are needed that compare GLP-1RA to other weight-loss methods, matching the magnitude and speed of weight loss, age, sex, and degree of photoaging, the only design capable of isolating the class effect from the confounding variable represented by the rate of weight loss. This same systematic review already signaled that the available body of literature is composed mostly of studies without an adequate comparison group (Daneshgaran et al., 2025).

The magnitude of the phenomenon as a clinical and public-health concern, evidenced by the growth of online searches for related procedures (Mnajjed; Mims, 2025) and by growing recognition in related specialties, such as otolaryngology (Seidel; Bode, 2025), makes the proposed agenda even more urgent. Likewise, the already-established characterization of the combined loss of elastin, collagen, adipose volume, and muscle (Montecinos et al., 2024) offers a descriptive starting point on which the comparative and translational studies proposed here could be built.

Second, there is a need for studies incorporating objective biomarkers of dermal turnover, such as type I to type III collagen ratios, elastin quantification, and oxidative stress markers, comparing users and non-users, to directly test the predictions of the receptor-specific hypothesis in human tissue, not only in cell culture (Anastasiou et al., 2025; Paschou et al., 2025). Third, longitudinal studies with standardized imaging-based facial volumetry are lacking, ones that would replace case reports and perceptual assessments with reproducible measures of compartmental volume change over time and after drug discontinuation, allowing evaluation of the reversibility of the changes (Sharma et al., 2025).

Fourth, the very nosological delimitation of the phenomenon deserves scrutiny: it is necessary to establish, with objective criteria, whether “Ozempic face” constitutes a distinct entity or a point on the continuous spectrum of facial changes associated with any rapid weight loss, avoiding premature consolidation of a clinical label (Sharp, 2026). Coordinated attention to these gaps would transform a debate currently sustained by plausibility and observation into a question amenable to empirical resolution.

5. Conclusions

The association between GLP-1RA-mediated weight loss and facial volume loss with soft-tissue laxity is consistent across the available reports, clinically relevant, and supported by facial volumetry data, clinical series, and the documented rise in demand for rejuvenation procedures. In this restricted sense, the answer to the question that motivates this review is affirmative: weight loss achieved with these drugs is accompanied by facial changes that patients and clinicians perceive as premature aging. The promise of a definitive causal explanation, however, has not yet been fulfilled.

The existence of a specific pharmacological mechanism of the GLP-1 pathway, mediated by receptors on ADSCs and fibroblasts, is biologically plausible and consistent with molecular data, but has not been demonstrated in a design capable of separating it from the magnitude and speed of weight loss, which remain uncontrolled confounding variables. Whether these changes exceed what would be expected from comparable weight loss achieved by other means therefore remains an open question. The evidence is informative about the association and useful for generating mechanistic hypotheses, but immature regarding causal attribution, which reinforces caution against the premature consolidation of “Ozempic face” as an autonomous clinical entity. Progress in the field depends less on new observations of the phenomenon, which is already sufficiently described, and more on comparative and translational studies designed specifically to dissociate the drug effect from the weight-loss effect.

6. Authors' Contributions

Ana Beatriz Neves Félix: investigation, data curation, writing – original draft. *Camila de Oliveira Zendram*: investigation, data curation, writing – original draft. *Isabela Cristina de Pinho Rosa*: investigation, data curation, writing – original draft. *Amir Horiquni Barbosa*: conceptualization, methodology, investigation, data curation,

writing – original draft, writing – review & editing. Érica Ferrari Calissi: supervision, validation, writing – review & editing.

7. Conflicts of Interest

No conflicts of interest.

8. Ethics Approval

Not applicable.

9. Artificial Intelligence Statement: Declaration of Generative AI and AI-Assisted Technologies in the Writing Process

The authors declare the use of generative artificial intelligence tools (Claude Sonnet 5 and Claude Opus 5, Anthropic, 2026) in the preparation of this manuscript. AI tools were used to (a) execute the predefined Boolean search strategy programmatically against the PubMed/MEDLINE, OpenAlex, Europe PMC, and Crossref APIs, and compile the resulting records; and (b) assist with language editing and formatting to the journal's requirements.

All decisions regarding study eligibility, inclusion, and exclusion were made by the authors. Every retrieved record was screened by the authors against the predefined criteria, and every included reference was independently verified by the authors for authorship, publication venue, and content accuracy against the primary source. AI tools were not used to interpret findings, formulate conclusions, or determine the direction of the arguments presented. All AI-assisted content was reviewed and approved by the corresponding author, who assumes full responsibility for the scientific accuracy and integrity of the manuscript.

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