https://www.scirp.org/journal/jbise
J. Biomedical Science and Engineering,
2025, Vol. 18, (No. 3), pp: 45-59

Investigating the Impact of GLP-1 Receptor Agonist-Induced Fat Loss on Collagen Synthesis and Skin Elasticity

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Keywords: GLP-1 Receptor Agonists, Semaglutide, Fat Loss, Collagen Synthesis, Skin Elasticity, Dermal Fibroblasts, Skin Aging, Weight Management, Obesity, Type 2 Diabetes, Skin Sagging, Collagen Turnover
Received: February 10, 2025 **Accepted:** March 25, 2025 **Published:** March 28, 2025

ABSTRACT

The increasing use of glucagon-like peptide-1 (GLP-1) receptor agonists, including semaglutide, for weight management has sparked interest in understanding their broader physiological effects, particularly on skin health. GLP-1 receptor agonists are effective at inducing fat loss in patients with obesity and type 2 diabetes, but their influence on collagen synthesis and skin elasticity remains underexplored. This literature review investigates the effects of fat loss induced by GLP-1 receptor agonists on dermal health, with a focus on collagen turnover and the skin's ability to maintain elasticity. Collagen, a critical structural protein, is essential for skin strength, elasticity, and overall integrity. The mechanical properties of skin can be altered by fat loss, which raises questions about the balance between weight reduction and skin health during GLP-1 receptor agonist treatment. This review synthesizes findings from studies examining the role of fat loss on collagen production and skin elasticity, including clinical trials, animal models, and *in vitro* experiments. Comparative data from other weight loss interventions, such as bariatric surgery and lifestyle changes, are also considered to provide a broader context for understanding how GLP-1 receptor agonists influence dermal fibroblasts, collagen synthesis, and the development of skin sagging or laxity. We highlight gaps in the current literature and propose potential mechanisms by which GLP-1 receptor agonists might modulate collagen turnover, skin aging, and dermal elasticity, offering new insights into the broader

effects of these medications.

1. INTRODUCTION

In recent years, the class of GLP-1 receptor agonist medications have surged in popularity. These medications are currently indicated for the use of Type 2 Diabetes Mellitus (T2DM), obesity, and Obstructive Sleep Apnea (OSA) [1]. There was a noted 40× increase in the use of semaglutide, a GLP-1 agonist affiliated brand name "Ozempic" and "Wegovy", for the treatment of T2DM from 2019 to 2022 [2]. This increase was observed, in part, because of the weight loss benefits and lowered cardiovascular risk factors affiliated with this class of medications [3]. This surge in popularity highlights the growing interest in exploring the multifaceted benefits of GLP-1 receptor agonists beyond their traditional indications, underscoring the need for further research into their broader physiological and clinical effects.

Semaglutide and other GLP-1 receptor agonists mimic the actions of endogenous glucagon-like peptide-1 (GLP-1)/incretin hormone by activating the GLP-1 receptor. This hormone is naturally released in a biphasic fashion from enteroendocrine L cells in response to the absorption of nutrients. As a result, GLP-1 induces the production of insulin and glucose-dependent insulin for the regulation of blood sugar after a meal. Additionally, GLP-1 promotes proinsulin gene expression and increases the response of GLUT2 and glucokinase receptors to enhance insulin sensitivity [4]. Furthermore, this hormone has also been indicated in delayed gastric emptying which contributes to a sensation of early satiety and decreased appetite [3-5]. In turn, these effects contribute to the desired outcome of lowered hemoglobin A1c and weight loss.

In addition to the affiliated cardiovascular risk factors, obesity is attributed to a variety of dermatological conditions such as acanthosis nigricans, xerosis, candidiasis, striae distensae, and keratosis pilaris [6]. These conditions occur more frequently in patients with a higher BMI because of the altered epidermal barrier, reduced water permeability, impaired wound healing, and low collagen concentration [6-9]. Obesity modifies the extracellular matrix by changing the collagen III expression and dysregulating the regenerative process [10]. Consequently, weight loss has revealed a reduction in the incidence, a significant improvement, and/or complete reversal in these affiliated dermatoses due to improved collagen expression and skin regeneration [10-12]. Consequently, these findings underscore the importance of addressing obesity not only to mitigate systemic health risks but also to improve dermatological outcomes and skin health through enhanced collagen production and skin regeneration.

Collagen plays a crucial role in skin structure, strength (from the molecule construction of triple helices), and elasticity [13]. It is deposited in the extracellular matrix where it contributes to the mechanical structure, shape, and organization of tissues. These mechanical and elastic properties of fibril-forming collagen are possible through cross-linking reactions which contribute to cell growth, differentiation, and migration in the skin, muscles, and bones [14]. As a result, increased collagen in the skin is associated with enhanced appearance through measurable factors of hydration, elasticity, and wrinkles [13]. Over time, collagen may be affected through intrinsic and extrinsic variables such as glycation (as seen in diabetes mellitus), oxidative stress, mechanical stress, and UV radiation [15]. This highlights collagen's pivotal role in maintaining the structural and functional integrity of the skin, emphasizing its importance in both aesthetic and medical contexts.

Thus, the turnover and synthesis of collagen contributes to the visible effects of skin aging and elasticity. As people age, the collagen in the extracellular matrix undergoes fragmentation which impairs the mechanical properties of the skin and dermal cell functions. This is evidenced by the reduction in basal keratinocyte proliferation and the flattening of the dermal-epidermal junction. Flattening of the dermal-epidermal junction is instrumental in making the epidermis more fragile by making it less resistant to shearing forces. In the fragmented collagen extracellular matrix, fibroblasts (cells that produce collagen) have reduced surface area and are unable to produce stronger collagen impacting skin strength and elasticity [16]. Therefore, enhancing collagen production has been attributed to improvement in skin hydration, skin elasticity, medical scaffold treatment, GERD, and various types of arthritis [17]. As such, promoting collagen synthesis and

reducing collagen fragmentation present promising avenues for improving skin strength, elasticity, and overall health, particularly in aging and disease-related contexts.

Although research has been conducted on the dramatic effects of weight loss on collagen following gastric bypass and other bariatric/cosmetic procedures, little research has focused on the impact of pharmacological-induced weight loss regarding dermatology-related issues [18]. Likewise, extensive research has been conducted on the effects of GLP-1 receptor agonists on cardiovascular risk factors but has failed to address dermatological concerns [19]. Therefore, to further assess whether GLP-1 receptor agonist medications affect collagen synthesis and skin elasticity (through their induction of visceral weight loss) additional discussion/research is necessary.

2. DISCUSSION

2.1. Fat Loss and Its Impact on Skin Structure

Fat loss significantly influences the architecture and composition of the skin, primarily affecting the dermal and subcutaneous layers. Adipose tissue, composed of white adipose tissue (WAT) and brown adipose tissue (BAT), provides insulation, cushioning, and energy storage. During fat loss, adipocytes release triglycerides into circulation through lipolysis, causing a reduction in the size of fat cells but not their number [20]. Additionally, the loss of subcutaneous fat exposes underlying musculoskeletal features, intensifying the appearance of wrinkles and sagging [21]. This reduction leads to decreased subcutaneous fat, compromising the skin's structural support.

2.1.1. Effects of Rapid Weight Loss on Collagen and Elasticity

Weight loss, especially rapid or massive, often results in decreased collagen synthesis and elasticity, as observed in patients after bariatric surgery. A study by Rocha *et al.*, examining individuals who experienced massive weight loss post-bariatric surgery, revealed notable changes in skin composition [22]. Patients with massive weight loss showed a significant reduction in thick collagen fibers (mean volume fraction reduced from 41% to 32%, $p = 0.048$) and a notable increase in thin collagen fibers (mean volume fraction increased from 34% to 45%, $p = 0.0085$), indicating collagen remodeling. Additionally, an increase in elastic fiber density was observed, which correlated with enhanced skin elasticity. Elastic fiber density increased significantly in the massive weight loss group, with a mean density of 0.01275 $\mu m/\mu m^2$ compared to 0.00797 $\mu m/\mu m^2$ in the morbid obesity group ($p < 0.0001$). This increase suggests an adaptive response to support increased skin elasticity after fat reduction. However, despite these changes, the skin often exhibited laxity due to the loss of underlying fat, leading to a less firm appearance.

When adipose tissue is lost, collagen synthesis generally decreases, as the process of fat loss often leads to a reduction in the production of extracellular matrix components like collagen, particularly collagen type VI, which is prevalent in adipose tissue [23]. Collagen is the most abundant structural component of the adipose tissue extracellular matrix (ECM) and provides tissue architecture and cellular function support, as well as morphogenesis. Adipose tissue contains several types of collagen, including type I, III, IV, and VI, which contribute to tissue integrity and elasticity [24]. During obesity, adipose tissue often experiences increased collagen deposition, leading to a condition called "adipose tissue fibrosis," where the extracellular matrix becomes stiffer due to excessive collagen production [25]. From this we can postulate that during rapid weight loss adipose tissue experiences decreased collagen deposition. Studies suggest that impaired cross-linking of collagen fibers leads to a weaker ECM and reduced mechanical stability of the skin. A clinical trial by Liu *et al.* found that fat mass reduction was negatively correlated with pericellular collagen accumulation and thus as fat mass decreases, collagen accumulation around adipocytes decreases as well [26]. Specific enzymes such as lysyl oxidase (LOX), lysyl oxidase-like 4 (LOXL4), transglutaminase 1 (TGM1), and procollagen-lysine, 2-oxoglutarate 5-dioxygenase 2 and 3 (PLOD2, PLOD3) were markedly reduced in transcriptomic analyses of genes encoding enzymes involved in collagen biosynthesis and cross-linking [26]. This suggests impaired cross-linking of collagen fibers, leading to a weaker extracellular matrix (ECM) and reduced mechanical stability of the skin. These structural changes led to reduced skin tension and increased

elasticity, contributing to skin laxity and the formation of folds in areas like the abdomen, arms, and thighs. Another study by Gallo *et al.* noted a decline in structural proteins like collagen XIV and vinculin, leading to reduced skin turgor and elasticity [27]. They found that the inflammatory state associated with obesity further altered the dermal matrix, with chronic inflammation persisting even after substantial weight loss.

2.1.2. GLP-1 Receptor Agonist's Role in Fat Loss and Skin Impact

GLP-1 Receptor Agonists promote weight loss through three primary mechanisms: appetite suppression, delayed gastric emptying, and improved glucose homeostasis. By mimicking incretin hormones, GLP-1 receptor agonists slow gastric emptying and reduce food intake, facilitating significant fat mass reduction [3-5]. Its effect on weight reduction is achieved by modulating the neural pathways responsible for hunger and satiety, leading to reduced caloric intake [28, 29]. By targeting GLP-1 receptors in the hypothalamus, these medications significantly decrease hunger while enhancing the sensation of fullness. This results in a caloric deficit that facilitates fat loss without the need for severe dietary restrictions. Additionally, GLP-1 receptor agonists slow gastric emptying, reducing postprandial glucose spikes and further reinforcing appetite control [28, 29]. Their ability to preferentially reduce fat mass, as opposed to lean body mass, distinguishes it from some other weight loss interventions.

2.1.3. Clinical Evidence on GLP-1 Receptor Agonist and Skin Effects

Anyiam *et al.* demonstrated that over a 12-week period, semaglutide achieved an average fat mass reduction of 4.0 kg, which represents over half of the total weight lost during this time [28]. This targeted reduction is particularly important for preserving metabolic health and maintaining physical functionality during weight loss. In addition to its effects on weight, semaglutide enhances metabolic health by increasing insulin sensitivity and reducing fasting glucose levels [29]. Hence these changes not only support weight loss but also improve the management of comorbid conditions such as type 2 diabetes. In clinical settings, semaglutide has shown greater efficacy in achieving significant weight loss compared to other pharmacological agents like liraglutide and orlistat. In the cohort study by Ghusn *et al.*, at doses of 1.7 and 2.4 mg, patients on semaglutide achieved a mean weight loss of 10.9% over six months, which surpassed the outcomes seen with lifestyle interventions alone [29]. This makes semaglutide a compelling option for addressing obesity and its associated complications. It is important to note that the weight loss induced by semaglutide can result in changes to skin structure similar to those observed with other weight loss methods, such as alterations in collagen composition and skin elasticity. A systematic review by Jafar *et al.* highlighted that patients on semaglutide experience regional fat loss, including reductions in cheek and temporal fat pads, contributing to noticeable changes in facial aesthetics [21]. However, specific studies directly examining semaglutide's impact on skin properties are limited, necessitating further research.

2.1.4. Comparison of Weight Loss Interventions on Skin

Comparative studies of bariatric surgery, lifestyle modifications, and pharmacological agents reveal distinct effects on skin structure. Bariatric surgery is one of the most effective interventions for rapid weight loss. However, the sudden reduction in subcutaneous fat often results in excess skin and reduced elasticity due to insufficient time for dermal remodeling [21, 22]. The proteomic analysis of skin in post-bariatric patients has shown a marked reduction in collagen-related proteins, emphasizing the need for targeted interventions to support skin health during and after weight loss. Post-bariatric surgery, the absorption of vitamins like A and D may be significantly reduced, leading to dryness, thinning, or even impaired wound healing [30]. The skin is directly impacted by the absorption of various nutrients that are crucial for collagen synthesis, cell turnover, and overall skin elasticity. For instance, vitamin A promotes keratinization and immune system function. Vitamin A deficiency is often associated with dry, keratotic skin, while vitamin D deficiency can impact cell growth and differentiation, affecting skin regeneration [30]. A multidisciplinary approach involving nutritional monitoring and appropriate supplementation is essential for preventing or managing these issues and supporting optimal skin health post-surgery.

In contrast, lifestyle changes that promote gradual weight loss tend to preserve skin integrity better,

albeit with less dramatic weight reduction outcomes. Manzoni *et al.* found that adequate hydration and a balanced diet rich in antioxidants, vitamins, and trace elements can support collagen synthesis and mitigate oxidative stress, which accelerates skin aging [30]. For instance, a review by Cao *et al.* reported that water promotes dermal hydration and elasticity, while copper and zinc aid in collagen stabilization and repair [31]. Nutrients such as iron and copper are vital for the synthesis of collagen and the overall health of skin and connective tissue. Iron deficiency, common post-bariatric surgery, may result in pallor, glossitis, and brittle nails, while copper deficiency can impair wound healing and lead to depigmentation and fragile hair [30]. In contrast, poor dietary habits can exacerbate skin aging. High-fat or high-sugar diets contribute to chronic inflammation and promote advanced glycation end-product (AGE) formation, which weaken collagen networks [31]. AGEs damage collagen and elastin, the proteins essential for maintaining skin firmness and elasticity. Addressing these dietary factors can significantly augment skin health during weight loss, making gradual, nutrition-focused lifestyle changes a cornerstone of both metabolic and dermatological well-being.

Pharmacological weight loss treatments, such as semaglutide and liraglutide, offer a middle ground between surgical and lifestyle approaches. While less invasive than surgery, the associated weight loss can result in similar aesthetic concerns, such as increased skin laxity and accelerated apparent aging due to subcutaneous fat loss. Semaglutide, in particular, induces a slower and more consistent fat loss, reducing the likelihood of severe skin laxity. By preserving lean body mass and enhancing fat mass reduction, semaglutide supports better skin structural integrity compared to bariatric surgery [22, 29]. Understanding the impact of these interventions on skin health provides insights into semaglutide's unique benefits. While bariatric surgery and rapid weight loss are associated with nutritional deficiencies which lead to skin aging due to structural disruptions, semaglutide's gradual and targeted fat loss minimizes these adverse effects. Ensuring supplementation, combining semaglutide with a nutrient-rich diet, can help preserve skin elasticity and overall health during weight loss [22, 29, 32]. However, some patients may still experience a reduction in overall food intake, potentially leading to deficiencies in essential nutrients such as vitamin D, B12, and protein, all of which are crucial for maintaining skin health and elasticity.

2.2. Collagen Synthesis and Skin Elasticity

Dermal fibroblasts (DFs) are the main cellular components of the skin responsible for the form and function of the extracellular matrix (ECM). They synthesize and remodel ECM components, including collagen (types I and III), elastin, proteoglycans, and glycoproteins, which provide strength, elasticity, and hydration to the skin. Skin immunity and angiogenesis are also regulated by DFs through control of lymphocyte differentiation and production of VEGFs and FGFs [33]. Additionally, DFs facilitate ECM remodeling to sustain fibroblasts. A combination of aging and environmental factors, particularly ultraviolet (UV) exposure, influences collagen synthesis by decreasing the number and activity of DFs. The production of collagen types I and III decreases, while matrix metalloproteinases (MMPs), which destroy the ECM through collagen fragmentation, become activated. While UV rays accelerate these processes through directly stimulating activating protein 1 (AP-1), MMP levels also naturally rise gradually in aging skin [34]. Over time, the accumulation of end products damages collagen fibers, reducing their turnover. The combination of these changes contribute to the visible signs of skin aging.

The relationship between collagen density, skin elasticity, and skin firmness is best represented by studies highlighting the impact of collagen supplementation on skin hydration, elasticity, wrinkles, and density. De Miranda, *et al.* reported improved skin hydration and elasticity and reduced facial wrinkles after only 60 to 90 days of collagen peptide supplementation. Doses as low as 2.5 grams per day of collagen peptides can show these improvements, which can persist for up to 30 days after supplementation ends [35]. These findings emphasize that optimal collagen levels play a critical role in maintaining skin elasticity, firmness, and smoothness. However, as dermal fibroblasts (DFs) decline and matrix metalloproteinases (MMPs) increase with age, collagen synthesis decreases, leading to visible signs of aging such as reduced elasticity, more wrinkles, and decreased hydration [33]. Intrinsic skin aging further contributes to the loss of elastic fibers. This, in combination with decreased collagen, reduces dermal volume, which is seen as fine wrinkles. When

compared to young skin, which has many, well-arranged collagen fibers, those in aged skin are fragmented and poorly distributed [36]. Factors such as fat loss and weight fluctuations can also influence collagen levels, further affecting skin firmness and appearance.

Glucagon-like peptide-1 receptor agonists (GLP-1RAs) impact dermal fibroblast function and collagen synthesis through various molecular mechanisms. GLP-1RAs can modulate fibroblast function by activating the GLP-1 receptor, a G protein-coupled receptor (GPCR). This activation leads to downstream signaling pathways, including the cyclic adenosine monophosphate (cAMP) pathway, that have the potential to influence collagen synthesis and fibroblast function [37, 38]. GLP-1RAs have also been shown to cross-activate the insulin-like growth factor 1 receptor (IGF-IR), which promotes elastin gene expression and elastic fiber production in fibroblasts [38].

Significant fat loss can affect collagen turnover and skin elasticity, exemplified by Rasmussen, *et al.* when using the aminoterminal propeptide of type III pro-collagen (S-PIIINP) as a marker for collagen over a period of weight loss. This demonstrated that type III collagen turnover was elevated in obesity, with higher levels of S-PIIINP, but decreased during times of weight loss [39]. This suggests there is reduced collagen synthesis after weight loss takes place and potentially less collagen production in those with lower body mass. Orpheu *et al.* focused on post-bariatric plastic surgery candidates, whose massive weight loss was associated with a depletion of collagen in abdominal skin, leading to a flaccid appearance. Although collagen amounts declined, elastic fibers did not, and there was no correlation with age [40]. This further supports the relationship between fat loss and collagen content. Aging further complicates fat and collagen balance as muscle mass decreases and fat mass increases with age. Collagen peptide supplementation is a potential solution to improve skin's elasticity and wrinkled appearance while aiding fat reduction, as shown by Park, *et al.*, who confirmed 15 grams per day of collagen supplementation can reduce body fat in adults age 50 and up [41]. Appropriate collagen supplementation is a strategy for maintaining skin health and weight loss during aging, while decreased collagen amounts may have the opposite effect.

2.3. Mechanisms by Which GLP-1 Receptor Agonists May Influence Collagen Synthesis

2.3.1. Direct Effects of GLP-1 Receptor Agonists on Fibroblast Activity

GLP-1 receptor agonists, including semaglutide, are known for their effectiveness in managing obesity and type 2 diabetes, but their effects on dermal fibroblasts and skin health remain underexplored. Dermal fibroblasts are responsible for synthesizing the extracellular matrix (ECM), including collagen and elastin, which provide structure and elasticity to the skin [42]. The volume loss associated with GLP-1 receptor agonist-induced fat reduction raises concerns about its impact on the skin's ability to maintain integrity, particularly in the face. Research indicates that GLP-1 receptor signaling may influence fibroblast activity by enhancing collagen production and ECM turnover, potentially mitigating the adverse effects of fat loss on skin elasticity [43, 44]. Preclinical studies suggest this signaling enhances the synthesis of type I and III collagen, vital for dermal structure [45]. However, these mechanisms are not fully understood, leaving significant gaps in knowledge regarding the direct role of GLP-1 receptor agonists in dermal health. For patients undergoing rapid weight loss, addressing these potential challenges is critical to preserving skin appearance and function. Determining whether GLP-1 receptor agonists have protective effects on fibroblast activity or whether additional interventions, such as topical treatments or supplements, are necessary to maintain dermal health remains a priority. This is especially relevant given the growing popularity of GLP-1 receptor agonists, which underscores the need for further research into their dermatologic implications.

2.3.2. GLP-1 Receptor Agonist-Induced Fat Loss and Dermal Health

The rapid weight loss facilitated by GLP-1 receptor agonists often leads to significant facial fat reduction, resulting in noticeable aesthetic changes like a hollow or gaunt appearance, colloquially termed "Ozempic face" or "Semaglutide face" [44, 46]. Facial fat pads, which provide youthful contours, diminish with fat loss, leading to skin sagging and an imbalance in facial harmony. This can create psychological distress, as patients who achieve weight loss may struggle with dissatisfaction regarding their facial appearance. While

anecdotal evidence highlights these concerns, clinical data on "Ozempic face" remain limited. The loss of subcutaneous fat beneath the skin further challenges skin elasticity, exacerbating visible aging signs [47]. Aesthetic treatments like biostimulatory dermal fillers, including calcium hydroxylapatite (CaHA) and poly-L-lactic acid (PLLA), have been shown to restore lost volume while stimulating collagen production, helping rebuild the skin's structure over time [48]. These interventions are crucial for patients experiencing rapid fat loss, offering a viable solution to counteract the aesthetic consequences and maintain facial symmetry [44]. Ultimately, an integrative approach addressing both physical and emotional well-being is essential to optimize outcomes for patients using GLP-1 receptor agonists.

2.3.3. Systemic Effects of Fat Loss on Skin Health

GLP-1 receptor agonist-induced fat loss impacts systemic factors such as inflammation and hormonal balance, both of which are critical to skin health. GLP-1 receptor agonists, including liraglutide, have demonstrated anti-inflammatory effects by reducing the expression of pro-inflammatory cytokines like tumor necrosis factor-α (TNF-α), a contributor to collagen degradation and skin aging [49, 50]. By inhibiting nuclear factor-kappa B (NF-κB), GLP-1 receptor signaling mitigates inflammation, which can otherwise accelerate skin aging and impair collagen synthesis. Clinical studies have shown reductions in TNF-α levels by as much as 20% with GLP-1 receptor activation, highlighting its potential dermatologic benefits [51]. Additionally, adipose tissue serves as a source of adipokines such as leptin and adiponectin, which regulate skin physiology and collagen production [51]. GLP-1 receptor agonist-induced fat loss alters adipokine signaling, potentially reducing their beneficial effects on skin integrity [52]. The systemic hormonal changes accompanying rapid weight loss can further challenge the skin's ability to maintain elasticity and structure. These findings emphasize the need for an integrated approach to managing skin health in patients undergoing GLP-1 receptor agonist therapy. A deeper understanding of the relationship between fat loss, inflammation, and hormonal changes is crucial to developing strategies that preserve skin quality.

2.3.4. Role of Adipokines in Skin Health

Adipokines, bioactive molecules secreted by adipose tissue, play a pivotal role in regulating skin physiology, including collagen synthesis and extracellular matrix remodeling [52]. GLP-1 receptor agonist-induced fat loss may alter adipokine signaling pathways, impacting the skin's regenerative processes and overall health [53]. Leptin and adiponectin, two key adipokines, are involved in maintaining dermal integrity by promoting collagen production and influencing fibroblast activity. Preclinical studies have also shown that GLP-1 receptor expression in skin cells, particularly around hair follicles, suggests a potential direct role in modulating dermal functions [45, 51]. However, as fat reserves diminish, the reduced secretion of adipokines may impair collagen synthesis, exacerbating visible signs of aging such as wrinkles and skin thinning. Emerging treatments like adipose collagen fragments (ACF) have shown promise in enhancing skin health, but their interaction with GLP-1 receptor agonist-induced adipokine changes remains unexplored. Furthermore, GLP-1 receptor agonists' influence on lipid metabolism, including their regulation of lipolysis and lipid storage, may contribute to skin changes [51]. These findings highlight the need for targeted research to fully understand the impact of GLP-1 receptor agonists on adipokine signaling and their implications for skin health.

2.4. Clinical Evidence and Research Findings

GLP-1 receptor agonists represent a class of medications that has revolutionized the approach to diabetes and obesity by providing unprecedented added value due to the induction of rapid weight loss. These metabolic steps forward have also raised awareness of dermatological sequelae, including facial fat loss and skin laxity, which may represent an unwanted consequence of weight loss.

One of the latest observations is the so-called "Semaglutide Face," first reported by Haykal *et al.* [44]. It describes a profound loss of facial fat within the subcutaneous layer, resulting in hollowing around the periorbital, temporal, and midface regions. This will eventually lead to an undefined, droopy look along the

mandible and mouth. As supportive fat pads become depleted, skin laxity is further demarcated, accelerating the apparent process of aging, with all the aesthetic and psychological burdens it carries for the patient. Haykal *et al.* emphasized that these changes are not injurious to health but constitute the cosmetic compromise that accompanies the dramatic weight reductions produced by semaglutide [44]. The psychological burden of these cosmetic changes underscores the need for strategies to manage or mitigate such effects in patients undergoing treatment.

Skin laxity is one more common result related to quick weight loss, meaning the loss of skin elasticity. The accelerated nature of weight loss mediated through the GLP-1 receptor agonist usually leaves no time for the skin to shrink along with changes in the composition of underlying fat. This usually leads to hanging sites, as evidenced on the face, neck, arms, abdomen, and thighs. According to Hany *et al.* (2024), the absence of underlying fat pads accentuates any deepened folds, wrinkles, and loss of elasticity. Beyond the aesthetic issues, severe skin laxity may also be functionally problematic, including limited mobility, physical discomfort due to skin folds, and impaired hygiene in the affected areas [44, 54]. It is important to note, however, that changes in collagen composition and skin elasticity observed with GLP-1RAs are reversible. Dermatologic treatments such as autologous fat transfers, composite fat grafting, and soft tissue filler injections can reverse these changes by providing adipose-derived stem cells (ADSCs) and volume and elasticity [55]. Addressing these challenges may require a multidisciplinary approach, including dermatological and surgical interventions, to improve patient outcomes.

2.4.1. Comparison with Other Weight-Loss Interventions

The effect of semaglutide and other GLP-1 receptor agonists on skin health is comparable to other weight loss interventions, such as bariatric surgery and lifestyle changes; however, there are some important differences. Bariatric surgery has conventionally been associated with extreme weight loss and consequent skin laxity. Manzoni *et al.* (2015) reported increased levels of type III collagen-an immature type of collagen-in the skin following bariatric surgery [30]. Though type III collagen is important during the initial stages of wound healing, its excessive production may cause disturbances in normal skin architecture, inhibit collagen remodeling, and thus result in diminished skin elasticity [55]. Similarly, Hany *et al.* (2024) performed a histological comparative study of skin samples from both surgical and non-surgical massive weight loss individuals [54]. Their findings indicated a significant decrease in elastic fibers in the abdominal skin of the SMWL group, underlining the lesser resilience of the skin after surgical interventions. On the other hand, the more gradual weight loss associated with lifestyle interventions-that is, diet and exercise-allows the skin more time to adapt, thus potentially mitigating risks of excess skin and laxity [56, 57]. Thus, while lifestyle interventions may reduce risk for skin laxity, they may not confer equivalent metabolic benefits or weight loss outcomes.

Other weight loss medications that may be comparable to semaglutide include phentermine-topiramate, orlistat, bupropion-naltrexone, and setmelanotide. Phentermine-topiramate causes slower weight loss than semaglutide, which may reduce the risk of excessive loose skin. A study by Gasoyan *et al.* reported that semaglutide resulted in an average weight loss of approximately more than 10% over 52 weeks [58]. In contrast, data from the CONQUER trial published by Enright *et al.* indicated that phentermine-topiramate led to a weight loss of about 10% over a similar period of 56 weeks [59]. Naltrexone-bupropion and orlistat also have slower weight reduction, which may allow for better skin adaptation. A systematic review conducted by Moiz *et al.* discovered that older anti-obesity medications like orlistat, phentermine-topiramate, and bupropion-naltrexone have not been as successful as semaglutide in achieving substantial weight loss and were associated with less produced weight loss outcomes [60]. There have been limited studies on phentermine-topiramate and setmelanotide's direct effect on collagen turnover. Given the absence of targeted research on the direct impact on collagen synthesis for orlistat and bupropion-naltrexone, it is unclear how these medications may influence collagen synthesis and skin elasticity. Further randomized control trials that directly compare the weight loss efficacy, collagen turnover, and skin elasticity of semaglutide versus other weight loss medications are needed.

2.4.2. Gaps in Knowledge and Future Research Directions

Despite the growing interest in its dermatological effects, there are still significant knowledge gaps with regard to the long-term effect of GLP-1 receptor agonists on skin health. Most current literature has focused on metabolic and weight-reduction benefits without consideration for how such changes may influence skin elasticity, collagen synthesis, and general dermatological health. Although the initial findings from studies indeed show that rapid weight loss associated with GLP-1 receptor agonists is often linked to skin laxity and compromised collagen integrity, few systematic or longitudinal studies have been conducted thus far.

It has yet to be determined whether GLP-1 receptor agonists act directly on collagen synthesis and skin remodeling or whether these changes occur as a consequence of the rapid fat loss. The influence of GLP-1 receptor activation on various molecular pathways, in turn, might explain the effects of GLP-1 on collagen homeostasis and skin integrity. In addition, comparative studies of semaglutide with other weight loss interventions, like bariatric surgery or lifestyle modifications, would go a long way in elucidating strategies for mitigating adverse dermatological effects. Novel strategies that may improve skin outcomes in the context of weight loss include adjunctive therapies targeting skin elasticity or fat redistribution. Such studies would help to address these knowledge gaps and give a better view of the pros and cons of GLP-1 receptor agonists, thus helping healthcare professionals in the management and satisfaction of patients.

GLP-1 receptor agonists have an unparalleled effect on weight loss, but the dermatological impacts, such as skin laxity and facial fat loss, require further attention. As clinicians and researchers continue to explore the many facets of the impact of GLP-1 receptor agonists, a balanced approach considering both metabolic benefits and dermatological outcomes is essential. GLP-1 receptor agonist treatments, with deep insight into the knowledge gap in skin health and collagen remodeling, will be critical to realizing its full therapeutic potential, considering aesthetic and functional skin changes in patients.

2.5. Implications for Dermatology Practice

While all GLP-1 receptor agonists are powerful for weight loss, they equally pose unique challenges to dermatological practice. Rapid weight loss often leads to excess loose skin, loss of facial volume, and prematurely aged features components of a condition popularly referred to in the media and social conversation as "Ozempic Face" [44]. These cosmetic concerns will often necessitate skin tightening procedures, injectable fillers, and other dermatological treatments to regain a healthy, more youthful appearance and improve overall patient outcomes. Media attention to the "Ozempic Face" has made some leery of GLP-1 receptor agonists as a treatment modality.

2.5.1. Skin Rejuvenation Therapies for Post-Weight Loss Patients

There are a myriad of therapies available that can serve to counteract skin laxity and collagen loss following rapid fat reduction. Popular treatments include laser resurfacing, microneedling, radiofrequency (RF) therapy, and ultrasound therapy [61]. Laser resurfacing promotes fibroplasia and collagen synthesis, tightening facial skin and rejuvenating its appearance [62]. Microneedling, also called percutaneous collagen induction therapy, creates controlled micro-injuries to stimulate collagen and elastin production, improving skin texture and elasticity [63]. Microneedling can be associated with RF energy to enhance collagen production in the deeper dermal layers [64]. These present solutions for wrinkled, scarred, and sagging skin of patients with sudden weight loss.

2.5.2. Ultrasound and Injectable Treatments for Collagen Stimulation

Ultrasound therapies, including high-intensity focused ultrasound (HIFU) and microfocused ultrasound (MFU), are increasingly used to improve collagen production and skin firmness. These technologies deliver targeted energy to specific tissue layers, sparing the epidermis while remodeling the deeper dermis and the superficial musculoaponeurotic system [65]. Injectable fillers, particularly those containing hyaluronic acid, have also gained popularity for restoring lost facial volume and contour. Hyaluronic acid, a polysaccharide naturally found in the dermis, is prized for its ability to retain moisture and improve skin elasticity [66]. For patients who have facial fat loss from GLP-1 agonists, injectable fillers will help balance out

these effects to provide a fresh, youthful appearance.

2.5.3. Platelet-Rich Plasma and Topical Interventions

Platelet-rich plasma (PRP) represents a versatile skin rejuvenation treatment which is derived from a patient's own blood. PRP's concentrated growth factors stimulate cell repair, angiogenesis, and collagen production, promoting a more youthful and revitalized skin texture [67]. PRP works even better when supplemented with other therapies such as injectable fillers, lasers, and ultrasound. Other less invasive options to enhance skin integrity include topical treatments of retinoids and collagen supplements. Retinoids stimulate collagen synthesis and inhibit enzymes that degrade collagen, while collagen supplements improve elasticity and counteract some aspects of age-related collagen loss. This is according to Bolke, 2019, and Quan, 2023 [68, 69]. Collectively, these interventions provide a multi-faceted approach to combat the visible effects of aging and restore a healthier skin appearance.

2.5.4. Future Directions in Dermatologic Research

Dermatologists involved in semaglutide treatment should always consider keeping the skin of the patient healthy. They should emphasize individualistic skincare by following an individualistic routine that includes hyaluronic acid, peptides, and ceramides for hydration, collagen support, and barrier protection, respectively. Daily use of sunscreen will protect against UV-induced photo-damage, and moisturizer will help in hydration and elasticity. Topical retinoids may also be prescribed for collagen production. Early education regarding the potential for facial volume loss will provide these patients with opportunities to consider prevention or correction options, which include injectable fillers or microneedling. Dietary recommendations, including antioxidant-rich foods and supplements containing collagen, can be provided to further support skin health.

Further studies are needed to elucidate the relationship between dermatologic health and rapid weight loss treatments. Longitudinal studies can assess changes in skin elasticity, skin hydration, and collagen density in patients on GLP-1 receptor agonists. Comparison studies using weight loss medications—semaglutide, liraglutide, and tirzepatide—may reveal drug-specific effects with respect to skin health. The molecular mechanism for the changes observed in the skin after weight loss may promote novel treatments aimed at reducing possible side effects. Such a finding might represent the beginning of adjunctive treatments or supplements aimed at maintaining skin elasticity and avoiding facial volume loss during weight reduction.

3. CONCLUSIONS

GLP-1 receptor agonist-induced fat loss presents significant implications for collagen synthesis, skin elasticity, and overall dermatologic health. These agents effectively promote fat reduction, which can alter dermal structure and contribute to changes in skin appearance. Collagen, a critical component for maintaining skin strength and elasticity, may be affected by fat loss, potentially impacting skin integrity and accelerating visible signs of aging, such as increased laxity and wrinkling. Additionally, reduced subcutaneous fat may exacerbate conditions like cellulite or contribute to a more aged or gaunt facial appearance, raising aesthetic concerns for patients undergoing rapid weight loss.

While current evidence suggests that GLP-1 receptor agonists may influence skin health, further research is needed to elucidate their long-term effects on collagen dynamics, fibroblast activity, and overall dermal remodeling. Studies investigating the molecular pathways linking GLP-1 receptor activation to extracellular matrix homeostasis, wound healing, and age-related skin changes would provide valuable insights. Moreover, controlled clinical trials assessing dermatologic outcomes in patients on long-term GLP-1 therapy are necessary to develop targeted interventions for maintaining skin integrity.

For dermatologists, understanding the systemic changes associated with GLP-1 receptor agonists is essential for managing the skin health of patients undergoing significant weight loss. This includes monitoring for potential reductions in skin elasticity, identifying individuals at higher risk for excessive skin sagging, and exploring adjunct therapies such as biostimulatory dermal fillers, microneedling with platelet-rich

plasma (PRP), collagen-stimulating peptides, or energy-based skin tightening modalities. Additionally, patient education on optimal skincare, including hydration, sun protection, and collagen-supportive nutrition, can help mitigate adverse dermatologic effects.

The increasing use of GLP-1 receptor agonists for weight management highlights the need for dermatologists to integrate these insights into patient care. By adopting a comprehensive, patient-centered approach, clinicians can proactively address both the aesthetic and dermatologic concerns associated with rapid weight loss. Collaboration between endocrinologists, dermatologists, and aesthetic specialists will be crucial in optimizing patient outcomes, ensuring that weight loss benefits are complemented by strategies to maintain skin health and resilience.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest regarding the publication of this paper.

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